Comparison of Clinical Characteristics of Stent Thrombosis Between the Right Coronary Artery and the Left Coronary Artery — A Subanalysis of the REAL-ST Registry —

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Background: Stent thrombosis (ST) remains a severe complication following stent implantation. We previously reported the risk factors for ST after 2nd-generation drug-eluting stent (DES) in the REAL-ST (Retrospective Multicenter Registry of ST After First- and Second-Generation DES Implantation) registry.

Methods and Results: In this subanalysis, we aimed to reveal the difference in ST between right coronary (RCA) and left (LCA) coronary arteries. A total of 307 patients with ST were divided into the RCA-ST group (n=93) and the LCA-ST group (n=214). Multivariate analysis revealed younger age (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.93–0.99, P=0.01), ostial lesion at the time of index percutaneous coronary intervention (OR 4.37, 95% CI 1.43–13.33, P=0.01), bifurcation lesion at the time of index PCI (OR 0.05, 95% CI 0.02–0.12, P<0.01), chronic total occlusion (CTO) lesion at the time of index PCI indication (OR 4.19, 95% CI 1.05–16.71, P=0.04), and use of prasugrel at the time of ST (OR 7.30, 95% CI 1.44–36.97, P=0.02) were significantly associated with RCA-ST.

Conclusions: Younger age, ostial or CTO lesion, and use of prasugrel at the time of ST were prominent factors in RCA-ST, whereas bifurcation lesion was associated with LCA-ST. We should pay attention to the differences between RCA-ST and LCA-ST to prevent ST.

Key Words: Bifurcation lesion; Chronic total occlusion (CTO) lesion; Ostial lesion; Right coronary artery; Stent thrombosis

S tent thrombosis (ST) is a serious complication following stent implantation, resulting in fatal or nonfatal acute myocardial infarction (AMI).1 The incidence of late or very late ST was greater with 1st-generation drug-eluting stents (DES) than with bare-metal stents,2 which dampened the enthusiasm for DES. Although several studies have demonstrated better clinical outcomes with 2nd-generation DES compared with 1st-generation DES,3,4 ST still occurred with 2nd-generation DES.5 Recently, our group reported on the REAL-ST (Retrospective Multicenter Registry of ST After First- and Second-Generation DES Implantation) registry to elucidate the risk factors and long-term outcomes of patients with definite ST after 2nd-generation DES implantation.6 The REAL-ST registry revealed that the risk factors for ST were different among early ST, late ST, and very late ST, and the long-term clinical outcomes were worse in patients with ST than in those without ST.6 However, we could not provide sufficient data to elucidate the mechanism of ST, which highlighted the need for a detailed subanalysis.
The pathophysiology of ST includes patient-, lesion-, procedure-, and stent-related factors. Because underlying plaques, such as calcified nodules, which are known to be associated with ST, are significantly different between the right coronary artery (RCA) and left coronary artery (LCA), the mechanism of ST may differ in the coronary arteries. Furthermore, the long-term outcomes following ST may also differ between the RCA and LCA, because left ventricular function and long-term outcomes are generally worse with LCA-AMI than with RCA-AMI.

The aim of this subanalysis of REAL-ST was to compare the clinical characteristics and outcomes between ST in the RCA and ST in the LCA, and to find the clinical factors associated with ST in the RCA.

### Methods

The REAL-ST registry was conducted as a retrospective multicenter registry, and the study design of the main analysis has been described elsewhere. Definite ST was defined according to the Academic Research Consortium criteria. The study protocol conformed to the Declaration of Helsinki principles, and was approved by the ethics committee of each participating institution. The present subanalysis has selected patients who had definite ST with 2nd-generation DES as the study population from the REAL-ST registry data, and they were divided into the RCA-ST and LCA-ST groups for comparison of clinical characteristics. We sought the factors that were related to RCA-ST by using a multivariate stepwise logistic regression.

### Table 1. Comparison of Baseline Characteristics of the RCA-ST and LCA-ST Patient Groups

| Variables                        | All patients (n=307) | RCA-ST group (n=93) | LCA-ST group (n=214) | P value |
|----------------------------------|---------------------|---------------------|----------------------|---------|
| **Age (years)**                  | 68.1±10.5           | 66.2±9.7            | 69.0±10.8            | 0.02    |
| **Male sex**                     | 247 (80.5)          | 73 (78.5)           | 174 (81.3)           | 0.57    |
| **BMI (kg/m²)**                  | 23.5±3.6 (n=294)    | 24.0±3.5 (n=89)     | 23.3±3.6 (n=205)     | 0.10    |
| **Hypertension**                 | 244 (79.5)          | 74 (79.6)           | 170 (79.4)           | 0.98    |
| **Diabetes mellitus**            | 145 (47.2)          | 43 (46.2)           | 102 (47.7)           | 0.82    |
| **Dyslipidemia**                 | 252 (82.1)          | 77 (82.8)           | 175 (81.8)           | 0.83    |
| **Current smoker**               | 97/306 (31.7)       | 26/93 (28.0)        | 71/213 (33.3)        | 0.35    |
| **Hemoglobin (mg/dL)**           | 13.0±2.1 (n=288)    | 12.8±1.9 (n=86)     | 13.1±2.2 (n=202)     | 0.33    |
| **eGFR (mL/min/1.73m²)**         | 59.1±30.8 (n=288)   | 52.6±31.4 (n=86)    | 61.9±30.2 (n=202)    | 0.07    |
| **Prior myocardial infarction**  | 99 (32.2)           | 31 (33.3)           | 68 (31.8)            | 0.79    |
| **Prior PCI**                    | 140 (45.6)          | 48 (51.6)           | 92 (43.0)            | 0.16    |
| **Prior CABG**                   | 13 (4.2)            | 6 (6.5)             | 7 (3.3)              | 0.22    |
| **Prior stroke**                 | 38 (12.4)           | 10 (10.8)           | 28 (13.1)            | 0.57    |
| **Prior PAD**                    | 48 (15.6)           | 19 (20.4)           | 29 (13.6)            | 0.13    |
| **Hemodialysis**                 | 43 (14.0)           | 21 (22.6)           | 22 (10.3)            | <0.01   |
| **STEMI**                        | 92 (30.0)           | 30 (32.2)           | 62 (29.0)            |         |
| **NSTEMI**                       | 19 (6.2)            | 6 (6.5)             | 13 (6.1)             |         |
| **Unstable angina**              | 36 (11.7)           | 10 (10.8)           | 26 (12.1)            |         |
| **Stable angina**                | 160 (52.1)          | 47 (50.5)           | 113 (52.8)           |         |
| **LVEF (%)**                     | 51.9±14.4 (n=294)   | 53.4±14.0 (n=89)    | 51.2±14.5 (n=205)    | 0.29    |
| **Clinical presentation at index PCI** |                |                     |                     |         |
| **Aspirin**                      | 303 (98.7)          | 93 (100)            | 210 (98.1)           | 0.32    |
| **Ticlopidine**                  | 12 (3.9)            | 5 (5.4)             | 7 (3.3)              | 0.52    |
| **Clopidogrel**                  | 276 (89.9)          | 79 (84.9)           | 197 (92.1)           | 0.06    |
| **Prasugrel**                    | 14 (4.6)            | 9 (9.7)             | 5 (2.3)              | 0.01    |
| **Cilostazol**                   | 28 (9.1)            | 5 (5.4)             | 23 (10.7)            | 0.13    |
| **Anticoagulation**              | 30 (9.8)            | 9 (9.7)             | 21 (9.8)             | 0.97    |
| **ACEI/ARB**                     | 194 (63.2)          | 57 (61.3)           | 137 (64.0)           | 0.65    |
| **β-blocker**                    | 144 (46.9)          | 44 (47.3)           | 100 (46.7)           | 0.93    |
| **Calcium-channel blocker**      | 107 (34.9)          | 36 (38.7)           | 71 (33.2)            | 0.35    |
| **Statin**                       | 215 (70.0)          | 65 (69.9)           | 150 (70.1)           | 0.97    |
| **Oral hypoglycemia agent**      | 80 (26.1)           | 25 (24.2)           | 55 (25.7)            | 0.83    |
| **Insulin**                      | 34 (11.1)           | 11 (11.8)           | 23 (10.7)            | 0.78    |

Categorical variables are expressed as number and (%). Continuous variables are shown as mean±SD. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; LCA, left coronary artery; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PAD, peripheral arterial disease; RCA, right coronary artery; ST, stent thrombosis; STEMI, ST-segment elevation myocardial infarction.
model. The incidence of all-cause death and recurrent ST within 4 years after the index ST were compared between the 2 groups.

Data are expressed as mean±SD or percentage. Categorical variables are presented as numbers (percentage) and compared with a Pearson’s χ² test or Fisher’s exact test. The Kolmogorov-Smirnov test was performed to determine if the continuous variables were normally distributed. Normally distributed continuous variables were compared between the groups using an unpaired Student’s t-test. Otherwise, continuous variables were compared using a Mann-Whitney U-test. Multivariate stepwise logistic regression analysis was performed to investigate variables associated with RCA-ST. In this model, RCA-ST was adopted as a dependent variable. Variables that had a marginal association (P<0.20) with RCA-ST in univariate logistic regression analyses were adopted as independent variables. Incidences of all-cause death and recurrent ST after the index ST events were estimated by the Kaplan-Meier method, and the differences between groups were assessed by log-rank test. The odds ratio (OR) and the 95% confidence interval (CI) were calculated. A P-value <0.05 was considered statistically significant. All analyses were performed using statistical software, SPSS 23.0/Windows (SPSS, Chicago, IL, USA).

Results

A total of 307 patients who had definite ST of native coronary arteries following 2nd-generation DES implantation were analyzed in the present study, and were divided into the RCA-ST group (n=93) and the LCA-ST group (n=214). The comparison of baseline patient characteristics between the 2 groups is shown in Table 1. As compared with the LCA-ST group, the RCA-ST group had the following clinical characteristics: younger age, higher prevalence of hemodialysis, more prasugrel users. General comorbidities such as hypertension, diabetes mellitus, and dyslipidemia were not different between the 2 groups.

The comparison of lesion and procedural characteristics at the time of index PCI between the 2 groups is shown in Table 2. An ostial lesion at the index PCI was more frequently observed in the RCA-ST group (16.1%) than in the LCA-ST group (4.7%) (P<0.01). Meanwhile, bifurcation lesion at the index PCI was significantly less frequent in the RCA-ST group (7.5%) than in the LCA-ST group (57.5%) (P<0.01). Total stent length tended to be longer in CTO lesions of the RCA-ST (n=8: 74.8±26.9 mm) than those of the LCA-ST group (n=8: 51.9±27.6 mm) without reaching statistical significance (P=0.10). The comparison of lesion and procedural characteristics at the time of ST is shown in Table 3. The use of prasugrel was significantly greater in the RCA-ST group (9.7%) than in the LCA-ST group (5.9%) (P<0.01). ST types, including early ST, late ST and very late ST, were comparable between the RCA-ST and LCA-ST groups (P=0.14). Treatments for ST were comparable between groups; 9 patients in the RCA-ST group used prasugrel at the time of ST and all 9 patients using prasugrel experienced early ST; 3 patients in the LCA-ST group used prasugrel at the time of ST and of them 2 cases were early ST and 1 was very late ST.

Table 4 shows the results of univariate logistic regression analysis and multivariate stepwise logistic regression analysis investigating the variables associated with RCA-ST. The multivariate stepwise logistic regression analysis showed that ostial lesion at the time of index PCI (OR

### Table 2. Comparison of Lesion and Procedural Characteristics at the Index PCI Between the RCA-ST and LCA-ST Groups

| Variables                        | All patients (n=307) | RCA-ST group (n=93) | LCA-ST group (n=214) | P value |
|----------------------------------|----------------------|---------------------|----------------------|---------|
| De novo lesion                   | 271 (88.3)           | 76 (81.7)           | 195 (91.1)           | 0.02    |
| In-stent restenosis              | 37 (12.1)            | 17 (18.3)           | 20 (9.3)             | 0.03    |
| Ostial lesion                    | 25 (8.1)             | 15 (16.1)           | 10 (4.7)             | <0.01   |
| Bifurcation lesion               | 130 (42.3)           | 7 (7.5)             | 123 (57.5)           | <0.01   |
| Treated with 1-stent technique   | 111 (36.2)           | 6 (6.5)             | 105 (49.1)           | <0.01   |
| Treated with 2-stent technique   | 19 (6.2)             | 1 (1.1)             | 18 (8.4)             | 0.01    |
| Lesion type                      |                      |                     |                      | 0.92    |
| A                                | 10 (3.3)             | 4 (4.3)             | 6 (2.8)              |         |
| B1                               | 33 (10.7)            | 10 (10.8)           | 23 (10.7)            |         |
| B2                               | 82 (26.7)            | 25 (26.9)           | 57 (26.6)            |         |
| C                                | 182 (59.3)           | 54 (58.1)           | 128 (59.8)           |         |
| Severe calcification             | 80 (26.1)            | 27 (29.0)           | 53 (24.8)            | 0.43    |
| Tortuous lesion                  | 64 (20.8)            | 24 (25.8)           | 40 (18.7)            | 0.16    |
| Chronic total occlusion          | 16 (5.2)             | 8 (8.6)             | 8 (3.7)              | 0.10    |
| Rotational ablation use          | 46 (15.0)            | 17 (18.3)           | 29 (13.6)            | 0.29    |
| Post-dilatation                  | 219 (71.3)           | 61 (65.6)           | 158 (73.8)           | 0.14    |
| Total stent length (mm)          | 34.5±20.2 (n=293)    | 35.5±23.0 (n=89)    | 34.1±27.6 (n=204)    | 0.82    |
| Max pressure of stent deployment (atm) | 15.1±4.7 (n=293) | 15.5±4.8 (n=89)    | 14.9±4.6 (n=204)    | 0.40    |
| Stent overlap                    | 111 (36.2)           | 31 (33.3)           | 80 (37.4)            | 0.50    |
| IVUS/OCT use at index PCI        | 245 (79.8)           | 72 (77.4)           | 173 (80.8)           | 0.49    |
| Stent edge dissection            | 2 (n=301, 0.7)       | 0 (n=91, 0.0)       | 2 (n=210, 1.0)       | 1.00    |
| Post-diameter stenosis ≥20%      | 86 (n=301, 28.6)     | 22 (n=91, 24.2)     | 64 (n=210, 30.5)     | 0.20    |

Categorical variables are expressed as number and (%). Continuous variables are shown as mean±SD. IVUS, intravascular ultrasound; OCT, optical coherence tomography. Other abbreviations as in Table 1.
Table 3. Comparison of Patient Characteristics, and Procedural and Lesion Characteristics at Time of ST in the RCA-ST and LCA-ST Groups

|                            | All patients (n=307) | RCA-ST group (n=93) | LCA-ST group (n=214) | P value |
|---------------------------|----------------------|---------------------|----------------------|---------|
| **Medications at ST**     |                      |                     |                      |         |
| Aspirin                   | 265 (86.3)           | 79 (84.9)           | 186 (86.9)           | 0.64    |
| Ticlopidine               | 10 (3.3)             | 5 (5.4)             | 5 (2.3)              | 0.18    |
| Clopidogrel               | 227 (73.9)           | 62 (66.7)           | 165 (77.1)           | 0.06    |
| Prasugrel                 | 12 (3.9)             | 9 (9.7)             | 3 (1.4)              | <0.01   |
| Cilostazol                | 13 (4.2)             | 3 (3.2)             | 10 (4.7)             | 0.76    |
| Non-antiplatelet therapy  | 31 (10.1)            | 9 (9.7)             | 22 (10.3)            | 0.87    |
| Anticoagulation           | 27 (8.8)             | 8 (8.6)             | 19 (8.9)             | 0.94    |
| ACEI/ARB                  | 171 (55.7)           | 45 (48.4)           | 126 (58.9)           | 0.09    |
| β-blocker                 | 130 (42.3)           | 39 (41.9)           | 91 (42.5)            | 0.92    |
| Calcium-channel blocker   | 102 (33.2)           | 37 (39.8)           | 65 (30.4)            | 0.11    |
| Statin                    | 196 (63.8)           | 61 (65.6)           | 135 (63.1)           | 0.67    |
| Oral hypoglycemia agent   | 73 (23.8)            | 25 (26.9)           | 48 (22.4)            | 0.40    |
| Insulin                   | 38 (12.4)            | 14 (15.1)           | 24 (11.2)            | 0.35    |
| **Clinical presentation at ST** |                      |                     |                      | 0.90    |
| STEMI                     | 217 (70.7)           | 67 (72.0)           | 150 (70.1)           |         |
| NSTEMI                    | 35 (11.4)            | 9 (9.7)             | 26 (12.1)            |         |
| Unstable angina           | 25 (8.1)             | 7 (7.5)             | 18 (8.4)             |         |
| Cardiac arrest            | 30 (10.8)            | 10 (10.8)           | 20 (9.3)             |         |
| **Procedural and lesion characteristics** |                      |                     |                      | 0.14    |
| ST type                   |                      |                     |                      |         |
| Early ST                  | 176 (57.3)           | 46 (49.5)           | 130 (60.7)           |         |
| Late ST                   | 64 (20.8)            | 25 (26.9)           | 39 (18.2)            |         |
| Very late ST              | 67 (21.8)            | 22 (23.7)           | 45 (21.0)            |         |
| Stent type at ST          |                      |                     |                      | 0.35    |
| Biolimus-eluting          | 68 (22.1)            | 17 (18.3)           | 51 (23.8)            |         |
| Cobalt-chromium everolimus-eluting | 124 (40.4) | 36 (38.7)           | 88 (41.1)            |         |
| Platinum-chromium everolimus-eluting | 45 (14.7) | 14 (15.1)           | 31 (14.5)            |         |
| Zotarolimus-eluting, Resolute | 18 (5.9)         | 9 (9.7)             | 9 (4.2)              |         |
| Zotarolimus-eluting, Endeavor | 52 (16.9)       | 17 (18.3)           | 35 (18.3)            |         |
| **Initial TIMI flow grade** |                      |                     |                      | 0.07    |
| 0                         | 224 (73.0)           | 60 (64.5)           | 164 (76.6)           |         |
| 1                         | 16 (5.2)             | 4 (4.3)             | 12 (5.6)             |         |
| 2                         | 40 (13.0)            | 18 (19.4)           | 22 (10.3)            |         |
| 3                         | 27 (8.8)             | 11 (11.8)           | 16 (7.5)             |         |
| **Final TIMI flow grade** |                      |                     |                      | 0.15    |
| 0                         | 3 (1.0)              | 2 (2.2)             | 1 (0.5)              |         |
| 1                         | 10 (3.3)             | 1 (1.1)             | 9 (4.2)              |         |
| 2                         | 33 (10.7)            | 7 (7.5)             | 26 (12.1)            |         |
| 3                         | 261 (85.0)           | 83 (89.2)           | 178 (83.2)           |         |
| Multivessel ST            | 10 (3.3)             | 0 (0.0)             | 10 (4.7)             | 0.04    |
| Stent fracture            | 12 (3.9)             | 7 (7.5)             | 5 (2.3)              | 0.05    |
| Peri-stent staining       | 5 (1.6)              | 1 (1.1)             | 4 (1.9)              | 1.00    |
| IABP use                  | 131 (42.7)           | 35 (37.6)           | 96 (44.9)            | 0.24    |
| PCPS use                  | 20 (6.5)             | 6 (6.5)             | 14 (6.5)             | 0.98    |
| IVUS/OCT use at ST        | 228 (74.3)           | 65 (69.9)           | 163 (76.2)           | 0.25    |
| Additional stent implantation | 103 (33.6)       | 32 (34.4)           | 71 (33.2)            | 0.83    |
| Thrombus aspiration       | 103 (33.6)           | 32 (34.4)           | 71 (33.2)            | 0.83    |
| Emergency CABG            | 12 (3.9)             | 5 (5.4)             | 7 (3.3)              | 0.52    |

Categorical variables are expressed as number and (%). Continuous variables are shown as mean ± SD. IABP, intra-aortic balloon pumping; PCPS, percutaneous cardiopulmonary support; TIMI, Thrombolysis in Myocardial Infarction. Other abbreviations as in Tables 1,2.
Table 4. Univariate Logistic Regression Analysis and Multivariate Stepwise Logistic Regression Analysis to Find Associations With \( \text{RCA-ST} \)

| Continuous variables | Univariate | Multivariate |
|----------------------|------------|--------------|
|                      | OR 95% CI  | P value      | OR 95% CI  | P value      |
| Age (per 1 year old) | 0.98 0.95–0.99 0.04 | 0.96 0.93–0.99 0.01 |
| BMI (per 1 kg/m\(^2\)) | 1.06 0.99–1.14 0.10 |    |
| Hemoglobin (per 1 mg/dL) | 0.94 0.84–1.06 0.32 |    |
| LDL cholesterol (per 1 mg/dL) | 1.00 0.99–1.01 0.93 |    |
| Hemoglobin A1c (per 1%) | 1.12 0.90–1.39 0.30 |    |
| eGFR (per 1 mL/min/1.73 m\(^2\)) | 0.99 0.98–0.99 0.02 |    |
| LVEF (per 1%) | 1.01 0.99–1.03 0.29 |    |
| Total stent length at index PCI (per 1 mm) | 1.00 0.99–1.02 0.60 |    |

| Categorical variables | Univariate | Multivariate |
|-----------------------|------------|--------------|
| Variables at index PCI |            |              |
| Hypertension | 1.01 0.55–1.84 0.98 |    |
| Dyslipidemia | 1.07 0.57–2.04 0.83 |    |
| Diabetes mellitus | 0.94 0.58–1.54 0.35 |    |
| Current smoking | 0.78 0.46–1.33 0.35 |    |
| AMI as clinical presentation | 1.34 0.81–2.20 0.25 |    |
| Prior PCI | 1.41 0.87–2.31 0.16 |    |
| Prior PAD | 1.64 0.87–3.10 0.13 |    |
| Hemodialysis | 2.55 1.32–4.91 <0.01 |    |
| In-stent restenosis lesion | 2.17 1.08–4.36 0.03 |    |
| Ostial lesion | 3.92 1.69–9.10 <0.01 | 4.37 1.43–13.33 0.01 |
| Bifurcation lesion | 0.06 0.03–0.14 <0.01 | 0.05 0.02–0.12 <0.01 |
| Bifurcation lesion treated with 2 stents | 0.12 0.02–0.90 0.04 |    |
| Chronic total occlusion lesion | 2.42 0.88–6.67 0.09 | 4.19 1.05–16.71 0.04 |
| Severely calcified lesion | 1.24 0.72–2.14 0.43 |    |
| Tortuous lesion | 1.51 0.85–2.70 0.16 | 1.99 0.95–4.18 0.07 |
| Post-dilatation | 0.68 0.40–1.14 0.14 |    |
| Rotational ablation | 1.43 0.74–2.75 0.29 |    |
| Stent overlap | 0.84 0.50–1.40 0.50 |    |
| IVUS/OCT use | 0.81 0.45–1.47 0.49 |    |
| Clopidogrel | 0.49 0.23–1.04 0.06 |    |
| Prasugrel | 4.48 1.46–13.76 <0.01 |    |
| Cilostazol | 0.47 0.17–1.28 0.14 |    |
| Variables at ST |            |              |
| Early ST | 0.63 0.39–1.03 0.07 |    |
| Stent fracture | 3.40 1.05–11.02 0.04 |    |
| Initial TIMI flow grade 3 (vs. 0, 1 and 2) | 2.10 1.20–3.68 0.01 | 2.04 0.99–4.15 0.05 |
| Final TIMI flow grade 3 (vs. 0, 1 and 2) | 1.68 0.80–3.55 0.17 |    |
| Emergency CABG | 1.68 0.52–5.44 0.39 |    |
| IABP use | 0.74 0.45–1.22 0.24 |    |
| PCPS use | 0.99 0.37–2.65 0.98 |    |
| Aspirin | 0.85 0.43–1.70 0.65 |    |
| Ticlopidine | 2.38 0.67–8.41 0.18 |    |
| Clopidogrel | 0.59 0.35–1.02 0.06 |    |
| Prasugrel | 7.54 1.99–28.52 0.03 | 7.30 1.44–36.97 0.02 |
| ACEI/ARB | 0.66 0.40–1.07 0.09 |    |
| Calcium-channel blocker | 1.52 0.91–2.52 0.11 |    |

Multivariate stepwise logistic regression analysis model included variables that had an association (P<0.2) with RCA ST in the univariate logistic analysis: ACEI/ARB at the time of ST, age per 1 year old, AMI as clinical presentation at index PCI, BMI per 1 kg/m\(^2\), bifurcation lesion, bifurcation lesion treated with 2 stents, calcium-channel blocker, chronic total occlusion lesion, cilostazol at index PCI, clopidogrel at index PCI, clopidogrel at the time of ST, early ST, final TIMI flow grade 3 (vs. 0, 1 and 2), hemodialysis, initial TIMI flow grade 3 (vs. 0, 1 and 2), in-stent restenosis lesion, ostial lesion, post-dilatation, prasugrel at index PCI, prasugrel at the time of ST, prior PAD, stent fracture, and tortuous lesion. AMI, acute myocardial infarction; LDL, low-density lipoprotein. Other abbreviations as in Tables 1–3.
Figure 1. Kaplan-Meier curves of cumulative event of all-cause death within 4 years after the index stent thrombosis (ST) event in the RCA-ST and LCA-ST groups. Log-rank test shows the RCA-ST group had relatively less death events than the LCA-ST group (P=0.08). LCA, left coronary artery; RCA, right coronary artery.

Figure 2. Kaplan-Meier curves of cumulative recurrent stent thrombosis (ST) within 4 years after the index ST event in the RCA-ST and LCA-ST groups. Log-rank test shows no significant difference between the groups (P=0.34). LCA, left coronary artery; RCA, right coronary artery.
The main findings of this study are that younger age, ostial lesion, bifurcation lesion, CTO lesion, and use of prasugrel at the time of ST were significantly associated with definite ST in the RCA. Moreover, the incidence of all-cause death tended to be lower in the RCA-ST group than in the LCA-ST group, whereas the incidence of recurrent ST was not different between the groups. Although several studies have reported risk factors of ST such as AMI, CTO lesion, long lesion, diabetes mellitus, chronic kidney disease and the RCA, the clinical differences between RCA-ST and LCA-ST have not been discussed in the literature. Our results suggest that the mechanism of ST is different between these coronary arteries.

First, we will discuss why ostial lesions were significantly associated with RCA-ST as compared with LCA-ST. It is well known that in-stent restenosis occurs more frequently in ostial RCA lesions than in non-ostial RCA lesions. Recent intravascular imaging studies have revealed the close association between in-stent restenosis and neoatherosclerosis, suggesting the possibility that in-stent plaque rupture caused by neoatherosclerosis is one of the reasons for ST in ostial RCA lesions. The aorto-ostial RCA has lower distensibility and excessive rigidity with a hinge motion, resulting in stent deformation, including recoil and fracture after stent implantation, in ostial lesions. Moreover, calcified nodules are frequently observed in the ostium of the RCA, which might be an important underlying plaque in ST. Although the literature regarding ST in the ostial LCA (left main ostium) is sparse, multiple mechanisms underlying ostial RCA lesions may be associated with RCA-ST.

Why were bifurcation lesions less frequently observed in the RCA-ST than in the LCA-ST? These lesions, which are a well-known risk factor of ST, occur less in the RCA than in the LCA. Furthermore, variations of bifurcation lesions are wider in the LCA than in the RCA, because the LCA has several bifurcations such as the left main distal, left anterior descending artery-diagonal branch, left circumflex artery-obtuse marginal branch, and left circumflex artery-posterolateral branch, whereas the RCA has only a few bifurcations such as the posterior descending branch-posterolateral branch. Therefore, the reason why bifurcation lesions were less frequently observed in the RCA-ST group could be less opportunities to treat bifurcation lesions during PCI to the RCA.

We now discuss why CTO lesions were more frequently observed in the RCA-ST than in the LCA-ST. The Canadian Multicenter CTO Registry revealed that CTO occurred more frequently located in the RCA than in the LCA. Furthermore, the total stent length was longer in RCA-CTO lesions than in LCA-CTO lesions. Several studies report that stent deployment to CTO lesions is an important risk factor of ST, and that longer stents are also a risk factor of ST. In the present study, total stent length in CTO lesions tended to be longer in the RCA-ST group than in the LCA-ST. The greater incidence of CTO and longer stent length might be the reason why CTO lesions were more frequently observed in the RCA-ST group.

The use of prasugrel was more frequently observed in the RCA-ST than in the LCA-ST group. Because STEMI patients treated with prasugrel are associated with favorable outcomes such as lower ST events as compared with STEMI patients treated with clopidogrel, prasugrel is considered to be a more potent thienopyridine than clopidogrel. One possible explanation for our results was that ST in the RCA was associated with mechanical reasons such as stent fracture or stent deformation rather than pharmacological reasons such as drug-non-responders, whereas the cause of ST in the LCA was associated with pharmacological rather than mechanical reasons.

Furthermore, all cases of prasugrel administration at the time of ST in the RCA-ST group were patients with early ST, which is considered to be associated with the PCI procedure rather than with antiplatelet medications. Although efficacy and safety have been confirmed in Japanese patients, the lower dose regimen of prasugrel (loading dose: 20 mg in Japan vs. 60 mg in Western countries, maintenance dose: 3.75 mg in Japan vs. 10 mg in Western countries) may be a possible explanation for the association between the use of prasugrel and ST in this study.

The RCA-ST group had relatively better outcomes compared with the LCA-ST in the present study. In general, AMI caused by LCA occlusion has worse clinical outcomes compared with AMI caused by RCA occlusion, partly because left ventricular function is more severely damaged by LCA than by RCA occlusion. Furthermore, because most of the patients with ST presented with acute coronary syndrome, LCA-ST might have more cases of fatal AMI than RCA-ST.

Study Limitations
This retrospective subanalysis of the REAL-ST registry has several limitations, which have been described elsewhere. Furthermore, the present study did not investigate gene polymorphism such as CYP2C19, which is closely associated with nonresponders to clopidogrel. Second, some quantitative coronary angiographic data, including minimal lumen diameter and reference diameter, were not available. Although we discussed the association of RCA-ST with use of prasugrel, the number of prasugrel users was much smaller than the number of clopidogrel users. Because we enrolled patients with ST after implantation of various 2nd-generation DES, it remains unclear whether the differences in ST between RCA and LCA are common across the various DES. Finally, there was a lack of some variables, including peak creatine phosphokinase levels and left ventricular function, at the time of ST events because of the nature of a retrospective registry.
Conclusions
Younger age, ostial lesion, CTO lesion, and use of prasugrel at the time of ST were significantly associated with definite ST in the RCA, whereas bifurcation lesion was significantly associated with definite ST in the LCA. The incidence of all-cause death tended to be lower with RCA-ST than with LCA-ST. We should pay attention to the differences between RCA-ST and LCA-ST to prevent and treat definite ST more effectively.

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