Title: Endothelial shear stress and vascular remodeling in BRS and metallic stent
Category: Interventional Cardiology

Abstract

Aims: The impact of endothelial shear stress (ESS) on arterial remodeling in vessels implanted with bioresorbable scaffold (BRS) as compared to metallic drug-eluting stent (DES) remains elusive. We aimed to determine whether the relationship between ESS and remodeling patterns differs in BRS from those seen in metallic DES at 3-year follow-up.
Methods and Results: In the ABSORB II randomized trial, lesions were investigated by serial coronary angiography and intravascular ultrasound (IVUS). Three-dimensional reconstructions of coronary arteries post-procedure and at 3-year were performed. ESS was quantified using non-Newtonian steady flow simulation. IVUS cross-sections in device segment were matched using identical landmarks.

Paired ESS calculations post-procedure and at 3 years were feasible in 57 lesions in 56 patients. Post-procedure, median ESS at frame level was higher in BRS than in DES, with marginal statistical significance (0.97±0.48 vs. 0.75±0.39 Pa, p=0.063). In the BRS arm, vessel area and lumen area showed larger increases in the highest tercile of median ESS post-procedure as compared to the lowest tercile. In contrast, in DES, no significant relationship between median ESS post-procedure and remodeling was observed. In multivariate analysis, smaller vessel area, larger lumen area, higher plaque burden post-procedure, and higher median ESS post-procedure were independently associated with expansive remodeling in matched frames. Only in BRS, younger age was an additional significant predictor of expansive remodeling.
Conclusions: In a subset of lesions with large plaque burden, shear stress could be associated with expansive remodeling and late lumen enlargement in BRS, while ESS had no impact on vessel dimension in metallic DES.

Figure-1: Analysis steps for computational fluid dynamics (CFD) simulation in coronary artery. This figure demonstrates the steps for CFD simulations in the study. Two orthogonal coronary projections displaying the treated vessel were processed in 3D-QCA software. After defining the reference points for the main vessel (which were the vessel ostium or just after the catheter tip -as in this case- for proximal reference point and one diameter of the main vessel after the distal side branch for distal reference point) for 3D-QCA,the luminal borders and the centerline were automatically detected by the software (**Panel-A**). For proximal and distal side branches, proximal reference point was the same as in main vessel reconstruction. After automatic luminal contour and centerline detection of the distal side-branch (**Panel-B**) and proximal side-branch (**Panel-C**), 3D-QCA models were transferred to the dedicated software for co-registration to mount the IVUS-derived lumen and vessel contours on the 3D centerline which comes from 3D-QCA of the main vessel (**Panel-D**). During co-registration step, longitudinal position of the IVUS contours was implemented by mapping the IVUS frames including side-branches on the orthogonal angiographic projections. The circumferential orientation of the IVUS cross-sections was adjusted by the side-branches (red asterisks in **Panel-D**). The rotation of cross-sections in-between was linearly interpolated. Following the co-registration, the model was transferred to the 3D workbench software to fuse the 3D-QCA models with IVUS contours in order to get luminal surface models (**Panel-E**). The 3D-QCA segment overlapping with IVUS segment was deleted in order to get the luminal surface data only from IVUS in device segment (right upper panel in **Panel-E**, the arrows show the proximal and distal edge of the IVUS segment). The luminal surface wall data was exported in*.stl* format. Following the workbench step, luminal volume was meshed and the meshed model was then processed in a CFD software to simulate the flow in the reconstructed vessel model (**Panel-F**).

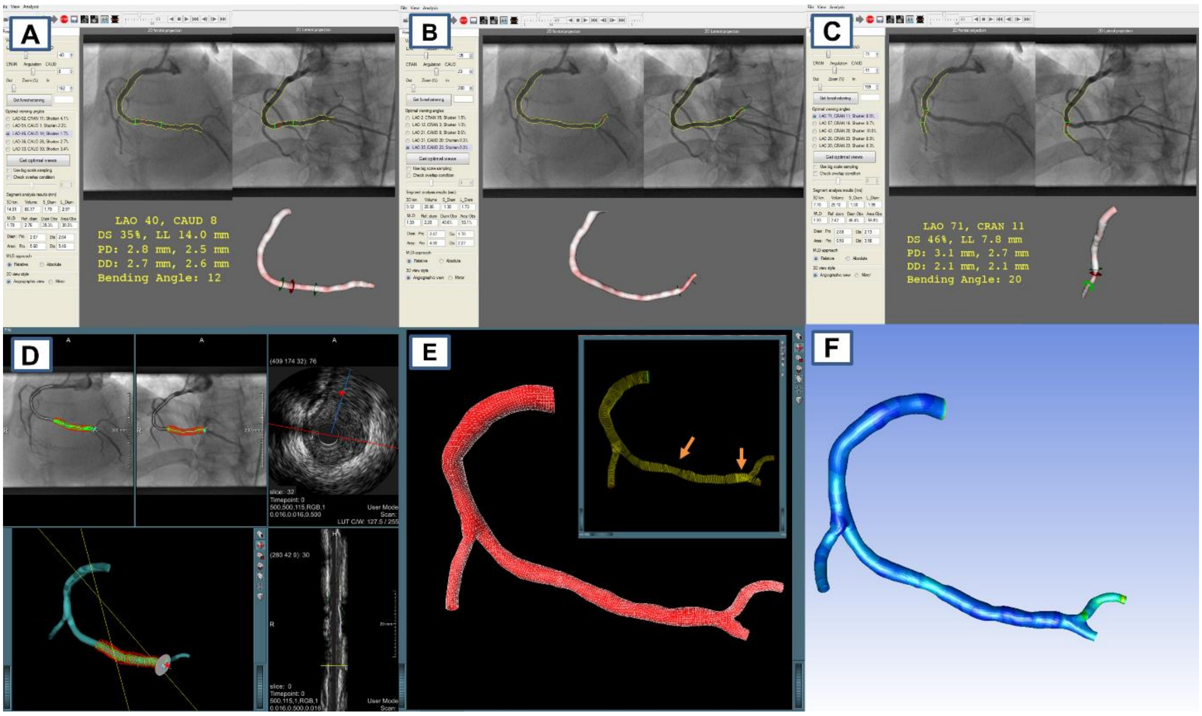

Figure-2: Study flow-chart.

CFD=computational fluid dynamics, ESS=endothelial shear stress, IVUS=intravascular ultrasound.

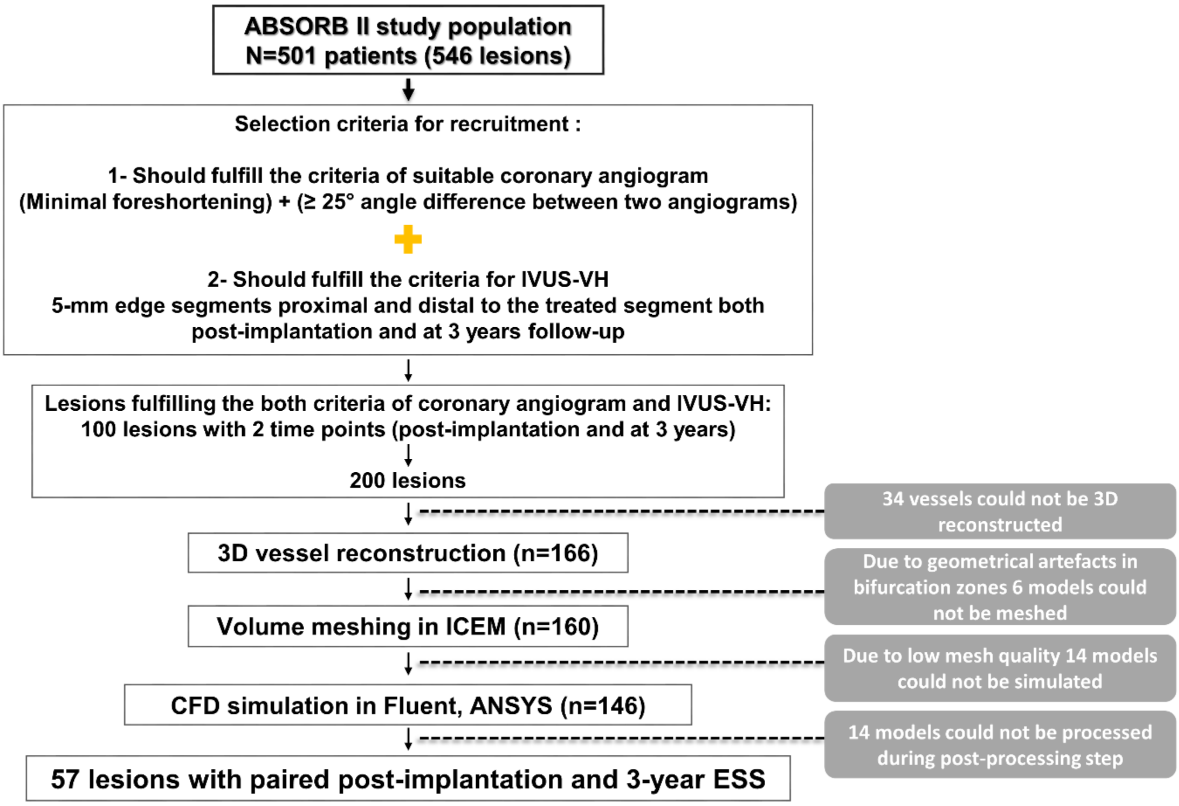

Figure-3: Changes in lumen, plaque, vessel area and plaque burden in matched frame stratified by terciles of median ESS post-procedure.

Stratification by terciles of median ESS post-procedure: ~0.658, 0.658~0.953, 0.953~ Pa. Thresholds of terciles were derived from frame-level data with all lesions pooled. There were 1753 and 954 frames (2:1 randomization) with paired ESS values post-procedure and at 3 years in the BRS and DES arm, respectively.

*P-value <0.05 (by linear mixed model, corrected for multiple comparisons). ESS=endothelial shear stress.

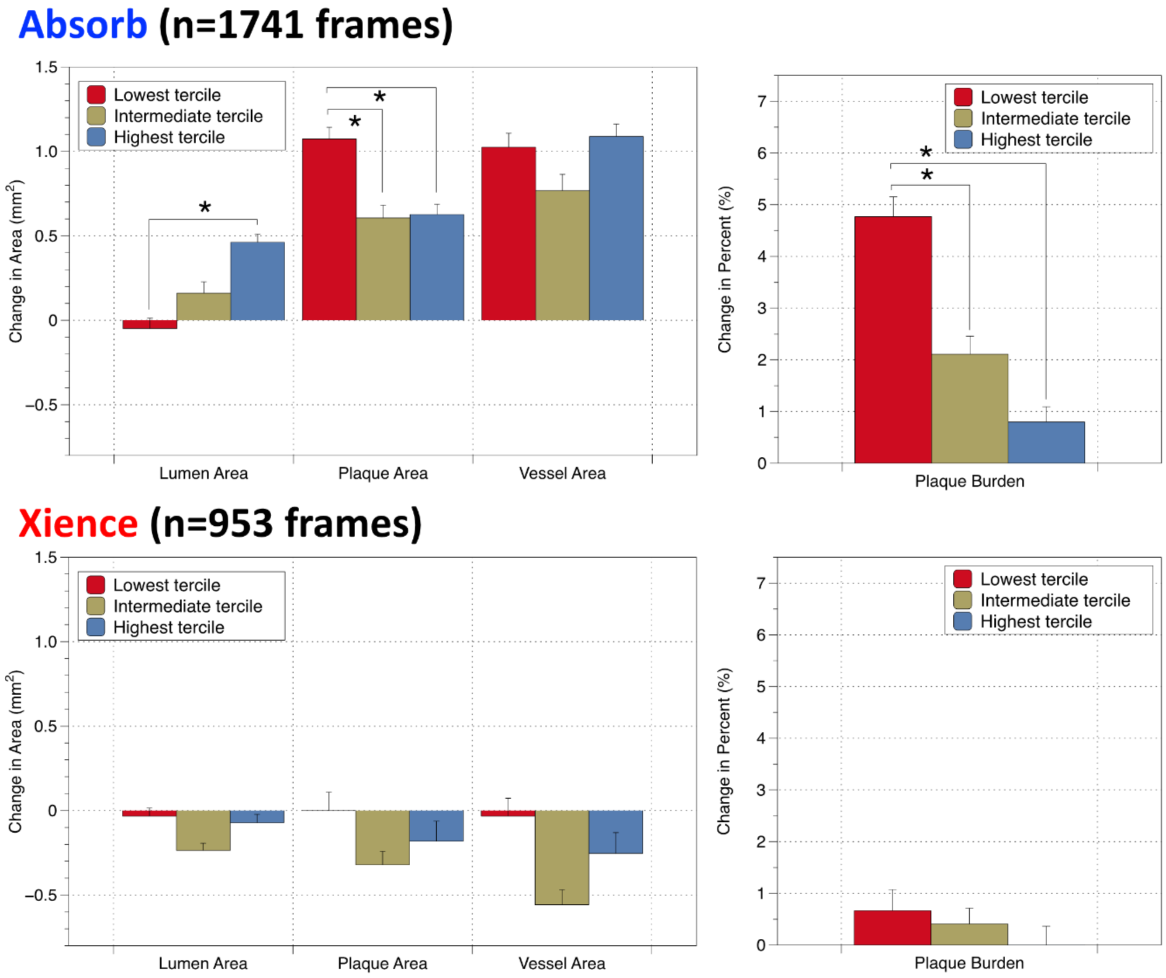

Figure-4: Correlations between change in vessel and lumen area, between relative change in lumen area and relative change in plaque burden, and between relative change in lumen area and change in median shear stress, in patients exhibiting expansive remodeling in Absorb and metallic Xience groups, respectively (analysis at frame level).

VE – vessel area, LA – lumen area, PB – plaque burden, WSS – wall shear stress

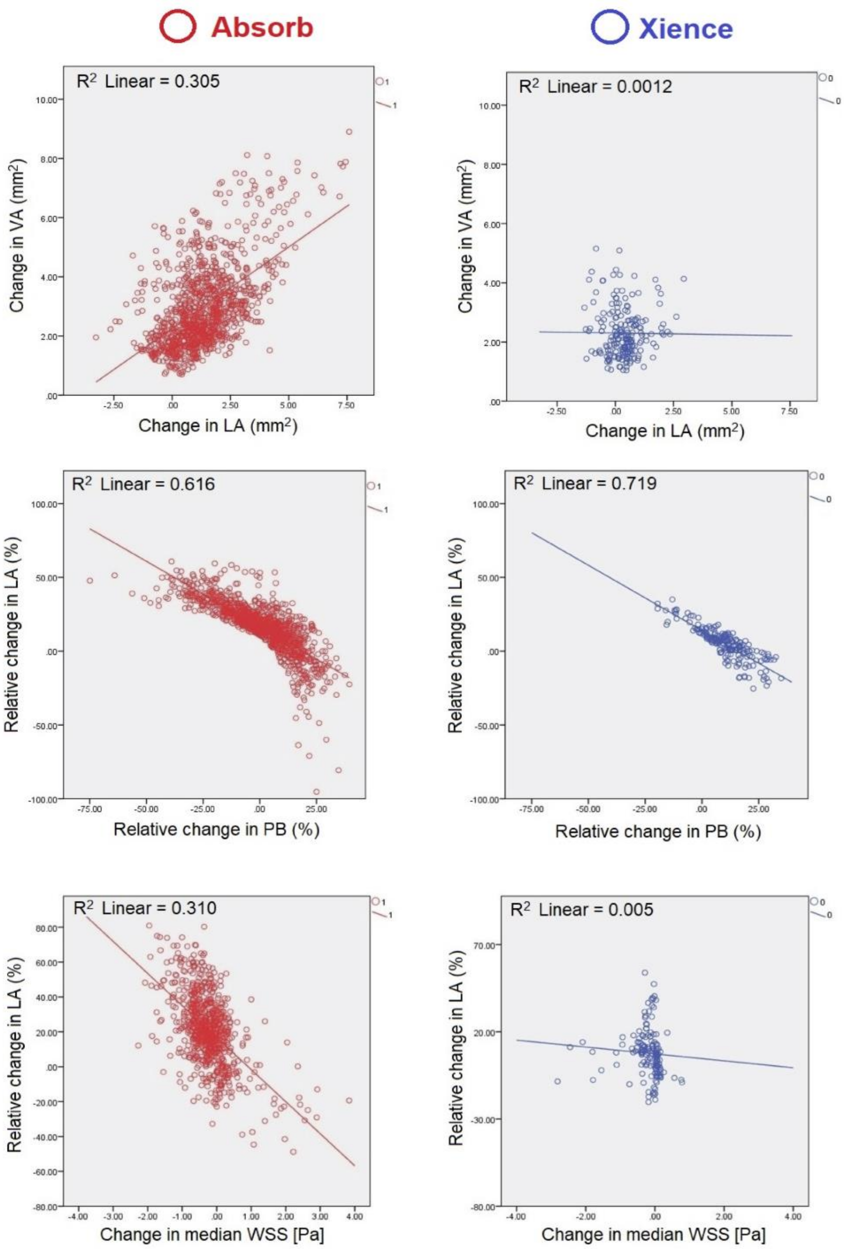

Figure-5: Post-procedural endothelial shear stress and changes in IVUS parameters during 3 years in a case of expansive remodeling in BRS.

Upper panels show 3D representation of endothelial shear stress (ESS) distribution post-procedure (left) and at 3-year (right) in a vessel implanted with bioresorbable scaffold (BRS). The scaffolded segment is located between white lines. The red line indicates matched sites whose cross-sectional images are shown in the lower panels. At this cross-section, median ESS post-procedure was 1.70 Pa (highest tercile in the analysis population). Subsequently, vessel area increased by 3.24 mm^2 with lumen enlargement of 1.83 mm^2

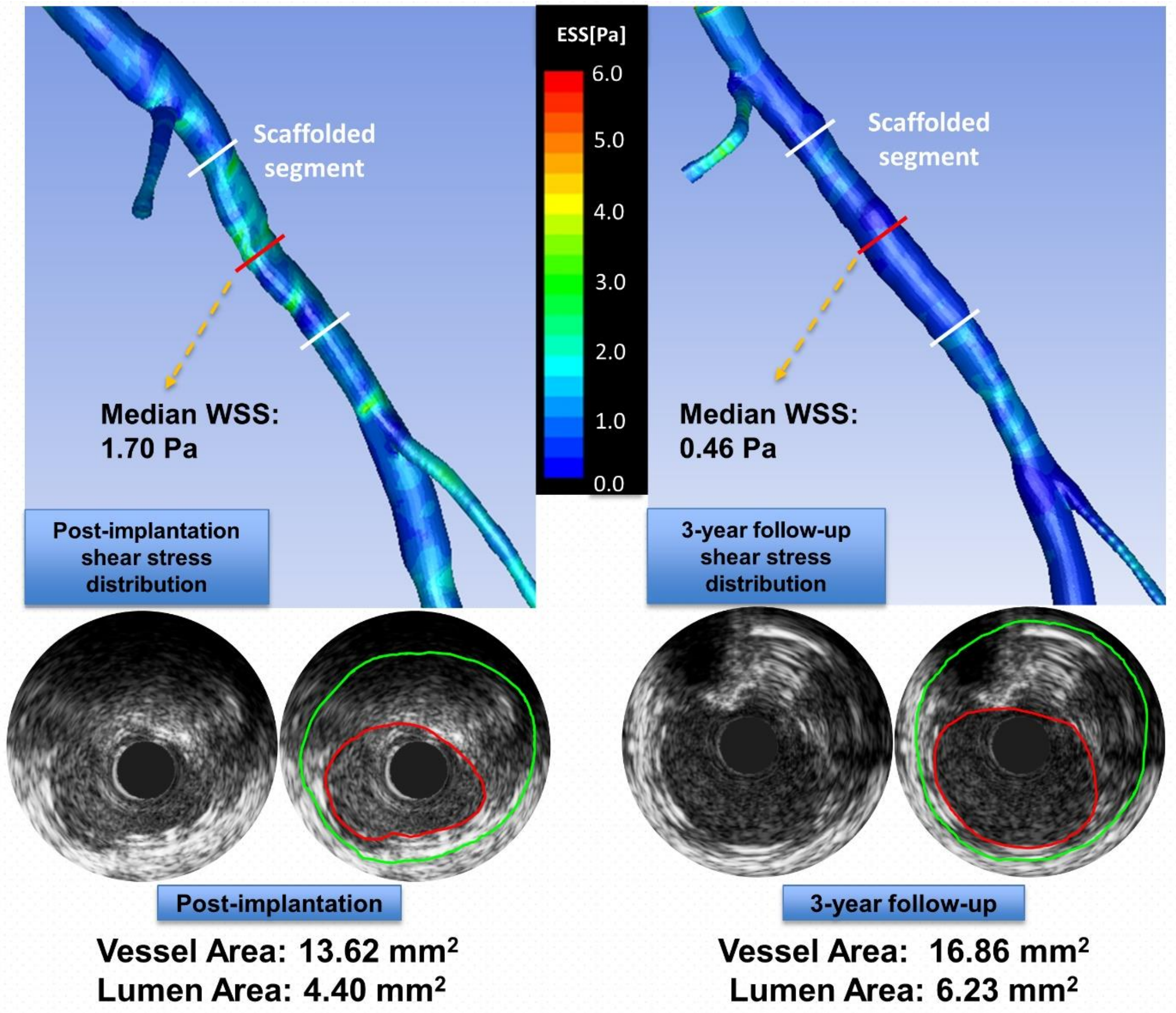

Figure-6: Cumulative frequency curves of endothelial shear stress (ESS) between devices post-procedure and at follow-up (frame-level statistics with all lesions pooled). Post-procedure median ESS was higher in the bioresorbable scaffold (BRS) arm, although the difference did not reach statistical significance. At 3 years, median ESS at frame level was significantly higher in the BRS arm than in the drug eluting stent (DES) arm.

ESS post-procedure was evaluated at the frame level (pooled analysis). Statistical test was performed using linear mixed effect model taking into account clustering within a lesion. ESS= endothelial shear stress.)

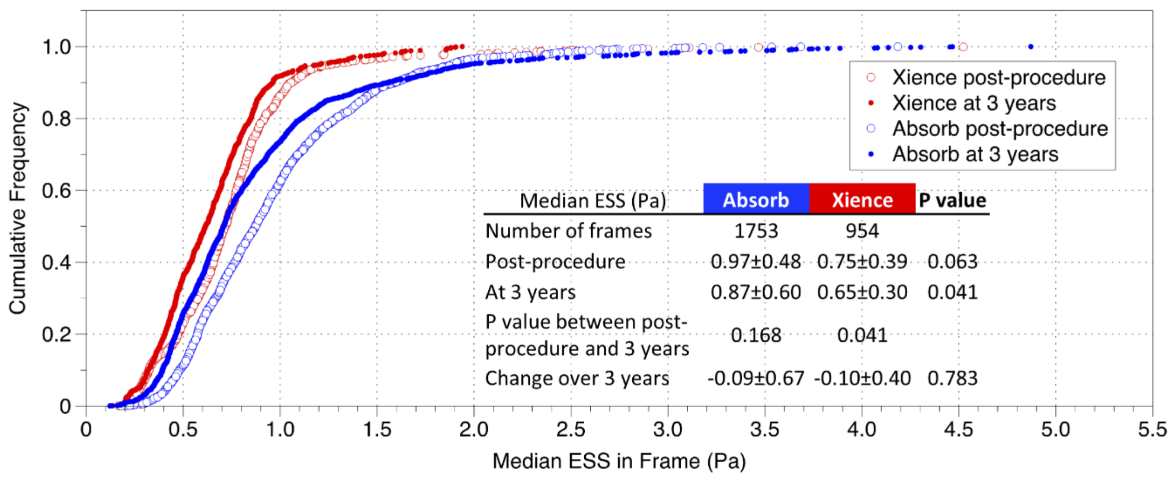

Table 1. Baseline patient, lesion characteristics and procedure details.

	BRS	DES	P value
Patient characteristics	35 patients	21 patients	
Age (years)	60.34±8.09	57.57±10.63	0.275
Male	20(57.1)	20(95.2)	0.002
Current smoking	9(25.7)	5(23.8)	1.000
Hypertension requiring medication	27(77.1)	15(71.4)	0.752
Dyslipidemia requiring medication	28(80.0)	13(61.9)	0.212
Diabetes	8(22.9)	1(4.8)	0.132
Unstable angina	4(11.4)	3(14.3)	1.000
Prior MI	8(22.9)	5(23.8)	1.000
Previous PCI	13(37.1)	9(42.9)	0.780
Obesity (BMI≥30kg/m^2)	8(22.9)	7(33.3)	0.534
Lesion characteristics	35 lesions	22 lesions	
Lesion location			
Right coronary artery	10(28.6)	7(31.8)	0.415
Left anterior descending	15(42.9)	12(54.5)	
Left circumflex artery	10(28.6)	3(13.6)	

Lesion classification			
A	1 (2.9)	0 (0.0)	0.628
B1	13 (37.1)	10 (45.5)	
B2	21 (60.0)	12 (54.5)	
Procedural details			
Pre-dilatation performed	35(100.0)	21(95.5)	0.386
Nominal diameter of pre-dilatation balloon(mm)	2.62±0.39	2.63±0.38	0.930
Maximal pressure during pre-dilatation(atm)	12.23±3.25	12.71±2.63	0.565
Nominal diameter of device(mm)	3.01±0.30	3.09±0.20	0.297
Length of implanted device(mm)	21.77±6.79	19.36±3.51	0.085
Maximal pressure during device implantation(atm)	13.91±2.37	13.36±2.56	0.411
Expected device diameter(mm)	3.36±0.32	3.30±0.28	0.523
Post-dilatation performed	23(65.7)	17(77.3)	0.391
Nominal diameter of post-dilatation balloon(mm)	3.16±0.37	3.29±0.30	0.234
Maximal pressure during post-dilatation(atm)	15.65±3.24	16.94±3.88	0.260
Expected diameter of post-dilatation balloon(mm)	3.29±0.39	3.39±0.32	0.431
Expected diameter of post-dilatation/device balloon throughout procedure(mm)	3.40±0.33	3.37±0.29	0.732
Expected balloon-artery ratio	1.21±0.13	1.17±0.12	0.176
Post-procedural patient related factors	35 patients	21 patients	
Mean LDL cholesterol(mmol/L)	2.35±0.62	2.52±0.84	0.374

BMI=body mass index, BRS=bioresorbable scaffold, DES=drug-eluting stent, LDL=low-density lipoprotein, MI=myocardial infarction, PCI=percutaneous coronary intervention.

Table 2. Changes in lumen, plaque, vessel area and plaque burden in matched frames stratified by median or minimum ESS.

BRS (n=741 frames)		Lowest tercile	Intermediate tercile	Highest tercile	p-value* Lowest vs. Intermediate tercile	Lowest vs. Highest tercile	Intermediate vs. Highest tercile
Median ESS	Range (Pa)	~0.658	0.658~0.953	0.953~			
	Number of frames	516	497	728			
	Delta Lumen Area (mm^2)	-0.26±1.46	0.18±1.39	0.57±1.28	0.003	<0.001	0.082
	Delta Plaque Area (mm^2)	0.92±1.54	0.58±1.79	0.76±1.59	0.249	0.283	1.000
	Delta Vessel Area (mm^2)	0.66±1.79	0.76±2.19	1.34±1.99	0.779	0.036	0.284
	Delta Plaque Burden (%)	5.36±8.98	1.86±8.09	0.72±7.46	0.011	<0.001	0.304

DES (n=953 frames)		Lowest tercile	Intermediate tercile	Highest tercile	p-value* Lowest vs. Intermediate tercile	Lowest vs. Highest tercile	Intermediate vs. Highest tercile
Median ESS	Range (Pa)	~0.658	0.658~0.953	0.953~			
	Number of frames	388	397	168			
	Delta Lumen Area(mm^2)	-0.04±0.90	-0.16±0.84	-0.23±0.73	1.000	1.000	1.000
	Delta Plaque Area(mm^2)	-0.01±2.06	-0.30±1.51	-0.21±1.85	0.487	1.000	1.000
	Delta Vessel Area(mm^2)	-0.05±2.05	-0.46±1.70	-0.43±1.79	0.367	1.000	1.000
	Delta Plaque Burden(%)	0.77±7.73	0.12±5.53	0.22±6.74	1.000	1.000	1.000

*P-values were by linear mixed model, corrected for multiple comparison. ESS=endothelial shear stress.

Table 3. Multivariate model predicting vessel area change (mm^2) over 3 years.

	Overall Coefficient	95% CI	P value	Absorb Coefficient	95% CI	P value	Xience Coeffi
Age (per year)	-0.07	(-0.21 , 0.07)	0.329	-0.22	(-0.39 , -0.04)	0.016	0.09
Female	0.57	(-2.61 , 3.75)	0.715	0.54	(-2.10 , 3.19)	0.676	3.11
Absorb implantation	0.04	(-2.67 , 2.75)	0.975	NA			
IVUS post-procedure							
Vessel area(per mm^2)	-0.74	(-0.92 , -0.56)	<0.001	-0.70	(-0.92 , -0.48)	<0.001	-0.92
Lumen area(per mm^2)	0.78	(0.43 , 1.13)	<0.001	0.66	(0.19 , 1.12)	0.006	1.16
Plaque area(per mm^2)	NA*						
Plaque burden(per %)	0.10	(0.06 , 0.15)	<0.001	0.10	(0.05 , 0.15)	<0.001	0.14

Median ESS post-procedure(per Pa)	0.45	(	0.01	,	0.89	)	0.046	0.59	(	0.16	,	1.01	)	0.009	0.21

* not shown because it is redundant.
CI=confidence interval, ESS=endothelial shear stress, IVUS=intravascular ultrasound, NA=not available.