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Acute Gain in Minimal Lumen Area Following Implantation of Everolimus-Eluting ABSORB Biodegradable Vascular Scaffolds or Xience Metallic Stents

Intravascular Ultrasound Assessment From the ABSORB II Trial

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ABSTRACT

OBJECTIVES The study compared, by intravascular ultrasound (IVUS), acute gain (AG) at the site of the pre-procedural minimal lumen area (MLA) achieved by either the Absorb (Abbott Vascular, Santa Clara, California) scaffold or the Xience stent and identified the factors contributing to the acute performance of these devices.

BACKGROUND It is warranted that the acute performance of Absorb matches that of metallic stents; however, concern exists about acute expansion and lumen gain with the use of Absorb.

METHODS Of a total of 501 patients (546 lesions) in the ABSORB II (ABSORB II Randomized Controlled Trial) randomized trial, 445 patients with 480 lesions were investigated by IVUS pre- and post-procedure. Comparison of MLA pre- and post-procedure was performed at the MLA site by matching pre- and post-procedural IVUS pullbacks.

RESULTS Lower AG on IVUS (lowest tertile) occurred more frequently in the Absorb arm than in the Xience arm (3.46 mm^2 vs. 4.27 mm^2, respectively; $p < 0.001$; risk ratio: 3.04; 95% confidence interval: 1.94 to 4.76). The plaque morphology at the MLA cross-section was not independently associated with IVUS acute gain. The main difference in AG in MLD by angiography was observed at the time of device implantation (Xience vs. Absorb, Δ+1.50 mm vs. Δ+1.23 mm, respectively), whereas the gain from post-dilation was similar between the 2 arms (Δ+0.16 mm vs. Δ+0.16 mm) when patients underwent post-dilation, although expected balloon diameter was smaller in the Absorb arm than in the Xience arm ($p = 0.003$) during post-dilation.

CONCLUSIONS At the site of the pre-procedural MLA, the increase of the lumen post-procedure was smaller in the Absorb-arm than in the Xience arm. To achieve equivalent AG to Xience, the implantation of Absorb may require more aggressive strategies at implantation, pre- and post-dilation than the technique used in the ABSORB II trial. (ABSORB II Randomized Controlled Trial [ABSORB II]; NCT01425281) (J Am Coll Cardiol Intv 2016;9:1216–27)

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The fully bioresorbable scaffold is a novel device to treat coronary artery stenosis, potentially minimizing the long-term complications seen with metallic drug-eluting stents. The everolimus-eluting Absorb bioresorbable vascular scaffold (Absorb, Abbott Vascular, Santa Clara, California) made of poly-L-lactide (PLLA) provides a temporary coronary scaffolding for at least 6 months and becomes fully resorbed by approximately 3 years (1). The first-in-humans trial using the Absorb showed excellent safety results with potential late benefits such as late lumen enlargement and restoration of vasomotion (2). The ABSORB II (ABSORB II Randomized Controlled Trial; NCT01425281) study is the first randomized trial between the Absorb scaffold and Xience metallic stents in patients with up to 2 de novo native coronary lesions (3,4).

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It is warranted that the acute performance of Absorb matches that of metallic stents; however, concern exists about acute expansion and lumen gain with the use of a polymeric device. In the ABSORB first-in-humans trial, post-procedural intravascular ultrasound (IVUS) imaging demonstrated that implantation of an Absorb scaffold resulted in a more eccentric lumen with nonhomogeneous scaffold expansion compared with metallic stents (5). Furthermore, nonrandomized matched population from the ABSORB and SPIRIT trials demonstrated that angiographic acute gain in lumen diameter tends to be smaller in the Absorb than in the Xience (6). This trend was also observed in the randomized Japanese ABSORB trial (7-9). In the ABSORB II randomized trial, pre-procedural and post-procedural documentary IVUS imaging were mandatory and provided a unique opportunity to evaluate the scaffold/stent expansion at the precise site of pre-procedural minimal lumen area (MLA) and to relate the degree of expansion to the mechanical performance of both devices, procedural parameters of implantation and tissue composition derived from IVUS analyses (4).

Therefore, the purpose of this study was to investigate the IVUS acute gain at the site of minimal lumen area between the Absorb scaffold and the Xience stent and to identify the factors contributing to the acute performance of these devices.

ABBREVIATIONS AND ACRONYMS

IVUS = intravascular ultrasound

MLA = minimal lumen area

MLD = minimal lumen diameter

QCA = quantitative coronary angiography

METHODS

STUDY DESIGN AND POPULATION. The ABSORB II study was a randomized controlled trial comparing the safety and efficacy of the Absorb everolimus-eluting bioresorbable vascular scaffold and the Xience everolimus-eluting metallic stent in patients with up to 2 de novo native coronary lesions. Details of the study are available elsewhere (3). After successful pre-dilation of the target lesion, 2:1 randomization was performed. Of a total of 501 patients (546 lesions), 335 patients (364 lesions) were randomly assigned to receive Absorb device, and 166 patients (182 lesions) were assigned to receive the Xience device. Grayscale IVUS and IVUS-virtual histology (VH) imaging pre-procedure and post-implantation was mandatory but documentary. No treatment recommendation on the basis of IVUS imaging was made in the protocol.

STUDY DEVICE. The Absorb device has an amorphous poly-DL-lactide (PDLLA) coating that contains and controls the release of the antiproliferative drug everolimus. The scaffold is made of semicrystalline PLLA. PLLA is completely biodegraded by hydrolysis into water and CO_2 via the Krebs cycle. Physically, the scaffold has struts with an approximate thickness of 150 μm. The Xience device is an everolimus-eluting, cobalt chromium alloy device with a platform consisting of serpentine rings connected by links fabricated from a single piece. The overall strut thickness including the drug coating is approximately 90 μm.

PROCEDURE AND IVUS ACQUISITION. Pre-procedural IVUS was mandatory before dilation of the target lesion. If it was not technically feasible (e.g., the IVUS catheter could not cross the lesion), pre-dilation with a small balloon was allowed to facilitate the IVUS catheter insertion.

IVUS images were obtained with a rotational 45-MHz IVUS catheter (Revolution, Volcano Corp.,

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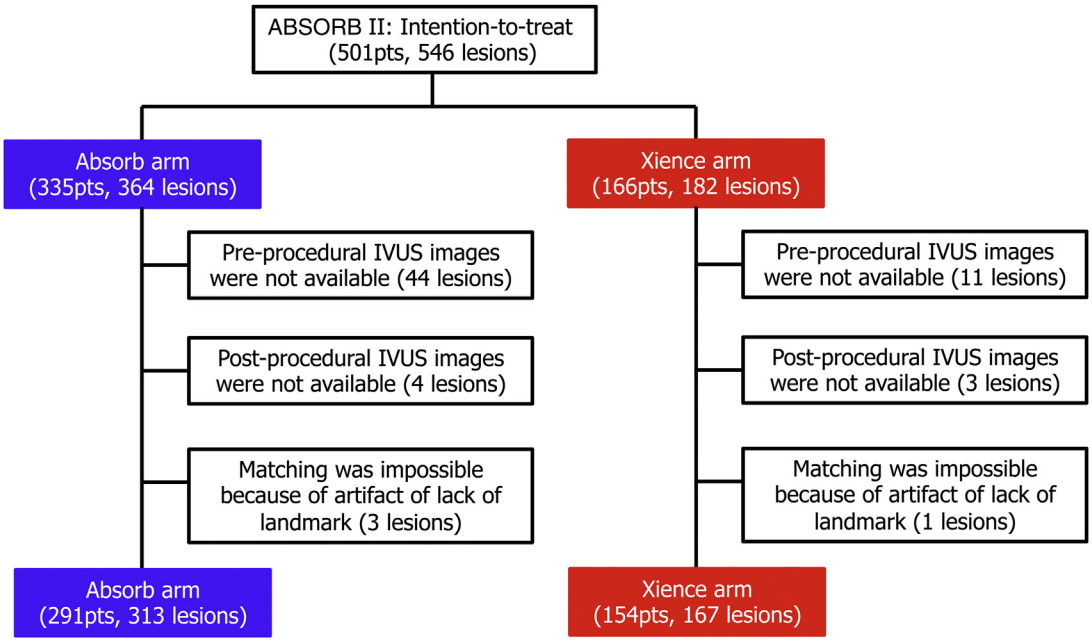
FIGURE 1 Study Flow Chart



Of 501 patients with 546 lesions, enrolled in the ABSORB II trial, 445 patients with 480 lesions (291 patients with 313 lesions in Absorb and 154 patients with 167 lesions in Xience) had both pre-procedural and post-procedural IVUS analyses for acute lumen area gain at the original minimal lumen area site. pts = patients.

Rancho Cordova, California). After intracoronary injection of 200 μg of nitroglycerin, IVUS pullbacks were performed with the use of an automated motorized device at a pullback speed of 0.5 mm/s. Lesions were treated with routine interventional techniques that included mandatory pre-dilation with a balloon shorter and 0.5 mm smaller in diameter than the study device. The size of stent/scaffold was determined by the target vessel diameter, which was measured by pre-procedural on-line quantitative coronary angiography (QCA) (3,10). All patients enrolled in the ABSORB II trial were treated as follows: 1) a 3.5-mm device was used when both the proximal and distal maximal lumen diameters were within an upper limit of 3.8 mm and a lower limit of 3.0 mm; 2) a 3.0-mm device was used when both the proximal and the distal maximal lumen diameters were within an upper limit of 3.3 mm and a lower limit of 2.5 mm; 3) a 2.5-mm device was used when both the proximal and the distal maximal lumen diameters were within an upper limit of 3.0 mm and a lower limit of 2.25 mm; and 4) scaffold/stent overlap was allowed. Post-dilation with a balloon shorter than the implanted scaffold/stent was performed at the discretion of the operators. Post-procedural IVUS images were obtained at the end of the procedure (post-device implantation or post-dilation). All pullbacks were analyzed offline by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) using commercially available software (QIvus version 2.2, Medis, Leiden, the Netherlands).

MEASUREMENT OF ACUTE GAIN ON IVUS. To assess the acute performance of the Absorb and Xience stent at the site of the worst stenosis pre-procedure, the difference of lumen area between pre- and post-procedural IVUS images at the site of the pre-procedural minimal lumen area (MLA) was measured as acute gain in MLA. Pre-procedural MLA was defined as the smallest lumen area within the target lesion. After identifying the frame of the pre-procedural MLA site, matching of pre- and post-procedural IVUS images was performed by identifying common landmarks, such as side branches, bifurcations, large calcifications, or echogenic metallic marker on the device. Matching was performed using a dedicated software (QCU-CMS software, Medis). The pre-procedural image of the MLA was matched and

compared with the post-procedural lumen area at the same site. The lower acute gain was defined as the lowest tertile from the whole population.

ANALYSIS OF IVUS AND PROCEDURAL PARAMETERS. Contour detection was performed by experienced IVUS core laboratory analysts who were unblinded to the device type. IVUS metrics including vessel, stent/scaffold, and lumen area were measured at 0.5-mm intervals. To identify the lesion factors in the evaluation of acute gain, analysis was also performed using the following parameters: plaque burden, lumen eccentricity, presence of calcium, remodeling index (11) from grayscale IVUS and tissue composition parameters (absolute value and percentage) from IVUS-VH. Plaque burden was obtained by the plaque plus medium cross-sectional area divided by the vessel cross-sectional area (12). Eccentricity index was calculated as the ratio of the projected minimal and maximal lumen or scaffold/stent diameter at the MLA cross-section (5,13). Pre-treatment reference segments were selected as sites with the least amount of plaque proximal and distal to the MLA sites before the take-off of any major side branch (11). The remodeling index (RI) was calculated as the vessel area at the MLA site divided by the average of the proximal and distal reference vessel areas. Negative remodeling was defined as an RI <0.88, intermediate remodeling as an RI of 0.88 to 1.00, and positive remodeling as an RI >1.00 (11).

Location and circumferential distribution of calcium was quantified in grayscale IVUS. Calcium was defined as bright echoes with acoustic shadowing. The location of the calcium was defined as superficial, deep, or both (14). If the leading edge of the acoustic shadowing appeared within the shallowest 50% of the plaque thickness, it was defined as superficial calcium. If the leading edge of the acoustic shadowing appeared within the deepest 50% of the plaque thickness, it was defined as deep calcium. The largest continuous arc of calcium and summed arc of calcium at the site of pre-interventional lumen area were measured in degrees with a protractor centered on the lumen. In addition, the arc of calcium was classified as 1 quadrant (≤90°), 2 quadrants (91° to 180°), 3 quadrants (181° to 270°), or 4 quadrants (271° to 360°). By IVUS-VH analysis, tissue at the site of pre-procedural MLA was divided into 4 basic plaque tissue components: fibrous tissue, fibrofatty tissue, necrotic core, and dense calcium (15).

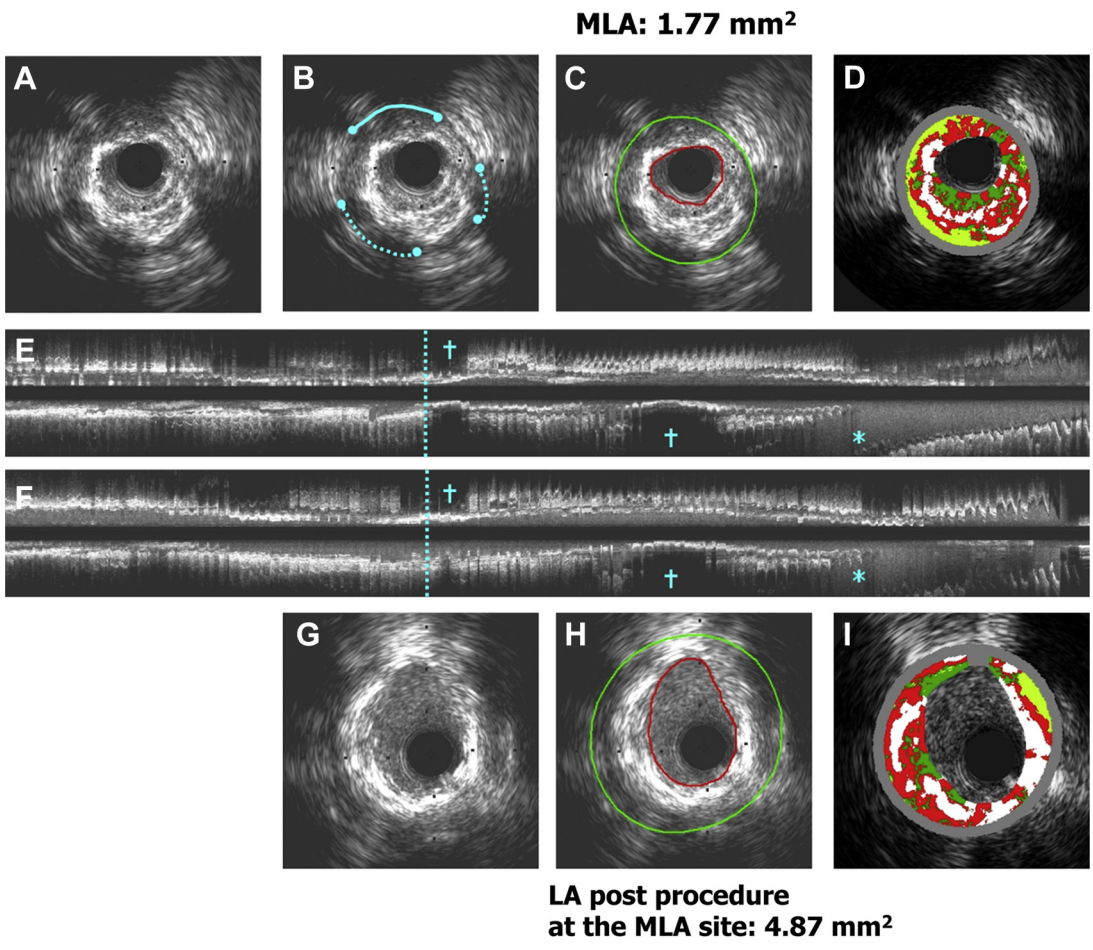
In the compliance charts (pressure-diameter relationships) for Absorb and Xience (Prime, Xpedition, and so forth) provided by the manufacturer, the inner

TABLE 1 Clinical Characteristics and Procedural Variables (N = 445)

	Absorb (N = 291)	Xience (N = 154)	p Value
Demographics			
Males	217 (74.6)	123 (79.9)	0.241
Age (y)	61 ± 10	61 ± 10	0.786
Current smoking	77 (26.5)	33 (21.4)	0.251
Lipid disorder requiring medication	201 (69.1)	116 (75.3)	0.258
Hypertension requiring medication	188 (64.6)	104 (67.5)	0.802
Diabetes mellitus	64 (22.0)	38 (24.7)	0.554
Stable angina	187 (64.3)	100 (64.9)	0.917
Body mass index (kg/m^2)	27.8 ± 4.1	28.1 ± 3.7	0.542
Obesity (BMI ≥30 kg/m^2)	67 (23.1)	44 (28.6)	0.208
Lesions (N = 480)	313 lesions	167 lesions	
Pre-procedural angiography			
Lesion location			0.184
Left anterior descending artery	146 (46.7)	81 (48.5)	
Left circumflex artery	88 (28.1)	35 (21.0)	
Right coronary artery	79 (25.2)	51 (30.5)	
Lesion classification†			0.456
A	4 (1.3)	1 (0.6)	
B1	181 (58.0)	85 (51.5)	
B2	125 (40.1)	78 (47.3)	
C	2 (0.6)	1 (0.6)	
Quantitative coronary angiography			
Interpolated percent diameter stenosis (%)	58.3 ± 11.1	59.1 ± 11.4	0.448
Minimal lumen diameter (mm)	1.08 ± 0.32	1.07 ± 0.31	0.627
Reference vessel diameter (mm)	2.60 ± 0.37	2.64 ± 0.40	0.327
Maximal diameter at proximal reference segment (mm)	2.84 ± 0.45	2.87 ± 0.46	0.476
Maximal diameter at distal reference segment (mm)	2.69 ± 0.45	2.74 ± 0.43	0.258
Procedural variables			
Pre-dilation			
Pre-dilation before IVUS	115 (36.7)	59 (35.3)	0.842
Pre-dilation performed	313 (100.0)	165 (98.8)	0.121
Nominal diameter of pre-dilation balloon (mm)	2.60 ± 0.36	2.64 ± 0.35	0.236
Maximal pressure during pre-dilation (atm)	12.2 ± 3.0	12.5 ± 3.1	0.300
Device implantation			
Nominal diameter of device			0.139
2.5 mm	52 (16.6)	17 (10.2)	
2.75 mm	0 (0)	1 (0.6)	
3.0 mm	190 (60.7)	107 (64.1)	
3.5 mm	71 (22.7)	42 (25.1)	
Maximal pressure during device implantation (atm)	13.1 ± 2.7	13.8 ± 2.5	0.008*
Expected inner device diameter (mm)	3.34 ± 0.33	3.28 ± 0.33	0.109
Post-dilation			
Post-dilation performed	194 (62.0)	102 (61.1)	0.844
Nominal diameter of post-dilation balloon (mm)‡	3.16 ± 0.34	3.28 ± 0.37	0.01*
Maximal pressure during post-dilation (atm)§	15.3 ± 3.2	16.7 ± 3.4	0.001*
Expected diameter of post-dilation balloon (mm)§	3.27 ± 0.35	3.40 ± 0.39	0.003*
Maximal expected diameter of balloon (with or without post-dilation) (mm)	3.37 ± 0.33	3.38 ± 0.36	0.896

Values are n (%) or mean ± SD. *p < 0.05. †Data were available in 477 lesions. ‡Data were available in 292 lesions. §Data were available in 290 lesions.

FIGURE 2 Representative Case of IVUS Acute Gain



Examples of IVUS pullbacks before **(A–E)** and after procedure **(F–I)**. Vessel and lumen contours were drawn **(C)** at the site of pre-procedural minimal lumen area (**dotted line** in longitudinal view **[E, F]**). Calcium, defined as bright echoes with acoustic shadowing, was measured in its circumferential extension (largest continuous arc of calcium **[solid arc]**: 101.3°, summed arc of calcium **[solid and dotted arcs]**: 214.1° **[B]**), and location (superficial calcium). Tissue component **(D)** was assessed by IVUS-VH. After matching pre- **(E)** and post-procedural IVUS pullbacks **(F)**, vessel and lumen areas were obtained at the corresponding site **(H)**. Lumen area in **C** was 1.77 mm^2 and 4.87 mm^2 in **H**. Therefore, acute lumen gain was 3.10 mm^2 (**green line** = vessel contour; **red line** = lumen contour; **blue asterisk** = side branch; **blue dagger** = calcification).
LA = lumen area; MLA = minimal lumen area; IVUS-VH = intravascular ultrasound-virtual histology.

diameters of the devices were described. Expected device diameter was obtained from the device compliance chart, using the nominal device diameter and the maximal pressure during implantation. During post-dilation, the expected balloon diameter was obtained from the balloon compliance chart data provided by the various manufacturers of balloons, using the nominal diameter of the balloon and the maximal pressure during the procedure. In case the pressure during the procedure exceeded the highest pressure on the chart, the highest diameter on the chart was used for the calculation.

ANGIOGRAPHIC ASSESSMENT. Online QCA analyses were undertaken by the sites before Absorb implantation to define Dmax (10), and pre- and post-procedural offline QCA were performed by an independent core laboratory (Cardialysis BV) using the coronary angiography analysis system (Pie Medical Imaging, Maastricht, the Netherlands). The minimal lumen diameter (MLD) changes at different phases of the procedure were measured before procedure, after device implantation, and immediately after post-dilation. Additionally, minimal diameter of balloon was measured during scaffold/stent implantation at

TABLE 2 IVUS Data at the Site of Pre-Procedural Minimal Lumen Area (N = 480)

Data	Pre-Procedure			Post-Procedure			Change From Pre to Post		
	Absorb (n = 313)	Xience (n = 167)	p Value	Absorb (n = 313)	Xience (n = 167)	p Value	Absorb (n = 313)	Xience (n = 167)	p Value
Grayscale IVUS									
Lumen area (mm^2)	2.08 ± 0.76	2.13 ± 0.85	0.502	5.55 ± 1.46	6.40 ± 1.68	<0.001	3.46 ± 1.35	4.27 ± 1.46	<0.001
Vessel area (mm^2)	10.71 ± 3.67	11.61 ± 3.89	0.014	13.05 ± 3.83	14.28 ± 4.01	0.001	2.34 ± 1.80	2.66 ± 1.82	0.066
Plaque area (mm^2)	8.63 ± 3.47	9.47 ± 3.71	0.016	7.51 ± 2.82	7.88 ± 2.94	0.181	−1.12 ± 1.75	−1.60 ± 1.76	0.005
Plaque burden (%)	79.0 ± 8.3	80.2 ± 8.5	0.143	56.4 ± 8.1	54.3 ± 7.8	0.007	−22.6 ± 8.2	−25.9 ± 7.3	<0.001
Minimal lumen diameter (mm)	1.47 ± 0.23	1.48 ± 0.25	0.660	2.41 ± 0.37	2.66 ± 0.45	<0.001			
Maximal lumen diameter (mm)	1.75 ± 0.37	1.77 ± 0.38	0.591	2.86 ± 0.40	3.00 ± 0.41	<0.001			
Lumen eccentricity	0.86 ± 0.10	0.85 ± 0.10	0.711	0.84 ± 0.08	0.89 ± 0.11	<0.001			
Presence or absence of calcium (%)			0.987						
No	114 (36.4)	61 (36.5)							
1 quadrant (1∼90°)	130 (41.5)	67 (40.1)							
2 quadrants (91∼180°)	41 (13.1)	24 (14.4)							
3 quadrants (181∼270°)	15 (4.8)	9 (5.4)							
4 quadrants (270∼360°)	13 (4.2)	6 (3.6)							
Largest continuous arc of calcium (°)	45.5 ± 58.8	51.8 ± 67.0	0.306						
Summed arc of calcium (°)	54.3 ± 69.3	60.7 ± 75.0	0.362						
Remodeling pattern (%)*			0.802						
Positive remodeling	94 (30)	46 (28)							
Intermediate remodeling	83 (27)	43 (26)							
Negative remodeling	132 (42)	75 (45)							
IVUS-VH									
Fibrous tissue (% of total plaque area)	27.70 ± 16.07	26.70 ± 14.69	0.504	27.30 ± 10.99	21.71 ± 8.86	<0.001	−0.41 ± 15.11	−4.99 ± 15.22	0.002
Fibrofatty tissue (% of total plaque area)	52.70 ± 22.81	54.00 ± 21.61	0.551	31.49 ± 19.77	30.08 ± 17.65	0.440	−21.25 ± 20.07	−23.92 ± 17.17	0.139
Necrotic core (% of total plaque area)	15.64 ± 10.23	15.48 ± 9.94	0.867	28.58 ± 10.70	30.65 ± 10.12	0.043	13.03 ± 10.96	15.17 ± 10.65	0.044
Dense calcium (% of total plaque area)†	3.95 ± 6.02	3.82 ± 5.81	0.822	12.56 ± 11.21*	17.56 ± 12.90*	<0.001	8.56 ± 10.13	13.74 ± 12.47	<0.001

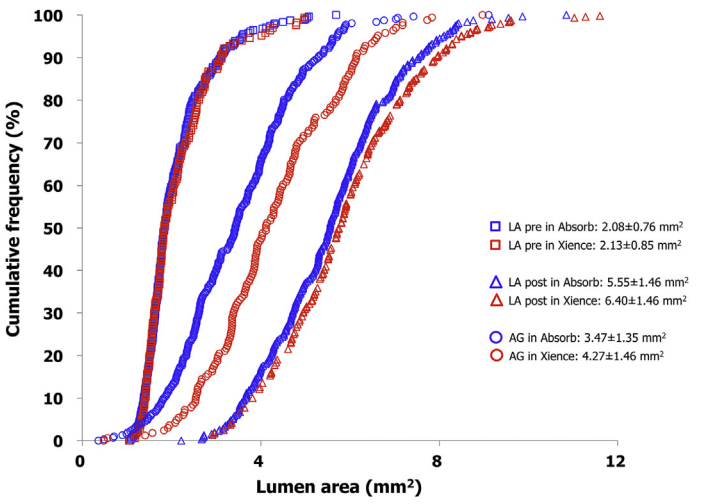
Values are mean ± SD or n (%). *7 are missing data. †The polymeric or metallic struts are detected as (pseudo)calcium on IVUS-VH.
IVUS-VH = intravascular ultrasound-virtual histology.

maximal inflation pressure and during post-dilation at maximal inflation pressure.

Acute recoil was defined as follows: When a stent/scaffold delivery balloon was used for stent/scaffold expansion, acute absolute stent/scaffold recoil was defined as the difference between the mean diameter of the stent/scaffold delivery balloon at the highest pressure at implantation of the stent/scaffold (X) and the mean luminal diameter of the stented/scaffolded segment after implantation (Y). Acute absolute stent/scaffold recoil was calculated as: [X - Y]. When a post-dilation balloon was used in the procedure, acute absolute recoil was defined as the difference between the mean diameter of the post-dilation balloon at the highest pressure in the post-dilated segment (X′) and the mean luminal diameter after post-dilation (Y′). The angiogram of X and Y was performed in the same angiographic view so that the 2 images were perfectly matched.

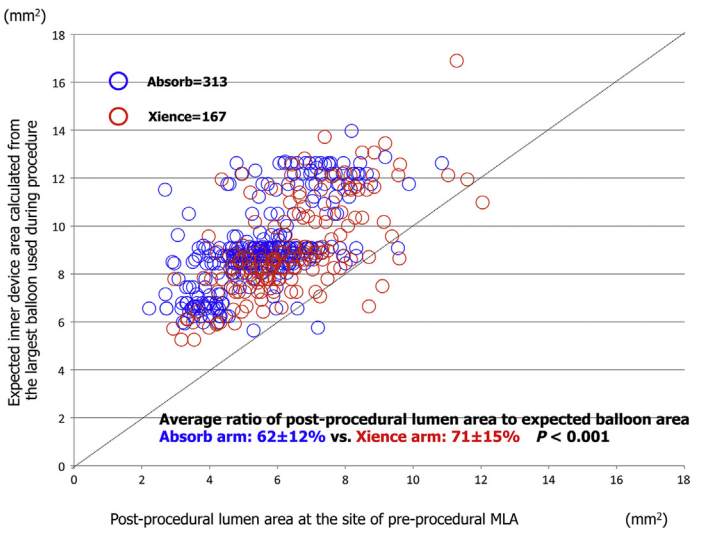
STATISTICAL ANALYSIS. Categorical variables are presented as counts and percentages. Continuous variables are presented as mean ± SD. A p value of <0.05 was considered statistically significant. Generalized estimating equations modeling was performed to take into an account the clustered nature of >1 stents/scaffolds per patient, which might result in unknown correlations among measurements within these scaffold clusters. Paired analysis was performed in the patients with analyzable pre- and post-procedural IVUS images. Logistic regression analysis was performed to find the relationship of the following factors with IVUS lower acute gain in lumen area: sex, age, obesity (body mass index ≥30 kg/m^2),

FIGURE 3 Cumulative Frequency Distribution Curve of Pre- and Post-MLA and Acute Gain



Cumulative frequency distribution curve of AG at the MLA site pre-procedure [AG = (MLA_{post} – MLA_{pre})] for Absorb and Xience. Pre-procedural MLA was similar between the 2 arms. The post-procedural lumen area at the site of the pre-procedural MLA was significantly smaller in the Absorb arm than in the Xience arm (5.55 mm^2 vs. 6.40 mm^2, respectively; $p < 0.001$). The amount of change in lumen area was significantly smaller in the Absorb arm than in the Xience arm (3.46 mm^2 vs. 4.27 mm^2, respectively; $p < 0.001$). AG = acute gain; MLA = minimal lumen area.

FIGURE 4 Device Expansion of Absorb and Xience



When device expansion was defined as the ratio of post-procedural lumen area at the site of the pre-procedural MLA to the expected inner device area calculated from the largest balloon used during procedure, the Absorb scaffold achieved, on average, 62 ± 12% only of the predicted lumen area, whereas the Xience stent achieved 71 ± 15% ($p < 0.001$). MLA = minimal lumen area.

treated vessel, pre-procedural MLA, pre-procedural lumen eccentricity, plaque area, and vessel area (all measurements at the site of MLA). In addition, presence or absence of calcium as well as arc of calcium at the site of MLA, tissue composition at the site of MLA, remodeling index (11), type of stent/scaffold, and maximal expected inner device or balloon diameter throughout procedure (in cases with or without post-dilation) were also included in the logistic regression analysis. In the multivariate model, MLA was not included due to strong interaction with plaque area and vessel area. Statistical analyses were performed with SPSS version 23.0.0 software (IBM, Armonk, New York).

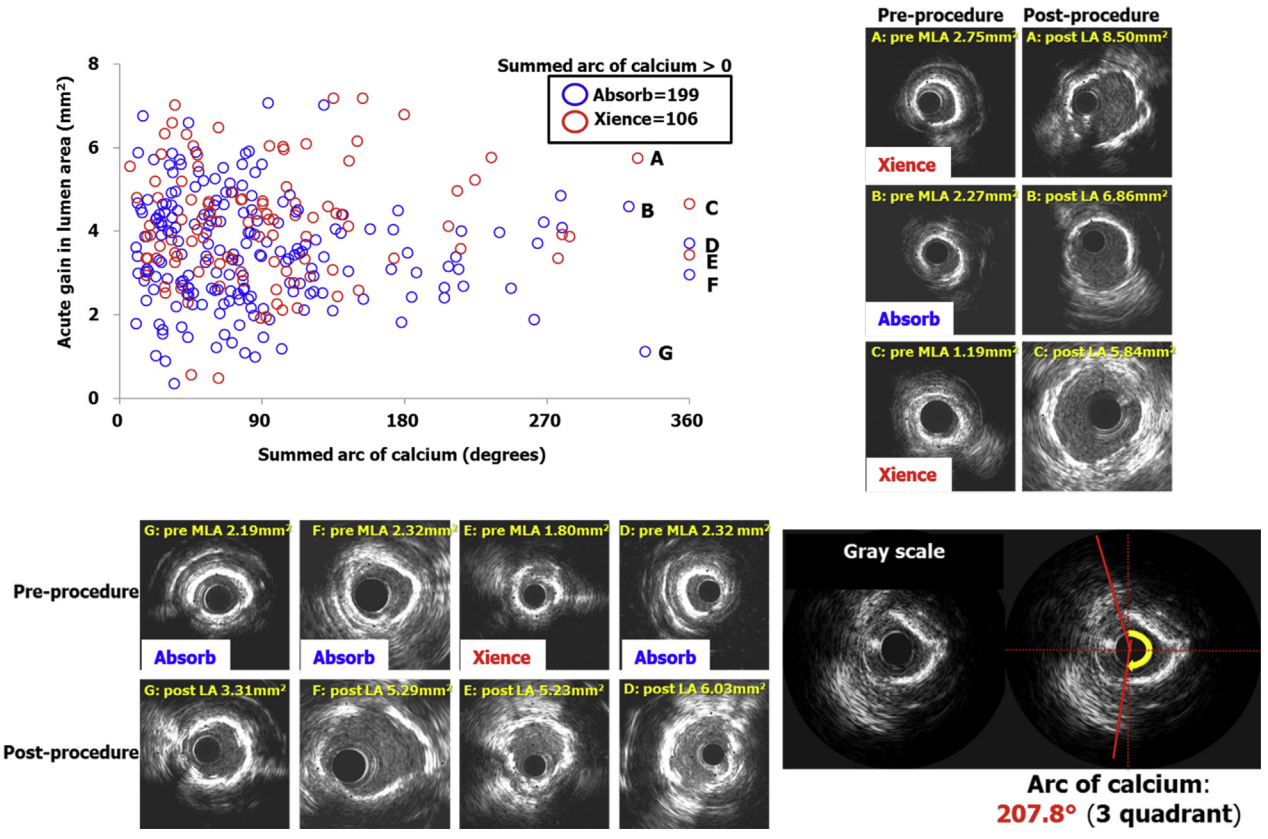
RESULTS

BASELINE CHARACTERISTICS. Of 501 patients with 546 lesions who were enrolled in the ABSORB II trial, 445 patients with 480 lesions (291 patients with 313 lesions in the Absorb arm and 154 patients with 167 lesions in the Xience arm) had both pre-procedural and post-procedural IVUS analyses for acute lumen area gain assessment (Figure 1). There were no significant differences in baseline patient demographics and pre-procedural angiography data (Table 1).

DIFFERENCES IN PROCEDURAL IMPLANTATION STRATEGY BETWEEN ABSORB AND XIENCE. Table 1 indicates the differences in procedural strategy between Absorb and Xience. Pre-dilation strategy was comparable between both arms. At the time of the device implantation, no differences in device size selection and expected inner device diameter were observed, whereas maximal pressure during device implantation was higher in Xience than in Absorb. At the time of post-dilation, nominal diameter of the balloon, maximal pressure, and expected balloon diameter were smaller in the Absorb arm than in the Xience arm.

IVUS ANALYSIS. A representative case of acute gain in MLA is presented in Figure 2. Overall, the pre-procedural MLA was comparable between the 2 arms. However, pre-procedural vessel area (Xience 11.61 mm^2 vs. Absorb 10.71 mm^2, respectively; $p = 0.014$) and plaque area (Xience 9.47 mm^2 vs. Absorb 8.63 mm^2, respectively; $p = 0.016$) at the site of MLA were significantly larger in the Xience arm than in the Absorb arm. The post-procedural lumen area at the site of pre-procedural MLA was significantly smaller in the Absorb arm (5.55 mm^2 vs. 6.40 mm^2, respectively; $p < 0.001$). The amount of change in plaque area and plaque burden was significantly smaller in

FIGURE 5 Relationship Between Circumferential Distribution of Calcium and Acute Gain



The relationship between circumferential distribution of calcium and acute gain (**blue circles** = Absorb; **red circles** = Xience). Presence or absence of calcium as well as the arc of calcium by IVUS grayscale did not affect acute gain and device expansion at the site of minimal lumen area. IVUS = intravascular ultrasound; MLA = minimal lumen area.

the Absorb arm than in the Xience arm (−1.12 mm² vs. −1.60 mm², respectively; p = 0.005; and −22.6% vs. −25.9%, respectively; p < 0.001). The increase of vessel area tended to be smaller in the Absorb arm (2.34 mm² vs. 2.66 mm², respectively; p = 0.066). As a result, there were significant differences in acute gain for the minimal lumen areas (3.46 mm² vs. 4.27 mm², respectively; p < 0.001) (Table 2, Figure 3).

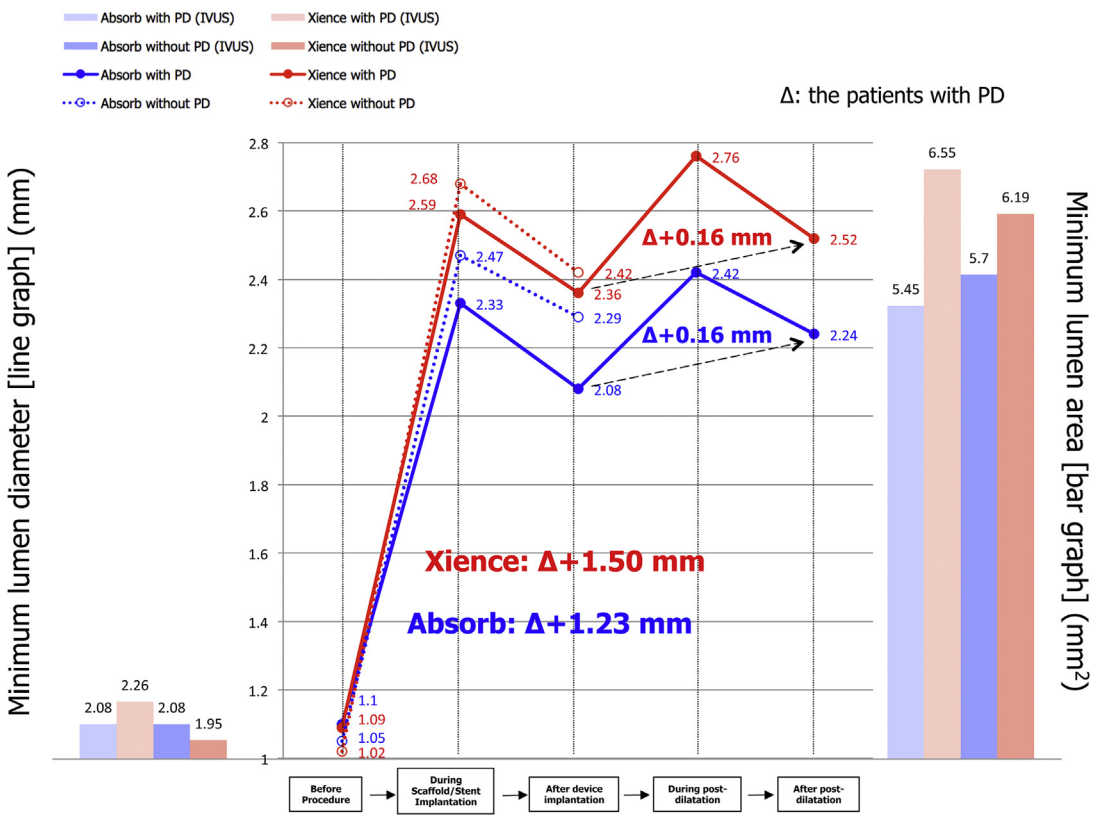
DEVICE EXPANSION IN MINIMAL LUMEN AREA. When device expansion (16,17) was defined as the ratio of post-procedural lumen area at the site of pre-procedural MLA to the expected inner device area calculated from the largest balloon used during procedure, the Absorb scaffold achieved on average 62 ± 12% of the predicted lumen area, whereas the Xience stent achieved 71 ± 15% (p < 0.001) (Figure 4). Location of calcium as well as the arc of calcium and the amount of NC did not affect device expansion (Figure 5).

QCA MLD CHANGES AT DIFFERENT PHASES DURING PROCEDURE. Figure 6 shows the MLD by QCA and MLA by IVUS changes at different phases during the procedure in the patients who had both pre- and post-procedural IVUS analyses.

The Main difference in acute gain in MLD by QCA was observed at the time of device implantation (Xience vs. Absorb, Δ+1.50 mm vs. Δ+1.23 mm, respectively), whereas the gain from post-dilation was similar between the 2 arms (Δ+0.16 mm vs. Δ+0.16 mm) when patients underwent post-dilation. Acute recoil during device implantation was similar in both devices (Xience vs. Absorb, 0.20 ± 0.18 mm vs. 0.19 ± 0.19 mm, respectively; p = 0.716), whereas acute recoil during post-dilation was larger in the Xience than in the Absorb (0.21 ± 0.21 mm vs. 0.13 ± 0.20 mm, respectively; p = 0.006).

PREDICTORS OF LOWER ACUTE GAIN. Lower acute gain (lowest tertile) occurred more frequently in

FIGURE 6 Minimal Lumen Diameter Changes by QCA and MLA Changes by IVUS at Different Phases of the Procedure



The minimal lumen diameter changes by QCA **(line graph)** and MLA changes by IVUS **(bar graph)** at different phases of the procedure in patients who had both pre- and post-procedural IVUS analyses. Change of MLD by QCA and MLA by IVUS of the Absorb and the Xience are depicted by **blue** and **red**, respectively. **Dotted lines** show minimal lumen diameter changes for those lesions that were not post-dilated, whereas **solid lines** show minimal lumen diameter change of the lesions that underwent post-dilation. Differences in acute gains were mainly observed at the time of device implantation (Δ+1.50 mm vs. Δ+1.23 mm), whereas the gain from post-dilation was similar between the 2 arms (Δ+0.16 mm vs. Δ+0.16 mm), when patients underwent post-dilation. IVSU = intravascular ultrasound; MLA = minimal lumen area; QCA = quantitative coronary angiography.

the Absorb arm than in the Xience arm (risk ratio: 3.04; 95% confidence interval [CI]: 1.94 to 4.76) (Table 3). Results of logistic regression analysis are summarized in Online Table 1. Sex, age, obesity, treated vessel, pre-procedural lumen eccentricity at the site of MLA, presence or absence of calcium as well as arc of calcium at the site of MLA, tissue composition at the site of MLA were not independent predictors for lower acute gain. The following variables were significantly associated with lower acute gain in the multivariate model: Absorb use, maximal inner device or balloon diameter throughout procedure, vessel and plaque areas at the MLA site, and negative remodeling. Differences in IVUS acute gain between Absorb and Xience were consistent across these variables (Table 3).

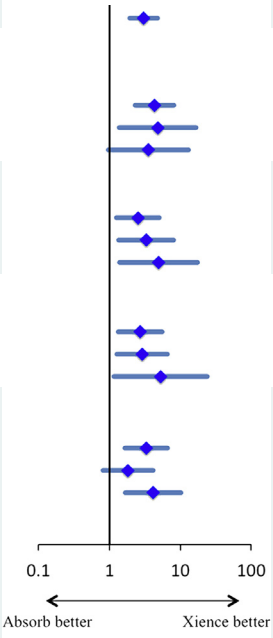
DISCUSSION

MAIN FINDINGS. The main findings of this study are: lower acute gain occurred more frequently in the Absorb arm than in the Xience arm (3.46 mm^2 vs. 4.27 mm^2, respectively; $p < 0.001$; risk ratio: 3.04; 95% CI: 1.94 to 4.76); plaque morphology at the MLA cross-section was not independently associated with acute gain; and on angiography, acute device recoil was comparable, but expansion of the device was different. The influence of post-dilation on MLD was somewhat limited.

IMPACT OF LESION MORPHOLOGY ON LUMEN ENLARGEMENT. There are conflicting data about the impact of lesion morphology on lumen enlargement. In

TABLE 3 Incidence of Lower Acute Gain

	Absorb	Xience	Risk Ratio	p Value for Interaction
All patients	41% (128/313)	19% (31/167)	3.04 (1.94-4.76)	
Maximal expected diameter of balloon with or without post-dilatation				
Lower tertile (≤3.28)	70% (78/112)	35% (25/72)	4.31 (2.30-8.10)	
Mid-tertile (>3.28, ≤3.40)	32% (37/117)	9% (3/34)	4.78 (1.37-16.64)	0.872
Higher tertile (>3.40)	16% (13/84)	5% (3/61)	3.54 (0.96-13.02)	
Vessel area at MLA site				
Lower tertile (≤9.10)	67% (75/112)	45% (21/47)	2.51 (1.25-5.04)	
Mid-tertile (>9.10, <12.30)	33% (35/105)	13% (7/53)	3.29 (1.35-8.02)	0.305
Higher tertile (≥12.30)	19% (18/96)	5% (3/67)	4.92 (1.39-17.46)	
Plaque area at MLA site				
Lower tertile (≤7.10)	69% (79/114)	46% (20/44)	2.71 (1.33-5.53)	
Mid-tertile (>7.10, <9.95)	35% (35/101)	16% (9/58)	2.89 (1.27-6.56)	0.475
Higher tertile (≥9.95)	14% (14/98)	3% (2/65)	5.25 (1.15-23.94)	
Remodeling*				
Negative (RI<0.88)	41% (54/132)	17% (13/75)	3.30 (1.65-6.59)	
Intermediate (0.88≤ RI≤1.00)	39% (32/83)	26% (11/43)	1.83 (0.81-4.13)	0.835
Positive (RI>1.0)	43% (40/94)	15% (7/46)	4.13 (1.67-10.18)	



*Remodeling index: 7 missing data.
MLA = minimal lumen area; RI = remodeling index.

previous reports, the expansion of drug-eluting stents was drastically influenced by IVUS (grayscale/virtual histology) plaque morphology (including the arc and length of lesion calcium) or quantitative lesion site geometry (lesion vessel area, plaque area, and plaque burden) (16-18). In the present study, the impact of plaque component on acute gain in lumen area was not retained in the multivariate analysis, although in univariate analysis, higher amounts of fibrotic plaque, necrotic core, and dense calcium showed lower acute gain in lumen area in both arms. In the present study, presence or absence of calcium as well as the arc of calcium by IVUS grayscale did not affect the acute gain and device expansion at MLA (**Figure 5**).

DIFFERENCES IN PROCEDURAL STRATEGY BETWEEN ABSORB AND XIENCE. Differences in acute performance can be driven not only by differences in the mechanical properties of the Absorb scaffold and the Xience metallic stent but also by different initial implantation strategies (6,19,20). Within precise boundaries of expansion (e.g., 3.0 to 3.5 mm for a device of 3.0 mm), the stress-strain relationship of the metallic and polymeric struts are comparable, and the mechanical strength of the Absorb scaffold is not different from that of the metallic stent (21). However, when the scaffold is over-expanded (>3.5 mm for a 3.0-mm device), the strut crowns begin approaching their geometrical limit. The radial support is maximized, while their tensile strength limit is also reached (22). Therefore, pre-dilation, optimal expansion, and avoidance of over-expansion are encouraged during the procedure with the Absorb device.

Maximal expected balloon diameters in cases with or without post-dilation were similar between Absorb and Xience. However, the ratio of post-procedural lumen area at the site of pre-procedural MLA to the expected inner device area calculated from the largest balloon used during procedure was smaller in the Absorb than in the Xience (**Figure 4**). This result might imply the necessity of more aggressive strategy during implantation and post-dilation of Absorb compared to Xience due to the device mechanical properties (i.e., tensile strength and radial force).

When QCA was performed to assess MLD changes at different phases during the procedure, differences between the 2 arms were already significant at the time of device balloon expansion (Δ+1.50 mm for Xience vs. Δ+1.23 mm for Absorb; $p < 0.01$) (**Figure 6**), despite the fact that the expected inner devices' diameters at implantation were similar in both arms. Acute device recoil amounts were comparable between the 2 arms (4). Despite less aggressive post-dilation in the Absorb

arm than in the Xience arm, the angiographic gains from post-dilation between the 2 arms were similar (Δ+0.16 mm vs. Δ+0.16 mm, respectively; p = 0.97) (**Figure 6**). These angiographic analyses implied differences of the mechanical properties of both devices and the necessity of different procedural strategies for implantation.

The issue of recoil in QCA and IVUS seemingly somewhat contradicted each other. Another possibility is that the limited accuracy of the measurements by QCA and IVUS due to their resolutions could cause this contradiction. Their accuracy could be affected differently in implanted polymeric scaffolds and metallic stents. Moreover, the recoils were assessed by QCA and IVUS in a different fashion and settings. With IVUS, post-procedural MLA was compared to the virtual expected balloon dimensions at the time of maximal balloon inflation. In QCA, recoil was assessed from the difference in diameter between inflation balloon device and stented/scaffolded diameter of the vessel post-implantation.

CLINICAL IMPLICATION. On the basis of previous reports (23) of disrupted polymeric scaffolds due to over-expansion, the protocol did not recommend post-dilation of the bioresorbable scaffold device. However, on angiography, a significant difference in the initial expansion was noted (Absorb < Xience). To achieve with the Absorb an acute lumen gain equivalent to that of the Xience, device balloon expansion with higher pressures and/or more aggressive post-dilation should be considered within the limits of the recommended diameters due to the difference in inherent device mechanical properties (i.e., tensile strength and radial force). Because the device balloon of the Absorb is semi-compliant, implantation with a high pressure might result in over-expansion of the device or edge dissection. One of the possible contributing factors to lower acute gain in the Absorb is the lack of systematic post-dilation with a noncompliant balloon with a diameter of 0.25 or 0.5 mm larger than the nominal diameter of the polymeric device.

The following 3 clinical questions remain: How does an aggressive lesion preparation (pre-dilation, rotational atherectomy or cutting/scoring balloon) impact acute gain? Can a high implantation pressure with the Absorb device improve acute gain? How does an aggressive post-dilation impact acute gain? These questions should be answered in future trials.

STUDY LIMITATIONS. If the IVUS catheter could not cross the lesion, pre-dilation with a small balloon was performed. The incidence of pre-dilation before IVUS was similar between the Absorb and Xience arms, but initial lesion geometry and morphology could not be evaluated in 12% of lesions. The analysts in core laboratory were not blinded to the device type, which could result in potential bias in data acquisition. Aorto-ostial lesions, bifurcations, chronic total occlusions, and lesions with heavy calcification on angiography were excluded from the present study. Thus, our conclusions should not be extrapolated to more complex lesion subsets. Lastly, in the present study, we did not evaluate—due to the small number of the events—the relationship between IVUS findings and clinical events such as scaffold thrombosis that is our current concern after implantation of Absorb.

CONCLUSIONS

At the site of pre-procedural MLA, the Absorb scaffold showed lower acute gain than Xience stents. To achieve acute gain equivalent to that of Xience, Absorb deployment may require preparation of the lesion and more aggressive strategies at implantation and post-dilation than the technique used in the ABSORB II trial due to the difference in inherent device mechanical properties.

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PERSPECTIVES

WHAT IS KNOWN? It is warranted that the acute performance of Absorb matches that of metallic stents; however, concern exists about acute expansion and lumen gain with the use of Absorb.

WHAT IS NEW? Lower IVUS acute gain occurred more frequently in the Absorb arm than in the Xience arm. The plaque morphology at the MLA cross-section was not independently associated with acute gain. On angiography, device acute recoil was comparable but expansion of the device was different.

WHAT IS NEXT? Further studies are needed to evaluate the impact of more aggressive strategies at implantation, pre- and post-dilation than the technique used in the ABSORB II trial on acute performance of Absorb.

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KEY WORDS bioresorbable vascular scaffold, drug-eluting stent(s), intravascular ultrasound

APPENDIX For a supplemental table, please see the online version of this article.