




ORIGINAL RESEARCH

Long-Term Outcomes and Clinical Predictors of Mortality Following Occurrence of Stent Thrombosis

Takayuki Ishihara , MD; Katsuki Okada, MD, PhD; Hirota Kida, MAS; Takuya Tsujimura, MD; Osamu Iida, MD; Shota Okuno, MD; Yosuke Hata, MD; Taku Toyoshima , MD; Naoko Higashino, MD; Atsushi Kikuchi, MD; Tetsuya Watanabe , MD, PhD; Takashi Morita , MD, PhD; Akihiro Tanaka, MD; Ryu Shutta, MD; Masami Nishino , MD, PhD; Shumpei Kosugi , MD; Yasunori Ueda, MD, PhD; Yasuhiro Ichibori, MD, PhD; Yoshiharu Higuchi, MD, PhD; Yohei Sotomi, MD, PhD; Daisuke Nakamura, MD; Masahiro Kumada, MD, PhD; Shungo Hikoso , MD, PhD; Daisaku Nakatani, MD, PhD; Toshiaki Mano, MD, PhD; Yasushi Sakata , MD, PhD; The OCV Long ST Registry Investigators[†]

BACKGROUND: Stent thrombosis (ST) remains a significant medical issue. In particular, longer-term mortality and clinical predictors after ST occurrence have yet to be elucidated.

METHODS AND RESULTS: This was a multicenter, retrospective, observational study. A total of 187 definite ST cases from January 2008 to December 2017 were enrolled, and the long-term clinical outcomes were investigated. The primary outcome measure was the cumulative mortality after ST occurrence. In addition, independent predictors of mortality were assessed. Among the stent types causing ST, bare-metal stent, first-generation drug-eluting stent, second-generation drug-eluting stent, and third-generation drug-eluting stent comprised 31.0%, 19.3%, 36.9%, and 6.4% of cases, respectively. Median duration from stent implantation to ST was 680.5 (interquartile range, 33.8–2450.5) days. Cumulative mortality was 14.6%, 17.4%, 21.2%, 24.4%, and 33.8% at 1, 2, 3, 5 and 10 years, respectively. The cumulative mortality did not significantly differ by type of stent, and mortality of late ST was higher than that of early ST and very late ST; however, it did not reach statistical significance after the multivariate analysis. Independent predictors of mortality were hemodialysis (hazard ratio [HR], 7.80; 95% CI, 3.07–19.81; $P < 0.001$), culprit lesions in the left main trunk (HR, 8.14; 95% CI, 1.71–38.75; $P = 0.008$), culprit lesions in the left coronary artery (HR, 2.77; 95% CI, 1.10–6.96; $P = 0.030$), and peak creatine kinase (HR, 1.017; 95% CI, 1.011–1.022; $P < 0.001$).

CONCLUSIONS: The 10-year cumulative mortality after ST reached 33.8%. Close follow-up is thus mandatory for patients with ST, especially with hemodialysis, culprit lesions in the left main trunk and left coronary artery, and high peak creatine kinase.

Key Words: long-term outcomes ■ mortality ■ stent thrombosis

See Editorial by Moukarbel.

Drug-eluting stents (DESs) are commonly used for the treatment of coronary artery disease. Although DESs have dramatically decreased the incidence of restenosis compared with bare-metal stents,¹ issues

associated with stent thrombosis (ST) have risen, especially late stent thrombosis and very late stent thrombosis, which occur 1 month and 1 year, respectively, after stent implantation and cause acute myocardial

Correspondence to: Takayuki Ishihara, MD, Kansai Rosai Hospital Cardiovascular Center, 3-1-69 Inabaso, Amagasaki, Hyogo 660-8511, Japan. E-mail: t.ishihara31@gmail.com

[†] A complete list of the OCV Long ST Registry Investigators can be found in the appendix at the end of the article.

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CLINICAL PERSPECTIVE

What Is New?

- In this multicenter registry, the 10-year cumulative mortality after stent thrombosis reached 33.8%, and independent predictors of all-cause death were hemodialysis, culprit lesions in the left main trunk and left coronary artery, and peak creatine kinase.
- Quantitative coronary angiography analysis showed that postprocedural in-segment diameter stenosis was higher in patients with than without major adverse cardiac event.
- Intravascular ultrasound demonstrated more frequent stent underexpansion before and immediately after percutaneous coronary intervention at the time of stent thrombosis in those with target lesion revascularization than those without.

What Are the Clinical Implications?

- Close follow-up is mandatory for patients with stent thrombosis, and stent underexpansion must be avoided.
- The strategy such as debulking of the calcified plaque using atherectomy devices should be performed at the time of the initial percutaneous coronary intervention as well as stent thrombosis.

Nonstandard Abbreviations and Acronyms

DES	drug-eluting stent
LMT	left main trunk
MACE	major adverse cardiac event
ST	stent thrombosis
TLR	target lesion revascularization

infarction and sudden death attributable to the sudden onset of thrombus.² A multicenter trial by Kimura et al³ reported that the 1-year mortality of patients with definite ST after implantation of a first-generation sirolimus-eluting stent was 10.5% for patients with very late stent thrombosis, 22.4% for those with early stent thrombosis, and 23.5% for those with late stent thrombosis. Another single-center trial showed that the 5-year mortality of patients with ST, the majority of whom received first-generation DES implants, reached 39.0%.⁴ However, no multicenter registry study has assessed the longer-term mortality. In addition, development of DES has reduced the incidence of ST, which is now \approx 1% 3 years after implantation of a second-generation DES.^{5,6} However, ST remains a medical issue, and the long-term mortality of patients with ST receiving a second-generation DES implant has not been elucidated. Further, adverse cardiac

events and recurrence of repeat interventions are significant issues that arise after the occurrence of ST.⁴ However, differences in angiographic and intravascular imaging findings between patients with and without major adverse cardiac event (MACE) and target lesion revascularization (TLR) have not been elucidated.

In this multicenter registry, we gathered data from ST cases and evaluated the long-term prognosis, including angiographic and intravascular imaging analysis findings.

METHODS

Our study data will not be made available to other researchers for purposes of reproducing the results because of institutional review board restrictions.

Patients

This was a multicenter, retrospective, observational study (Long-term Outcomes following Occurrence of Stent Thrombosis registry). Coronary angiography performed from January 2008 to December 2017 was retrospectively evaluated in each hospital, and cases with definite ST were extracted. Subjects in the current registry were definite ST cases, with angiographic confirmation of ST according to the Academic Research Consortium definition.⁷ Specifically, definite ST cases were defined as those with a thrombus that originated in the stent or in a segment 5 mm proximal or distal to the stent and at least 1 of the following within a 48-hour time window: acute onset of ischemic symptoms at rest; new ischemic ECG changes that suggest acute ischemia; typical rise and fall in cardiac biomarkers.⁷ Patients with all types of stent (bare-metal stent, first-generation DES, second-generation DES, third-generation DES) and ST onset (<30 days, early ST; 31 days to 1 year, late ST; >1 year, very late ST) were included. DES generation was defined as follows: first-generation DES, Cypher (Cordis, Miami, FL) or Taxus (Boston Scientific, Natick, MA); second-generation DES, Endeavor (Medtronic, Minneapolis, MN), Nobori (Terumo, Tokyo, Japan), Promus (Boston Scientific), Resolute (Medtronic), or Xience (Abbott Vascular, Abbott Park, IL); third-generation DES: Synergy (Boston Scientific) or Ultimaster (Terumo). Cases without angiographic evaluation were excluded from this registry. The study was approved by the medical ethics committee of each hospital. The requirement for the patients' written informed consent was waived because this was observational research without intervention or invasiveness and did not use human biological specimens, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Instead, relevant information regarding the study has been made available to the public.

Clinical Follow-Up

We collected the clinical outcomes, including all-cause death, cardiac death, nonfatal myocardial infarction, TLR, target vessel revascularization, and recurrent ST, as follows: (1) We collected the outcome information from the medical record of each hospital during the data-collecting period (from November 2019 to January 2020); (2) for patients who continuously attended the hospital at the time point of data collection, we collected the outcome data at that time; (3) for patients who stopped to attend the hospital at the time point of data collection, we confirmed the outcome information by telephone if possible; when we could not confirm the information, we input the outcome information by the medical record till the last visit. Myocardial infarction was defined as type 1 to type 3 or type 4b on the basis of the Third Universal Definition of Myocardial Infarction.⁸ ST was defined according to the Academic Research Consortium definition.⁷ Only Academic Research Consortium –defined ST was included in the current study.

Angiographic Analysis

We gathered coronary angiography data obtained at the time of initial percutaneous coronary intervention (PCI) and ST. The view showing the most severe stenosis was selected for quantitative coronary angiography (QCA), which was performed using a computerized angiographic analysis system (QAngioXA 7.3; Medis Medical Imaging Systems, Leiden, the Netherlands) at the same angle of projection before and immediately after PCI.⁹ Two of the authors (T.T. and N.H.) performed the QCA analysis.

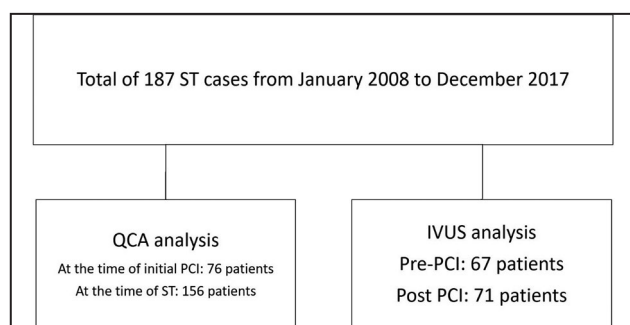


Figure 1. Study flowchart.

A total of 187 cases with ST from January 2008 to December 2017 were enrolled in this registry. Quantitative coronary angiography analysis was possible for 76 patients and 156 patients at the time of initial PCI and ST, respectively. Pre- and post-PCI intravascular ultrasound analyses at the time of ST were available for 67 patients and 71 patients, respectively. IVUS indicates intravascular ultrasound; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; and ST, stent thrombosis.

Intravascular Imaging Analysis

We gathered intravascular imaging data obtained at the time of ST. Because of the limited optical coherence

Table 1. Baseline Patient and Lesion Characteristics at the Time of Initial PCI

Variable	
Number of patients	187
Patient characteristics	
Age, y	64.7±10.7
Male	161 (86.1)
Body mass index, kg/m ²	23.3±4.1
Ejection fraction, %	56.8±13.0
Primary disease	
Stable angina pectoris	58 (31.0)
Silent myocardial ischemia	18 (9.6)
Unstable angina pectoris	33 (17.6)
Non-ST-segment-elevation myocardial infarction	9 (4.8)
ST-segment-elevation myocardial infarction	53 (28.3)
Unknown	16 (8.6)
Coronary risk factors	
Hypertension*	138 (73.8)
Dyslipidemia†	106 (56.7)
Current smoking/Past smoking	66 (35.3)/62 (33.2)
Diabetes	79 (42.2)
Chronic kidney disease	42 (22.5)
Hemodialysis	17 (9.1)
Family history	17 (9.1)
History of PCI	71 (38.0)
History of CABG	9 (4.8)
History of myocardial infarction	43 (23.0)
History of chronic heart failure	19 (10.2)
History of atrial fibrillation	12 (6.4)
History of stroke	13 (7.0)
Lesion characteristics	
ACC/AHA classification	
Type A/B1	13 (7.0)/35 (18.7)
B2/C/unknown	57 (30.5)/50 (26.7)/32 (17.1)
Target vessel	
Left anterior descending artery	83 (44.4)
Right coronary artery	72 (38.5)
Left circumflex artery	26 (13.9)
Left main trunk	6 (3.2)
Bifurcation	64 (34.2)
Calcification	35 (18.7)
Chronic total occlusion	6 (3.2)

Data are presented as mean±SD or number (%). ACC indicates American College of Cardiology; AHA, American Heart Association; CABG coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

*Receiving antihypertensive medication, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg.

†Treatment with medication, total cholesterol ≥220 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, or triglycerides ≥150 mg/dL.

Table 2. Baseline Patient and Lesion Characteristics at the Time of ST

Variable	
Number of patients	187
Patient characteristics	
Age, y	68.8±11.6
Duration from PCI to ST, d	680.5 (33.8–2450.5)
Type of stent thrombosis	
Early stent thrombosis	43 (23.0)
Late stent thrombosis	29 (15.5)
Very late stent thrombosis	102 (54.5)
Type of disease at presentation	
Unstable angina pectoris	28 (15.0)
Non-ST-segment-elevation myocardial infarction	29 (15.5)
ST-segment-elevation myocardial infarction	130 (69.5)
Medication use	
Aspirin	138 (73.8)
Clopidogrel	65 (34.8)
Ticlopidine	13 (7.0)
Prasugrel	12 (6.4)
Cilostazol	15 (8.0)
Warfarin	15 (8.0)
Direct oral anticoagulant	3 (1.6)
Statin	77 (41.2)
ACEi/ARB	67 (35.8)
β blocker	70 (37.4)
Dual antiplatelet therapy	84 (44.9)
Aspirin alone	54 (28.9)
P2Y12 inhibitor alone	6 (3.2)
No aspirin nor P2Y12 inhibitor	43 (23.0)
Lesion characteristics	
ACC/AHA classification	
Type A/B1/B2/C	7 (3.7)/46 (24.6)/83 (44.4)/51 (27.3)
Type of stent at culprit lesion*	
Bare-metal stent	58 (31.0)
First-generation DES	36 (19.3)
Cypher	29 (15.5)
Taxus	8 (4.3)
Second-generation DES	69 (36.9)
Endeavor	3 (1.6)
Nobori	18 (9.6)
Promus	14 (7.5)
Resolute	7 (3.7)
Xience	28 (15.0)
Third-generation DES	12 (6.4)
Synergy	4 (2.1)
Ultimaster	8 (4.3)
Unknown	12 (6.4)

(Continued)

Table 2. (Continued)

Variable	
Pre-TIMI flow grade	
Grade 0/1/2/3	109 (58.3)/6 (3.2)/26 (13.9)/46 (24.6)
Final TIMI flow grade	
Grade 0/1/2/3	3 (1.6)/2 (1.1)/8 (4.3)/171 (91.4)

Data are presented as mean±SD, median (interquartile range) or number (%). ACC indicates American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin II receptor blocker; DES, drug-eluting stent; PCI, percutaneous coronary intervention; ST, stent thrombosis; and TIMI, Thrombolysis in Myocardial Infarction.

*Two patients developed ST with multiple stents.

tomography (OCT), near infrared spectroscopy and coronary angiography data, we evaluated only intravascular ultrasound (IVUS) data. Before and immediately after PCI, IVUS analyses were performed using a computerized IVUS analysis system (QIvus3.1.18.0; Medis Medical Imaging Systems).¹⁰ First, the external elastic membrane cross-sectional area (CSA), lumen CSA, and plaque media CSA were evaluated at proximal and distal reference segment sites. The reference segment was defined at the site with the largest lumen proximal or distal to the stent but within the same segment (usually within 10 mm of the stent with no major intervening branches). The proximal or distal reference may or may not be the site with the fewest plaques. Plaque media CSA was calculated by subtracting the lumen area from the external elastic membrane area. Second, total stent length, external elastic membrane CSA, stent CSA, lumen CSA, neointimal area, persistent plaque CSA, minimum stent diameter, maximum stent diameter, stent symmetry index, lumen volume, stent volume, vessel volume, neointimal volume, and neointimal volume obstruction were evaluated in the stent segment. Neointimal area was calculated by subtracting the lumen CSA from the stent CSA. Persistent plaque CSA was calculated by subtracting the stent CSA from the external elastic membrane CSA. Stent symmetry index was defined as the minimum stent diameter divided by the maximum stent diameter. Neointimal volume was calculated by subtracting the lumen volume from the stent volume. Neointimal volume obstruction was defined as the neointimal volume divided by the stent volume. Third, stent expansion index was defined as the minimum stent area divided by the average reference lumen area. Stent underexpansion is an area of inadequately expanded stent compared with the adjacent normal reference segment, defined by stent expansion <80% of the reference vessels. Fourth, symmetric stent expansion was defined as stent symmetry index ≥0.7.¹¹ Two of the authors (T.I. and T.T.) performed the IVUS analysis.

Primary and Secondary Outcomes

The primary outcome measure was the cumulative mortality after ST occurrence. Secondary outcome measures were comparison of mortality associated with the type of stent and type of ST; the cumulative incidence of MACE, defined as the composite of cardiac death, nonfatal myocardial infarction, and TLR; the cumulative incidence of cardiac death, nonfatal myocardial infarction, TLR, target vessel revascularization, and recurrent ST; and the independent predictors of mortality. We also compared angiographic and IVUS findings between patients with and without MACEs and TLRs, respectively.

Evaluation of Inter- and Intraobserver Reproducibility

The inter- and intraobserver intraclass correlation coefficients for evaluating QCA and IVUS findings were determined for 20 randomly selected cases.

Statistical Analysis

All results are expressed as mean±SD and median (interquartile range) for continuous variables with and without normal distribution. Continuous variables with and without homogeneity of variance were analyzed using the Student *t*-test and the Welch *t*-test, respectively. Categorical variables were analyzed using Fisher's exact test for 2 × 2 comparisons. Multivariate analysis was performed using Cox regression analysis. Variables in the univariate analysis with *P* values <0.05 were selected for multivariate analysis. Censored cases were analyzed as noninformative censoring. Statistical

significance was defined as *P*<0.05. Bonferroni correction was performed for multiple comparisons. All calculations were performed using the IBM SPSS Statistics package ver. 26 (IBM Corp., Armonk, NY).

RESULTS

Patient Flow Chart

A total of 187 ST cases were investigated in this registry (Figure 1). QCA analysis was possible at the time of initial PCI and ST for 76 patients and 156 patients, respectively. Pre- and post-PCI IVUS analyses were possible for 67 patients and 71 patients, respectively.

Baseline Characteristics at the Time of Initial PCI

Baseline patient and lesion characteristics at the time of initial PCI are shown in Table 1. Half of patients suffered from acute coronary syndrome as the primary disease. Approximately half of patients had type B2/C lesions. Baseline medication use and procedural characteristics at the time of initial PCI are shown in Table S1.

Baseline Characteristics at the Time of ST

Baseline patient and lesion characteristics and medication use at the time of ST are summarized in Table 2. Median duration from stent implantation to ST was 680.5 (interquartile range, 33.8–2450.5) days. ST type was early ST, late ST, and very late ST in 23.0%, 15.5%, and 54.5% of cases, respectively. The stent type of

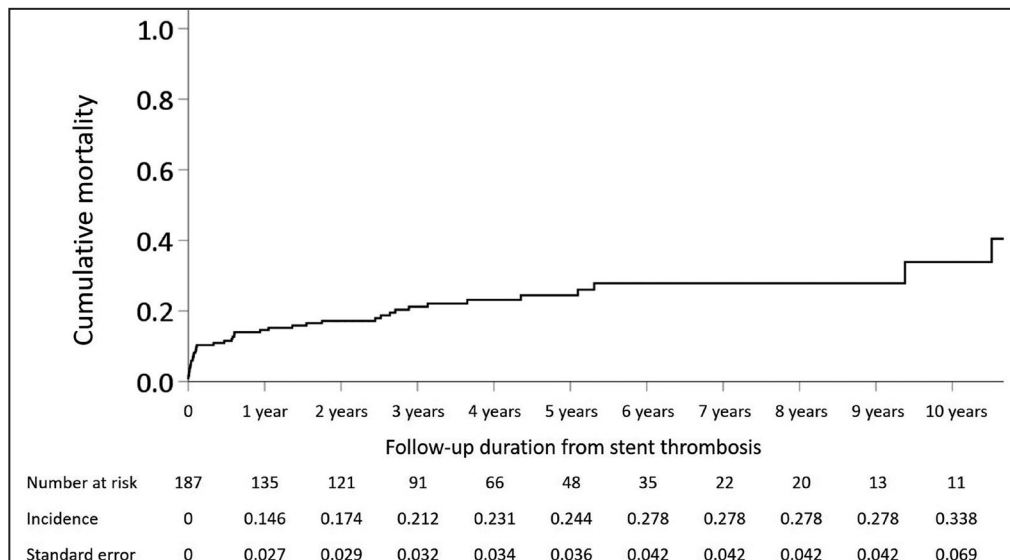


Figure 2. Cumulative mortality after the occurrence of stent thrombosis.

The cumulative incidence of all-cause death was 14.6%, 17.4%, 21.2%, 24.4%, and 33.8% at 1, 2, 3, 5, and 10 years, respectively.

culprit lesion was bare-metal stent, first-generation DES, second-generation DES, and third-generation DES in 31.0%, 19.3%, 36.9%, and 6.4% of cases, respectively. Dual antiplatelet therapy was continued in 44.9% of patients at the time of ST. Laboratory data and procedural characteristics at the time of ST are shown in Table S2. IVUS was most frequently used for PCI at the time of ST.

Primary and Secondary Outcomes

The median follow-up duration was 1054.0 (interquartile range, 239.5–1850.0) days. The cumulative incidence of all-cause death was 14.6%, 17.4%, 21.2%, 24.4%, and 33.8% at 1, 2, 3, 5, and 10 years,

respectively (Figure 2). Mortality associated with the type of stent and type of ST is compared in Figure 3. Although third-generation DES tended to be used more frequently than that the other stent types, the difference did not reach statistical significance after Bonferroni correction. Mortality of late ST was higher than that of early ST and very late ST. Figure 4 shows the cumulative incidence of secondary outcomes. The 10-year incidence of MACE, cardiac death, non-fatal myocardial infarction, TLR, target vessel revascularization, and recurrent ST was 41.9%, 14.7%, 7.3%, 31.0%, 35.1%, and 7.5%, respectively (Figure 4). Independent predictors of mortality were hemodialysis (hazard ratio [HR], 7.80; 95% CI, 3.07–19.81; $P < 0.001$),

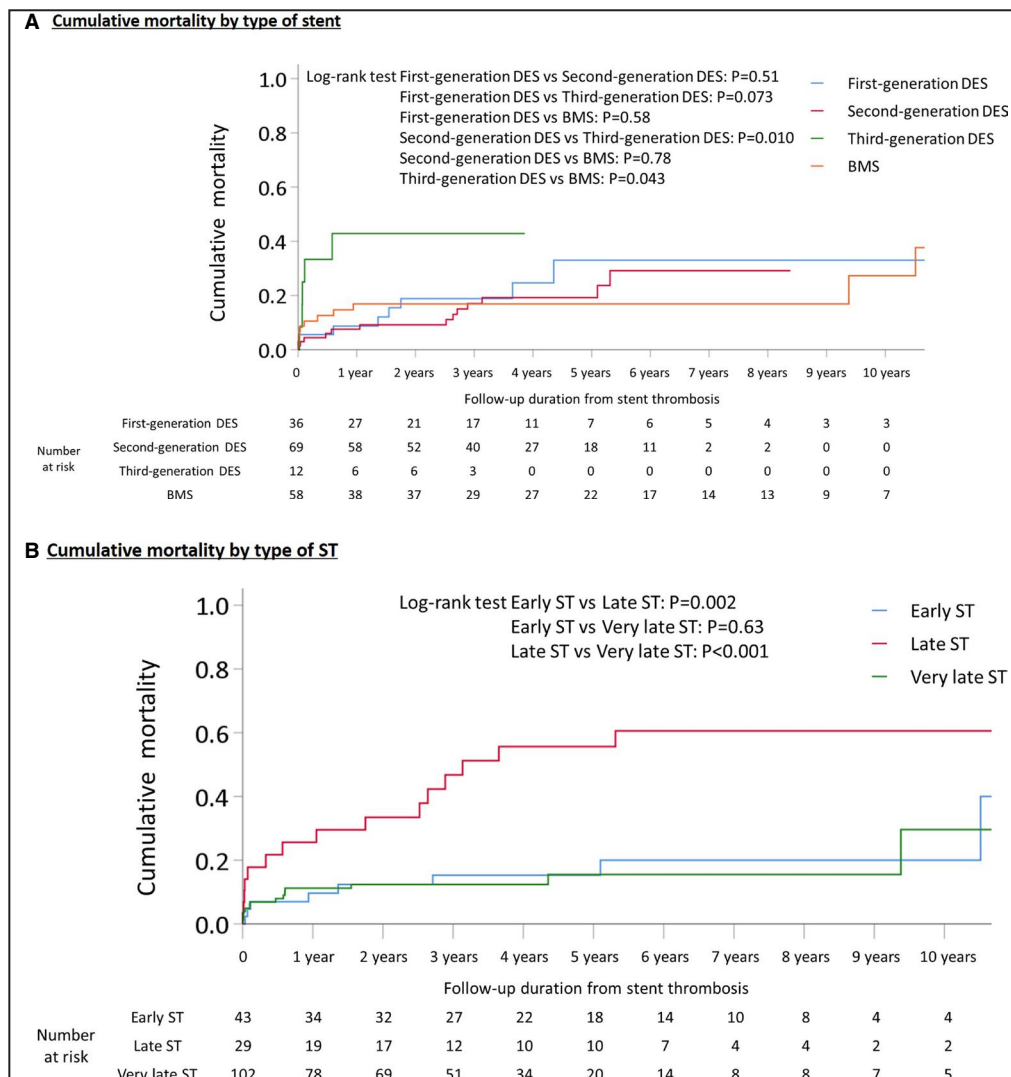


Figure 3. Cumulative mortality by type of stent and ST.

A, Cumulative mortality by type of stent. Although cumulative mortality tended to be higher among patients with third-generation DES, differences among the stent types did not reach statistical significance after Bonferroni correction. **B**, Cumulative mortality by type of ST. Mortality of late ST was higher than that of early ST and very late ST. BMS indicates bare-metal stent; DES, drug-eluting stent; and ST, stent thrombosis.

culprit lesions in the left main trunk (LMT; HR, 8.14, 95% CI, 1.71–38.75; $P=0.008$), culprit lesions in the left coronary artery (LCA; HR, 2.77; 95% CI, 1.10–6.96; $P=0.030$), and peak creatine kinase (CK; 100 U/L increase; HR, 1.017; 95% CI, 1.011–1.022; $P<0.001$) (Table 3). In the comparison of QCA analysis results, while pre-PCI lesion length was shorter, post-PCI in-segment and in-segment minimum lumen diameters were smaller, and post-PCI in-segment diameter stenosis was higher in patients with than without MACE, all

parameters were similar between patients with and without TLR except for the pre-PCI lesion length at the time of ST (Table 4). At the time of initial PCI, all parameters of QCA analysis were similar between patients with and without MACE and TLR (Table S3). Using IVUS, while all parameters were similar between patients with and without MACE, stent underexpansion before and immediately after PCI at the time of ST was more frequently observed in patients with than without TLR (Table 5, Table S4). Among 39 patients

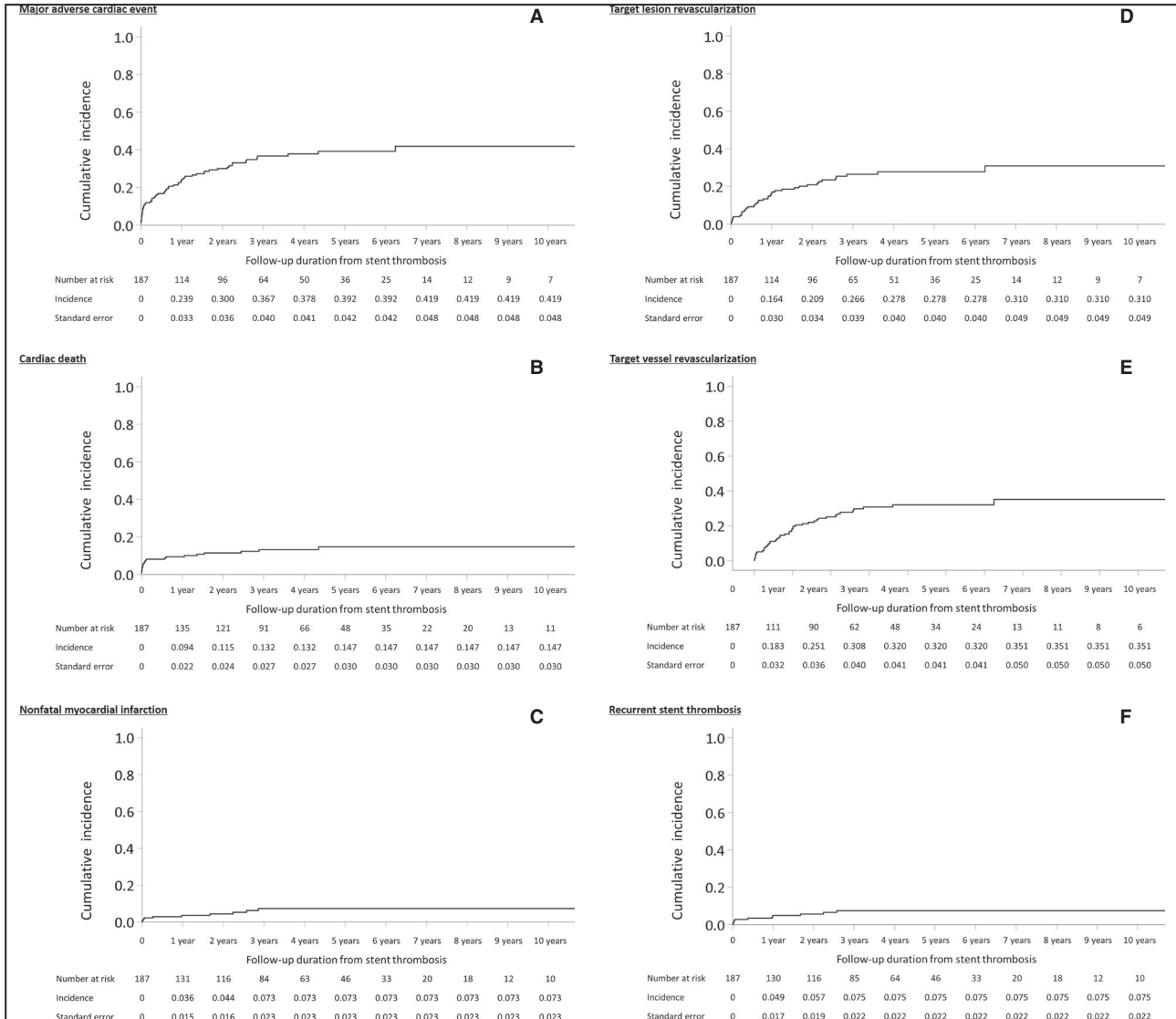


Figure 4. Cumulative incidence of secondary outcomes.

A, Cumulative incidence of major adverse cardiac events. The cumulative incidence was 23.9%, 30.0%, 36.7%, 39.2%, and 41.9% at 1, 2, 3, 5, and 10 years, respectively. **B**, Cumulative incidence of cardiac death. The cumulative incidence was 9.4%, 11.5%, 13.2%, and 14.7% at 1, 2, 3, and 5 years, respectively. No events occurred after 5 years. **C**, Cumulative incidence of nonfatal myocardial infarction. The cumulative incidence was 3.6%, 4.4%, and 7.3% at 1, 2, and 3 years, respectively. No events occurred after 3 years. **D**, Cumulative incidence of target lesion revascularization. The cumulative incidence was 16.4%, 20.9%, 26.6%, 27.8%, and 31.0% at 1, 2, 3, 5, and 10 years, respectively. **E**, Cumulative incidence of target vessel revascularization. The cumulative incidence was 18.3%, 25.1%, 30.8%, 32.0%, and 35.1% at 1, 2, 3, 5, and 10 years, respectively. **F**, Cumulative incidence of recurrent stent thrombosis. The cumulative incidence was 4.9%, 5.7%, and 7.5% at 1, 2, and 3 years, respectively. No events occurred after 3 years.

Table 3. Univariate and Multivariate Cox Regression Analysis for Predictors of Mortality

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Male	1.28	0.50–3.26	0.61			
Age (1-y increase)	1.01	0.98–1.03	0.71			
BMI (1 kg/m ² increase)	1.04	0.96–1.12	0.39			
Hypertension	1.12	0.52–2.44	0.77			
Dyslipidemia	0.57	0.30–1.08	0.085			
Diabetes	1.92	1.04–3.55	0.036	1.24	0.56–2.74	0.60
No smoking (reference)	1.00					
Current	0.84	0.39–1.78	0.65			
Past	0.97	0.46–2.03	0.93			
Hemodialysis	5.48	2.71–11.11	<0.001	7.80	3.07–19.81	<0.001
Family history	0.83	0.28–2.45	0.73			
Prior PCI	1.03	0.54–1.95	0.93			
Prior CABG	2.17	0.66–7.09	0.20			
OMI	1.40	0.68–2.90	0.36			
CHF	2.05	0.90–4.66	0.087			
Atrial fibrillation	1.22	0.42–3.52	0.72			
Stroke	2.32	0.97–5.53	0.058			
Target vessel						
RCA (reference)	1.00			1.00		
LCA (LAD+LCX)	2.93	1.35–6.36	0.007	2.77	1.10–6.96	0.030
LMT	4.56	1.20–17.26	0.026	8.14	1.71–38.75	0.008
Type of stent						
First-generation DES (reference)	1.00					
Second-generation DES	0.81	0.34–1.94	0.64			
Third-generation DES	2.61	0.86–7.98	0.092			
Bare-metal stent	0.76	0.31–1.85	0.54			
Initial stent average diameter (1-mm increase)	0.42	0.17–1.04	0.062			
Initial stent total length (1-mm increase)	1.01	0.99–1.03	0.50			
Timing of ST						
Early ST (reference)	1.00					
Late ST	3.31	1.42–7.68	0.005	2.50	0.90–6.95	0.079
Very late ST	0.81	0.35–1.88	0.62			
Type of disease at the time of ST						
UAP (reference)	1.00					
NSTEMI	0.83	0.23–2.98	0.78			
STEMI	1.37	0.57–3.27	0.48			
Initial TIMI flow grade at the time of ST						
TIMI 0 (reference)	1.00					
TIMI 1	0.79	0.11–5.85	0.82			
TIMI 2	1.05	0.43–2.57	0.91			
TIMI 3	1.11	0.54–2.25	0.78			
Final TIMI flow grade at the time of ST						
TIMI 0 (reference)	1.00					
TIMI 1	1.28	0.077–21.09	0.87			
TIMI 2	1.31	0.14–12.66	0.82			
TIMI 3	0.69	0.095–5.06	0.72			

(Continued)

Table 3. Continued

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Peak CK (100 U/L increase)	1.012	1.008–1.016	<0.001	1.017	1.011–1.022	<0.001

BMI indicates body mass index; CABG, coronary artery bypass grafting; CHF, chronic heart failure; CK, creatine kinase; DES, drug-eluting stent; HR, hazard ratio; LCA, left coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk; NSTEMI, non–ST-segment–elevation myocardial infarction; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; ST, stent thrombosis; STEMI, ST-segment–elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; UAP, unstable angina pectoris.

with TLR, 20 patients (51.3%) underwent TLR simultaneously with diagnostic coronary angiography and 19 patients (49.7%) did it 27.7±18.3 days after coronary angiography. The clinical presentation at the time of TLR was stable angina pectoris (28.2%), silent myocardial ischemia (43.6%), unstable angina pectoris (5.1%), non–ST-segment–elevation myocardial infarction (2.6%), and ST-segment–elevation myocardial infarction (20.5%). As a strategy for TLR, PCI and coronary artery bypass grafting were performed for 35 patients (89.7%) and 4 patients (10.3%), respectively.

Inter- and Intraobserver Reproducibility

The inter- and intra-observer intraclass correlation coefficients ranged from 0.735 to 0.961 and from 0.745 to 0.996 for QCA and IVUS findings, respectively. The intraclass correlation coefficients for each parameter of QCA and IVUS findings are shown in Table S5.

DISCUSSION

In this multicenter registry, our findings revealed that (1) the 10-year cumulative mortality after ST was 33.8%;

(2) the cumulative mortality did not significantly differ by type of stent, and mortality of late ST was higher than that of early ST and very late ST but did not reach statistical significance after the multivariate analysis; (3) the independent predictors for all-cause death were hemodialysis, culprit lesions in the LMT and left coronary artery, and peak CK; and (4) QCA analysis suggested that post-PCI in-segment diameter stenosis was higher in patients with than without MACE, while IVUS findings implied that stent underexpansion before and immediately after PCI at the time of ST was more frequently observed in patients with than without TLR (Figure 5). This is the first report to describe the long-term outcomes and QCA and IVUS findings after ST occurrence.

A multicenter registry by Kuramitsu et al¹² reported that the 4-year cumulative mortality was 33.0% after ST occurrence associated with second-generation DES. Another single-center data study showed that the 5-year mortality was 39.0% after ST occurrence.⁴ Data from the current registry demonstrated that the cumulative mortality after ST occurrence associated with second-generation DES was 19.2% at 4 years and that the 5-year mortality after ST occurrence was 24.4% in the entire population. The hospitals enrolled in

Table 4. Quantitative Coronary Angiography at the Time of ST

	MACE	No MACE	P value	TLR	No TLR	P value
Number of patients	50	106		33	123	
Pre-PCI						
Lesion length, mm	12.1±5.9	16.2±7.3	0.048	11.3±5.9	15.9±7.1	0.040
Minimum lumen diameter, mm	0.31±0.42	0.22±0.48	0.27	0.35±0.45	0.22±0.46	0.15
Reference vessel diameter, mm	2.99±0.59	3.09±0.91	0.39	2.99±0.58	3.08±0.88	0.59
Diameter stenosis, %	88.6±16.4	92.8±14.7	0.12	86.7±17.8	92.7±14.4	0.090
Post-PCI						
In-segment						
Minimum lumen diameter, mm	1.60±0.65	1.89±0.56	0.007	1.76±0.57	1.81±0.61	0.66
Reference vessel diameter, mm	2.57±0.62	2.78±0.70	0.096	2.67±0.63	2.72±0.70	0.73
Diameter stenosis, %	38.6±18.2	31.0±14.5	0.017	34.7±14.1	33.1±16.7	0.61
In-stent						
Minimum lumen diameter, mm	1.79±0.69	2.06±0.54	0.013	1.88±0.65	2.01±0.59	0.31
Reference vessel diameter, mm	2.68±0.56	2.99±1.03	0.061	2.74±0.62	2.94±0.98	0.28
Diameter stenosis, %	34.0±19.3	28.7±14.9	0.109	31.9±16.1	29.9±16.7	0.56

Data are presented as mean±SD.

MACE indicates major adverse cardiac event; PCI, percutaneous coronary intervention; ST, stent thrombosis; and TLR, target lesion revascularization.

Table 5. Intravascular Ultrasound Findings on Stent Expansion at the Time of ST

	MACE	No MACE	P value	TLR	No TLR	P value
Pre-PCI						
Number of analyzed lesions	19	48		12	55	
Stent expansion index, %	95.7±42.9	103.7±43.9	0.50	77.1±24.5	106.7±45.0	0.032
Stent underexpansion	9 (47.4)	13 (27.1)	0.097	8 (66.7)	14 (25.5)	0.014
Symmetric stent expansion	10 (52.6)	28 (58.3)	0.44	5 (42)	33 (60)	0.34
Post-PCI						
Number of analyzed lesions	21	50		13	58	
Stent expansion index, %	94.1±25.1	99.0±23.2	0.43	87.7±24.0	99.8±23.3	0.099
Stent underexpansion	8 (38.1)	12 (24.0)	0.18	7 (53.8)	13 (22.4)	0.038
Symmetric stent expansion	11 (52.4)	30 (60.0)	0.37	6 (46.2)	35 (60.3)	0.37

Data are presented as mean±SD or n (%).

MACE indicates major adverse cardiac event; PCI, percutaneous coronary intervention; ST, stent thrombosis; and TLR, target lesion revascularization.

this registry are located in urban areas. Shorter onset to balloon time was associated with not only less impaired myocardial perfusion but also better long-term clinical outcome in patients with ST-segment elevation myocardial infarction having primary PCI.^{13,14} The urban location of the hospitals could make it possible to achieve shorter onset to balloon time, which would contribute to the lower mortality in this registry compared with that reported in previous studies.

Univariate and multivariate analyses demonstrated that cumulative mortality did not significantly differ by

type of stent and type of ST. Kimura et al³ showed that the 2-year mortality of very late ST was better than that of early ST and late ST. In contrast, Kuramitsu et al¹² demonstrated that the 4-year mortality was similar among early, late, and very late ST. It is possible that the sample size was too small to obtain statistical significance in the current study, and further investigation with a larger sample size is needed to confirm these findings.

Multivariate analysis identified several independent predictors of mortality. Hemodialysis is a major predictor of poor clinical outcomes after Cypher stent

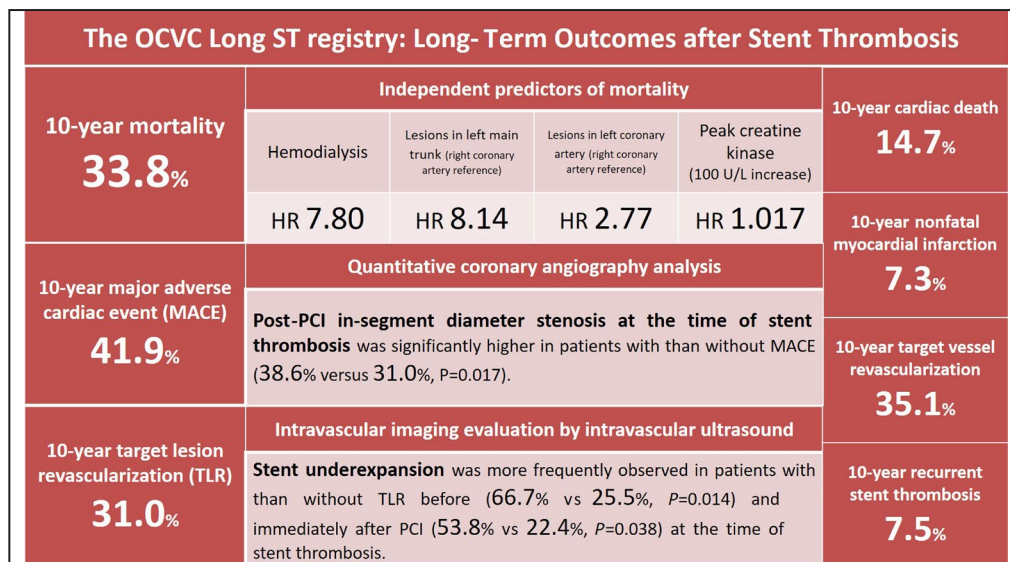


Figure 5. Visual overview.

The 10-year cumulative mortality after stent thrombosis was 33.8%. The independent predictors for all-cause death were hemodialysis, culprit lesions in left main trunk and left coronary artery, and peak creatine kinase. The 10-year incidence of major adverse cardiac event (MACE), cardiac death, nonfatal myocardial infarction, target lesion revascularization (TLR), target vessel revascularization, and recurrent stent thrombosis was 41.9%, 14.7%, 7.3%, 31.0%, 35.1%, and 7.5%. Quantitative coronary angiography analysis suggested that post-PCI in-segment diameter stenosis was higher in patients with than without MACE, while intravascular ultrasound findings implied that stent underexpansion before and immediately after PCI at the time of stent thrombosis was more frequently observed in patients with than without TLR. HR indicates hazard ratio; OCVC, Osaka CardioVascular Conference; and PCI, percutaneous coronary intervention.

implantation.¹⁵ The worst prognosis cannot be improved even using second- and third-generation DES.¹⁶ Similarly, occurrence of ST leads to poor prognosis in patients with hemodialysis, indicating that closer follow-up and medical care are mandatory. In those with ST-segment-elevation myocardial infarction, patients with culprit lesions in LMT had the worst prognosis, while those with lesions in the right coronary artery had the best.¹⁷ Consistent with this, patients with ST with LMT lesions had the highest mortality while those with lesions in the right coronary artery had the lowest mortality in the current registry. Peak CK indicates the range of myocardial infarction and is a powerful predictor of future prognosis among patients with acute myocardial infarction.¹⁸ Similarly, our registry data demonstrated that peak CK was an independent predictor of mortality among patients with ST.

Comparison using QCA and IVUS evaluation suggested that post-PCI in-segment diameter stenosis was higher among patients with than without MACE and the rate of pre- and post-PCI stent underexpansion at the time of ST was higher among patients with than without TLR. Although the precise mechanism of the positive relationship between post-PCI in-segment diameter stenosis and future MACE was unknown, stent underexpansion may be related to unfavorable results such as MACE and TLR. Inadequate stent expansion is a known predictor of TLR.¹⁹ Stent underexpansion can easily occur when a stent is implanted without optimal lesion preparation, especially if the lesion has severe calcification. In addition, even after ST occurrence, stent underexpansion is sometimes difficult to overcome using only balloon angioplasty, mainly attributable to severe calcification. Debulking of the calcified plaque using rotational atherectomy is effective for lesions with severe calcification; this strategy should be performed at the time of the initial PCI as well as ST.^{20,21}

Limitations

This study had several limitations. First, it was a retrospective, observational study; however, because of the multicenter design, the sample size was relatively large compared with that of previous studies. Second, QCA and IVUS evaluations were impossible for some cases because of poor image quality. In addition, since this study included data from a substantially older period, coronary angiography and IVUS imaging data available for analysis did not exist in some cases at the time of initial PCI and even at the time of ST. Third, the small number of cases observed using OCT prevented evaluation of the mechanism of ST. Finally, although the detailed medication during the follow-up period, the achievement degree of optimal medical therapy, and the presence of cancer would impact on the long-term prognosis, it was difficult to collect the data of these factors.

CONCLUSIONS

In this multicenter registry, the 10-year cumulative mortality after ST reached 33.8% and the independent predictors of all-cause death were hemodialysis, culprit lesions in the LMT and left coronary artery, and peak CK. Furthermore, post-PCI in-segment diameter stenosis at the time of ST was higher in patients with than without MACE, and stent underexpansion at the time of ST was more frequently observed in patients with than without TLR. Our findings indicate that close follow-up is mandatory for patients with ST, and that stent underexpansion must be avoided.

APPENDIX

Osaka CardioVascular Conference Long-term Outcomes following Occurrence of Stent Thrombosis Registry Investigators

Takayuki Ishihara, Takuya Tsujimura, Osamu Iida, Shota Okuno, Yosuke Hata, Taku Toyoshima, Naoko Higashino, and Toshiaki Mano, Kansai Rosai Hospital, Amagasaki, Japan; Shumpei Kosugi, Yasunori Ueda, Motoo Date, Tatsuhisa Ozaki, and Kohtaro Takayasu, Osaka National Hospital, Osaka, Japan; Yoshiharu Higuchi, Yasuhiro Ichibori, Naoki Mori, Tomoaki Kobayashi, and Yuma Hamanaka, Osaka Police Hospital, Osaka, Japan; Takahisa Yamada, Takashi Morita, Tetsuya Watanabe, and Atsushi Kikuchi, Osaka General Medical Center, Osaka, Japan; Masami Nishino, Ryu Shutta, Akihiro Tanaka, Naotaka Okamoto, and Masaki Tsuda, Osaka Rosai Hospital, Sakai, Japan; Osamu Nakagawa, and Masahiro Kumada, Toyonaka Municipal Hospital, Toyonaka, Japan; Isamu Mizote, Daisuke Nakamura, Kensuke Yokoi, Tatsuya Shiraki, Taiki Sato, Akihiro Sunaga, Bolrathanak Oeun, Hirota Kida, Yohei Sotomi, Tomoharu Dohi, Katsuki Okada, Shinichiro Suna, Tomohito Ohtani, Toshihiro Takeda, Daisaku Nakatani, Hiroya Mizuno, Shungo Hikoso, Yasushi Matsumura and Yasushi Sakata, Osaka University Graduate School of Medicine, Suita, Japan.

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Affiliations

Kansai Rosai Hospital Cardiovascular Center, Amagasaki, Japan (T.I., T.T., O.I., S.O., Y.H., T.T., N.H., T.M.); Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan (K.O., H.K., Y.S., D.N., S.H., D.N., Y.S.); Division of Cardiology, Osaka General Medical Center, Osaka, Japan (A.K., T.W., T.M.); Division of Cardiology, Osaka Rosai Hospital, Osaka, Japan (A.T., R.S., M.N.); Cardiovascular Division, National Hospital Organization Osaka National Hospital, Osaka, Japan (S.K., Y.U.); Cardiovascular Division, Osaka Police Hospital, Osaka, Japan (Y.I., Y.H.); and Department of Cardiology, Toyonaka Municipal Hospital, Toyonaka, Japan (M.K.).

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Supplemental Material

Tables S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Baseline medication use and procedural characteristics at the time of initial percutaneous coronary intervention.

Number of patients	187
Medication use	
Aspirin, n (%)	140 (74.9)
Clopidogrel, n (%)	80 (42.8)
Ticlopidine, n (%)	38 (20.3)
Prasugrel, n (%)	14 (7.5)
Cilostazol, n (%)	11 (5.9)
Warfarin, n (%)	10 (5.3)
Direct oral anticoagulant, n (%)	3 (1.6)
Statin, n (%)	72 (38.5)
ACEi/ARB, n (%)	68 (36.4)
β blocker, n (%)	67 (35.8)
Procedural characteristics	
Intravascular imaging device, n (%)	
Intravascular ultrasound	111 (59.4)
Optical coherence tomography	3 (1.6)
Pre-dilatation, n (%)	87 (46.5)
Pre-dilatation balloon diameter, mm	2.59 \pm 0.47
Pre-dilatation balloon pressure, atm	13.0 \pm 4.0
Average stent diameter, mm	3.11 \pm 0.41
Total stent length, mm	26.5 \pm 14.4
Post-dilatation, n (%)	71 (38.0)

Post-dilatation balloon diameter, mm	3.20±0.57
Post-dilatation balloon pressure, atm	15.4±3.8
Type of stent (N=224)	
Bare-metal stent	65 (29.0)
First-generation DES	50 (22.3)
Cypher™	41 (18.3)
Taxus™	9 (4.0)
Second-generation DES	84 (37.5)
Endeavor™	5 (2.2)
Nobori™	22 (9.8)
Promus™	14 (6.2)
Resolute™	7 (3.1)
Xience™	36 (16.1)
Third-generation DES	12 (5.4)
Synergy™	4 (1.8)
Ultimaster™	8 (3.6)
Unknown	13 (5.8)

Data are presented as mean ± SD or number (%). ACEi = angiotensin converting enzyme inhibitor,

ARB = angiotensin II receptor blocker, DES = drug-eluting stent.

Table S2. Laboratory data and procedural characteristics at the time of stent thrombosis.

Number of patients	187
Laboratory data	
White blood cell, $\times 10^3 / \mu\text{L}$	9.6 \pm 3.9
Red blood cell, $\times 10^6 / \mu\text{L}$	4.12 \pm 0.81
Hemoglobin, g/dL	12.7 \pm 2.3
Hematocrit, %	38.5 \pm 6.9
Platelet, $\times 10^3 / \mu\text{L}$	215.1 \pm 76.6
Creatinine, mg/dL	0.93 [0.79, 1.24]
Blood sugar, mg/dL	179.8 \pm 87.5
Hemoglobin A _{1c} , %	6.4 \pm 1.3
Total cholesterol, mg/dL	161.3 \pm 41.5
Triglyceride, mg/dL	110.8 \pm 67.6
High-density lipoprotein cholesterol, mg/dL	42.9 \pm 12.1
Low-density lipoprotein cholesterol, mg/dL	95.1 \pm 33.5
Peak creatine kinase, U/L	1030.0 [372.0, 3017.0]
Peak creatine kinase-MB, U/L	110.0 [39.0, 251.8]
Procedural characteristics	
Intravascular imaging device, n (%)	
Intravascular ultrasound	150 (80.2)
Optical coherence tomography	27 (14.4)
Access site, n (%)	
Radial artery	63 (33.7)

Common femoral artery	117 (62.6)
Brachial artery	5 (2.7)
Unknown	2 (1.1)
Aspiration, n (%)	136 (72.7)
Distal protection, n (%)	35 (18.7)
Pre-dilatation, n (%)	155 (82.9)
Pre-dilatation balloon diameter, mm	2.83±0.53
Pre-dilatation balloon pressure, atm	13.8±4.7
Bare-metal stent, n (%)	16 (8.6)
Drug-coated balloon, n (%)	35 (18.7)
Drug-eluting stent, n (%)	67 (35.8)
Average stent diameter, mm	3.16±0.46
Total stent length, mm	23.2±10.3
Post-dilatation, n (%)	49 (26.2)
Post-dilatation balloon diameter, mm	3.30±0.49
Post-dilatation balloon pressure, atm	16.1±4.2

Data are presented as mean ± SD, median (interquartile range) or number (%).

Table S3. Quantitative coronary angiography at the time of initial percutaneous coronary intervention.

	MACE	No MACE	P value	TLR	No TLR	P value
Number of patients	29	47		24	52	
Pre-PCI						
Lesion length, mm	17.2±10.9	15.5±9.3	0.54	17.1±10.2	15.6±9.9	0.60
Minimum lumen diameter, mm	0.55±0.41	0.71±0.60	0.22	0.59±0.41	0.68±0.59	0.52
Reference vessel diameter, mm	2.81±0.69	2.93±0.72	0.46	2.88±0.72	2.89±0.71	0.93
Diameter stenosis, %	79.8±15.0	75.6±19.2	0.32	78.4±15.2	76.7±18.8	0.69
Post-PCI						
In-segment						
Minimum lumen diameter, mm	2.05±0.58	2.20±0.72	0.37	2.06±0.59	2.18±0.70	0.51
Reference vessel diameter, mm	2.80±0.67	3.12±0.72	0.059	2.82±0.70	3.08±0.72	0.16

Diameter stenosis, %	26.2±14.6	28.1±13.6	0.59	26.4±15.2	27.9±13.4	0.69
In-stent						
Minimum lumen diameter, mm	2.22±0.54	2.43±0.57	0.11	2.24±0.54	2.40±0.57	0.25
Reference vessel diameter, mm	3.01±0.60	3.24±0.69	0.15	2.96±0.64	3.23±0.66	0.11
Diameter stenosis, %	25.7±14.0	24.2±13.3	0.65	24.1±13.2	25.1±13.8	0.76

Data are presented as mean ± SD. MACE = major adverse cardiac event, PCI = percutaneous coronary intervention, TLR = target lesion revascularization.

Table S4. Intravascular ultrasound findings other than stent expansion at the time of stent thrombosis.

	MACE	No MACE	P value	TLR	No TLR	P value
Pre-PCI						
Number of analyzed lesions	19	48		12	55	
Proximal reference site						
EEM CSA, mm ²	16.78±6.35	18.03±4.89	0.39	18.16±7.11	17.57±4.93	0.73
Lumen CSA, mm ²	6.19±2.85	6.02±2.63	0.82	7.01±3.09	5.86±2.56	0.18
Plaque media CSA, mm ²	10.60±4.35	12.01±3.80	0.19	11.15±4.75	11.71±3.84	0.66
Distal reference site						
EEM CSA, mm ²	13.10±4.30	12.67±5.14	0.75	12.60±4.47	12.84±5.01	0.88
Lumen CSA, mm ²	4.96±2.37	4.70±2.35	0.69	5.54±2.61	4.61±2.27	0.22
Plaque media CSA, mm ²	8.14±3.68	7.97±3.77	0.86	7.06±2.85	8.22±3.87	0.33

Stent implantation site

Total stent length, mm	26.3±15.0	26.1±13.5	0.97	29.0±15.7	25.5±13.5	0.44
EEM CSA, mm ²	15.28±4.16	15.69±4.15	0.72	15.56±4.61	15.57±4.06	1.0
Stent CSA, mm ²	7.10±1.84	7.31±2.05	0.70	7.37±2.23	7.22±1.94	0.81
Lumen CSA, mm ²	4.12±1.23	3.92±1.68	0.65	4.28±1.14	3.91±1.64	0.47
Minimum stent CSA, mm ²	4.91±1.87	5.12±2.01	0.69	4.75±2.14	5.13±1.93	0.55
Maximum stent CSA, mm ²	9.69±3.27	9.95±3.60	0.79	10.46±3.80	9.75±3.44	0.53
Neointimal area, mm ²	2.98±1.55	3.30±1.72	0.37	3.10±1.81	3.31±1.66	0.69
Peri-stent plaque area, mm ²	8.19±3.11	8.37±2.95	0.82	8.19±2.99	8.35±3.00	0.87
Minimum stent diameter, mm	2.54±0.57	2.58±0.68	0.82	2.53±0.68	2.57±0.64	0.85
Maximum stent diameter, mm	3.80±1.54	3.65±1.06	0.65	4.12±1.88	3.60±1.00	0.18
Stent symmetry index	0.70±0.15	0.72±0.13	0.67	0.65±0.13	0.73±0.14	0.072

Lumen volume, mm ³	101.5±47.3	98.2±66.7	0.85	116.5±47.9	95.4±63.8	0.29
Stent volume, mm ³	179.7±94.5	181.0±92.7	0.96	204.7±99.2	175.4±91.1	0.32
Vessel volume, mm ³	396.1±227.0	396.9±219.2	0.99	434.3±215.7	388.4±221.7	0.52
Neointimal volume, mm ³	78.3±63.1	82.7±49.6	0.76	88.2±68.6	80.0±50.0	0.63
Neointimal volume obstruction, %	40.7±17.2	45.7±18.8	0.32	39.5±17.5	45.3±18.6	0.32

Post-PCI

Number of analyzed lesions	21	50		13	58	
Proximal reference site						
EEM CSA, mm ²	17.06±5.11	18.16±4.40	0.36	17.43±5.81	17.92±4.36	0.73
Lumen CSA, mm ²	6.93±4.28	6.86±3.02	0.94	7.96±5.08	6.64±2.91	0.38
Plaque media CSA, mm ²	10.13±2.84	11.30±3.08	0.14	9.47±2.58	11.29±3.06	0.051

Distal reference site

EEM CSA, mm ²	12.48±5.83	13.32±4.98	0.54	13.51±6.25	12.97±5.01	0.74
Lumen CSA, mm ²	5.06±2.30	5.07±2.39	0.98	5.52±2.45	4.96±2.34	0.45
Plaque media CSA, mm ²	7.42±4.51	8.25±3.42	0.40	7.99±5.06	8.01±3.46	0.99

Stent implantation site

Total stent length, mm	30.8±14.1	32.1±12.8	0.72	31.8±14.0	31.7±13.0	0.99
EEM CSA, mm ²	14.90±4.60	16.30±4.53	0.24	15.28±5.06	16.02±4.48	0.60
Stent CSA, mm ²	7.33±2.27	7.76±2.30	0.47	7.55±2.44	7.64±2.27	0.90
Minimum stent CSA, mm ²	5.28±2.10	5.70±2.08	0.44	5.44±2.14	5.61±2.14	0.79
Maximum stent CSA, mm ²	10.10±3.55	10.22±3.23	0.89	10.67±4.10	10.08±3.13	0.56
Lumen CSA, mm ²	5.05±2.04	5.34±2.27	0.62	5.27±1.80	5.25±2.28	0.98
Minimum lumen CSA, mm ²	3.37±1.27	3.43±1.51	0.88	3.47±1.09	3.39±1.51	0.87

EEM CSA at MLA site, mm ²	14.01±5.42	14.12±5.34	0.94	13.83±5.16	14.15±5.41	0.86
Area stenosis at MLA site, %	74.41±8.06	73.99±11.07	0.88	73.31±7.81	74.30±10.69	0.76
Neointimal area, mm ²	2.27±1.20	2.41±1.28	0.66	2.28±1.31	2.39±1.25	0.78
Peri-stent plaque CSA, mm ²	7.58±2.67	8.55±3.00	0.20	7.73±2.99	8.38±2.92	0.47
Minimum stent diameter, mm	2.63±0.60	2.83±0.77	0.29	2.72±0.64	2.78±0.75	0.79
Maximum stent diameter, mm	3.69±0.74	4.36±2.60	0.25	3.86±0.85	4.23±2.43	0.60
Stent symmetry index	0.71±0.10	0.71±0.14	0.91	0.70±0.07	0.71±0.14	0.86
Lumen volume, mm ³	148.5±72.2	161.0±79.7	0.54	164.4±78.5	155.7±77.6	0.72
Stent volume, mm ³	216.1±86.9	240.3±101.4	0.34	229.2±87.8	234.0±100.3	0.88
Vessel volume, mm ³	442.1±184.9	514.1±229.7	0.21	463.0±176.4	499.4±227.8	0.59
Neointimal volume, mm ³	67.5±43.4	79.3±51.6	0.36	64.8±37.6	78.3±51.5	0.38
Neointimal volume obstruction, %	31.8±15.6	32.4±16.7	0.89	29.7±14.4	32.8±16.8	0.54

Data are presented as mean \pm SD or n (%). Stent symmetry index is defined as the minimum stent diameter divided by the maximum stent diameter. CSA = cross sectional area, EEM = external elastic membrane, MACE = major adverse cardiac event, PCI = percutaneous coronary intervention, TLR = target lesion revascularization.

Table S5. Inter- and intra-observer intraclass correlation coefficients for quantitative coronary angiography and intravascular ultrasound findings.

	ICC (1, 1) (Inter-observer reproducibility)	ICC (2, 1) (Intra-observer reproducibility)
QCA		
Pre-PCI		
Lesion length	0.896	0.802
Minimum lumen diameter	0.886	0.898
Reference vessel diameter	0.834	0.846
Diameter stenosis	0.84	0.916
Post-PCI		
In-segment		
Minimum lumen diameter	0.917	0.881
Reference vessel diameter	0.961	0.884
Diameter stenosis	0.735	0.746
In-stent		
Minimum lumen diameter	0.823	0.839
Reference vessel diameter	0.967	0.867
Diameter stenosis	0.74	0.779

IVUS

Proximal reference site

EEM CSA	0.847	0.855
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Lumen CSA	0.939	0.935
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Distal reference site

EEM CSA	0.858	0.907
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Lumen CSA	0.92	0.908
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Stent implantation site

Total stent length	0.991	0.996
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EEM CSA	0.942	0.761
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Stent CSA	0.991	0.982
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Minimum stent CSA	0.974	0.941
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Maximum stent CSA	0.917	0.954
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Lumen CSA	0.847	0.745
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Minimum lumen CSA	0.917	0.852
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Lumen volume	0.915	0.834
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Stent volume	0.982	0.969
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Vessel volume	0.900	0.802
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Stent expansion

Stent expansion index	0.893	0.809
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CSA = cross sectional area, EEM = external elastic membrane, ICC = intraclass correlation

coefficients, IVUS = intravascular ultrasound, PCI = percutaneous coronary intervention, QCA =

quantitative coronary angiography.