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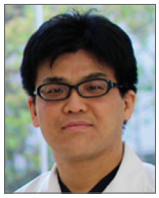
Long-term (7 to 10 years) clinical outcome after first-generation sirolimus-eluting stent implantation



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KEYWORDS

- coronary artery disease
- sirolimus-eluting stent
- stent thrombosis
- target lesion revascularisation

Abstract

Aims: Late adverse events such as very late stent thrombosis (VLST) or late target lesion revascularisation (TLR) after sirolimus-eluting stent (SES) implantation remain an important concern. However, clinical outcomes beyond five years after SES implantation remain unclear. We sought to assess the very long-term (7-10 years) clinical outcome after SES implantation.

Methods and results: Between April 2004 and March 2008, a total of 985 consecutive patients with 1,307 lesions underwent percutaneous coronary intervention only with SES. Cumulative incidence of TLR within the first year was 11.8%. Late TLR beyond one year continued to occur without attenuation or acceleration up to 10 years (2.6%/year, and cumulative 10-year incidence, 35.2%). Cumulative incidence of definite stent thrombosis was low (30 days, 0.31%; one year, 0.63%; five years, 1.1%; and 10 years, 2.6%), whereas definite VLST also continued to occur without attenuation or acceleration (0.22%/year).

Conclusions: Late adverse events such as VLST and late TLR beyond one year after SES implantation continue to occur up to 10 years without attenuation or acceleration of their annual incidences. Careful clinical follow-up is mandatory in patients who have already been treated with SES.

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Abbreviations

ARC	Academic Research Consortium
CABG	coronary artery bypass graft
CREDO-Kyoto	Coronary Revascularisation Demonstrating Outcome study in Kyoto
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
eGFR	estimated glomerular filtration rate
ISA	incomplete stent apposition
IVUS	intravascular ultrasound
LST	late stent thrombosis
MI	myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
PSS	persistent contrast staining
SES	sirolimus-eluting stent
SF	stent fracture
ST	stent thrombosis
TLR	target lesion revascularisation
VLST	very late stent thrombosis

Introduction

The sirolimus-eluting stent (SES) was the most widely used first-generation drug-eluting stent (DES) and dramatically reduced the rate of in-stent restenosis and subsequent target lesion revascularisation (TLR) compared with bare metal stents (BMS)[1]. Pivotal randomised clinical trials have demonstrated that the efficacy of SES was sustained without any significant increase of stent thrombosis (ST) up to four to five years after implantation[2,3]. However, in real-world clinical practice, late adverse events such as very late ST (VLST) and late TLR beyond one year have emerged as unsolved issues after SES implantation[4-8]. The j-Cypher Registry demonstrated that VLST and late TLR beyond one year continued to occur without attenuation up to five years after SES implantation (0.26%/year and 2.2%/year, respectively)[8]. Furthermore, the CREDO-Kyoto (Coronary Revascularisation Demonstrating Outcome study in Kyoto) percutaneous coronary intervention (PCI)/coronary artery bypass graft (CABG) registry cohort-2 also reported that VLST and late TLR beyond one year after SES implantation occurred constantly and without attenuation up to seven years (0.24%/year and 2.0%/year, respectively)[9]. Although these findings suggested that late adverse events such as VLST and late TLR beyond one year are a continuous hazard, lasting at least up to seven years after SES implantation, there is a paucity of reports evaluating clinical outcomes beyond seven years after SES implantation. Therefore, we sought to assess very long-term (7 to 10 years) clinical outcomes of SES in the present single-centre study.

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Methods

PATIENT POPULATION AND PROCEDURAL PROTOCOL

From April 2004 to March 2008, a total of 4,603 consecutive patients with 5,514 lesions underwent percutaneous coronary intervention with stent implantation in Kokura Memorial Hospital, Kitakyushu, Japan. Of these, 985 consecutive patients (1,307 lesions) treated only with SES (CYPHER®; Cordis, Johnson & Johnson, Warren, NJ, USA) were enrolled in the present study **(Figure 1)**. All interventions were performed using standard techniques. Predilatation, post-dilatation, and the use of intravascular ultrasound (IVUS) were left to the operator's discretion. After the procedure, all patients were advised to continue aspirin (81-162 mg daily) for life unless contraindicated. Either ticlopidine (200 mg daily) or clopidogrel (75 mg daily) was also prescribed for at least three months after stent implantation. A routine follow-up angiography six to 12 months after SES implantation was recommended to the patients regardless of clinical symptoms. All patients gave written informed consent for the procedure and the follow-up protocol, which was approved by the ethics committee of Kokura Memorial Hospital.

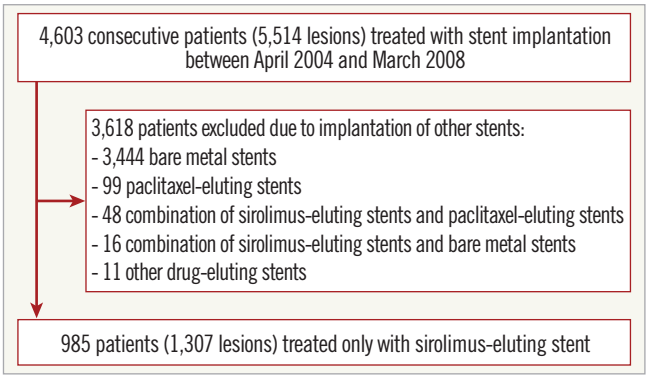


Figure 1. *Study flow chart.*

STUDY ENDPOINTS AND DEFINITIONS

The major study endpoints included VLST, late TLR beyond one year, and clinically driven late TLR beyond one year. All-cause death, cardiac death, non-cardiac death, myocardial infarction (MI), stroke, CABG, and any coronary revascularisation were also assessed as endpoints. Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. MI was defined according to the Academic Research Consortium (ARC) definition[10]. TLR was defined as either PCI or CABG resulting from restenosis or thrombosis of the SES-treated target lesion that included the proximal and distal edge to the stent (within 5 mm) and the ostium of side branches[8]. Clinically driven TLR was defined as TLR performed because of ischaemic symptoms, electrocardiographic changes at rest or positive stress test results[8]. Clinically driven TLR on a patient basis was censored when non-clinically driven TLR was performed in all the target lesions. The timing and diagnostic certainty of ST were assessed according to the ARC definition[10]. Stroke during the follow-up was defined as ischaemic or haemorrhagic stroke requiring hospitalisation with symptoms lasting >24 hours.

CLINICAL FOLLOW-UP

Clinical follow-up data were obtained either from a review of the hospital records or by telephone contacts with the patients, relatives,

or referring physicians. Patients who were lost to follow-up were censored on the last day with follow-up information. Follow-up intervals were calculated from the day of the index procedure.

STATISTICAL ANALYSIS

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean±SD or median (interquartile range). Cumulative incidences were estimated by the Kaplan-Meier method. To evaluate the late events beyond one year, we used landmark analysis at one year. Those patients with individual endpoint events before one year were excluded in the landmark analysis. A Cox proportional hazards model was used to identify independent risk factors of TLR (within the first year and beyond one year). We used the 23 variables listed in **Table 1** as potential independent variables **(Online Table 1)**. The continuous variables were dichotomised by clinically meaningful reference values. To determine the independent risk factors, we first selected variables with p-values <0.10 in the univariate Cox models. We then included them simultaneously in the multivariable models and obtained the adjusted hazard ratios and their 95% confidence intervals. To evaluate the risk factors for TLR beyond one year, we included only those patients who completed the one-year follow-up without TLR. Statistical analysis was performed with the use of JMP software, version 10.0 (SAS Institute Inc., Cary, NC, USA). A two-sided p-value of <0.05 was considered statistically significant.

Results

BASELINE CHARACTERISTICS

The current study population included predominantly patients with stable coronary artery disease. However, the great majority of patients had high-risk features such as advanced age, diabetes mellitus, prior PCI, prior MI, and multivessel disease **(Table 1)**. Also, the great majority of patients had AHA/ACC type B2/C lesions with complex lesion characteristics such as bifurcation, in-stent restenosis, severe calcification, and chronic total occlusion **(Table 2)**. The prevalence of post-dilatation after SES implantation was low, and intravascular ultrasound was used infrequently **(Table 2)**. The prescription rates of the evidence-based medications such as statins and beta-blockers were low at the time of hospital discharge **(Table 1)**. Median follow-up duration of survivors was 8.6 (first and third quartiles [Q1-Q3]: 7.6-9.4; and range: 0-11.0) years. Ten-year clinical follow-up was completed in 138 patients (90.2%) among 153 patients eligible for 10-year follow-up.

Table 1. Patient characteristics.

Characteristics		
Number of patients		985
Age (years)		68.7±9.6
>80 years		103 (10.5%)
Male		756 (76.8%)
Hypertension		756 (76.8%)
Diabetes mellitus		479 (48.6%)
Insulin-treated		83 (8.4%)
Dyslipidaemia		534 (54.2%)
Chronic kidney disease	eGFR <30 ml/min/1.73 m^2 without haemodialysis	48 (4.9%)
	Haemodialysis	61 (6.2%)
Current smoker		151 (15.3%)
Multivessel disease		350 (35.5%)
Target lesion involving chronic total occlusion		116 (11.8%)
Target lesion involving in-stent restenosis		331 (33.6%)
Target lesion involving bifurcation treated with two stents		38 (3.9%)
Target lesion involving ostial right coronary artery		68 (6.9%)
Target lesion involving severe calcification		69 (7.0%)
Total stent length >28 mm		298 (30.3%)
Number of diseased vessels	1	635 (64.5%)
	2	272 (27.6%)
	≥3	78 (7.9%)
Prior myocardial infarction		333 (33.8%)
Prior percutaneous coronary intervention		664 (67.4%)
Prior coronary artery bypass grafting		67 (6.8%)
Prior stroke		77 (7.8%)
Clinical status	Stable coronary artery disease	962 (97.7%)
	Acute coronary syndrome	23 (2.3%)
Left ventricular ejection fraction (%)		61.0 (50.0-68.0)
≤40%		106 (10.8%)
Medications at discharge	Aspirin	985 (100%)
	Thienopyridine	985 (100%)
	Beta-blockers	264 (26.9%)
	ACE-I/ARB	544 (55.2%)
	Statins	512 (52.1%)
	Oral hypoglycaemic agent	317 (32.1%)

Data are presented as mean±SD, median (interquartile range), or number (%). ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker

CLINICAL OUTCOMES

The cumulative 10-year incidence of all-cause death and cardiac death was 30.3% and 8.1%, respectively **(Table 3, Figure 2A)**. Cardiac death constituted 23.9% of all-cause death. The cumulative 10-year incidence of MI was low (annual incidence of 0.6%).

In this cohort, 88.0% of patients underwent angiographic follow-up within one year. The cumulative incidence of TLR within the first year was relatively high (11.8%). Among the 201 patients undergoing TLR within the first year, 74 patients (66.7%) underwent plain old balloon angioplasty, 27 patients (24.3%) another SES implantation, eight patients (7.2%) coronary artery bypass graft, and two patients (1.8%) paclitaxel-eluting stent implantation. Late TLR beyond one year also continued to occur constantly without attenuation or acceleration up to 10 years (2.6%/year) **(Figure 2B, Figure 3)**. Clinically driven TLR within the first year was relatively low (5.2%), but it continued to occur with

Table 2. Lesion and procedural characteristics.

Characteristics		
Number of lesions		1,307
Location of target lesion	LAD	628 (48.1%)
	RCA	385 (29.5%)
	LCX	328 (25.1%)
	LMCA	38 (2.9%)
	SVG	6 (0.5%)
AHA/ACC lesion type	A	34 (2.6%)
	B1	304 (23.2%)
	B2	385 (29.5%)
	C	584 (44.7%)
In-stent restenosis		368 (28.2%)
Severe calcification		89 (6.8%)
Bifurcation		454 (34.7%)
Treated with two stents		53 (4.1%)
Ostial location		93 (7.1%)
Chronic total occlusion		119 (9.1%)
Procedural characteristics		
Number of stents per lesion	1	1,003 (76.8%)
	2	244 (18.7%)
	≥3	60 (4.5%)
Total stent length (mm)		23.0 (18.0-33.0)
Overlapping stent		313 (24.0%)
Post-dilatation		463 (37.3%)
Maximal inflation pressure (atm)		16.5±2.6
IVUS use		217 (16.6%)

Data are presented as mean±SD, median (interquartile range), or number (%). AHA/ACC: American Heart Association/American College of Cardiology; IVUS: intravascular ultrasound; LAD: left anterior descending coronary artery; LCX: left circumflex artery; LMCA: left main coronary artery; RCA: right coronary artery; SVG: saphenous vein graft

a constant rate of 1.6%/year beyond one year **(Figure 2B)**. Non-TLR continued with a similar frequency to TLR with an annual incidence of 2.3% **(Figure 2B)**.

The cumulative incidence of definite ST was also low (30-day, 0.31%; one-year, 0.63%; five-year, 1.1%; and 10-year, 2.6%). VLST continued to occur constantly without attenuation or acceleration up to 10 years after SES implantation (0.22%/year) **(Table 3, Figure 4A, Figure 4B)**. Among 19 ST events up to 10 years, 18 (94.7%) resulted in MI. ST was the cause of MI during follow-up in 39.1% of 46 MI episodes. All patients with early ST and late ST had continued dual antiplatelet therapy (DAPT) at the time of ST, whereas DAPT had been continued in seven (53.8%) of 13 patients with VLST. No patient had discontinued both aspirin and thienopyridine before the onset of ST.

Stent fracture (SF) was observed in 43 (13.3%) of 323 TLR lesions and in four (21.1%) of 19 ST lesions (one LST and three VLST). The incidence of SF as a cause for TLR or ST was higher in the right coronary artery than in other vessels (30 [69.8%] of 43 SF-related TLR lesions; three [75.0%] of four SF-related ST lesions).

Independent risk factors for TLR within one year included such target lesions as the ostial RCA, total stent length >28 mm, in-stent restenosis, age >80 years, bifurcation lesions treated with two stents **(Table 4)**. Independent risk factors for late TLR beyond one year included such target lesions as in-stent restenosis, total stent length >28 mm, estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 without haemodialysis **(Table 4)**.

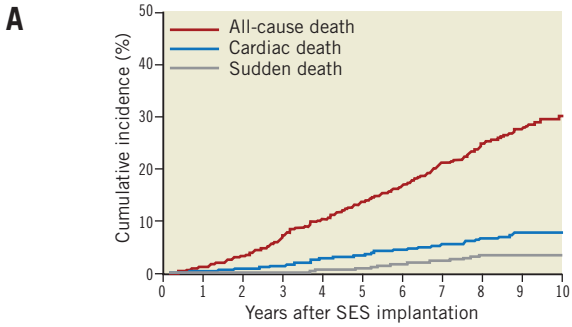
Discussion

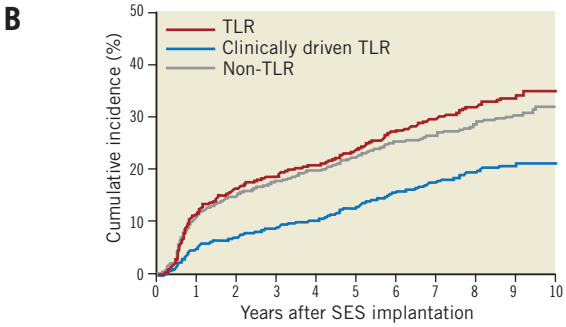
The main finding of the present study is that late adverse events such as VLST and late TLR beyond one year after SES implantation continue to occur up to 10 years without attenuation or acceleration of their annual incidences.

Table 3. Clinical event rates up to 10 years.

		Number of patients with events (Cumulative incidence)			
		30-day	1-year	5-year	10-year
Death	All-cause death	0 (0%)	13 (1.4%)	128 (14.0%)	244 (30.3%)
	Cardiac death	0 (0%)	5 (0.51%)	32 (3.7%)	60 (8.1%)
	Sudden death	0 (0%)	1 (0.11%)	9 (1.1%)	27 (3.7%)
Myocardial infarction		3 (0.31%)	10 (1.2%)	25 (2.9%)	46 (6.5%)
Stent thrombosis	Definite	3 (0.31%)	6 (0.63%)	10 (1.1%)	19 (2.6%)
	Definite/probable	3 (0.31%)	7 (0.73%)	11 (1.2%)	20 (2.7%)
	Definite/probable/possible	3 (0.31%)	7 (0.73%)	22 (2.5%)	46 (6.4%)
Stroke		4 (0.41%)	6 (0.63%)	24 (2.7%)	36 (6.2%)
Target lesion revascularisation		4 (0.41%)	111 (11.8%)	220 (24.2%)	290 (35.2%)
Clinically driven target lesion revascularisation		4 (0.41%)	48 (5.2%)	112 (13.5%)	159 (21.7%)
Non-target lesion revascularisation		5 (0.51%)	107 (11.6%)	207 (23.0%)	259 (32.5%)
Coronary artery bypass grafting		1 (0.10%)	13 (1.5%)	27 (4.3%)	58 (7.4%)
Any coronary revascularisation		8 (0.82%)	217 (23.0%)	381 (41.7%)	475 (57.0%)

Cumulative incidences of events were calculated by the Kaplan-Meier method.



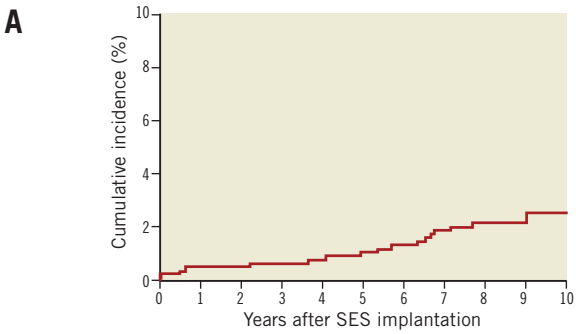


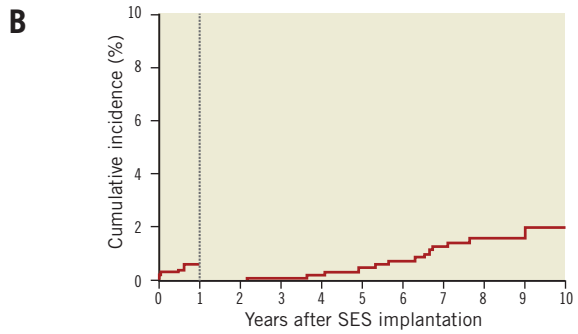
Intervals	0 day	30 days	1 year	5 years	10 years
All-cause death					
No. of patients at risk	985	964	918	775	87
No. of patients with events	0	4	13	128	251
Cumulative incidence	0%	0.41%	1.4%	14.0%	30.3%
Cardiac death					
No. of patients at risk	985	964	915	774	87
No. of patients with events	0	4	5	32	60
Cumulative incidence	0%	0.41%	0.51%	3.7%	8.1%
Sudden death					
No. of patients at risk	985	967	924	780	87
No. of patients with events	0	0	1	9	27
Cumulative incidence	0%	0%	0.11%	1.1%	3.7%

Intervals	0 day	30 days	1 year	5 years	10 years
TLR					
No. of patients at risk	985	964	817	604	53
No. of patients with events	0	4	111	220	290
Cumulative incidence	0%	0.41%	11.8%	24.2%	35.2%
Clinically driven TLR					
No. of patients at risk	985	964	817	605	52
No. of patients with events	0	4	48	112	159
Cumulative incidence	0%	0.41%	5.2%	13.5%	21.7%
Non-TLR					
No. of patients at risk	985	963	813	608	55
No. of patients with events	0	5	107	207	259
Cumulative incidence	0%	0.51%	11.6%	23.0%	32.5%

Figure 2. *Cumulative incidence of clinical events up to 10 years after SES implantation. A) All-cause death, cardiac death and sudden death. B) TLR, clinically driven TLR, and non-TLR. SES: sirolimus-eluting stent; TLR: target lesion revascularisation*

Widespread use of first-generation DES has raised several unresolved, clinically relevant issues. Particular concerns have been the late complications including VLST and late TLR. VLST is a reassuringly rare, but potentially life-threatening complication. Recently, several large-scale DES registries have demonstrated that the annual incidences of VLST were 0.21 to 0.53%/year up to three to five years[3-8]. More recently, Natsuaki et al reported from the CREDO-Kyoto 2 registry that VLST beyond one year after SES implantation occurred constantly and without attenuation up to seven years (0.24%/year)[9]. Although these results suggested that the risk of VLST is sustained without attenuation up to seven years after SES implantation, there are few data evaluating >7 years' follow-up of SES. In the present study, VLST continued to occur without attenuation up to 10 years after SES implantation (0.22%/year). This annual incidence of VLST is consistent with that reported from the j-Cypher Registry and the CREDO-Kyoto 2 registry[8,9]. Considering these findings, VLST remains a concerning problem at least up to 10 years after SES implantation, while it was reassuring that we did not see a signal suggesting acceleration in the occurrence of VLST, although a pathological study

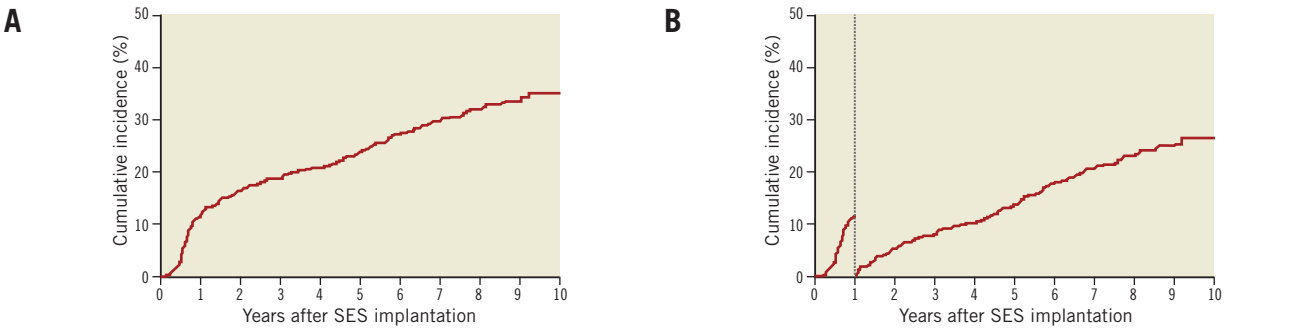




Intervals	0 day	30 days	1 year	5 years	10 years
No. of patients at risk	985	965	918	774	86
No. of patients with events	0	3	6	10	19
Cumulative incidence	0%	0.31%	0.63%	1.1%	2.6%

Intervals	0 day	30 days	1 year	5 years	10 years
No. of patients at risk	985	965	918	774	86
No. of patients with events	0	3	6	4	13
Cumulative incidence	0%	0.31%	0.63%	0.49%	2.0%

Figure 3. *Cumulative incidence of TLR during the entire follow-up period (A), within one year, and between one and 10 years by the one-year landmark analysis (B). SES: sirolimus-eluting stent; TLR: target lesion revascularisation*



Intervals	0 day	30 days	1 year	5 years	10 years
No. of patients at risk	985	964	817	604	53
No. of patients with events	0	4	111	220	290
Cumulative incidence	0%	0.4%	11.8%	24.2%	35.2%

Intervals	0 day	30 days	1 year	5 years	10 years
No. of patients at risk	985	964	817	604	53
No. of patients with events	0	4	111	109	179
Cumulative incidence	0%	0.4%	11.8%	14.2%	26.7%

Figure 4. *Cumulative incidence of definite stent thrombosis during the entire follow-up period (A), within one year, and between one and 10 years by the one-year landmark analysis (B). SES: sirolimus-eluting stent*

suggested more pronounced neoatherosclerosis formation with longer time intervals after coronary stent implantation[11-13].

In the present study, late TLR beyond one year also continued to occur constantly without attenuation up to 10 years after SES implantation with an annual incidence of 2.6%/year. This annual incidence of late TLR is also consistent with that reported from previous large-scale DES registries[8,9]. Recently, Palhais et al were the first to report a 10-year clinical follow-up of 200 patients with SES implantation, demonstrating that the cumulative 10-year incidence of TLR was 8% and the risk of TLR was maximal at three to six years after SES implantation and decreased thereafter[14]. Compared with the present study, the cumulative incidence of TLR was much lower and the trend was quite different. The current study had a larger study population with a higher-risk patient profile and more complex lesion characteristics, such as a high prevalence of DM, ISR, bifurcation lesion, chronic total occlusion, and long total stent length. After the introduction of SES in real-world clinical practice, SES were widely used in high-risk patients as shown in the current study, which might have led to the sustained occurrence of late TLR.

The underlying mechanisms for the continuous occurrence of late adverse events after SES implantation have not been fully understood. Previous studies have demonstrated that inflammatory reaction, hypersensitivity, endothelial dysfunction, and

Table 4. Univariate and multivariable Cox models for target lesion revascularisation.

Variables	Present events/ patients, n (%)	Absent events/ patients, n (%)	Univariate		Multivariable	
			HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
TLR within 1 year						
Target lesion involving ostial RCA	22/68 (35.0)	88/917 (10.0)	3.92 (2.40-6.13)	<0.001	3.60 (2.17-5.75)	<0.001
Total stent length >28 mm	48/298 (16.8)	62/687 (9.5)	1.81 (1.24-2.64)	0.002	1.84 (1.24-2.72)	0.003
Target of ISR	50/331 (15.9)	60/654 (9.6)	1.73 (1.19-2.52)	0.005	1.72 (1.17-2.52)	0.006
Age ≥80 years	5/103 (5.2)	105/882 (12.4)	0.41 (0.14-0.90)	0.02	0.38 (0.13-0.85)	0.02
Target of a bifurcation lesion treated with two stents	10/38 (26.3)	100/947 (11.1)	2.58 (1.26-4.69)	0.01	2.43 (1.17-2.52)	0.02
Haemodialysis	14/61 (25.8)	96/924 (10.8)	2.73 (1.49-4.62)	0.002	1.92 (0.99-3.49)	0.054
Insulin use	16/83 (19.7)	94/902 (10.9)	1.90 (1.08-3.13)	0.03	1.74 (0.97-2.91)	0.06
Target lesion involving severe calcification	13/69 (21.4)	97/916 (11.0)	2.10 (1.12-3.61)	0.02	1.40 (0.72-2.55)	0.31
TLR beyond 1 year						
Target lesion involving ISR	70/257 (34.0)	108/560 (22.9)	1.44 (1.06-1.94)	0.02	1.43 (1.05-1.93)	0.02
Total stent length >28 mm	59/234 (29.6)	119/583 (25.1)	1.35 (0.98-1.83)	0.07	1.41 (1.02-1.92)	0.036
eGFR <30 ml/min/1.73 m^2 without haemodialysis	10/33 (48.0)	167/783 (25.7)	2.09 (1.03-3.76)	0.04	2.06 (1.01-3.71)	0.046
Target lesion involving ostial RCA	13/40 (46.2)	165/777 (25.3)	1.83 (0.99-3.09)	0.056	1.71 (0.92-2.89)	0.09
Prior stroke	18/62 (36.3)	160/755 (25.7)	1.62 (0.96-2.57)	0.07	1.48 (0.87-2.35)	0.14

Only variables with univariate $p<0.10$ are shown. Incidences of events were calculated by the Kaplan-Meier method. CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; ISR: in-stent restenosis; RCA: right coronary artery.

neoatherosclerosis could be suggested as the causes of VLST as well as late TLR beyond one year[15-19]. Recently, an OCT analysis in 50 patients with ISR after DES implantation demonstrated that 52% of lesions had at least one thin-cap fibroatheroma containing neointima, 58% had in-stent neointimal rupture, and 58% showed intraluminal thrombi[20]. More recently, Kang et al reported that, using OCT, VLST was associated with in-stent neointimal rupture in 63% of DES-treated lesions[21]. Furthermore, stent fracture (SF) is also one of the risk factors for ST and TLR after DES implantation and may be likely to occur due to increased metallic fatigue over time[22,23]. Indeed, Ohya et al reported that SF after SES implantation was consistently associated with higher rates of VLST and TLR during eight-year follow-up[24]. In the present study, SF was observed in a significant proportion of lesions with TLR and/or ST. Furthermore, persistent contrast staining (PSS), which might be related to inflammation and remodelling of the stented vessel, was reported to be a potent risk factor for VLST of SES[25]. These findings support the belief that neoatherosclerosis, SF and PSS are the causes of late adverse events in some SES-treated patients. Long-term DAPT after SES implantation might be necessary in some selected patients with potent angiographic risk factors of VLST such as SF and/or PSS.

The current study showed that late adverse events such as VLST and late TLR beyond one year after SES implantation continue to occur up to 10 years without attenuation or acceleration of their annual incidences. These findings indicate that there may be no end in sight for the late adverse events after SES implantation. Therefore, further careful follow-up is mandatory to assess the very long-term outcomes of patients who have already received SES implantation. Although the mechanisms for late adverse events after SES implantation are multifactorial, the most significant contributing factor might be different according to the timing and type of late adverse events. Indeed, the j-Cypher Registry suggested that the risk factors of late TLR are similar to those of early TLR, whereas the predictors for VLST are quite different from those for early ST and LST[8]. Although the current study could not provide the predictors for VLST, target lesions involving in-stent restenosis, total stent length, and eGFR <30 ml/min/1.73 m^2 without haemodialysis were independent predictors for late TLR beyond one year. Therefore, more careful follow-up may be required in those patients.

Limitations

There are several limitations in the present study. First, this study was a retrospective, single-centre study that did not include a control group. Therefore, we could not assess whether the very long-term outcomes of SES are different from those of BMS and/or second-generation DES based on the results of the current study. Second, the present study included a very small number of patients with acute coronary syndrome. Third, the overall incidence and clinical impact of SF and PSS, which are reported to be strong risk factors for ST after SES implantation, were not assessed in the present study[24,25]. Fourth, we did not have information on bleeding complications and antiplatelet therapy during the follow-up. Finally, first-generation SES are no longer used in current practice. However, many millions of patients have already undergone first-generation SES implantation. Therefore, it is important to continue evaluating the very long-term clinical outcomes of patients receiving first-generation SES implantation to improve the care of these patients.

Impact on daily practice

Late adverse events such as VLST and late TLR beyond one year after SES implantation continue to occur up to 10 years without attenuation or acceleration of their annual incidences. Careful clinical follow-up is mandatory in patients who have already been treated with SES.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Online Table 1. Univariate Cox model for target lesion revascularisation.

This paper also includes supplementary data published online at: www.asiaintervention.org

Supplementary data

Online Table 1. Univariate Cox model for target lesion revascularisation.

Variables	Univariate			
	TLR within 1 year		TLR beyond 1 year	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age ≥80 years	0.41 (0.14-0.90)	0.02	0.63 (0.31-1.14)	0.13
Male	1.10 (0.67-1.77)	0.67	1.32 (0.14-1.94)	0.14
Hypertension	0.94 (0.61-1.48)	0.79	1.21 (0.85-1.77)	0.30
Insulin-treated diabetes mellitus	1.90 (1.08-3.13)	0.03	1.13 (0.62-1.88)	0.67
Dyslipidaemia	1.11 (0.76-1.63)	0.58	0.84 (0.62-1.12)	0.24
eGFR <30 ml/min/1.73 m^2 without haemodialysis	1.51 (0.63-3.00)	0.32	2.09 (1.03-3.76)	0.04
Haemodialysis	2.73 (1.49-4.62)	0.002	1.53 (0.73-2.83)	0.24
Current smoker	0.80 (0.43-1.35)	0.41	1.02 (0.67-1.49)	0.92
Target of chronic total occlusion	1.40 (0.80-2.32)	0.23	1.37 (0.87-2.06)	0.17
Target of ISR	1.73 (1.19-2.52)	0.005	1.44 (1.06-1.94)	0.02
Target of bifurcation lesion treated with two stents	2.58 (1.26-4.69)	0.01	1.40 (0.60-2.76)	0.41
Target of ostial RCA	3.92 (2.40-6.13)	<0.001	1.83 (0.99-3.09)	0.053
Target of severe calcification	2.10 (1.12-3.61)	0.02	1.05 (0.50-1.93)	0.89
Total stent length >28 mm	1.81 (1.24-2.64)	0.002	1.35 (0.98-1.83)	0.07
Prior myocardial infarction	1.23 (0.83-1.80)	0.29	0.98 (0.71-1.33)	0.88
Prior percutaneous coronary intervention	1.30 (0.86-2.00)	0.22	1.16 (0.85-1.61)	0.37
Prior coronary artery bypass grafting	1.29 (0.61-2.41)	0.48	1.34 (0.73-2.27)	0.33
Prior stroke	1.18 (0.58-2.15)	0.62	1.62 (0.96-2.57)	0.07
Acute coronary syndrome	0.80 (0.13-2.51)	0.74	0.82 (0.20-2.15)	0.72
Left ventricular ejection fraction ≤40%	0.98 (0.49-1.74)	0.94	1.40 (0.87-2.15)	0.15
Beta-blocker use	1.12 (0.73-1.67)	0.60	1.23 (0.81-1.72)	0.41
ACE-I/ARB use	1.19 (0.81-1.75)	0.38	1.03 (0.77-1.39)	0.85
Statins use	1.39 (0.95-2.05)	0.10	1.11 (0.83-1.50)	0.48

ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; ISR: in-stent restenosis; RCA: right coronary artery