ORIGINAL RESEARCH

Risk Factors and Outcomes of Recurrent Drug-Eluting Stent Thrombosis: Insights From the REAL-ST Registry

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BACKGROUND: Stent thrombosis (ST) after drug-eluting stent (DES) implantation remains a life-threatening complication. Recurrent ST (RST) is not a rare phenomenon, potentially contributing to high mortality after the index ST events. However, little evidence is available about the incidence, risk factors, and clinical outcomes of definite RST after DES thrombosis.

METHODS AND RESULTS: From REAL-ST (Retrospective Multicenter Registry of ST After First- and Second- Generation DES Implantation), this study evaluated 595 patients with definite ST (first-generation DES thrombosis, n=314; second-generation DES thrombosis, n=281). During a median follow-up of 31 months, we identified 32 patients with definite RST after first-generation DES thrombosis (n=18) and second-generation DES thrombosis (n=15). Cumulative incidence of RST was 4.5% and 6.0% at 1 and 5 years, respectively, which did not significantly differ between first-generation DES thrombosis and second-generation DES thrombosis. Independent predictors of definite RST were early ST (hazard ratio [HR], 2.38; 95% CI, 1.06–5.35 [*P*=0.035]) and multivessel ST (HR, 3.47; 95% CI, 1.03–11.7 [*P*=0.044]). Definite RST was associated with a 2.8-fold increased risk of mortality (adjusted HR, 2.78; 95% CI, 1.35–5.73 [*P*=0.006]).

CONCLUSIONS: Cumulative incidence of definite RST did not significantly differ between first-generation DES thrombosis and second-generation DES thrombosis. Early ST and multivessel ST were risk factors of definite RST. Definite RST significantly increased mortality after DES thrombosis, highlighting the clinical importance of preventing RST to improve outcomes of patients with ST.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: UMIN000025181.

Key Words: drug-eluting stent ■ percutaneous coronary intervention ■ recurrent stent thrombosis

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See Editorial by Panaich and Girotra

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] REAL-ST (Retrospective Multicenter Registry of ST After First- and Second-Generation DES Implantation) revealed that definite ST in patients led to unfavorable long-term outcomes compared with those without definite ST, regardless of the timing of ST.[3] Furthermore, this registry

CLINICAL PERSPECTIVE

What Is New?

- Cumulative incidence of definite recurrent stent thrombosis (RST) did not significantly differ between first- and second-generation drug-eluting stents.
- Early stent thrombosis and multivessel stent thrombosis were risk factors of definite RST after drug-eluting stents thrombosis. Definite RST was independently associated with mortality after the index stent thrombosis events.

What Are the Clinical Implications?

- Definite RST is not a rare complication, contributing independently to mortality after drug-eluting stents thrombosis. Therefore, preventing RST may assist in the improvement of outcomes associated with stent thrombosis.
- Insufficient platelet inhibition is perhaps the most important contributor to definite RST. More potent $P2Y_{12}$ inhibitors (eg, prasugrel or ticagrelor) should be considered in the absence of identifiable mechanical causes (eg, stent underexpansion, stent malapposition, or edge dissection).

Nonstandard Abbreviations and Acronyms

DES	drug-eluting stent
EST	early stent thrombosis
G1-ST	first-generation drug-eluting stent thrombosis
G2-ST	second-generation drug-eluting stent thrombosis
LST	late stent thrombosis
REAL-ST	Retrospective Multicenter Registry of ST After First- and Second-Generation DES Implantation
RST	recurrent stent thrombosis
ST	stent thrombosis
VLST	very late stent thrombosis

demonstrated that the 1-year mortality rate after ST was equivalent between first- and second-generation DES, highlighting that ST remains a life-threatening complication in the second-generation DES era.[4]

Recurrent ST (RST) remains an unsolved issue after the index ST events.[2–6] Recently, Armstrong et al[5] reported that the 3-year mortality rate tended to be higher in patients with RST than those without RST; and advanced age, bifurcation lesion, and

a larger proximal reference vessel diameter were predictors of RST. However, this study had a small number of patients with definite RST, especially after second-generation DES thrombosis. Also, it remains unclear whether RST is independently associated with mortality after the index ST events. In the present study, we sought to assess the incidence, risk factors, and clinical outcomes of patients with RST after first- and second-generation DES thrombosis by analyzing REAL-ST.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

This study is a post hoc analysis of REAL-ST (http://www.umin.ac.jp; unique identifier, UMIN000025181), which was a retrospective multicenter registry of patients with definite ST after first- and second-generation DES implantation at 46 Japanese percutaneous coronary intervention institutions (Appendix). 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 percutaneous coronary intervention with first-generation DES from April 2004 to December 2013 or second-generation DES from May 2009 to December 2016; or (2) who had definite ST of first- or second-generation DES from April 2004 to March 2017. Finally, a total of 655 patients with ST (first-generation DES thrombosis [G1-ST], n=342; second-generation DES thrombosis [G2-ST], n=313) were enrolled in the registry.

For this study, we evaluated RST events after the index ST occurrence. Patients with cardiac arrest and final thrombolysis in myocardial infarction flow grade 0 at the time of ST were excluded from this study. The study protocol was approved by the ethics committees at all participating centers and was in accordance with the Declaration of Helsinki. Written informed consent was waived because of the retrospective study design.

Definitions and Study End Points

Definite ST was defined according to the Academic Research Consortium criteria.[7] ST was categorized according to the timing of ST occurrence as early ST (EST; within 30 days), late ST (LST; between 31 and 365 days), and very late ST (VLST; >1 year). Patients who presented with recurrent acute coronary syndrome and angiographic evidence of thrombus in the

same stent were defined as having definite RST. The main objective of this study was to assess the incidence, risk factors, and clinical outcomes of RST after the index ST events. All-cause death was assessed as the clinical end point during the follow-up.

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 ST events.

Statistical Analysis

Categorical variables were presented as numbers and percentages, and continuous variables were expressed as median and interquartile range. Cumulative incidence risk of RST was estimated by the Kaplan–Meier method. As RST is a time-varying indicator, its association of patient characteristics at baseline or index ST events were assessed using a univariable Cox regression model, with time to first RST censoring as the response variable and each covariate as the explanatory variables. A multivariable model was developed for the association of RST with 4 clinically relevant variables (age, bifurcation
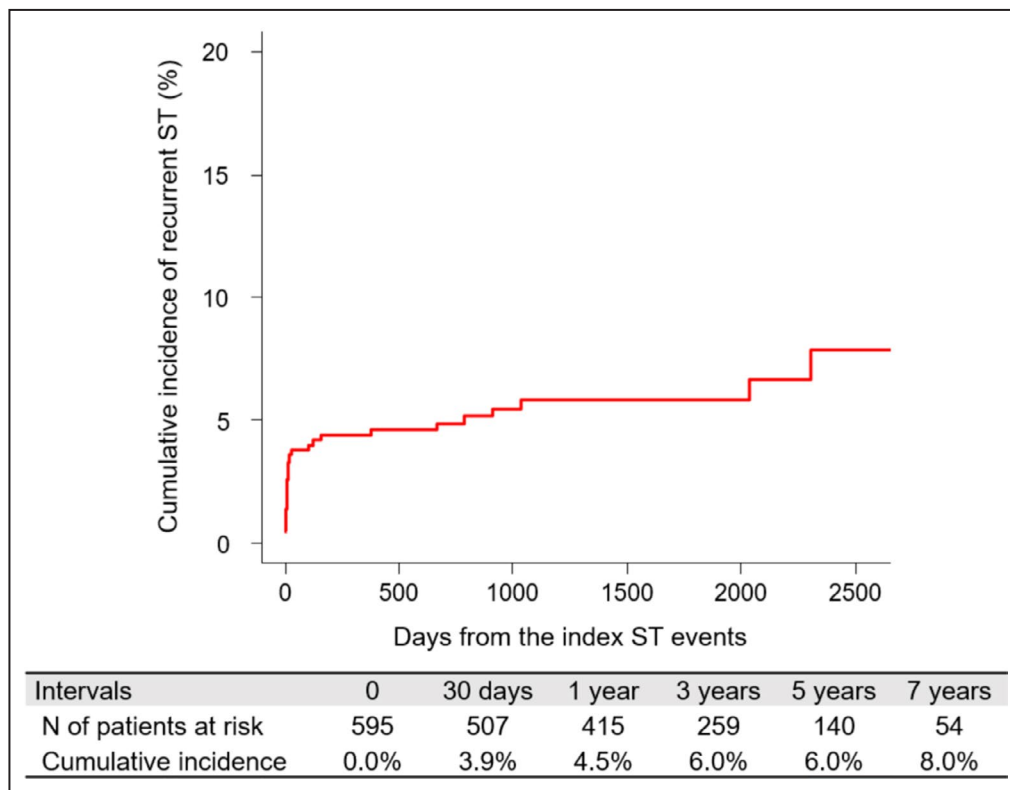
lesion, ST type [EST, LST, VLST], and multivessel ST).[6] To assess the association of RST during the follow-up with all-cause death, we used Cox regression models with RST during the follow-up as a time-dependent covariate. Once RST occurred, the indicator for RST was turned on for the remainder of follow-up. Unadjusted and adjusted hazard ratios (HRs) for the association of RST with all-cause death were estimated. Adjustment variables were based on factors most associated with RST from the multivariable model and on factors identified to be important for RST. The survival probabilities before and after RST development were visualized by the Simon-Makuch survival estimates for the time-dependent RST and non-RST statuses.[8]

All statistical analyses were performed by a physician (S.K.) and a statistician (T.S.) using R software version 3.5.2 (R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute). A value of $P<0.05$ was considered statistically significant.

RESULTS

Study Population

Among 655 patients, 60 were excluded for the following reasons at the time of ST: cardiac arrest (n=52) and final thrombolysis in myocardial

Intervals	0	30 days	1 year	3 years	5 years	7 years
N of patients at risk	595	507	415	259	140	54
Cumulative incidence	0.0%	3.9%	4.5%	6.0%	6.0%	8.0%

Figure 1. Cumulative incidence of recurrent stent thrombosis (ST).

Table 1. Baseline Clinical Characteristics

	RST (n=32)	Non-RST (n=563)	Univariable Cox Regression HR (95% CI)	*P* Value
Age, y*	68 (61–77)	69 (62–76)	1.01 (0.98–1.05)	0.52
Men*	23 (71.9)	458 (81.3)	0.60 (0.28–1.30)	0.20
Hypertension*	26 (81.2)	448 (79.9)	1.12 (0.46–2.72)	0.80
Diabetes mellitus*	17 (53.1)	255 (45.5)	2.31 (0.70–7.57)	0.36
Dyslipidemia*	29 (90.6)	451 (80.4)	1.38 (0.69–2.77)	0.17
Current smoker*	8 (25.0)	157 (28.1)	0.90 (0.40–2.01)	0.80
Hemodialysis*	2 (6.2)	46 (8.2)	0.84 (0.20–3.51)	0.81
Prior myocardial infarction*	13 (40.6)	195 (34.8)	1.23 (0.60–2.48)	0.57
Prior PCI*	19 (59.4)	280 (49.9)	1.33 (0.66–2.70)	0.43
Prior CABG*	0 (0.0)	26 (4.6)	NA	NA
Multivessel disease*	14 (43.8)	210 (37.5)	1.44 (0.71–2.89)	0.31
LVEF, %	50.0 (40.8–63.0)	56.2 (46.0–65.0)	0.98 (0.95–1.00)	0.046
≤40.0%*	6 (18.8)	77 (14.3)	1.60 (0.66–3.89)	0.30
DES type*				
First-generation DES	17 (53.1)	297 (52.8)	0.88 (0.44–1.78)	0.72
Second-generation DES	15 (46.9)	266 (47.2)	1.13 (0.56–2.29)	0.72
Clinical presentation at baseline*				
Stable angina	16 (50.0)	344 (61.1)	1.00 [reference]	
Unstable angina	4 (12.5)	78 (13.9)	1.18 (0.39–3.53)	0.77
NSTEMI	2 (6.2)	31 (5.5)	1.75 (0.40–7.62)	0.46
STEMI	10 (31.2)	110 (19.5)	2.05 (0.93–4.51)	0.08
Target coronary vessel*				
Left main	1 (3.1)	27 (4.8)	0.69 (0.09–5.06)	0.72
Left anterior descending	21 (65.6)	302 (53.6)	1.71 (0.82–3.54)	0.15
Left circumflex	2 (6.2)	92 (16.3)	0.35 (0.08–1.48)	0.16
Right	8 (25.0)	156 (27.7)	0.83 (0.37–1.85)	0.65
In-stent restenosis*	5 (15.6)	88 (15.6)	0.96 (0.37–2.50)	0.94
Ostial lesion*	1 (3.1)	45 (8.0)	0.37 (0.05–2.70)	0.33
Bifurcation lesion*	13 (40.6)	219 (38.9)	1.08 (0.53–2.19)	0.83
Severe calcification*	6 (18.8)	100 (17.8)	1.08 (0.44–2.62)	0.87
Chronic total occlusion*	3 (9.4)	49 (8.7)	1.01 (0.31–3.33)	0.98
Total stent length, mm	24.0 (18.0–34.3)	28.0 (18.0–41.0)	0.99 (0.97–1.02)	0.56
Total stent length >38 mm*	8 (25.0)	156 (27.7)	0.90 (0.41–2.01)	0.81
Stent overlap*	9 (28.1)	195 (34.6)	0.74 (0.34–1.61)	0.45

Categorical variables are expressed as number and percentage. Continuous variables are indicated as median and interquartile range. CABG indicates coronary artery bypass graft; DES, drug-eluting stent; HR, hazard ratio; LVEF, left ventricular ejection fraction; NA, not applicable; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Variables used for the multivariable analysis assessing the association of recurrent stent thrombosis (RST) with all-cause death.

infarction flow grade 0 (n=8). Finally, 595 patients were analyzed (G1-ST, n=314; G2-ST, n=281) in the present study. During a median follow-up of 31 months, we identified 32 patients with RST after G1-ST (n=17) and G2-ST (n=15). RST events mostly occurred within the 30 days after the index ST occurrence (Figure 1).

Baseline Clinical Characteristics

The baseline patient and lesion characteristics are shown in Table 1. There were no significant associations with the time to onset of RST except for left ventricular ejection fraction. In terms of clinical characteristics at the time of ST, patients with EST or multivessel ST experienced RST more frequently (Table 2 and Table S1).

Table 2. Clinical Presentation, Medication, and Treatment at the Time of ST

	RST (n=32)	Non-RST (n=563)	Univariable Cox Regression HR (95% CI)	P Value
ST type*				
Early	18 (56.2)	214 (38.0)	2.94 (1.29–6.73)	0.026
Late	5 (15.6)	78 (13.9)	2.18 (0.71–6.65)	0.25
Very late	9 (28.1)	271 (48.1)	1.00 [reference]	
Multivessel ST*	3 (9.4)	19 (3.4)	4.08 (1.24–13.4)	0.02
Status of antiplatelet				
Dual antiplatelet therapy	25 (78.1)	339 (60.3)	1.00 [reference]	
Aspirin alone	3 (9.4)	131 (23.3)	0.31 (0.09–1.03)	0.06
Thienopyridine alone	0 (0.0)	19 (3.4)	NA	NA
None	4 (12.5)	73 (13.0)	0.80 (0.28–2.29)	0.67
Medication				
Anticoagulation	0 (0.0)	48 (8.5)	NA	NA
ACEI/ARB	20 (62.5)	325 (57.8)	1.17 (0.57–2.39)	0.67
β-Blocker	11 (34.4)	215 (38.3)	0.85 (0.41–1.77)	0.67
Statin	22 (68.8)	354 (63.0)	1.25 (0.59–2.63)	0.56
Oral hypoglycemia agent	8 (25.0)	127 (22.6)	1.15 (0.52–2.56)	0.73
Insulin	4 (12.5)	55 (9.8)	1.37 (0.48–3.90)	0.56
Clinical presentation*				
Unstable angina	2 (6.2)	41 (7.3)	1.00 [reference]	
NSTEMI	4 (12.5)	76 (13.5)	1.20 (0.22–6.55)	0.83
STEMI	26 (81.2)	446 (79.2)	1.30 (0.31–5.46)	0.72
Cardiogenic shock*	8 (25.8)	112 (20.5)	1.43 (0.66–3.10)	0.25
Final TIMI flow grade				
1	2 (6.2)	16 (2.8)	2.83 (0.67–11.9)	0.16
2	3 (9.4)	51 (9.1)	1.15 (0.35–3.80)	0.81
3	27 (84.4)	496 (88.1)	1.00 [Reference]	
Final TIMI flow grade ≤ 2*	5 (15.6)	67 (11.9)	1.51 (0.58–3.93)	0.40
Treatment*				
PCI	32 (100.0)	560 (99.5)	NA	NA
Emergent CABG	1 (3.1)	12 (2.1)	1.70 (0.23–12.4)	0.60

Categorical variables are expressed as number and percentage. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; HR, hazard ratio; NA, not applicable; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis; STEMI, ST-segment–elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

*Variables used for the multivariable analysis assessing the association of recurrent stent thrombosis (RST) with all-cause death.

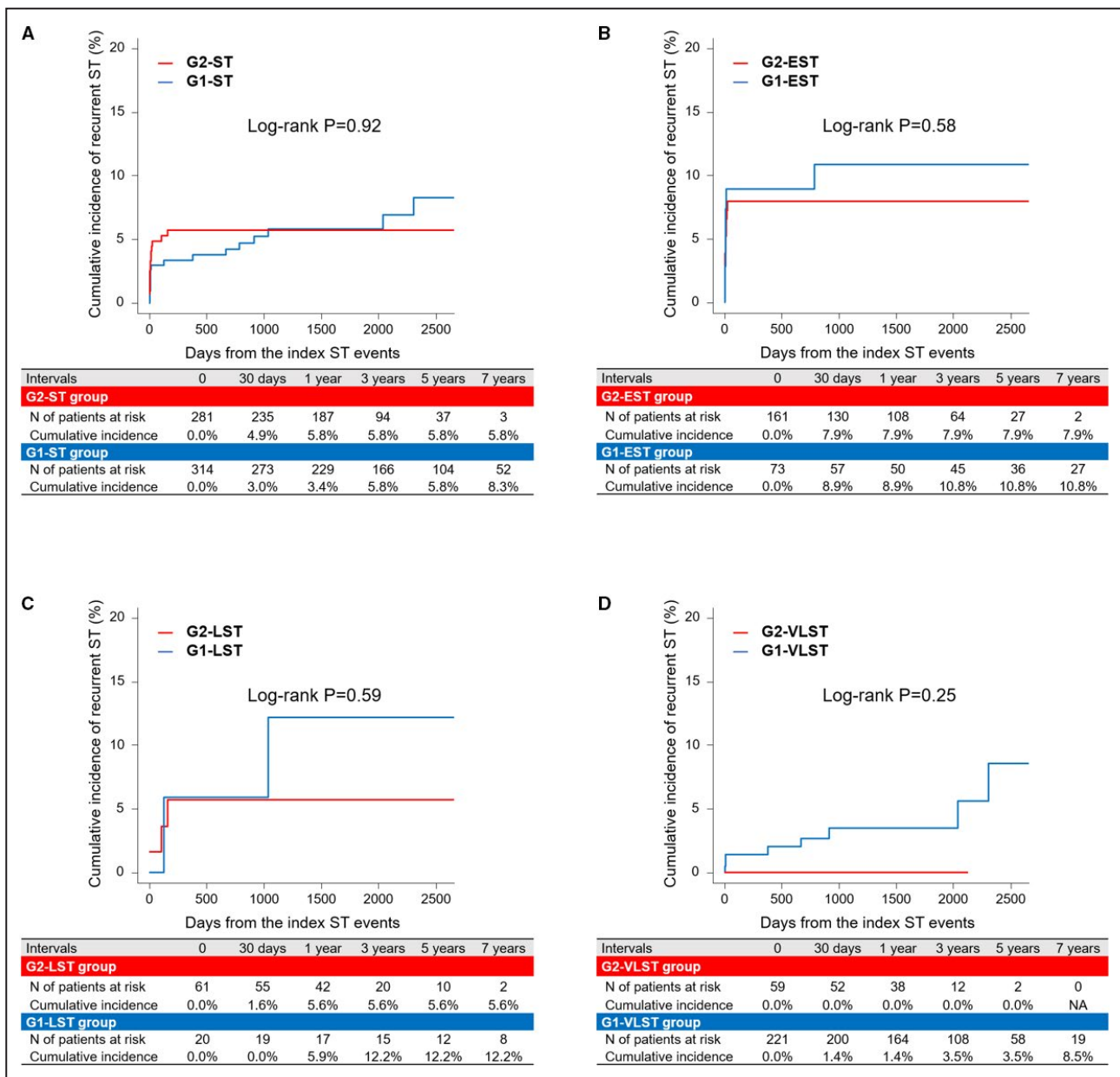## Comparison of Incidence of RST After G1-ST and G2-ST

Cumulative incidence of definite RST did not significantly differ between G1-ST and G2-ST, regardless of the timing of ST (Figure 2). Although 8.5% of patients with G1-VLST experienced definite RST events during the follow-up, those with G2-VLST did not.

Risk Factors and Outcomes of RST

Martingale residual plots did not give any evidence against the linearity assumption for all models. Independent predictors of definite RST were EST (HR,

2.38; 95% CI, 1.06–5.35 [P=0.035]) and multivessel ST (HR, 3.47; 95% CI, 1.03–11.7 [P=0.044]) (Figure 3). The Schoenfeld residuals for each variable suggested that proportional hazards assumption was approximately met except for EST; the HR of EST versus VLST seemed to get smaller over the follow-up period. Table 3 shows the association of definite RST with all-cause death. Definite RST was associated with a 2.8-fold increased risk of mortality (adjusted HR, 2.78; 95% CI, 1.35–5.73 [P=0.006]). Estimates of HRs for all variables in the time-dependent Cox models are presented in Table S2. Figure 4 depicts this increase in hazard after the development of RST (P=0.007 by the Mantel-Byer test).

Figure 2. Comparison of incidence of recurrent stent thrombosis (RST) after first-generation drug-eluting stent thrombosis (G1-ST) and second-generation drug-eluting stent thrombosis (G2-ST).
ST indicates stent thrombosis. **A**, Early ST (EST), (**B**) late ST (LST), and (**C**) very late ST (VLST).

DISCUSSION

The main findings of the present study were as follows: (1) the cumulative incidence of definite RST did not significantly differ between G1-ST and G2-ST; (2) EST and multivessel ST were risk factors of definite RST; and (3) definite RST was independently associated with an increased risk of mortality after the index ST events.

RST remains an unsolved issue after index ST events.[2–6,8] Previous studies reported that the RST rate was 4.6% to 5.3% at 1 year[2,9] and 15% to 20% at 5 years.[1,6] However, these data had a small number of

definite RST, especially after G2-ST. In addition, some studies included RST after bare-metal stent thrombosis. In the present study, the cumulative incidence of RST was 4.5% and 6.0% at 1 and 5 years, respectively, which did not significantly differ between G1-ST and G2-ST. Of note, however, definite RST did not occur beyond 6 months after G2-ST. Furthermore, definite RST after G1-VLST continued to occur up to 7 years, despite no occurrence of definite RST after G2-VLST. These findings suggest that there are some differences in the cause of definite RST between G1-ST and G2-ST, particularly after VLST. Indeed, an optical coherence
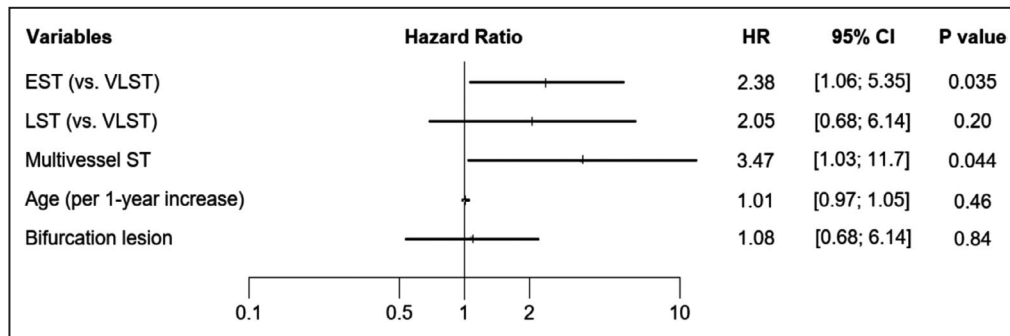
Figure 3. Risk factors associated with recurrent stent thrombosis (ST).
EST indicates early stent thrombosis; HR, hazard ratio; LST, late stent thrombosis; ST, stent thrombosis; and VLST, vary late stent thrombosis.

tomography study revealed that the dominant findings were somewhat different between G1-VLST and G2-VLST.[10] Although the underlying mechanism of definite RST remains poorly understood, we recognize the difference in the timing of definite RST between G1-ST and G2-ST.

Advanced age, bifurcation lesion, and a larger proximal reference vessel diameter were reportedly associated with definite or probable RST,[6] whereas limited evidence is available regarding the risk factors of definite RST after DES thrombosis. The current study demonstrated that EST and multivessel ST were risk factors of definite RST after G1-ST and G2-ST. EST is more common than LST and VLST, accounting for ≈50% to 70% of all ST cases.[1–3] Riegger et al[11] reported that EST patients had a higher level of platelets and C-reactive protein at the time of ST than those with LST and VLST, suggesting that platelets may be more activated at the time of EST. Multivessel ST is reported in ≈3% of patients with ST.[2–4] As ST simultaneously occurs within the multiple stents, platelet activation potentially plays a crucial role in the occurrence of multivessel ST. Considering these findings, increased platelet activation may contribute mainly to definite RST. It is intriguing that our results were not in line with the previous study.[6] Possible explanations for this include the following: (1) the previous study included RST after bare-metal stent or unknown ST; and (2) the 2-stent approach for bifurcation lesions was more frequently performed in the previous study than the current studies (31.3% versus 18.5%).[6] Nevertheless, we

could not identify the risk factors of definite RST after G2-ST because of its small number of patients enrolled in the current study. Further studies are warranted to assess these differences.

ST is less likely to occur in the second-generation DES era but remains a life-threatening complication.[3,4] A previous study reported a higher rate of major cardiovascular events in patients with RST than those without RST,[6] whereas it remains unclear whether RST would significantly increase mortality after the index ST events. To our knowledge, the present study firstly demonstrated that definite RST contributed independently to mortality after ST. Accordingly, preventing RST may assist in the improvement of outcomes associated with ST. Given that EST and multivessel ST were risk factors of definite RST in the present study, intracoronary imaging is mandatory to identify the underlying mechanism of ST. When mechanical causes, including stent underexpansion, stent malapposition, or edge dissection, are evident, they should be appropriately fixed with imaging guidance.[12] Insufficient platelet inhibition is perhaps the most important contributor to definite RST. More potent $P2Y_{12}$ inhibitors, such as prasugrel or ticagrelor, are preferred in the absence of identifiable mechanical causes.[13,14] Although the optimal duration of dual antiplatelet therapy) after the index ST events remains unclear, it should be continued for at least 6 months after G2-ST according to our results. Furthermore, prolonged dual antiplatelet therapy beyond 1 year might be considered in patients with G1-VLST.

Table 3. Mortality Rates Following Recurrent ST

	Patient-y	Death	Mortality Rate (Per 10 Patient-y)	Crude HR (95% CI)	P Value	Adjusted HR (95% CI)*	P Value
Non-RST	1795.3	133	0.74	1.00		1.00	
RST	68.6	10	1.46	2.38 (1.25–4.56)	0.009	2.78 (1.35–5.73)	0.006

HR indicates hazard ratio; RST, recurrent stent thrombosis; and ST, stent thrombosis.
*Adjusted for variables presented with asterisk (*) in Table 1 and Table 2.
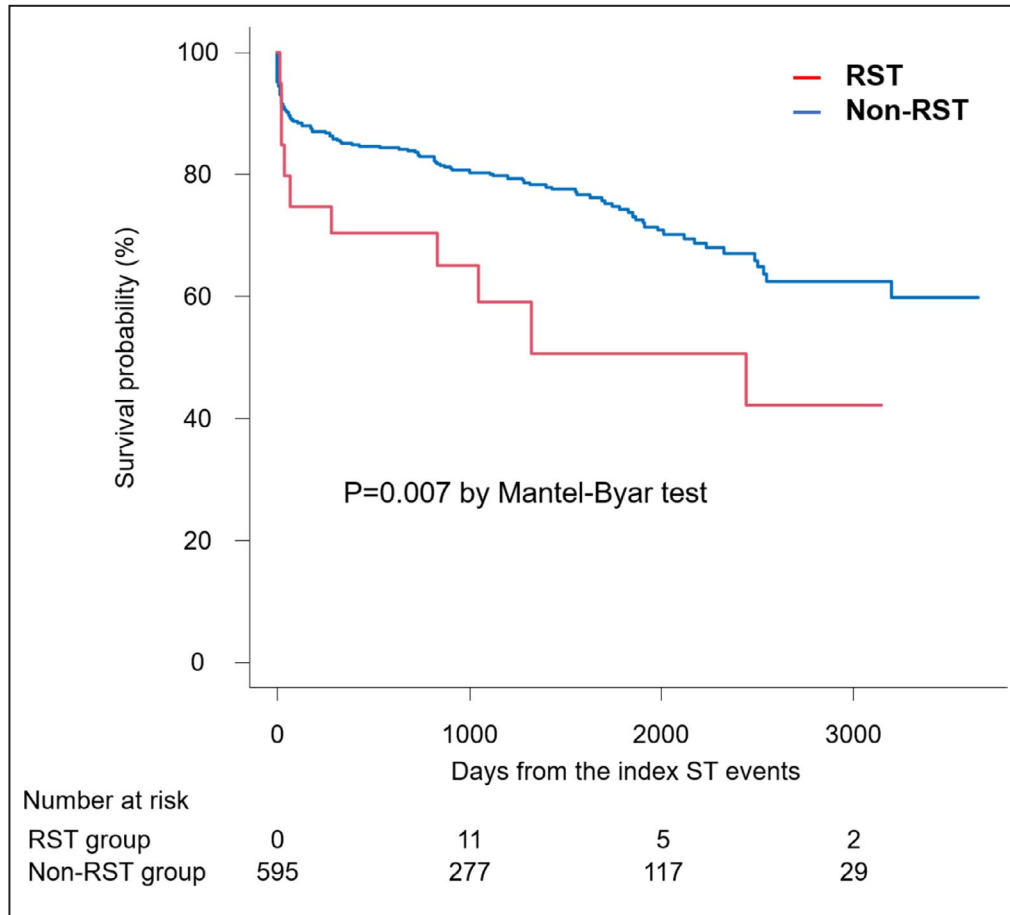
Figure 4. Survival probabilities before and after recurrent stent thrombosis (RST) development. ST indicates stent thrombosis.

Study Limitations

There are several limitations in the present study. First, we retrospectively collected clinical data on definite RST after G1-ST and G2-ST self-reported by the site investigators in this study. Therefore, we could not guarantee consecutive enrollment of patients with definite RST in all of the participating centers, which may result in the underestimation of RST incidence. Second, the study population was relatively small, and thereby we could not separately assess the risk factors of definite RST after G1-ST and G2-ST in the present study. Third, the current study did not include patients with probable and possible RST. Forth, antiplatelet therapy plays a crucial role in the reduction of the occurrence of RST. However, we could not obtain information on antiplatelet therapy after the index ST events in the present study. Further studies should assess the optimal antiplatelet therapy to prevent RST. Fifth, the proportional hazards assumption for EST versus VLST did not even approximately hold in the present study, whereas its HR should

be at best interpreted as an approximate value for a time-averaged HR.[15] Indeed, Figure 2 includes the cumulative incidence functions for EST, LST, and VLST, which directly shows the distributions of time to RST from the first onset of ST. These findings suggest that this violation of proportional hazards assumption did not affect the conclusions in the present study. Sixth, intravascular imaging devices help us identify the underlying mechanism of RST. However, the detailed information on these findings were not available in this study. Finally, the follow-up duration was shorter in patients with G2-ST than in those with G1-ST, especially with VLST, which may result in the underestimation of RST incidence after G2-ST.

CONCLUSIONS

Cumulative incidence of definite RST did not significantly differ between G1-ST and G2-ST. EST and multivessel ST were risk factors of definite RST after DES thrombosis. Definite RST significantly increased

mortality after the index ST events, highlighting the clinical importance of preventing RST to improve outcomes of patients with ST.

APPENDIX

List of Participating Centers and Investigators

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SUPPLEMENTAL MATERIAL

Table S1. Angiographical Findings and Treatment at the Time of the Index Stent Thrombosis Events.

	RST (n=32)	Non-RST (n=563)	Univariate Cox Regression HR (95% CI)	P value
Thrombus aspiration	20 (62.5)	386 (68.6)	0.71 (0.35-1.46)	0.36
Plain balloon angioplasty	22 (68.8)	393 (69.8)	0.91 (0.42-1.92)	0.80
Drug-coated balloon	2 (6.3)	40 (7.1)	1.02 (0.24-4.30)	0.98
Additional stenting	11 (34.3)	239 (42.5)	0.70 (0.34-1.45)	0.34
BMS	3 (9.4)	51 (9.1)	1.00 (0.30-3.29)	1.00
DES	9 (28.1)	189 (33.6)	0.77 (0.35-1.66)	0.50
IVUS/OCT use	23 (71.9)	391 (69.4)	1.18 (0.54-2.54)	0.68
Angiographical findings				
PSS	3 (9.4)	31 (5.5)	1.60 (0.49-5.24)	0.44
Stent fracture	2 (6.3)	45 (8.0)	0.69 (0.17-2.90)	0.62

BMS indicates bare-metal stent; CI, confidence intervals; DES, drug-eluting stent; HR, hazard ratio; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PSS, peri-stent contrast staining; and RST, recurrent stent thrombosis.

Table S2. The Estimates of Time-Dependent Cox Regression Models for Mortality After Stent Thrombosis Onset.

	Adjusted HR (95% CI) *	P value
Time-varying variable		
Recurrent ST	2.78 (1.35-5.73)	0.006
Baseline variables		
Age (per 1-year)	1.06 (1.04-1.09)	<0.001
Male sex	1.82 (1.05-3.17)	0.03
Hypertension	0.98 (0.61-1.60)	0.94
Diabetes mellitus	1.10 (0.75-1.61)	0.61
Dyslipidemia	0.88 (0.57-1.37)	0.57
Current smoker	1.34 (0.86-2.09)	0.19
Hemodialysis	1.62 (0.74-3.53)	0.22
Prior myocardial infarction	1.34 (0.86-2.09)	0.20
Prior PCI	0.79 (0.50-1.23)	0.29
Prior CABG	0.95 (0.35-2.55)	0.92
Multivessel disease	1.63 (1.11-2.40)	0.013
LVEF ≤40%	2.98 (1.93-4.60)	<0.001

G2-ST (versus G1-ST)	1.26 (0.78-2.01)	0.34
Clinical presentation at baseline (versus SAP)		
UAP	1.45 (0.86-2.46)	0.17
NSTEMI	1.38 (0.63-3.01)	0.42
STEMI	0.75 (0.43-1.33)	0.33
Target vessel		
Right coronary artery	0.47 (0.18-1.22)	0.12
Left anterior descending coronary artery	0.57 (0.23-1.43)	0.23
Left circumflex coronary artery	0.64 (0.25-1.64)	0.35
Left main coronary artery	1.79 (0.87-3.67)	0.11
In-stent restenosis	1.37 (0.81-2.30)	0.24
Ostial lesion	0.62 (0.28-1.39)	0.25
Bifurcation lesion	0.89 (0.59-1.33)	0.57
Severe calcification	1.34 (0.81-2.20)	0.25
Chronic total occlusion	0.64 (0.31-1.35)	0.24
Total stent length >38-mm	1.89 (1.10-3.23)	0.02
Stent overlap	0.86 (0.50-1.47)	0.57

Variables measured at ST

ST type (versus very late ST)

Early ST	0.79 (0.48-1.29)	0.35
Late ST	0.87 (0.45-1.70)	0.68
Multivessel ST	0.34 (0.09-1.22)	0.10

Clinical presentation at ST (versus UAP)

NSTEMI	1.62 (0.56-4.68)	0.37
STEMI	2.47 (1.01-6.04)	0.048
Cardiogenic shock at ST	1.07 (0.68-1.69)	0.77
Final TIMI ≤2 at ST	2.07 (1.27-3.38)	0.004

Treatment at ST

PCI	7.29 (0.61-86.39)	0.12
CABG	3.41 (1.10-10.55)	0.03

G1-ST indicates first-generation drug-eluting stent thrombosis; and G2-ST, second-generation drug-eluting stent thrombosis. Other abbreviations as in Tables 1 and 2.

Unless indicated otherwise, the reference category was set at "none."

*Adjusted for covariates below by including them as regressors of multivariable Cox models: age, baseline clinical presentation, bifurcation lesion, cardiogenic shock at stent

thrombosis (ST), chronic total occlusion, clinical presentation at ST, current smoker,

drug-eluting stent type, diabetes mellitus, dyslipidemia, final TIMI flow grade ≤2,

hemodialysis, hypertension, in-stent restenosis, left ventricular ejection fraction ≤40%,

male sex, multivessel disease, multivessel ST, ostial lesion, prior coronary artery bypass

graft (CABG), prior myocardial infarction, prior percutaneous coronary intervention

(PCI), recurrent ST, severe calcification, stent overlap, ST type, target coronary vessel,

treatment at ST (PCI or CABG), and total stent length ≥38-mm.