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Fate and clinical significance of angiographically visible stent malapposition (peri-stent contrast staining) after drug-eluting stent implantation: a long-term clinical follow-up study

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KEYWORDS

- drug-eluting stent (DES)
- intravascular ultrasound (IVUS)
- stent fracture
- stent malapposition
- stent thrombosis

Abstract

Aims: Peri-stent contrast staining (PSS) is thought to represent angiographically visible incomplete stent apposition, and may be associated with adverse clinical sequelae. We investigated the prognostic significance of PSS in patients with sirolimus-eluting stents (SES).

Methods and results: Consecutive patients undergoing SES implantation with follow-up angiography (n=807, 644 male, mean age 66.0 years) at >6 months were studied. The primary endpoint was major adverse cardiac events (MACE), defined as a composite of death, myocardial infarction, stent thrombosis, and target lesion revascularisation. Twenty patients (2.48%) exhibited PSS at follow-up angiography. After a median of five years (3,744 patient-years) of follow-up, seven (35.0%) in the PSS group reached the primary endpoint versus 117 (14.9%) in the non-PSS group (p=0.013). Together with diabetes, renal failure, unstable angina, saphenous vein graft and longer total stent length, PSS independently predicted the primary endpoint (HR: 2.94, 95% confidence interval 1.36 to 6.35, p=0.006). PSS was also significantly associated with very late stent thrombosis (VLST), which occurred in three (15.0%) patients with PSS versus 13 (1.7%) patients without PSS (p=0.006).

Conclusions: PSS is an uncommon but significant angiographic finding in patients treated with SES implantation, which independently predicts MACE, and may contribute to an increased risk of VLST.

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Introduction

The initial success of drug-eluting stents in ameliorating restenosis has been tempered by the recognition of an apparently higher incidence of late stent-related complications relative to bare metal stents, including very late stent thrombosis (VLST)[1-10]. Amongst other factors, VLST has been linked to incomplete stent apposition as detected by intravascular ultrasound and/or optical coherence tomography[11-16]. However, these invasive imaging modalities are not in widespread routine clinical use, and the majority of coronary interventions remain guided by conventional x-ray angiography alone.

While Alfonso and co-workers reported that three patients suffered from VLST associated with angiographic coronary aneurysm, Imai et al described the phenomenon of peri-stent contrast staining (PSS), which they defined as contrast staining outside stent struts insufficient to fulfil the definition of a coronary artery aneurysm (localised dilatation of the lumen; >50% of the diameter of associated reference vessel segment) in a single-centre retrospective cohort study[17,18]. Imai and colleagues found an association between PSS within 12 months of sirolimus-eluting stent (SES) implantation and subsequent major adverse cardiac events (MACE), including target lesion revascularisation (TLR) and VLST[18]. The finding of PSS may therefore potentially identify patients at increased risk requiring prompt remedial intervention. However, their study was limited by low event rates and clinical follow-up was for up to only three years. Before the widespread recognition of PSS as a harbinger of increased risk, there is a need to confirm these findings in other centres. We sought to determine the longer-term clinical significance of PSS with follow-up up to five years, and to explore its relationship with stent strut fracture[19,20]. We further sought to determine the baseline clinical and procedural factors predisposing to PSS.

Editorial, see page 12

Methods

STUDY POPULATION, OUTCOME MEASURES AND FOLLOW-UP

We prospectively enrolled 939 consecutive patients undergoing percutaneous coronary intervention (PCI) with sirolimus-eluting stents to examine long-term angiographic and clinical outcome at the Fujita Health University Hospital, Toyoake, Japan, from June 2004 to August 2009. Patients with a target lesion in a native coronary artery undergoing elective stent implantation with agreement to follow-up coronary angiography were included in the study. Patients were excluded from the study if they had a contraindication to anticoagulation and antiplatelet therapy. Overall, 132 patients did not undergo follow-up angiography and were excluded from the study cohort, giving rise to a final study population of 807 patients **(Figure 1)**. Patients underwent routine follow-up angiography after a minimum of six months and were followed up clinically for a minimum of four years (median five years, interquartile range from four years to six years) with a total of 3,744 patient-years accrued and 100% clinical follow-up. The study was approved by our institutional ethics committee and was carried out in accordance with the guidelines set out in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Our primary endpoint was a composite of MACE, defined as subacute stent thrombosis (≤30 days after the procedure); late stent thrombosis (>30 days after the procedure); very late stent thrombosis (VLST, defined as stent thrombosis >1 year after the procedure); death, Q-wave and non-Q-wave myocardial infarction, and need for target lesion revascularisation (TLR).

All patients were followed up for the study endpoint by a combination of telephone interviews, review of medical records, and consultation with referring cardiologists and patients' primary care physicians. All events were adjudicated by an endpoint committee blinded to the angiographic data.

PERCUTANEOUS CORONARY INTERVENTION PROCEDURES

According to standard patient care, treatment with aspirin at a dose of 100-200 mg daily was started before the procedure and continued indefinitely. Treatment with a thienopyridine was begun before the procedure and continued for at least one year to avoid subacute and late stent thrombosis.

Sirolimus-eluting stent (CYPHER®; Cordis, Johnson & Johnson, Miami Lakes, FL, USA) implantation was performed according to standard clinical practice with radial or femoral approaches using

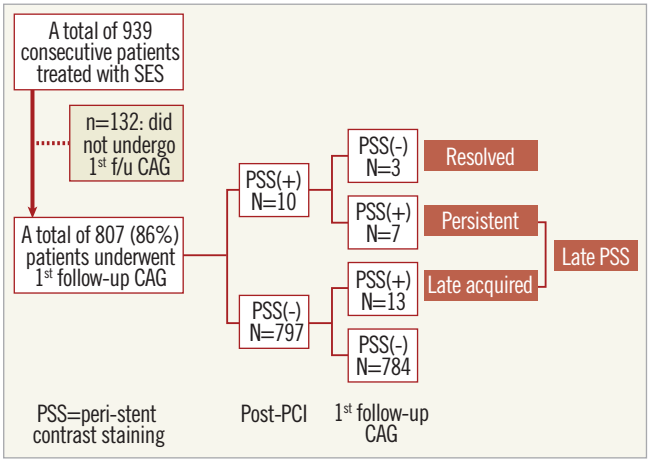

Figure 1. *Study flow chart illustrating study design. PSS: peri-stent contrast staining; SES: sirolimus-eluting stent*

guide catheters 6 Fr or greater in a size to facilitate subsequent quantitative coronary angiographic (QCA) analysis[21,22]. A bolus of 8,000-10,000 IU of heparin was administered during the procedure. To ensure full expansion of the stent, high-pressure intra-stent balloon inflation was performed. Stent and balloon sizes were determined using measurements of vessel dimension and plaque distribution made with IVUS, where technically possible. A total of 766 (95%) patients underwent IVUS-guided PCI. The IVUS criteria for optimal stenting were originally derived from the MUSIC study: (1) good stent apposition with symmetric stent expansion; (2) full stent expansion with sufficient lumen area (i.e., lumen area 80% or greater of the average reference lumen area pre-intervention); and (3) the absence of major dissection[23]. To fulfil these criteria, repeated high-pressure intra-stent balloon inflation or additional stenting was performed if necessary.

QCA analysis

QCA analyses were performed using the computer-based edge-detection Coronary Angiography Analysis System (CAAS II; Pie Medical Imaging, Maastricht, The Netherlands)[21,24]. Coronary angiograms were obtained in multiple views matched after intracoronary injection of nitrates. Interpolated reference vessel diameter, minimal lumen diameter (MLD) and percentage diameter stenosis were obtained at baseline (pre stenting), post-stenting, and at follow-up using the guiding catheter from the QCA system as a scaling device. QCA analyses were performed at the independent core laboratory of the Fujita Health University. QCA measurements of the target lesion were obtained in the "in-stent" (including only the stented segment) and in the 5 mm adjacent segments (the stent margins 5 mm proximal and distal to the stent). Late loss was defined as the change in MLD at follow-up (MLD post-stenting minus MLD at follow-up). Restenosis was defined as ≥50% diameter stenosis at follow-up by QCA.

PERI-STENT CONTRAST STAINING AND STENT FRACTURE DEFINITIONS

PSS was defined as contrast staining outside of the stent struts extending to >20% of the diameter of the corresponding reference vessel segments[18]. Stent fracture was defined as the significant disappearance of stent struts in the stent at follow-up angiography in comparison with the presence of stent struts immediately after stent implantation, or by newly developed fluoroscopic discontinuity of stent struts at follow-up[20]. The presence of PSS and stent fracture was determined in the core laboratory independently by two experienced observers blinded to all clinical data, with adjudication by a panel in cases of disagreement.

STATISTICAL ANALYSIS

All continuous variables are expressed as mean±SD for normally distributed variables or as medians and interquartile ranges for non-parametric data. Normality was assessed using the Kolmogorov-Smirnov test. The unpaired t-test or Mann-Whitney U test was used to assess differences in continuous variables between two groups as appropriate. Categorical data are presented as frequencies and percentages. Differences in categorical variables were assessed using the chi-square test or Fisher's exact test where appropriate. Cumulative event-free survival for MACE was assessed using the Kaplan-Meier method, and comparison between groups was performed using the log-rank test. Where appropriate, a multivariable Cox proportional hazards model was used to adjust for potentially confounding variables with $p<0.05$ on univariable analysis using a forward stepwise variable selection procedure. The validity of the proportionality of hazards assumption was appropriately checked. To evaluate the predictors of PSS, multivariable binary logistic regression analysis including variables with $p<0.05$ by univariable analysis was performed using a forward stepwise variable selection procedure. All data were analysed using SPSS Version 21 (IBM Corp., Armonk, NY, USA). Only a single culprit lesion was evaluated per patient to avoid the effects of intra-cluster correlation (ICC). Two-tailed values of $p<0.05$ were considered significant.

Results

Overall, there were 23 cases of PSS identified in the study cohort – 10 immediately after SES implantation and a further 13 cases identified at follow-up **(Figure 1)**. Of the 10 initial cases, three had resolved at pre-planned follow-up angiography. The final number of patients with PSS was therefore 20 (2.48%).

Table 1. Baseline demographic and clinical characteristics of the study cohort.

		Late PSS (n=20)	Non-PSS (n=787)	*p*-value
No. of lesions		20	787	–
Age (years)		64.8±8.8	66.3±9.4	0.771
Male (%)		16 (80.0)	626 (79.5)	0.962
Body mass index (kg/m^2)		23.6±2.4	24.0±3.1	0.645
Diabetes (%)		5 (25.0)	258 (32.8)	0.463
Hypertension (%)		11 (55.0)	490 (62.3)	0.509
Hypercholesterolaemia (%)		9 (45.0)	446 (56.7)	0.299
Renal insufficiency (%)		3 (15.0)	109 (13.9)	0.750
Current smoking (%)		11 (55.0)	251 (31.9)	0.029
Prior infarction (%)		9 (45.0)	305 (38.8)	0.572
Previous angioplasty (%)		13 (65.0)	379 (48.2)	0.137
Previous bypass surgery (%)		1 (5.0)	54 (6.9)	0.793
Clinical status (%)	Stable angina	15 (75.0)	571 (72.6)	0.809
	Unstable angina	1 (5.0)	105 (13.3)	0.499
	Acute myocardial infarction	3 (15.0)	86 (10.9)	0.476
	Recent myocardial infarction	1 (5.0)	25 (3.2)	0.485
Emergency PCI		5 (25.0)	153 (19.0)	0.567
Left ventricular ejection fraction (%)		59.4±10.7	57.6±12.5	0.492
Medical treatment (%)	Statins	12 (60.0)	470 (59.7)	0.979
	Beta-blockers	6 (30.0)	310 (39.3)	0.395

Values are expressed as mean±SD or n (%). PCI: percutaneous coronary intervention

Table 1 summarises the baseline demographic and clinical characteristics of the PSS and non-PSS groups. There was a significantly higher proportion of current smokers amongst the PSS patients but the two groups were otherwise comparable. With respect to vessel and lesion characteristics, patients in the PSS group exhibited greater vessel tortuosity **(Table 2)**. The procedural characteristics for the two groups were largely similar; however, the reference vessel diameter at baseline was greater in the PSS group **(Table 3)**. None of the patients had stent strut fracture at baseline. However, patients in the PSS group had a significantly higher incidence of stent strut fracture at follow-up relative to the non-PSS group (20.0% versus 5.7% respectively, p=0.008).

CLINICAL FOLLOW-UP

At the end of follow-up, of the 20 patients with PSS, seven (35%) reached the primary endpoint of MACE versus 117 (14.9%) in the non-PSS group (p=0.013) **(Figure 2A)**, a difference largely driven by myocardial infarction and the need for target lesion revascularisation **(Figure 2B, Figure 2C, Table 4)**. Overall, three patients (15.0%) in the PSS group experienced VLST versus 13 patients (1.7%) in the non-PSS group (p=0.006) **(Figure 2D, Table 4)**. After adjusting for the presence of stent fracture and other baseline clinical and angiographic differences, the presence of PSS remained a significant independent predictor of the primary outcome of MACE (hazard ratio [HR]: 2.94, 95% confidence interval [CI] 1.36 to 6.35, p=0.006) **(Figure 3, Table 5)**. The presence of diabetes, renal failure, unstable angina, saphenous vein graft and longer total stent length were also significant independent predictors of outcome.

Table 2. Baseline angiographic characteristics of the study cohort.

		Late PSS (n=20)	Non-PSS (n=787)	*p*-value
Location of target lesion (%)	Right coronary	6 (30.0)	232 (29.5)	0.960
	Left anterior descending	8 (40.0)	360 (45.7)	0.611
	Circumflex	5 (25.0)	172 (21.9)	0.784
	Left main	1 (5.0)	19 (2.4)	0.398
	Saphenous vein graft	0 (0.0)	7 (0.9)	0.675
In-stent restenosis (%)		3 (15.0)	81 (10.3)	0.454
De novo (%)		16 (80.0)	681 (86.5)	0.337
Eccentric (%)		18 (90.0)	574 (72.9)	0.122
Severe calcification (%)		4 (20.0)	118 (15.0)	0.552
Tortuosity (%)		8 (40.0)	154 (19.6)	0.024
Bifurcation (%)		13 (65.0)	367 (46.6)	0.104
Ostial location (%)		2 (10.0)	123 (15.6)	0.755
Chronic total occlusion (%)		1 (5.0)	25 (3.2)	0.485
Thrombosis (%)		2 (10.0)	84 (10.7)	0.924
Angle >60°		2 (10.0)	62 (7.9)	0.668
Multiple bending (%)		2 (10.0)	57 (7.2)	0.652
Type B2/C (%)		17 (85.0)	541 (68.7)	0.145

Values are expressed as n (%).

Table 3. Angiographic, procedural, and quantitative coronary angiography (QCA) data.

	Late PSS (n=20)	Non-PSS (n=787)	*p*-value
Procedural characteristics			
Stent size (mm)	3.1±0.3	3.0±0.4	0.488
Maximum inflation pressure (atm)	16.1±3.3	15.9±3.0	0.765
No. of stents per lesion	1.3±0.5	1.3±0.6	0.814
Total stent length (mm)	27.6±12.4	24.5±10.4	0.592
IVUS use (%)	19 (95.0)	747 (94.9)	0.998
Direct stenting (%)	6 (30.0)	310 (39.4)	0.396
Crush stenting (%)	1 (5.0)	29 (3.7)	0.536
Bifurcation stenting (%)	7 (35.0)	166 (21.1)	0.134
Kissing balloon technique (%)	1 (5.0)	34 (4.3)	0.592
Angle alteration			
Angle (°)	148.9±17.5	147.3±18.2	0.786
Post-angle (°)	162.5±13.2	160.1±12.6	0.626
Reduction angle (°)	13.6±11.0	12.8±12.2	0.563
Follow-up angle (°)	154.9±15.0	155.0±16.1	0.568
Increased angle (°)	7.6±6.8	5.3±9.4	0.047
Acute angiographic outcome			
Angiographic success (%)	19 (95.0)	776 (98.6)	0.262
TIMI 3 (%)	19 (95.0)	774 (98.3)	0.298
QCA			
Reference diameter at baseline (mm)	2.89±0.58	2.54±0.56	0.029
Lesion length (mm)	19.8±12.7	16.9±8.8	0.430
Minimal lumen diameter (mm)			
At baseline	1.06±0.64	0.89±0.45	0.360
After procedure	2.49±0.43	2.47±0.49	0.839
At follow-up	2.22±0.78	2.33±0.61	0.422
Acute gain (mm)	1.43±0.83	1.58±0.57	0.478
Late loss (mm)	0.27±0.60	0.14±0.53	0.529
Stent fracture at follow-up			
Stent fracture (%)	4 (20.0)	45 (5.7)	0.008
Complete fracture (%)	2 (10.0)	30 (3.8)	0.166
Partial fracture (%)	2 (10.0)	15 (1.9)	0.012

Values are expressed as mean±SD or n (%). IVUS: intravascular ultrasound; QCA: quantitative coronary angiography; TIMI: Thrombolysis In Myocardial Infarction

PREDICTORS OF PSS

Multivariable logistic regression analysis revealed that the presence of smoking, stent fracture and a larger reference diameter pre-procedure, all independently predict PSS **(Table 6)**. On pre-specified exploratory analysis, the presence of a circumflex lesion, in-stent restenosis, or chronic total occlusion did not predict subsequent late PSS.

Discussion

We found that PSS was an uncommon occurrence after SES implantation with a net incidence of 2.48% at follow-up angiography. However, it was nonetheless significantly associated with adverse

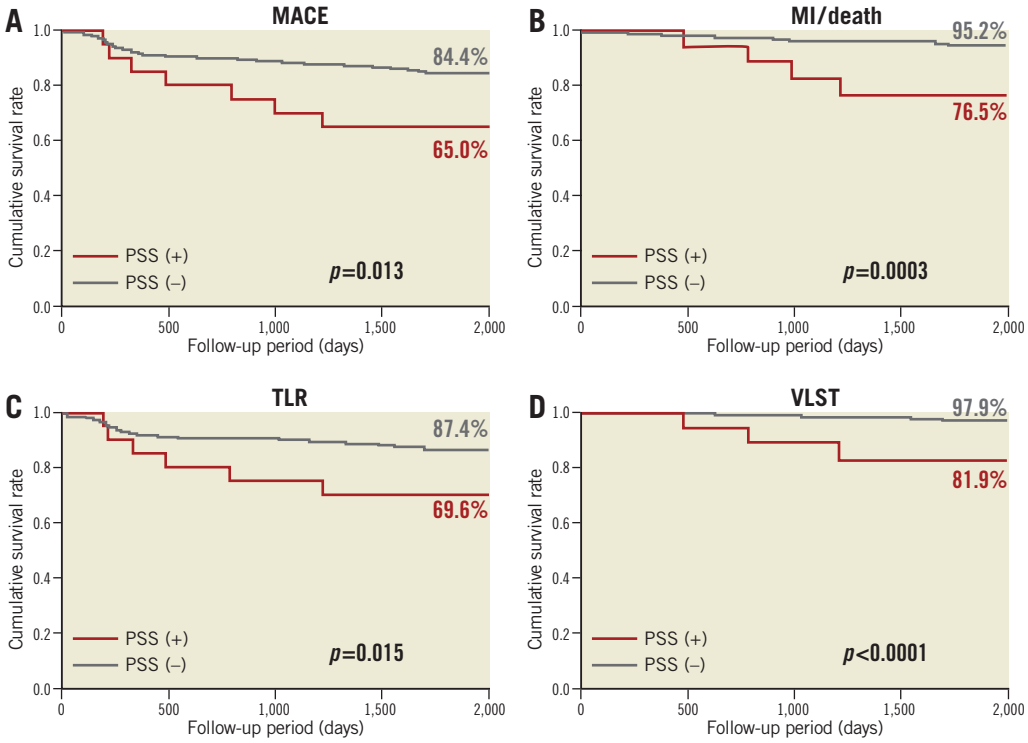

Figure 2. *Kaplan-Meier event-free survival rate for each clinical outcome. A) Kaplan-Meier estimates of event-free survival for the primary endpoint of major adverse cardiac events (MACE) stratified according to the presence or absence of peri-stent contrast staining (PSS). B) Kaplan-Meier estimates of event-free survival for myocardial infarction and death stratified according to the presence or absence of peri-stent contrast staining (PSS). C) Kaplan-Meier estimates of event-free survival from target lesion revascularisation (TLR) stratified according to the presence or absence of peri-stent contrast staining (PSS). D) Kaplan-Meier estimates of event-free survival for the secondary endpoint of very late stent thrombosis (VLST) stratified according to the presence or absence of peri-stent contrast staining (PSS).*

Table 4. Breakdown of study events stratified according to the presence or absence of peri-stent contrast staining (PSS).

	Late PSS (n=20)	Non-PSS (n=787)	*p*-value
In-stent restenosis, n (%)			
Focal	3 (15.0)	70 (8.9)	0.415
Diffuse	3 (15.0)	26 (3.3)	0.032
Overall	6 (30.0)	96 (12.2)	0.018
In-segment restenosis, n (%)			
Overall	7 (35.0)	127 (16.1)	0.025
Stent thrombosis, n (%)			
Definite	3 (15.0)	14 (1.8)	0.007
Probable	0 (0.0)	2 (0.3)	0.824
Possible	0 (0.0)	3 (0.4)	0.786
Definite/probable	3 (15.0)	16 (2.0)	0.010
All	3 (15.0)	19 (2.4)	0.015
Phase of stent thrombosis, n (%)			
Early	0 (0.0)	4 (0.5)	0.750
Late	0 (0.0)	2 (0.3)	0.823
Very late	3 (15.0)	13 (1.7)	0.006
Late/very late	3 (15.0)	15 (1.9)	0.008

Table 5. Summary of the results of univariable and multivariable analysis of the predictors of major adverse cardiac events (MACE) for the study cohort.

	Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Late PSS	2.54 (1.18-5.44)	0.016	2.94 (1.36-6.35)	0.006
Body mass index	0.94 (0.89-0.99)	0.032		
Diabetes	2.00 (1.41-2.84)	0.001	1.98 (1.35-2.89)	0.001
Renal failure	2.84 (1.94-4.18)	<0.001	2.89 (1.91-4.35)	<0.001
Previous MI	1.55 (1.09-2.21)	0.013		
Prior CABG	2.34 (1.38-3.97)	0.002		
Unstable angina	1.68 (1.08-2.63)	0.021	1.90 (1.19-3.01)	0.004
LVEF	0.97 (0.96-0.99)	0.002		
Saphenous vein graft	6.28 (2.31-17.0)	0.001	5.13 (1.83-14.32)	0.002
Ostial location	1.58 (1.03-2.42)	0.035		
Stent fracture	2.08 (1.17-3.70)	0.012		
Number of stents	1.49 (1.17-1.90)	0.002		
Total stent length	1.02 (1.01-1.04)	0.003	1.27 (1.09-1.48)	0.003

Multivariable model included all baseline covariates with $p<0.05$ on univariable analysis, and was performed using a forward stepwise selection procedure. CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PSS: peri-stent contrast staining

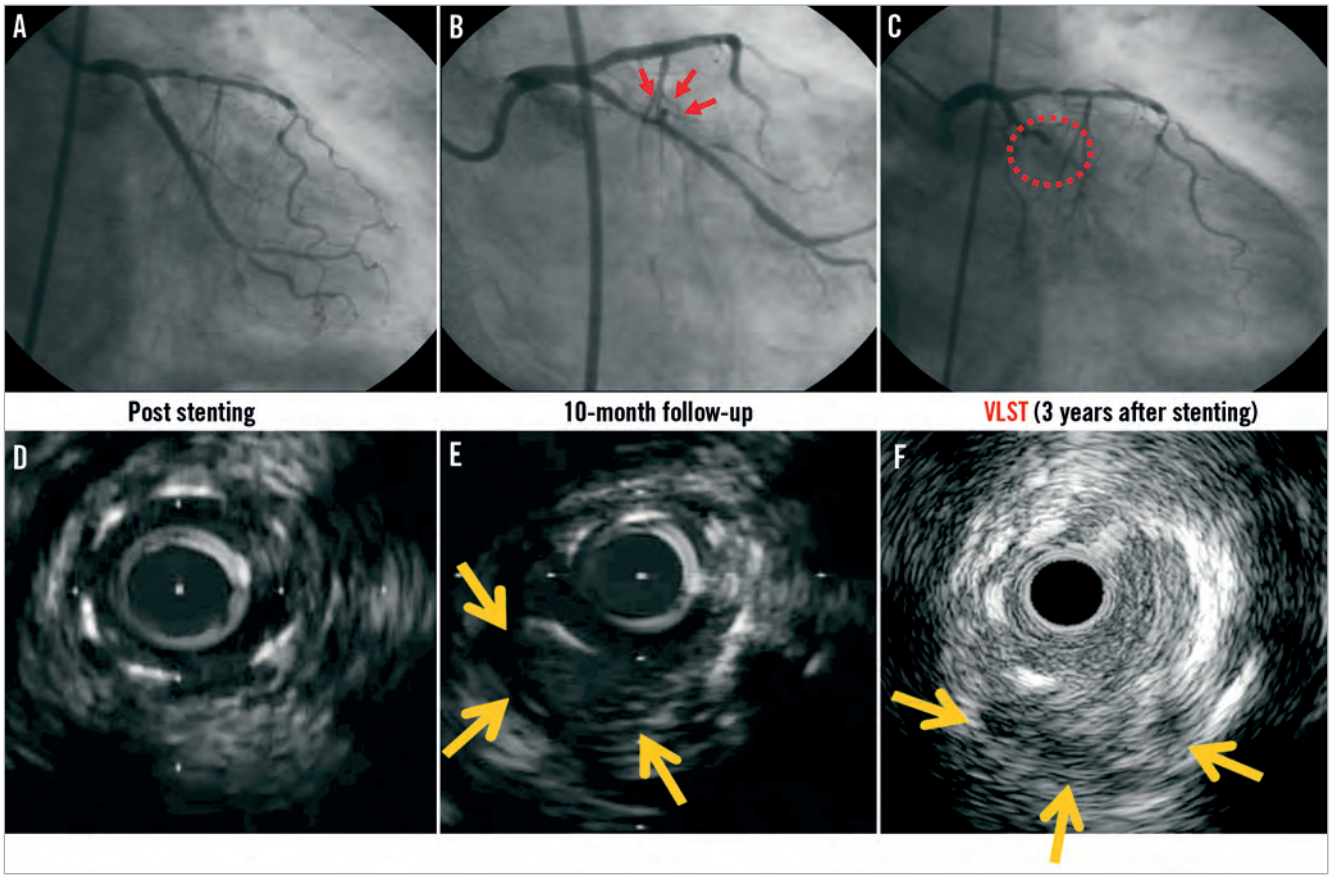

Figure 3. *Late acquired PSS and subsequent VLST. A 72-year-old female with stable angina underwent single stent implantation (3.0×18.0 mm) to the middle segment of the left circumflex coronary artery followed by high-pressure intra-stent balloon dilatation up to 14 atmospheres. Successful stent implantation was performed without significant residual stenosis by angiography (A). At 10-month follow-up, angiographically visible stent malapposition (i.e., peri-stent staining [PSS]) was observed without any significant clinical symptoms (B). At 1,416 days after initial stent implantation, she suddenly developed chest pain and hypotension. Emergent coronary angiography revealed thrombotic occlusion in the stented segment, representing very late stent thrombosis (C). Corresponding IVUS images are shown in the lower panels. These demonstrate a widely patent lumen without stent strut collapse immediately after the stent implantation (D). At 10-month follow-up, IVUS reveals that the external elastic membrane (EEM) is markedly increased and is associated with an incompletely apposed stent strut. This phenomenon produced significant lumen behind the stent strut from 6 o'clock to 9 o'clock (arrows in E). Follow-up IVUS demonstrates that thrombus occupies the lumen both inside the stent as well as behind the stent strut from 5 o'clock to 8 o'clock (arrows in F).*

Table 6. Results of logistic regression analysis of the predictors of peri-stent contrast staining (PSS).

	Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Current smoking	2.61 (1.07-6.38)	0.035	2.51 (1.01-6.21)	0.047
Tortuosity	2.74 (1.10-6.82)	0.030		
Stent fracture	4.12 (1.32-12.84)	0.014	3.64 (1.13-11.79)	0.031
Reference diameter	2.32 (1.12-4.85)	0.024	2.42 (1.13-5.18)	0.023

Multivariable model included all baseline covariates with $p<0.05$ by univariable analysis, and was performed using a forward stepwise selection procedure.

clinical sequelae. For the first time, we were able to demonstrate that PSS is a significant independent predictor of MACE after adjusting for potential confounding variables, including stent fracture.

Imai et al first described the phenomenon of PSS and suggested an association between this finding and adverse outcomes, including TLR and VLST[18]. The incidence of PSS in the present study mirrors that reported by Imai et al. However, despite the fact that they studied 3,081 lesions in total from 1,998 patients, their median follow-up was only three years, and therefore their overall event rate was too low to allow meaningful statistical analysis of their principal study outcomes (TLR after one year and VLST), leaving uncertainty about the long-term clinical significance of this finding. In contrast, the median of five years (3,744 patient-years) of follow-up achieved in the present study, together with our broader but clinically relevant endpoint of MACE, allowed us to evaluate the independent prognostic significance of PSS whilst adjusting for potential confounders, including stent fracture. Furthermore, by studying

only one lesion per patient, we avoided the potential problem of intra-cluster correlation between lesions within patients, which limits the previous work by Imai et al.

Our findings are discordant with those of Yakushiji et al who examined the significance of late PSS in a subgroup of patients from the HORIZONS-AMI study[25]. They found a similar incidence of PSS at follow-up (2.1%) to the present study; however, in contrast to the present study, none of these patients experienced stent thrombosis. There are a number of potential explanations for this discrepancy. Firstly, the patients studied were treated with a mixture of bare metal and paclitaxel-eluting stents, whereas, in the present study, only patients undergoing SES implantation were studied. Secondly, patients with PSS had a higher rate of thienopyridine use at three years compared with those without PSS (50% versus 27%, respectively, p=0.016) with 21/22 (96%) also receiving aspirin. This prolonged use of dual antiplatelet therapy may have abrogated any thrombotic risk associated with PSS in their cohort. Thirdly, their median follow-up duration was three years from enrolment versus five years in the present study. This significantly shorter duration of follow-up will have reduced their power to detect any difference in event rates between those with and without PSS.

We found that current smoking, stent fracture and a larger reference vessel diameter were significantly associated with the development of PSS. These findings are discordant with those of Imai et al who identified chronic total occlusions, circumflex lesions, and in-stent restenosis as predictors of PSS. However, the latter associations should be treated with caution, as multiple lesions were analysed within patients without adjustment for intra-cluster correlation, resulting in potential overestimation of the significance of these associations.

Our analysis revealed that active smoking was one of the most important predictors for the occurrence of PSS. We speculate that the endothelial dysfunction engendered by smoking could predispose to the appearance of PSS in long-term follow-up; however, further work is required to elucidate the exact mechanisms responsible.

The phenomenon of PSS is likely to be an angiographic correlate of incomplete stent apposition. Its association with stent strut fracture is in keeping with this. However, stent malapposition is likely to be multifactorial in aetiology, and our finding that stent fracture was not an independent predictor of outcome is supportive of this. We have previously shown that, amongst other mechanisms, incomplete stent strut apposition can occur as a result of failure of neointimal hyperplasia as well as lesion remodelling[15]. Our present work confirms that, whilst PSS and stent fracture are associated, only PSS is of independent prognostic value for the outcome of MACE.

The significant association between PSS and thrombotic sequelae identified in the present study is in accord with the work of Cook et al, who, using IVUS, identified a high prevalence of incomplete stent apposition in patients with drug-eluting stents presenting with VLST[13]. More recently, we reported that incomplete stent apposition without neointimal hyperplasia by OCT was significantly associated with the presence of OCT-detected thrombus at follow-up, and may constitute a potent substrate for late stent thrombosis[15]. Although OCT and IVUS are likely to be significantly more sensitive at detecting incomplete stent apposition, the majority of patients undergoing PCI are not evaluated with these intracoronary imaging techniques[26]. Thus, the ability potentially to identify significant PSS with the more widely available conventional angiography alone affords the opportunity for remedial intervention.

In our cohort, we observed a VLST rate of ~2% after five years (0.4% per annum), implying a need for continued vigilance in patients treated with drug-eluting stents.

Although rare, this complication can be potentially devastating. We speculate that the presence of PSS may identify a subgroup of patients at higher risk who may benefit from prolonged or lifelong dual antiplatelet therapy; however, this hypothesis requires formal evaluation. The finding by Yakushiji et al that patients with PSS do not experience a greater rate of VLST in a setting where a significant number of these patients were on dual antiplatelet therapy is circumstantially supportive of such a strategy[25].

Study limitations

As PSS is a recently described phenomenon, our study is by necessity retrospective in nature. It was also conducted at a high-volume tertiary referral centre incurring the possibility of selection bias. Additionally, our study was not carried out in multicentre randomised fashion. Nevertheless, this also allowed us to standardise patient assessment and achieve a high rate of follow-up angiography (86%), and 100% clinical follow-up.

Our primary endpoint was a composite of MACE. Despite our large sample size and long minimum follow-up duration, we were underpowered to address specifically the independent prognostic significance of PSS for VLST with adjustment for potential confounders. However, given the rarity of the latter, this is only likely to be possible in the setting of a large multicentre international registry study.

Furthermore, while our primary endpoint was MACE defined as various stages of stent thrombosis, death, myocardial infarction, and need for target lesion revascularisation (TLR), some investigators might prefer to use only death and myocardial infarction. However, we feel that even VLST and TLR would also have significant impact on patients' clinical course because lesions with PSS may be associated with in-stent or in-segment restenosis requiring revascularisation due to abnormal vessel healing response following the SES implantation.

Although our study only evaluated patients undergoing SES implantation, peri-stent staining has also been described with more contemporary stents such as everolimus-eluting devices[27]. However, given the large number of patients who have received first-generation SES and the widespread current use of second-generation products, which have also been afflicted with this complication, we feel our data retain continuing relevance for current clinical practice. Indeed, given the long-term nature of the risk associated with peri-stent contrast staining, we feel it is important to alert the interventional cardiology community to this finding, which may be

present but apparently clinically silent amongst patients undergoing repeat angiography or intervention.

Conclusions

PSS is an uncommon but significant angiographic finding in patients treated with SES which independently predicts MACE, and may contribute to the increased risk of VLST in these patients. Further work is required to clarify the optimum management of patients with angiographically visible incomplete stent apposition and to investigate the mechanisms responsible for it.

Impact on daily practice

While peri-stent contrast staining (PSS) is thought to represent angiographically-visible incomplete stent apposition, previous IVUS/OCT studies revealed that incomplete stent apposition plays a role in thrombus formation following drug-eluting stent implantation[13-15]. However, previous studies have provided conflicting circumstantial evidence concerning the role of PSS in very late stent thrombosis[1,25]. Our study clearly and statistically demonstrated for the first time that PSS independently predicted major adverse cardiac events including death, MI, stent thrombosis and target lesion revascularisation, together with diabetes, renal failure, unstable angina, saphenous vein graft and longer total stent length. Furthermore, PSS was also significantly associated with very late stent thrombosis. Given that millions of patients around the world have been treated with the first generation sirolimus-eluting CYPHER® stent, PSS is a serious concern and should be recognised as a potential risk-marker for very late drug-eluting stent failure.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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