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Randomized clinical trial of abluminus DES+ sirolimus-eluting stent versus everolimus-eluting DES for percutaneous coronary intervention in patients with diabetes mellitus: An optical coherence tomography study

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Abstract

Background: Diabetic patients are at higher risk of recurrent adverse events following percutaneous coronary intervention (PCI) than the nondiabetics. Despite the introduction of new generation drug-eluting stents, their efficacy in the diabetics is still limited.

Aims: To evaluate the efficacy of the Abluminus DES+ biodegradable polymer sirolimus-eluting stent in reducing neointimal hyperplasia in diabetic patients, compared to a durable polymer everolimus-eluting stent (DP-EES).

Methods: A total of 131 patients with diabetes and coronary artery disease were enrolled in six Italian centers and randomized in a 2:1 fashion to PCI with Abluminus DES+ or DP-EES: 85 were assigned to Abluminus DES+ and 46 to DP-EES. The primary endpoint was optimal coherence tomography (OCT)-derived neointimal volume at 9–12 months. Secondary endpoints included OCT-derived neointimal area, neointimal volume obstruction and adverse clinical events.

Results: The primary endpoint, neointimal volume, did not differ between Abluminus DES+ and DP-EES ($29.11 \pm 18.90\ mm^3$ vs. $25.48 \pm 17.04\ mm^3$, $p = 0.40$) at 9–12-month follow-up. This finding remained consistent after weighing for the sum of stents lengths ($1.14 \pm 0.68\ mm^3$ vs. $0.99 \pm 0.74\ mm^3$ for Abluminus DES+ and DP-EES, respectively, $p = 0.38$). Similarly, other OCT-derived and clinical secondary endpoints did not significantly differ between the two groups. Rate of target lesion failure was high in both groups (21.2% for Abluminus DES+ and 19.6% for DP-EES).

Conclusions: This preliminary study failed to demonstrate the superiority of the Abluminus DES+ over the DP-EES in diabetic patients in terms of neointimal proliferation.

KEYWORDS
diabetes mellitus, drug-eluting stent, everolimus, optimal coherence tomography, percutaneous coronary intervention, sirolimus

1 | INTRODUCTION

Diabetes mellitus (DM) negatively impacts on outcomes following percutaneous coronary intervention (PCI). Compared to the non-diabetics, patients affected by DM are at higher risk of in-stent restenosis and adverse clinical events.[1,2]

Late stent thrombosis was a serious concern of first-generation drug-eluting stents (DES).[3–5] The introduction of new-generation DES, characterized by thinner struts, biocompatible polymers with reduced impact on platelet activity or polymers coating limited to the abluminal surface of the struts, contributed to reduce the incidence of adverse events and late stent thrombosis.[6–8] Nevertheless, available data about the performance of new-generation DES in diabetic patients are heterogenous.[9,10] Thus, there is a strong and still unmet need for a dedicated device for these patients.

The Abluminus DES+ (Envision Scientific) is a sirolimus-eluting stent (SES) with biodegradable polymer (BP) carrier applied to the abluminal surface and a proprietary eluting matrix on the stent balloon which release sirolimus to the vessel endothelium. To simplify, this device is designed as a DES mounted on a drug-coated delivery balloon. This combination results in enhanced and uniform release of sirolimus, that may have an increased antiproliferative efficacy with potential benefit in the diabetics.

The study hypothesis of this randomized pilot study is to investigate whether the use of the Abluminus DES+ compared to the durable polymer everolimus-eluting stent (DP-EES) Xience (Abbot Vascular) is associated with a reduced in-stent neointimal volume in diabetic patients. The Xience DP-EES was chosen as a comparator as EES were one of the most reputable DES in clinical practice at the time of the study protocol design.

2 | METHODS

2.1 | Study design and patient selection

The ABILITY (Abluminus DES+ Sirolimus-eluting stent vs. Everolimus-eluting DES for Percutaneous Coronary Intervention in Patients with Diabetes Mellitus) study was a prospective, randomized, multicenter, Italian, open label, 2-arm parallel group trial comparing Abluminus DES+ versus Xience DP-EES in patients with DM, and coronary artery disease (CAD) undergoing PCI.

The study was approved by the Ethical Committees of each participating hospital and registered with ClinicalTrials.gov (NCT03399994). The study sponsor was Fondazione Evidence per Attività e Ricerche Cardiovascolari ONLUS.

The trial population included patients with DM and CAD with stable angina, silent ischemia with a positive functional study, or acute coronary syndrome (ACS) except ST-segment elevation myocardial infarction (STEMI). Patients were deemed eligible for randomization if they had one or more culprit "de novo" lesion in a native coronary artery with significant stenosis (>50% by visual estimate). There were no limitations on the number of treated lesions and lesion length. Implanted DES diameter ranged between 2.5 and 4.0 mm. Patients were enrolled in six Italian hospitals. List of participating centers and trial personnel are reported in the Supporting Information: Table 1.

Exclusion criteria included: contraindication to Abluminus DES+ implantation (hypersensitivity to sirolimus drug, allergy to L605 Cobalt-Chromium alloy, sensitivity to contrast agents that cannot be controlled prophylactically before Abluminus DES+ implantation, or contraindications to antiplatelet and/or anticoagulant therapy), chronic total occlusion, LM stenosis or in-stent restenosis as target lesion, STEMI or cardiogenic shock as clinical presentation, left ventricular ejection fraction <30%, history of severe bleeding or known coagulopathy, and previous PCI in the target vessel within the preceding 3 months.

2.2 | Study device

The Abluminus DES+ was specifically conceived for the diabetics. The device is a balloon expandable stent made with a cobalt-chromium alloy with a strut thickness of 73 µm. The active antiproliferative compound sirolimus is delivered by a BP. The coating polymers poly L-lactide 50–50, poly DL-lactide-co-glycolide and polyvinylpyrrolidone are applied to the abluminal surface only, targeting the endothelium and reducing the inflammatory response. The polymeric carrier releases 40%–50% of sirolimus in the first 3–4 days, while the remaining drug is released more slowly within 48 days, during BP degradation. Moreover, the stent delivery balloon is covered with sirolimus with the same delivery polymer used for stent coating. The drug loading varies from 42 to 330 µg (on stent and balloon) according to stent diameter and length. This combination allows a more uniform delivery of sirolimus to the vessel wall, in both the areas in contact with the stent and those between the stent struts and at the edges of the device.[11] These characteristics are expected to be particularly beneficial in the diabetics, who often present long and diffuse CAD.[12–15] After preclinical evaluation,[16] the Abluminus DES+ was tested in the en-ABL-1 first-in-human study on 40 Indian patients, showing optimal late lumen loss at 6 months with persistent good results at 3 years.[17] Later, the larger en-ABL e-registry on 2500 Indian patients showed excellent 1 and 2-year

safety and efficacy with low rates of major adverse cardiovascular events (MACE), and revascularization.[18–20]

2.3 | Study procedures

After recruitment, patients were randomized in a 2:1 ratio to PCI with either Abluminus DES+ or Xience DP-EES. Randomization was performed using a web-based system after diagnostic angiography, before any lesion preparation procedure. PCI was performed according to local practice. The choice of whether and how to perform lesion preparation and postimplant stent optimization was left to the discretion of the operator; however, stent postdilation was encouraged. When implanting the Abluminus DES+, the operator was prescribed to perform an inflation of at least 45 s to allow complete drug delivery from the delivery balloon to the vessel. For each patient, all the enrolled lesions were treated in one single procedure.

Before the procedure, patients underwent pre-medication according to local practice. If not already on chronical antiplatelet therapy, patients received aspirin and a loading dose of clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg), depending on clinical setting and risk profile. Adequate intraprocedural anticoagulation was achieved according to current practice. After PCI, double antiplatelet therapy was prescribed according to current guidelines.[21]

Angiographic and optimal coherence tomography (OCT) follow-up was scheduled at 9 months after PCI, while clinical follow-up was performed at discharge and at 12 months. Due to the coronavirus disease (COVID)-19 pandemic, a protocol amendment was introduced allowing the 9-month angiography and OCT follow-up between 9 and 12 months and performing the 12-month clinical follow-up via phone call.

2.4 | Study endpoints

The primary efficacy endpoint was OCT-measured in-stent neointimal volume at 9–12-month follow-up. Neointimal volume was calculated in all the analyzed cross sections of the OCT run and then weighed by the sum of lengths of implanted stents.

Secondary efficacy endpoints included OCT-measured neointimal area at the site of minimal lumen area (MLA), and neointimal volume obstruction, defined as the ratio between neointimal hyperplasia volume and stent volume × 100. Neointimal volume obstruction was also weighed by the sum of lengths of implanted stents. Although the study was not powered for clinical events, the following clinical endpoints were evaluated at 12 months: target lesion failure (TLF) (composite of cardiac death, target vessel myocardial infarction [TVMI], and target lesion revascularization [TLR]) and its single components, and probable or definite stent thrombosis. All clinical endpoints were defined in accordance with the Academic Research Consortium-2 Consensus Document.[22] Moreover, device, lesion, and procedural success were assessed at 24 h. Device success was defined as deployment of the assigned stents without system failure or device-related complication, lesion success was defined as attainment of <30% residual stenosis of the target lesion after PCI, whereas procedural success was defined as lesion success without the occurrence of MACE (composite of death, MI, and target vessel revascularization) during hospital stay.

2.5 | Angiography and OCT analysis

Anonymized copies of the OCT images and coronary angiograms were collected and sent to a Central Corelab (Euroimage Research) to be analyzed by expert reviewers who were blinded to patient information and allocated stent. Reviewers evaluated the quality of each OCT run and only analyzed acquisitions that met prespecified quality requirements. Stents with more than 10% of suboptimal total struts visualization (i.e., inability of OCT to address all the struts in a specific cross-section) were excluded from the analysis. Conventional definitions derived from expert consensus OCT documents were applied.[23] Analyses were performed using an offline software (LightLab Consolle) every two cross-sections (0.40 mm intervals, at a pull-back speed of 20 mm/s). Neointimal thickness was calculated as the difference between the stent and the luminal contoured areas, while volumetric measurements were obtained applying the Simpson rule. Quantitative coronary angiography analyses of the coronary angiograms were performed by the Corelab to evaluate the minimal lumen diameter, reference vessel diameter, and percent diameter stenosis at baseline, postprocedure and at follow-up.

2.6 | Statistical analysis

Sample size calculation was based on data from more than 1500 lesions extracted from the Central Corelab database. A mean value of in-stent neointimal volume formation of 15 ± 7.5% in the DP-EES group and a significant volume reduction of 30% with the Abluminus DES+ were assumed. Thus, aiming for a two-tailed α of 0.05% and 80% power, sample size was fixed to 135 patients (45 in DP-EES group and 90 in Abluminus DES+ group). Considering a 10%–15% drop-out rate and a 3% rate of suboptimal OCT acquisitions, the final sample size was raised to 165.

All the analyses were conducted in the modified intention to treat (m-ITT) population, defined as all randomized patients that received at least one allocated study stent and with at least one assessment point after the index procedure, independently from other protocol violations. Subjects withdrawing from the study and/or lost to follow-up were evaluated up to the last visit available for review.

Categorical variables and endpoints were summarized as absolute and relative frequencies. Continuous variables and endpoints were presented as mean ± standard deviation for normally distributed data, or median and interquartile range for non-normally distributed data. Categorical variables and endpoints were compared with the χ^2

TABLE 1 Baseline clinical characteristics.

	Abluminus DES+ (*N* = 85)	DP-EES (*N* = 46)	All (*N* = 131)
Age, years	67.59 ± 8.64	67.48 ± 9.74	67.55 ± 9.00
Female sex	24 (28.2%)	10 (21.7%)	34 (26.0%)
Ethnicity			
Caucasian	83 (97.6%)	44 (95.7%)	127 (96.9%)
Black	1 (1.2%)	0 (0.0%)	1 (0.8%)
Asian	0 (0.0%)	1 (2.2%)	1 (0.8%)
Other	1 (1.2%)	1 (2.2%)	2 (1.5%)
BMI, kg/m^2	27.33 ± 3.76	28.06 ± 4.87	27.59 ± 4.18
Prior MI	26 (30.6%)	16 (34.8%)	42 (32.1%)
Prior PCI	35 (41.2%)	19 (41.3%)	54 (41.2%)
Arterial hypertension	74 (87.1%)	39 (84.8%)	113 (86.3%)
Smoker (current or former)	46 (54.1%)	27 (58.7%)	73 (55.7%)
Hypercholesterolemia	65 (76.5%)	38 (82.6%)	103 (78.6%)
Family history of cardiovascular disease	18 (22%)	17 (37.8%)	35 (27.6%)
eGFR ≤ 60 mL/min	12 (14.1%)	17 (37%)	29 (22.1%)
Peripheral vascular disease	19 (22.4%)	13 (28.3%)	32 (24.4%)
Liver disease[a]	3 (3.5%)	2 (4.3%)	5 (3.8%)
Glycated Hb (%)	6.86 ± 0.83	7.18 ± 0.84	6.96 ± 0.83
Glucose, mg/dL	148.21 ± 59.08	147.18 ± 62.45	147.84 ± 59.98
Total cholesterol, mg/dL	140.36 ± 40.71	143.33 ± 35.59	141.52 ± 38.54
Hemoglobin, mg/dL	13.42 ± 1.55	13.06 ± 1.83	13.29 ± 1.66
Cardiac status			
Silent ischemia	49 (57.6%)	21 (45.7%)	70 (53.4%)
Stable angina	14 (16.5%)	13 (28.3%)	27 (20.6%)
Unstable angina	11 (12.9%)	3 (6.5%)	14 (10.7%)
NSTEMI	11 (12.9%)	9 (19.6%)	20 (15.3%)
Heart failure[b]	4 (4.7%)	11 (23.9%)	15 (11.5%)
Type of diabetes			
Missing	1 (1.2%)	0 (0.0%)	1 (0.8%)
Type 1	1 (1.2%)	1 (2.2%)	2 (1.5%)
Type 2	83 (97.6%)	45 (97.8%)	128 (97.7%)
Diabetes therapy			
No	3 (3.5%)	2 (4.3%)	5 (3.8%)
Insulin	15 (17.6%)	10 (21.7%)	25 (19.1%)
Oral antidiabetics	62 (72.9%)	28 (60.9%)	90 (68.7%)
Both	5 (5.9%9	6 (13.0%)	11 (8.4%)

Note: Values are mean ± SD or *n* (%).

Abbreviations: BMI, body mass index; DP-EES, durable polymer everolimus-eluting stent; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

[a]Defined as abnormal liver enzyme levels, imaging evidence of liver abnormalities, or histopathological confirmation of liver damage.

[b]Including both heart failure with reduced and preserved ejection fraction.

TABLE 2 Procedural characteristics.

	Abluminus DE + (*N* = 85)	DP-EES (*N* = 46)	All (*N* = 131)
Radial access	77 (90.6%)	39 (84.8%)	116 (88.5%)
No. of vessels with critical stenosis	1.80 ± 1.40	1.87 ± 1.05	1.82 ± 1.29
Total no. of treated lesions	120	64	184
Total no. of implanted stents	151	83	234
No. of implanted stents per patients	1.78 ± 1.11	1.80 ± 0.98	1.79 ± 1.06
No. of implanted stents per lesion	1.27 ± 0.53	1.30 ± 0.61	1.28 ± 0.56
Stent diameter (mm)	2.97 ± 0.40	2.90 ± 0.46	2.94 ± 0.42
Total stent length (mm)	40.47 ± 26.25	43.76 ± 27.70	41.63 ± 26.69
Lesion length (mm)	22.62 ± 11.30	23.13 ± 15.87	22.80 ± 13.06
Bifurcation[a]	18 (15.0%)	11 (17.2%)	29 (15.8%)
Tortuosity (45°–90°)[a]	31 (25.8%)	17 (26.6%)	48 (26.1%)
Calcium (moderate or severe)[a]	15 (12.5%)	12 (18.8%)	27 (14.7%)
Treated lesion[a]			
LAD	53 (44.2%)	30 (46.9%)	83 (45.1%)
Circumflex	32 (26.7%)	17 (26.6%)	49 (26.6%)
RCA	35 (29.2%)	17 (26.6%)	52 (28.3%)
Predilatation[b]	111 (73.5%)	55 (66.3%)	166 (70.9%)
Postdilatation[b]	93 (61.6%)	51 (61.4%)	144 (61.5%)
Residual diameter stenosis (%)[a]			
Missing	1 (0.8%)	0	1 (0.5%)
0	113 (94.2%)	61 (95.3%)	174 (94.6%)
0–10	3 (2.5%)	0 (0.0%)	3 (1.6%)
10–20	3 (2.5%)	3 (4.7%)	6 (3.3%)
>20	0 (0.0%)	0 (0.0%)	0 (0.0%)
Post-PCI TIMI flow[a]			
0	2 (1.7%)	0 (0.0%)	2 (1.1%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	1 (1.6%)	1 (0.5%)
3	118 (98.3%)	63 (98.4%)	181 (98.4%)
Implanted stent size (mm)			
2.25	3 (2.0%)	8 (9.8%)	\
2.50	38 (25.2%)	24 (29.3%)	\
2.75	15 (9.9%)	7 (8.5%)	
3.00	59 (39.1%)	25 (30.1%)	\
3.25	0 (0%)	1 (1.2%)	\
3.50	32 (21.2%)	14 (16.9%)	\
4.00	4 (2.6%)	4 (4.9%)	\
APT at discharge			
Aspirin	82 (98.8%)	45 (97.8%)	127 (98.4%)
Clopidogrel	65 (78.3%)	35 (76.1%)	100 (77.5%)

(Continues)

TABLE 2 (Continued)

	Abluminus DE + (*N* = 85)	DP-EES (*N* = 46)	All (*N* = 131)
Prasugrel	4 (4.8%)	0 (0.0%)	4 (3.1%)
Ticagrelor	13 (15.7%)	10 (21.7%)	23 (17.8%)
Concomitant drugs at discharge			
Beta-blockers	58 (69.9%)	33 (71.7%)	91 (70.5%)
OAC	14 (16.9%)	5 (10.9%)	19 (14.7%)
Statins	74 (89.2%)	43 (93.5%)	117 (90.7%)

Note: Lesion characteristics are based on quantitative coronary angiography analysis.Values are mean ± SD or *n* (%).

Abbreviations: APT, antiplatelet therapy; DP-EES, durable polymer everolimus-eluting stent; LAD, left-anterior descending; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

[a]Percentages are calculated on total of treated lesions.

[b]Percentages are calculated on total of implanted stents.

or Fisher's exact test, as appropriate, while Student's *t* test or Mann–Whitney *U* test were used for continuous variables. All tests were two-sided with an α level of 0.05 considered statistically significant.

The analysis on the time of the occurrence of TLF was made according to the following hierarchical order of its components: cardiac death, TVMI and TLR. The probability of not occurrence of the secondary endpoints was estimated using the Kaplan–Meier method and comparison between the two groups was performed with the log-rank test. A multivariable analysis with the Cox's proportional hazard regression method was carried out to explore the possibility of no-event according to prespecified variables (stent type, sex, age, number of lesions, vessel size, stent length, number of stents).

Statistical analyses were performed using STAT-SAS System v. 9.4 (SAS Institute).

2.7 | Data management and event adjudication

Data acquisition was managed through an electronic case report form compliant with current regulations concerning data protection and security. Clinical events were initially assessed by the treating physicians at each participating center, and subsequently adjudicated by an independent event adjudication committee composed of three interventional cardiologists who were blinded to the treatment group. Data management was performed by an independent research organization (Mediolanum Cardiovascular Research).

3 | RESULTS

Between May 21, 2018, and May 10, 2021, 134 diabetic patients from six Italian centers consented to study participation. Prespecified sample size was not reached due to difficulties in enrollment caused by the COVID-19 pandemic. A total of 133 patients were randomized in a 2:1 fashion to either Abluminus DES+ (86 patients) or DP-EES (47 patients). One patient was enrolled but not randomized due to screening failure. Of the 133 randomized patients, two were excluded from the m-ITT population: one did not undergo PCI since a conservative strategy was preferred and one due to nonadherence to the allocated stent type. Thus, the final m-ITT population was composed of 131 patients.

Baseline clinical characteristics are reported in Table 1. Mean age was 67.6 ± 9 years and 74% of patients were males. Most patients (53.4%) had silent ischemia, while 20.6% and 26% presented with stable angina or ACS, respectively.

3.1 | Procedural and discharge characteristics

Overall, 184 coronary lesions were treated: 120 in 85 patients allocated to Abluminus DES+ and 64 in 46 patients randomized to DP-EES. A total of 234 stents were implanted, with a per patient average of 1.78 ± 1.11 and 1.80 ± 0.98 stents implanted, and a per lesion average of 1.27 ± 0.53 and 1.3 ± 0.61 stents implanted in the Abluminus DES+ and in the DP-EES group, respectively. At discharge, most of the patients were prescribed statins (90.7%) and betablockers (70.5%). A total of 98.4% of the patients were prescribed aspirin, while clopidogrel was the most used $P2Y_{12}$ inhibitor (77.5%). Detailed data are reported in Table 2.

3.2 | Course of the follow-up

The COVID-19 pandemic severely impacted on the course of the study. As aforementioned, a protocol amendment was introduced to widen the follow-up period. Coronary angiography was performed at 9–12 months in 78 patients (59.5%) and OCT in 69 patients. OCT images deemed suitable for the analysis were available for 65 out of 131 (49.6%) patients: 46/85 (54.1%) and 19/46 (41.3%) in the Abluminus DES+ and DP-EES groups,

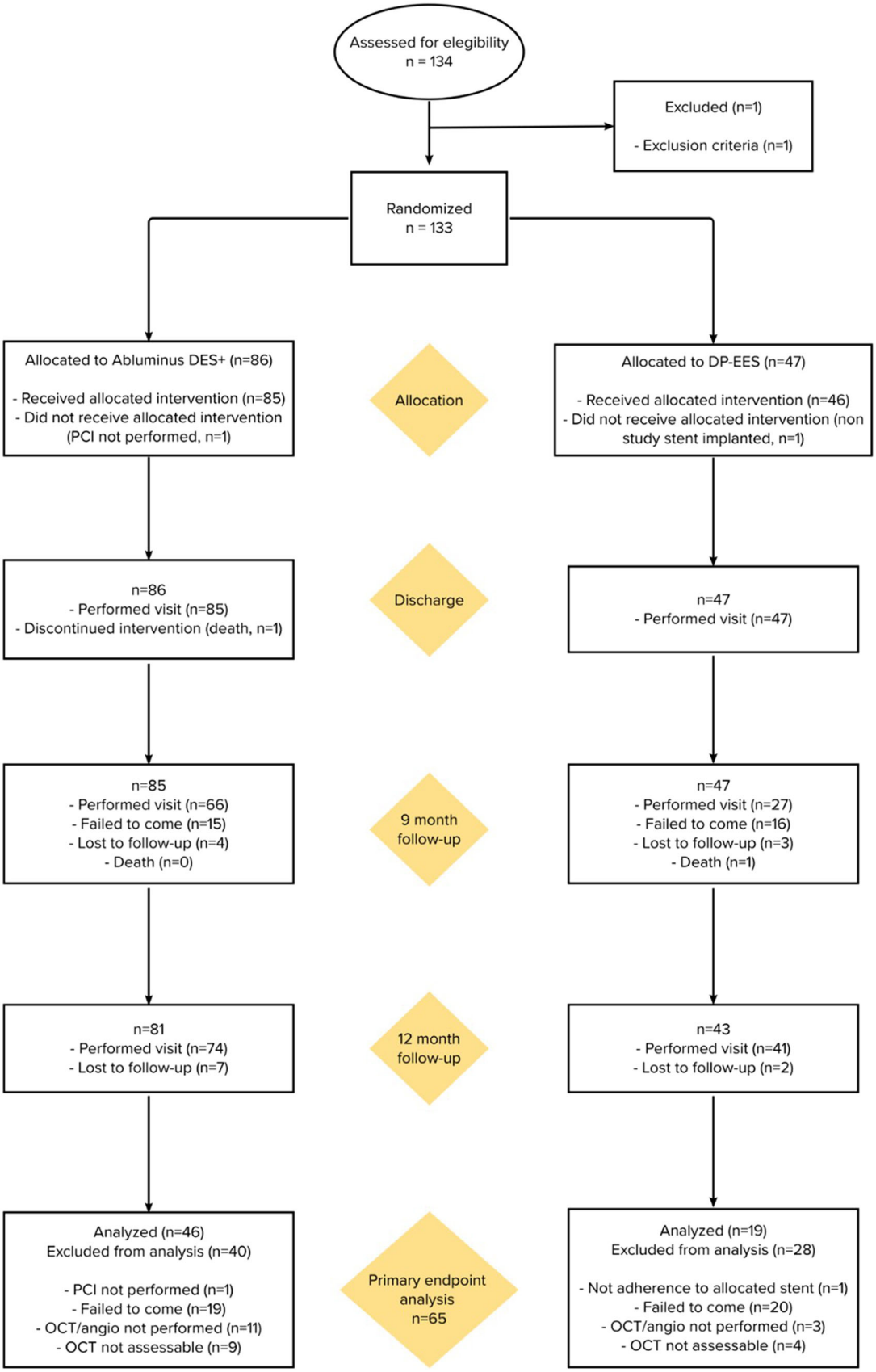


FIGURE 1 Patient disposition at follow-ups—randomized population. DP-EES, durable-polymer everolimus-eluting stent; OCT, optimal coherence tomography; PCI, percutaneous coronary intervention. [Color figure can be viewed at wileyonlinelibrary.com]

respectively. Since some patients underwent revascularization in more than one lesion, OCT analysis on the primary and the secondary endpoints were performed in 59 and 26 lesions in the two groups, respectively. At 12 months, clinical follow-up was performed in 113/131 (86.3%) patients, via telephone contact in most of the cases (72.6%). A comprehensive diagram of patients' dispositions up to 12-month follow-up is provided by Figure 1.

3.3 | Optimal coherence tomography outcomes

No significant difference for the primary endpoint was observed between the Abluminus DES+ and DP-EES group (neointimal volume: 29.11 ± 18.9 mm^3 vs. 25.48 ± 17.04 mm^3, $p = 0.40$). This finding remained consistent after weighing neointimal volume by the sum of lengths of implanted stents (1.14 ± 0.68 mm^3/mm vs. 0.99 ± 0.74 mm^3/mm, $p = 0.38$).

The OCT-derived secondary endpoint neointimal area at the site of MLA did not differ significantly between the two study groups (1.77 ± 1.42 vs. 1.89 ± 1.46 mm^2, $p = 0.73$). Similarly, no significant difference between the two study stents was found with respect to neointimal volume obstruction (19.36 ± 9.85% vs. 15.02 ± 7.28%, $p = 0.07$). Figures 2 and 3 show examples of different qualitative OCT findings, while the Central Illustration 1 provides a comprehensive overview of the results. Complete data about the OCT analysis are shown in Table 3.

3.4 | Secondary clinical endpoints

Secondary clinical endpoints are reported in Table 4. Procedural success at 24 h was 98.8% and 100% in the Abluminus DES+ and in the DP-EES group, respectively.

At last available follow-up all patients were asymptomatic for angina or dyspnea. Secondary clinical endpoints occurred in a total of

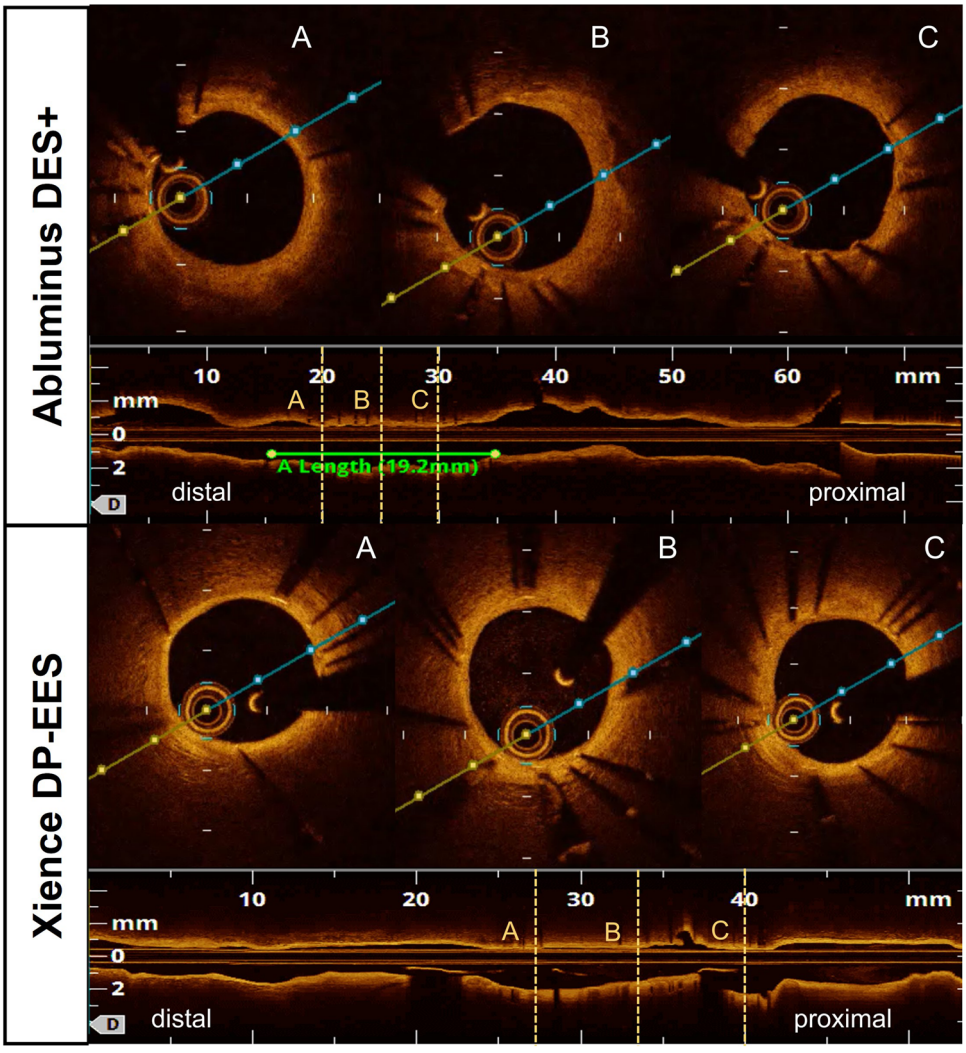


FIGURE 2 OCT follow-up images revealing good stent performance, without significant neointimal hyperplasia for both Abluminus DES+ and Xience DP-EES at the distal, mid, and proximal segments of the stent (Panel A, B, C respectively). DP-EES, durable-polymer everolimus-eluting stent. [Color figure can be viewed at wileyonlinelibrary.com]

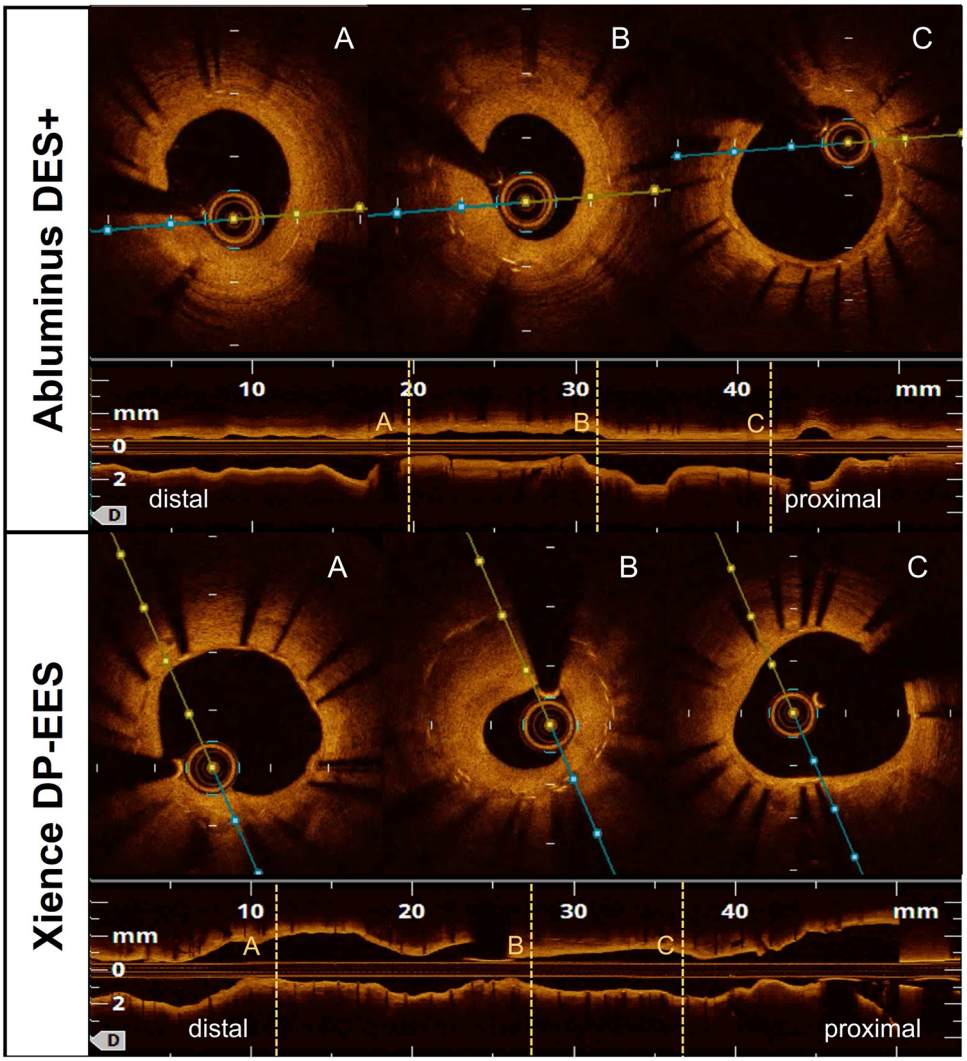
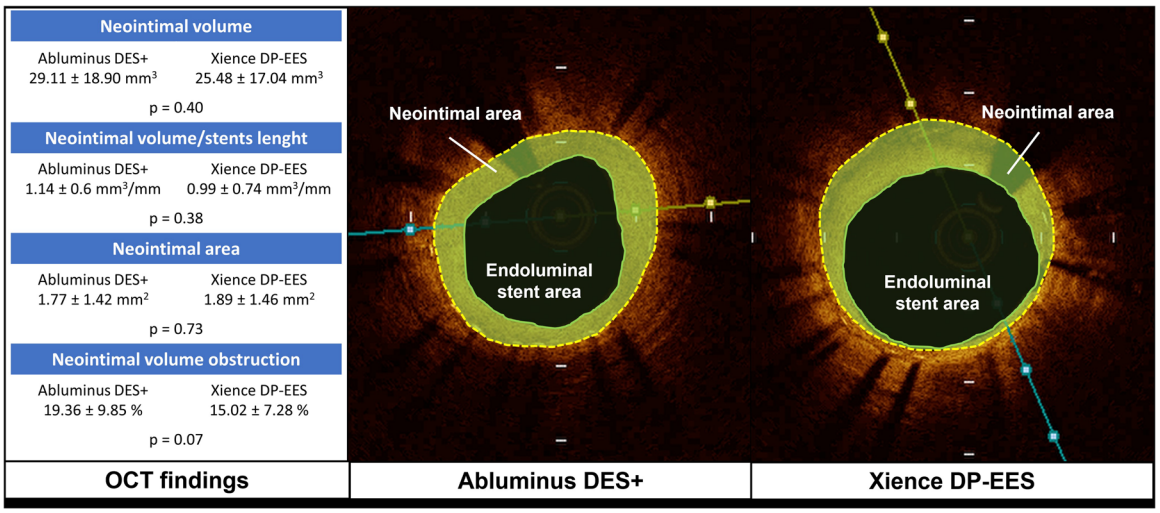


FIGURE 3 OCT follow-up images revealing significant neointimal hyperplasia formation for both Abluminus DES+ and Xience DP-EES at the distal, mid, and proximal segments of the stent (Panel A, B, C respectively). DP-EES, durable-polymer everolimus-eluting stent. [Color figure can be viewed at wileyonlinelibrary.com]



CENTRAL ILLUSTRATION 1 Summary of the study OCT findings and representative follow-up OCT cross sections of Abluminus DES+ and Xience DP-EES with endoluminal stent area (black area inside the green line) and neointimal area (green area inside the yellow dotted line). DP-EES, durable polymer everolimus-eluting stent; OCT, optimal coherence tomography. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Optimal coherence tomography results.

	Abluminus DES+ 46 patients/59 OCT pullbacks	DP-EES 19 patients/26 OCT pullbacks	*p* Value
Primary endpoint			
In-stent NI volume (mm^3)	29.11 ± 18.90	25.48 ± 17.04	0.40
In-stent NI volume/sum of lengths of implanted stents (mm^3/mm)	1.14 ± 0.68	0.99 ± 0.74	0.38
Secondary endpoint			
In-stent NI area (mm^2)	1.77 ± 1.42	1.89 ± 1.46	0.73
NI volume obstruction (%)	19.36 ± 9.85	15.02 ± 7.28	0.07

Note: Values are mean ± SD or *n* (%).

Abbreviations: DES, drug-eluting stent; DP-EES, durable polymer everolimus-eluting stent; NI, neointimal; OCT, optimal coherence tomography.

TABLE 4 Secondary clinical efficacy endpoints.

	Abluminus DES+ (*N* = 85)	DP-EES (*N* = 46)	ALL (*N* = 131)
Outcomes at 24 h			
Discharged from hospital	84 (98.8%)	46 (100%)	130 (99.2%)
Device success	85 (100%)	46 (100%)	131 (100%)
Lesion success	84 (98.8%)	46 (100%)	130 (99.2%)
Procedural success	84 (98.8%)	46 (100%)	130 (99.2%)
Clinical events at follow-up			
TLF	18 (21.2%)	9 (19.6%)	26 (19.8%)
Cardiac death	1 (1.2%)	0 (0.0%)	1 (0.8%)
TVMI	3 (3.5%)	1 (2.2%)	4 (3.0%)
TLR	17 (20.0%)	8 (17.4%)	25 (19.1%)
Stent thrombosis (probable or definite)	2 (2.4%)	0 (0.0%)	2 (1.5%)

Note: Values are *n* (%).

Abbreviations: DP-EES, durable polymer everolimus-eluting stent; TLF, target lesion failure; TLR, target lesion revascularization; TVMI, target vessel myocardial infarction.

27 patients: 1 cardiac death (Abluminus DES+ group), 4 TVMI (3 Abluminus DES+, 1 DP-EES), 25 TLR (17 Abluminus DES+, 8 DP-EES), and 2 stent thrombosis (both in the Abluminus DES+ group).

Kaplan–Meier estimates of the probability of not occurrence of TLF and TLR are depicted in Figures 4 and 5. The log-rank test did not disclose significant differences between the two study groups ($p = 0.67$ for TLF and $p = 0.59$ for TLR). The only variable significantly associated with the occurrence of TLF after adjustment at multivariable analysis was the number of target lesions treated (>1 lesion vs. 1 lesion: HR = 2.61; 95% CI: 1.22–5.56; $p = 0.013$).

3.5 | Adverse events

Assessment of safety in terms of adverse events did not disclose safety concerns. At 12-month follow-up at least one serious adverse event was reported in 30 and 18 patients in the Abluminus DES+ and DP-EES group, respectively. Two patients died: one patient in the Abluminus DES+ group had a dissection of the LM (nontarget vessel) during the index procedure after Abluminus DES + deployment which required stenting (Megatron Synergy DES; Boston Scientific) and died on the same day following stent thrombosis extended from the LM to the mid-left anterior descending artery and to the ostium of the circumflex. The second patient (DP-EES group) died for respiratory failure before 12-month follow-up. All serious adverse events are summarized in the Supporting Information: Table 2.

4 | DISCUSSION

The main findings of the ABILITY OCT trial are as follows:

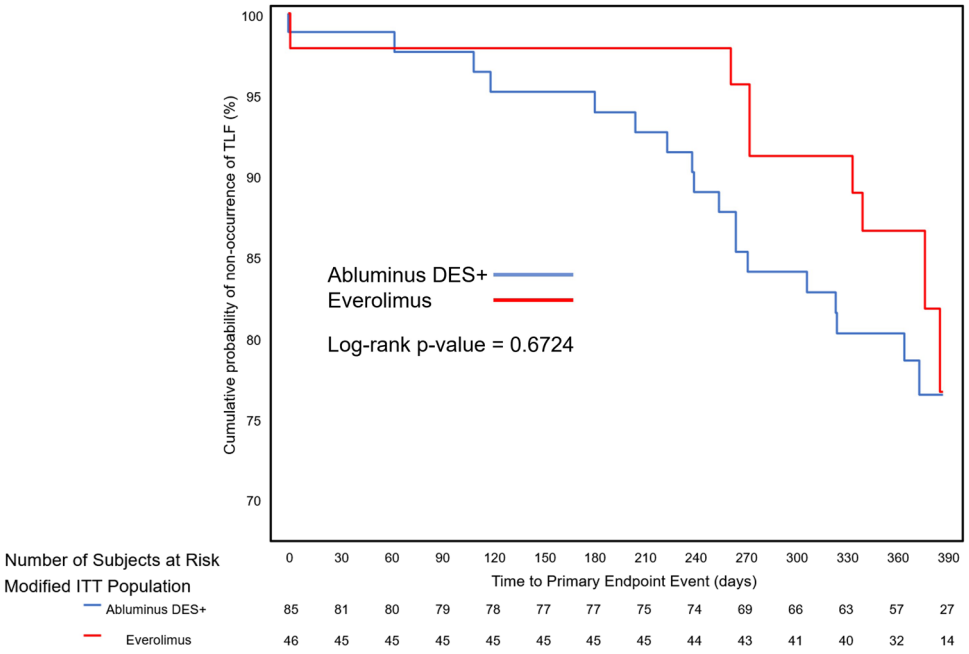


FIGURE 4 Cumulative frequency of TLF nonoccurrence at 12 months. TLF, target lesion failure. [Color figure can be viewed at wileyonlinelibrary.com]

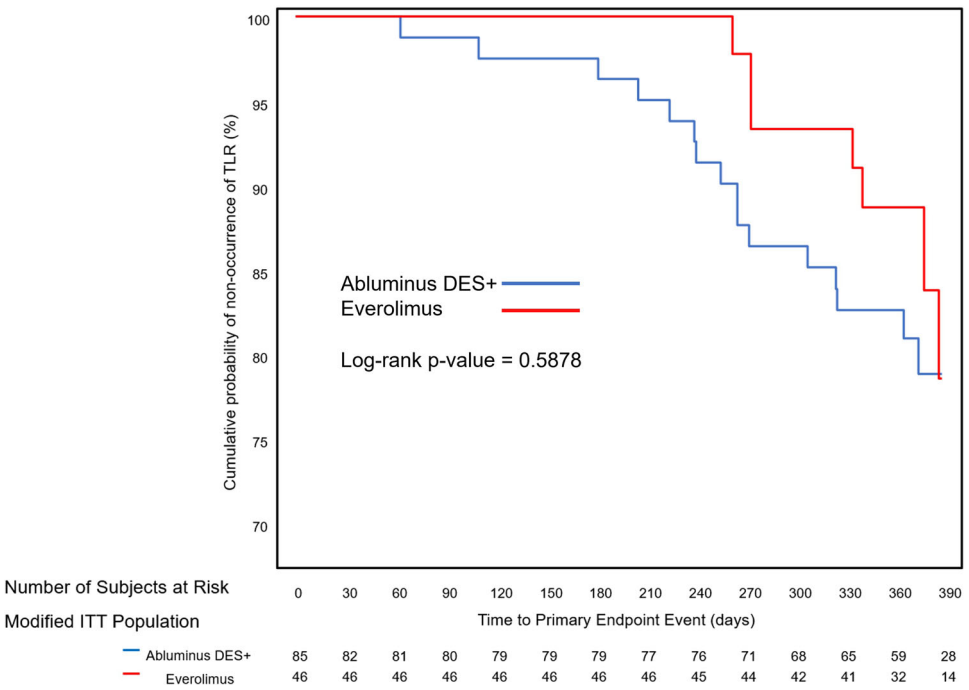


FIGURE 5 Cumulative frequency of TLR nonoccurrence at 12 months. TLR, target lesion revascularization. [Color figure can be viewed at wileyonlinelibrary.com]

1. There was no significant difference in neointimal volume between the lesions treated with Abluminus DES+ and those treated with DP-EES. This result remained consistent when neointimal volume was weighed by the sum of lengths of implanted stents. Equally, no significant difference between the two study stents was evidenced with respect to neointimal volume obstruction.
2. No significant difference with respect to clinical endpoints was found between the two study stents, with a similar incidence of TLR in both groups.

Our study does not support the initial hypothesis of a higher antiproliferative efficacy of the Abluminus DES+ as compared with

the Xience DP-EES up to 12 months after PCI in diabetic patients. Our results suggest that the attempt to increase the sirolimus supply to the endothelium through the combination of a thin-strut DES and a delivering drug coated balloon has no effect in reducing neointimal hyperplasia, as compared to DP-EES. In a previous study by Costa and colleagues, diabetic patients were randomized to PCI using a DES with standard (SD) or double dose (DD) sirolimus. Notably, the authors found no significant difference between DD- and SD-SES in terms of neointimal hyperplasia at 6-month follow-up.[24] A possible explanation relies on the metabolism of diabetic cells: as compared with normal smooth muscle cells, those cultured in high glucose concentration require more than 10-fold sirolimus concentration to reach similar antiproliferative suppression.[25] In addition, both the glucose uptake and oxidation are impaired in the diabetic heart, which is forced to derive adenosine triphosphate from fatty acids. These considerations led to the hypothesis that the diabetic endothelium may benefit from a more efficient drug carrier rather than from an increase in active drug dosage and constituted the rationale for using fatty acids as carriers. This technology is exploited by the Cre8 polymer free amphilimus-eluting stent (PF-AES), which was successfully tested in patients with DM. The RESERVOIR trial showed a lower neointimal volume obstruction in the Cre8 PF-EAS group as compared to Xience DP-EES among patients with poor diabetes control,[26] while the SUGAR trial showed a lower rate of primary endpoint TLF among diabetic patients undergoing PCI with Cre8 PF-AES, as compared to Resolute Onyx durable-polymer zotarolimus-eluting stent DP-ZES.[27] However, the promising results of the SUGAR trial were not confirmed at 2-year follow-up.[28] Notably, these studies were conducted in patients with relatively simple lesions and confirmatory data in a large and more complex diabetic population are needed.

The average 9 to 12-month OCT-derived neointimal volume of $29.11 \pm 18.90\,mm^3$ with Abluminus DES+ and $25.48 \pm 17.04\,mm^3$ with DP-EES confirms the excess of neointimal proliferation following DES implantation in the diabetics. The RESERVOIR study reported a 9-month neointimal volume of $16.0 \pm 9.1\,mm^3$ and $15.1 \pm 7.6\,mm^3$ for PF-AES and DP-EES, respectively.[26] In addition, the TARGET All Comers and the RESET-OCT studies including both diabetic and nondiabetic patients reported neointimal volume values of $19.3 \pm 26.0\,mm^3$ (Firehawk BP-SES) and $16.5 \pm 10.7\,mm^3$ (Xience DP-EES) at 3 months, and $26.6 \pm 23.1\,mm^3$ (Cypher DP-SES) and $34.0 \pm 30.1\,mm^3$ (Xience DP-EES) at 9 months, respectively.[29,30] Since many factors of diversity may impact on the neointimal volume, we weighed neointimal volume by the sum of implanted stents lengths, but no significant difference between the two devices was evidenced. Finally, we considered the percentage of neointimal volume obstruction, which better reflects the relation between neointimal hyperplasia and vessel dimension, but still no relevant difference was found between Abluminus DES + and DP-EES.

Even if ABILITY-OCT study was not powered for clinical outcomes, the lack of any difference in clinical events was expected according to the angiographic and OCT findings. Of note, an overall TLR rate of 19.1% at 12-month is higher than shown by prior studies in patients with DM undergoing PCI with new-generation DES. In the RESERVOIR study, the rates of TLR at 12 months were 5.2% and 12.1% for PF-AES and DP-EES,[26] while in the recent SUGAR trial 12-month TLR happened in 2.4% and 3.9% with PF-AES and DP-ZES, respectively.[27] The higher incidence of events reported in our study compared to other reports may be a consequence of both the mandatory invasive follow-up and the increased lesion complexity of our study. Notably, compared to the RESERVOIR trial, the number of implanted stents per lesion in our study appears higher and the stent diameters slightly smaller. In addition, our population seems to be affected by more severe CAD, as the number of diseased vessels per patient is higher.

4.1 | Study limitations

We acknowledge several limitations in this study. The main limitation is related to the lack of complete enrollment and incomplete angiographic and OCT follow-up due to the impact of the early phase of COVID-19. As a consequence, apart from the clinical events, the study should be regarded as underpowered for the primary endpoint as well. Nevertheless, the available findings suggest that it would be unlikely that the Abluminus DES+ would outperform the DP-EES even if a larger number of patients were enrolled and the follow-up would have been complete. Another limitation of our study is that OCT analysis was limited to the quantitative evaluation of neointimal hyperplasia, while other qualitative parameters such as characteristics of neointimal tissue (homogeneous vs. nonhomogeneous) or the percentage of uncovered struts were not assessed.

4.2 | On-going investigations

The ongoing ABILITY Diabetes Global (NCT04236609) trial is randomizing diabetic patients to PCI with either Abluminus DES+ or Xience DP-EES. The two coprimary endpoints at 1-year follow-up are: rate of ischemia-driven TLR (powered for noninferiority and sequentially superiority), and rate of TLF (powered for noninferiority). The trial will provide pivotal information about the clinical performance of the Abluminus DES+ device in the diabetics.

5 | CONCLUSIONS

This preliminary mechanistic study failed to demonstrate that the use of the Abluminus DES+, a DES with sirolimus coating on the delivering balloon and on the outer surface of the stent, is associated with a lower neointimal volume at 9 to 12-month follow-up as compared with Xience DP-EES in diabetic patients.

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CONFLICTS OF INTEREST STATEMENT

Dr Luca Testa has received consultant fee from and served as a proctor for Abbott, Boston Scientific, Medtronic, and Merrill. Dr Matteo Montorfano has received consultant fee from Abbott, Boston, Kardia and Medtronic. Dr. Reimers has received speaker honoraria from Boston Scientific. Dr Azeem Latib has served as a consultant for Abbott, Medtronic, Edwards Lifesciences, Boston Scientific, Neovasc, Shifamed, and Philips. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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