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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)

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ABSTRACT

OBJECTIVES This study examined whether coronary angioscopy-verified in-stent yellow plaque at 1 year after drug-eluting stent (DES) implantation is associated with future event of very late stent failure (VLSF).

BACKGROUND Atherosclerosis detected as yellow plaque by angioscopy has been associated with future events of acute coronary syndrome. Development of in-stent neoatherosclerosis is a probable mechanism of VLSF.

METHODS This study included 360 consecutive patients who received successful angioscopic examination at 1 year after implantation of a DES. They were clinically followed up for VLSF defined as cardiac death, acute myocardial infarction or unstable angina, or need for revascularization associated with the stent site.

RESULTS The follow-up interval was 1,558 ± 890 days (4.3 ± 2.4 years). The incidence of VLSF was significantly higher in the patients with yellow plaque than in those without (8.1% vs. 1.6%; log rank $p = 0.02$). Multivariable analysis revealed the presence of yellow plaque (hazard ratio [HR]: 5.38; $p = 0.02$) and absence of statin therapy (HR: 3.25; $p = 0.02$) as risks of VLSF.

CONCLUSIONS In-stent atherosclerosis evaluated by yellow plaque at 1 year after the implantation of DES and the absence of statin therapy were risks of VLSF. The underlying mechanism of VLSF appeared to be the progression of atherosclerosis as demonstrated by the yellow plaque. (J Am Coll Cardiol Intv 2015;8:814–21) © 2015 by the American College of Cardiology Foundation.

Although introduction of drug-eluting stent (DES) use substantially reduced early target lesion revascularization (TLR) as compared to bare-metal stent use by restricting development of neointima hyperplasia, DES have been associated with increased the risk of stent thrombosis and TLR after 1 year, that is, very late stent failure (VLSF) (1). The incidence of VLSF has been reduced with the use of newer DES than with first-generation DES (2–8), but VLSF remains an unresolved problem associated with DES and its mechanism is not well understood.

Although coronary angioscopy has not become a mainstream intravascular imaging technique, it has provided substantial information pertaining to macroscopic pathology in living patients. It has reliably detected atherosclerosis as yellow plaques, and especially those with high-grade yellow color have been regarded high-risk plaques and demonstrated to be associated with future coronary events

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by many clinical studies (9–12). Neoatherosclerosis or atherosclerosis progression has been proposed to be associated with VLSF (13). In the present prospective follow-up study, we examined whether the presence of in-stent yellow plaque at 1 year after DES implantation would predict the risk of subsequent VLSF associated with the original stent site.

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METHODS

STUDY DESIGN. We performed a single-center prospective follow-up study (DESNOTE [Detect the Event of Very Late Stent Failure From the Drug-Eluting Stent Not Well Covered by Neointima Determined by Angioscopy]) to demonstrate that the angioscopic findings of the stented segment, especially the presence of in-stent yellow plaque, at 1 year after DES implantation would be at risk of future VLSF.

All patients who received successful angioscopic examination at planned 1-year follow-up after the DES implantation in the native coronary artery without any event of earlier stent failure were enrolled from July 20, 2004 to August 8, 2013 and clinically followed up for the occurrence of VLSF. Yellow color, neointima coverage, and thrombus at the site of DES implantation were examined by angioscopy. VLSF was defined as follows: 1) cardiac death; 2) myocardial infarction or unstable angina at the target stent; or 3) TLR at the target stent. Written informed consent was obtained from all enrolled patients. Although angioscopic examination at 1-year follow-up was encouraged for all patients who received DES at our hospital, it was not performed in the following situations: 1) when an angioscopic specialist was not available; 2) when there was not adequate time for the examination; or 3) when the informed consent could not be obtained.

Catheterization was performed by femoral, brachial, or radial artery approach using a 6-F or 7-F sheath and catheters. Coronary angiogram was recorded by the Innova Cardiovascular imaging system (GE Healthcare Japan, Tokyo, Japan). Glycoprotein IIb/IIIa inhibitors were not used because they were not approved in Japan for clinical use. Cypher sirolimus-eluting stent (SES) (Cordis, Bridgewater, New Jersey) and Taxus paclitaxel-eluting stent (Boston Scientific, Natick, Massachusetts) were defined as the first-generation DES, and the other DES used were defined as second-generation DES.

The data on the patient demographics were acquired from the clinical record at the time of enrollment for the angioscopic examination (Table 1). Some data on the patient background were additionally acquired at the end of follow-up. Lipid profile was recorded with low-density lipoprotein cholesterol calculated from high-density lipoprotein cholesterol and triglyceride levels. Hypertension was defined as the blood pressure >140/90 mm Hg or current antihypertensive drug use. Diabetic patients were defined as the patients with fasting blood glucose >126 mg/dl or those already taking oral drugs for diabetes

ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

HR = hazard ratio

SES = sirolimus-eluting stent(s)

TLR = target lesion revascularization

VLSF = very late stent failure

ZES = zotarolimus-eluting stent(s)

TABLE 1 Patient Characteristics

	All (n = 360)	YP (n = 235)	No YP (n = 125)	p Value
Male	297 (83)	195 (83)	102 (82)	0.7
Age, yrs	66 ± 9	66 ± 8	67 ± 10	0.1
Risk factor				
Diabetes mellitus	148 (41)	92 (39)	56 (45)	0.3
Hypertension	303 (84)	193 (82)	110 (88)	0.1
Hypercholesterolemia	313 (87)	202 (86)	111 (89)	0.5
Current smoking	57 (16)	39 (17)	18 (15)	0.6
Body mass index	25 ± 3	25 ± 3	25 ± 4	0.1
Diagnosis for stenting				0.5
ACS	62 (17)	43 (18)	19 (15)	
Non-ACS	298 (83)	192 (82)	106 (85)	
Target vessel				0.4
Left anterior descending coronary artery	166 (46)	100 (43)	66 (53)	
Left circumflex coronary artery	53 (15)	36 (15)	17 (14)	
Right coronary artery	141 (39)	99 (42)	42 (33)	
Stent type				<0.001
Cypher SES	224 (62)	163 (69)	61 (49)	
Taxus PES	68 (19)	36 (15)	32 (26)	
Endeavor ZES	18 (5)	6 (3)	12 (10)	
Xience EES	39 (11)	21 (9)	18 (14)	
Nobori BES	11 (3)	9 (4)	2 (2)	
Stent diameter, mm	3.0 ± 0.4	3.0 ± 0.4	3.0 ± 0.3	0.1
Total stent length, mm	26 ± 15	27 ± 16	25 ± 12	0.2
Serum lipid profile, mg/dl				
Total cholesterol	180 ± 33	182 ± 34	176 ± 32	0.1
Low-density lipoprotein cholesterol	99 ± 30	102 ± 31	95 ± 28	0.04
High-density lipoprotein cholesterol	49 ± 12	50 ± 12	48 ± 13	0.1
Triglycerides	157 ± 112	151 ± 98	169 ± 134	0.1
Angioscopic finding				
Yellow plaque	235 (65)	235 (100)	0 (0)	N/A
Thrombus	99 (28)	82 (35)	17 (14)	<0.001
Minimal neointima coverage grade	0.5 ± 0.6	0.5 ± 0.5	0.6 ± 0.6	0.6
Minimal neointima coverage grade	1.6 ± 0.5	1.6 ± 0.5	1.5 ± 0.5	0.9
Medication				
Statin	267 (74)	173 (74)	94 (75)	0.8
Aspirin	338 (94)	220 (94)	118 (94)	0.8
Clopidogrel/ticlopidine	307 (85)	196 (83)	111 (89)	0.2

Values are n (%) and mean ± SD.

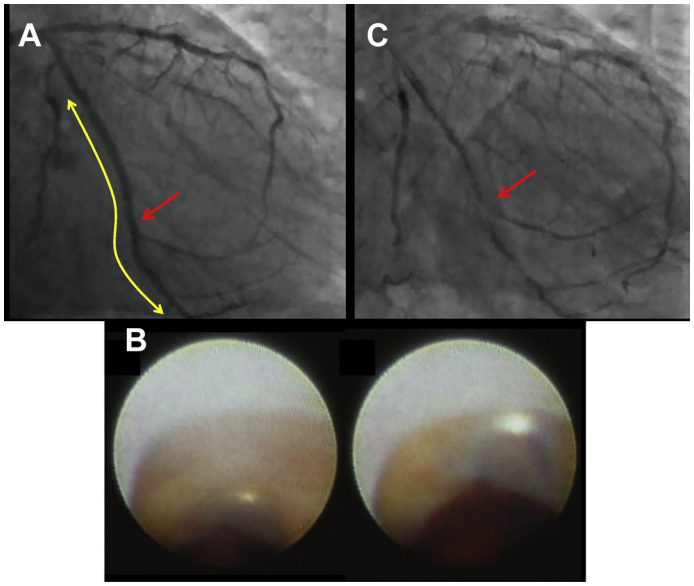
ACS = acute coronary syndrome(s); BES = biolimus-eluting stent(s); EES = everolimus-eluting stent(s); N/A = not applicable; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); YP = yellow plaque; ZES = zotarolimus-eluting stent(s).

mellitus or receiving insulin therapy. Acute coronary syndrome included acute myocardial infarction with or without ST-segment elevation defined by the Joint European Society of Cardiology/American College of Cardiology Committee and unstable angina was defined according to the Braunwald classification. This study was approved by the Osaka Police Hospital Ethical Committee.

ANGIOSCOPIC EXAMINATION AND EVALUATION. The RX-3310A and MV-5010A nonobstructive coronary angioscopes (Machida, Tokyo, Japan) and DAG-2218 LN optic fiber (Machida) were used. Angioscopic observation of the stented lesions was done while blood was cleared away from the viewing area by the injection of 3% dextran-40 as we previously reported (14). Yellow color was classified into 4 grades (0: white, 1: slight yellow, 2: yellow, and 3: intensive yellow) compared with the standard colors as we previously reported (9,10). Neointima coverage was classified into 3 grades (0: no coverage, 1: poor coverage, 2: complete coverage) as we previously reported (15,16). Thrombus was defined as white or red material that had cotton-like or ragged appearance or that presented fragmentation with or without protrusion into lumen or adherent to the luminal surface. Maximum and minimum neointima coverage grade, maximum yellow color grade, and presence or absence of thrombus was determined for each stented lesion. Presence of yellow plaque was defined as the maximum yellow color grade ≥2. Two specialists of angioscopy, who were blinded to patients' characteristics, evaluated the angioscopic images. In the case of disagreement, a third reviewer served as an arbitrator. The inter observer and intraobserver reproducibility for the interpretation of angioscopic images (16) was 95% and 95% for stent coverage, 85% and 95% for plaque color, and 90% and 100% for thrombus, respectively.

STATISTICAL ANALYSIS. Continuous data were presented as mean ± SD. Patients were divided into 2 groups according to the presence or absence of yellow plaque at the site of stent implantation. Comparisons between the groups were performed by unpaired Student *t*-test or chi-square test. The incidence of VLSF was compared between the groups using Kaplan-Meier methods and log rank test. Multivariable Cox proportional hazards regression analysis was performed to determine the risk factors of VLSF; the variables included were as follow: stent type (first vs. second generation); age; sex; hypertension; diabetes mellitus; current smoking; stenting for acute coronary syndrome; serum low-density lipoprotein cholesterol; serum high-density lipoprotein cholesterol; serum triglyceride; aspirin use; ticlopidine/clopidogrel use; statin use; stent diameter; total stent length; presence of yellow plaque; presence of thrombus; and minimum neointima coverage grade. Proportionality assumptions were tested by graphic approaches. A p value of <0.05 was regarded as statistically significant. Analysis was performed with SPSS (version 16.0 J for Windows, SPSS Inc., Chicago, Illinois).

FIGURE 1 A Case of the Patient With Yellow Plaque Who Experienced VLSF



A 58-year-old male patient who had been treated by Cypher sirolimus eluting stent for stable effort angina received 1-year follow-up catheterization. Angiography **(A)** revealed no in-stent restenosis in the circumflex coronary artery and angioscopy **(B)** detected yellow plaque in the stent **(red arrow)**. The **yellow line** indicates the segment where the stent was implanted. The patient experienced recurrence of effort angina at 23 months after the follow-up examination and received catheterization again. Then, angiography **(C)** revealed in-stent restenosis especially at the site where yellow plaque had been detected at 1-year follow-up **(red arrow)**. VLSF = very late stent failure.

RESULTS

PATIENTS' CHARACTERISTICS. During the study period, 360 patients were enrolled, and 235 (65%) of them had yellow plaque. The follow-up interval was 1,558 ± 890 days (4.3 ± 2.4 years). The patient demographics presented in **Table 1** compare patients with and without yellow plaque. The patient characteristics were similar between the groups except that the distribution of stent type was different, and that serum low-density lipoprotein cholesterol was higher and the frequency of thrombus was higher in the

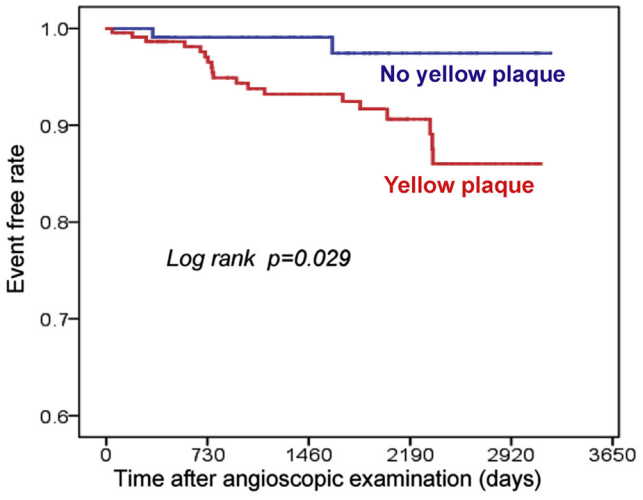
patients with yellow plaque than in those without. A case of the patient with yellow plaque who experienced VLSF is presented in Figure 1.

INCIDENCE OF VLSF. The incidence of VLSF was significantly higher in the patients with in-stent yellow plaque than in those without during the follow-up interval of 4.3 ± 2.4 years (8.1% vs. 1.6%; log rank p = 0.02) (Figure 2). The incidence of VLSF and TLR were both significantly higher in the patients with yellow plaque than in those without, although the incidence of cardiac death, acute myocardial infarction, unstable angina, and the combination of cardiac death, acute myocardial infarction, and unstable angina were not significantly different between the groups (Table 2). The sensitivity, specificity, positive predictive value, and negative predictive value of yellow plaque for VLSF were 90.5%, 36.3%, 8.1%, and 98.4%, respectively.

RISK FACTORS FOR THE OCCURRENCE OF VLSF. Multivariable Cox regression analysis revealed that presence of yellow plaque, absence of statin therapy, smaller stent diameter, and serum low-density lipoprotein cholesterol level were significantly correlated to VLSF risk (Table 3).

ADDITIONAL ANALYSIS USING THE DATA AT THE END OF FOLLOW-UP. The serum lipid profile and medications at the end of follow-up were collected from the clinical record (Table 4). The serum low-density lipoprotein cholesterol was still significantly higher in the patients with yellow plaque. Multivariable Cox regression analysis using these data revealed that the presence of yellow plaque and the increase in the serum low-density lipoprotein cholesterol level from baseline to the end of follow-up were the significant risk factors for VLSF (Table 5).

FIGURE 2 Kaplan-Meier Analysis on the Incidence of VLSF



N	0	730 (2 yrs)	1460 (4 yrs)	2190 (6 yrs)	2920 (8 yrs)
Yellow plaque	235	181	145	64	17
No yellow plaque	125	89	70	23	7

The incidence of very late stent failure (VLSF) was significantly higher in the patients with in-stent yellow plaque than in those without during the follow-up interval of 1,558 ± 890 days (4.3 ± 2.4 years) (8.1% vs. 1.6%; log rank p = 0.029).

DISCUSSION

We observed a significant association between the angioscopic findings of yellow plaque in the DES-implanted lesion at 1 year after implantation and the subsequent VLSF. The incidence of VLSF was significantly higher in the patients with yellow plaque than in those without during the follow-up period of more than 4 years; a multivariable analysis demonstrated presence of yellow plaque (hazard ratio [HR]: 5.38; p = 0.02) and absence of statin therapy (HR: 3.25; p = 0.02) as risks of VLSF. Because statin therapy is known to reduce the yellow color of plaques, these findings suggest that the progression of yellow plaque would be an important mechanism for the occurrence of VLSF. This is the first study that linked angioscopic identification of in-stent yellow plaque to actual hard events of VLSF.

YELLOW PLAQUE FORMATION AFTER DES IMPLANTATION. Higo et al. (15) had originally reported that in living humans Cypher-SES accelerated the formation of yellow plaque at 10 months after implantation. A recent histopathologic study by Nakazawa et al. (13) confirmed the presence of neoatherosclerosis after bare-metal stent and DES implantation with

TABLE 2 Incidence of Primary Endpoint and its Components

	All	YP	No YP	p Value
Primary endpoint	21 (5.8)	19 (8.1)	2 (1.6)	0.01
Combination of cardiac death, acute myocardial infarction, and unstable angina	11 (3.1)	10 (4.3)	1 (0.8)	0.07
Components of primary endpoint				
Cardiac death	5 (1.4)	5 (2.1)	0 (0)	0.1
Acute myocardial infarction	3 (0.8)	2 (0.9)	1 (0.8)	0.9
Unstable angina	3 (0.8)	3 (1.3)	0 (0)	0.2
Target lesion revascularization	15 (4.2)	14 (6.0)	1 (0.8)	0.02

Values are n (%).
YP = yellow plaque.

TABLE 3 Multivariable Cox Regression Analysis To Evaluate the Risk Factors of VLSF

	HR (95% CI)	p Value
Presence of yellow plaque	5.38 (1.24–23.3)	0.02
Without statin use	3.25 (1.18–8.92)	0.02
Stent diameter, mm	0.27 (0.08–0.90)	0.03
Low-density lipoprotein cholesterol, mg/dl	0.97 (0.96–0.99)	<0.001

Stent type (first vs. second generation), age, sex, hypertension, diabetes mellitus, current smoking, stenting for acute coronary syndrome, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, serum triglyceride, aspirin use, ticlopidine/clopidogrel use, statin use, stent diameter, total stent length, presence of yellow plaque, presence of thrombus, and minimum neointima coverage grade were included as variables.

CI = confidence interval; HR = hazard ratio.

the shorter implantation duration for DES to develop neoatherosclerosis. Cypher SES is known to accelerate the formation of yellow plaque; Xience everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, California) does not change the yellow color of the stented lesion; and Endeavor zotarolimus-eluting stent (ZES) (Medtronic, Minneapolis, Minnesota) (17) leads to formation of thick fibrous white neointima similar to BMS. The formation of thick fibrous white neointima over atherosclerotic yellow lesions might contribute to stability of plaques. Xience EES has a very thin neointima and may not shield the yellow plaque under the stent; however, it does not accelerate the formation of yellow plaque.

Yellow plaque formation could be accelerated by various coronary risk factors and reduced by medical therapy like statins. Therefore, in combination with these systemic factors and medications, the characteristics of each DES may influence the formation of yellow plaque at the stent site.

TABLE 4 Patients' Characteristics at the End of Follow-Up

	All	YP	No YP	p Value
Serum lipid profile, mg/dl				
Low-density lipoprotein cholesterol	87 ± 26	90 ± 28	81 ± 22	0.003
High-density lipoprotein cholesterol	46 ± 13	47 ± 12	45 ± 13	0.1
Triglycerides	138 ± 91	137 ± 76	139 ± 115	0.8
Low-density lipoprotein cholesterol change*	−12 ± 31	−11 ± 34	−13 ± 24	0.6
High-density lipoprotein cholesterol change*	−3 ± 9	−3 ± 9	−3 ± 9	0.7
Triglyceride change*	−20 ± 94	−14 ± 87	−31 ± 106	0.1
Medication				
Statin	279 (78)	183 (78)	96 (77)	0.8
Aspirin	323 (90)	213 (91)	110 (88)	0.4
Clopidogrel/ticlopidine	247 (69)	159 (68)	88 (70)	0.6

Values are mean ± SD or n (%). *Change from baseline to the end of follow-up.

YP = yellow plaque.

INCIDENCE OF VLSF IN VARIOUS CLINICAL TRIALS. According to the results of clinical trials with up to 5-year follow-up available in previous reports and at ClinicalTrial.gov, TLR rates at 1 and 5 years are 4.9% and 9.4% in Cypher SES (18,19); 4.4% and 9.1% in Taxus paclitaxel-eluting stents (20,21); 5.9% and 7.5% in Endeavor ZES (22,23); and 3.4% and 8.9% in Xience EES (24), respectively. The VLSF as shown by the yearly TLR between 1 and 5 years is 1.1%, 1.2%, 0.4%, and 1.4% per year in Cypher SES, Taxus paclitaxel-eluting stents, Endeavor ZES, and Xience EES, respectively, which favors Endeavor ZES as the DES to use. A recent report (3) clarified that, in the ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions), although higher angiographic restenosis was observed with Endeavor ZES than with Cypher SES at 9 months, cumulative outcomes through 5 years demonstrated that the composite endpoint of MACE, cardiac death, and myocardial infarction, were lower with Endeavor ZES use than with Cypher SES use. Furthermore, the rate of TLR beyond 9 months was significantly lower in Endeavor ZES than with Cypher SES. The higher incidence of VLSF with Cypher SES than with Endeavor ZES may possibly be explained by the fact that Cypher SES increases the yellow color of the lesion and Endeavor ZES reduces it.

ASSOCIATION BETWEEN ANGIOSCOPIC FINDINGS AND FUTURE EVENTS OF VLSF. Development of neoatherosclerosis has been proposed as a cause of very late stent thrombosis (25) and of restenosis after DES implantation (26). As demonstrated in the present analysis, the presence of yellow plaque at 1 year was a significant risk of future VLSF, although the presence of thrombus or the minimum neointima coverage grade was not detected as a significant risk. The absence of statin therapy also presented a significant risk, suggesting that prevention of atherosclerosis progression would be an important mechanism for the prevention of VLSF. This is consistent with a report from the CREDO-Kyoto Registry Cohort 2 (Comparison of three-year outcome after PCI and CABG stratified by the SYNTAX score in patients with triple vessel coronary artery disease: an observation from the CREDO-Kyoto PCI/CABG registry Cohort-2) that statin use was associated with the lower risk of late TLR after Cypher SES implantation (27). Being consistent with a previous report (28), the smaller stent diameter was also a risk for

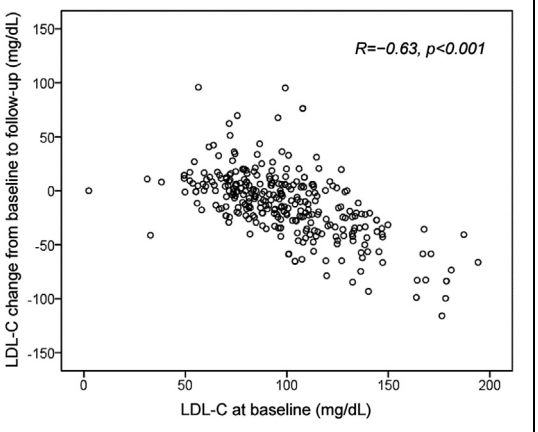
TABLE 5 Multivariable Cox Regression Analysis To Evaluate the Risk Factors of VLSF Including the Data at the End of Follow-Up

	HR (95% CI)	p Value
Presence of yellow plaque	8.55 (1.13–66.7)	0.03
Low-density lipoprotein cholesterol change from baseline to the end of follow-up, mg/dl	1.03 (1.01–1.04)	0.001
Low-density lipoprotein cholesterol at the end of follow-up, mg/dl	0.98 (0.97–1.00)	0.07
Stent diameter, mm	0.28 (0.08–1.00)	0.05

Stent type (first vs. second generation), age, sex, hypertension, diabetes mellitus, current smoking, stenting for acute coronary syndrome, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, serum triglyceride, serum low-density lipoprotein cholesterol change from baseline to follow-up, serum high-density lipoprotein cholesterol change from baseline to follow-up, serum triglyceride change from baseline to follow-up, aspirin use, ticlopidine/clopidogrel use, statin use, stent diameter, total stent length, presence of yellow plaque, presence of thrombus, and minimum neointima coverage grade were included as variables.

Abbreviations as in Table 3.

FIGURE 3 Correlation Between the LDL-C at Baseline and Its Change by Follow-Up



The value of low-density lipoprotein cholesterol (LDL-C) measured at the time of angioscopic examination (baseline) was inversely correlated with its change by the time of follow-up ($R = -0.63$; $p < 0.001$). Therefore, the patients with the higher LDL-C level at baseline possibly achieved the lower risk of VLSF. The higher the value, the patient and doctor might have made a stronger effort to reduce it.

VLSF in the present study. Although it appeared strange that the higher low-density lipoprotein cholesterol was associated with the lower risk of VLSF, it might be explained by the fact that the value of low-density lipoprotein cholesterol used in the multivariable analysis was measured at the time of angioscopic examination and that the higher value was reduced more by the end of clinical follow-up ($R = -0.63$; $p < 0.001$) (Figure 3), possibly achieving the lower risk of VLSF. The higher the value, both the patient and doctor might have made a stronger effort to reduce it. When the data at the end of follow-up were included in the multivariable analysis, the presence of yellow plaque and the increase in the serum low-density lipoprotein cholesterol level from baseline to the end of follow-up were selected as being at significant risk of VLSF. This suggests that the extent of baseline in-stent atherosclerosis and its progression induced by increased serum low-density lipoprotein cholesterol level might have determined the occurrence of VLSF.

ATHEROSCLEROSIS DEFINED BY YELLOW PLAQUE EVALUATED BY ANGIOSCOPIC STUDIES. Angioscopically detected yellow plaque has been commonly detected at the culprit lesions of spontaneous acute coronary syndrome (10). Yellow plaques, especially those with high yellow color grade, are regarded as vulnerable plaques, because they have high prevalence of disruption-causing thrombus formation and because they have thin fibrous caps (9,29). The patients with more yellow plaques in their coronary arteries have been demonstrated to have higher risk of future acute coronary syndrome by a prospective study (30).

Like the culprit lesions of spontaneous acute coronary syndrome, the culprit lesions of very late stent thrombosis are known to have disrupted yellow plaque (31). Furthermore, the culprit lesions of both thrombosis and restenosis in the very late phase after stent implantation have been reported by angioscopic and optical coherence tomography studies to have advanced atherosclerosis (11,32,33). Therefore, the results of DESNOTE study are very important and informative, which have demonstrated that having yellow plaque at the site of stent implantation is a risk of future VLSF, suggesting that regression of yellow plaque by statin or other antiatherosclerotic therapy may be an effective treatment to prevent VLSF. Furthermore, the intracoronary imaging at 1 year after implantation of DES may identify the risk of future VLSF before the long-term clinical data become available. We would like to emphasize again that this is the first study to link angioscopic identification of in-stent yellow plaque to the actual hard events of VLSF in the future.

STUDY LIMITATIONS. Although we included all types of DES available, more first-generation DES were included than the newer DES during the study period. The data on the newer DES may become available in the future. Although the patients with

tortuous or small vessels not suitable for angioscopic examination or those with renal dysfunction were not excluded, they were unlikely to be included. The number of patients included was too small for the more detailed subanalysis. Indeed, among the components of primary endpoints, only TLR was significantly different between the groups, whereas the study at this time point might be underpowered to clarify whether the other components were truly different. With a larger study population and longer follow-up interval, this study will clarify these questions in the future. Angioscopy could not acquire the images of whole vessel wall due to the blood flow and might have missed some yellow plaques.

CONCLUSIONS

In-stent atherosclerosis evaluated by the presence of yellow plaque at 1 year after the implantation of DES and the absence of statin therapy was demonstrated as a risk of VLSF. A main mechanism of VLSF was suggested to be the progression of atherosclerosis as shown by yellow plaque.

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PERSPECTIVES

WHAT IS KNOWN? The findings of neoatherosclerosis are often detected at the sites of DES failure. However, its correlation to the occurrence of future event is unknown.

WHAT IS NEW? This study demonstrated that the in-stent atherosclerosis evaluated by yellow plaque at one year after the implantation of DES and the absence of statin therapy were the risks of very-late DES failure, suggesting that the underlying mechanism of very-late DES failure appeared to be the progression of atherosclerosis as demonstrated by the yellow plaque.

WHAT IS NEXT? Because the presence of in-stent atherosclerotic yellow plaque at one year after the implantation of DES and the absence of statin therapy were identified in this study as the risk of future DES failure, the medical treatments to prevent the formation of atherosclerotic yellow plaque would be expected to reduce the risk of DES failure. Therefore, the statin therapy and other anti-atherosclerotic therapies would be recommended for the prevention of very-late DES failure. Large randomized trials are required to test if the aggressive anti-atherosclerotic therapies can really reduce the incidence of very-late DES failure.

REFERENCES

1. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.

2. Eisenstein EL, Wijns W, Fajadet J, et al. Long-term clinical and economic analysis of the Endeavor drug-eluting stent versus the Driver bare-metal stent: 4-year results from the ENDEAVOR II trial (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv 2009;2:1178–87.

3. Kandzari DE, Mauri L, Popma JJ, et al. Late-term clinical outcomes with zotarolimus- and sirolimus-eluting stents: 5-year follow-up of the ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv 2011;4:543–50.

4. Leon MB, Kandzari DE, Eisenstein EL, et al., for the ENDEAVOR IV Investigators. Late safety, efficacy, and cost-effectiveness of a zotarolimus-eluting stent compared with a paclitaxel-eluting stent in patients with de novo coronary lesions: 2-year follow-up from the ENDEAVOR IV trial (Randomized, Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv 2009;2:1208–18.

5. Garg S, Serruys P, Onuma Y, et al., for the SPIRIT II Investigators. 3-year clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: the SPIRIT II trial (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv 2009;2:1190–8.

6. Stone GW, Midei M, Newman W, et al., for the 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.

7. Stone GW, Rizvi A, Sudhir K, et al., for the 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.

8. Onuma Y, Miquel-Hebert K, Serruys PW, for the 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.

9. 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.

10. 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.

11. Yokoyama S, Takano M, Yamamoto M, et al. 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.

12. Hasegawa K, Tamai H, Kyo E, et al. Histopathological findings of new in-stent lesions developed beyond five years. Catheter Cardiovasc Interv 2006;68:554–8.

13. Nakazawa G, Vorpahl M, Finn AV, Narula J, Virmani R. One step forward and two steps back with drug-eluting-stents: from preventing restenosis to causing late thrombosis and nouveau atherosclerosis. J Am Coll Cardiol Img 2009;2:625–8.

14. 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.

15. Higo T, Ueda Y, Oyabu J, et al. Atherosclerotic and thrombogenic neointima formed over sirolimus drug-eluting stent: an angioscopic study. J Am Coll Cardiol Img 2009;2:616–24.

16. Oyabu J, Ueda Y, Ogasawara N, Okada K, Hirayama A, Kodama K. Angioscopic evaluation of neointima coverage: sirolimus drug-eluting stent versus bare metal stent. Am Heart J 2006;152:1168–74.

17. Matsuo K, Ueda Y, Nishio M, et al. A higher colour grade yellow plaque was detected at one year after implantation of an everolimus-eluting stent than after a zotarolimus-eluting stent. Heart Asia 2013;5:192–6.

18. Holmes DR Jr., Leon MB, Moses JW, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation 2004;109:634–40.

19. Weisz G, Leon MB, Holmes DR Jr., et al. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) Trial. J Am Coll Cardiol 2009;53:1488–97.

20. Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. Circulation 2004;109:1942–7.

21. Ellis SG, Stone GW, Cox DA, et al., for the TAXUS IV Investigators. Long-term safety and efficacy with paclitaxel-eluting stents: 5-year final results of the TAXUS IV clinical trial (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent). J Am Coll Cardiol Intv 2009;2:1248–59.

22. Fajadet J, Wijns W, Laarman GJ, et al., for the ENDEAVOR II Investigators. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. Circulation 2006;114:798–806.

23. Fajadet J, Wijns W, Laarman GJ, et al. Long-term follow-up of the randomised controlled trial to evaluate the safety and efficacy of the zotarolimus-eluting driver coronary stent in de novo native coronary artery lesions: five year outcomes in the ENDEAVOR II study. EuroIntervention 2010;6:562–7.

24. Stone GW, Midei M, Newman W, et al., for the SPIRIT III Investigators. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903–13.

25. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41.

26. Liistro F, Stankovic G, Di Mario C, et al. First clinical experience with a paclitaxel derivate-eluting polymer stent system implantation for in-stent restenosis: immediate and long-term clinical and angiographic outcome. Circulation 2002;105:1883–6.

27. Natsuaki M, Nakagawa Y, Morimoto T, et al., for the CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators. Impact of statin therapy on late target lesion revascularization after sirolimus-eluting stent implantation (from the CREDO-Kyoto Registry Cohort-2). Am J Cardiol 2012;109:1387–96.

28. Choi IJ, Park HJ, Seo SM, et al. Predictors of early and late target lesion revascularization after drug-eluting stent implantation. J Interv Cardiol 2013;26:137–44.

29. Kubo T, Imanishi T, Takarada S, et al. Implication of plaque color classification for assessing plaque vulnerability: a coronary angioscopy and optical coherence tomography investigation. J Am Coll Cardiol Intv 2008;1:74–80.

30. Ohtani T, Ueda Y, Mizote I, et al. Number of yellow plaques detected in a coronary artery is associated with future risk of acute coronary syndrome: detection of vulnerable patients by angioscopy. J Am Coll Cardiol 2006;47:2194–200.

31. Matsuo K, Ueda Y, Nishio M, et al. Very late stent thrombosis at 2.5 years after sirolimus-eluting stent implantation with prior angioscopic image of culprit lesion: a case report. J Cardiol Cases 2012;5:e12–5.

32. Kang SJ, Lee CW, Song H, et al. OCT analysis in patients with very late stent thrombosis. J Am Coll Cardiol Img 2013;6:695–703.

33. Kang SJ, Mintz GS, Akasaka T, et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. Circulation 2011;123:2954–63.

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