



Vulnerable struts with **CRE8**, **Biomatrix** and **Xience** stents assessed with **OCT** and their correlation with clinical variables at 6-month follow-up: the CREBX-OCT study

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Abstract

First-generation drug eluting stents (DES) reduced the incidence of restenosis and need for repeated target lesion revascularization but, in autoptic studies, frequently resulted in incomplete endothelial coverage, which is an important predictor of late adverse events and increased mortality after stent implantation. More recently, not only uncovered, but also malapposed or protruding struts have been considered vulnerable structures, as they are deemed to perturb blood flow, whereas only struts well embedded into the vessel wall are considered stable. We compared the number of uncovered and of other vulnerable (protruding or malapposed) struts among three different second-generation drug-eluting stents (DES) (Cre8, Biomatrix, Xience), using optical coherence tomography (OCT) 6 months after implantation. Moreover, we analyzed the relationship between the percentage of vulnerable struts and the clinical characteristics of patients. 60 patients with stable angina or non-ST-Elevation acute coronary syndrome and indication to percutaneous angioplasty were randomly assigned to receive one of the three DES. After 6 months, OCT images were obtained. After 6 months, OCT images were obtained (1289 cross sections; 10,728 struts). None of the three DES showed non-coated struts or areas of stent thrombosis. Significant differences in the average number of protruding struts (Cre8: 33.9 ± 12.6 ; Biomatrix: 26.2 ± 18.1 ; Xience: 13.2 ± 8.5 ; $p < 0.001$) and in the proportion of malapposed struts (Cre8: 0.7%; Biomatrix: 0.9%; Xience: 0.0%; $p = 0.040$) and of incomplete stent apposition area (Cre8: 10.4%; Biomatrix: 4.7%; Xience: 0.7%; $p < 0.001$) were observed. No significant difference was found in neointimal hyperplasia area with a not significant tendency toward greater minimal and maximal struts thickness for Biomatrix. In comparison with Cre8 and Biomatrix, Xience showed a significantly lower proportion of vulnerable struts in all clinical sub-groups considered. In the group of 60 patients a significant relation was found between age and number of vulnerable struts ($p = 0.014$). The three second-generation DES were similarly effective in permitting neo-intimal formation and complete struts coating 6 months after implantation, but Cre8 and Biomatrix showed a greater proportion of protruding and malapposed struts.

Trail Registry: Clinical Trials.gov Identifier: NCT02850497.

Keywords Second generation drug eluting stent · Optical coherence tomography · Follow-up · Malapposition · Protruding strut · Neo-intimal coverage

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Introduction

First-generation drug eluting stents (DES) reduced the incidence of restenosis and need for repeated target lesion revascularization [1, 2] but, in autoptic studies [3], frequently resulted in incomplete endothelial coverage, which is an important predictor of late adverse events and increased mortality after stent implantation [4–8]. Such incomplete endothelial coverage was mainly ascribed to the inflammatory effect of the “drug-polymer binomial” used in these

stents [9, 10]. This hypothesis stimulated the search for new technologies which led to the development of second-generation DES, with reduced inflammatory effect on the vessel wall and unchanged power in preventing restenosis [9–11]. More recently, not only uncovered, but also malapposed or protruding struts have been considered vulnerable structures, as they are deemed to perturb blood flow, whereas only struts well embedded into the vessel wall are considered stable [12–15].

Second-generation DES are largely heterogeneous, differing in the type and location of anti-proliferative drugs and polymers on their platform surface. Therefore, interventional cardiologists may find it difficult to select the stent providing the best immediate and mid-term clinical results. We therefore conducted a randomized, prospective trial using optical coherence tomography (OCT), aimed at comparing, the number of uncovered struts and that of other vulnerable (malapposed or protruding) struts among three second-generation DES, 6 months after their implantation during percutaneous coronary intervention (PCI). Moreover, we analyzed the relationship between the proportion of vulnerable struts and clinical and demographic characteristics of patients.

Methods

The CREBX-OCT study (Comparison of uncovered, malapposed, or protruding struts with three types of second-generation DES: **CRE8**, **Biomatrix** and **Xience** with **OCT** at 6-month follow-up of patients submitted to PCI) is a non-profit, single center, 3-arm, prospective randomized study (Clinical Trials.gov Identifier: NCT02850497; Fig. 1).

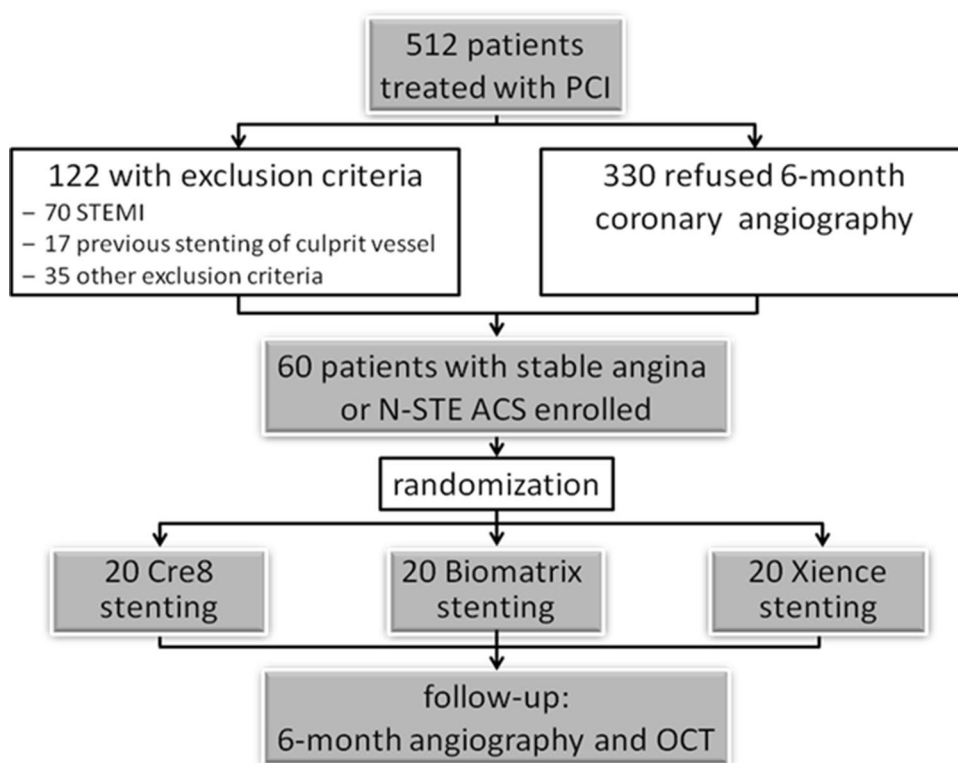
Endpoints

The primary endpoint of the trial was to compare, at 6-month follow-up, the number of uncovered struts as assessed by OCT among the three groups. The co-primary endpoint also included other characteristics (malapposition or protrusion) recently reported in the literature [12–15] as indicating struts' vulnerability and their relationship to clinical variables.

Patients

Patients > 18-year-olds planned to be treated with PCI for stable angina (SA) or non-ST segment elevation acute coronary syndrome (N-STE ACS) by a single operator at the catheterization laboratory of the University of Florence from September, 2015 to July, 2017, were considered eligible for the study, provided they did not meet any of the following

Fig. 1 Study flow chart. *PCI* percutaneous coronary intervention, *STEMI* ST segment elevation myocardial infarction, *N-STE ACS* non-ST segment elevation acute coronary syndrome, *OCT* optical coherence tomography



exclusion criteria: (1) ST segment elevation myocardial infarction; (2) contraindication to dual antiplatelet therapy; (3) surgical intervention planned < 6 months; (4) indication to anticoagulant therapy; (5) comorbidities with expected survival < 6 months; (6) cardiogenic shock; (7) unwillingness to sign informed consent or to undergo 6-month coronary angiography. Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Randomization to Cre8, Biomatrix, or Xience was performed in computer-generated sequences after coronary angiography resulting in indication to DES implantation. In case of multivessel coronary artery disease, only one vessel was chosen for the study, at operator's discretion. Further angiographic exclusion criteria were: (1) visually estimated diameter of target vessel ≤ 2.5 mm; (2) target vessel previously treated with stent implantation. Over the study period, 60 patients without exclusion criteria consented to participate in the trial and were hence enrolled, 20 in each randomization arm (Fig. 1).

Stents implantation and OCT imaging

The polymer-free Cre8™ stent (CID s.p.a., Saluggia, Italy) has a cobalt-chromium platform, coated with “carbofilm”, eluting amphilius™, which is composed of sirolimus and a mixture of long-chain fatty acids, contained in grooves on stent's outer surface (Strut's thickness 80 μm). The BioMatrix Flex™ stent (Biosensors EUROPE SA, Morges, Switzerland) has a steel platform, eluting biolimus A9™, which is a semi-synthetic sirolimus derivative with improved pharmacokinetic properties. Its poly-lactic acid polymer is biodegradable: the drug and the polymer are present only on stent's abluminal surface (Strut's thickness 112 μm ; polymer's thickness 11 μm). The Xience™ V stent (Abbott Vascular, Santa Clara, California, USA) has a cobalt-chromium platform, eluting everolimus and with a non-biodegradable polymer: the drug and the polymer are present on the intraluminal as well as the abluminal stent's surface (Strut's thickness 81 μm ; polymer's thickness 3.9 $\mu\text{m} \times 2$).

In all three arms, DES were deployed at a pressure selected at operator's discretion according to the characteristics of the lesion, and eventual optimization with non-compliant balloon was based on qualitative assessment of post-deployment angiographic images.

OCT was performed with ILUMIENT™ PCI Optimization System-St. Jude Medical (resolution power 20 μm) after completion of index PCI and at 6-month follow-up coronary angiography. Briefly, the imaging catheter (Dragonfly™ Duo Imaging Catheter, LightLab Imaging, Inc. Westford, USA) was advanced on a standard 0.014 inch PCI guide

wire, with the light source distal to the stent. The guide catheter was well engaged into the coronary ostium so as to minimize the reflow into the aorta of contrast medium injected during image acquisition. The OCT catheter was then pulled-back at 20 mm/s by an automated device, while intracoronary injecting contrast medium (20 ml at 4 ml/s or 3 ml/s for left or right coronary artery, respectively). A first, OCT qualitative analysis was performed in the catheterization laboratory, immediately after the index PCI, in order to determine whether stent implantation had to be further optimized with non-compliant balloons. The off-line analysis of OCT data was performed by ILUMENT™ OPTISTM St. Jude Medical workstation by two different investigators (C.F. and E.C.), who were blinded to each other's assessment and to the type of implanted stent. From baseline OCT, only the presence of calcified plaques in the treated segments and the number of malapposed struts in the three groups of patients were recorded. For the 6-month OCT analysis that represented the primary study end-point, each OCT final measure represented the average of measures acquired by the two independent investigators. To this purpose, stents were analyzed by OCT at each millimeter of length, using one frame every 5 acquired frames, the number of measures for each patient thereby depending on the length of implanted stent. Patients with two or more overlapping stents had a number of analyzed frames that was smaller than the sum of individual stent length, because of the overlapping zone. After machine calibration, vessel luminal area, stent area, number of struts, neointimal thickness at each strut level (defined as the distance between luminal surface of strut and vessel lumen, with exclusion of strut thickness), were measured from each analyzed frame. In particular, neointimal area was calculated as: stent area–lumen area. Struts were classified as covered when at the 6-month OCT analysis they had lost the brightness observed at the OCT performed immediately after the stent implantation or if they appeared partially or completely covered by a layer of tissue. Struts were classified as uncovered when they showed the same brightness observed at the OCT analysis performed immediately after stent implantation or if they appeared in any part uncovered by a layer of tissue. Moreover, struts were classified as apposed or malapposed in relation to their adherence to the vessel wall [16, 17].

The thickness of struts was different in the three type of stents in relation to the different structural characteristics and to the polymer presence: and malapposition was determined by adding the actual strut thickness and polymer thickness to the OCT resolution limit as mentioned above. On the basis of this definition the cutoff to consider a strut malapposed is different in the three types of stents. For malapposed struts, the maximum distance between the external strut surface and vessel wall was calculated. Well-apposed struts were further classified as embedded in the vessel wall or as protruding

into vessel lumen. Struts were considered embedded when buried into the vessel wall, with a coverage thickness not reducing the vessel lumen, and protruding when, though covered by tissue, the strut boundary was located above the level of the luminal surface [17].

Pharmacological treatment

Before PCI, all patients received ASA 325 mg orally or 250 mg intravenously and intravenous unfractionated heparin as an initial bolus of 70 UI/kg. Patients treated for SA also received a 600 mg clopidogrel loading dose, those treated for N-STE ACS a 180 mg ticagrelor or a 60 mg prasugrel loading dose. After PCI, all patients were prescribed ASA 100 mg indefinitely and clopidogrel 75 mg daily for 6 months if treated for SA, or ticagrelor 180 mg or prasugrel 10 mg daily for 12 months if treated for N-STE ACS. Other drugs such as statins, beta-blockers, angiotensin-converting enzyme inhibitors, were prescribed in accordance with international guidelines [18, 19].

Response to the Dual antiplatelet therapy was evaluated by light transmittance aggregometry (LTA) using 10 μ M/L adenosine-diphosphate (ADP) and 1 mM arachidonic acid (AA) as agonists. Patients with high on-treatment platelet reactivity (HPR) by ADP ($\geq 70\%$) were switched to another P2Y₁₂ antagonist; in patients with high on-treatment platelet reactivity HPR by AA ($\geq 20\%$) acetylsalicylic acid dose was increased if not contraindicated. Platelet function analysis was repeated 48 h after therapy variation [20].

A clinical follow-up at 6 months was performed to evaluate Major Cardiovascular events (MACE) a composite of cardiovascular death, myocardial infarction, stroke, recurring angina or need for target lesion revascularization [21].

Statistical analysis

Data were stored in a dedicated database and analyzed with SPSS 20 for Windows statistical software (SPSS Inc, Chicago, IL, USA). Categorical and continuous variables were reported respectively as percentages, or as mean \pm SD, or median and interquartile range (IQR) for non-normal distributions, and compared with Chi square test or with ANOVA or Kruskal-Wallis test. A two-tailed $p < 0.05$ was considered statistically significant. Association of the continuous variables with the percentage of vulnerable struts was analyzed with a linear or not linear regression on the basis of the best fitting.

Sample size calculation

The sample size needed to achieve a good statistical power was difficult to be obtained a priori because it required the knowledge of how many struts we would have analyzed in

our series, that in turn depended on the number and length of stents implanted in our study population. We could only hypothesize, on the basis of previous studies, that a percentage as high as 85% of struts would result embedded at 6 month follow-up, with a difference of $\pm 10\%$ (with a SD 10) between a group with respect to each other. On this basis, it was estimated that 16 patients per group would be enough to reach a power of 80% and a two sided level of significance of 0.05. We choose to enrol four more patients per group (+ 25%) in order to prevent drop-outs at follow-up.

Results

The main baseline demographic, clinical, and angiographic characteristics (Table 1) were all similar across the three randomization groups. The main laboratory tests at baseline and at 6-month follow-up, including the prevalence of responders to ASA and to P₂Y₁₂, were also similar (data not reported).

OCT imaging after the index PCI showed 12, 5 and 12 calcified plaques in the Cre8, the Biomatrix and the Xience group, respectively; moreover, two, one and two patients in the Cre8, Biomatrix and Xience group had some malapposed struts, with an overall number of 8, 6 and 7 malapposed struts, respectively : $P = NS$ for all comparisons (Table 2). The 6-month follow-up OCT data deriving from the analysis of 1289 cross sections and 10,728 struts, with similar numbers of frames and struts analyzed across the three groups, are reported in Table 2. The proportion of cross sections with incomplete stent apposition (ISA) was lower in the Xience-group, compared to the other two groups. No uncovered struts, or struts with evidence of thrombus formation, were observed in any of the three groups, whereas the proportion of malapposed struts was smaller, and the maximum distance of malapposition shorter, in the Xience than in the Cre8 or the Biomatrix group. Overall, some malapposed struts were present in 13/60 patients (21.6%), but in five of them (38.4%) some struts had resulted already malapposed in OCT at baseline. The proportion of protruding struts was greater in the Cre8 than in the other two groups. The Xience group also had a higher proportion of well-embedded struts, compared to the other two groups. No significant difference was observed, across the three groups, in neointimal area or in struts' coverage thickness. Correlations of percentage of vulnerable struts with continuous variables in all patients and in the three groups of treatment are reported in Table 3. A direct linear relation was found between the age of all sixty patients and the percentage of vulnerable struts (Fig. 2)

Comparisons between and within groups of percentage of vulnerable struts regarding clinical characteristics are reported in Table 4. Patients treated with Xience showed

Table 1 Baseline clinical, biohumoral, coronary angiographic and PCI characteristics

	Cre8	Biomatrix	Xience	p value
Gender M/F, n (%)	15/5 (75/25)	15/5 (75/25)	16/4 (80/20)	0.911
Age (years), mean \pm SD	68 \pm 10.4	65.4 \pm 11.9	62.5 \pm 11.7	0.318
BMI (Kg/m ²), mean \pm SD	26 \pm 3.4	25.5 \pm 2.7	28.5 \pm 3.4	0.016
Hypertension, n (%)	17 (85)	18 (90)	18 (90)	0.851
Diabetes, n (%)	4 (20)	5 (25)	5 (25)	0.911
Hyperlipidemia, n (%)	15 (75)	16 (80)	15 (75)	0.911
Ever smoker, n (%)	13 (65)	11 (55)	14 (70)	0.605
Familial history of CAD, n (%)	7 (35)	6 (30)	4 (20)	0.563
Previous CAD, n (%)	5(25)	3 (15)	2 (10)	0.432
Previous PCI, n (%)	2 (10)	2 (10)	0 (0)	0.343
Previous CABG, n (%)	0 (0)	1 (5)	0 (0)	0.362
Previous TIA/stroke, n (%)	2 (10)	0 (0)	0 (0)	0.126
Chronic kidney disease, n (%)	1 (5)	1 (5)	1 (5)	1
COPD, n (%)	3 (15)	2 (10)	1 (5)	0.574
Sinus rhythm, n (%)	19 (95)	17 (85)	19 (95)	0.418
Atrial fibrillation, n (%)	1 (5)	3 (15)	1(5)	
Heart failure, n (%)	1 (5)	4 (29)	1 (5)	0.189
LVEF (%), mean \pm SD	57.3 \pm 8.5	56.4 \pm 10.6	54.9 \pm 7.8	0.748
Total cholesterol (mg/dL)	165 \pm 39	158 \pm 27	178 \pm 47	0.360
HDL cholesterol (mg/dL)	42 \pm 13	37 \pm 9	39 \pm 16	0.696
LDL cholesterol (mg/dL)	96 \pm 37	86 \pm 34	104 \pm 43	0.438
Triglycerides (mg/dL)	123 \pm 66	137 \pm 60	185 \pm 104	0.091
proBNP (pg/mL), median (IQR)	896 (294–1663)	591 (100–1017)	604 (162–1780)	0.601
Troponin (μ g/L), median (IQR)	0.60 (0.17–1.84)	1.08 (0.53–2.06)	2.36 (0.41–7.24)	0.279
Hemoglobin (g/dL)	12.3 \pm 1.9	12.3 \pm 1.3	13.1 \pm 1.7	0.178
Leukocyte ^a (109/L)	7.65 \pm 2.42	7.45 \pm 1.58	7.53 \pm 1.60	0.950
Platelets ^a (109/L)	191 \pm 67	187 \pm 54	191 \pm 52	0.355
Creatinine (mg/dL)	1.35 \pm 1.35	0.95 \pm 0.23	1.37 \pm 1.38	0.432
eGFR (mL/min/1.73 m ²)	78 \pm 25	98 \pm 29	84 \pm 26	0.062
Stable angina, n (%)	3 (15)	5 (25)	4 (20)	0.732
Acute coronary syndrome ^a , n (%)	17 (85)	15 (75)	16 (70)	
Multivessel disease	12 (60)	14 (70)	13 (65)	0.136
2, n (%)	6 (30)	11(55)	4 (20)	
3, n (%)	6 (30)	3 (15)	9 (45)	
Target lesion coronary artery				0.268
Left anterior descending	6 (30)	11 (55)	15 (75)	
Left circumflex	2 (10)	3 (15)	4 (20)	
Right	6 (30)	6 (30)	1 (5)	
Number of stents, n (%)				0.445
1, n (%)	17 (85)	15 (75)	12 (60)	
2, n (%)	3 (15)	4 (20)	7 (35)	
3, n (%)	0 (0)	1 (5)	1 (5)	
Total length (mm), mean \pm SD	22.9 \pm 9.9	28.6 \pm 11.4	30.0 \pm 14.8	0.182
Overlapping stents, n (%)	3 (15)	5 (25)	8 (40)	0.198

BMI body mass index, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention, *CABG* coronary artery by-pass graft, *TIA* transient ischemic attack, *COPD* chronic obstructive pulmonary disease, *LVEF* left ventricle ejection fraction, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *proBNP* pro-brain natriuretic peptide, *eGFR* estimated glomerular filtration rate

^aPatients with STEMI were excluded from enrollment

Table 2 Results of OCT analysis at follow-up (mean values of all the measurements in all patients)

	CRE8	BIOMATRIX	XIENCE	<i>p</i> value
Cross sections analyzed, (n)	414	427	448	n/a
Luminal area (mm ²), mean ± SD	8.62 ± 2.16	8.07 ± 2.65	6.76 ± 1.78	0.031
Stent area (mm ²), mean ± SD	9.26 ± 2.27	8.93 ± 2.56	7.60 ± 1.92	0.057
NIH area (mm ²), mean ± SD	0.80 ± 0.25	0.97 ± 0.43	0.85 ± 0.28	0.254
Min neointimal thickness (mm), mean ± SD	0.05 ± 0.11	0.09 ± 0.19	0.04 ± 0.01	0.424
Max neointimal thickness (mm), mean ± SD	0.15 ± 0.12	0.21 ± 0.21	0.15 ± 0.05	0.315
Cross sections with ISA, n	43	20	3	<0.001
%	10.4	4.7	0.7*	
Struts analyzed (n)	3442	3313	3975	n/a
Apposed struts, n	3311	3240	3941	n/a
%	96.2	97.8	99.1	<0.001
100 mm ² of lateral surface, mean ± SD	37.5 ± 17.0	34.7 ± 15.6	42.9 ± 25.7	0.478
Embedded struts, n	2189	2360	3445	<0.001
%, mean ± SD	66.1 ± 12.7	72.8 ± 19.1	87.4 ± 8.5*	
100 mm ² of lateral surface, mean ± SD	24.6 ± 12.4	24.9 ± 15.5	37.1 ± 21.5	0.053
Protruding struts, n	1121	848	521	<0.001
%, mean ± SD	33.9 ± 12.6	26.2 ± 18.1	13.2 ± 8.5*	
100 mm ² of lateral surface, mean ± SD	12.9 ± 9.3	9.5 ± 6.2	6.0 ± 5.6**	0.025
Covered by thrombus, n	0	0	0	n/a
Uncovered struts, n	0	0	0	n/a
Malapposed struts, n	99	57	5	n/a
%	8 [§]	6 [§]	7 [§]	n/a
% median (IQR)	0.7 (0.0–2.1)	0.9 (0.0–2.9)	0.0 (0.0–0.0)*	0.040
100 mm ² lateral surface, median (IQR)	0.22 (0.00–0.91)	0.00 (0.00–0.76)	0.00 (0.00–0.00)*	0.005
Covered by NIH, n	99	57	5	n/a
Covered by thrombus, n	0	0	0	n/a
Uncovered, n	0	0	0	n/a
Malapposition distance				
Maximum (mm)	1.13	0.71	0.69	0.007
Median (IQR)	0.43 (0.12–1.13)	0.16 (0.02–0.71)	0.00 (0.00–0.00)*	
Side branch zone struts, n	32	16	29	n/a
Covered by NIH, n	32	16	29	n/a
Uncovered, n	0	0	0	n/a
Covered by Thrombus, n	0	0	0	n/a

NIH neointimal hyperplasia, ISA incomplete stent apposition, IQR interquartile range (25°–75° percentile)

**p* < 0.05 compared to Biomatrix and Cre8

***p* < 0.05 compared to Cre8

§Malapposed Struts at the index procedure. Data available on 51/60 patients

a significantly lower proportion of vulnerable struts in all clinical subgroups analyzed.

Over the 6-month follow-up, no patient died or had a myocardial infarction or stroke. However, MACEs occurred in 9/60 patients as recurring angina (*n* = 6: 1 in the Cre8, 3 in the Biomatrix and 2 in the Xience group, respectively) or as a need for repeated PCI in the target vessel (*n* = 3; 1 in each group) (*P* = NS for all comparisons). Overall, 11/60 patients had a second PCI of a

coronary branch different from the target one (3 in Cre8, 3 in the Biomatrix, and 5 in the Xience group, respectively).

Discussion

The main findings of this prospective, randomized trial, aimed at comparing OCT images across three second-generation DES (Cre8, Biomatrix and Xience) 6 months

Table 3 Correlations of percentage of vulnerable struts with anthropometric-functional and biohumoral data in all patients and with respect to the type of stent implanted

	CRE8	BIOMATRIX	XIENCE	All patients
Age (years)	0.09 (0.714)	0.38 (0.113)	0.28 (0.255)	0.32 (0.014)*
BMI (kg/m ²)	0.29 (0.301)	0.04 (0.872)	0.29 (0.253)	−0.07 (0.660)
LVEF post PCI (%)	−0.42 (0.105)	−0.26 (0.307)	−0.08 (0.772)	−0.17 (0.232)
Hemoglobin (g/dL)				
Post PCI	0.08 (0.748)	−0.32 (0.196)	−0.05 (0.838)	−0.21 (0.126)
At follow-up	−0.11 (0.651)	−0.04 (0.866)	−0.05 (0.851)	−0.16 (0.232)
WBC (n/μL × 10 ³)				
Post PCI	−0.26 (0.287)	0.06 (0.815)	0.02 (0.951)	−0.06 (0.660)
At follow-up	0.01 (0.956)	−0.14 (0.571)	0.19 (0.445)	−0.02 (0.880)
Glucose (g/L), mean ± SD				
Post PCI	−0.06 (0.825)	−0.20 (0.534)	0.19 (0.511)	−0.22 (0.157)
At follow-up	−0.05 (0.874)	0.06 (0.872)	−0.02 (0.944)	−0.09 (0.608)
Total cholesterol (mg/dL)				
Post PCI	0.35 (0.221)	−0.40 (0.113)	−0.50 (0.085)	−0.18 (0.237)
At Follow-up	−0.08 (0.784)	0.15 (0.644)	−0.05 (0.878)	−0.01 (0.931)
HDL cholesterol (mg/dL)				
Post PCI	0.40 (0.179)	−0.19 (0.460)	0.30 (0.276)	0.15 (0.327)
At follow-up	0.30 (0.236)	−0.23 (0.478)	0.38 (0.248)	0.08 (0.605)
LDL cholesterol (mg/dL)				
Post PCI	0.30 (0.295)	−0.36 (0.153)	−0.58 (0.023)*	−0.19 (0.201)
At follow-up	−0.05 (0.860)	0.25 (0.436)	−0.22 (0.509)	−0.002 (0.990)
Triglycerides (mg/dL)				
Post PCI	−0.01 (0.975)	0.13 (0.607)	−0.13 (0.635)	−0.08 (0.580)
At follow-up	−0.28 (0.317)	0.05 (0.880)	−0.24 (0.486)	−0.06 (0.731)
EGFR (mL/min/1.73 m ²)				
Post PCI	−0.14 (0.581)	−0.03 (0.897)	0.41 (0.081)	0.02 (0.905)
At follow-up	−0.28 (0.317)	0.05 (0.880)	−0.24 (0.486)	−0.06 (0.731)
TnI (ng/mL)				
Post PCI	0.07 (0.781)	0.19 (0.463)	−0.36 (0.155)	−0.09 (0.499)
NT-proBNP (p g/ml)				
Post PCI	−0.05 (0.894)	0.53 (0.064)	0.33 (0.347)	0.25 (0.148)
At follow-up	−0.17 (0.612)	0.19 (0.651)	−0.29 (0.535)	0.20 (0.327)

All values are reported as Pearson's R (p value) but TnI and NT-proBNP, when Spearman's rho was used
BMI body mass index, *LVEF* left ventricle ejection fraction, *PCI* percutaneous coronary intervention, *WBC* white blood cells, *HDL* high density lipoproteins, *LDL* low density lipoproteins, *EGFR* estimated glomerular filtration rate, *TnI* NT-proBNP

*p < 0.05 in all patients and in the three groups

after their implantation, are the following: (1) no uncovered struts were observed with any DES, with no difference in neointimal thickness; (2) the proportion of vulnerable (malapposed and/or protruding) struts was lower in patients randomized to receive the Xience than the other two DES, with the Cre8 showing the highest proportion; moreover, the Xience was also associated with a higher proportion of stable, well-embedded struts; (3) age and the number of vulnerable struts were in direct linear relationship; (4) these differences did not translate into different risk of MACEs over the 6-month follow-up (Fig. 3).

In our study population, no uncovered struts were found at 6-month follow-up OCT, reinforcing the concept that all three different second-generation DES ensured a complete neointimal coverage of struts over a relatively short follow-up, irrespective of whether they were implanted in patients with SA or N-STE ACS. Although late-stent thrombosis is a multi-factorial phenomenon in which the uncovered struts, ascribed to delayed and incomplete endothelialization, represent only one element [3, 6], this result indirectly reinforces the claim of greater anti-thrombogenic effectiveness of second-generation DES. This finding also confirms

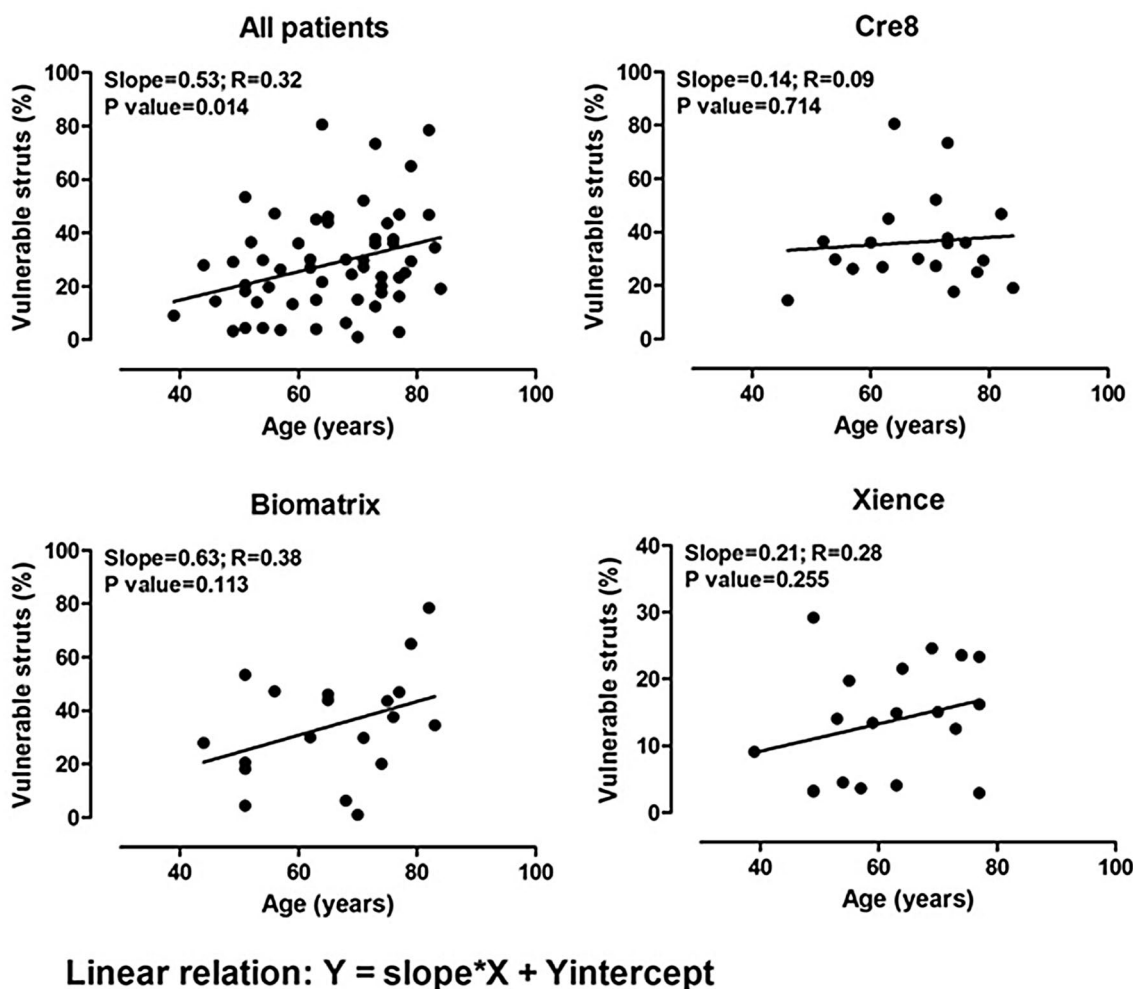


Fig. 2 A direct linear relation was found between age and the percentage of vulnerable struts (all 60 patients and sub-groups DES)

previously published data about earlier re-endothelization of second-generation DES that, at 2-week and at 3-month OCT analysis, showed a proportion of uncovered struts similar to that observed at 1-month with bare metal stents [15, 22–26].

Although the true ratio of uncovered struts may be underestimated with OCT because of its partial ability to distinguish a neointimal layer from fibrin, several studies analyzing the healing of second generation DES with OCT, found a ratio of covered struts between 95 and 100% similar to our results [15, 24–27] (Fig. 4).

Moreover, according to imaging technologies and autopsy studies, the concept of “vulnerable” struts has been extended to include not only the uncovered, but also the malapposed or protruding struts [12–15, 28, 29]. Although recent analyses of several stent thrombosis registries found that extensively malapposed struts were frequently identified in patients who experienced stent thrombosis, the clinical effects of stent malapposition remain controversial [30–34].

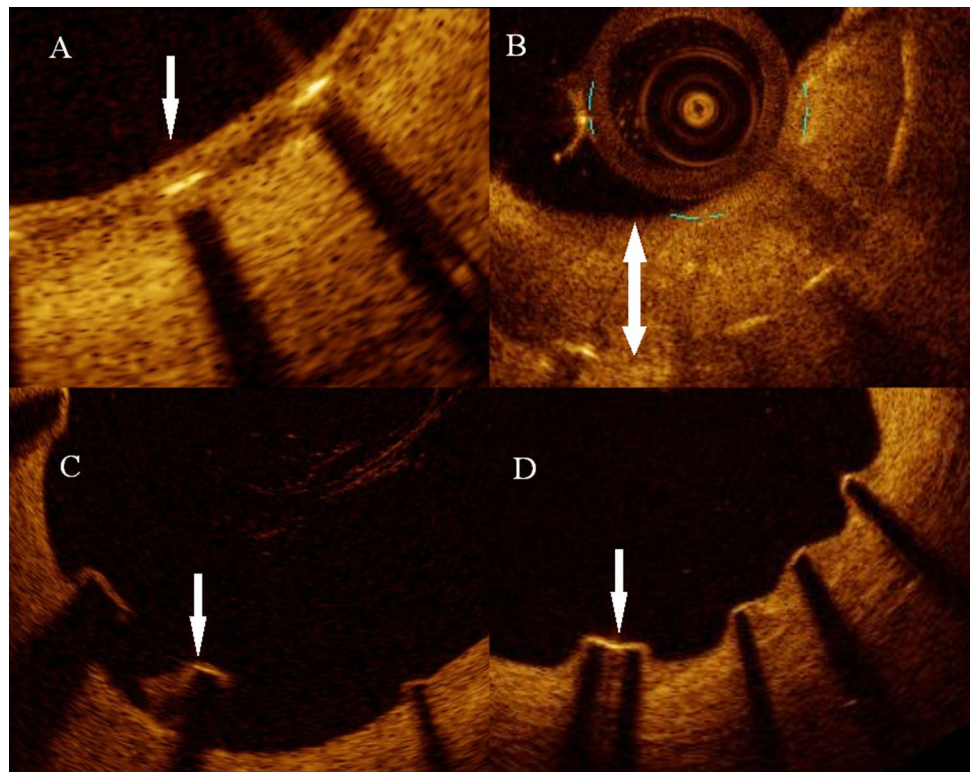
Struts’ malapposition may be acquired or may result from incomplete stent expansion during the index procedure, especially in the presence of calcified plaques. Late, or acquired malapposition may be due either to the presence of thrombus or dissection between stent and plaque at stent implantation, which eventually disappeared at follow-up, or to positive vessel remodeling [35]. In our study population, the number of malapposed struts observed after the index procedure was similar across the three groups. Therefore, the differences observed at OCT follow-up cannot be attributed to potential differences in stent deployment during index PCI. In particular, the lower percentage of malapposed struts found in our study in the Xience group is in agreement with that found by Katayama et al. [36], that comparing healing between everolimus and biolimus stent. These authors observed that a late-acquired malapposition, due to a positive vessel-remodeling, was less frequent in the permanent fluoropolymer-coated everolimus stents than in the

Table 4 Comparisons, between (with ANOVA) and within groups (with Student's t-test), of the percentage of vulnerable struts regarding anthropometric-anamnestic data

	CRE8	BIOMATRIX	XIENCE	Between groups p-value
Age				
≤ 70 years	36.2 ± 18.7	27.2 ± 18.7	12.9 ± 8.6	0.004
> 70 years	36.4 ± 16.3	44.6 ± 19.1	15.7 ± 8.6	0.017
Within groups p value	0.981	0.064	0.536	
Gender				
Male	35.4 ± 16.6	36.3 ± 18.5	13.0 ± 9.0	0.375
Female	39.1 ± 19.6	30.6 ± 25.3	16.8 ± 4.5	< 0.001
Within groups p value	0.688	0.582	0.497	
Body mass index				
≤ 29 kg/m ²	35.7 ± 16.4	33.3 ± 22.5	10.6 ± 8.1	0.004
> 29 kg/m ²	51.0 ± 27.1	37.6 ± 13.6	18.6 ± 6.9	0.029
Within groups p value	0.220	0.797	0.0497	
Arterial hypertension				
Yes	20.2 ± 6.3	9.7 ± 12.2	26.9 ± 3.3	0.194
No	39.2 ± 16.6	37.4 ± 19.2	12.6 ± 7.3	< 0.001
Within groups p value	0.071	0.066	0.017	
Diabetes				
Yes	38.0 ± 18.5	34.1 ± 23.1	14.1 ± 8.5	0.001
No	29.5 ± 4.9	35.8 ± 10.8	12.0 ± 9.4	0.008
Within groups p value	0.382	0.873	0.682	
Dyslipidemia				
Yes	36.3 ± 22.4	24.4 ± 18.8	18.0 ± 10.7	0.356
No	36.4 ± 15.6	37.2 ± 20.5	13.1 ± 7.6	< 0.001
Within groups p value	0.993	0.275	0.319	
Smoking Habit				
Yes	31.2 ± 6.9	30.3 ± 23.6	15.4 ± 5.2	0.220
No	39.1 ± 20.1	38.3 ± 17.2	13.8 ± 9.4	< 0.001
Within groups p value	0.329	0.409	0.718	
Family History of CAD				
Yes	39.4 ± 20.1	39.0 ± 19.8	13.2 ± 7.4	< 0.001
No	30.6 ± 6.4	24.8 ± 19.4	17.7 ± 11.5	0.335
Within groups p value	0.275	0.161	0.355	
Previous CAD				
Yes	35.2 ± 15.1	34.4 ± 17.3	13.9 ± 8.6	< 0.001
No	39.8 ± 23.2	35.2 ± 38.3	17.1 ± 6.4	0.623
Within groups p value	0.614	0.955	0.621	
Renal failure				
Yes	36.3 ± 17.9	36.2 ± 20.9	15.5 ± 8.0	< 0.001
No	36.9 ± 1.1	20.4 ± 0.3	4.3 ± 0.3	< 0.001
Within groups p value	0.961	0.311	0.071	
Comorbidity				
≤ 3	35.8 ± 16.1	35.4 ± 23.4	14.2 ± 8.3	0.005
> 3	37.4 ± 19.5	33.1 ± 15.2	14.2 ± 9.1	0.038
Within groups p value	0.840	0.822	0.992	

CAD coronary artery disease

Fig. 3 Example of optical coherence tomography findings obtained from our study population. Arrows indicate each type of vulnerable struts. **a** Embedded struts; **b** neo-intimal hyperplasia; **c** malapposed struts; **d** protruding struts



biodegradable polymer-coated biolimus stents suggesting that the Xience polymer may have a higher biocompatibility.

In our trial, protrusion was defined as struts projecting into the lumen in the absence of an obvious separation from vessel wall. Although the concept of struts protrusion with potentially altered flow pattern is not widely recognized, it is likely that a foreign body protruding into the coronary lumen may disturb the flow at the blood-intima interface, with complex and turbulent flow patterns potentially associated with delayed endothelialization and/or thrombogenic effects [37–41]. For this reason, Moore et al. [12] suggested that stent protrusion ratio is an important parameter to be taken into account when evaluating stent's safety. Moreover, protruding struts, even when properly covered by neointima, may impair coronary flow by reducing vessel lumen because of the greater thickness of tissue needed to cover them. Protruding struts may represent a stage of healed, formerly malapposed struts related to incomplete stent apposition at the time of DES implantation or may be the result of an outward remodeling of vessel wall giving the appearance of coronary evagination between the struts. Hypothetically, coronary evaginations may represent an early stage of positive remodeling [13, 36].

In contrast, embedded struts are considered “stable” because they are buried into the vessel wall and well covered by a neointima layer without significant lumen loss. In our study, the Xience group showed the lowest proportion of malapposed or protruding, and the highest proportion of

well-embedded struts in all clinical sub-groups considered, whereas the Cre8 group showed the highest proportion of protruding or malapposed struts and the highest proportion of cross sections with incomplete stent apposition. Despite these differences, the neointimal thickness measured by OCT was similar across the three groups, supporting a similar efficacy of all three DES types in preventing re-stenosis. However, the Biomatrix stent was associated with a minimal and maximal coverage thickness that were largely greater, although not significantly (so, because of large SD and variability coefficients, togliere?) than those observed in the other two groups. In particular, the mean value of the minimal thickness observed in the Biomatrix group was almost twice that observed in the Xience and Cre8 groups, suggesting a lower efficacy of this stent in limiting neointimal hyperplasia.

It could be hypothesized that the different percentage of vulnerable struts observed at 6-month OCT analysis in the three groups of patients was related to differences in the flexibility, elasticity and geometric structure of the metallic platform which may have affected the stent apposition to the vessel wall in addition to the different type and location of anti-proliferative drugs and polymers [35–38].

Moreover, a direct relation was found between the age of the overall group and the percentage of vulnerable struts probably reflecting the increased stiffness due to a more extensive atherosclerotic disease of the vessel wall, with the increase in age.

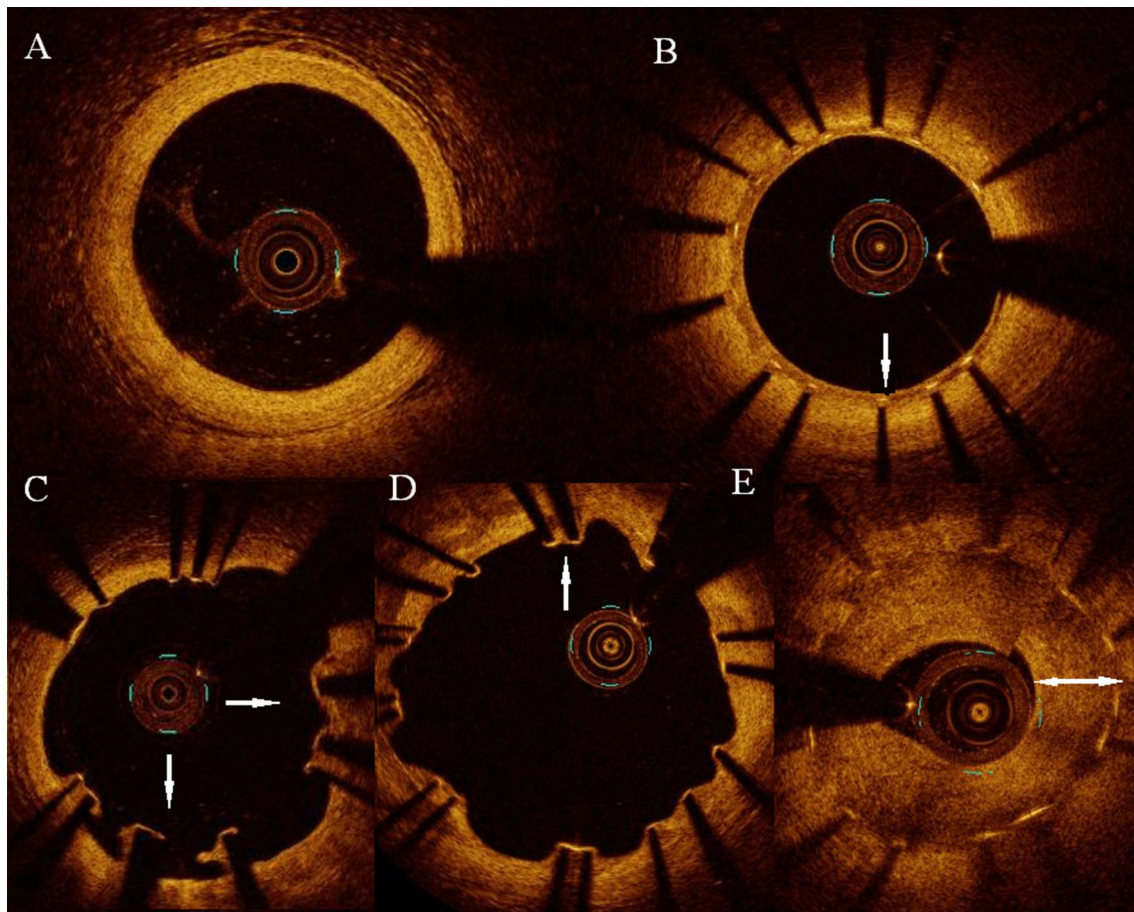


Fig. 4 Example of optical coherence tomography cross section obtained from our study population. Arrows indicate each type of vulnerable struts. **a** Vessel cross section; **b** Optimal stent apposition

and embedded struts; **c** Drug Eluting Stent malapposition with Incomplete Stent Apposition area; **d** Vessel cross section with protruding struts; **e** In stent restenosis

Clinical implications

The results of the present study may also have implications in the current interventional practice; they suggest that all three types of stent used can be safely implanted but Xience showed a lower percentage of protruding and malapposed struts at follow-up. These results can be translated in the daily use of Xience as the best option of drug eluting stent with respect to the other two ones analyzed. Moreover, our study suggests that struts vulnerability may be mainly determined by structural characteristics of the stent independently of implantation technique.

Limitations

Some limitations of our study have to be acknowledged. First, the study enrolled only 60 patients and was therefore not powered for detecting differences in the clinical outcomes and MACE.

Secondly, OCT analysis performed at the index procedure was not analyzed, with the exception of data, available for 51/60 patients (85%) and relating to malapposed struts only.

Future directions

Studies performed in a wider population of patients will provide further informations on the relation among stents structure, their healing and adverse events at follow-up.

Conclusion

The results of this study demonstrate that all the three DES used are safe since they allow a complete strut coverage at 6-month OCT follow-up. However, the use of Cre8 and Biomatrix with respect to Xience, have been associated with a higher proportion of malapposed and protruding struts at follow-up in all clinical subgroups considered showing a differential healing among the three stents analyzed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest to declare.

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