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Study on the potential clinical significance of subclinical stent edge effects after drug-eluting stent implantation

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The edge effect (EE) of isolated restenosis at one or both ends of a stent is not reduced by drug-eluting stent (DES). The purpose of the study was to investigate the long-term outcome of 1-year subclinical DES-EE (sDES-EE), which was defined as any reduction in the minimal lumen area (MLA) at stent edge without any evidence of clinical ischemia. A total of 252 patients were enrolled from one of our previous randomized controlled studies, who were detected by optical coherence tomography (OCT) immediately after DES implantation and 1 year later. The primary endpoint was EE-related target lesion failure (EE-TLF) at 5 years. Secondary endpoints were the changes of morphologies and composition of stent edge plaque, and each component of EE-TLF. sDES-EE at 1 year was significantly correlated with EE-TLF at 5 years by binary logistic regression analysis after propensity scoring. The most valuable cutoff value of sDES-EE at 1 year was a 25% MLA reduction at the stent edge, according to receiver operating characteristic analysis, which showed a major increase in lipid normalized total volume (0.99 ± 0.25 mm^3 vs. -0.21 ± 0.06 mm^3, $p = 0.025$) and lipid percent atheroma volume (3.92 ± 1.34% vs. -1.22 ± 0.78%, $p = 0.029$). EE-TLF at 5 years was significantly higher in the sDES-EE group than in the non-sDES-EE group (15.6% vs. 4.1%, $p = 0.001$). sDES-EE with MLA reduction ≥ 25% at the stent edge at 1 year after PCI was an independent predictor of EE-TLF at 5 years, which was mainly caused by the progression of lipid components measured by OCT.
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Keywords Optical coherence tomography, Drug-eluting stent, Subclinical, Edge effect, Target lesion failure

Percutaneous coronary intervention (PCI) with new-generation drug-eluting stents (DESs) implantation has improved the efficacy and safety of treatment for obstructive coronary artery disease compared to bare metal stents (BMSs)[1,2]. In-stent restenosis (ISR) is still a stumbling block in the field of coronary intervention[3–6].

At present, the most accepted ISR classification is the Mehran classification[7]. Among them, ISR limited to the 5-mm edge segment of the stent, which was the transitional area between the stent struts and native coronary artery, is also known as the edge effect (EE) belongs to Type IB in the Mehran classification, the mechanism of this kind of restenosis appears to be different from that in the other Mehran types (the former occurs in a location that is not covered by the stent struts, while the latter is covered by the stent struts)[7,8]. This difference is also demonstrated by the fact that the incidence of the 1st generation DES-EE is not significantly lower than that of BMS-EE[6,9]. Even with the use of a new-generation DES, there is no significant reduction in the incidence of clinical stent EE[6,9,10].

Although the application of intravascular imaging technology has made the mechanism of ISR much clearer[6,11,12], few interventions specifically target DES-EE[8,13], and most of them focus on how to select the stent

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landing zone to reduce the occurrence of clinical DES-EE[11,12,14]. Recently, software based on optical coherence tomography (OCT) image analysis with an artificial intelligence framework, the optical flow ratio (OFR) version OctPlus, V2.0 (URL: http://www.pulse-imaging.com) designed by Pulse Medical Imaging Technology (Shanghai, Chinia), has gradually become prominent in clinical studies on the natural outcome of coronary plaques[15,16]. Its histological function enables the quantitative analysis of various components of coronary plaques and their propotions[17]. We aimed to analyze the plaque characteristics of subclinical DES-EE (sDES-EE) 1 year after PCI and the associated rate of target lesion failure (TLF) 5 years later.

Patients and methods

Study design and patient selection

This is a subgroup analysis of one of our previous randomized studies (ClinicalTrials.gov. Number: NCT02140801)[18]. The design and organization of this study are shown in Fig. 1. Consecutive patients with acute coronary syndrome presenting with *de novo* lesions treated by DES(s) implantation were enrolled preliminarily. Patients were included if they were >18 years old, they presented with unstable angina or myocardial infarction > 24 h prior to treatment, only one vessel was implanted with DES(s), and OCT detection was performed at baseline after PCI and after 1 year. Patients were excluded if they had an estimated life expectancy of < 1 year, they were pregnant or breastfeeding women, or they had multiple-vessel stenting, bifurcation lesions treated with a 2-stent strategy, any history of severe renal or hepatic dysfunction (hepatic failure, cirrhosis, portal hypertension and active hepatitis), in-stent restenosis lesions, chronic total occlusion, thrombus-containing lesions, or any edge dissection or hematoma that was not covered by another DES. Finally, a total of 252 patients met the criteria and completed 5 years of clinical follow-up. The study was approved by the ethics committee of Nanjing First Hospital, and all patients provided written informed consent. All study was performed in accordance with relevant guidelines and regulations.

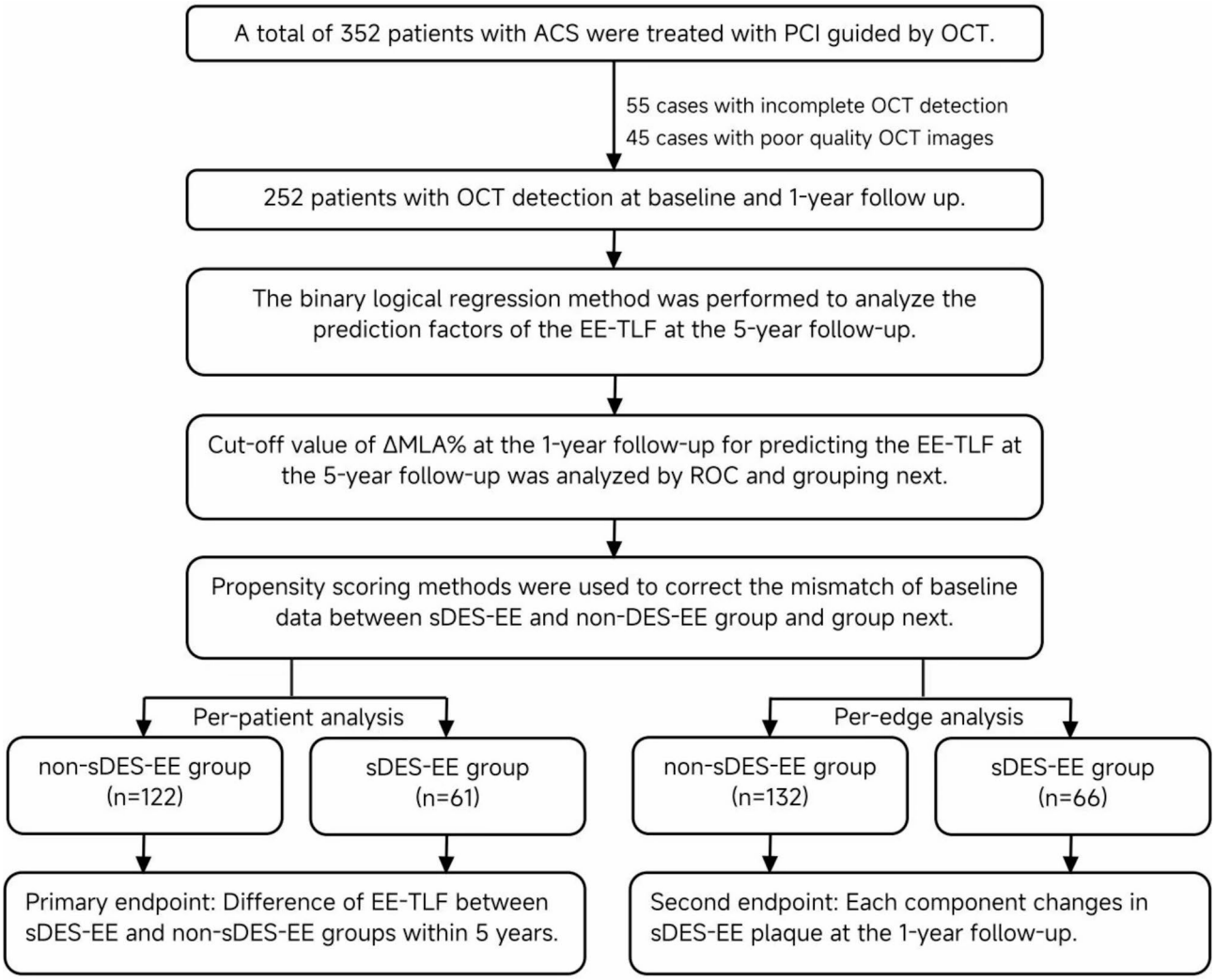

Fig. 1. Study flow chart and study design. ACS, acute coronary syndrome; DES, drug eluting stent; EE, edge effect; ΔMLA%, the percent changes of minimal luminal area; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; ROC, receiver-operating characteristic; TLF, target lesion failure.

Medical therapy and clinical follow-up

All enrolled patients received dual antiplatelet therapy (aspirin 100 mg qd + clopidogrel 75 mg qd or ticagrelor 90 mg bid) for at least 1 year and were switched to aspirin antiplatelet monotherapy for life. More critically, all enrolled patients received statin-based lipid-lowering therapy, which could be combined with ezetimibe depending on the doctors' discretion based on the level of low-density lipoprotein cholesterol (LDL-C). No patients received proprotein convertase subtilisin/kexin type 9 inhibitors. Control of other risk factors, such as hypertension and diabetes mellitus, was determined by the treating physician and was guided by local guidelines. Detailed information and the effectiveness of lipid profile risk factor control, such as total cholesterol (T-CH), LDL-C, high-density lipoprotein cholesterol (HDL-C) and non-HDL-C, were collected for analysis. Changes in T-CH (ΔT-CH) were defined as the T-CH level at the 1-year follow-up minus the T-CH level at baseline. Changes in LDL-C (ΔLDL-C), HDL-C (ΔHDL-C), non-HDL-C (Δnon-HDL-C), and triglycerides (Δtriglycerides) were calculated in the same way. Percent ΔLDL-C (ΔLDL-C%) was calculated as ΔLDL-C/baseline LDL-C × 100. All patients underwent outpatient or telephone clinical follow-up at 1, 3, 6, 12, 24, 36 and 60 months after PCI for collecting EE-related TLF (EE-TLF), including cardiac death, target vessel myocardial infarction (TVMI), and clinically driven target lesion revascularization (TLR).

OCT image acquisition and OFR analysis

OCT images of the post-PCI stenting segment were acquired after adequate amounts of nitroglycerin intracoronary injection. Both ILUMIEN OPTIS and C7-XR (Lightlab Imaging Incorporated, Westford, MA) could be applied with a 2.7-F catheter (Dragonfly OPTIS or Dragonfly Duo imaging catheter, Westford, MA) with automatic pullback at a speed of 36 mm/s with continuous contrast injection (3–4 ml/s) to flush the blood cells to obtain high-quality OCT images. All OCT images are finally saved in DICOM format and input into OFR software for offline analysis (which is feasible to quantitatively analyze the composition and properties of coronary plaques derived from OCT images frame by frame, and to measure external elastic membrane area (EEM_a) of the target lesion segment by delineating the clear vascular boundary proximally and distally measured by OCT and the principle of Murry formula at the bifurcation site)[19]. Quantitative and qualitative analyses of local coronary plaque on the stent edge were obtained by automatic border detection followed by manual correction frame by frame. After manual multiaspect coregistration based on the stent strut boundary, precise measurement of plaque components within 5 mm of the stent, the quantitative indexes of each plaque component are described in accordance with previous studies:[15,16,20] EEM_a was defined as the cross-sectional area of the EEM, and lumen area was defined as the cross-sectional area of the lumen. Normalized total atheroma volume (TAVn) =Σ(EEM_a-Lumen area)/number of frames of target segment×100, the same calculation method is used for the calculation of lipid TAVn, fibrous TAVn, calcium TAVn, and macrophage TAVn. Percent atheroma volume (PAV) =Σ(EEM_a-Lumen area)/ΣEEM_a×100, =Σlipid area/number of frames of target segment×100), the same calculation method is used for the calculation of lipid PAV, fibrous PAV, calcium PAV, and macrophage PAV. The change in TAVn (ΔTAVn) was defined as the TAVn at the 1-year follow-up minus the baseline TAVn, and likewise for the change in lipid TAVn (lipid ΔTAVn), the change in fibrous TAVn (fibrous ΔTAVn), the change in calcium TAVn (calcium ΔTAVn) and the change in macrophage TAVn (macrophage ΔTAVn). The change in PAV (ΔPAV) was defined as the PAV at the 1-year follow-up minus the baseline PAV, and likewise for the change in lipid PAV (lipid ΔPAV), the change in fibrous PAV (fibrous ΔPAV), the change in calcium PAV (calcium ΔPAV) and the change in macrophage PAV (macrophage ΔPAV). The stent edge minimal lumen area (MLA) was measured on the peri-stent segments within 5 mm of the stent edge, and the change in MLA (ΔMLA) was defined as the MLA at the 1-year follow-up minus the baseline MLA. Percent ΔMLA (ΔMLA%) was defined as the ΔMLA/MLA at baseline. The thinnest fibrous cap thickness (TFCT) was calculated by the OFR automatically in each measured segment.

All OCT image quality determinations and final measurements using OFR software were performed by 2 experienced technicians independently (both were trained and certified by Pulse Medical Imaging Technology, Shanghai, Co., Ltd), who were blinded to the patients' clinical information. Intra- and interobserver variability of the OCT image analysis by OFR were evaluated by the kappa statistic (for categorical variables such as lipid, fibrous, calcium and macrophage characteristics) or the intraclass correlation coefficient (ICC) (for continuous variables such as TAVn, PAV and TFCT). Finally, all kappa and ICC values were > 0.9 by consistency tests before final formal measurements.

Definitions and endpoints

sDES-EE was defined as any reduction in the MLA measured by OFR of the peri-stent segments within 5 mm of the stent edge during the 1-year follow-up without evidence of clinical ischemia. The primary endpoint was the EE-TLF at the 5-year follow-up. The secondary endpoints were the differences in ΔTAVn and ΔPAV in the lipid, fibrous, calcium and macrophage components between the sDES-EE group and the non-sDES-EE group, as well as each component of EE-TLF (such as cardiac death, TVMI, and clinically driven TLR related to DES-EE) at 5 years. The remodeling index (RI) was calculated as usual.

Statistical analysis

Baseline characteristics are reported as count (percentage) for categorical data, as mean ± standard deviation for normally distributed continuous data, and as median (interquartile range) for nonnormally distributed data. The χ^2 test or Fisher's exact test was used to compare categorical variables. Student's t test for normal data or the Wilcoxon rank sum score for nonnormal data was used to compare continuous variables. Univariate correlation analysis was performed first, and then binary logistic regression analysis was performed based on the stepwise regression method to estimate the association between DES-EE-related TLF at 5 years and basic clinical characteristics and subclinical DES-EE at 1 year. The odds ratio (OR) and 95% its confidence intervals (CI) were

calculated to evaluate the strength of each correlation. Receiver operating characteristic (ROC) curves were drawn to compare the prognostic ability of the variables to predict the EE-TLF at 5 years, and the area under each curve (AUC) was calculated. The cutoff value of variables derived from the ROC analysis was selected as the basis for the next group analysis. To eliminate the interference of baseline data mismatching between the two groups, we used the method of propensity scoring to correct the baseline data. Differences in EE-TLF at 5 years in the sDES-EE group and non-DES-EE group at 1 year were calculated by the Kaplan–Meier method and were compared by the log-rank test. All statistical tests were two-tailed, and $P < 0.05$ was considered to indicate statistical significance. All analyses were performed using R software for Windows version 4.1.2 (https://www.r-project.org/).

Results

Preliminary exploration of the correlation between sDES-EE at 1 year and EE-TLF at 5 years

After accounting for each risk factor for coronary artery disease, medication and changes in the lipid profile from baseline to the 1-year follow-up, univariate correlation analysis showed that hypertension, HDL-C, T-CH, angiotensin-converting enzyme inhibitor (ACEI)/ angiotensin receptor blocker (ARB), calcium channel blocker (CCB) or beta-blocker use, and ΔMLA% from baseline to 1 year were potentially correlated with EE-TLF at the 5-year follow-up. Then, all these indicators were reanalyzed by multivariate binary logistic regression analysis to find independent predictors of EE-TLF at 5 years. Finally, only ΔMLA% was verified to be independently related to 5-year EE-TLF (Table 1). ROC curve analysis demonstrated that the cutoff value of ΔMLA% at the 1-year follow-up for predicting EE-TLF at the 5-year follow-up was − 24.44%, which had a sensitivity of 60.0%, specificity of 69.0%, positive predictive value (PPV) of 14.8%, negative predictive value (NPV) of 95.1% and AUC of 0.658 (0.519–0.797, $p < 0.001$). For ease of memorization and calculation, we adjusted the cutoff value of -24.44% to an integer − 25% (Fig. 2).

Based on the original definition of sDES-EE in this study with any reduction in MLA at the stent edge without evidence of ischemia at 1 year, in the per-edge analysis, a total of 178 (70.63%) sDES-EEs occurred at the 1-year follow-up detected by OCT, which was more distal than proximal sDES-EEs (58.33% vs. 30.56%, $p < 0.001$) that occurred at the 1-year follow-up in a total of 252 patients. The total sDES-EE ratio decreased significantly after we used the criteria of 25% ΔMLA% reduction (23.4% vs. 70.63%, $p < 0.001$), but the distal sDES-EE incidence was still significantly higher than that of proximal sDES-EE (16.27% vs. 9.92%, $p < 0.001$).

Baseline clinical characteristics and EE-TLF at 5 years after grouping according to -25% ΔMLA% at stent edge at 1 year

To reduce the imbalance of baseline data between the groups, we used a propensity scoring method to adjust the groups' baseline clinical characteristics. After this, all coronary artery disease risk factors, such as hypertension, diabetes mellitus, dyslipidemia, current smoking ratio, and lipid profiles at baseline and at the 1-year follow-up, were comparable between the sDES-EE and non-sDES-EE groups (Table 2).

Kaplan–Meier analysis (Fig. 3a) showed that EE-TLF at the 5-year follow-up was higher in the sDES-EE group at 1 year than in the non-sDES-EE group (15.9% vs. 4.1%, $p = 0.001$). Further landmark analysis (Fig. 3b) showed no differences in EE-TLF within one year between the two groups. After that, the two curves gradually separated, and the incidence of EE-TLF at 5 years increased significantly in the sDES-EE group compared to the non-sDES-EE group (14.3% vs. 3.6%, $p = 0.002$), which were caused by increased TVMI (11.4% vs. 3.0%, $p = 0.001$) and clinical triven TLR (9.4% vs. 2.0%, $p = 0.030$) significantly, but no significant difference of cardiac death (3.1% vs. 0.5%, $p = 0.088$) was found between two groups within 5 years (Fig. 4).

Morphologies and component changes in sDES-EE at the 1-year follow-up

All morphologies and components of plaque (or the coronary wall) within 5 mm of the DES edges were measured by OFR software offline at baseline and at the 1-year follow-up (Table 3). Morphological analysis showed that no differences in TAVn or ΔTAVn were found between the sDES-EE and non-sDES-EE groups at baseline or 1 year in

	Univariate analysis		Multivariate binary logistic regression			
				95% CI		
Variables	*r*	*P*-value	OR	low	high	*P*-value
Hypertension	0.159	0.025	0.251	0.046	1.369	0.110
HDL-C at 1-year	-0.199	0.006	0.318	0.015	6.618	0.459
T-CH at 1-year	-0.148	0.044	0.429	0.177	1.043	0.062
ACEI/ARB	0.259	0.000	0.118	0.013	1.054	0.056
Beta-blocker	0.176	0.013	0.134	0.016	1.146	0.066
ΔMLA%	-0.179	0.012	0.012	0.000	0.308	0.008

Table 1. Univariate and multivariate binary logistic regression analysis for correlation between the variables and EE-TLF at the 5-year follow-up. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence intervals; EE, edge effect; HDL-C, high-density lipoprotein cholesterol; MLA, minimal lumen area; ΔMLA%, percent ΔMLA; OR, odds ratio; T-CH, total cholesterol; TLF, target lesion failure.

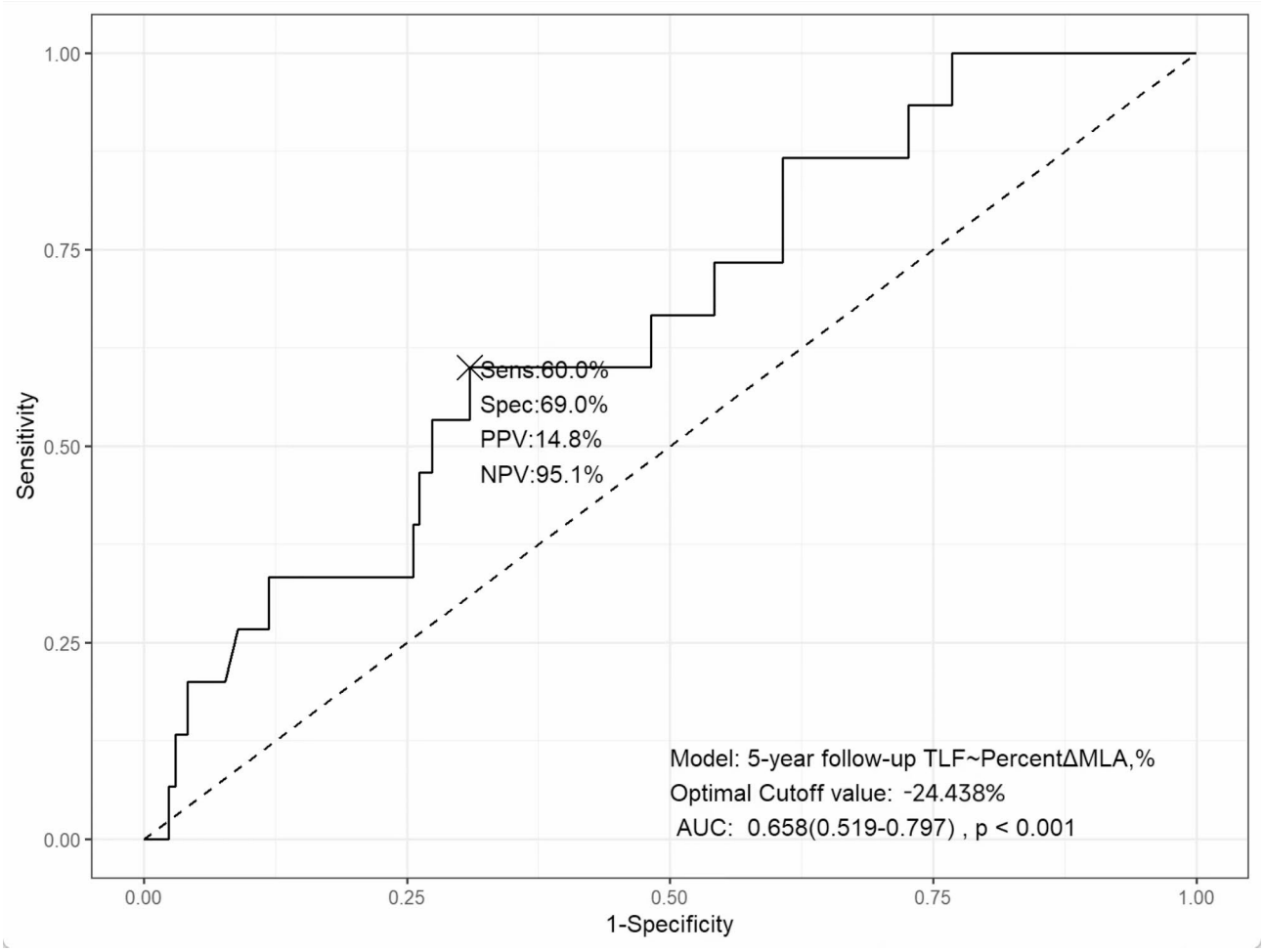

Fig. 2. Receiver-operating characteristic (ROC) analysis for ΔMLA% predicting EE-TLF within 5 years. AUC, area under the curve; ΔMLA%, the percent changes of minimal lumen area; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver-operating characteristic; TLF, target lesion failure.

the per-edge analysis after propensity scoring matching, but TAVn increased significantly in both the non-sDES-EE group (11.75 [7.45, 19.13] mm^3 vs. 13.45 [8.60, 19.65] mm^3, $p = 0.034$) and the sDES-EE group (13.50 [7.15, 20.23] mm^3 vs. 14.65 [8.53, 24.53] mm^3, $p = 0.008$) from baseline to 1 year. Interestingly, no difference in PAV at baseline was found between the two groups, but PAV was significantly higher in the sDES-EE group than in the non-sDES-EE group at 1 year. PAV increased significantly in both the sDES-EE group (27.80 [21.23, 37.00]% vs. 36.20 [26.55, 44.65]%, $p < 0.001$) and the non-sDES-EE group (29.00 [22.98, 40.90]% vs. 30.95 [25.05, 41.50]%, $p < 0.05$), but clearly more in the former. Even baseline MLA at stent edge was comparable between two groups, it reduced in both sDES-EE group (4.48 ± 1.82 mm^2 vs. 6.51 ± 2.33 mm^2, $p < 0.001$) and non-sDES-EE group (5.91 ± 2.45 mm^2 vs. 6.37 ± 2.73 mm^2, $p = 0.005$) at 1 year compared to baseline, ΔMLA, ΔMLA% and MLA at 1 year were significantly lower in the sDES-EE group compared to the non-sDES-EE group. EEM_a was reduced significantly in the sDES-EE group (11.79 ± 4.70 mm^2 vs. 9.82 ± 4.18 mm^2, $p = 0.008$); however, no significant changes were found in the non-sDES-EE group (10.83 ± 4.41 mm^2 vs. 11.45 ± 4.32 mm^2, $p = 0.296$) from baseline to the 1-year follow-up. RI and ΔRI were lower in the sDES-EE group than in the non-sDES-EE group at 1 year, which showed that RI decreased significantly in the sDES-EE group (0.95 ± 0.14 vs. 0.89 ± 0.22, $p = 0.009$) but not in the non-sDES-EE group (0.95 ± 0.10 vs. 0.97 ± 0.15, $p = 0.070$). Component analysis showed that baseline lipid, fibrous, calcium and macrophage TAVn and PAV were comparable between the two groups, but lipid TAVn (0.88 ± 1.89 mm^3 vs. 1.83 ± 0.12 mm^3, $p = 0.018$) and lipid PAV (3.46 ± 1.34% vs. 7.24 ± 2.42%, $p < 0.01$) increased significantly in the sDES-EE group; however, there were no significant changes in lipid TAVn (1.40 ± 0.69 mm^3 vs. 1.20 ± 0.90 mm^3, $p = 0.864$) or lipid PAV (6.08 ± 2.01% vs. 4.91 ± 1.03%, $p = 0.745$) in the non-sDES-EE group from baseline to 1 year. The lipid components of both TAVn and PAV were higher in the sDES-EE group than in the non-sDES-EE group at the 1-year follow-up. No significant differences in other components, such as fibrous, calcium, macrophages and TFCT, were found between them (Representative case with 1-year sDES-EE and EE-TLF between 1 ~ 5 years was shown in Fig. 5).

	Total ($n=183$)	non-sDES-EE ($n=122$)	sDES-EE ($n=61$)	*P* Value
Age, yrs	62.81 ± 9.67	62.51 ± 9.45	63.72 ± 10.34	0.178
Men, *n*(%)	127 (69.4)	84 (69.0)	43 (70.3)	0.847
BMI	24.67 ± 2.89	24.81 ± 3.09	24.39 ± 2.44	0.359
Hypertension, *n*(%)	112 (61.2)	77 (63.1)	35 (57.4)	0.453
Diabetes mellitus, *n*(%)	45 (24.6)	30 (24.4)	15 (24.3)	0.957
Dyslipidemia, *n*(%)	123 (67.2)	83 (67.9)	40 (65.6)	0.741
Smoking, *n*(%)	78 (42.6)	48 (47.3)	30 (49.2)	0.926
Baseline medical therapy				
Statin, *n*(%)	183 (100.0)	122 (100.0)	61 (100.0)	NA
Ezetimibe, *n*(%)	68 (37.2)	42 (34.7)	26 (42.2)	0.396
Antiplatelet therapy, *n*(%)	183 (100.0)	122 (100.0)	61 (100.0)	NA
ACEI/ARB, *n*(%)	101 (55.2)	72 (58.9)	29 (46.9)	0.381
CCB, *n*(%)	47 (25.7)	35 (28.7)	12 (19.7)	0.551
Beta-blocker, *n*(%)	87 (47.5)	62 (50.8)	25 (41.8)	0.484
Baseline lipid profile				
T-CH, mmol/L	3.71 [3.01, 4.55]	3.74 [2.99 4.57]	3.61 [3.02, 4.37]	0.899
LDL-C, mmol/L	2.02 [1.62, 2.65]	2.05 [1.60, 2.80]	1.98 [1.65, 2.48]	0.759
HDL-C, mmol/L	1.01 [0.87, 1.23]	1.02 [0.86, 1.22]	0.99 [0.87, 1.22]	0.529
non-HDL-C, mmol/L	2.71 [2.06, 3.32]	2.75 [2.06, 3.43]	2.61 [2.07, 3.09]	0.693
Triglycerides, mmol/L	1.32 [1.02, 2.01]	1.32 [1.02, 1.89]	1.31 [1.01, 2.18]	0.675
Serum creatinine, μmol/L	72.00 [61.00, 83.50]	71.30 [62.00, 82.15]	74.0 [58.50, 81.00]	0.688
eGFR, mL/(min*1.73m^2)	90.73 [80.67, 100.74]	92.56 [83.89, 101.30]	86.89 [76.61, 97.81]	0.137
Serum calcium, mmol/L	2.19 [2.12, 2.22]	2.20 [2.12, 2.23]	2.16 [2.09, 2.16]	0.380
Serum phosphorus, mmol/L	1.27 [1.01, 1.35]	1.25 [0.97, 1.30]	1.30 [1.08, 1.38]	0.471
Serum uric acid, μmol/L	330.5 [272.3, 379.00]	350.50 [293.27, 378,34]	321.2 [258.70, 384.30]	0.316
1-year Follow up lipid profile				
T-CH, mmol/L	3.48 [2.94, 4.00]	3.48 [2.92, 4.11]*	3.28 [2.95, 3.81]	0.505
LDL-C, mmol/L	1.70 [1.36, 2.15]	1.74 [1.38, 2.20]***	1.69 [1.34, 2.09]**	0.570
HDL-C, mmol/L	1.14 [0.98, 1.38]	1.16 [0.98, 1.39]*	1.11 [1.00, 1.36]**	0.882
non-HDL-C, mmol/L	2.21 [1.81, 2.85]	2.21 [1.82, 2.90]*	2.21 [1.80, 2.83]**	0.739
Triglycerides, mmol/L	1.20 [0.93, 1.66]	1.22 [0.94, 1.68]	1.14 [0.85, 1.52]**	0.224
Serum creatinine, μmol/L	74.00 [63.12, 83.50]	72.10 [63.00, 83.07]	75.00 [60.50, 89.06]	0.659
eGFR, mL/(min*1.73m^2)	88.35 [78.36, 101.12]]	90.84 [82.49, 100.20]	84.78 [75.21, 94.76]	0.341
Change in lipid profile between index and 1-year follow-up				
ΔT-CH, mmol/L	-0.26 [-0.95, 0.38]	-0.26 [-0.89, 0.38]	-0.26 [-1.05, 0.41]	0.855
ΔLDL-C, mmol/L	-0.32 [-0.94, 0.14]	-0.31 [-0.99, 0.16]	-0.29 [-0.83, 0.09]	0.878
ΔLDL-C, %	-0.15 [-0.35, 0.08]	-0.15 [-0.34, 0.09]	-0.15 [-0.35, 0.05]	0.825
LDL-C < 1.4mmol/L, %	50 (27.3)	40 (32.5)	10 (16.4)	0.711
Δnon-HDL-C, mmol/L	-0.34 [-1.03, 0.21]	-0.34 [-1.03, 0.24]	-0.34 [-1.05, 0.17]	0.853
ΔHDL-C, mmol/L	0.13 [-0.01, 0.27]	0.14 [0.00, 0.27]	0.11 [-0.06, 0.23]	0.136
ΔTriglycerides, mmol/L	-0.11 [-0.54, 0.25]	-0.07 [-0.47, 0.26]	-0.23 [-0.77, 0.18]	0.158
Serum creatinine, μmol/L	1.05 [-0.98, 2.71]	0.80 [-0.10, 1.66]	1.63 [-0.98, 3.90]	0.157
ΔeGFR, mL/(min*1.73m^2)	-1.07 [-2.08, 0.15]	-1.34 [-1.89, 0.02]	-1.70 [-2.13, -1.19]	0.165

Table 2. Patients' clinical characteristics at baseline and 1-year follow-up. $^{***}P<0.001$;$^{**}P<0.01$;$^{*}P<0.05$. Values are expressed as the median (interquartile range) for continuous variables with abnormal distribution and described as the mean ± standard deviation with normal distribution, or frequency (percentage) for categorical variables in the table. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body Mass Index; CCB, calcium channel blocker; DES, drug eluting stent; EE, edge effect; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; T-CH, total cholesterol.

Discussion

The findings of this study are mainly reflected in the following three points: (1) sDES-EE with stent-edge MLA reduction by > 25% at 1 year predicted a significant increase in EE-TLF at 5 years' follow-up; (2) the isolated sDES-EE at the 1-year follow-up was mainly due to the increase in lipid component; and (3) negative remodeling of the stent edge may trigger sDES-EE.

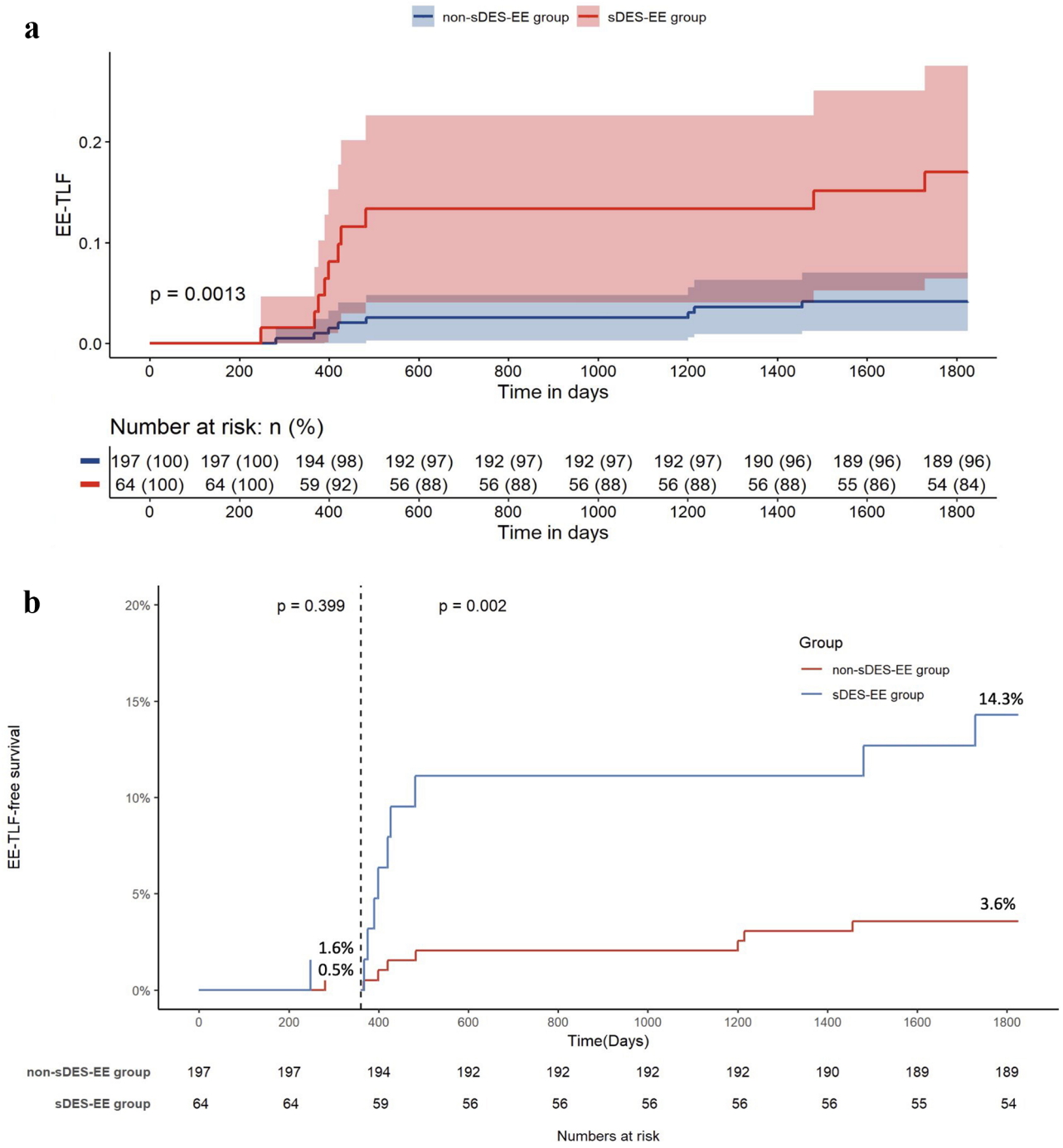

Fig. 3. Kaplan Meier and Landmark analysis of sDES-EE versus non-sDES-EE at 1 year for EE-TLF at 5 years. **a** Kaplan Meier analysis. **b** Landmark analysis.

Stent EE, as a prominent clinical problem in the era of intracoronary brachytherapy, has started to get attention from cardiovascular interventionalists[21]. The performance of stent EE was early defined as localized lesions with angiographic diameter stenosis ≥ 50% within 5 mm of the stent edge at follow-up[7,10]. Clinical DES-EE (combined with ischemia symptoms and evidence associated with stent-edge lesions) has received more attention because it often requires repeat revascularization, while those without clinical ischemia evidence are defined as sDES-EE[22]. Despite the use of new-generation DESs and intravascular imaging to guide PCI, the incidence of clinical DES-EE is still about 2.1%~4.4% between 6 and 12 months after PCI[23–25]. DES-EE is caused by multiple factors, such as stent edge plaque burden, plaque characteristics, presence of hinge motion, and the presence of myocardial bridges[13,26,27]. These factors are interrelated and sometimes cannot be avoided. With the technological development of PCI and the use of intravascular imaging, more patients present with sDES-EE within 1 year[6,14]. Even if we performed PCI guided by OCT, sDES-EE occurred at a total of 70.63% of sites based

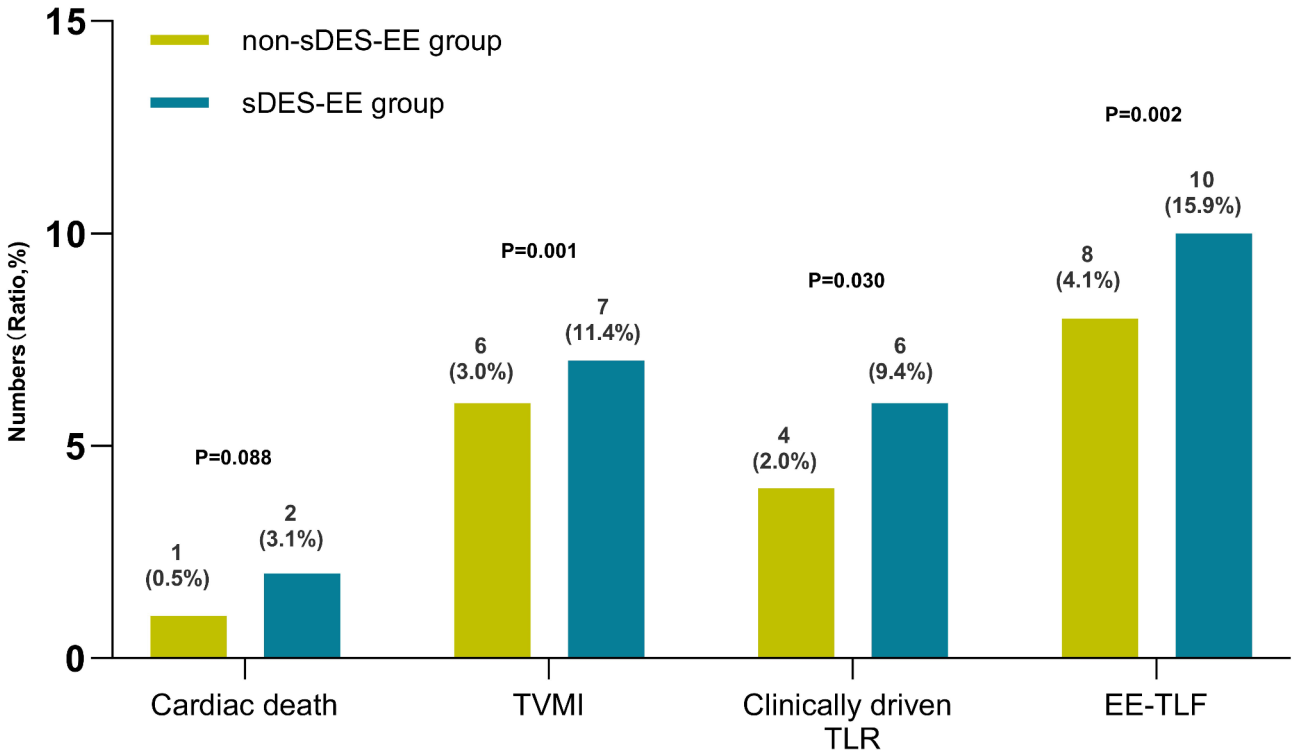

Fig. 4. sDES-EE associated with total EE-TLF and each component of EE-TLF within 5 years. DES, drug eluting stent; EE, edge effect; sDES-EE, subclinical DES-EE; TLF, target lesion failure; TLR, target lesion revascularization; TVMI, target vessel myocardial infarction.

on the original definition in the present study, and 23.4% of sDES-EE with stent edge MLA reduction > 25% at 1 year had a predictive value of significant EE-TLF within 5 years. When we interpret the clinical significance of 25%MLA reduction, we should pay attention to its PPV and NPV 14.8% and 95.1%, respectively. In other words, if no more than 25%MLA reduction occurs in stent edge effect at 1-year post-PCI, the incidence of EE-TLF will be significantly reduced within 5 years. But if more than 25% MLA reduction occurred at the stent edge after one year, EE-TLF at 5 years would not necessarily occur. We believe that the occurrence of sDES-EE at 1 year after PCI is a potential indication that the proliferation of stent-edge plaques caused by multiple factors is a chronic process. If multiple factors are not detected and corrected in time, this stimulation will act on the stent edge over a long period of time, eventually leading to an increased EE-TLF. It may explain that most of EE-TLF events occurred after 400 days post PCI for patients with sDES-EE at 1-year. We analyzed the correlation between clinical factors and 1-year sDES-EE with ΔMLA% >25% by univariate logistic regression, but no indicators have been found to predict MLA reduction > 25% at 1 year (Supplement table 1).

Few studies have been conducted on the plaque components of the DES-EE site. The main cause of BMS-EE was the increase in plaque and media, and the lumen area was reduced within 1 ~ 2 mm from the edge of the stent[28–31] One intravascular ultrasound (IVUS) study showed that the fibrofatty component increase was the main cause of DES-EE[32], and further studies based on virtual histology IVUS demonstrated that thin cap fibroatheroma and large necrotic core were more often at the proximal DES-EE plaque[33,34]. Our study focused on the morphology and component changes of the sDES-EE plaque from baseline to 1-year follow-up. Interestingly, we found that compared with non-sDES-EE, the plaque components at the stent edge of sDES-EE were significantly increased by lipid components, which manifested as greater lipid TAVn and lipid PAV, whereas fibrous, calcium and macrophage component changes were not significantly different. The baseline data of the two groups indicated that the plaque burden at the stent edge site did not exceed 40%, and the lipid composition did not exceed 10%, which met the current recommended standards[11,14,35]. That meant that even we performed PCI according to the 'LightLab' criteria guided by OCT[14], the plaque characteristics at the DES landing zone have no prediction value for sDES-EE at 1 year. If the MLA at the stent edge was reduced by > 25%, this indicated a significant increase in EE-TLF in the next 4 years, which is consistent with the previous viewpoint that even if the newest generation of DES is adopted, DES-EE still cannot be completely avoided[10,13,25]. An artificial intelligence concept-based software system, the OFR, has been used to quantitatively analyze plaque morphology and components more accurately in current study[15–18,27]. After comparing the baseline and 1-year follow-up data, the increase in lipid components was the main cause of sDES-EE. However, the average LDL-C control of patients in our study did not meet the guideline standards[36], so it cannot be concluded that future clinical studies should pursue this possibility.

Vascular remodeling appears to have a role in the process of DES-EE, but previous studies results have been inconsistent[28,37–41]. Our study found a significant reduction in RI in the sDES-EE group compared to the non-

Parameter	non-sDES-EE ($n=132$)	sDES-EE ($n=66$)	*P* Value
TAVn, mm^3			
baseline	11.75 [7.45, 19.13]	13.50 [7.15, 20.23]	0.260
1-year follow-up	13.45 [8.60, 19.65]*	14.65 [8.53, 24.53]**	0.249
ΔTAVn	0.89 [-1.45, 3.13]	2.25 [-0.32, 4.73]	0.170
PAV, %			
baseline	29.00 [22.98, 40.90]	27.80 [21.23, 37.00]	0.481
1-year follow-up	30.95 [25.05, 41.50]*	36.20 [26.55, 44.65]***	0.002
ΔPAV	1.90 [-2.35, 4.94]	8.45 [6.42, 10.48]	< 0.001
Lipid TAVn, mm^3			
baseline	1.40 ± 0.69	0.88 ± 0.09	0.474
1-year follow-up	1.20 ± 0.90	1.83 ± 0.12*	0.013
Lipid ΔTAVn	-0.21 ± 0.06	0.99 ± 0.25	0.025
Lipid PAV, %			
baseline	6.08 ± 2.01	3.46 ± 1.34	0.655
1-year follow-up	4.91 ± 1.03	7.24 ± 2.42**	0.012
Lipid ΔPAV	-1.22 ± 0.78	3.92 ± 1.34	0.029
Fibrous TAVn, mm^3			
baseline	11.08 ± 5.86	11.43 ± 5.92	0.340
1-year follow-up	11.86 ± 5.69	12.55 ± 6.10	0.517
Fibrous ΔTAVn	0.79 ± 0.40	1.12 ± 0.17	0.872
Fibrous PAV, %			
baseline	82.80 ± 10.92	80.00 ± 10.71	0.064
1-year follow-up	82.77 ± 11.61	78.41 ± 13.64	0.080
Fibrous ΔPAV	-0.05 ± 0.04	-2.03 ± 1.97	0.189
Calcium TAVn, mm^3			
baseline	0.00 [0.00, 0.01]	0.01 [0.00, 0.03]	0.299
1-year follow-up	0.03 [0.00, 0.06]	0.05 [0.01, 0.08]	0.659
Calcium ΔTAVn	0.01 [0.00, 0.02]	0.03 [0.01, 0.04]	0.473
Calcium PAV, %			
baseline	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.260
1-year follow-up	0.00 [0.00, 0.01]	0.01 [0.00, 0.02]	0.663
Calcium ΔPAV	0.00 [0.00, 0.00]	0.00 [0.00, 0.01]	0.412
Macrophage TAVn, mm^3			
baseline	0.00 [0.00, 0.04]	0.00 [0.00, 0.00]	0.616
1-year follow-up	0.00 [0.00, 0.03]	0.00 [0.00, 0.02]	0.636
Macrophage ΔTAVn	0.01 [0.00, 0.02]	0.02 [0.01, 0.03]	0.426
Macrophage PAV, %			
baseline	0.10 [0.00, 0.20]	0.00 [0.00, 0.00]	0.503
1-year follow-up	0.12 [0.00, 0.21]	0.00 [0.00, 0.10]	0.747
Macrophage ΔPAV	0.03 [0.01, 0.05]	0.03 [0.01, 0.04]	0.510
TFCT, μm			
baseline	154.00 [100.00,239.00]	170.00 [136.00,251.50]	0.588
1-year follow-up	186.00 [133.00,243.75]	200.00 [127.75,270.75]	0.274
ΔTFCT	37.82 [-15.25, 91.25]	22.50 [-10.25,54.75]	0.619
MLA, mm^2			
baseline	6.37 ± 2.73	6.51 ± 2.33	0.753
1-year follow-up	5.91 ± 2.45**	4.48 ± 1.82***	< 0.001
ΔMLA	-0.46 ± 0.30	-2.03 ± 1.61	< 0.001
ΔMLA%, %	-1.30 ± 0.80	-36.81 ± 16.35	< 0.001
EEM_a, mm^2			
baseline	10.83 ± 4.41	11.79 ± 4.70	0.770
1-year follow-up	11.45 ± 4.32	9.82 ± 4.18**	0.021
Continued			

Parameter	non-sDES-EE ($n=132$)	sDES-EE ($n=66$)	P Value
ΔEEM_a	0.58 ± 0.28	-1.84 ± 0.41	0.001
RI			
baseline	0.95 ± 0.10	0.95 ± 0.14	0.816
1-year follow-up	0.97 ± 0.15	0.89 ± 0.22**	0.001
ΔRI	0.05 ± 0.03	-0.06 ± 0.26	0.013

Table 3. Per-edge analysis of sDES-EE morphologies and components measured by OFR. ***$P<0.001$; **$P<0.01$; *$P<0.05$; these values were compared between baseline and 1-year follow-up. Values are expressed as the median (interquartile range) for continuous variables with abnormal distribution and described as the mean ± standard deviation with normal distribution, or frequency (percentage) for categorical variables in the table. DES, drug eluting stent; EE, edge effect; EEMa, external elastic membrane area; MLA, minimal luminal area; OFR, optical flow ratio; PAV, percent atheroma volume; ΔMLA%, percent ΔMLA; RI, remodeling index; TAVn, normalized total atheroma volume; TFCT, thinnest fibrous cap thickness.

sDES-EE group, which caused significant negative remodeling in the sDES-EE group. Even though we cannot explain the mechanism of this phenomenon, we hypothesize that this chronic remodeling in conjunction with the growth of plaque volume is involved in the development of EE-TLF over 5 years.

In addition, we continue to believe that the increase in EE-TLF resulting from the development of sDES-EE is a chronic and multifactorial process, and although it is not possible to reduce the frequency of sDES-EE from the optimized stent landing zone by screening patients for their baseline data, we should emphasize that if sDES-EE is detected at the 1-year follow-up, more intensive lipid-lowering therapy should be prescribed to patients as quickly as possible, or intensive lipid-lowering therapy should be adopted right after PCI routinely to reduce EE-TLF for 5 years. This concept is worthy of further research.

Conclusions

sDES-EE with MLA reduction ≥ 25% at the stent edge at 1-year post-PCI was an independent predictor of EE-TLF at 5 years post-PCI, which was mainly caused by the progression of lipid components measured by OFR.

Limitations

1. The number of cases was relatively small. We think that all patients in this study are patients with acute coronary syndrome, the conclusions of this study cannot be generalized to chronic coronary syndrome patients.
2. All plaque characteristics at the stent landing zone were simple lesions, which caused 0% EE-TLF at 1 year.
3. The average LDL-C level post-PCI had not reached the recommendations of guidelines in most patients, so we did not find a correlation between LDL-C reduction and the decrease in sDES-EE at 1 year.
4. We focused on the indicators for sDES-EE morphology and component changes, which might be different from those of clinical DES-EE.
5. Although OFR software is a novel artificial intelligence framework that can measure plaque components automatically, its clinical value needs to be confirmed by more studies.

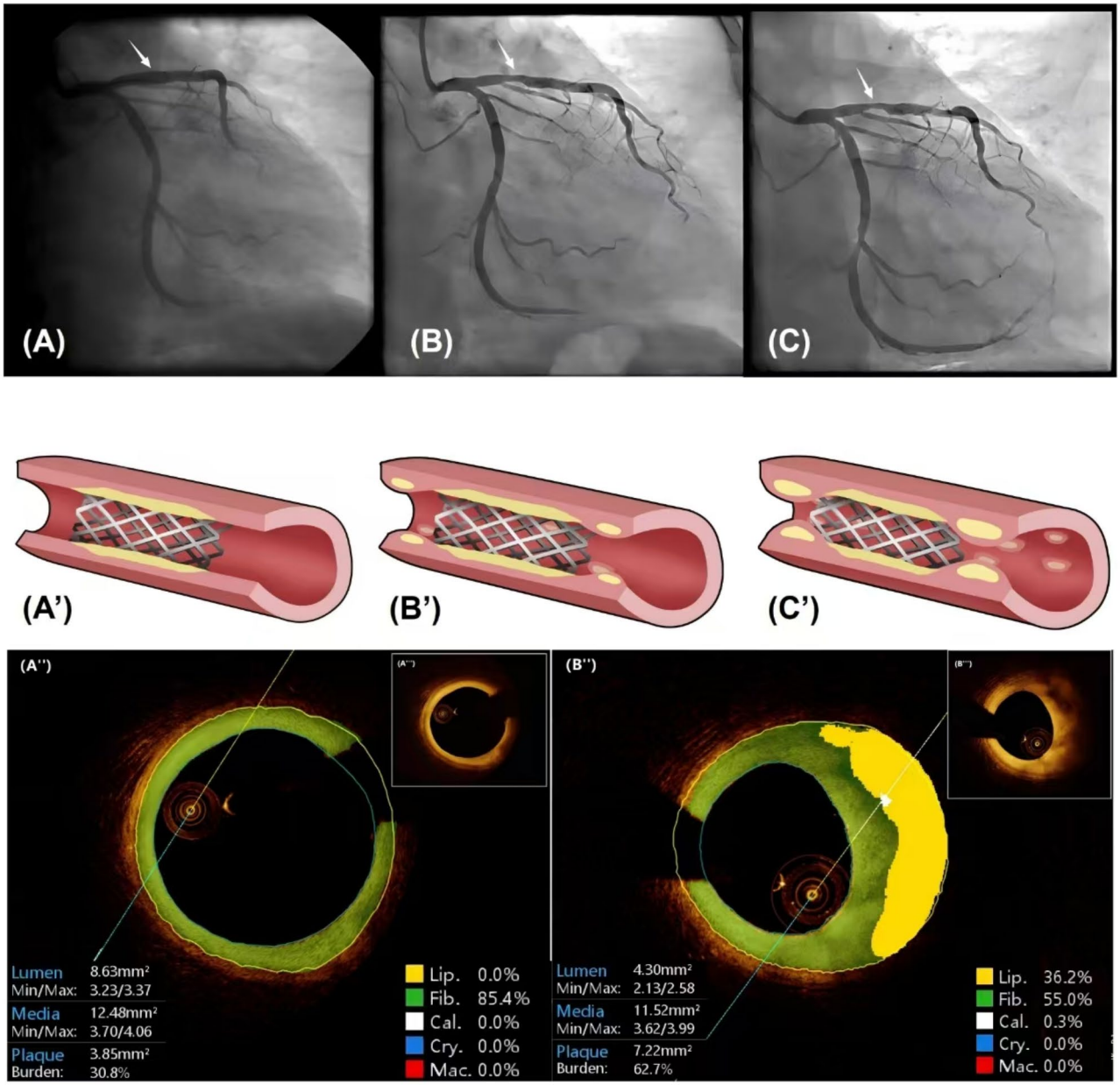

Fig. 5. Representative case with 1-year sDES-EE and EE-TLF between 1 ~ 5 years. The figure in the upper row shows the angiography results of the right anterior oblique foot position, and the white solid arrow points to the proximal part of DES in the anterior descending branch; **(A)** indicates immediately result after the implantation of DES; **(B)** indicates the angiographic sDES-EE results at 1-year follow-up after PCI; **(C)** indicates that EE-TLF occurred between 1 year and 5 years after PCI. The figure in the middle row shows the Simulated diagram. (A'), (B') and (C') simulates the result of **(A)**, **(B)** and **(C)** separately. The figure in the lower row shows the cross-sectional OCT image of the white solid arrow points in the upper figure. (A") corresponds to **(A)**, showing that the plaque area was 3.85 mm^2 and plaque burden was 30.8% at the proximal DES edge immediately after PCI, of which fibrous components accounted for 85.4% and lipid components accounted for 0.0%. (B") corresponds to **(B)**, showing that the plaque area increased to 7.22 mm^2 and plaque burden increased to 62.7% at the same site 1 year after PCI, of which fibrous components accounted for 55.0% and lipid components increased to 36.2%. DES, drug eluting stent; EE, edge effect; PCI, percutaneous coronary intervention; sDES-EE, subclinical DES-EE; TLF, target lesion failure.

Data availability

Data supporting the findings of our study are available from Nanjing Hospital, Nanjing Medical University. If someone wants to request the data from this study, data are available from the correspondence authors upon reasonable request and with permission from Nanjing Hospital, Nanjing Medical University.

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Author contributions

Yi Xu, Wei You, Tian Xu, Pei-Na Meng, Xiang-Qi Wu, Zhi-Ming Wu, Xiao-Han Kong, De-Lu Yin and Mei-En Zhan performed data curation. Yi Xu, Yi-Fei Wang and Meng-Yao Zhao performed formal analysis.Yi Xu, Yi-Fei Wang, Meng-Yao Zhao, Wei You and Xiang-Qi Wu performed visualization and wiring original draft.Hai-Bo Jia, Bin Liu and Fei Ye performed conceptualization, methodology, validation, writing review and editing, supervision and project administration.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Nanjing First Hospital.

Competing interests

The authors declare no competing interests.

Conflict of interest

There are no conflicts of interest in this study.

Additional information

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