博士学位論文

薬剤溶出性ステント留置後のステント内血栓の評価
―血管内視鏡検査と血小板機能検査を用いた検討―

近畿大学大学院
医学研究科医学系専攻

松浦 剛郎

Doctoral Dissertation

Impact of neointimal condition and platelet reactivity on intrastent thrombus at long-term follow-up after 2nd- and 3rd-generation drug-eluting stent implantation -Insights from a coronary angioscopy and pharmacodynamic study-

November 2020

Department of Cardiology, Major in Medical Sciences
Kindai University Graduate School of Medical Sciences

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博士学位論文

論　文　目　録

近畿大学大学院
医学研究科医学系専攻

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論　文　目　録

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学 位 論 文

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-Insights from a coronary angioscopy and pharmacodynamic study-
（薬剤溶出性ステント留置後のステント内血栓の評価
-血管内視鏡検査と血小板機能検査を用いた検討-）

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副　論　文

題　名

Importance of sympathetic nervous system activity during left ventricular functional recovery and its association with in-hospital complications in Takotsubo syndrome

Takero Matsuura MD, Masafumi Ueno, MD, PhD, Yoshitaka Iwanaga, MD, PhD
Shunichi Miyazaki, MD, PhD

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博士学位論文

論　文　要　旨

薬剤溶出性ステント留置後のステント内血栓の評価
―血管内視鏡検査と血小板機能検査を用いた検討―

令和 2 年 11 月

近　畿　大　学　大　学　院

医学研究科医学系専攻

松　浦　剛　郎

論 文 内 容 の 要 旨

【目的】
薬剤溶出性ステント留置後の患者において、ステント内血栓の存在と、ステントストラットの被膜状況と血小板反応性の関連を評価する。
【方法】
急性冠症候群に対して第 2・第 3 世代の薬剤溶出性ステントを留置した患者を対象に、追跡造影検査施行時に血管内視鏡検査と血小板機能検査を行う。血管内視鏡検査でステントストラットの被膜状況や内膜の色調やステント内血栓の有無を評価する。また血小板機能検査も同時に行い、血小板反応性を評価する。
【結果】
第 2 世代薬剤溶出性ステントを留置された患者 50 例と、第 3 世代薬剤溶出性ステントを留置された患者 50 例の、連続 100 症例を対象とした。第 3 世代の薬剤溶出性ステントを留置された群では、第 2 世代の薬剤溶出性ステントを留置された群と比較して、有意にステントストラットは良好に被膜されており内膜の色調も有意に白色であった。またステント内血栓も少ない傾向にあった。ステント内血栓を認める群はステント内血栓を認めない群と比較して、血小板反応性が有意に亢進していた。多変量解析ではステントストラットの露出と血小板反応性の亢進が、ステント内血栓の独立した予測因子であった。また、ステントストラットが露出と血小板反応性の亢進の両方を認める群と、その内の片方だけを認める群と、両方とも認めない群とで比較した場合、両方を認める群で有意にステント内血栓を高頻度に認めた。
【考察】
過去の報告で、ステント内血栓の存在は将来的なステント血栓症と関連していると言われている。本研究での結果から、ステントストラットの露出に代表される局所的な要因と、血小板反応性の亢進に代表される全身の要因との両方ともが、ステント内血栓の存在と関連していると考えられる。
【結論】
第 3 世代の薬剤溶出性ステントは第 2 世代の薬剤溶出性ステントと比較して、ステントストラットは良好に被膜されていた。またステントストラットの被膜に代表される局所的な要因と、血小板反応性の亢進に代表される全身の問題の両方ともが、将来的な遅発性ステント血栓症に関与しているかもしれない。

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課博

同　意　書

2020 年 11 月 13 日

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ORIGINAL ARTICLE
Imaging

Impact of Neointimal Condition and Platelet Reactivity on Intrastent Thrombus at Long-Term Follow-up After 2nd- and 3rd-Generation Drug-Eluting Stent Implantation

— Insights From a Coronary Angioscopy and Pharmacodynamic Study —

Takero Matsuura, MD; Masafumi Ueno, MD, PhD; Heitaro Watanabe, MD, PhD; Masakazu Yasuda, MD, PhD; Toru Takase, MD, PhD; Takashi Nakamura, MD, PhD; Kenji Yamaji, MD, PhD; Yoshitaka Iwanaga, MD, PhD; Shunichi Miyazaki, MD, PhD; Gaku Nakazawa, MD, PhD

Background: Although the incidence of very late stent failure (VLSF) is reduced with newer generation drug-eluting stent (DES), the mechanism of VLSF has not been fully explored.

Methods and Results: This study evaluated both local vascular healing using coronary angioscopy and systemic factors determined by platelet reactivity at long-term follow-up after 2nd- and 3rd-generation DES implantation in patients with acute coronary syndrome. Coronary angioscopy was performed to assess neointimal coverage (NIC), yellow color (YC) grade and presence of thrombus. The obtained findings were compared with 2nd- and 3rd-DES. Platelet aggregation was assessed by light transmittance aggregometry. 100 consecutive patients were prospectively enrolled: 2nd- (n=50) and 3rd-DES (n=50). 3rd-DES patients had significantly higher NIC grade and lower YC grade compared with 2nd-DES. The presence of thrombus was tended to be lower with 3rd-DES than with 2nd-DES (8% vs. 18%, P=0.11). Patients with thrombus had significantly higher maximum platelet aggregation and higher prevalence of high on-treatment platelet reactivity (HPR) than those without thrombus. Multivariable analysis showed stent strut exposure and HPR as independent predictors of thrombus.

Conclusions: Newer generation DES contribute to better vascular healing depending on the degree of neointimal coverage. In addition to local factors at the stented lesion, systemic factors such as degree of platelet reactivity might also contribute to VLSF.

Key Words: Coronary angioscopy; In-stent thrombus; Neointimal coverage; Platelet reactivity

Drug-eluting stents (DES) have substantially reduced the need for early target lesion revascularization (TLR) compared with bare-metal stents (BMS) by inhibiting neointima hyperplasia.[1] However, the early generation DES have been associated with an increased risk of very late stent failure (VLSF) due to stent thrombosis and TLR after 1 year.[2–4] Although the incidence of VLSF is reduced with newer generation DES, it remains an unresolved problem and its mechanism has not been fully explored.[5,6] As one of the reasons, the lifelong presence of a durable polymer (DP) might induce arterial wall inflammation, delayed vascular healing, and long-term endothelial dysfunction.[7] To overcome this, 3rd-generation (3rd-) DES were developed with an ultrathin abluminal biodegradable polymer (BP) coating that is completely absorbed within 4 months, and have shown favorable clinical outcomes in large clinical trials.[8,9] Evaluating the differences in intrastent conditions among each era of stents using intravascular imaging is important for the optimal medical management of patients with coronary artery disease (CAD). Of the available imaging techniques, coronary angioscopy is the only modality that can directly visualize local conditions, and provide insights on the pathophysiology and treatment of CAD.

In addition, antiplatelet therapy also plays a pivotal role in preventing acute and late stent thrombosis (ST) as a

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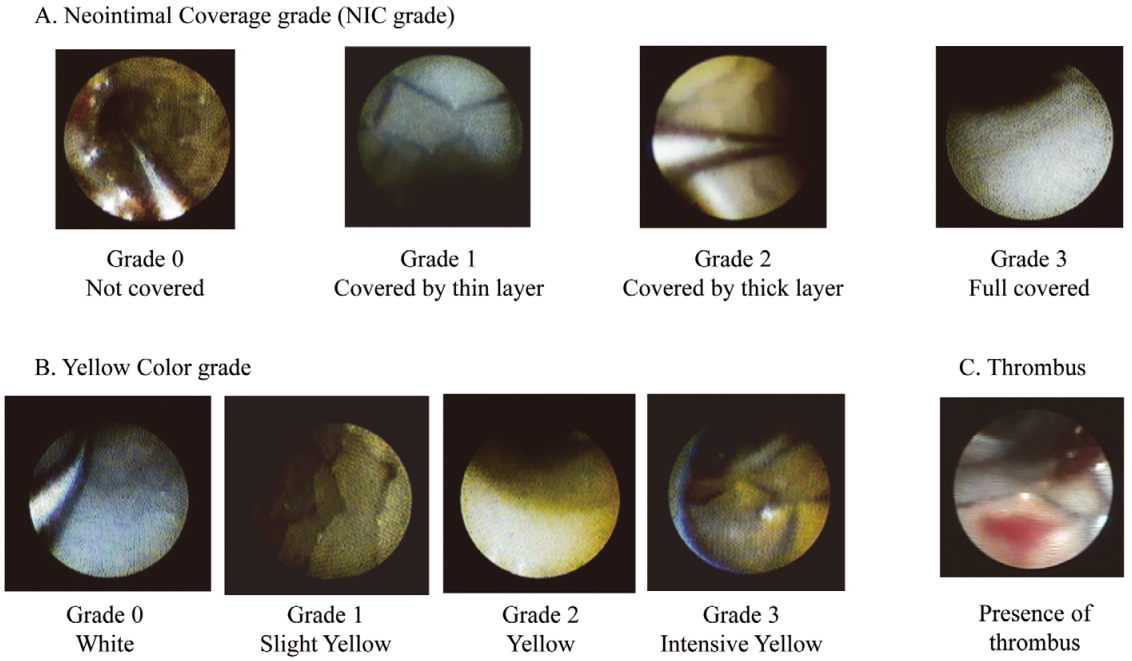

Figure 1. Definitions of neointimal coverage (NIC) grade, yellow color (YC) grade and intra-stent thrombus. (**A**) NIC grade: 0, stent struts fully visible; 1, stent struts visible through thin neointima; 2, stent struts slightly visible through thick neointima; 3, stent struts not visible under neointima. (**B**) YC grade: 0, white; 1, slight yellow; 2, yellow; 3, intense yellow. (**C**) Representative case of intrastent thrombus.

systemic factor after DES implantation.[10] Several investigations have demonstrated the presence of high on-treatment platelet reactivity (HPR) using platelet function tests, despite the use of dual antiplatelet therapy (DAPT), and that it is an independent predictor of adverse outcomes, including ST.[11,12]

Therefore, the purpose of this study was to evaluate both the quality and quantity of neointima and the presence of intrastent thrombus as local factors using coronary angioscopy, and platelet reactivity using platelet function test as a systemic factor in patients who experienced an acute coronary syndrome (ACS) treated with 2nd- or 3rd-DES on DAPT.

Methods

Study Population and Study Design

This was a prospective observational study comparing the angioscopic findings of stented lesions in patients with ACS on DAPT at long-term follow-up after 2nd-DES and 3rd-DES. Patients were recruited in the Division of Cardiology at Kindai University Hospital, and were eligible if they met all of the inclusion criteria: (1) with ACS and after 2nd-DES (everolimus-eluting stent (EES): Xience V®, PRIME, Xpedition and Sierra; Abbott Vascular, Santa Clara, CA, USA) or 3rd-DES (EES: Synergy™; Boston Scientific, Natick, MA, USA) implantation; (2) on standard DAPT with aspirin (100 mg/daily) and $P2Y_{12}$ receptor inhibitor such as clopidogrel (75 mg/daily) or prasugrel (3.75 mg/daily) at follow-up angioscopy; and (3) anatomically suitable for angioscopy. Patients were excluded if any of the following criteria were encountered: in-stent restenosis; concomitant use of oral anticoagulant drugs, cilostazol, or dipyridamole; on hemodialysis; or platelet count $<100\times10^3$/mL. We prospectively enrolled consecutive patients who underwent coronary angioscopy at 1-year follow-up catheterization. Additionally, we performed pharmacodynamic assessments by measuring platelet reactivity using light transmission aggregometry (LTA) to identify the response to DAPT in patients treated with 2nd- and 3rd-DES. A sample size calculation was not performed because this study was exploratory in nature; however, we hypothesized that a total of 100 patients would be required based on a previous study that was similar in design to ours.[13,14]

This study was conducted in compliance with the Declaration of Helsinki for investigations in human subjects, and the study protocol was approved by the Institutional Review Board of the Kindai University Faculty of Medicine.

Angioscopic Examination

Coronary angioscopic examination was performed using a balloon occlusion type of angioscopy (Fullview NEO; i Heart Medical, Tokyo, Japan) through a radial or femoral approach using a 6Fr catheter after administration of unfractionated heparin (5,000 IU). Briefly, the fiberscopy was placed at the distal of the stent and manually pulled back to the proximal end of the stent under fluoroscopic guidance. Visualization of the coronary lumen was accomplished during low-pressure inflation of a proximal, distensible occlusion cuff with continuous hand-operated flushing of fluid (room-temperature lactated Ringers solution)

Table 1. Clinical and Lesion Characteristics

	2nd-DES (n=50)	3rd-DES (n=50)	P value
Time to angioscopy (days)	293±46	293±31	1.00
Age (years)	64.4±11.5	67.7±11.3	0.15
Male	36 (72.0%)	41 (82.0%)	0.23
BMI (kg/m^2)	23.7 [21.2–26.4]	23.8 [21.5–25.7]	0.90
Type of ACS			0.02
STEMI	34 (68.0%)	22 (44.0%)	
NSTE-ACS	16 (32.0%)	28 (56.0%)	
Target lesion			0.20
LAD	24 (48.0%)	29 (58.0%)	
LCX	13 (26.0%)	6 (12.0%)	
RCA	13 (26.0%)	15 (30.0%)	
Coronary risk factors			
Hypertension	36 (72.0%)	40 (80.0%)	0.35
Diabetes mellitus	21 (42.0%)	18 (36.0%)	0.54
Hyperlipidemia	35 (70.0%)	33 (66.0%)	0.67
Smoking	11 (22.0%)	3 (6.4%)	0.02
Medications			
β-blockers	43 (86.0%)	42 (84.0%)	0.78
Statins	50 (100%)	50 (100%)	1.0
Insulin	3 (6.0%)	2 (4.0%)	0.65
Antiplatelet therapy			
Aspirin+clopidogrel	36 (72.0%)	25 (50.0%)	0.02
Aspirin+prasugrel	14 (28.0%)	25 (50.0%)	0.02
Stent characteristics			
Diameter (mm)	3.25 [3–3.5]	3.5 [3–3.63]	0.28
Length (mm)	18 [15–28]	22 [16–28]	0.29
Laboratory findings			
HbA1c (%)	6.1 [5.8–6.7]	6.1 [5.9–6.4]	0.68
LDL-C (mg/dL)	71.5 [56–91.3]	73.5 [57–85.3]	0.96

2nd-DES, 2nd-generation drug-eluting stent; 3rd-DES, 3rd-generation drug-eluting stent; BMI, body mass index; LAD, left anterior descending artery; LCX, left circumflex branch; LDL-C, low-density lipoprotein cholesterol; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; RCA, right coronary artery; STEMI, ST-segment-elevation myocardial infarction.

through the irrigation channel of the angioscope.[15] Since August 2017, we have been using a different angioscopic fiber of a non-occlusive and short monorail type (smart-I; i Heart Medical), because the Fullview NEO was discontinued. To remove blood from the field of view, low-molecular dextran was continuously injected by auto injector (3–4 mL/s, total 30–40 mL) through a guide extension catheter (Guideliner; Japan Lifeline, Tokyo, Japan). Angioscopic images were digitally recorded.[16]

Angioscopic Analysis

Two experienced observers assessed neointimal coverage (NIC) grade, yellow color (YC) grade and presence of intrastent thrombus. The NIC grade was classified as: grade 0=no coverage; grade 1=partial coverage with thin neointima; grade 2=partial coverage with thick neointima; grade 3=complete coverage (**Figure 1**).[14] The maximum, minimum, and dominant NIC grades were determined for each stented lesion. YC was classified into 4 grades: grade 0=white; grade 1=slight yellow; grade 2=yellow; grade 3=intense yellow (**Figure 1**).[17] We defined reddish material around the stent strut and within the neointima as intrastent thrombus (**Figure 1**)[18]. Angioscopic evaluations were made by 2 experienced independent specialists in coronary intervention and angioscopy who were blinded to the patient's clinical status.

Blood Sampling and Platelet Function Testing

Blood samples were collected before cardiac catheterization from an antecubital vein using a 21-gauge needle. The first 2–4 mL of blood was discarded to avoid spontaneous platelet activation. Samples were processed within 1 h after blood drawing.

Platelet reactivity was measured with LTA, which was performed according to standard protocols as previously described.[19] Briefly, blood was collected in sodium citrate (3.8%) tubes and platelet aggregation was assessed using platelet-rich plasma (PRP) by the turbidimetric method in a 2-channel aggregometer (MCM HEMA TRACER 313M, MC Medical Inc, Tokyo, Japan). PRP was obtained as a supernatant after centrifugation of citrated blood at 13.3 s^{-1} for 10 min and kept at 37ºC before use. Platelet-poor plasma (PPP) was obtained by a 2nd centrifugation at 50 s^{-1} for 15 min. Finally, light transmission was adjusted to 0% with PRP and to 100% with PPP for each measurement. Adenosine diphosphate (ADP) and collagen were used as

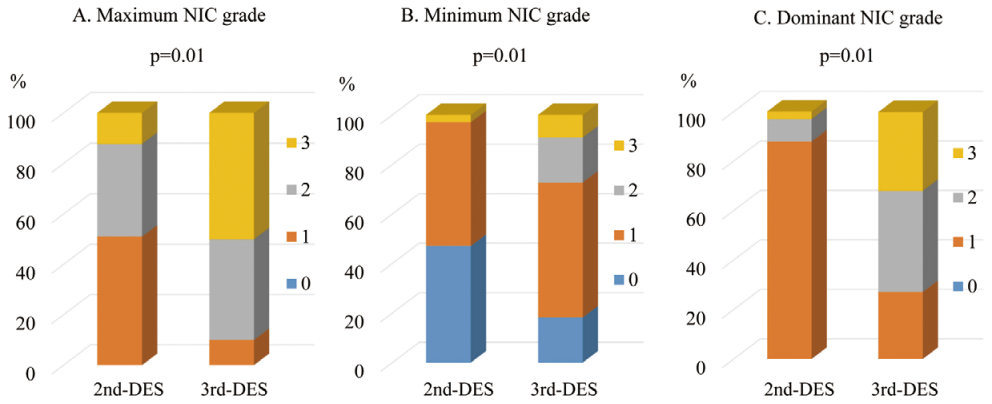

Figure 2. Distribution of neointimal coverage (NIC). (**A**) Maximum NIC grade. The 3rd generation drug-eluting stent (DES) had higher maximum NIC grade than the 2nd-generation (2nd)-DES (P=0.001). (**B**) Minimum NIC grade. 3rd-DES had higher minimum NIC grade than 2nd-DES (P=0.001). (**C**) Dominant NIC grade was higher in 3rd-DES than in 2nd-DES (P=0.001).

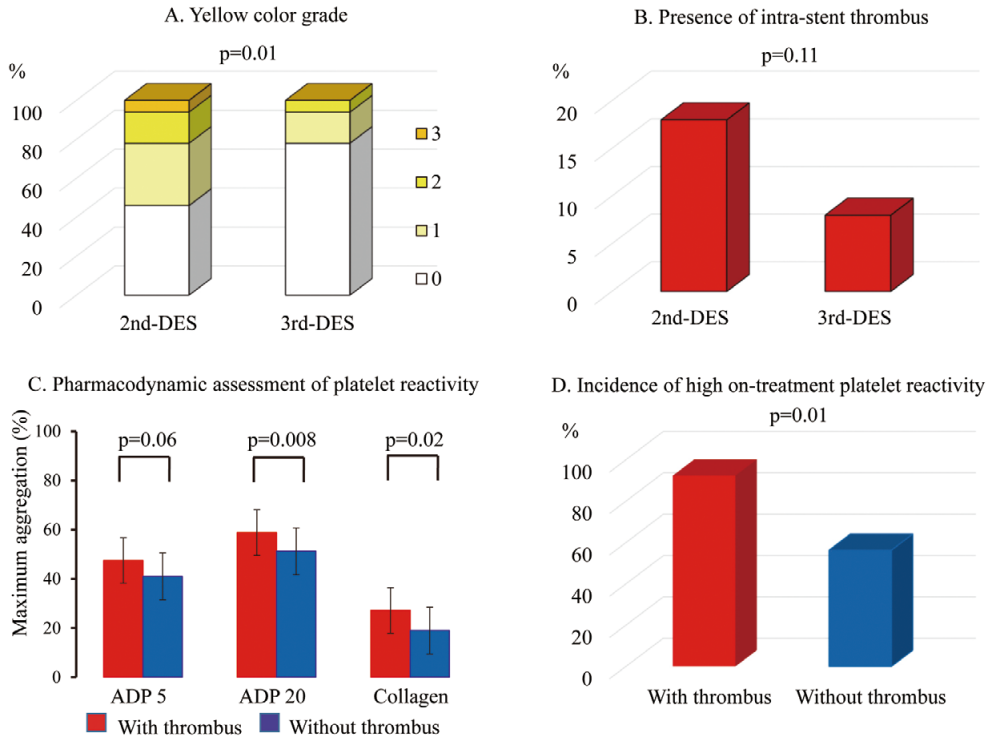

Figure 3. Yellow color (YC) grade of neointima, incidence of intrastent thrombus and light transmittance aggregometry (LTA) findings. (**A**) YC grade was significant lower in 3rd-generation drug-eluting stent (DES) than in 2nd-generation (2nd)-DES (P=0.003). (**B**) Lower tendency for intrastent thrombus with 3rd-DES than with 2nd-DES (P=0.11). (**C**) LTA induced by 5 and 20 μmol/L ADP and 10 μg/mL collagen in patients with and without thrombus. Data are presented as mean and standard deviation. (**D**) Comparison of incidence of high on-treatment platelet reactivity in patients with and without thrombus.

platelet agonists to evaluate the effects of $P2Y_{12}$ inhibitors and aspirin, respectively. Maximal platelet aggregation (MPA) was measured after stimuli with ADP (5 μmol/L and 20 μmol/L), and collagen (10 μg/mL) (MC Medical Inc., Tokyo, Japan). Curves were recorded for 7 min. HPR was defined when MPA was ≥50% with 20 μmol/L ADP.[20]

Statistical Analysis

Continuous variables were analyzed for normal distribution with the Kolmogorov-Smirnov test and presented as

Table 2. Univariate Analysis for Presence of Intrastent Thrombus

	With thrombus (n=13)	Without thrombus (n=87)	P value
Age (years)	65.8±11.3	67.6±12.3	0.60
Male	6 (46.2%)	71 (81.6%)	0.01
BMI (kg/m^2)	22.9 [20.4–24.4]	23.8 [21.6–26.6]	0.31
Type of ACS			0.45
STEMI	6 (46.2%)	50 (57.5%)	
NSTE-ACS	7 (53.9%)	37 (42.5%)	
Target lesion			0.19
LAD	4 (30.8%)	49 (56.3%)	
LCX	3 (23.1%)	16 (18.4%)	
RCA	6 (46.1%)	22 (25.3%)	
Coronary risk factors			
Hypertension	11 (84.6%)	65 (74.7%)	0.42
Diabetes mellitus	4 (30.8%)	35 (40.2%)	0.51
Hyperlipidemia	10 (76.9%)	58 (66.7%)	0.45
Smoking	2 (15.4%)	12 (13.8%)	0.89
Medications			
β-blockers	12 (92.3%)	73 (83.9%)	0.39
Statins	13 (100%)	87 (100%)	1.0
Insulin	1 (7.7%)	4 (4.6%)	0.65
Antiplatelet therapy			
Aspirin+clopidogrel	9 (69.2%)	52 (59.8%)	0.51
Aspirin+prasugrel	4 (30.8%)	35 (40.2%)	0.51
Stent characteristics			
Diameter (mm)	3.25 [3–3.5]	3.25 [3–3.5]	0.49
Length (mm)	23 [16.5–28]	20 [16–28]	0.94
Laboratory findings			
HbA1c (%)	5.9 [5.7–6.7]	6.1 [5.9–6.5]	0.41
LDL-C (mg/dL)	86 [46.5–93.5]	72 [57–88]	0.65
Minimum NIC grade			0.01
0	9 (69.2%)	19 (21.8%)	
1	3 (23.1%)	51 (58.6%)	
2	0 (0%)	15 (17.3%)	
3	1 (7.7%)	2 (2.3%)	
Yellow color grade			0.67
0	8 (61.5%)	54 (62.1%)	
1	2 (15.4%)	22 (25.3%)	
2	2 (15.4%)	9 (10.3%)	
3	1 (7.7%)	2 (2.3%)	

Abbreviations as in Table 1.

mean±standard deviation or as median and interquartile range (IQR) if a normal distribution was present or not, respectively. Student's t-test or the Mann-Whitney U test was used for comparisons of continuous variables where appropriate. Categorical variables are expressed as frequencies and percentages. Categorical variables were tested by chi-square test or Fisher's exact test. Multivariate logistic regression analysis was performed to investigate risk factors for intrastent thrombus. Odds ratio (OR) and 95% confidence interval (CI) were calculated. All univariate variables with $P<0.05$ and those deemed of clinical interest were included in the statistical model. Statistical analysis was performed using JMP v13.0 software (SAS Institute Inc., Cary, NC, USA).

Results

Study Population

A total of 100 consecutive patients were prospectively enrolled: 50 patients treated with 2nd-DES, and 50 with 3rd-DES. Their clinical characteristics are shown in **Table 1**. Patients were similar for all clinical characteristics, except for a higher prevalence of ST-segment elevation myocardial infarction (STEMI) and smoking, and more clopidogrel use in the 2nd-DES group.

Angioscopic Findings

The angioscopic NIC grade at each stent are shown in **Figure 2**. Max- and Min-NIC grades were significantly different between groups: 3rd-DES had higher Max- and Min-NIC grade than 2nd-DES (Max-NIC: P=0.001, Min-

Table 3. Multivariate Logistic Regression Analysis for Presence of Intrastent Thrombus Including Both Angioscopic Findings and Pharmacodynamic Response to DAPT

	OR	95% CI	P value
Stent strut exposure	5.77	1.53–27.86	0.03
HPR in LTA	14.52	1.53–137.96	0.02
Female sex	5.01	1.09–22.98	0.04
Use of 3rd-DES	0.69	0.15–3.28	0.64
Use of clopidogrel as $P2Y_{12}$ inhibitor	1.26	0.27–5.89	0.77

CI, confidence interval; DAPT, dual antiplatelet therapy; HPR, high on-treatment platelet reactivity; LTA, light transmission aggregometry; OR, odds ratio. Other abbreviations as in Table 1.

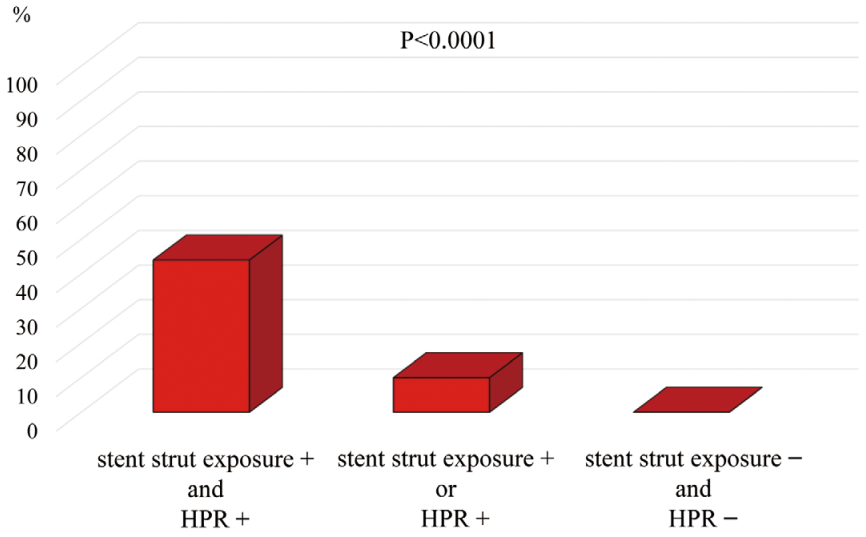

Figure 4. Difference in the incidence of intrastent thrombus according to stent strut exposure and high on-treatment platelet reactivity (HPR): 44.4% in patients with both stent strut exposure and HPR, 10% in patients with stent strut exposure or HPR, and 0% in patients without stent strut exposure and HPR (P<0.0001).

NIC: P=0.001). Dominant NIC grade was also higher for 3rd-DES than for 2nd-DES (P=0.001). The kappa values for inter- and intra-observer agreement on angioscopic evaluations were 0.76 and 0.84, respectively.

YC grade and incidence of intrastent thrombus foreach type of stent are shown in **Figure 3A**,**B**. The Max-YC grade was significantly lower for 3rd-DES than for 2nd-DES (P=0.003). A higher YC grade of the stented lesion was associated with higher frequency of STEMI (P<0.001) and lower Max-NIC grade (P=0.006). In the entire study population there were 13 patients (13%) with intrastent thrombus. The presence of intrastent thrombus showed a lower tendency with 3rd-DES than with 2nd-DES (8% vs. 18%, P=0.11) (**Figure 3B**).

To assess the independent predictors of intrastent thrombus, we first conducted univariate logistic regression analysis including the angioscopic findings. Univariate analysis for the presence of intrastent thrombus is shown in **Table 2**. The presence of intrastent thrombus was associated with sex (P=0.01) and Min-NIC grade (P=0.01).

Pharmacodynamic Assessment of Platelet Reactivity

Platelet reactivity using LTA was assessed in the 100 patients treated with 2nd- (n=50) or 3rd-DES (n=50). Mean MPA was 41±14% with 5 μmol/L ADP, 52±12% with 20 μmol/L ADP and 20±12% with 10 μg/mL collagen. The prevalence of HPR was 61 (61%) in the entire study population. Patients with HPR showed significantly higher HbA1C levels and a tendency to higher body mass index in comparison with non-HPR patients (6.4±0.8 vs. 6.1±0.7; P=0.03, 24.5±3.4 vs.23.3±4.1; P=0.1). The other clinical characteristics were not significantly different between HPR and non-HPR patients.

Patients with intrastent thrombus had significantly higher MPA values at 5 and 20 μmol/L ADP and 10 μg/mL collagen stimuli compared with those without thrombus (**Figure 3C**). The prevalence of HPR was significantly higher in patients with intrastent thrombus in comparison with those without thrombus (**Figure 3D**). Considering the differences in $P2Y_{12}$ receptor inhibitor, the MPA values at 5 and 20 μmol/L ADP and 10 μg/mL collagen were not significantly different between clopidogrel and prasugrel (5 μmol/L ADP: P=0.32, 20 μmol/L ADP: P=0.72, and 10 μg/mL collagen: P=0.79).

Prediction of Intrastent Thrombus Including Pharmacodynamic Response

Multivariate logistic regression analysis was performed to investigate the independent predictors of intrastent thrombus including both angioscopic findings and pharmacodynamic response to DAPT in patients treated with 2nd- and 3rd-DES. A multivariable logistic regression analysis including sex, 3rd-DES, use of clopidgrel, stent strut exposure, and presence of HPR as covariates showed that stent strut

exposure, HPR for $P2Y_{12}$ receptor inhibitor and female sex were independent predictors of intrastent thrombus (**Table 3**). In consideration of the results of multivariate analysis, we also evaluated the rate of intrastent thrombus if the patients had stent strut exposure and HPR. The incidence of intrastent thrombus was significantly different as follows; 44.4% in patients with both stent strut exposure and HPR, 10% in patients with stent strut exposure or HPR, and 0% in patients without both stent strut exposure and HPR ($P<0.0001$) (**Figure 4**). In the patients with intrastent thrombus, the incidence of patients with both stent strut exposure and HPR, only HPR, and only stent strut exposure was 61.5%, 30.8%, and 7.7%, respectively.

Discussion

This is the first study, to the best of our knowledge, to evaluate the relationships among the quality and quantity of neointima and the presence of intrastent thrombus by using coronary angioscopy, and platelet reactivity using a platelet function test at long-term follow-up after 2nd- or 3rd-DES implantation in patients with ACS on DAPT. The key findings were as follows: (1) Max- and Min-NIC grades were significantly higher in 3rd-DES than in 2nd-DES; (2) YC grade was significantly lower in 3rd-DES than in 2nd-DES; (3) the presence of intrastent thrombus showed a lower tendency with 3rd-DES than with 2nd-DES, and was associated with significantly lower grades of Max- and Min-NIC; (4) HPR was also strong independent predictor of intrastent thrombus; and (5) patients presenting with both stent strut exposure and HPR had a significantly higher rate of intrastent thrombus compared with only one of these factors being present. These findings indicated that 3rd-DES have a more favorable vascular response than 2nd-DES. In addition to local factors such as the stented lesion, systemic factors such as the pharmacodynamic response to antiplatelet therapy might also be associated with VLSF.

DES plays a pivotal role in reducing clinical restenosis but have a higher incidence of VLSF such as ST and restenosis due to neoatherosclerosis, especially with 1st-DES. From a histopathological point of view, the mechanisms of VLSF have been evaluated in several studies. Finn et al[21] reported that the ratio of uncovered to total stent struts and heterogeneity of neointimal healing after 1st-DES implantation were predictors of late ST. The mechanism was thought to be that the DP of 1st-DES provokes a chronic inflammatory response in the arterial wall, which plays a role in delayed healing.[21] The presence of neoatherosclerosis was also a contributing factor in VLSF with both BMS and DES. Nakazawa et al reported that neoatherosclerosis is a frequent finding in DES and occurs earlier than in BMS, possibly because of stent polymer- or metal-induced endothelial dysfunction.[22] Currently, various coronary imaging techniques are being used to clarify the mechanisms of VLSF, but of them, only coronary angioscopy can provide detailed information of the luminal surface by direct visualization, which plays an important role in elucidating the morphological interaction between plaque and thrombus. Higo et al reported that sirolimus-eluting stent implantation in 57 patients had poor neointimal coverage and promoted formation of yellow plaque observed by angioscopy in the stented lesion within 10 months of follow-up.[23] Thrombus was detected more often on yellow neointima than on white neointima, suggesting yellow neointima reflects neoatherosclerotic change.[24] However, in the present study there was no relationship between intrastent thrombus and YC intensity. The etiology of intrastent thrombus is multifactorial. Compared with previous studies, the present study population had lower YC grade of neointima, more intensive statin therapy, more potent antiplatelet therapy, use of thinner strut stents, and lower low-density lipoprotein cholesterol levels. These factors may be reasons for the discrepancy between previous studies and ours.

Several previous investigations have demonstrated that the angioscopic findings of stented lesions predict future clinical outcomes. In the DESNOTE (Detect the Event of Very late Stent Failure From the Drug-Eluting Stent Not Well Covered by Neointima Determined by Angioscopy) study, 360 patients, who were examined by coronary angioscopy 1 year after DES implantation, were classified according to the presence of yellow neointima in the stented lesion, and the incidences of VLSF, cardiac death, myocardial infarction related to the target lesion, and TLR, were compared. During 4.3±2.4 years of follow-up, VLSF occurred more frequently in patients with yellow neointima than in those without yellow neointima, suggesting that early detection of neoatherosclerosis using coronary angioscopy can predict VLSF.[6] The present study demonstrated that 3rd-DES had a significantly lower YC grade of neointima than 2nd-DES. However, we could not conclude whether this finding indicated neoatherosclerosis or underlying yellow plaque that had existed before stent implantation because we did not evaluate YC grade at the time of stent implantation. Regarding the relationship between subclinical intrastent thrombus detected by angioscopy and clinical outcomes, Okuno et al reported that intrastent thrombus at 9 months after 2nd-DES implantation was independently associated with poor clinical outcomes.[25] Considering that finding, assessment of vascular healing of the stented lesion using coronary angioscopy is important for predicting future coronary events. The previous investigations using a variety of coronary imaging have demonstrated that neointima and vascular healing after stent implantation are determined by several factors such as underlying lesion factors, patient factors, and the percutaneous coronary intervention (PCI) procedure. Strut thickness, type of polymer, stent platform material, drugs, and stent under-expansion and malapposition of struts to the vascular wall as well as accompanying diseases such as diabetes mellitus have been reported as risk factors.[26–28] In particular, polymer-induced hypersensitivity reaction, incomplete strut re-endothelialization, stent malapposition, and accelerated neoatherosclerosis have been noted with the DP of 1st-DES.[29] Consequently, 2nd DP-DES were developed, with novel antiproliferative drugs, more biocompatible polymer coating, and thinner stent struts made from cobalt-chromium or platinum-chromium instead of stainless steel. Although 2nd DP-DES showed greater strut coverage with less inflammation, less fibrin deposition, and less late and very late ST compared with 1st DP-DES, the incidence of neoatherosclerotic events was comparable to that observed with 1st DP-DES, and is still considered as a mechanism of VLSF. [30] To overcome the current limitations of DP, BP-3rd-DES were developed, designed to have a similar safety profile to that of BMS to reduce the risk of ST, while maintaining the efficacy profile of DP-DES to reduce the risk of TLR. To prove these theories, the SENIOR (Drug-eluting stents in elderly patients

with coronary artery disease) trial randomized BP-DES (Synergy™) vs. a BMS with short DAPT in patients with CAD who were older than 75 years. The study demonstrated that use of BP-DES rather than BMS resulted in lower adverse clinical event rates at 1 year even with 1-month DAPT.[31] Our angioscopic findings demonstrated that BP-DES achieved the aim of overcoming the limitation of 2nd DP-DES, and neointimal coverage was better than with 2nd-DES, representing an ideal degree of healing.

In addition to local factors, antiplatelet therapy also plays an important role in preventing ST. Several investigations have demonstrated that increased platelet reactivity and impaired pharmacodynamic response to antiplatelet therapy contribute to an increased risk of cardiovascular events.[11,32,33] Therefore, the antiplatelet response is thought to be associated with intrastent thrombus. However, only a few studies have considered the relationship between the pharmacodynamic response to antiplatelet therapy and intrastent thrombus detected by coronary angioscopy.[26] In the present study, HPR was observed in ≈60% patients, which was similar to a previous study using the same definition of HPR.[20] Interestingly, most cases of intrastent thrombus occurred when there was both stent strut exposure and HPR but not when just one of these factors was present. That finding suggested that both local and systemic factors contribute to the presence of intrastent thrombus, an hypothesis that must be validated in larger cohort studies.

Study Limitations

First, this was a single-center prospective cohort study. Second, patients with coronary artery anatomy unsuitable for angioscopic examination were not included. Third, we could not acquire angioscopic images for the entire stented segment in some patients because of a limited field of view. Fourth, angioscopy can only show luminal surface morphology and pigmentation of the plaque, therefore the YC grade would depend on the position of the lipid core within plaques.

Conclusions

Newer generation DES platforms with thinner struts and BP contribute to better vascular healing, depending on the degree of neointimal coverage. In addition to local factors at the stented lesion, systemic factors such as the degree of platelet reactivity assessed by the pharmacodynamic response to antiplatelet therapy might also contribute to VLSF. Further prospective trials are warranted to confirm our study's findings.

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IRB Information

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