Stent Thrombosis and Intrastent Thrombus Formation in Patients Undergoing Elective PCI: Results of an Angioscopic Substudy of the Randomized Trial PRASFIT-Elective (PRASugrel for Japanese PatIenTs with Coronary Artery Disease Undergoing Elective PCI)

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Background: Angioscopy was performed in a group of patients in the PRASugrel For Japanese PatIenTs with Coronary Artery Disease Undergoing Elective PCI (PRASFIT-Elective) study to determine the incidence and clinical features of stent thrombosis. Stent thrombosis is an infrequent, but potentially severe event that may require revascularization or lead to other clinically significant events. Its incidence and clinical features in Japanese patients undergoing elective percutaneous coronary intervention (PCI) are poorly understood, especially in those receiving dual antiplatelet therapy with prasugrel or clopidogrel in combination with aspirin.

Methods: Coronary angioscopy was performed before and at 36 weeks after elective PCI in 19 and 14 patients treated with prasugrel and clopidogrel, respectively, across eight participating institutions. Coronary angioscopic images were adjudicated by independent staff at a central laboratory to assess intrastent thrombus, neointimal coverage, and plaque color.

Results: The proportion of stents with a red thrombus decreased from 57.9% (11/19) to 21.1% (4/19) in the prasugrel group ($P = 0.0082$) and from 50.0% (7/14) to 35.7% (5/14) in the clopidogrel group ($P = 0.3173$) at stenting to the follow-up visit. Platelet reactivity at 4 weeks was similar between patients with or without a red intrastent thrombus. Stent coverage was classified as Grade 1 in most of the patients, and the yellow plaque classification was Grade 0–2 in most of the patients.

Conclusions: Prasugrel and clopidogrel were associated with low rates of red thrombus after 36 weeks of dual-antiplatelet therapy after PCI. Stent coverage and yellow plaque classification were similar in prasugrel- and clopidogrel-treated patients.

Key words: angioscopy, clopidogrel, percutaneous coronary intervention, prasugrel
Introduction

The mortality rate attributable to cardiovascular diseases, including stroke and coronary artery disease, is very high. Each year, around 250,000 patients undergo percutaneous coronary intervention (PCI) in Japan. Patients are routinely prescribed dual antiplatelet therapy (DAPT) comprising aspirin and thienopyridine following this procedure. However, despite the use of antiplatelet drugs and drug-eluting stents (DES), stent thrombosis remains a challenge. Stent thrombosis may also necessitate revascularization or result in other clinically significant events.

To improve the management of patients, several studies have investigated possible risk factors for stent thrombosis to help detect patients at risk or facilitate its earlier detection.

The Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study, which included 8582 patients who underwent successful PCI, showed that anatomically complex lesions and the presence of thrombus were strong predictors of stent thrombosis based on analyses of 92 patients with stent thrombosis within the 2-year follow-up. In addition, a pooled analysis of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) and Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) studies showed that the presence of thrombotic events occurring during PCI was independently associated with 30-day mortality, major bleeding, major adverse cardiovascular events, and intraprocedural stent thrombosis (i.e., thrombosis related to stent deployment).

According to the International Drug-Eluting Stent Event Registry of Thrombosis (DESSERT), most stent thrombosis events occurred within 1 year, but some were detected up to 7.3 years after PCI. The authors investigated the potential predictors of late/very late DES thrombosis. They reported that younger age, African-American race, current smoking, multivessel disease, long length stents, overlapping stents, and percutaneous coronary intervention of vein graft lesions were independently correlated with late/very late stent thrombosis in a cohort of 378 case-control pairs. Several angiographic parameters were also associated with late/very late stent thrombosis, including lesions within the left anterior descending artery or a bypass graft, thrombus, and a larger residual diameter stenosis after DES implantation.

Some studies have also investigated the characteristics of patients who required revascularization following DES failure. For example, Kotani et al. performed coronary angiography in patients who underwent urgent revascularization following thrombus-related DES failure. They reported that thrombus formation was due to a delayed healing process in most patients, but other triggers included restenosis, insufficient DAPT duration, neoatherosclerosis, and vasospasm.

The efficacy and safety of DAPT with either prasugrel or clopidogrel added to aspirin following elective PCI in Japanese patients was examined in the PRASugrel For Japanese PatIenTs with Coronary Artery Disease Undergoing Elective PCI (PRASFIT-Elective) study. The primary endpoint, the incidence of major cardiovascular events, such as cardiovascular death, non-fatal myocardial infarction, or non-fatal ischemic stroke, occurred in 4.1% (15/370) and 6.7% (25/372) of patients in the prasugrel and clopidogrel groups, respectively. Revascularization was performed in 2.2% (8/370) and 2.4% (9/372) of patients, respectively. The purpose of this analysis is to gain insight into the incidence and clinical features of intrastent thrombus after stent implantation, and find the relationship between intrastent thrombus and cardiovascular events. This study was conducted as a part of PRASFIT-Elective in which a subgroup of patients underwent coronary angiography.

Materials and Methods

PRASFIT-Elective study design and patients

The design and results of the PRASFIT-Elective study are reported in more detail elsewhere. Briefly, Japanese patients aged ≥20 years who were scheduled for elective PCI to treat coronary artery disease (e.g., stable angina or prior MI with stenosis) were enrolled and randomly treated with either prasugrel (loading/maintenance doses: 20/3.75 mg) or clopidogrel (300/75 mg) in combination with aspirin (81–100 mg/day). Patients were treated for 24–48 weeks in accordance with the stent label and continued DAPT until the end of the follow-up.

The present study was conducted in accordance with applicable ethical guidelines, including the Declaration of Helsinki. Patients provided written informed consent to participate in the larger study, and those enrolled in the larger study signed an additional informed consent form for the additional procedures. This study was planned and conducted in parallel with the larger study. This trial was registered in the Japan Pharmaceutical Information Center database (JapicCTI-111550). This study was performed at eight institutions.

The pharmacodynamic effects of prasugrel and clopidogrel on platelet function were assessed using the VerifyNow assay (Accumetrics, San Diego, CA, USA), which yields P2Y12 reaction units (PRU).

Coronary angiography

Coronary angiography was to be performed at 36 weeks after PCI. Institutions could also perform angiography before and after PCI (optional), and any time between 24 and 36 weeks. Each institutions used its own coronary angiographic system. Angiography
was performed at least once and could be performed up to three times, depending on the individual patient’s clinical status and available resources. The procedure was done using a guide catheter with a diameter of ≥6 Fr, and patients were administered ≥5000 U of heparin, depending on the local procedures. Based on the patient’s blood pressure, nitrogen could be administered if necessary. Images were taken for the entire stent and included a 10-mm margin at both ends of the stent.

The presence/absence of red, white, and mixed thrombi was determined for each stent according to location (distal, central, and proximal segments). Stent features were graded and compared between the two groups with intrastent thrombus assessed using the Ermenonville classification.8 The degree of neointimal coverage was classified using a 4-grade system, as previously described,9 where grade 0 is no neointimal coverage; grade 1 is when stent struts bulge into the lumen but are covered and still translucently visible; grade 2 is when stent struts are visible but not translucent; and grade 3 is when stent struts are not visible because they were embedded in the neointima. Plaque color was graded as 0 (white), 1 (light yellow), 2 (yellow), or 3 (bright yellow), as previously described.10,11 Stent thrombosis was defined according to the Academic Research Consortium criteria.12 Intrastent thrombus was defined as a thrombus inside the stent that did not occlude the stent lumen.

All coronary angioscopic images were adjudicated at a central laboratory by independent staff who were blinded to the patients’ personal information.

Statistical analysis

Statistical analyses were performed in all patients who underwent coronary angioscopy at the follow-up visit (week 36). The characteristics of patients were examined descriptively to determine the mean ± standard deviation or n (%) of patients as appropriate. The McNemar test was used to compare the proportions of stents with red thrombus formation between PCI and the follow-up visit. Statistical comparisons were not made between the clopidogrel and prasugrel groups, owing to the small sample size and because clopidogrel was not indicated for use in elective PCI at the time of the study, as previously described.7

Results

Patients

Figure 1 shows the disposition of patients. Overall, 35 and 30 patients in the prasugrel and clopidogrel groups provided informed consent, and follow-up angiography was performed in 28 and 26 patients, respectively. Seven patients (nine stents) in the prasugrel group and four patients (five stents) in the clopidogrel group withdrew from the study after providing informed consent due to adverse events in three patients, consent withdrawal in three patients, and investigator’s decision in one patient in the prasugrel group, and consent withdrawal in two patients, adverse event in one patient, and investigator’s decision in one

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Fig. 1  Patient disposition.
CAS, coronary angiography; PCI, percutaneous coronary intervention; PRASFIT-Elective, PRASugrel For Japanese PatIenTs with Coronary Artery Disease Undergoing Elective PCI; PRU, P2Y12 reaction units; TLR, target lesion revascularization
patient in the clopidogrel group. Target lesion revascularization was performed in one patient (two stents) in the prasugrel group and in three patients (eight stents) in the clopidogrel group. Coronary angioscopy was also performed before PCI in 19 and 14 patients in the prasugrel and clopidogrel groups, respectively. The characteristics of patients were generally comparable in the prasugrel and clopidogrel groups, including the proportion of females, age, body weight, disease classification, medical history, stent type, and target lesion (Table 1). However, Body Mass Index (BMI) and dyslipidemia incidence were higher in the clopidogrel group (Table 1). In total, there were 47 and 39 stents in the prasugrel and clopidogrel groups, respectively. Of these, 46 (97.9%) and 35 (89.7%), in the prasugrel and clopidogrel groups, respectively were examined immediately after implantation, and 37 (78.7%) and 31 (79.5%), respectively, were examined during follow-up.

Thrombus formation and relationship to platelet inhibition

The proportion of stents with a red thrombus decreased significantly from 57.9% (11/19) at stenting to 21.1% (4/19) at the follow-up visit in the prasugrel group (P = 0.0082). The incidence of red thrombi before stent implantation was 25.0% (5 of 20 patients) in the prasugrel group and 30.8% (4 of 13 patients) in the clopidogrel group. Although the proportion of stents with a red thrombus decreased in the clopidogrel group (from 50.0% [7/14] to 35.7% [5/14]), the difference was not significant (P = 0.3173). We then examined whether PRU at week 4 was associated with the presence of a red intrastent thrombus. The mean ± standard deviation PRU at week 4 was 196.9 ± 67.62 (range 101–299; n = 9) in patients with a red intrastent thrombus versus 197.7 ± 52.34 (range 61–293; n = 23) in patients without a red thrombus. In prasugrel-treated patients, the values in patients with and without red intrastent thrombus were 163.3 ± 59.67 (n = 4) and 184.9 ± 53.27 (n = 14). The corresponding values in clopidogrel-treated patients were 223.8 ± 66.62 (n = 5) and 217.8 ± 46.70 (n = 9). There was no significant difference in week 4 PRU values between patients with and without red thrombi at follow-up, in either the prasugrel or clopidogrel group (Fig. 2). Among the nine patients with a red thrombus, one patient developed a new thrombus at the follow-up visit (Fig. 3A). The patient received clopidogrel, and their PRU was 270. No patient taking prasugrel had developed a new thrombus at the time of the follow-up visit. The mean PRU in eight patients with no change in red thrombi or thrombus was 187.8. The details of platelet inhibition among the nine patients who developed intrastent red thrombi are shown in Table 2. No difference in LDL-C between patients with and without red thrombi was observed in either group. In the prasugrel group, mean PRU was 124.3 ± 8.50 (n = 3) in patients with red thrombi, and 111.9 ± 29.42 (n = 14) in patients without red thrombi, respectively (P = 0.4902). In the clopidogrel group, mean PRU was 101.3 ± 29.43 (n = 4) in patients with red thrombi, and 115.0 ± 45.34 (n = 8) in patients without red thrombi, respectively (P = 0.5978). Typical angioscopic images showing no change are shown in Fig. 3B–E. The mean PRU in nine patients whose thrombi disappeared was 191.8. Typical angioscopic images showing disappearance of a thrombus are

![Fig. 2 PRU values at week 4 by treatment (A) and by presence or absence of red thrombi at follow-up (B). The analysis was conducted in patients who underwent endoscopy both immediately after stent implantation and at follow-up and also in whom PRU was measured at Week 4. The t-test was used for the comparison of PRU values between patients with and without red thrombi at follow-up. Statistical comparisons between the clopidogrel and prasugrel groups were not made owing to the small sample size and because clopidogrel was not indicated for use in elective PCI at the time of the study. PCI, percutaneous coronary intervention; PRU, P2Y12 reaction units](image)
### Table 1. Patient characteristics in the study cohort and in patients with complete endoscopic and PRU data

|                                | Patients undergoing CAS at follow-up or for whom TLR was available | Patients undergoing CAS at follow-up and for whom PRU at week 4 was available |
|--------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------|
|                                | Prasugrel (n = 28) | Clopidogrel (n = 26) | P-value | Prasugrel (n = 18) | Clopidogrel (n = 14) | P-value |
| Female (%)                     | 8 (28.6)           | 9 (34.6)            | ND      | 6 (33.3)          | 6 (42.9)            | 0.5809  |
| Age                            |                   |                     |         |                   |                     |         |
| Mean (years)                   | 66.6 ± 9.0        | 70.2 ± 9.2          | 0.1489  | 67.9 ± 7.6        | 70.1 ± 9.4          | 0.4589  |
| ≥75 years (%)                  | 5 (17.9)          | 10 (38.5)           | 0.0912  | 4 (22.2)          | 5 (35.7)            | 0.3997  |
| Body weight                    |                   |                     |         |                   |                     |         |
| Mean (kg)                      | 60 ± 9.6          | 65.9 ± 12.8         | 0.0600  | 59.6 ± 7.7        | 63.9 ± 8.4          | 0.1390  |
| ≤50 kg (%)                     | 4 (14.3)          | 1 (3.8)             | 0.1860  | 2 (11.1)          | 0                   | 0.1977  |
| ≤60 kg (%)                     | 12 (42.9)         | 7 (26.9)            | 0.2205  | 7 (38.9)          | 4 (28.6)            | 0.5421  |
| BMI (kg/m²)                    | 23.1 ± 2.9        | 26.2 ± 3.9          | 0.0015  | 22.8 ± 2.3        | 26.1 ± 2.2          | 0.0004  |
| Current smoker (%)             | 6 (21.4)          | 1 (3.8)             | 0.1182  | 4 (22.2)          | 1 (7.1)             | 0.4298  |
| Disease classification (%)     |                   |                     |         |                   |                     |         |
| Stable angina                  | 21 (75.0)         | 21 (80.8)           | 0.6104  | 15 (83.3)         | 9 (64.3)            | 0.2170  |
| Prior myocardial infarction    | 2 (7.1)           | 1 (3.8)             | 0.5972  | 0                  | 1 (7.1)             | 0.2493  |
| Unstable angina                | 3 (10.7)          | 1 (3.8)             | 0.3356  | 2 (11.1)          | 1 (7.1)             | 0.7024  |
| Silent myocardial Ischemia     | 2 (7.1)           | 3 (11.5)            | 0.5777  | 1 (5.6)           | 3 (21.4)            | 0.1780  |
| Medical history (%)            |                   |                     |         |                   |                     |         |
| Hypertension                   | 19 (67.9)         | 21 (80.8)           | 0.2793  | 14 (77.8)         | 11 (78.6)           | 0.9570  |
| Dyslipidemia                   | 18 (64.3)         | 23 (88.5)           | 0.0379  | 12 (66.7)         | 11 (78.6)           | 0.4575  |
| Diabetes mellitus              | 11 (39.3)         | 7 (26.9)            | 0.3356  | 7 (38.9)          | 4 (28.6)            | 0.5421  |
| Creatinine clearance (%)       |                   |                     |         |                   |                     |         |
| >60 mL/min                     | 19 (79.2)         | 18 (78.3)           | 0.9395  | 11 (68.8)         | 9 (75.0)            | 0.7171  |
| ≥30 to ≤60 mL/min              | 5 (20.8)          | 5 (21.7)            | 0.356   | 5 (31.3)          | 3 (25.0)            |         |
| <30 mL/min                     | 0                  | 0                   | 0       | 0                  | 0                   |         |
| Primary treatment (%)          |                   |                     |         |                   |                     |         |
| LD                             | 16 (57.1)         | 15 (57.7)           | 0.9675  | 8 (44.4)          | 9 (64.3)            | 0.2645  |
| MD                             | 12 (42.9)         | 11 (42.3)           | 0.556   | 10 (55.6)         | 5 (35.7)            |         |
| Type of stent (%)              |                   |                     |         |                   |                     |         |
| BMS                            | 1 (3.6)           | 0                   | ND      | 1 (5.6)           | 0                   | ND      |
| DES                            | 27 (96.4)         | 26 (100.0)          | 0       | 17 (94.4)         | 14 (100.0)          |         |
| Target lesion (%)              |                   |                     |         |                   |                     |         |
| RCA                            | 11 (39.3)         | 5 (19.2)            | 0.1068  | 8 (44.4)          | 4 (28.6)            | 0.3575  |
| LAD                            | 17 (60.7)         | 18 (69.2)           | 0.5126  | 10 (55.6)         | 7 (50.0)            | 0.7547  |
| LCX                            | 6 (21.4)          | 6 (23.1)            | 0.8843  | 3 (16.7)          | 4 (28.6)            | 0.4190  |
| Multivessel treatment (%)      | 9 (32.1)          | 12 (46.2)           | 0.2913  | 4 (22.2)          | 3 (21.4)            | 0.9570  |
| Concomitant medications (%)    |                   |                     |         |                   |                     |         |
| PPI                            | 14 (50.0)         | 17 (65.4)           | 0.2533  | 8 (44.4)          | 9 (64.3)            | 0.2645  |
| Statin                         | 16 (57.1)         | 16 (61.5)           | 0.7426  | 9 (50.0)          | 7 (50.0)            | 1.0000  |
| Ca blocker                     | 14 (50.0)         | 14 (53.8)           | 0.7775  | 10 (55.6)         | 6 (42.9)            | 0.4760  |
| ARB                            | 8 (28.6)          | 13 (50.0)           | 0.1065  | 7 (38.9)          | 6 (42.9)            | 0.8206  |
| β-blocker                      | 12 (42.9)         | 9 (34.6)            | 0.5348  | 9 (50)            | 3 (21.4)            | 0.0977  |

Values are expressed as the n (%) or mean ± standard deviation.

ARB, angiotensin receptor blocker; BMI, Body Mass Index; BMS, bare metal stent; CAS, coronary angiography; DES, drug-eluting stent; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PPI, proton pump inhibitor; LD, loading dose; MD, maintenance dose; ND, not determined; PRU, P2Y₁₂ reaction units; RCA, right coronary artery; TLR, target lesion revascularization
Fig. 3  Representative coronary angiography findings in patients receiving clopidogrel (A, C, E, G) or prasugrel (B, D, F). (A) This patient developed a new thrombus that was visible at the follow-up visit (36 weeks; right panel). (B, C) Patients with a red thrombus both immediately after PCI (left panels) and at 36 weeks after PCI (right panels). (D, E) Patients with no thrombus both immediately after PCI (left panels) and at 36 weeks after PCI (right panels). (F, G) Patients whose thrombus disappeared between immediately after PCI (left panels) and 36 weeks after PCI (right panels). PCI, percutaneous coronary intervention

Table 2.  Thrombus change in relation to platelet inhibition in patients developing intrastent red thrombi

| Patient | Treatment group | Presence or absence of thrombi immediately after stent implantation | Presence or absence of thrombi at follow-up | Thrombus change                           |
|---------|-----------------|---------------------------------------------------------------------|---------------------------------------------|-------------------------------------------|
| 20324   | Prasugrel       | Present                                                             | Present                                     | No change                                 |
| 20550   | Prasugrel       | Present                                                             | Present                                     | No change                                 |
| 20911   | Clopidogrel     | Present                                                             | Present                                     | No change                                 |
| 20917   | Clopidogrel     | Present                                                             | Present                                     | No change                                 |
| 20981   | Clopidogrel     | Absent                                                              | Present                                     | Additional thrombus formation             |
| 20982   | Clopidogrel     | Present                                                             | Present                                     | No change                                 |
| 20984   | Prasugrel       | Present                                                             | Present                                     | No change                                 |
| 20987   | Prasugrel       | Present                                                             | Present                                     | No change                                 |
| 21004   | Clopidogrel     | Present                                                             | Present                                     | No change                                 |
shown in Fig. 3F and G. These findings suggest that the presence of red thrombi is partly related to platelet function. None of the patients had white thrombi.

Stent coverage and yellow plaque grade
Table 3 shows stent coverage and yellow plaque classification in the prasugrel and clopidogrel groups. As shown in this table, most of the stent coverage-related parameters were classified as Grade 1, and the grades showed similar distributions in patients treated with prasugrel or clopidogrel. The yellow plaque grades of the central region, distal end, and proximal end of the stent were uniformly distributed across Grades 0–2, with ≤1 stent classified as Grade 3.

### Table 3. Stent coverage and yellow plaque grade among stents analyzed during follow-up

|                      | Dominant grade of coverage: center | Maximum grade of coverage: center | Minimum grade of coverage: center |
|----------------------|-----------------------------------|----------------------------------|-----------------------------------|
|                      | Prasugrel | Clopidogrel | Prasugrel | Clopidogrel | Prasugrel | Clopidogrel |
| Number of stents analyzed | 37    | 31         | 37        | 31         | 37        | 31         |
| Unassessable          | 4      | 2          | 4         | 2          | 4         | 2          |
| Grade 0               | 2 (6.1)| 1 (3.4)    | 0 (0)     | 1 (3.4)    | 7 (21.2)  | 9 (31.0)   |
| Grade 1               | 15 (45.5)| 16 (55.2) | 12 (36.4) | 7 (24.1)   | 19 (57.6) | 16 (55.2)  |
| Grade 2               | 8 (24.2)| 7 (24.1)   | 8 (24.2)  | 10 (34.5)  | 7 (21.2)  | 4 (13.8)   |
| Grade 3               | 8 (24.2)| 5 (17.2)   | 13 (39.4) | 11 (37.9)  | 0 (0.0)   | 0 (0.0)    |
| Mean ± SD grade       | 1.7 ± 0.92| 1.6 ± 0.83 | 2.0 ± 0.88| 2.1 ± 0.88 | 1.0 ± 0.66| 0.8 ± 0.66 |

|                      | Dominant grade of coverage: distal end | Dominant grade of coverage: proximal end | Heterogeneity of neointimal coverage |
|----------------------|----------------------------------------|------------------------------------------|-------------------------------------|
|                      | Prasugrel | Clopidogrel | Prasugrel | Clopidogrel | Prasugrel | Clopidogrel |
| Number of stents analyzed | 37    | 31         | 37        | 31         | 37        | 31         |
| Unassessable          | 7      | 7          | 7         | 8          | 4         | 2          |
| Grade 0               | 2 (6.9)| 3 (12.5)   | 3 (10.0)  | 2 (8.7)    | 7 (21.2)  | 7 (24.1)   |
| Grade 1               | 14 (48.3)| 10 (41.7)| 17 (56.7) | 14 (60.9)  | 16 (48.5) | 11 (37.9)  |
| Grade 2               | 7 (24.1)| 4 (16.7)   | 6 (20.0)  | 2 (8.7)    | 8 (24.2)  | 8 (27.6)   |
| Grade 3               | 6 (20.7)| 7 (29.2)   | 4 (13.3)  | 5 (21.7)   | 2 (6.1)   | 3 (10.3)   |
| Mean ± SD grade       | 1.6 ± 0.91| 1.6 ± 1.06 | 1.4 ± 0.85| 1.4 ± 0.95 | 1.2 ± 0.83| 1.2 ± 0.95 |

|                      | Yellow plaque grade: center | Yellow plaque grade: distal end | Yellow plaque grade: proximal end |
|----------------------|----------------------------|---------------------------------|----------------------------------|
|                      | Prasugrel | Clopidogrel | Prasugrel | Clopidogrel | Prasugrel | Clopidogrel |
| Number of stents analyzed | 37    | 31         | 37        | 31         | 37        | 31         |
| Unassessable          | 4      | 2          | 7         | 4          | 7         | 8          |
| Grade 0               | 10 (30.3)| 10 (34.5)| 11 (36.7) | 17 (63.0)  | 11 (36.7) | 7 (30.4)   |
| Grade 1               | 13 (39.4)| 7 (24.1) | 13 (43.3) | 4 (14.8)   | 11 (36.7) | 6 (26.1)   |
| Grade 2               | 9 (27.3)| 11 (37.9) | 6 (20.0)  | 6 (22.2)   | 8 (26.7)  | 9 (39.1)   |
| Grade 3               | 1 (3.0)| 1 (3.4)    | 0 (0.0)   | 0 (0.0)    | 0 (0.0)   | 1 (4.3)    |
| Mean ± SD grade       | 1.0 ± 0.85| 1.1 ± 0.94 | 0.8 ± 0.75| 0.6 ± 0.84 | 0.9 ± 0.80| 1.2 ± 0.94 |

Results are presented as the n (%) or mean ± standard deviation (SD).

Discussion
The clinical characteristics of intrastent thrombus observed in the present study are perhaps unsurprising when we consider the results of prior studies and the pathogenesis of intrastent thrombus. In particular, intrastent thrombus occurring in the chronic period (up to 36 weeks) after PCI is generally unlikely to cause stent thrombosis, considering that the incidences of stent thrombosis and intrastent thrombus differ.

The endothelium plays a significant role in intrastent thrombus formation. For example, Mitsutake et al. reported that poor endothelial function in the stent distal region was associated with poor neointimal coverage at 9 and 24 months after implantation.
of a first-generation DES.13,14

Newer DES, like everolimus-eluting stents,16 were associated with favorable arterial healing responses in patients with ST-segment elevation myocardial infarction or stable angina, but the healing process was still delayed in these patients. It is also notable that Mizoguchi et al. observed differences in the frequency of malapposed struts, neointimal unevenness score, and neointimal color grade between patients with ST-segment elevation myocardial infarction and patients with stable angina, indicative of differences in the healing process between these conditions.14

A multicenter registry by Gao et al. focused on the incidence and morphological predictors of intrastent coronary thrombus after DES implantation.15 They reported that the minimal lumen cross-sectional area was significantly smaller in the thrombus group than in the non-thrombus group, while thin-cap fibroatheroma and heterogeneous neointima were more common in the thrombus group. They also found that second-generation DES were associated with lower incidences of thrombus, uncovered struts, and extrastent lumen compared with first-generation DES.

Considering the role of platelets and their interactions with the epithelium in thrombosis formation, platelet reactivity (i.e., PRU) may be an important predictor of stent thrombosis in patients treated with P2Y12 inhibitors.16 The mean PRU was similar in patients with and without red thrombi in the prasugrel and clopidogrel groups in this study. Since the sample size is limited, we cannot clearly explain the reason for this lack of difference. In addition, in patients in whom PRU was measured at week 4 (prasugrel: n = 18, clopidogrel: n = 14), the proportion of patients with dyslipidemia and the mean LDL-C level, determined at baseline, were compared between the treatment groups, showing no differences. BMI was higher in the clopidogrel group, but BMI did not appear to have any effect on PRU. However, although the protocol of this study does not allow statistical comparisons of events and PRU between the prasugrel and clopidogrel groups, prasugrel is considered to produce a stable decrease in PRU in comparison with clopidogrel on the basis of the following result. In prasugrel-treated patients, the values in patients with and without red intrastent thrombus were 163.3 ± 59.67 (n = 4) and 184.9 ± 53.27 (n = 14). The corresponding values in clopidogrel-treated patients were 223.8 ± 66.62 (n = 5) and 217.8 ± 46.70 (n = 9). Therefore, sustained decreases in PRU are likely to contribute to a decrease in the incidence of red thrombi.

In the present study of Japanese patients undergoing elective PCI, the incidence of intrastent thrombus was highest just after stenting, even though an antiplatelet effect was clearly achieved, and a DES was used in almost all patients. The incidence of thrombus may appear higher than expected in this study. However, angioscopy differentiates thrombi based on color and allows the detection of microthrombus formation around the stent immediately after PCI. Since endoscopic data on thrombus formation immediately after PCI are limited, it may not be simply concluded that the incidence of red thrombus is higher in this study. Furthermore, the incidence of intrastent thrombus decreased over time, and intrastent thrombus formation is likely to be suppressed during chronic antiplatelet therapy. It is also intriguing to note that, in an observational study using optical coherence tomography, the authors reported a higher incidence of intrastent thrombus in asymptomatic patients with high platelet reactivity despite using clopidogrel.17 These results suggest that platelet reactivity may predict the risk of intrastent thrombus in some patients, but more studies are needed to examine this putative association and whether platelet reactivity or endothelial activity play predominant roles in the pathology of intrastent thrombus formation.

There are some limitations in this study. Clopidogrel was used as a reference drug, and we did not assess whether the differences between the two groups were statistically significant. Another limitation is the small sample size compared with the sample size of the main study. However, this was unavoidable, as angioscopy was only available at a small number of clinics with well-trained operators. Furthermore, the additional procedures were quite costly in terms of the time required and the interpretation of imaging at a central laboratory. We must also acknowledge that angioscopy could not be performed before and after PCI and during follow-up in all patients for several reasons. First and foremost, patient consent was required each time, and some patients did not consent to undergo the procedure repeatedly. Other reasons were that investigators did not wish to prolong the duration of PCI unnecessarily, and the angioscope and operator were not available when required.

**Conclusion**

We found that prasugrel was associated with low rates of red thrombus and revascularization after 24–36 weeks of dual-antiplatelet therapy after PCI. We also found that stent coverage and yellow plaque classification were similar between the prasugrel and clopidogrel groups. Larger studies, including patient registries, may be required to verify the present results.

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