Outcomes After First- Versus Second-Generation Drug-Eluting Stent Thrombosis (from the REAL-ST Registry)

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Limited data exist on the comparison of clinical outcomes after first- and second-generation drug-eluting stent (DES) thrombosis. From the Retrospective Multicenter Registry of Stent Thrombosis (ST) After First- and Second-Generation DES Implantation registry, this study evaluated 655 ST patients (first-generation DES thrombosis [G1-ST], n = 342; second-generation DES thrombosis [G2-ST], n = 313). After propensity score matching, the final study population consisted of 159 matched patients. The primary end point was the cumulative 1-year incidence of mortality. The mortality after G2-ST at 1 year was similar to that after G1-ST (23.0% vs 22.9%, p = 0.76). Also, the G2-ST group showed a significantly lower rate of target lesion revascularization than the G1-ST group (9.7% vs 17.1%, p = 0.01). Risk factors of 1-year mortality included cardiogenic shock or arrest at the time of ST, multivessel ST, left ventricular ejection fraction ≤40%, advanced age, and final thrombolysis in myocardial infarction flow grade ≤2. In conclusion, patients with G2-ST showed a similar 1-year mortality to those with G1-ST, highlighting that ST remains a life-threatening complication in the second-generation DES era. **(Am J Cardiol 2020;132:52−58)**

Stent thrombosis (ST) emerges as a major safety concern with first-generation drug-eluting stent (DES) in clinical practice because of the high incidences of death, myocardial infarction, and repeat revascularization.[1,2] Recently, the REAL-ST (Retrospective Multicenter Registry of ST After First- and Second-Generation DES Implantation) registry revealed that definite ST patients led to unfavorable long-term outcomes compared with those without definite ST, regardless of the timing of ST.[3] These findings highlight that ST is a life-threatening complication in both first- and second-generation DES, whereas little data are available regarding the comparison of clinical outcomes after first- and second-generation DES thrombosis.[4] Furthermore, the risk factors of mortality associated with ST remain unclear. In the present study, we sought to assess 1-year clinical outcomes after first- and second-generation DES thrombosis and their risk factors by analyzing the REAL-ST registry.

Methods

This study was a post hoc analysis of the REAL-ST registry, which was a retrospective multicenter registry of patients with definite ST after first- and second-generation DES implantation at 46 Japanese percutaneous coronary intervention (PCI) institutions (Methods in the Data Supplement). The study design and main results have been reported elsewhere.[3] In brief, we retrospectively attempted to enroll patients who fulfilled the following criteria: (1) who underwent PCI with first-generation DES from April 2004 to December 2013 or second-generation DES from May 2009 to December 2016; (2) who had definite ST of first- or second-generation DES from April 2004 to March 2017. Finally, a total of 655 ST patients (first-generation DES-ST [G1-ST], n = 342; second-generation DES-ST [G2-ST], n = 313) were enrolled in this registry. The study protocol was approved by the ethic committee at all participating centers and was in accordance with the Declaration of Helsinki. Written informed consent was waived because of the retrospective study design. This study was registered with http://www.umin.ac.jp, unique identifier UMIN000025181.

Definite ST was defined according to the Academic Research Consortium criteria.[5] ST was categorized according to the timing of ST occurrence as early ST (within 30 days), late ST (between 31 and 365 days), and very late ST (>1 year). The primary study end point was the cumulative

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incidence of all-cause death within 1 year after ST. Cardiac death, target lesion revascularization (TLR), and recurrent ST were also assessed. Death was regarded as cardiac death unless other noncardiac death could be identified. TLR was defined as a repeated PCI or repeated coronary artery bypass graft on the target lesion.

In this study, a propensity score (PS) matching analysis was performed to adjust for the differences in baseline clinical characteristics between the 2 groups. The PS was estimated by a logistic regression model that included patient and lesion characteristics listed in Tables 1 and 2 as exploratory variables. The matching was performed using the nearest-neighbor method with a caliper of 0.20. Categorical variables were presented as numbers (percentages) and compared using the chi-squared or Fisher's exact tests. Continuous variables were expressed as mean ± SD or median (interquartile range) and compared using the Student's *t* test or the Mann-Whitney U test based on their distributions. In the matched population, the cumulative incidence of study end points was estimated by the Kaplan-Meier method. Hazard ratio (HR) for all-cause death, cardiac death, TLR, and recurrent ST were compared between G1-ST and G2-ST groups, adjusting for clinically determined possible risk factors (listed in Tables 1 and 2) using a multivariable Cox model. To identify possible risk factors of all-cause death, multivariable Cox model was constructed using clinically relevant 7 variables (age, bifurcation lesion, cardiogenic arrest or shock at the time of ST, final thrombolysis in myocardial infarction [TIMI] flow grade ≤2, and left ventricular ejection fraction [LVEF] ≤40%, multivessel ST).[1,6-8]

Table 1
Baseline clinical characteristics

Variables	Overall population			Matched population		
	G1-ST (n = 342)	G2-ST (n = 313)	p	G1-ST (n = 159)	G2-ST (n = 159)	p
Age (years)*,†	68.9 ± 10.2	68.1 ± 10.6	0.31	68.2 ± 10.1	68.2 ± 11.4	0.97
Men*,†	277 (81.0%)	251 (80.2%)	0.84	129 (81.1%)	125 (78.6%)	0.68
Hypertension*,†	270 (78.9%)	248 (79.2%)	1.00	130 (81.8%)	131 (82.4%)	1.00
Diabetes mellitus*,†	156 (45.6%)	150 (47.9%)	0.58	82 (51.6%)	81 (50.9%)	1.00
Dyslipidemia*,†,‡	263 (76.9%)	257 (82.1%)	0.10	121 (76.1%)	122 (76.7%)	1.00
Current smoker*,†	83 (24.3%)	98 (31.3%)	0.045	51 (32.1%)	45 (28.3%)	0.54
Hemodialysis*,†	14 (4.1%)	45 (14.4%)	<0.001	12 (7.5%)	17 (10.7%)	0.44
eGFR (ml/min/1.73 m^2)	63.0 (50.3, 77.4)	62.8 (42.0, 76.7)	0.11	61.4 (43.9, 78.9)	64.8 (45.0, 79.4)	0.71
≤30 ml/min/1.73 m^2 without hemodialysis*,†	10 (2.9%)	12 (3.8%)	0.53	6 (3.8%)	6 (3.8%)	1.00
Prior myocardial infarction*,†	133 (38.9%)	103 (32.9%)	0.12	59 (37.1%)	63 (39.6%)	0.73
Prior PCI*,†	189 (55.3%)	145 (46.3%)	0.02	80 (50.3%)	87 (54.7%)	0.50
Prior CABG*,†	10 (2.9%)	18 (5.8%)	0.08	6 (3.8%)	4 (2.5%)	0.75
Prior stroke*,†	30 (8.8%)	39 (12.5%)	0.13	11 (6.9%)	15 (9.4%)	0.54
Multivessel coronary disease*,†	131 (38.3%)	124 (39.6%)	0.75	69 (43.4%)	69 (43.4%)	1.00
Left ventricular ejection fraction (%)	57.0 (48.0, 65.0)	53.2 (42.0, 63.0)	0.002	55.0 (45.0, 62.0)	55.0 (45.0, 65.2)	0.62
≤40.0%*,†	32 (9.4%)	67 (21.4%)	<0.001	24 (15.1%)	28 (17.6%)	0.65
Presentation at baseline*,†			<0.001			0.76
STEMI	39 (11.4%)	92 (29.4%)		24 (15.1%)	20 (12.6%)	
NSTEMI	15 (4.4%)	19 (6.1%)		9 (5.7%)	8 (5.0%)	
Unstable angina pectoris	54 (15.8%)	36 (11.5%)		27 (17.0%)	23 (14.5%)	
Stable angina pectoris	234 (68.4%)	166 (53.0%)		99 (62.3%)	108 (67.9%)	
Target coronary vessel*,†			0.16			0.97
Left main	16 (4.7%)	24 (7.7%)		10 (6.3%)	13 (8.2%)	
Left anterior descending	180 (52.6%)	147 (47.0%)		78 (49.1%)	78 (49.1%)	
Left circumflex	53 (15.5%)	43 (13.7%)		28 (17.6%)	26 (16.4%)	
Right	91 (26.6%)	93 (29.7%)		41 (25.8%)	40 (25.2%)	
Bypass graft	2 (0.6%)	6 (1.9%)		2 (1.3%)	2 (1.3%)	
In-stent restenosis*,†	69 (20.2%)	40 (12.8%)	0.01	29 (18.2%)	28 (17.6%)	1.00
Ostial lesion*,†	35 (10.2%)	27 (8.6%)	0.51	20 (12.6%)	15 (9.4%)	0.47
Bifurcation lesion*,†	138 (40.4%)	131 (41.9%)	0.75	67 (42.1%)	77 (48.4%)	0.31
Severe calcification*,†	43 (12.6%)	80 (25.6%)	<0.001	27 (17.0%)	29 (18.2%)	0.88
Chronic total occlusion*,†	38 (11.1%)	17 (5.4%)	0.008	11 (6.9%)	15 (9.4%)	0.54
Total stent length (mm)	28.0 (18.0, 40.0)	28.0 (18.0, 45.0)	0.19	28.0 (18.0, 41.0)	28.0 (18.0, 42.0)	0.97
Total stent length ≥38-mm*,†	87 (25.5%)	97 (31.0%)	0.14	47 (29.6%)	45 (28.3%)	0.90
Stent overlap*,†	119 (34.8%)	112 (35.8%)	0.81	59 (37.1%)	59 (37.1%)	1.00

Categorical variables are expressed as number and percentage. Continuous variables are indicated as mean ± SD or median (interquartile range).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration ratio; G1-ST = first-generation drug-eluting stent thrombosis; G2-ST = second-generation drug-eluting stent thrombosis; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

* Variables included in the multivariable analysis to estimate propensity score.

† Variables used for multivariable analyses comparing hazard ratio of G1-ST and G2-ST for the study end points.

‡ Defined as having at least 1 following feature: total cholesterol level ≥220 mg/dl, low-density lipoprotein cholesterol level ≥140 mg/dl, or medical treatment for dyslipidemia.

Table 2
Clinical presentation and treatment at the time of ST

Variable	Overall population			Matched population		
	G1-ST (n = 342)	G2-ST (n = 313)	p	G1-ST (n = 159)	G2-ST (n = 159)	p
ST type*,†			<0.001			0.83
Early ST	83 (24.3%)	178 (56.9%)		74 (46.5%)	70 (44.0%)	
Late ST	24 (7.0%)	67 (21.4%)		21 (13.2%)	25 (15.7%)	
Very late ST	237 (68.7%)	68 (21.7%)		64 (40.3%)	64 (40.3%)	
Multi-vessel ST*,†	19 (5.6%)	10 (3.2%)	0.18	7 (4.4%)	7 (4.4%)	1.00
Status of APT*,†			<0.001			0.93
Dual antiplatelet therapy	165 (48.3%)	240 (76.7%)		109 (68.6%)	106 (66.7%)	
Aspirin alone	118 (34.5%)	28 (9.0%)		28 (17.6%)	27 (17.0%)	
Thienopyridine alone	9 (2.6%)	11 (3.5%)		3 (1.9%)	4 (2.5%)	
None	50 (14.6%)	34 (10.9%)		19 (11.9%)	22 (13.8%)	
Medication						
Anticoagulation	27 (7.9%)	28 (8.9%)	0.67	12 (7.5%)	13 (8.2%)	1.00
ACE-I/ARB	206 (60.2%)	174 (55.6%)	0.24	90 (56.6%)	89 (56.0%)	1.00
Beta-blocker	126 (36.8%)	132 (42.2%)	0.17	56 (35.2%)	52 (32.7%)	0.72
Statin	206 (60.2%)	200 (63.9%)	0.38	85 (53.5%)	89 (56.0%)	0.74
Oral hypoglycemia agent	73 (21.3%)	76 (24.3%)	0.40	38 (23.9%)	42 (26.4%)	0.70
Insulin	31 (9.1%)	40 (12.8%)	0.13	15 (9.4%)	24 (15.1%)	0.17
Clinical presentation*,†			0.29			0.83
STEMI	253 (74.0%)	222 (70.9%)		112 (70.4%)	113 (71.1%)	
NSTEMI	46 (13.5%)	35 (11.2%)		21 (13.2%)	18 (11.3%)	
Unstable angina pectoris	19 (5.6%)	26 (8.3%)		11 (6.9%)	13 (8.2%)	
Cardiac arrest*,†	24 (7.0%)	30 (9.6%)	0.26	15 (9.4%)	15 (9.4%)	1.00
Cardiogenic shock*,†	91 (26.6%)	88 (28.1%)	0.73	46 (28.9%)	46 (28.9%)	1.00
Final TIMI flow grade*,†			0.70			1.00
0	4 (1.2%)	3 (1.0%)		3 (1.9%)	3 (1.9%)	
1	11 (3.2%)	10 (3.2%)		5 (3.1%)	4 (2.5%)	
2	28 (8.2%)	34 (10.9%)		10 (6.3%)	11 (6.9%)	
3	302 (87.5%)	266 (85.0%)		141 (88.7%)	141 (88.7%)	
Treatment						
PCI*,†	340 (99.4%)	307 (98.1%)	0.16	157 (98.7%)	155 (97.5%)	0.69
Emergent CABG*,†	4 (1.2%)	12 (3.8%)	0.04	3 (1.9%)	5 (3.1%)	0.72
IABP use*,†	88 (25.7%)	131 (41.9%)	<0.001	50 (31.4%)	47 (29.6%)	0.81
PCPS use*,†	14 (4.1%)	20 (6.4%)	0.22	8 (5.0%)	9 (5.7%)	1.00

Categorical variables are expressed as number and percentage.

APT = antiplatelet therapy; IABP = intra-aortic balloon pumping; PCPS = percutaneous cardiopulmonary support; TIMI = thrombosis in myocardial infarction; ST = stent thrombosis. Other abbreviations as in Table 1.

* Variables included in the multivariable analysis to estimate propensity score.

† Variables used for multivariable analyses comparing hazard ratio of G1-ST and G2-ST for the study end points.

All statistical analyses were performed by 2 physicians (Dr. Horie and Dr. Kuramitsu) using the JMP version 14 (SAS Institute, Cary, NC) and R software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). A value of $p < 0.05$ was considered statistically significant.

Results

After PS matching, the final study population consisted of 159 matched patients in each group (Figure 1). Baseline patient and lesion characteristics at the index PCI procedure before and after PS matching are provided in Table 1. Before PS matching, no significant differences in baseline clinical characteristics were observed between G1-ST and G2-ST groups except for current smoking, hemodialysis, prior PCI, LVEF, clinical presentation, lesion characteristics including in-stent stenosis, severe calcification, and chronic total occlusion. After PS matching, baseline patient and lesion characteristics were well balanced between the 2 groups. Table 2 shows clinical presentation and treatment at the time of ST. Before PS matching, significant differences were observed between the 2 groups for ST type, antiplatelet therapy, emergent coronary artery bypass graft, and intra-aortic balloon pumping use. After PS matching,

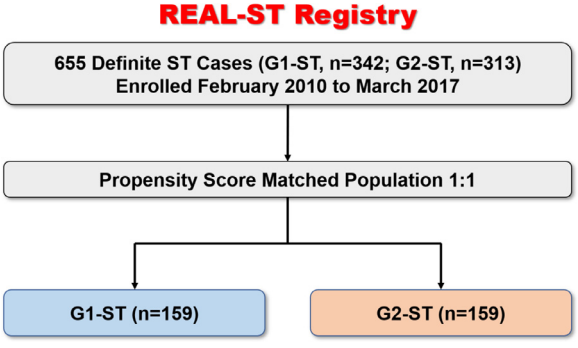
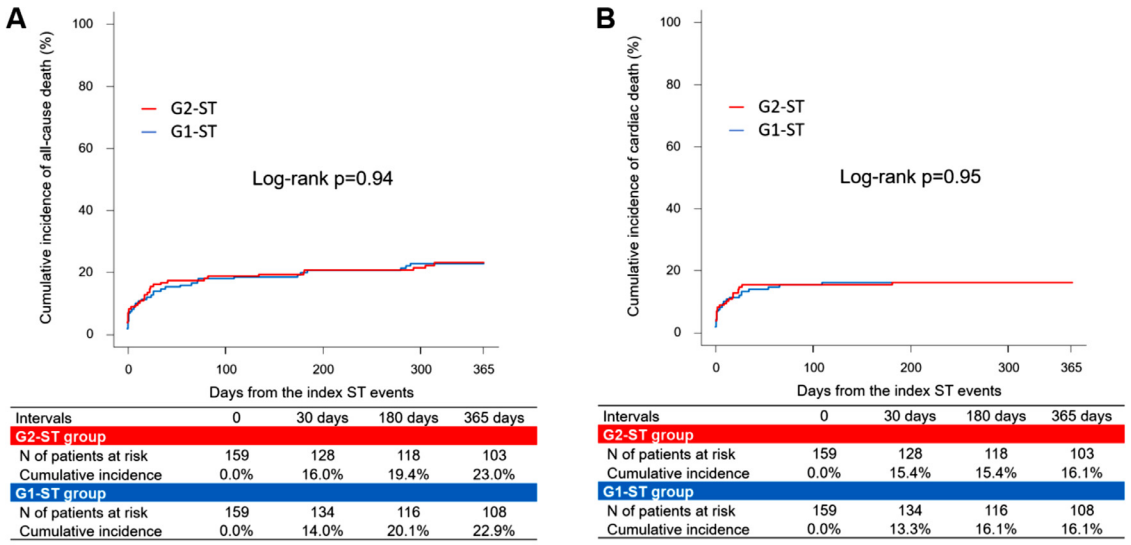


Figure 1. Study flowchart. G1-ST = first-generation drug-eluting stent thrombosis; G2-ST = second-generation drug-eluting stent thrombosis; ST = stent thrombosis.



Intervals	0	30 days	180 days	365 days
G2-ST group				
N of patients at risk	159	128	118	103
Cumulative incidence	0.0%	16.0%	19.4%	23.0%
G1-ST group				
N of patients at risk	159	134	116	108
Cumulative incidence	0.0%	14.0%	20.1%	22.9%

Intervals	0	30 days	180 days	365 days
G2-ST group				
N of patients at risk	159	128	118	103
Cumulative incidence	0.0%	15.4%	15.4%	16.1%
G1-ST group				
N of patients at risk	159	134	116	108
Cumulative incidence	0.0%	13.3%	16.1%	16.1%

Intervals	0	30 days	180 days	365 days
G2-ST group				
N of patients at risk	159	141	111	93
Cumulative incidence	0.0%	2.0%	7.9%	9.7%
G1-ST group				
N of patients at risk	159	132	106	92
Cumulative incidence	0.0%	6.2%	12.7%	17.1%

Intervals	0	30 days	180 days	365 days
G2-ST group				
N of patients at risk	159	126	118	103
Cumulative incidence	0.0%	2.2%	2.9%	2.9%
G1-ST group				
N of patients at risk	159	132	116	108
Cumulative incidence	0.0%	5.4%	5.4%	5.4%

Figure 2. Clinical events after stent thrombosis through 1 year. (*A*) All-cause death, (*B*) cardiac death, (*C*) target lesion revascularization, and (*D*) recurrent stent thrombosis. CI = confidence intervals; HR = hazard ratio.

clinical presentation and treatment at the time of ST were well balanced between the 2 groups.

One-year follow-up information was obtained in 145 G1-ST patients (91.2%) and in 136 G2-ST patients (85.5%). At 1 year, all-cause death rate was similar between the G1-ST and G2-ST groups (22.9% vs 23.0%; HR 1.01, 95% confidence intervals [CI]: 0.64 to 1.63, p = 0.94; Figure 2). Cumulative incidence of cardiac death and recurrent ST were also not significantly different between the 2 groups, whereas TLR rate tended to be lower in the G2-ST group than in the G1-ST group (9.7% vs 17.1%; HR 0.54, 95% CI: 0.27 to 1.08, p = 0.08; Figure 2). After adjustment for baseline characteristics, there were no significant differences in the rate of all-cause death, cardiac death, and recurrent ST between both groups (Table 3). On the other hand, TLR occurred less frequently in the G2-ST group as compared with the G1-ST group during the 1-year follow-up (adjusted HR 0.34, 95% CI: 0.14 to 0.81, p = 0.01; Table 3).

Independent risk factors of 1-year mortality were cardiogenic shock at the time of ST (HR 4.05, 95% CI: 2.31 to 7.71, p <0.001), multivessel ST (HR 3.96, 95% CI: 1.80 to 8.73, p <0.001), cardiac arrest at the time of ST (HR 3.17, 95% CI: 1.72 to 5.84, p <0.001), age (per 1.0 increase; HR 1.06, 95% CI: 1.03 to 1.09, p <0.001), LVEF ≤40% (HR 2.36, 95%CI: 1.40 to 3.97, p = 0.001), and final TIMI flow grade ≤2 (HR 2.02, 95% CI: 1.06 to 3.83, p = 0.03; Table 4).

Discussion

The main findings of the present study were as follows: (1) the mortality after G2-ST at 1 year was similar to that after G1-ST; (2) patients with G2-ST had a significantly lower incidence of TLR than those with G1-ST; and (3) clinical presentation (cardiogenic shock, cardiac arrest, multivessel ST, and final TIMI flow grade ≤2) at the time of ST, advanced age, and LVEF ≤40% were associated with 1-year mortality.

ST has emerged as a safety concern with first-generation DES in clinical practice due to the high incidence of

Table 3
Adjusted risk of clinical events associated stent thrombosis

Outcome	Total number of events (%)		Crude HR (95% CI)			Multivariable adjusted HR (95% CI)*		
	G1-ST	G2-ST	HR	95% CI	p	HR	95% CI	p
All-cause death	35 (22.9)	35 (23.0)	1.01	0.64-1.63	0.94	1.09	0.62-1.93	0.76
Cardiac death	25 (16.1)	25 (16.1)	1.02	0.58-1.77	0.95	1.37	0.67-2.80	0.39
TLR	22 (17.1)	12 (9.7)	0.54	0.27-1.08	0.08	0.34	0.14-0.81	0.01
Recurrent ST	8 (5.4)	4 (2.9)	0.50	0.15-1.66	0.26	0.35	0.05-2.29	0.28

CI = confidence intervals; HR = hazard ratio; ST = stent thrombosis; TLR = target lesion revascularization.

* Adjusted for covariates below by including them as regressors of multivariable Cox models: age, bifurcation lesion, cardiogenic shock at the time of stent thrombosis (ST), clinical presentation at baseline and at the time of ST, chronic total occlusion lesion, current smoking, diabetes mellitus, dyslipidemia, final thrombolysis in myocardial infarction flow grade at the time of ST, estimated glomerular filtration rate ≤30 ml/min/1.73 m^2 without hemodialysis, hemodialysis, hypertension, in-stent stenosis lesion, intra-aortic balloon pumping use at the time of ST, left ventricular ejection fraction ≤40%, male gender, multivessel disease, multivessel ST, ostial lesion, percutaneous cardiopulmonary support use at the time of ST, prior coronary artery bypass graft (CABG), prior percutaneous coronary intervention (PCI), prior myocardial infarction, prior stroke, status of antiplatelet therapy at the time of ST, lesion with severe calcification, stent overlap, target vessel, treatment (PCI or CABG) at the time of ST, total stent length ≥38-mm.

Table 4
Predictors of 1-year mortality

Variable	Univariable			Multivariable*		
	HR	95% CI	p	HR	95% CI	p
Age	1.04	1.01-1.06	0.004	1.06	1.03-1.09	<0.001
Men	1.12	0.61-2.04	0.72			
Hypertension	1.54	0.76-3.10	0.23			
Dyslipidemia	0.75	0.45-1.27	0.28			
Diabetes mellitus	1.11	0.69-1.78	0.66			
Current smoker	0.78	0.46-1.34	0.37			
Hemodialysis	1.63	0.81-3.29	0.17			
GFR ≤30 ml/min/1.73 m^2 without hemodialysis	1.75	0.64-4.83	0.27			
Prior myocardial infarction	1.39	0.87-2.22	0.17			
Prior PCI	1.17	0.73-1.88	0.51			
Prior CABG	1.94	0.71-5.32	0.20			
Prior stroke	1.44	0.69-3.00	0.33			
Multivessel coronary disease	1.99	1.24-3.21	0.004			
Left ventricular ejection fraction ≤40%	2.96	1.80-4.88	<0.001	2.36	1.40-3.97	0.001
In-stent restenosis lesion	1.24	0.70-2.19	0.47			
Ostial lesion	2.19	1.20-4.01	0.01			
Bifurcation lesion	1.43	0.90-2.29	0.13	1.39	0.85-2.30	0.19
Severe calcification	1.73	1.01-2.96	0.045			
Chronic total occlusion	0.14	0.02-1.02	0.052			
Total stent length ≥38-mm	1.10	0.66-1.82	0.72			
Stent overlap	1.1	0.68-1.77	0.71			
G2-ST (vs G1-ST)	1.02	0.64-1.63	0.94			
Multi-vessel ST	6.47	3.27-12.7	<0.001	3.96	1.80-8.73	<0.001
ST type (vs VLST)						
EST	1.37	0.82-2.27	0.23			
LST	0.92	0.42-2.04	0.84			
Clinical presentation at the time of ST (vs UAP)						
NSTEMI	1.85	0.19-17.8	0.59			
STEMI	5.26	0.73-38.1	0.10			
Cardiac arrest at the time of ST	26.8	3.58-200.4	<0.001	3.17	1.72-5.84	<0.001
Cardiogenic shock at the time of ST	5.77	3.55-9.38	<0.001	4.05	2.31-7.11	<0.001
Final TIMI flow grade ≤2 at the time of ST	2.41	1.34-4.33	0.003	2.02	1.06-3.83	0.03
Treatment at the time of ST						
PCI	0.63	0.16-2.59	0.53			
Emergent CABG	1.88	0.59-5.91	0.29			

EST = early stent thrombosis; LMCA = left main coronary artery; LST = late thrombosis; VLST = very late stent thrombosis. Other abbreviations as in Tables 1 and 2.

* Multivariable Cox model was constructed using clinically relevant 7 variables (age, bifurcation lesion, cardiogenic arrest or shock at the time of ST, final thrombosis in myocardial infarction flow grade ≤2, and left ventricular ejection fraction ≤40%, multivessel ST).

mortality associated with ST.[1,2] In the REAL-ST registry, patients with G2-ST showed unfavorable long-term mortality compared with those without ST, regardless of the timing of ST.[3] Furthermore, a previous study, including both G1-ST and G2-ST, demonstrated that cardiac death or recurrent ST occurred in 21.4% of patients during the first year after the index ST events.[4] Although these findings underscore that ST after first- and second-generation DES implantation results in worse clinical outcomes, little data exist on the comparison of clinical outcomes after G1-ST and G2-ST. The present study demonstrated that the mortality associated with G2-ST at 1-year was similar to that with G1-ST, highlighting that ST is less likely to occur in the second-generation DES era, but remains a life-threatening complication.

Recurrent ST and TLR after ST contribute to high mortality in patients with ST after DES implantation. Previous studies reported that recurrent ST occurred in 5%-8% during the 1-year follow-up.[2-4] However, the difference in the incidence of recurrent ST between G1- and G2-ST remains poorly understood. Furthermore, the TLR rate after ST has not yet been fully evaluated. In the current study, the G2-ST group demonstrated a significantly lower incidence of TLR than the G1-ST group. Possible explanations for this include the following: (1) the underlying mechanism may be somewhat different between G1- and G2-ST[9]; and (2) PCI strategy at the time of ST may affect clinical outcomes. Particularly, drug-coated balloon angioplasty has been introduced in clinical practice over the last decade and now emerges as an effective therapeutic option for in-stent restenosis.[10] Further studies are warranted to establish the optimal PCI strategy at the time of ST.

Final TIMI flow grade ≤2, low LVEF, cardiogenic shock or arrest, and advanced age are recognized as risk factors of mortality associated with ST.[1,6-8] Among them, the achievement of final TIMI flow grade 3 can be a procedural goal at the time of ST to reduce the mortality of ST patients. A large thrombus burden mainly causes the difficulty in restoring antegrade coronary flow when performing emergent PCI for ST lesions due to the frequent occurrence of distal embolization after balloon dilatation or additional stenting.[11] Although the clinical benefits of thrombus aspiration and distal protection devices in the acute myocardial infarction setting remain controversial, they should be considered as a therapeutic option in the presence of a huge thrombus.[12,13] Notably, an optical coherence tomography study revealed uncovered struts as the dominant finding for each ST, whereas stent underexpansion and severe restenosis were also frequently noted in early ST and late ST.[9] To improve outcomes associated with ST, we should identify the main cause of ST with intravascular imaging and choose the optimal PCI strategy with a goal of final TIMI flow grade 3.

There are several limitations in the present study. First, this study was a post hoc analysis of the REAL-ST registry and not a randomized comparison between G1-ST and G2-ST. Although we performed PS matching to adjust for differences in baseline clinical and procedural characteristics between the 2 groups, the potential of bias is inevitable in the present study, which might have affected the conclusions. Second, the risk factors of TLR could not be assessed in the present study. Finally, we could not investigate the relation between intravascular imaging findings and clinical outcomes due to the lack of imaging analysis in the present study.

In conclusion, patients with G2-ST showed a similar 1-year mortality to those with G1-ST, highlighting that ST is less likely to occur in the second-generation DES era, but remains a life-threatening complication.

Authors' Contributions

Kazunori Horie: Conceptualization, Methodology, Data Curation, Writing - Original Draft. Shoichi Kuramitsu: Project administration, Writing - Review & Editing. Tomohiro Shinozaki: Formal analysis. Masanobu Ohya: Investigation. Hiromasa Otake: Investigation. Futoshi Yamanaka: Investigation. Hiroki Shiomi: Investigation. Masahiro Natsuaki: Investigation, Validation. Gaku Nakazawa: Investigation. Norio Tada: Supervision. Kenji Ando: Supervision. Kazushige Kadota: Supervision. Shigeru Saito: Supervision. Takeshi Kimura: Supervision.

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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Supplementary materials

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