

Peri-stent contrast staining and very late stent thrombosis after sirolimus-eluting stent implantation: an observation from the RESTART (REgistry of Stent Thrombosis for review And Re-evaluATion) angiographic substudy

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KEYWORDS

- angiography
- drug-eluting stents
- incomplete stent apposition
- stent fracture
- stent thrombosis

Abstract

Aims: The aim of the study was to clarify the angiographic characteristics of stent thrombosis (ST) in relation to sirolimus-eluting stents (SES).

Methods and results: RESTART is a Japanese registry of SES-associated ST. As an angiographic substudy, coronary angiograms at baseline, at six to 12 months and at the time of ST were analysed. Angiograms of 313 patients (early ST [EST] 169 patients, late ST [LST] 59 patients, and very late ST [VLST] 85 patients) were investigated. Residual dissection post procedure was more frequently seen in the EST group. Stent fracture was more frequently seen in the VLST group than in the EST and LST groups (16.5%, 3.0%, and 3.4%, respectively; $p < 0.001$). Peri-stent contrast staining (PSS), defined as contrast staining outside the stent contour extending to $\geq 20\%$ of the stent diameter, was remarkably more prevalent in the VLST group than in the EST and LST groups (34.1%, 4.7%, and 6.8%, respectively; $p < 0.001$).

Conclusions: Abnormal angiographic findings such as PSS and stent fracture were found significantly more frequently in lesions with VLST than in lesions with EST and LST.

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Introduction

Stent thrombosis (ST) is one of the most serious complications of percutaneous coronary intervention (PCI). It has been reported that very late ST (VLST) beyond one year after stent implantation occurred more frequently after drug-eluting stent (DES) implantation than after bare metal stent (BMS) implantation¹. VLST has been reported as continuing to occur until three to four years of follow-up without any signs of attenuation of its incidence²⁻⁵. Mechanisms of VLST are currently very poorly understood, and even clinical and angiographic features of VLST after DES implantation have not yet been adequately described, mainly due to its low incidence and emergent situation. We have reported the differences in baseline demographic features, TIMI flow grade and mortality rate, according to the timing of ST in the RESTART registry (REgistry of Stent Thrombosis for review And Re-evaluATion)⁶. In addition, we previously demonstrated that peri-stent contrast staining (PSS) found within 12 months after sirolimus-eluting stent (SES) implantation seemed to be associated with subsequent VLST⁷. However, in the previous study, the prevalence of PSS in patients with VLST was not clarified due to the very small number of definite ST cases in patients with prior PSS diagnosis, and the lack of detailed angiographic analysis at the time of VLST.

In the current angiographic substudy of the RESTART registry, we sought to evaluate the detailed angiographic findings at the time of SES implantation, at six to 12 months follow-up, and at the time of ST. Qualitative and quantitative angiographic parameters were compared according to the timing of ST.

Methods and design

STUDY POPULATION

The RESTART registry is a nationwide Japanese registry of patients with ST after SES implantation. Design and patient enrolment of the RESTART registry have been published previously⁶. In the current angiographic substudy, coronary angiograms at baseline and at the time of ST were analysed in an angiographic core laboratory (Cardiocore, Tokyo, Japan). In cases of VLST, scheduled follow-up angiograms performed at six to 12 months were also analysed. The study protocol was approved by the ethics committees of the two centres to which the two principal investigators are affiliated (Kyoto University Hospital and Teikyo University Hospital). Because this study was conducted retrospectively, written informed consent was waived according to the guidelines for epidemiologic studies issued by the Ministry of Health, Labour and Welfare of Japan.

Among 235 centres reporting ST cases in the RESTART registry, 154 centres agreed to participate in the angiographic substudy (**Online Appendix**). The study population of the angiographic substudy consisted of 313 patients with ST out of the entire cohort of 611 patients enrolled in the RESTART registry. All angiograms with ST from centres participating in the angiographic substudy were analysed. There were 169 patients with early ST (EST), 59 patients with late ST (LST), and 85 patients with VLST (**Figure 1**). Angiograms both at baseline procedure and at the time of ST were analysed in all cases. Follow-up angiograms at six to 12 months were performed based on the sites' discretion and analysed in 57 cases (67%) out of 85 cases with VLST.

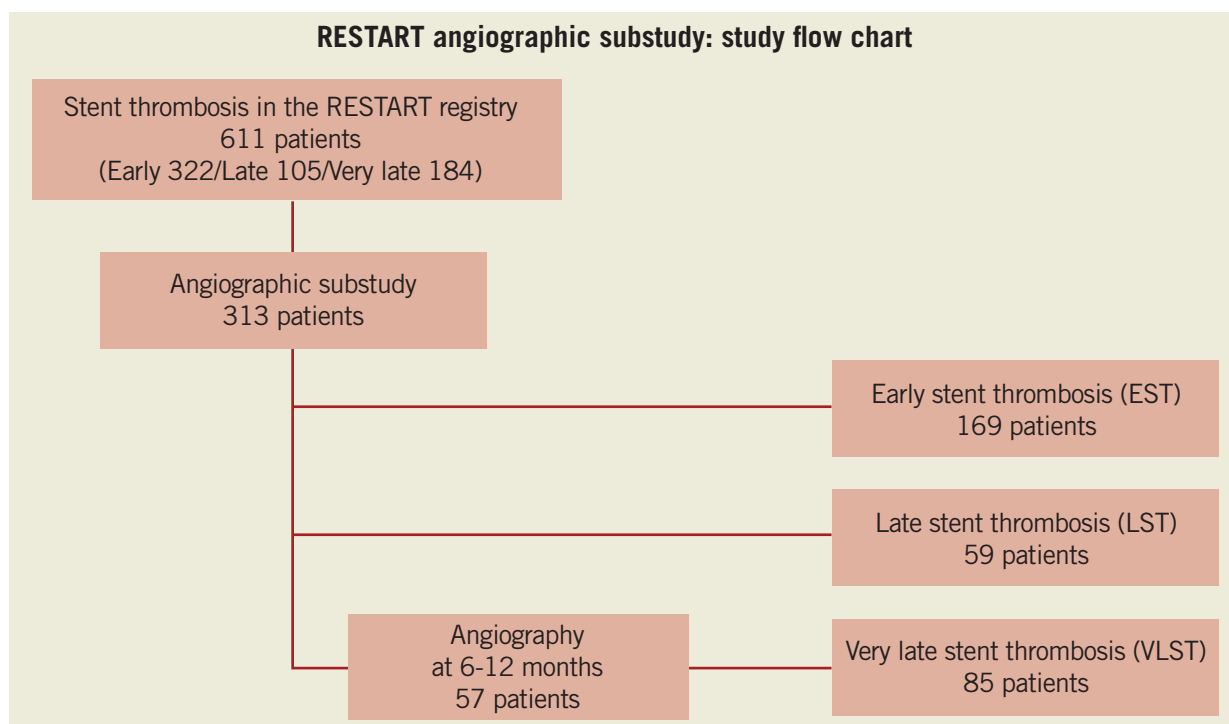


Figure 1. Study flow chart for the angiographic substudy of the RESTART registry. RESTART: registry of stent thrombosis for review and re-evaluation; CAG: coronary angiography; EST: early stent thrombosis; LST: late stent thrombosis; VLST: very late stent thrombosis

DEFINITIONS

ST was defined according to the Academic Research Consortium (ARC) definition⁸. Only patients with ARC definite ST were enrolled in the RESTART registry. ST was judged by the site investigators to have occurred if thrombolysis in myocardial infarction (TIMI) flow was grade 0 or 1 with occlusion originating in the peristent region, or grade 2 or 3 in the presence of angiographic evidence of thrombus associated with signs and symptoms of acute coronary syndrome (ACS). ST was categorised according to the timing of the occurrence of ST into EST (within 30 days), LST (between 31 and 365 days) and VLST (beyond one year).

ANGIOGRAPHIC ANALYSIS

Each angiogram was assessed both qualitatively and quantitatively by two experienced interventional cardiologists in an independent angiographic core laboratory (Cardiocore, Tokyo, Japan). Quantitative coronary angiographic analysis (QCA) was carried out with the CAAS 5.4 (Pie Medical Imaging, Maastricht, The Netherlands). The target segment was defined as the entire segment involving the implanted stent and the 5 mm proximal and distal edges adjacent to the stent. Angiographic analysis at the time of ST included angiographic evidence of thrombus, TIMI flow grade, stent fracture and PSS. Stent fracture was detected on coronary angiography according to the previously reported definition⁹, which was either partial strut fracture or complete separation of the stented segment. At the time of ST, PSS was evaluated after thrombus aspiration and/or balloon angioplasty. PSS was defined by discussion among

six investigators (Kimura, Kadota, Imai, Tada, Suzuki and Kozuma) as contrast staining outside the stent contour extending to $\geq 20\%$ of the stent diameter, considering the resolution of QCA (3 pixels exceeding the stent border from the 3.0 mm stent), as previously described⁷. Timing of PSS was classified as resolved PSS (PSS observed at post-stenting but not at follow-up), persistent PSS (PSS observed both at post-stenting and follow-up) and late acquired PSS (PSS observed at follow-up but not at post-stenting). In the current analysis, only late acquired PSS was evaluated. Angiograms of typical PSS and subsequent ST are demonstrated in **Figure 2**. The extent of PSS was measured using the caliper method of QCA software to determine whether the depth of the contrast staining exceeded 20% of the stent diameter. When a discrepancy between the two observers was found, the final decision was made by discussion and consensus in the angiographic core laboratory. In 98% of the cases (306 out of 313 lesions), the two observers agreed on the presence or absence of PSS.

IVUS ANALYSIS

IVUS data of VLST cases have been collected to clarify the mechanism of PSS findings, retrospectively. Maximum vessel area and the remodelling index were measured by means of PC-based software (EchoPlaque; Indec Systems Inc., Santa Clara, CA, USA). Incomplete stent apposition (ISA) was evaluated according to the previous definition¹⁰. IVUS analysis was conducted in an independent core laboratory at Stanford University Medical Center (Cardiovascular Core Analysis Laboratory, Stanford, CA, USA).

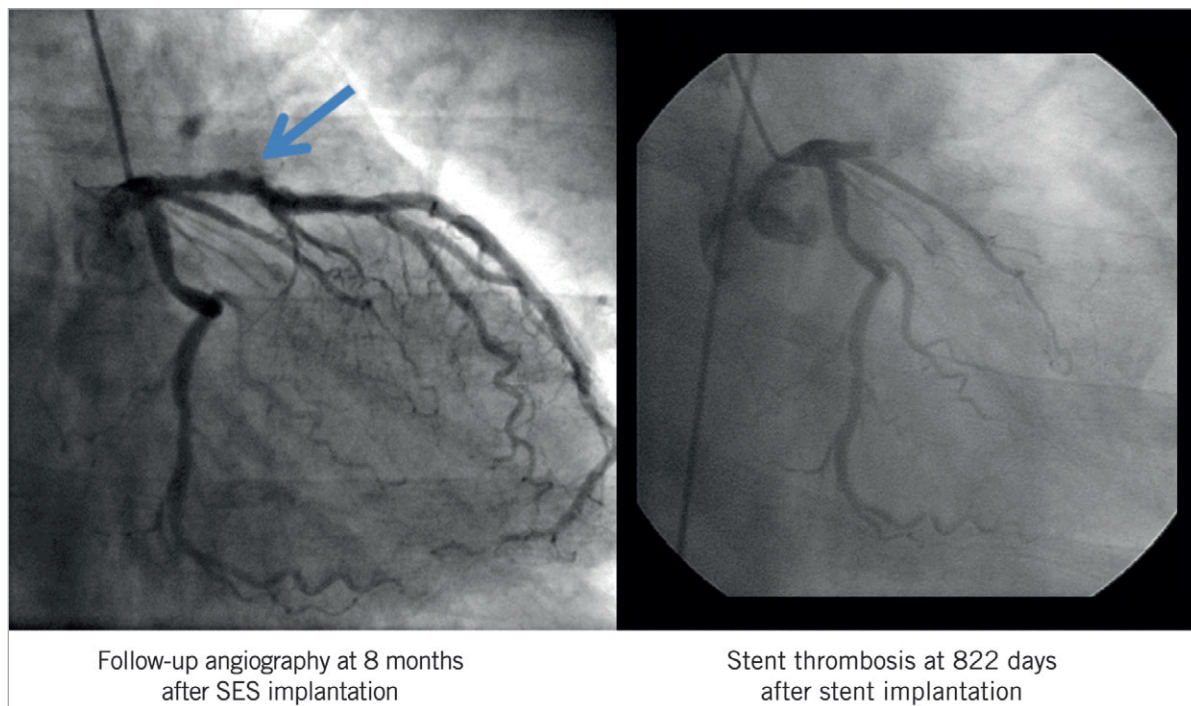


Figure 2. A representative case of PSS diagnosed at 8-month angiographic follow-up with subsequent VLST at 822 days after SES implantation. Arrow indicates the area of PSS. PSS could not be identified at the time of VLST. PSS: peri-stent contrast staining; SES: sirolimus-eluting stent; VLST: very late stent thrombosis

STATISTICAL ANALYSIS

Categorical variables were compared with the chi-square test. Continuous variables were expressed as mean value \pm standard deviation, unless otherwise indicated. Continuous variables were compared using the analysis of variance (ANOVA).

All analyses were performed with the use of SPSS software version 16 (SPSS Inc., Chicago, IL, USA) and all reported p-values were two-sided. A p-value of <0.05 was regarded as statistically significant.

Results

BASELINE CLINICAL CHARACTERISTICS

Baseline patient characteristics were significantly different according to the timing of ST, which was consistent with the results in the entire cohort of the RESTART registry (Table 1 and Table 2)⁶. In brief, patients in the VLST group were younger and were less often diabetics. Patients on haemodialysis and patients with diabetes were more prevalent in the LST group.

Table 1. Baseline patient characteristics according to the timing of stent thrombosis.

	EST	LST	VLST	p-value
Number of patients	169	59	85	
Age (years)	67.9 \pm 10.6	68.2 \pm 10.4	63.4 \pm 11.4	0.007
Male	139 (82%)	47 (80%)	73 (86%)	0.6
Prior MI	50 (30%)	20 (35%)	27 (32%)	0.78
Prior PCI	66 (39%)	26 (44%)	45 (53%)	0.11
Prior CABG	7 (4%)	7 (12%)	4 (5%)	0.08
Heart failure	31 (19%)	16 (28%)	13 (16%)	0.21
Diabetes mellitus	71 (42%)	31 (53%)	21 (25%)	0.002
Insulin-treated	20 (12%)	13 (24%)	4 (5.0%)	0.005
Hypertension	117 (70%)	47 (81%)	60 (71%)	0.24
Current smoker	56 (33%)	16 (27%)	37 (44%)	0.1
Haemodialysis	11 (7%)	16 (27%)	6 (7%)	<0.001
Stroke	15 (9%)	7 (12%)	8 (10%)	0.85
PAD	18 (11%)	7 (12%)	8 (10%)	0.9
ACS	86 (51%)	32 (54%)	36 (42%)	0.3

ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; EST: early stent thrombosis; LST: late stent thrombosis; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; VLST: very late stent thrombosis

Table 2. Baseline patient characteristics according to the timing of stent thrombosis. Difference between angiographic substudy and total cohort.

	EST			LST			VLST		
	Angio substudy	Total cohort	p-value	Angio substudy	Total cohort	p-value	Angio substudy	Total cohort	p-value
Number of patients	169	322		59	105		85	184	
Age	68 \pm 11	67 \pm 11	0.16	68 \pm 10	68 \pm 11	0.44	63 \pm 11	63 \pm 12	0.46
Male	82%	81%	0.67	80%	77%	0.49	86%	86%	1.00
Prior MI	30%	32%	0.40	35%	36%	0.84	32%	36%	0.36
Prior PCI	39%	42%	0.36	44%	50%	0.24	53%	54%	0.88
Prior CABG	4%	6%	0.17	12%	11%	1.00	5%	5%	1.00
Heart failure	19%	19%	0.88	28%	33%	0.21	16%	13%	0.38
Diabetes mellitus	42%	43%	1.00	53%	54%	0.85	25%	32%	0.08
Insulin-treated	12%	11%	0.46	24%	22%	0.81	5%	5%	1.00
Hypertension	70%	72%	0.38	81%	84%	0.59	71%	69%	0.87
Current smoker	33%	31%	0.47	27%	27%	1.00	44%	42%	0.88
Haemodialysis	7%	4%	0.06	27%	29%	0.83	7%	5%	0.31
Stroke	9%	10%	0.85	12%	11%	0.75	10%	8%	0.60
PAD	11%	12%	0.73	12%	12%	1.00	10%	11%	0.81
ACS	51%	51%	1.00	54%	48%	0.17	42%	47%	0.24

ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; EST: early stent thrombosis; LST: late stent thrombosis; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; VLST: very late stent thrombosis

ANGIOGRAPHIC FINDINGS AT BASELINE

Angiographic findings at baseline were also different in several aspects. Residual dissection post procedure was more frequently seen in the EST group. Chronic total occlusion was more prevalent and severe calcification was less prevalent in the VLST group. The prevalence of well-known risk factors of ST such as bifurcations and overlapping long stents was high and was not different according to the timing of ST (Table 3). Minimal lumen diameter post stenting was significantly greater and percent diameter stenosis post stenting was significantly smaller in the VLST group (Table 4).

ANGIOGRAPHIC FINDINGS AT THE TIME OF STENT THROMBOSIS AND AT SIX TO 12 MONTHS AFTER SES IMPLANTATION

At the time of ST, angiographic evidence of thrombus was confirmed in 301 lesions (96.2%). TIMI 2/3 flow was observed more frequently in the LST group (Table 5). Stent fracture was more frequently seen

in the VLST group than in the EST and LST groups (16.5%, 3.0%, and 3.4%, respectively; $p=0.050$). PSS was remarkably more prevalent in the VLST group than in the EST and LST groups (34.1%, 4.7%, and 6.8%, respectively; $p<0.001$) (Figure 3). A case of PSS at VLST is shown in Figure 4. Mean depth of PSS measured by QCA was 0.87 ± 0.30 mm. The extent of PSS was 3.13 ± 1.54 mm in length. Among 29 PSS cases, four lesions (13.8%) were aneurysms (>1.5 times of reference diameter). In lesions with PSS at the time of VLST, PSS had already been demonstrated in 14 lesions (56%) at six to 12 months angiographic follow-up. Even in lesions without PSS at the time of VLST, PSS had also been observed in 13 lesions (41%) at six to 12 months angiographic follow-up. Therefore, PSS was documented at least once during follow-up in 42 lesions (69% of 61 lesions with six to 12 months angiographic follow-up and 49% of 85 lesions with VLST) (Figure 5). Persistent PSS was observed in one patient with VLST and in three patients with early and late ST. Dual antiplatelet therapy was maintained at the time of ST in only five out

Table 3. Baseline angiographic and procedural characteristics according to the timing of stent thrombosis.

		EST	LST	VLST	p-value
Number of lesions		169	59	85	
Lesion location	LMCA	3 (2%)	1 (2%)	1 (1%)	0.70
	LAD	97 (57%)	32 (54%)	42 (49%)	
	LCX	21 (12%)	12 (20%)	14 (167%)	
	RCA	48 (28%)	14 (24%)	28 (33%)	
ACC/AHA type	A	2 (1%)	0 (0%)	1 (1%)	0.72
	B1	6 (4%)	3 (5%)	6 (7%)	
	B2	63 (37%)	27 (46%)	33 (39%)	
	C	98 (58%)	29 (49%)	45 (53%)	
Pre TIMI flow	0	32 (19%)	9 (15%)	21 (25%)	0.36
	1	12 (7%)	7 (12%)	3 (4%)	
	2	21 (12%)	10 (17%)	14 (17%)	
	3	104 (62%)	33 (56%)	47 (55%)	
Lesion length	Discrete	22 (13%)	9 (15%)	7 (8.2%)	0.60
	Tubular	56 (33%)	22 (37%)	34 (40%)	
	Diffuse	91 (54%)	28 (48%)	44 (52%)	
Number of stents		1.54±0.8	1.53±0.6	1.61±1.04	0.77
Overlapping stents		68 (40%)	31 (53%)	34 (40%)	0.22
Thrombus		36 (21%)	13 (22%)	16 (19%)	0.87
Severe calcification		64 (38%)	25 (42%)	19 (22%)	0.02
Eccentric lesion		119 (70%)	44 (75%)	60 (71%)	0.82
Ostial lesion		46 (27%)	21 (36%)	17 (20%)	0.11
Chronic total occlusion		12 (7%)	7 (12%)	16 (19%)	0.02
Saphenous vein graft		1 (1%)	1 (2%)	2 (2%)	0.48
Bifurcation lesion		87 (52%)	28 (48%)	43 (51%)	0.87
Two stents for bifurcation		15 (9%)	7 (12%)	5 (6%)	0.45
Residual dissection post procedure		28 (17%)	3 (5%)	3 (4%)	0.002
Residual stenosis ≥30% post procedure		12 (7%)	2 (3%)	2 (2%)	0.22

ACC: American College of Cardiology; AHA: American Heart Association; EST: early stent thrombosis; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LMCA: left main coronary artery; LST: late stent thrombosis; RCA: right coronary artery; TIMI: Thrombolysis In Myocardial Infarction; VLST: very late stent thrombosis

Table 4. Quantitative coronary angiographic analysis.

	EST	LST	VLST	p-value
Number of lesions	169	59	85	
Lesion length (mm)	22.0±14.1	18.4±10.5	19.4±10.2	0.15
Stent length (mm)	28.2±15.4	29.5±13.7	32.1±22.8	0.237
RVD in segment (mm)				
Pre-procedure	2.47±0.54	2.50±0.61	2.62±0.56	0.26
MLD (mm)				
Pre-procedure	0.56±0.44	0.53±0.40	0.58±0.46	0.81
Post in-segment	1.88±0.44	1.83±0.53	1.95±0.43	0.37
Post in-stent	2.22±0.40	2.25±0.43	2.37±0.39	0.03
Percent DS (%)				
Pre-procedure	77.2±17.2	78.9±17.6	78.0±17.9	0.8
Post in-segment	25.1±12.2	28.8±12.2	24.8±10.2	0.08
Post in-stent	15.6±8.7	15.9±8.6	12.9±8.9	0.04

DS: diameter stenosis; EST: early stent thrombosis; LST: late stent thrombosis; MLD: minimal luminal diameter; RVD: reference vessel diameter; VLST: very late stent thrombosis

of 27 VLST patients with the finding of PSS (18.5%), and in four out of 14 VLST patients (28.6%) showing stent fracture.

CORRELATION WITH IVUS ANALYSIS

IVUS data at VLST were available in 14 patients among 85 patients with VLST. Of these, four cases presented PSS in angiography, which was confirmed by IVUS as ISA in three cases (75%). Maximum vessel area was 31.2±12.2 mm² in patients with PSS and 23.4±5.8 mm² in patients without PSS, although serial data were obtained in only one case. Maximum vessel area of PSS cases was 24.11 mm², 20.34 mm², 47.84 mm², and 32.32 mm², respectively (Figure 4). Regarding the non-PSS cases at VLST (n=10), ISA was observed in six cases (60%).

Discussion

The main findings of this study are the following: (1) abnormal angiographic findings named PSS were found frequently at the time

Table 5. Angiographic findings at the time of stent thrombosis.

	EST	LST	VLST	p-value	
Number of lesions	169	59	85		
Initial TIMI flow at ST	0	140 (83%)	30 (51%)	58 (68%)	<0.001
	1	10 (6%)	8 (14%)	10 (12%)	
	2	7 (4%)	11 (19%)	9 (11%)	
	3	12 (7%)	10 (17%)	8 (9%)	
Thrombus	165 (98%)	55 (93%)	81 (95%)	0.28	
Final TIMI flow	0	5 (3%)	1 (2%)	7 (8%)	0.29
	1	4 (2%)	2 (3%)	1 (1%)	
	2	11 (7%)	2 (3%)	7 (8%)	
	3	145 (88%)	53 (91%)	68 (82%)	
Additional stenting	57 (34%)	20 (34%)	36 (42%)	0.37	

EST: early stent thrombosis; LST: late stent thrombosis; TIMI: Thrombolysis In Myocardial Infarction; VLST: very late stent thrombosis

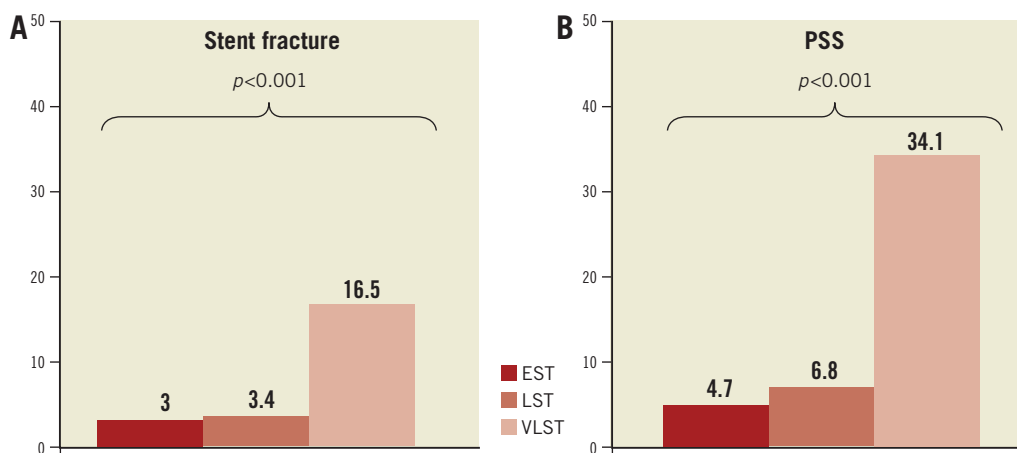


Figure 3. Prevalence of stent fracture (A) and PSS (B) according to the timing of ST. EST: early stent thrombosis; LST: late stent thrombosis; PSS: peri-stent contrast staining; ST: stent thrombosis; VLST: very late stent thrombosis

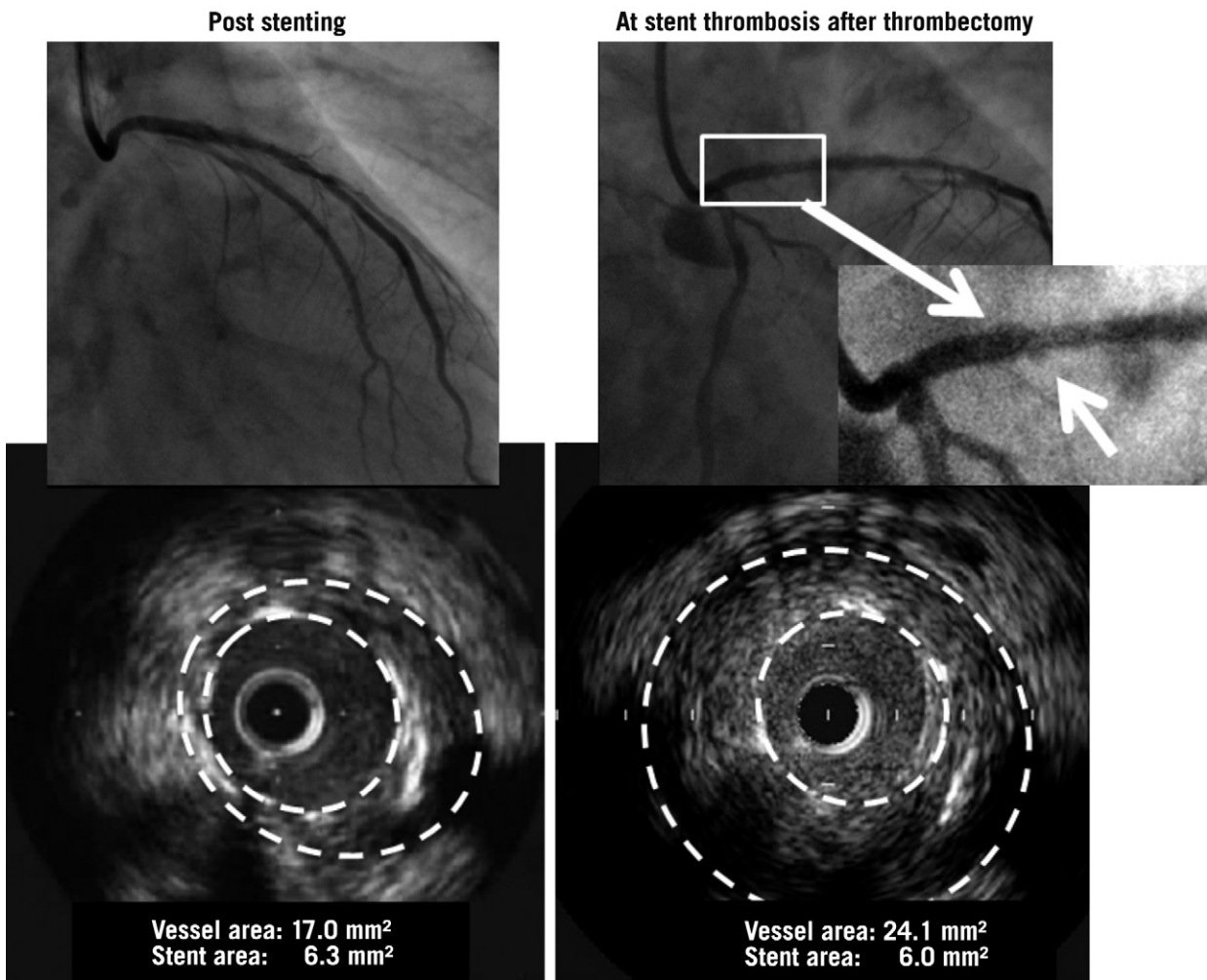


Figure 4. A representative case of very late stent thrombosis with diagnosis of PSS at the time of stent thrombosis (arrow). PSS was not identified post procedure. Maximum vessel area was enlarged from 17.0 mm² to 24.1 mm² and the remodelling index increased from 1.13 to 1.60 by IVUS analysis. PSS: peri-stent contrast staining; SES: sirolimus-eluting stent

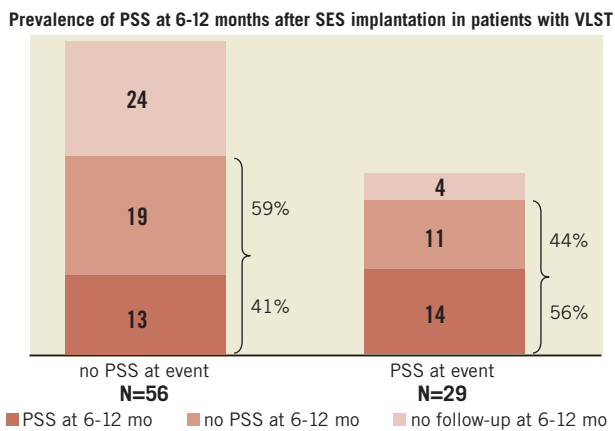


Figure 5. Prevalence of PSS at 6-12 months follow-up angiography in lesions with and without PSS at the time of VLST. PSS had already been diagnosed in 56% of lesions with PSS at event and in 41% of lesions without PSS at event. PSS: peri-stent contrast staining; VLST: very late stent thrombosis

of VLST, but not at the time of EST and LST; (2) stent fracture was also significantly more prevalent in lesions with VLST than in lesions with EST and LST.

In several intravascular ultrasound (IVUS) studies, late acquired ISA with positive remodelling was reported to be seen in 5-13% of lesions treated with SES, but was rarely seen in lesions treated with BMS¹⁰⁻¹². More recently, an association between late acquired ISA and VLST has been suggested by several IVUS studies demonstrating a very high prevalence (73-77%) of ISA in the setting of VLST¹³⁻¹⁶. PSS might be an angiographic counterpart of ISA observed by IVUS. The observed prevalence of PSS (34%) at the time of VLST was lower than the reported prevalence of ISA by IVUS (73-77%) reflecting the higher sensitivity of IVUS in detecting ISA. Difficulty in detecting PSS at the time of ST due to thrombotic material filling the space behind the stents could also explain the different prevalence of ISA or PSS between angiography and IVUS. Actually, even in lesions without PSS at the time of VLST, PSS had been observed in 41% of lesions at six to 12 months angiographic follow-up.

Although IVUS demonstrated higher sensitivity in detecting ISA, it is not realistic to perform a follow-up IVUS examination in order to identify incomplete apposition and stent fracture in routine clinical practice. Routine angiographic follow-up at six to 12 months after stent implantation is still commonly performed in Japan, even in the DES era. Considering the very low incidence of VLST, it seemed to be an inefficient way to conduct systematic angiographic follow-up to detect PSS and stent fracture. However, if PSS and/or severe stent fracture could predict future VLST, detection of these abnormal angiographic findings would be clinically relevant, although we do not recommend systematic scheduled follow-up angiography. We have previously demonstrated that PSS found within 12 months after SES implantation seemed to be associated with subsequent VLST⁷. Therefore, when PSS is observed at clinically-driven follow-up angiography, meticulous care including prolonged dual antiplatelet therapy may be required to prevent the occurrence of ST, considering the fact that dual antiplatelet therapy is stopped in the majority of VLST patients with a PSS finding.

It is intriguing that stent fracture was also significantly more prevalent in lesions with VLST than in lesions with EST and LST, although stent fracture is usually caused by fatigue of the devices. In the current study, the prevalence of stent fracture in lesions with VLST was much higher than the previously reported incidence (1-3%) during follow-up after DES implantation¹⁷. A human autopsy study in 177 DES-treated lesions reported a very high incidence of stent fracture (29%) and adverse pathologic reaction such as thrombosis and/or inflammation associated with severe stent fracture¹⁸. In an IVUS study of 20 consecutive lesions with IVUS evidence of stent fracture, stent fracture was reported to be associated with coronary aneurysm in five lesions (all treated with SES)¹⁹. It was postulated that biological reactions to the drug-eluting stent may cause positive remodelling with aneurysm formation and malapposition; aneurysm formation and malapposition may allow motion and/or kinking of the stent within the aneurysm, leading to stent fracture. Therefore, stent fracture seemed not to be the cause of PSS, but the consequence of PSS.

Delayed arterial healing has been considered to be the major cause of DES thrombosis²⁰. However, patient characteristics and angiographic findings at the time of ST were markedly different according to the timing of ST in the current study. Suspected mechanisms for EST included procedural factors such as residual dissection, platelet activation, and thrombotic milieu present in acute myocardial infarction. Differences in endothelial regeneration between DES and BMS might be a cause of LST²⁰. However, the high prevalence of PSS and ISA with positive remodelling in lesions with VLST might suggest that major mechanisms of VLST are different from delayed endothelial healing, although PSS and ISA with positive remodelling could be a continuous process resulting from delayed healing. Cook et al evaluated 10 patients with VLST by histologic examination of the thrombi aspirated, demonstrating that VLST was associated with inflammation¹⁴. They also demonstrated that eosinophilic infiltrates were more common in thrombi harvested from patients with VLST as compared with other causes of myocardial infarction, suggesting the presence of hypersensitivity in these lesions with VLST of DES.

Virmani et al reported a patient with VLST of SES, demonstrating histopathologic findings of extensive inflammation in the intima, media, and adventitia, consisting predominantly of lymphocytes and eosinophils associated with aneurysmal dilatation of the vessel wall, malapposition of the stent struts and thick fibrin thrombus between the stent struts and arterial wall^{21,22}. More recently, Kon et al reported a case with VLST of SES demonstrating serial changes in contrast staining outside the stent border leading to aneurysm formation as well as histopathologic evidence of hypersensitivity vasculitis in the stented segment²³. Therefore, accumulating evidence suggests that chronic inflammation may play the cardinal role in the pathogenesis of VLST. If hypersensitivity reaction and inflammation are the main cause of VLST, it may be reasonable that younger patients with less calcified lesions are dominant in VLST cases.

Limitations

There are several important limitations in the current study. First and most importantly, although the current angiographic analysis included the largest number of patients with SES-associated ST, we did not have data on control patients without ST. Therefore, we could not evaluate the risk factors of ST according to the timing after SES implantation. Second, there is a possibility of selection bias because only half of the patients in the RESTART registry were enrolled for the angiographic substudy. Furthermore, we have to admit that we could not guarantee all consecutive enrolments of ST patients in the RESTART registry by all centres, because case submission was conducted by the voluntary efforts of the sites. Third, six to 12-month angiograms were analysed only in 67% of VLST cases (**Table 6**). In addition, routine angiographic follow-up, which is a common practice in Japan, may have influenced the outcome

Table 6. Baseline patient characteristics based on availability of the follow-up angiograms in VLST patients.

	Follow-up angio (+)	Follow-up angio (-)	p-value
Number of patients	57	28	
Age	62±12	67±10	0.027
Male	83%	93%	0.32
Prior MI	37%	21%	0.22
Prior PCI	49%	61%	0.36
Prior CABG	5%	4%	1.00
Heart failure	19%	11%	0.53
Diabetes mellitus	23%	29%	0.60
Insulin-treated	2%	12%	0.09
Hypertension	67%	79%	0.32
Current smoker	47%	36%	0.36
Haemodialysis	4%	14%	0.09
Stroke	9%	11%	1.00
PAD	9%	11%	1.00
ACS	53%	68%	0.23

ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; EST: early stent thrombosis; LST: late stent thrombosis; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; VLST: very late stent thrombosis

since investigators may have altered their treatment according to the angiographic findings. However, the majority of hospitals performed routine angiographic follow-up after drug-eluting stent implantation regardless of initial angiographic results and recurrent ischaemic signs. Fourth, stent fracture could easily have been missed due to insufficient resolution of QCA, particularly when the stent was not heavily disrupted or image quality was not sufficient. In addition, assessment of PSS after balloon dilatation was challenging, since balloon dilatation sometimes induces dissection outside the stent. Fifth, IVUS analysis was not intended to be included in this angiographic substudy. Therefore, collection of IVUS images was insufficient and IVUS analysis may have less relevance in the current study. Finally, only a large-scale longitudinal follow-up study in patients with PSS and/or stent fracture could address the real clinical impact of these abnormal angiographic findings after SES implantation.

Conclusions

Abnormal angiographic findings such as PSS and stent fracture were found significantly more frequently in lesions with VLST than in lesions with EST and LST. The underlying mechanisms of VLST might be different from those of EST and LST.

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Conflict of interest statement

The following relationships with the sponsors of the study (Cordis Cardiology, Japan; Johnson & Johnson, Tokyo, Japan) were reported by the authors: K. Kozuma: receipt of honoraria; T. Kimura: advisory board member, speaker, and recipient of research grants; T. Aizawa: advisory board member, receipt of honoraria; S. Miyazaki: advisory board member; T. Yamaguchi: advisory board member; T. Isshiki: advisory board member, receipt of honoraria. The other authors reported no conflicts of interest.

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Online data supplement

Appendix. List of the participating centres and investigators of the RESTART registry angiographic substudy.

Online data supplement

Appendix. List of the participating centres and investigators of the RESTART registry angiographic substudy.

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