ORIGINAL RESEARCH

Comparison of Long-Term Clinical Outcomes of Lesions Exhibiting Focal and Segmental Peri-Stent Contrast Staining

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***Background*—**Peri-stent contrast staining (PSS) after metallic drug-eluting stent deployment is associated with target lesion revascularization and very late stent thrombosis. However, the type of PSS that influences the clinical outcomes is unknown. Therefore, we aimed to reveal which PSS type was influencing clinical outcomes.

***Methods and Results*—**This study included 5580 de novo lesions of 4405 patients who were implanted with a first- or second-generation drug-eluting stent and who were evaluated using follow-up angiography within 12 months after stent implantation. We compared the clinical outcomes of patients divided into focal PSS and segmental PSS groups for 6 years after stent implantation. Total PSS was observed in 97 lesions (2.2%), of which 42 and 55 lesions were focal and segmental PSS, respectively. Baseline characteristics were similar between groups, except for intraoperative chronic total occlusion (segmental PSS=47.3% versus focal PSS=11.9%, P=0.0001). The incidence of segmental PSS tended to be higher in patients with a first-generation drug-eluting stent (83.6% versus 16.4%, P=0.05). The cumulative incidence of stent thrombosis in the 6 years of segmental PSS group was significantly higher than that of the focal PSS group (13.9% versus 0%, P=0.04). The cumulative incidence of overall target lesion revascularization for restenosis, excluding target lesion revascularization procedures for stent thrombosis, was significantly higher in the segmental PSS group (38.0% versus 0%, P=0.01).

***Conclusions*—**The incidence of segmental PSS tended to be higher in patients with a first-generation drug-eluting stent and appeared to be significantly associated with target lesion revascularization and stent thrombosis. **(*J Am Heart Assoc*. 2016;5: e002878 doi: 10.1161/JAHA.115.002878)**

Key Words: peri-stent contrast staining • segmental peri-stent contrast staining • stent thrombosis

Stent thrombosis (ST) is one of the most serious complications of percutaneous coronary intervention in clinical practice. Very late-stent thrombosis (VLST) has been reported as continuing to occur until 3 to 4 years of follow-up without any signs of attenuation of its incidence.[1–4] Peri-stent contrast staining (PSS)—contrast staining outside of stent struts after metallic drug-eluting stent (DES) implantation—occurs at low frequency. However, PSS that occurs after sirolimus-eluting stent (SES) implantation is associated with increased risks of in-stent restenosis and VLST.[5]

This study showed the potential relevance to PSS and VLST, and another study revealed correlation between PSS and VLST.[6] These studies did not show the solution if we found PSS accidentally. Some studies concluded that continuation of dual antiplatelet therapy (DAPT) seemed not to be an effective treatment to prevent VLST.[7,8] Although an effective treatment was important, risk stratification of PSS was also important to prevent cardiac adverse events.

In the first-generation DES era, PSS might cause in-stent restenosis and VLST.[5,6,8] In the second-generation DES era, the incidence of PSS after everolimus-eluting stent (EES) implantation is less than after SES implantation.[7] We reported that PSS after second-generation DES implantation was associated with subsequent target-lesion revascularization (TLR) but VLST was not observed.[9]

To date, there were 4 PSS types,[5] but the type of PSS after metallic DES implantation that causes in-stent restenosis or VLST is unknown. To fill this gap in our knowledge, the goal of

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the present study was to identify which type of PSS after metallic DES implantation affected its clinical outcomes.

Methods

Study Design and Patients

From April 2007 to February 2013, 4405 patients (5580 lesions) underwent percutaneous coronary intervention using metallic DES implantation at Saiseikai Yokohama City Eastern Hospital. The stents used were as follows: SES (Cypher®, Cypher select®), paclitaxel-eluting stent (PES: taxus®, taxus element®), EES (Xience®, Xience V®, Xience Prime®, Promus®, and Promus element®), zotarolimus-eluting stents (ZES; Endeavor®, Endeavor Sprint®, and Resolute integrity®), and biolimus-eluting stent (BES; Nobori®). First-generation DESs were defined as SES or PES, and second-generation DESs were defined as an EES, ZES, or BES.

Of the 4405 patients, 938 patients (1180 lesions) were excluded because of a lack of follow-up angiography. The remaining 3467 patients (78.9%, 4400 lesions) underwent follow-up angiography within 12 months after stent implantation regardless of their symptoms. Based on angiographic findings at follow-up, the patients were divided into a focal PSS or segmental PSS group (Figure 1). We compared the patient characteristics in each group, including lesions, procedures, and clinical outcomes (cumulative incidence of TLR and ST 6 years after stent implantation). The recommended antiplatelet regimen after DES implantation was aspirin (100 mg daily, indefinitely) and thienopyridine (200 mg ticlopidine or 75 mg clopidogrel daily) for at least 3 months. The duration of DAPT was determined by each attending physician. Stringent adherence to continued DAPT was recommended when PSS was detected using follow-up angiography.

This study was an investigator-driven initiative. The study protocol was approved by the Institutional Review Board of Saiseikai Yokohama City Eastern Hospital. Because of the retrospective enrollment, the requirement for obtaining written informed consent from patients was waived.

Follow-up information until September 2015 was collected either from regular hospital consultation or by contacting patients and/or referring physicians.

Qualitative and Quantitative Angiographic Analyses

Lesions were defined as areas covered by single or multiple overlapping stents. When 2 stents were placed without overlap, these 2 areas were regarded as 2 separate lesions. Lesion complexity was classified according to the criteria of the American Heart Association/American College of Cardiology.[10] Quantitative angiographic analysis was performed through the in-stent segment and adjacent proximal and distal 5-mm vessel segments. Quantitative measurements included reference-vessel diameter, minimal luminal diameter, percentage stenosis diameter, and lesion length. Restenosis was defined as 50% of the diameter of the stenosis at follow-up. To confirm the diagnosis of PSS, 2 experienced interventional cardiologists who were uninformed of the clinical and procedural data independently analyzed the angiograms. Statistical analysis evaluated the extent of diagnostic agreement to determine inter- and intraobserver variability.[11] Disagreements were resolved according to the decision of a third observer, and the final diagnosis of PSS was made according to the consensus judgment.

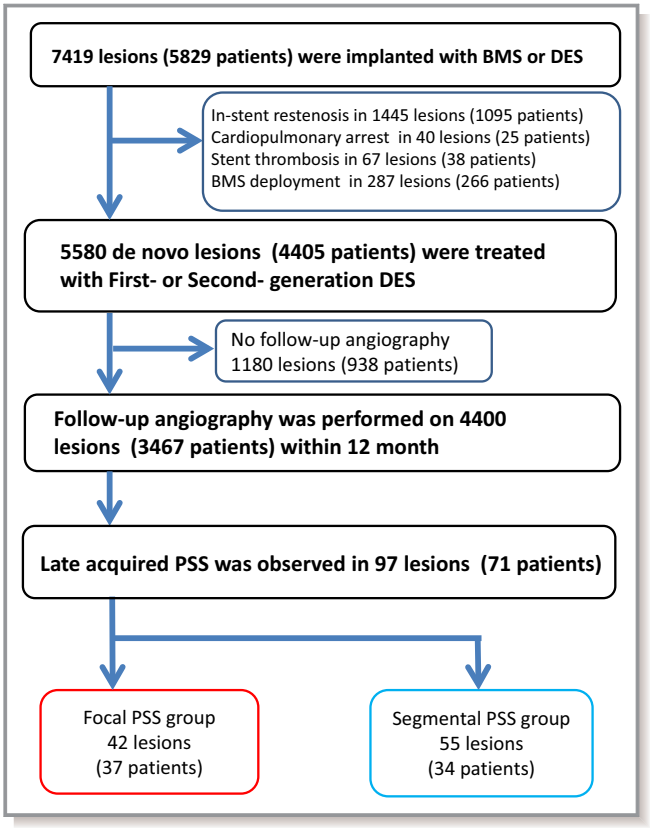


Figure 1. Study flow chart. BMS indicates bare metal stent; DES, drug-eluting stent; PSS, peri-stent contrast staining

Definition and Morphological Classification of Peri-Stent Contrast Staining

PSS was measured using quantitative coronary angiography and was defined as contrast-staining outside the stent contour, extending to >20% of the stent diameter. PSS was classified according to a published classification system[1] into the morphological groups as follows: monofocal, multifocal, segmental with irregular contour, and segmental with smooth

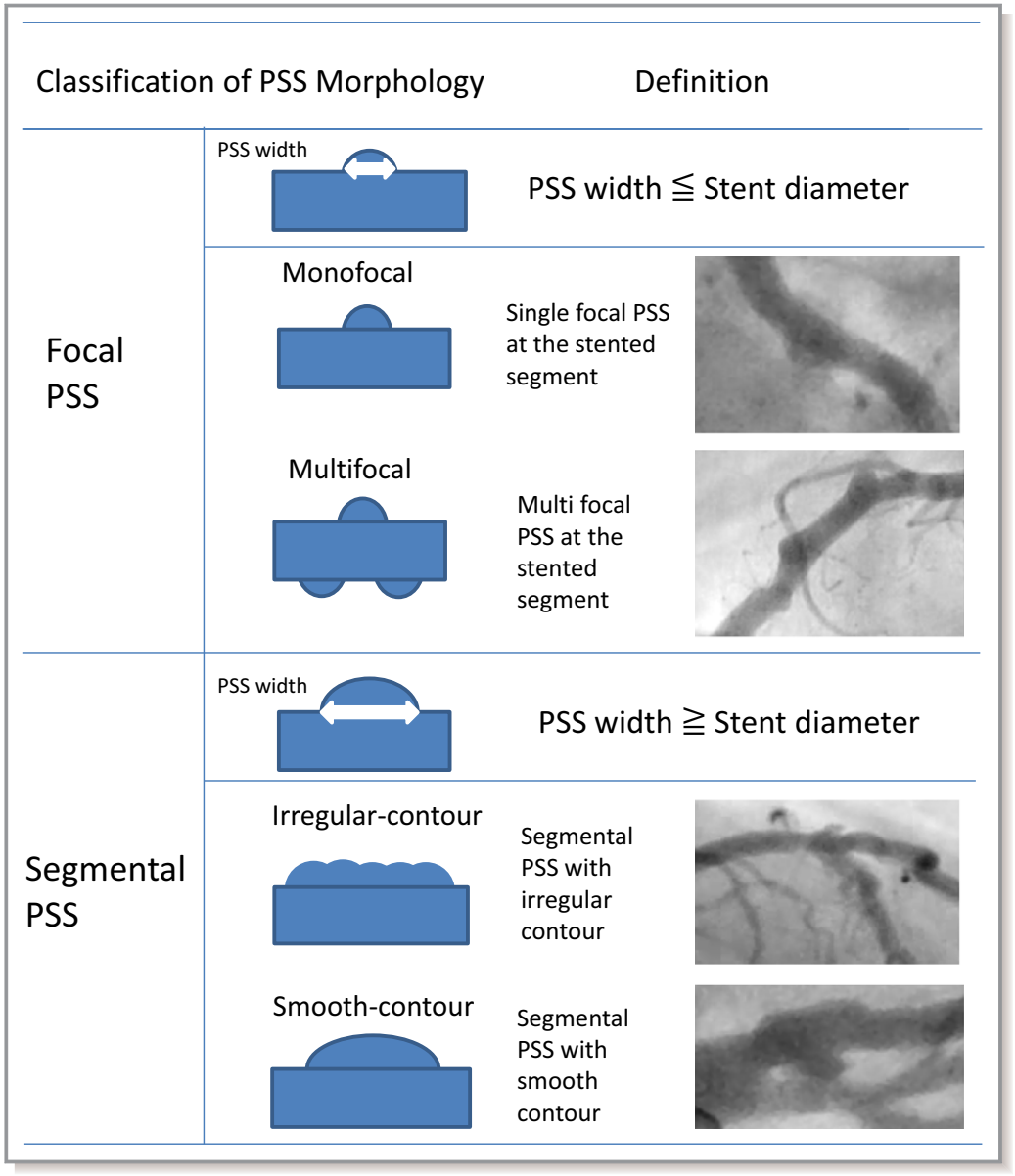


Figure 2. Definition and morphological classification of PSS. PSS indicates peri-stent contrast staining. Modified Imai PSS classification.[5]

contour (Figure 2). The focal PSS group included patients with monofocal or multifocal PSS, and the segmental PSS group included patients with irregular and smooth-contour PSS.

Definition of Stent Fracture, Target-Lesion Revascularization, and Stent Thrombosis

Stent fracture was defined as complete or partial separation of stent segments observed using fluoroscopy without contrast upon follow-up angiography.[12,13] A clinically driven TLR was defined as re-intervention of the target lesion due to presence of a symptomatic >50% diameter stenosis during follow-up. Overall TLR was defined as a clinically driven TLR or a >70% diameter stenosis upon follow-up angiography in the presence of signs of myocardial ischemia. The timing and diagnostic accuracy of ST were assessed according to the definition of the Academic Research Consortium.[14]

Statistical Analysis

Statistical analysis was performed using JMP version 10.0.2 (SAS Institute Inc, Cary, NC). Data are presented as values and percentages, mean± SD, or median (interquartile range). Categorical variables were compared between groups using the χ^2 or Fisher's exact tests, as appropriate. Continuous variables were compared between groups using the Student

paired *t* test or Mann–Whitney test, according to the normality of data distribution.

Cumulative incidence of overall TLR, clinically driven TLR, and ST of the focal PSS and segmental PSS was estimated by using Kaplan–Meier method and the differences were evaluated with the log-rank test. We additionally performed generalized estimating equations as a sensitivity analysis, to confirm the association of the PSS type with the prognostic outcomes. Generalized estimating equations analysis was performed using R software Program Version 3.1.0 (R Development Core Team).

All statistical analyses were 2-tailed and $P<0.05$ was considered statistically significant. All statistical analyses were conducted by a physician (T. Tokuda) and by an independent statistician (M. Takahara).

Inter- and Intraobserver Variability of the Diagnosis of Peri-Stent Contrast Staining

For the interobserver variability analysis, PSS was judged to be present by the first observer, but not by the second observer in 5 lesions. For the intraobserver variability analysis, PSS was judged to be present at the initial evaluation, but not at the second evaluation in 3 lesions. Values for inter- and intraobserver variability were 0.97 and 0.98, respectively, suggesting an almost perfect degree of agreement.

Results

Patients' Characteristics

Patients' baseline characteristics are shown in Table 1. There were no significant differences between the focal and segmental PSS groups, except for prior coronary artery bypass graft (focal PSS=0% versus segmental PSS=11.8%, $P=0.01$). The duration of DAPT was not significantly different between groups (1357±121 days versus 1436±142 days, $P=0.68$). In contrast, the lesions and procedural characteristics significantly differed between groups (Table 2). For example, chronic total occlusion (CTO) at the time of treatment was more frequent in the segmental PSS group (47.3% versus 11.9%, $P=0.0001$). The minimum lumen diameter was smaller, the percentage-diameter stenosis was larger, and lesions were significantly longer in the segmental PSS group (0.62±0.63 mm versus 0.98±0.62 mm, $P=0.008$; 80.7±20.2% versus 67.2±18.7%, $P=0.001$; 31.5±14.4 mm versus 21.9±10.0 mm, $P=0.0004$). Stent diameters and lengths were greater in the segmental PSS group (Table 2). There was no significant difference between stent types. However, segmental PSS was more frequent in patients with a first-generation DES (83.6% versus 16.4%, $P=0.05$).

Table 1. Patient Characteristics

	Focal PSS	Segmental PSS	*P* Value
Number of patients	37	34	
Age, y	71.0±10.5	69.0±9.7	0.42
Male, n (%)	29 (78.4)	30 (88.2)	0.26
Hypertension, n (%)	28 (75.7)	27 (79.4)	0.71
Diabetes mellitus, n (%)	9 (24.3)	13 (38.2)	0.20
Dyslipidemia, n (%)	24 (64.9)	19 (55.9)	0.44
Current smoking, n (%)	3 (8.1)	8 (23.5)	0.07
Dialysis, n (%)	4 (10.8)	3 (8.8)	0.78
Cerebrovascular disease, n (%)	2 (5.4)	2 (5.9)	0.93
Prior MI, n (%)	8 (21.6)	10 (29.4)	0.45
Prior CABG, n (%)	0 (0)	4 (11.8)	0.01
Acute coronary syndrome	3 (8.1%)	1 (2.9%)	0.33
Ejection fraction <30%	0 (0%)	0 (0%)	–
DAPT duration, days	1357±121	1436±142	0.68

Continuous data are presented as the mean±SD; categorical data are shown as counts (percentage). Categorical variables were compared using χ^2 and continuous variables were compared using *t* test. CABG indicates coronary artery bypass grafting; DAPT, dual antiplatelet therapy; MI, myocardial infarction; PSS, peri-stent staining.

Clinical Outcomes

The average follow-up period was 1680±698 days. Subsequent TLR was performed to treat 4 (9.5%) and 21 lesions (38.2%) in the focal PSS and segmental PSS groups, respectively. The cumulative incidence of subsequent TLR was significantly higher for the segmental PSS group (45.5% versus 9.5% at 6 years, $P=0.002$) (Figure 3A). The cumulative incidence of TLR, excluding TLR procedures for ST, was significantly higher for the segmental PSS group (38.0% versus 0.0%, $P=0.01$) (Figure 3B) and cumulative incidence of symptomatic TLR was also significantly higher for the segmental PSS group (15.6% versus 0.0%, $P=0.02$) (Figure 3C). Subsequent ST occurred in 4 patients in the segmental PSS group, and we did not detect ST in the focal PSS group. Of the ST patients, 3 patients and the remaining 1 patient were VLST and late ST, respectively. Late stent thrombosis in 1 patient was caused by the cessation of DAPT. The cumulative incidence of ST was significantly higher in the segmental PSS group (13.9% versus 0% at 6 years, $P=0.04$) (Figure 4). Representative angiograms of a patient with VLST with segmental PSS are shown in Figure 5.

We additionally adopted a generalized estimating equations approach to confirm the association of the PSS type with the prognostic outcomes. Consequently, the hazard ratio of the segmental versus focal PSS was calculated to be 4.5 (95% CI: 1.6–12.5, $P=0.004$) for all TLR including stent thrombosis, and 3.3 (95% CI: 1.1–9.5, $P=0.025$) for all TLR

Table 2. Types of Lesions and Procedures

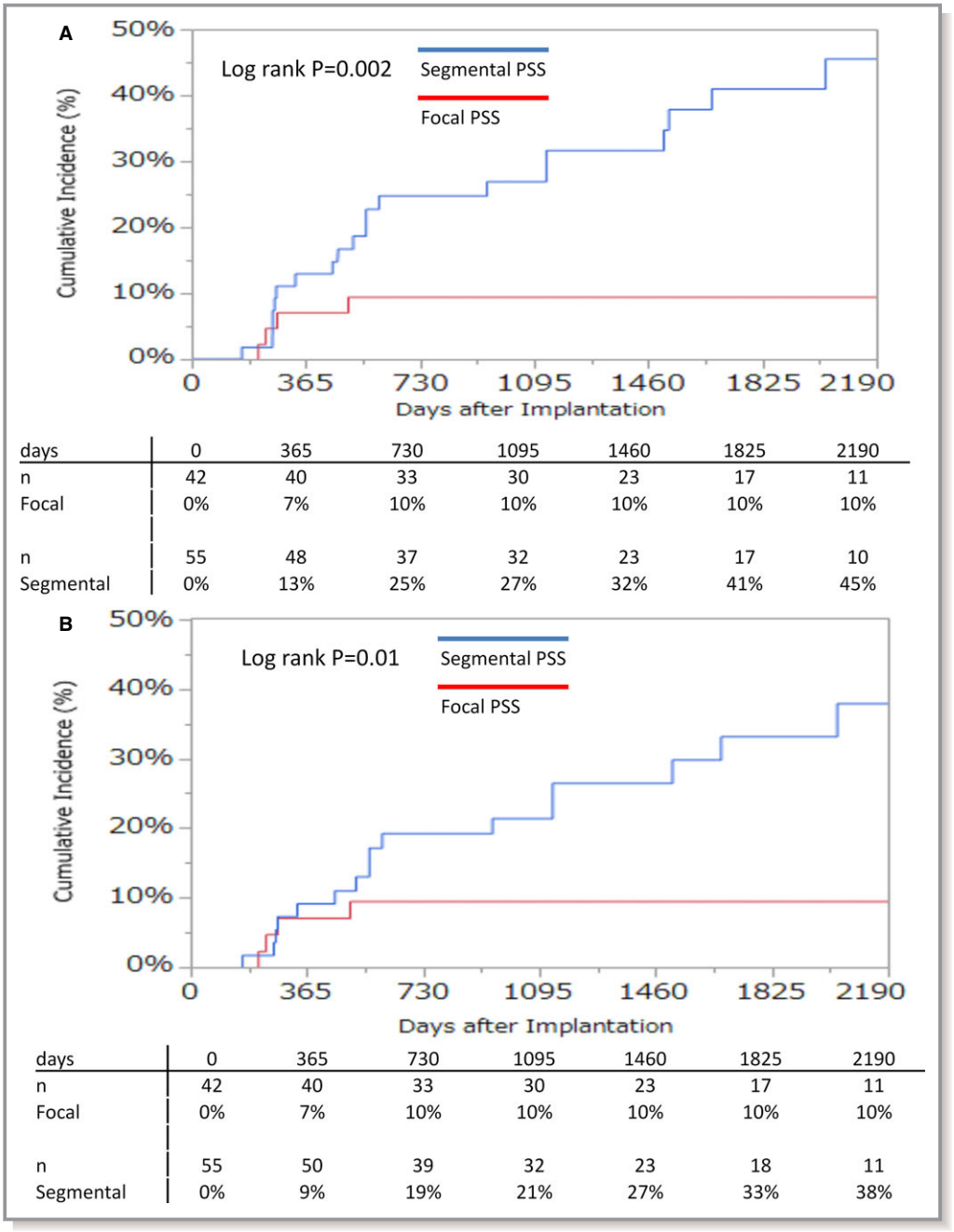
	Focal PSS	Segmental PSS	*P* Value
Lesion number, n	42	55	
LMT, n (%)	1 (2.4)	2 (3.6)	0.98
LAD, n (%)	15 (35.7)	18 (32.7)	
LCX, n (%)	4 (9.5)	5 (9.1)	
RCA, n (%)	22 (52.8)	30 (54.6)	
Ostial lesion, n (%)	6 (14.3)	10 (18.2)	0.61
Bifurcation lesion, n (%)	8 (19.1)	5 (9.1)	0.16
Severe calcification, n (%)	7 (16.7)	12 (21.8)	0.52
Severely angulated, n (%) (<90°)	3 (7.1)	4 (7.3)	0.98
CTO, n (%)	5 (11.9)	26 (47.3)	<0.01
Stent fracture, n (%)	6 (14.3)	10 (18.2)	0.61
Reference vessel diameter, mm	2.88±0.80	2.70±0.90	0.31
Minimum lumen diameter pre/postprocedure, mm	0.98±0.62/2.74±0.56	0.62±0.63/2.75±0.60	<0.01/0.94
% Diameter stenosis pre/postprocedure (%)	67.2±18.7/9.7±8.8	80.7±20.2/10.2±9.6	<0.01/0.81
Lesion length, mm	21.1±7.0	24.6±6.4	0.01
Stent diameter, mm	3.19±0.37	2.97±0.40	<0.01
Stent length, mm	24.9±8.0	31.5±7.5	<0.01
Number of implanted stents	1.32±0.56	1.45±0.60	0.31
Postdilation (%)	33 (78.6%)	48 (87.3%)	0.25
Implanted stent type			
EES (%)	10 (23.8%)	5 (9.1%)	0.17
ZES (%)	3 (7.1%)	1 (1.8%)	
BES (%)	1 (2.4%)	3 (5.7%)	
SES (%)	19 (45.2%)	31 (56.4%)	
PES (%)	9 (21.4%)	15 (27.2%)	
1st generation DES	28 (66.7%)	46 (83.6%)	0.05
2nd generation DES	14 (33.3%)	9 (16.4%)	

Lesion distribution and implanted stent type were compared using Fisher's exact test and the other categorical variables were compared using χ^2 and continuous variables were compared using *t* test. Continuous data are presented as the means±SD; categorical data are given as the counts (percentage). BES indicates biolimus-eluting stent; CTO, chronic total occlusion; DES, drug-eluting stent; EES, everolimus-eluting stent; LAD, left ascending coronary artery; LCX, left circumflex coronary artery; LMT, left main trunk; PES, paclitaxel-eluting stent; PSS, peri-stent staining; RCA, right coronary artery; SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent.

excluding stent thrombosis, indicating that the segmental PSS was significantly associated with TLR, even after taking the within-subject correlation into account (Figure 6). The hazard ratio for clinically driven TLR and ST could not be estimated since neither of these events were observed in the focal PSS group.

Discussion

The major findings of the present study are as follows: (1) Lesions with segmental PSS were more common in patients with CTO lesions and after implantation of a first-generation DES, and (2) Lesions with segmental PSS were associated with a higher rate of subsequent TLR and ST after 6 years than lesions with focal PSS. CTO is one of the independent predictors of PSS, and the cumulative incidence of VLST is significantly higher in lesions with PSS after SES implantation.[5,8] Some studies identified the mechanism that causes lesions with PSS.[15–17] However, devising a treatment for lesions with PSS remains an unsolved problem, partly because PSS occurs at a low frequency. Thus, lesions with PSS that may cause ST should be stratified to prevent major adverse events. This is the first report to our knowledge that compared lesions with focal PSS and segmental PSS during a 6-year follow-up of clinical outcomes after stent implantation.



days	0	365	730	1095	1460	1825	2190
n	42	40	33	30	23	17	11
Focal	0%	7%	10%	10%	10%	10%	10%
n	55	48	37	32	23	17	10
Segmental	0%	13%	25%	27%	32%	41%	45%

days	0	365	730	1095	1460	1825	2190
n	42	40	33	30	23	17	11
Focal	0%	7%	10%	10%	10%	10%	10%
n	55	50	39	32	23	18	11
Segmental	0%	9%	19%	21%	27%	33%	38%

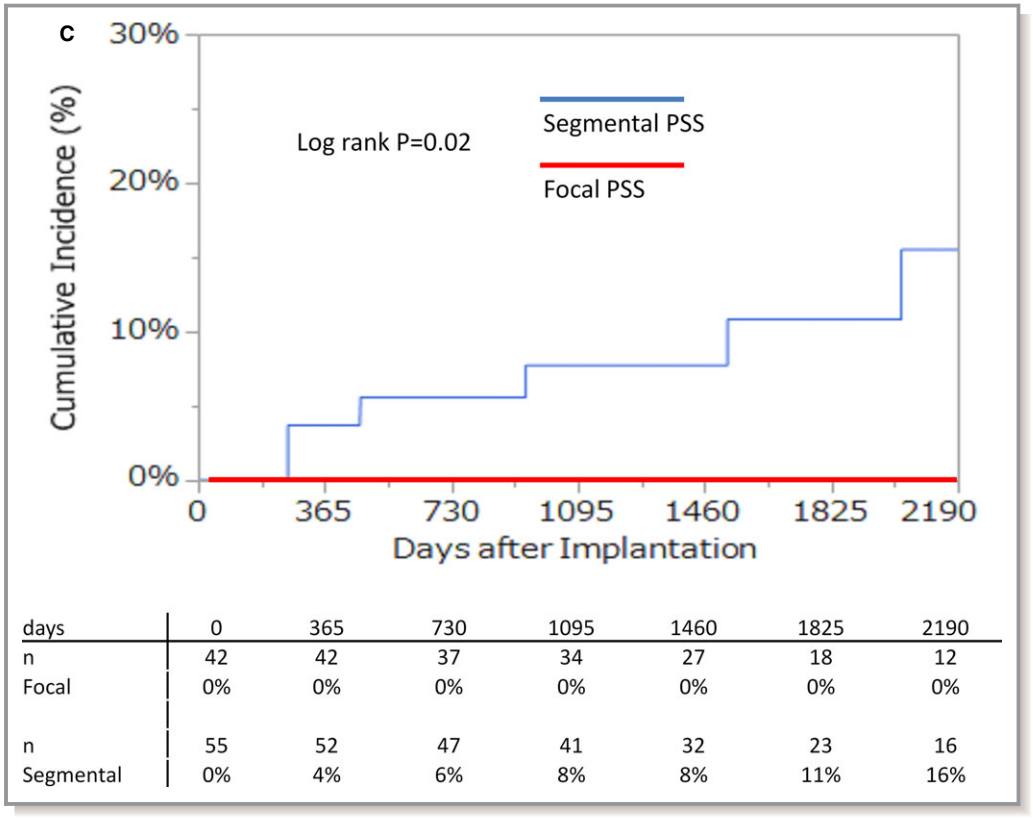
Figure 3. Cumulative incidence of overall TLR including those TLR procedures for stent thrombosis (A), overall TLR excluding those TLR procedures for stent thrombosis (B). Cumulative incidence of symptomatic TLR (C). PSS indicates peri-stent contrast staining; TLR, target lesion revascularization

Characteristics of Lesions With PSS

CTO is a risk factor for PSS[5,8] and consistent with the findings of the present study because longer lesions with CTO were more frequent in patients with segmental PSS. Furthermore, uncovered struts, malapposed struts, and red thrombus are frequently observed in lesions with PSS.[15] Moreover, incomplete stent apposition (ISA) occurs at a PSS site.[18,19] These results suggest that the range of frequencies of uncovered or malapposed struts are observed more often in lesions with segmental PSS than in lesions with focal PSS.

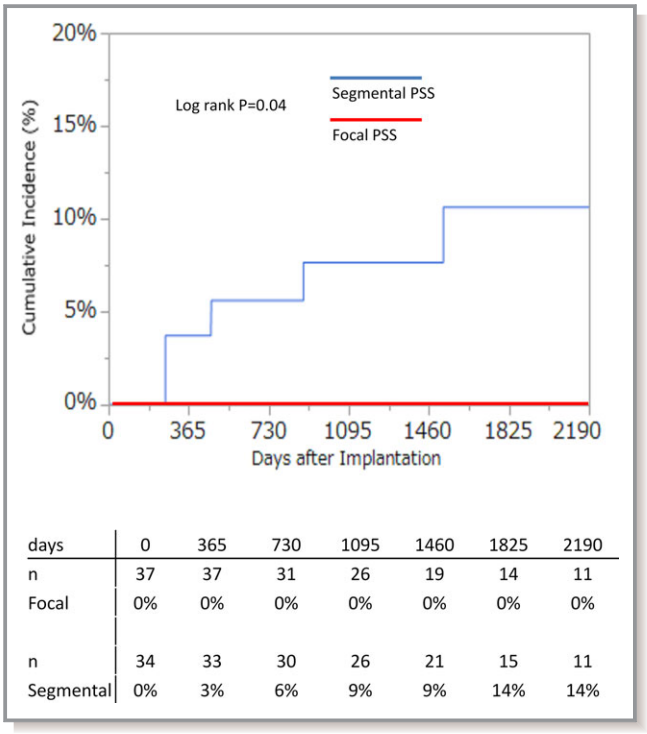
In this second generation of the DES era, lesions with focal PSS are frequently observed. For example, acute ISA decreases in patients with a second-generation DES compared with those with a first-generation DES.[20]

The rate of PSS after EES implantation is lower than that after SES implantation, and the incidence of PSS after EES implantation is 1.2%.[7] One reason to account for the lower



days	0	365	730	1095	1460	1825	2190
n	42	42	37	34	27	18	12
Focal	0%	0%	0%	0%	0%	0%	0%
n	55	52	47	41	32	23	16
Segmental	0%	4%	6%	8%	8%	11%	16%

Figure 3. continued



days	0	365	730	1095	1460	1825	2190
n	37	37	31	26	19	14	11
Focal	0%	0%	0%	0%	0%	0%	0%
n	34	33	30	26	21	15	11
Segmental	0%	3%	6%	9%	9%	14%	14%

Figure 4. Cumulative incidence of ST after DES deployment. DES indicates drug-eluting stent; PSS, peri-stent contrast staining; ST, stent thrombosis.

incidence of segmental PSS after second-generation DES implantation compared with a first-generation DES is a reduced reactive response in the coronary arteries to the second-generation DES. The thinner stent struts of a second-generation DES may be less likely to cause chronic inflammation. Thus, segmental PSS was observed less frequently in patients with a second-generation DES associated with PSS.

Prognosis of Lesions With Segmental PSS

In the present study, the cumulative incidence of TLR, excluding TLR procedures for treating ST, was significantly higher in association with segmental PSS than that previously reported.[5,8] As mentioned above, uncovered or malapposed struts leading to incomplete endothelial coverage and neoatherosclerosis are frequently observed in lesions with PSS.[15,21] Because the width of PSS is greater in a segmental PSS than in a focal PSS, we suggest that uncovered or malapposed struts may be frequently observed in lesions with segmental PSS. This explains why lesions with segmental PSS are more likely to develop neoatherosclerosis as well as in-stent restenosis compared with lesions with focal PSS.

In the present study, the cumulative incidence of TLR was higher in the segmental PSS group than in the focal PSS group

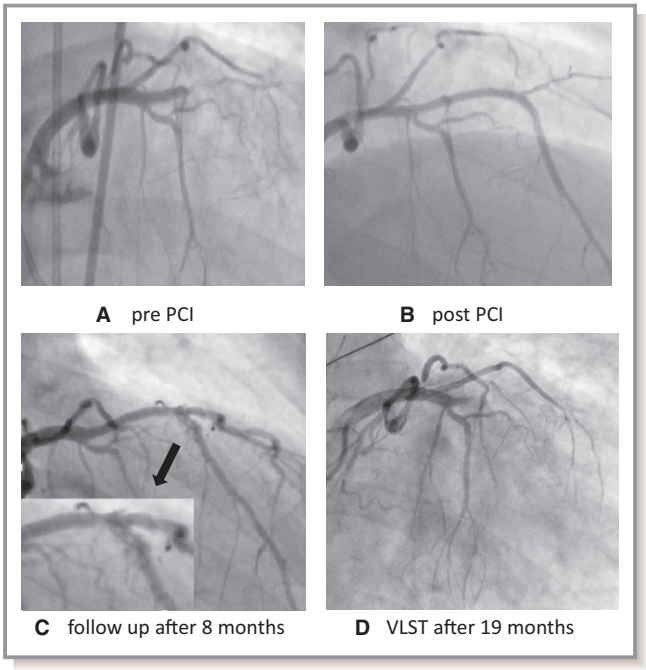


Figure 5. Representative case of PSS with very late-stent thrombosis (VLST). A, A 61-year-old man presented with effort angina. B, SES was placed in the left ascending coronary artery chronic total occlusion site. C, Segmental PSS was found by follow-up angiography at 8 months. D, VLST had occurred at 19 months after SES deployment. PCI indicates percutaneous coronary intervention; PSS, peri-stent contrast staining; SES, sirolimus-eluting stent.

because lesions with focal PSS are likely to have fewer uncovered struts and ISA than those with segmental PSS. Lesions with segmental PSS may have more malapposed struts compared with those with focal PSS, which causes a high shear-flow disturbance and the formation of more thrombi.[22] This might explain the mechanism of thrombus formation and ST in lesions with segmental PSS. Moreover, evidence indicates that an abnormal vascular response associated with inflammation may be prolonged at the PSS site. Thus, segmental PSS incurs a high risk for ST when flow disturbances are related to anatomical structures.

We detected one late stent thrombosis patient and 3 VLST patients. The cessation of DAPT caused late stent thrombosis; however, we were unable to determine the cause of VLST. A previous study indicated that PSS contributes to the mechanism of VLST.[6] The frequencies of TLR and ST do not increase in lesions with PSS after treatment for acute myocardial infarction;[17] however, these results are not relevant to those of the present study because the target lesions studied here included those caused by acute coronary syndrome as well as de novo lesions associated with acute coronary syndrome–induced lesions.

An effective treatment for lesions with PSS is not available at this time. The continuous administration of DAPT decreases the risk of ST[23,24]; however, this cannot be generalized to the decrease of ST for lesions with PSS because there was not a significant difference in the duration of DAPT between the 2 groups. The implantation Endeavor ZES to treat VLST associated with ISA is useful[25] and may provide effective treatment for lesions with segmental PSS because of full neointimal proliferation after Endeavor ZES implantation at the ISA site. However, we focused here on identifying the type of PSS that confers high risk for developing VLST. If segmental PSS is incidentally detected, our findings indicate that constant follow-up is mandatory to facilitate early identification of ischemia at the site of PSS, and DAPT continuation might not be an effective therapy. If segmental PSS increases gradually with repeat angiography, that is one of the risk factors for VLST and full neointimal proliferation might be needed with percutaneous coronary intervention for the site of segmental PSS to prevent VLST. Further studies are required to better understand the mechanisms, treatment options, and clinical course of PSS.

Clinical Implications

Segmental PSS seemed to be related to TLR and VLST in this study. To prevent in-stent restenosis, constant follow-up is mandatory if segmental PSS is incidentally detected. DAPT therapy itself might not be effective to prevent VLST. If

	Focal PSS	Segmental PSS	Adjusted HR	P value
Lesion number-no.	42	55	(95% CI)	
All TLR including ST	4 (9.5%)	21 (38.2%)	4.5 (1.6 to 12.5)	0.004
ALL TLR excluding ST	4 (9.5%)	21 (30.9%)	3.3 (1.1 to 9.5)	0.025

Figure 6. Adjusted 6-year outcomes of TLR comparing Focal PSS vs Segmental PSS. HR indicates hazard ratio; PSS, peri-stent contrast staining; ST, stent thrombosis; TLR, target lesion revascularization.

segmental PSS increases gradually with repeat angiography, Endeavor ZES implantation might lead to full neointimal proliferation at the site of PSS, which prevents occurrence of VLST.

Study Limitations

There are several limitations to the present study. First, this was a single-center study, and follow-up angiography was not performed for all patients. Therefore, selection bias may exist and may have biased the conclusions. Second, the number of patients with PSS was insufficient to investigate the correlation between segmental PSS and clinical outcomes. The actual incidences and risk factors for ST and TLR after the diagnosis of PSS require the evaluation of a larger number of patients that must be subjected to longer follow-up.

Conclusions

The frequency of segmental PSS tended to be higher in patients with CTO, after patients were implanted with a first-generation DES, and appeared to be significantly associated with TLR and ST.

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Disclosures

None.

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