EuroIntervention 2019;15:631-639 published online November 2018

Impact of the one-year angioscopic findings on long-term clinical events in 504 patients treated with first-generation or second-generation drug-eluting stents: the DESNOTE-X study

Yohei Sotomi[1], MD, PhD; Satoshi Suzuki[1], MD; Tomoaki Kobayashi[1], MD; Yuma Hamanaka[1], MD; Shimpei Nakatani[1], MD, PhD; Akio Hirata[1], MD, PhD; Yasuharu Takeda[1], MD, PhD; Yasunori Ueda[2], MD, PhD; Yasushi Sakata[3], MD, PhD; Yoshiharu Higuchi[1]*, MD, PhD

1. Department of Cardiology, Osaka Police Hospital, Osaka, Japan; 2. Cardiovascular Division, National Hospital Organization Osaka National Hospital, Osaka, Japan; 3. Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

KEYWORDS

- clinical research
- drug-eluting stent
- other imaging modalities

Abstract

Aims: We aimed to test the hypothesis that the presence of in-stent yellow plaque (YP) assessed by angioscopy would be a risk of very late stent failure (VLSF) of the cobalt-chromium everolimus-eluting stent (CoCr-EES) in comparison with first-generation drug-eluting stents (DES).

Methods and results: DESNOTE-X was a prospective cohort study, an extended study of the DESNOTE study (UMIN000013515). All patients who received successful angioscopic examination at planned one-year follow-up of DES were clinically followed. The primary endpoint was VLSF defined as a composite of cardiac death, target vessel myocardial infarction, and target lesion revascularisation. A total of 504 patients with 549 lesions were enrolled over a period of 12.5 years. At one-year follow-up, the incidence of YP was significantly higher in the first-generation DES than in the CoCr-EES (199/292 [68%] vs 80/257 [31%], p<0.001). Maximum yellow colour grade on coronary angioscopy at one-year follow-up was an independent predictor of future VLSF in the first-generation DES (HR 2.604 [95% CI: 1.265-5.361], p=0.009), whereas it was not in the CoCr-EES (p for interaction 0.022).

Conclusions: The incidence of in-stent atherosclerosis identified as YP on angioscopy was lower and its impact on late clinical events appeared smaller in the CoCr-EES than in the first-generation DES.

**Corresponding author: Department of Cardiology, Osaka Police Hospital, 10-31, Kitayama, Tennoji, Osaka, 543-0035, Japan. E-mail: yhiguchi-ja@umin.net*

SUBMITTED ON 25/06/2018 - REVISION RECEIVED ON 1st 07/10/2018 / 2nd 28/10/2018 - ACCEPTED ON 31/10/2018

DOI: 10.4244/EIJ-D-18-00660

Abbreviations

CoCr-EES	cobalt-chromium everolimus-eluting stent
DES	drug-eluting stent
IVUS	intravascular ultrasound
PCI	percutaneous coronary intervention
TLR	target lesion revascularisation
TVMI	target vessel myocardial infarction
VLSF	very late stent failure

Introduction

Although the introduction of drug-eluting stents (DES) substantially reduced early target lesion revascularisation (TLR) as compared to bare metal stents by restricting development of neointimal hyperplasia, DES have been associated with an increased risk of stent thrombosis and TLR after one year, that is, very late stent failure (VLSF)[1]. In the DESNOTE study in which mainly the first-generation DES was evaluated (86%), neoatherosclerosis identified as an in-stent yellow plaque (YP) on coronary angioscopy one year after the implantation of DES and the absence of statin therapy were risks of VLSF[1]. The underlying mechanism of VLSF appeared to be the progression of neoatherosclerosis as demonstrated by the YP. However, the incidence of VLSF has been reduced with the use of newer-generation DES[2-4]. Therefore, it would be interesting for physicians to know whether the cause of VLSF of the second-generation DES is also associated with the progression of neoatherosclerosis.

Coronary angioscopy provides substantial information pertaining to macroscopic pathology in living patients. It has reliably detected atherosclerosis as YPs, and especially those with a high-grade yellow colour have been regarded as high-risk plaques and demonstrated to be associated with future coronary events[5,6].

The purpose of the present study was to test the hypothesis that the angioscopic findings of the stented segment, especially the presence of in-stent YP, one year after stent implantation would be a risk of future VLSF in the second-generation best-in-class DES, cobalt-chromium everolimus-eluting stent (CoCr-EES) as was demonstrated in first-generation DES.

Methods

STUDY DESIGN AND POPULATION

DESNOTE-X (Detect the Event of very late Stent failure from the angioscopic fiNdings Of drug-eluTing stEnt - XIENCE) was a single-centre prospective cohort study. The present study focusing on the difference between first-generation DES and CoCr-EES was an extended study of the DESNOTE study (UMIN000013515). All patients who received successful angioscopic examination at planned one-year follow-up (±3 months) after DES implantation in the native coronary artery irrespective of clinical presentation (silent myocardial ischaemia, stable or unstable angina, ST-elevation myocardial infarction, or non-ST-elevation myocardial infarction) without any earlier event of stent failure were enrolled from July 2004 to January 2017 and clinically followed up for the occurrence of VLSF. The following DES were defined as first-generation DES: CYPHER® sirolimus-eluting stent (Cordis, Cardinal Health, Milpitas, CA, USA) and TAXUS™ paclitaxel-eluting stent (Boston Scientific, Marlborough, MA, USA). The cobalt-chromium everolimus-eluting stent (CoCr-EES; XIENCE V®, XIENCE PRIME®, XIENCE Xpedition® or XIENCE Alpine™; Abbott Vascular, Santa Clara, CA, USA) was evaluated as a best-in-class second-generation DES. Written informed consent was obtained from all enrolled patients. This study was approved by the Osaka Police Hospital Ethics Committee.

STUDY ENDPOINTS

The primary endpoint of the present study was VLSF, defined as a composite of cardiac death, target vessel myocardial infarction (TVMI), or target lesion revascularisation (TLR)[7]. The secondary endpoints were all individual components of the primary endpoint and definite or probable stent thrombosis (ST) according to the ARC definition[7]. An independent clinical events committee adjudicated all clinical events.

PROCEDURE

The PCI strategy was left to the discretion of the individual operators. Dual antiplatelet therapy (DAPT, aspirin and $P2Y_{12}$ inhibitor) was encouraged for at least one year after the PCI, followed by single antiplatelet therapy with aspirin (100 mg/day). Prolongation of DAPT beyond one year was left to the discretion of the outpatient clinician. All patients and treating physicians were asked to adhere to the Guideline of the Japanese Society of Cardiology in terms of tobacco usage, exercise, healthy food intake, maintenance of an adequate body weight, and medications for the achievement of target blood lipid concentrations, and blood pressure control. One-year invasive follow-up (±3 months) of coronary angiography, mainly via the radial approach, was planned for all patients. Imaging assessment of the stented segment was routinely performed with coronary angioscopy.

ANGIOSCOPIC EXAMINATION

Yellow colour grade, neointimal coverage, and thrombus at the site of DES implantation were examined by angioscopy. The non-occlusion type of angioscopy, VISIBLE (FiberTech Co., Ltd., Tokyo, Japan), was used. Angioscopic observation of the stented lesions was carried out while blood was cleared away from the viewing area by the injection of 3% dextran-40[8]. Cases with complete pullback and good image quality, as defined by >70% of analysable stent length, were included in this analysis[9].

Yellow colour grade was classified into four grades (0: white, 1: slight yellow, 2: yellow, and 3: intense yellow) compared with the standard colours[6]. Neointimal coverage was classified into three grades (0: no coverage, 1: poor coverage, 2: complete coverage)[10]. Thrombus was defined as white or red material that had a cotton-like or ragged appearance or that presented fragmentation with or without protrusion into the lumen or adherent to the luminal surface[11]. Image examples are presented in **Figure 1**. Maximum and minimum neointima coverage grade, maximum yellow colour grade, and the presence or absence of thrombus were determined

Figure 1. *Image examples of coronary angioscopy. Image examples of yellow colour grade, stent coverage grade and thrombus on coronary angioscopy.*

for each stented lesion. The presence of YP was defined as the maximum yellow colour grade ≥2 [1]. Four analysts of angioscopy (Y. Sotomi, S. Suzuki, T. Kobayashi, and Y. Hamanaka) who were blinded to patients' characteristics evaluated the angioscopic images. The inter-observer and intra-observer reproducibility (percent agreement) for the interpretation of angioscopic images in our institution was 95% and 95% for stent coverage, 85% and 95% for plaque colour, and 90% and 100% for thrombus, respectively[1]. When a patient had multiple lesions, the lesion with the worst values was chosen as representative for that patient.

STATISTICAL ANALYSIS

Lesions were divided into four groups according to the presence or absence of YP at the site of stent implantation on coronary angioscopy at one-year follow-up and generation of DES (first-generation DES vs second-generation CoCr-EES). Normality of data distribution was tested by the Kolmogorov-Smirnov test. Data are expressed as mean±SD or median and interquartile range. Group means for continuous variables with normal and non-normal distributions were compared using Student's t-tests and Mann-Whitney U tests, respectively. Categorical variables were compared using the Pearson's chi-square test or Fisher's exact test, as appropriate. A multivariate Cox proportional hazards analysis was performed to determine the independent determinants of VLSF stratified by first-generation DES or second-generation CoCr-EES. The model was constructed with forward stepwise Cox multivariable regression analysis, entry, and removal criteria of 0.05 and 0.10, respectively. Age, sex, hypertension, diabetes mellitus, current smoking, stenting for acute coronary syndrome, serum high-density lipoprotein cholesterol at baseline, serum triglyceride at baseline, aspirin use, prolonged DAPT use defined as continuous DAPT usage beyond one year after index PCI, statin use, maximum stent diameter, total stent length, maximum YP colour grade, presence of thrombus, minimum neointima coverage grade, and reduction of serum low-density lipoprotein cholesterol from baseline to last follow-up were included as variables. The incidence of VLSF was compared between the groups using Kaplan-Meier methods and the log-rank test. A p-value of <0.05 was regarded as statistically significant. A significant level for each paired comparison in the log-rank test was 0.025 after adjustment for multiplicity using the Bonferroni correction. All statistical analyses were performed with SPSS, Version 24.0.0 (IBM Corp., Armonk, NY, USA).

Results

STUDY POPULATION

A total of 504 patients with 549 lesions were enrolled over a period of 12.5 years. The median follow-up duration was 1,748 days (interquartile range: 1,079, 2,338 days). **Table 1** shows patient and lesion demographics, risk factors, and medication.

ANGIOSCOPIC FINDINGS

Angioscopic findings are shown in **Figure 2**. At one-year follow-up, the prevalence of in-stent YP was significantly higher in the first-generation DES than in the second-generation CoCr-EES (199/292 [68%] vs 80/257 [31%], p<0.001). In-stent thrombus was also more frequently observed in the first-generation

Table 1. Patient demographics.

	First-generation DES	Second-generation CoCr-EES	*p*-value
Patient level	**No. of patients=254**	**No. of patients=250**	
Age, years	65.9±8.9, 67 [59.8, 73]	67.3±9.2, 68 [62, 74.5]	0.086
Body mass index	24.6±3.4, 24.4 [22.5, 26.4]	24.9±3.3, 24.5 [22.7, 26.8]	0.340
Male	208/254 (82.4)	214/250 (85.6)	0.259
Diabetes mellitus	98/254 (38.6)	132/250 (52.8)	0.001
Hypertension	211/254 (83.1)	237/250 (94.8)	<0.001
Current smoker	38/250 (15.2)	32/250 (12.8)	<0.001
Acute coronary syndrome	52/219 (23.7)	54/245 (22.0)	0.663
Serum lipid profile at baseline, mg/dL			
Low-density lipoprotein cholesterol	102.4±27.3, 100 [83, 118]	85.2±22.2, 82 [68.75, 98]	<0.001
High-density lipoprotein cholesterol	49.4±13.2, 48 [40, 57]	47.2±11.0, 45 [39, 53.5]	0.043
Triglycerides	155.7±98.5, 131.5 [89.8, 189.5]	151.2±108.5, 120.5 [85.5, 186.3]	0.626
Serum lipid profile at last follow-up, mg/dL			
Low-density lipoprotein cholesterol	88.1±24.5, 86 [72.3, 102]	82.8±24.3, 79.5 [65.75, 97]	0.019
High-density lipoprotein cholesterol	46.1±13.1, 44 [38, 53.3]	47.2±12.2, 46 [39, 55.3]	0.320
Triglycerides	138.1±84.1, 116 [84, 171.8]	141.5±110.6, 119 [82, 158]	0.703
Lipid profile change from baseline to last follow-up			
Reduction of low-density lipoprotein cholesterol	14.9±29.7, 15 [–1.8, 33]	2.5±21.1, 2 [–8, 15]	<0.001
Reduction of high-density lipoprotein cholesterol	3.5±9.8, 2 [–2, 9]	0.1±8.9, 0 [–5, 5]	<0.001
Reduction of triglycerides	17.8±86.1, 10 [–27.8, 53.8]	9.7±95.5, 1 [–22, 34]	0.325
Medication at baseline			
Statin	179/254 (70.5)	220/250 (88.0)	<0.001
Aspirin	235/254 (92.5)	240/250 (96.0)	0.093
DAPT	202/254 (79.5)	214/250 (85.6)	0.073
Medication at last follow-up			
Statin	196/254 (77.2)	212/250 (84.8)	0.029
Aspirin	227/254 (89.4)	210/250 (84.0)	0.076
Prolonged DAPT	151/254 (59.4)	110/250 (44.0)	0.001
Follow-up duration, days	2,210±705, 2,285 [1,749, 2,786]	1,301±616, 1,174 [810, 1,695]	<0.001
Lesion level	**No. of lesions=292**	**No. of lesions=257**	
Target vessel			
Right coronary artery	112/292 (38.4)	91/257 (35.4)	0.233
Left anterior descending artery	134/292 (45.9)	138/257 (53.7)	
Left circumflex artery	44/292 (15.1)	28/257 (10.9)	
Left main trunk	1/292 (0.3)	0/257 (0.0)	
Saphenous vein graft	1/292 (0.3)	0/257 (0.0)	
ACC/AHA classification			
A	17/291 (5.8)	18/257 (7.0)	<0.001
B1	59/291 (20.3)	39/257 (15.2)	
B2	126/291 (43.3)	72/257 (28.0)	
C	89/291 (30.6)	128/257 (49.8)	
Stent type			
XIENCE EES	–	257/257 (100.0)	
CYPHER SES	224/292 (76.7)	–	
TAXUS PES	68/292 (23.3)	–	
Total stent length, mm	25.1±14.8, 23 [18, 28]	36.2±19.1, 33 [23, 47]	<0.001
Maximum stent diameter, mm	3.0±0.4, 3 [2.75, 3.5]	2.9±0.4, 3 [2.5, 3]	0.068

Data are expressed as number (%) or mean±standard deviation, median (interquartile range). DAPT: dual antiplatelet therapy

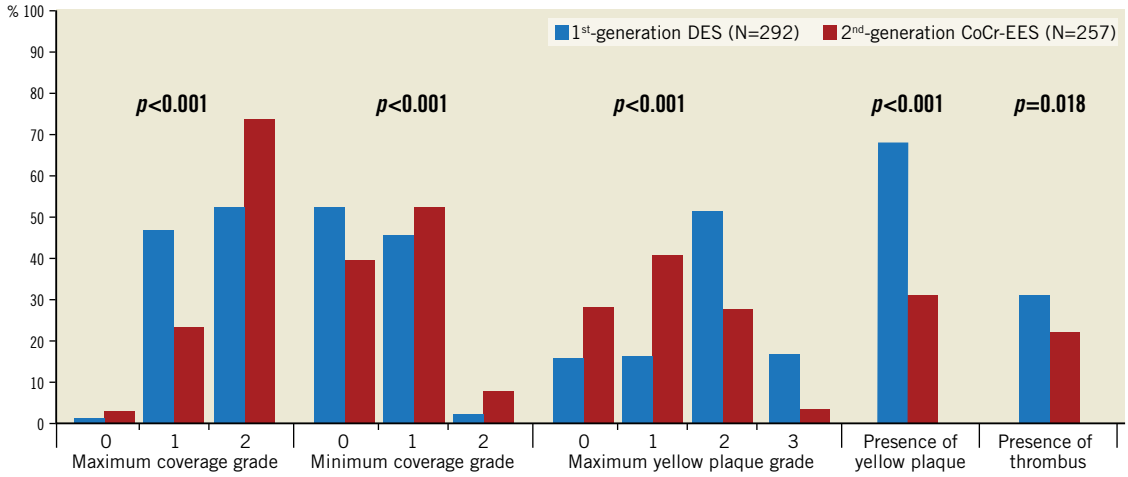


Figure 2. *Angioscopic findings. Percentages of each angioscopic finding are presented as bar graphs (chi-square test).*

DES than in the CoCr-EES (91/292 [31.2%] vs 57/257 [22.2%], p=0.018). Stent uncoverage (minimum coverage grade=0) was more frequently found in the first-generation DES as compared to the CoCr-EES (153/292 [52.4%] vs 102/257 [39.7%], p=0.002).

CLINICAL OUTCOMES

Figure 3 and **Figure 4** summarise the clinical endpoints. In the first-generation DES, the incidence of VLSF was significantly higher in the YP (+) group than in the YP (–) group (19/199 [9.5%] vs 0/93 [0%], log-rank test p=0.003), which was driven by the higher incidence of TLR in the YP (+) group. In the second-generation CoCr-EES, the incidence of VLSF did not differ significantly between the groups (2/80 [2.5%] vs 11/177 [6.2%], log-rank test p=0.249). Lesion characteristics stratified by the presence of YP in first- and second-generation DES are shown in **Table 2**.

Independent predictors of VLSF in first- and second-generation DES are presented in **Table 3**. Maximum yellow colour grade on coronary angioscopy at one-year follow-up was an independent predictor of future VLSF in the first-generation DES (HR 2.604 [95% CI: 1.265-5.361], p=0.009), whereas it was not in the CoCr-EES (p for interaction=0.022). In the second-generation CoCr-EES, age and prolonged DAPT were independently associated with late clinical events.

Discussion

The main findings of the present study can be summarised as follows. 1) At one-year follow-up, the incidence of in-stent YP was significantly higher in the first-generation DES than in the second-generation CoCr-EES (p<0.001). 2) In patients without early clinical events after implantation of first-generation DES, VLSF occurred more frequently in the YP (+) group than in the YP (–)

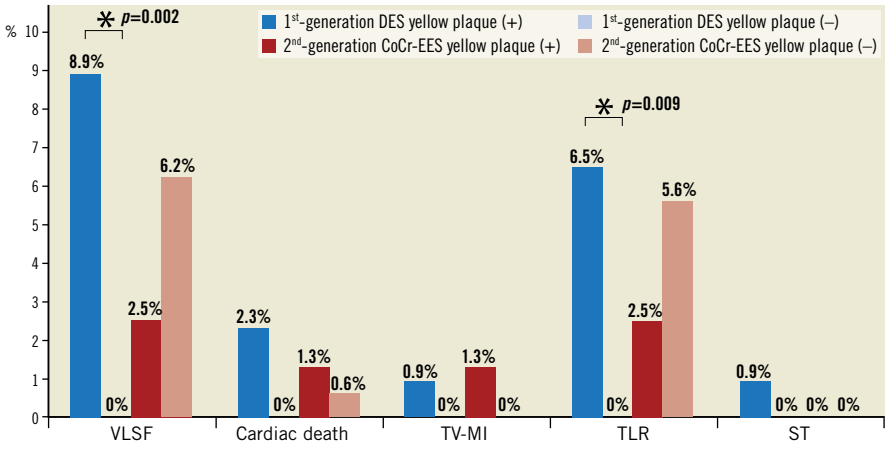


Figure 3. *Clinical endpoints. The incidence of the primary and secondary endpoints. *Only p-values <0.05 are presented. The other comparison was not statistically significant. DES: drug-eluting stent; ST: stent thrombosis; TLR: target lesion revascularisation; TV-MI: target vessel myocardial infarction; VLSF: very late stent failure*

Table 2. Lesion characteristics stratified by the presence of yellow plaque.

Variables		1st-generation DES			2nd-generation CoCr-EES		
		Yellow plaque (–)	Yellow plaque (+)		Yellow plaque (–)	Yellow plaque (+)	
		75 patients, 93 lesions	179 patients, 199 lesions	*p*-value	171 patients, 177 lesions	79 patients, 80 lesions	*p*-value
Age		67.0±9.8	65.5±8.5	0.215	66.8±9.5	68.4±8.4	0.182
Male gender		60/75 (80.0)	148/179 (82.7)	0.613	146/171 (85.4)	68/79 (86.1)	0.884
Body mass index		25.4±4.1	24.3±3.0	0.034	25.2±3.5	24.5±2.9	0.122
Hypertension		65/75 (86.7)	146/179 (81.6)	0.323	164/171 (95.9)	73/79 (92.4)	0.246
Diabetes mellitus		35/75 (46.7)	63/179 (35.2)	0.087	87/171 (50.9)	45/79 (57.0)	0.370
Current smoker		11/74 (14.9)	27/176 (15.3)	0.924	23/171 (13.5)	9/79 (11.4)	0.547
Acute coronary syndrome		14/75 (18.7)	38/144 (26.4)	0.203	35/171 (20.5)	19/74 (25.7)	0.367
Target vessel	Right coronary artery	32/93 (34.4)	80/199 (40.2)	0.741	60/177 (33.9)	31/80 (38.8)	0.356
	Left anterior descending artery	46/93 (49.5)	88/199 (44.2)		100/177 (56.5)	38/80 (47.5)	
	Left circumflex artery	15/93 (16.1)	29/199 (14.6)		17/177 (9.6)	11/80 (13.8)	
	Left main trunk	0/93 (0)	1/199 (0.5)		0/177 (0)	0/80 (0)	
	Saphenous vein graft	0/93 (0)	1/199 (0.5)		0/177 (0)	0/80 (0)	
Total stent length, mm		23.1±12.0	25.3±15.9	0.276	35.7±19.1	38.1±19.2	0.346
Maximum stent diameter, mm		3.0±0.3	3.1±0.4	0.041	2.9±0.4	2.9±0.4	0.997
ACC/AHA classification	A	4/93 (4.3)	13/198 (6.6)	0.713	10/177 (5.6)	8/80 (10.0)	0.436
	B1	22/93 (23.7)	37/198 (18.7)		30/177 (16.9)	9/80 (11.3)	
	B2	41/93 (44.1)	85/198 (42.9)		50/177 (28.2)	22/80 (27.5)	
	C	26/93 (28.0)	63/198 (31.8)		87/177 (49.2)	41/80 (51.2)	
Medication at baseline	Statin	51/75 (68.0)	128/179 (71.5)	0.576	151/171 (88.3)	69/79 (87.3)	0.828
	Aspirin	69/75 (92.0)	166/179 (92.7)	0.839	164/171 (95.9)	76/79 (96.2)	0.912
	DAPT	63/75 (84.0)	139/179 (77.7)	0.253	148/171 (86.5)	66/79 (83.5)	0.529
Lipid profile at baseline (mg/dL)	Low-density lipoprotein cholesterol	100.2±26.2	103.2±27.7	0.425	85.8±20.8	84.0±25.1	0.549
	High-density lipoprotein cholesterol	47.7±14.6	50.2±12.6	0.179	47.6±11.2	46.4±10.5	0.411
	Triglycerides	156.2±90.5	155.5±102.0	0.959	158.9±119.7	134.4±77.2	0.097
Medication at last follow-up	Statin	55/75 (73.3)	141/179 (78.8)	0.346	147/171 (86.0)	66/79 (82.3)	0.450
	Aspirin	66/75 (88.0)	161/179 (89.9)	0.647	139/171 (81.3)	71/79 (89.9)	0.085
	DAPT (prolonged DAPT)	46/75 (61.3)	105/179 (58.7)	0.692	74/171 (43.3)	36/79 (45.6)	0.734
Lipid profile at 1-year follow-up (mg/dL)	Low-density lipoprotein cholesterol	84.2±21.6	89.5±25.4	0.150	82.6±23.2	83.1±26.8	0.873
	High-density lipoprotein cholesterol	44.9±13.9	46.5±12.7	0.383	47.5±12.0	46.5±12.6	0.551
	Triglycerides	134.1±97.1	139.7±78.5	0.646	146.8±123.7	130.0±74.3	0.266
Reduction of low-density lipoprotein cholesterol		18.0±25.4	13.7±31.2	0.338	3.3±18.2	0.9±26.2	0.404
Reduction of high-density lipoprotein cholesterol		3.1±10.3	3.6±9.7	0.718	0.1±8.9	0.1±9.0	0.993
Reduction of triglycerides		22.2±76.6	16.0±89.8	0.617	12.1±108.5	4.3±58.4	0.553
Follow-up duration, days		2,198.8±625.9	2,214.7±736.8	0.870	1,348.6±634.8	1,197.8±561.4	0.072

Data are expressed as number (%) or mean±standard deviation, median (interquartile range). DAPT: dual antiplatelet therapy

group (p=0.003), whereas, in the second-generation CoCr-EES, the incidence of VLSF did not differ significantly between the groups (p=0.249). 3) Yellow plaque colour grade on coronary angioscopy at one-year follow-up was an independent predictor of VLSF in the first-generation DES, whereas it was not in the CoCr-EES.

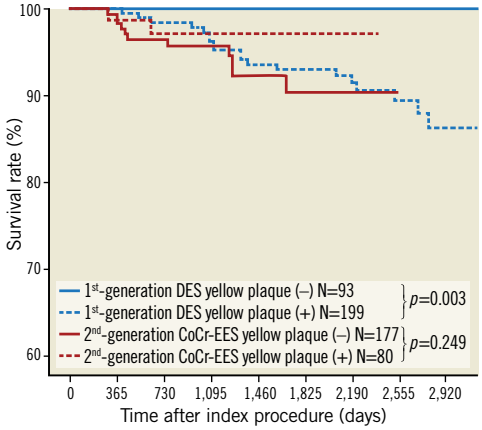
IMPACT OF IN-STENT YP ON VLSF IN FIRST-GENERATION DES AND SECOND-GENERATION CoCr-EES

Yellow plaque has commonly been detected at the culprit lesions of acute coronary syndrome patients[6,12]. Yellow plaques, especially those with a high yellow colour grade, are regarded as

Table 3. Multivariable Cox regression analysis to evaluate the risk factors for VLSF.

	Predictors	Hazard ratio (95% confidence interval)	*p*-value
1st-generation DES	Maximum yellow colour grade on angioscopy	2.604 [1.265-5.361]	0.009
	Low-density lipoprotein cholesterol reduction, mg/dL	0.984 [0.972-0.995]	0.006
2nd-generation CoCr-EES	Age, years	1.083 [1.008-1.163]	0.029
	Prolonged DAPT	3.717 [1.134-12.187]	0.030

A multivariate Cox proportional hazards analysis was performed to determine the independent determinants of VLSF stratified by first- and second-generation drug-eluting stents. The model was constructed with forward stepwise Cox multivariable regression analysis, entry, and removal criteria of 0.05 and 0.10, respectively. Age, sex, hypertension, diabetes mellitus, current smoking, stenting for acute coronary syndrome, serum high-density lipoprotein cholesterol at baseline, serum triglyceride at baseline, aspirin use, prolonged DAPT use, statin use, maximum stent diameter, total stent length, maximum yellow plaque colour grade, presence of thrombus, minimum neointima coverage grade, and reduction of serum low-density lipoprotein cholesterol from baseline to last follow-up were included as variables.



Number at risk	Index procedure	730 (2 years)	1,460 (4 years)	2,190 (6 years)	2,920 (8 years)
1st-g DES yellow plaque (–)	93	91	84	51	15
1st-g DES yellow plaque (+)	199	190	165	117	39
2nd-g CoCr-EES yellow plaque (–)	177	138	59	30	0
2nd-g CoCr-EES yellow plaque (+)	80	60	23	6	0

Figure 4. *Kaplan-Meier analysis for very late stent failure. Kaplan-Meier analysis for the primary endpoint (very late stent failure, a composite of cardiac death, target vessel myocardial infarction, and target lesion revascularisation) stratified by generation of DES and the presence of yellow plaque on coronary angioscopy.*

vulnerable plaques, because they have a high prevalence of disruption-causing thrombus formation and because they have thin fibrous caps[12].

Our previous study (the DESNOTE study) demonstrated that in-stent atherosclerosis, evaluated by the presence of YP one year after implantation of DES, was a risk factor for VLSF[1]. In the DESNOTE study, however, mainly the first-generation DES was evaluated (86%). The second-generation DES can provide better clinical outcomes than the first-generation DES[2-4,13], which drove us to conduct the current study. In the present study, as compared to the first-generation DES (68%), the prevalence of in-stent YP of the second-generation CoCr-EES XIENCE (31%) decreased to half, despite the fact that the rate of acute coronary syndrome was similar between the groups (22.8% vs 21.5%, p=0.721). This difference observed at follow-up would suggest that a certain part of the in-stent YP was associated with neoatherosclerosis. Progression of neoatherosclerosis might not be so apparent, at least at one-year imaging follow-up, in the CoCr-EES[14].

In contrast to the first-generation DES, no significant difference was found in VLSF between patients with in-stent YP and those without **(Figure 3, Figure 4)**. Progression of in-stent atherosclerosis seemed to be strongly associated with VLSF of the first-generation DES, whereas the impact of the progression of in-stent atherosclerosis would seem to be relatively small in the second-generation CoCr-EES. The reason for the negative impact of prolonged DAPT in the second-generation CoCr-EES is a matter of debate. Unlike the DAPT trial, in which myocardial infarction was reduced in the prolonged DAPT arm, TV-MI did not differ in the present study (prolonged DAPT 1/113 [0.9%] vs one-year DAPT 0/144 [0%], p=0.258)[15]. The negative impact of prolonged DAPT was driven by the high incidence of TLR in the prolonged DAPT patients (prolonged DAPT 9/113 [8.0%] vs one-year DAPT 3/144 [2.1%], p=0.027). It could be speculated that prolonged DAPT might be a surrogate representing physicians' considerations for high-risk procedures and/or angioscopic findings, and prolonged DAPT itself might not impact negatively on late clinical events. A further prospective large-scale study is warranted to investigate the predictors of VLSF of the newer-generation DES.

NEOATHEROSCLEROSIS FOLLOWING IMPLANTATION OF THE FIRST-GENERATION DES AND SECOND-GENERATION CoCr-EES

At one-year follow-up, the incidence of in-stent YP was significantly higher in the first-generation DES than in the second-generation CoCr-EES. A more modern strategy for dyslipidaemia in patients with CoCr-EES and the difference in lipid profile between groups probably influenced the lower prevalence of atherosclerotic change in neointima among lesions with CoCr-EES. Another possibility could be a device-related mechanism. Incompetent and dysfunctional endothelial coverage of the stented segment could contribute to the neoatherosclerosis[16]. Poorly formed cell junctions underlie the impaired barrier function of the endothelium, which allows a greater amount of lipoproteins to enter the subendothelial space, leading to the development of

neoatherosclerosis[17,18]. The expression of the platelet endothelial cell adhesion molecule-1 (PECAM-1) was greater in CoCr-EES when compared with the first-generation DES, sirolimus-eluting stent, paclitaxel-eluting stent, and zotarolimus-eluting stent in an animal model[19]. Therefore, second-generation DES CoCr-EES might not accelerate the formation of YP as compared to the first-generation DES[20]. The present study would support the validity of this concept in the human coronary artery during very long-term follow-up. On the other hand, human autopsy analysis presented a comparable frequency of neoatherosclerosis in CoCr-EES, sirolimus-eluting stents, and paclitaxel-eluting stents[21]. The study by Otsuka et al could suffer from the inevitable selection bias due to the principle of being a case control study. However, the study suggested that the main mechanism of the late stent failure could be the same (neoatherosclerosis), in cases where a late clinical event occurs. Progression of neoatherosclerosis might be slower in the second-generation DES than in the first-generation DES, at least up to one-year follow-up. Neoatherosclerosis of the newer-generation biodegradable polymer DES could be the next subject of scientific interest[22].

Study strength and limitations

The present study has, to date, the largest study population with the longest follow-up with prospective angioscopic evaluation in patients treated with first-generation DES and the best-in-class second-generation DES, XIENCE CoCr-EES.

However, some limitations of the present study need to be acknowledged. First, although the comparison in the first-generation DES was sufficiently powered, the comparison in the second-generation DES was underpowered in spite of the similar sample size between first- and second-generation DES, presumably due to the unexpected incidence of clinical events. Nevertheless, it is worth noting that significant interaction in the generation of DES existed. The results of the multivariate Cox regression analysis should be interpreted with caution and considered as hypothesis-generating. Second, patients with tortuous or small vessels not suitable for angioscopic examination were excluded, resulting in selection bias. Third, coronary angioscopy could not acquire the images of the whole vessel wall due to the blood flow and might have missed some yellow plaques and thrombus. Finally, although the amount of plaque may impact on VLSF, coronary angioscopy can evaluate only the surface of the plaque and cannot assess the plaque volume precisely.

Conclusions

The incidence of yellow plaque was smaller in the second-generation CoCr-EES than in the first-generation DES. The YP was independently associated with very late clinical events in the first-generation DES, whereas it was not in the second-generation CoCr-EES. The incidence of in-stent atherosclerosis identified as YP on angioscopy was lower and its impact on late clinical events appeared smaller in the CoCr-EES than in the first-generation DES. A further prospective large study is warranted to investigate the underlying mechanisms of the adverse events following newer-generation DES implantation.

Impact on daily practice

At one-year follow-up, the incidence of yellow plaque was significantly higher in the first-generation DES than in the second-generation CoCr-EES. Maximum yellow colour grade on coronary angioscopy at one-year follow-up was an independent predictor of future stent failure in the first-generation DES, whereas it was not in the second-generation CoCr-EES. Progression of neoatherosclerosis might be slower in the second-generation DES than in the first-generation DES, at least up to one-year follow-up. Neoatherosclerosis of the newer-generation biodegradable polymer DES could be the next subject of scientific interest.

Conflict of interest statement

Y. Sotomi and S. Nakatani have received speaker honoraria from Abbott Vascular Japan, Boston Scientific Japan, Terumo, Cardinal Health, and Medtronic. Y. Ueda has received a research grant and lecture fee from Abbott Vascular. The other authors have no conflicts of interest to declare.

References

1. Ueda Y, Matsuo K, Nishimoto Y, Sugihara R, Hirata A, Nemoto T, Okada M, Murakami A, Kashiwase K, Kodama K. In-Stent Yellow Plaque at 1 Year After Implantation Is Associated With Future Event of Very Late Stent Failure: The DESNOTE Study (Detect the Event of Very late Stent Failure From the Drug-Eluting Stent Not Well Covered by Neointima Determined by Angioscopy). *JACC Cardiovasc Interv.* 2015;8:814-21.

2. Stone GW, Rizvi A, Sudhir K, Newman W, Applegate RJ, Cannon LA, Maddux JT, Cutlip DE, Simonton CA, Sood P, Kereiakes DJ; SPIRIT IV Investigators. Randomized comparison of everolimus- and paclitaxel-eluting stents. 2-year follow-up from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV trial. *J Am Coll Cardiol.* 2011;58:19-25.

3. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Caputo R, Xenopoulos N, Applegate R, Gordon P, White RM, Sudhir K, Cutlip DE, Petersen JL; SPIRIT III Investigators. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. *Circulation.* 2009;119:680-6.

4. Onuma Y, Miquel-Hebert K, Serruys PW; SPIRIT II Investigators. Five-year long-term clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery disease: the SPIRIT II trial. *EuroIntervention.* 2013;8:1047-51.

5. Yokoyama S, Takano M, Yamamoto M, Inami S, Sakai S, Okamatsu K, Okuni S, Seimiya K, Murakami D, Ohba T, Uemura R, Seino Y, Hata N, Mizuno K. Extended follow-up by serial angioscopic observation for bare-metal stents in native coronary arteries: from healing response to atherosclerotic transformation of neointima. *Circ Cardiovasc Interv.* 2009;2:205-12.

6. Ueda Y, Asakura M, Yamaguchi O, Hirayama A, Hori M, Kodama K. The healing process of infarct-related plaques. Insights from 18 months of serial angioscopic follow-up. *J Am Coll Cardiol.* 2001;38:1916-22.

7. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M,

Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

8. Ueda Y, Nanto S, Komamura K, Kodama K. Neointimal coverage of stents in human coronary arteries observed by angioscopy. *J Am Coll Cardiol.* 1994; 23:341-6.

9. Sotomi Y, Onuma Y, Suwannasom P, Tateishi H, Tenekecioglu E, Zeng Y, Cavalcante R, Jonker H, Dijkstra J, Foin N, Koon JN, Collet C, de Winter RJ, Wykrzykowska JJ, Stone GW, Popma JJ, Kozuma K, Tanabe K, Serruys PW, Kimura T. Is quantitative coronary angiography reliable in assessing the lumen gain after treatment with the everolimus-eluting bioresorbable polylactide scaffold? *EuroIntervention.* 2016;12:e998-1008.

10. Higo T, Ueda Y, Oyabu J, Okada K, Nishio M, Hirata A, Kashiwase K, Ogasawara N, Hirotani S, Kodama K. Atherosclerotic and thrombogenic neointima formed over sirolimus drug-eluting stent: an angioscopic study. *JACC Cardiovasc Imaging.* 2009;2:616-24.

11. Suzuki S, Nakatani S, Sotomi Y, Shiojima I, Sakata Y, Higuchi Y. Fate of Different Types of Intrastent Tissue Protrusion: Optical Coherence Tomography and Angioscopic Serial Observations at Baseline and 9-Day and 3-Month Follow-Up. *JACC Cardiovasc Interv.* 2018;11:95-7.

12. Ueda Y, Ohtani T, Shimizu M, Hirayama A, Kodama K. Assessment of plaque vulnerability by angioscopic classification of plaque color. *Am Heart J.* 2004;148:333-5.

13. Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, Cutlip DE, Sudhir K, Hou L, Koo K, Stone GW. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv.* 2013;6:1263-6.

14. Nishimoto Y, Ueda Y, Sugihara R, Murakami A, Ueno K, Takeda Y, Hirata A, Kashiwase K, Higuchi Y, Yasumura Y. Comparison of angioscopic findings among second-generation drug-eluting stents. *J Cardiol.* 2017;70: 297-302.

15. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med.* 2014;371:2155-66.

16. Otsuka F, Byrne RA, Yahagi K, Mori H, Ladich E, Fowler DR, Kutys R, Xhepa E, Kastrati A, Virmani R, Joner M. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. *Eur Heart J.* 2015;36:2147-59.

17. Otsuka F, Finn AV, Yazdani SK, Nakano M, Kolodgie FD, Virmani R. The importance of the endothelium in atherothrombosis and coronary stenting. *Nat Rev Cardiol.* 2012;9:439-53.

18. Mitsutake Y, Ueno T, Ikeno F, Yokoyama S, Sasaki K, Nakayoshi T, Itaya N, Chibana H, Sasaki M, Fukumoto Y. Serial changes of coronary endothelial function and arterial healing after paclitaxel-eluting stent implantation. *Cardiovasc Interv Ther.* 2016;31:21-8.

19. Joner M, Nakazawa G, Finn AV, Quee SC, Coleman L, Acampado E, Wilson PS, Skorija K, Cheng Q, Xu X, Gold HK, Kolodgie FD, Virmani R. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol.* 2008;52:333-42.

20. Akazawa Y, Matsuo K, Ueda Y, Nishio M, Hirata A, Asai M, Nemoto T, Wada M, Murakami A, Kashiwase K, Kodama K. Atherosclerotic change at one year after implantation of Endeavor zotarolimus-eluting stent vs everolimus-eluting stent. *Circ J.* 2014;78:1428-36.

21. Otsuka F, Vorpahl M, Nakano M, Foerst J, Newell JB, Sakakura K, Kutys R, Ladich E, Finn AV, Kolodgie FD, Virmani R. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation.* 2014;129:211-23.

22. Ishihara T, Awata M, Iida O, Fujita M, Masuda M, Okamoto S, Nanto K, Kanda T, Tsujimura T, Uematsu M, Mano T. Satisfactory arterial repair 1 year after ultrathin strut biodegradable polymer sirolimus-eluting stent implantation: an angioscopic observation. *Cardiovasc Interv Ther.* 2019;34:34-9.