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ORIGINAL ARTICLE
Coronary Intervention

Clinical Outcomes After Percutaneous Coronary Intervention in East Asian Patients

— 30-Month Results of the PENDULUM Registry —

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Background: The 12-month results of the PENDULUM registry showed that after implantation of second-generation drug-eluting stents (DES), high $P2Y_{12}$ reaction unit (HPR) were independently associated with ischemic but not bleeding events.

Methods and Results: This study analyzed cumulative incidences of major adverse cardiac and cerebrovascular events (MACCE) and major bleeding (Bleeding Academic Research Consortium type 3 and 5) at 30 months after index percutaneous coronary intervention (PCI) (primary endpoints). Of 6,422 patients undergoing PCI with DES, 5,796 completed the 30-month follow up. The continuation rate of dual antiplatelet therapy decreased to 59.3% at 12 months and 26.4% at 30 months. At 30 months, the cumulative incidence of MACCE increased linearly and reached 9.5% (95% confidence interval 8.8–10.2) and that of major bleeding had the inflection point at 12 months and was 4.4% (3.9–5.0). MACCE and bleeding events were higher in HPR patients (unadjusted P value). After covariate adjustment, $P2Y_{12}$ reactivity units measured immediately after index PCI was not an independent risk factor for MACCE or major bleeding at 30 months.

Conclusions: MACCE consistently increased after 12 months post-PCI, whereas the increase in major bleeding events slowed down after 12 months in Japanese PCI patients in a real-world clinical setting. HPR patients had increased MACCE and bleeding complications, but HPR was not an independent risk factor of events at 30 months.

Key Words: Dual antiplatelet therapy; Major adverse cardiovascular and cerebrovascular events; Major bleeding; Percutaneous coronary intervention; Platelet reactivity

The consensus on antiplatelet therapy after stenting for percutaneous coronary intervention (PCI) has changed dramatically over the past few years. With the advancement of drug-eluting stent (DES) technology and the implementation of the concept of risk management by optimal medical therapy,[1,2] the incidence of stent thrombosis after PCI has become extremely low, allowing

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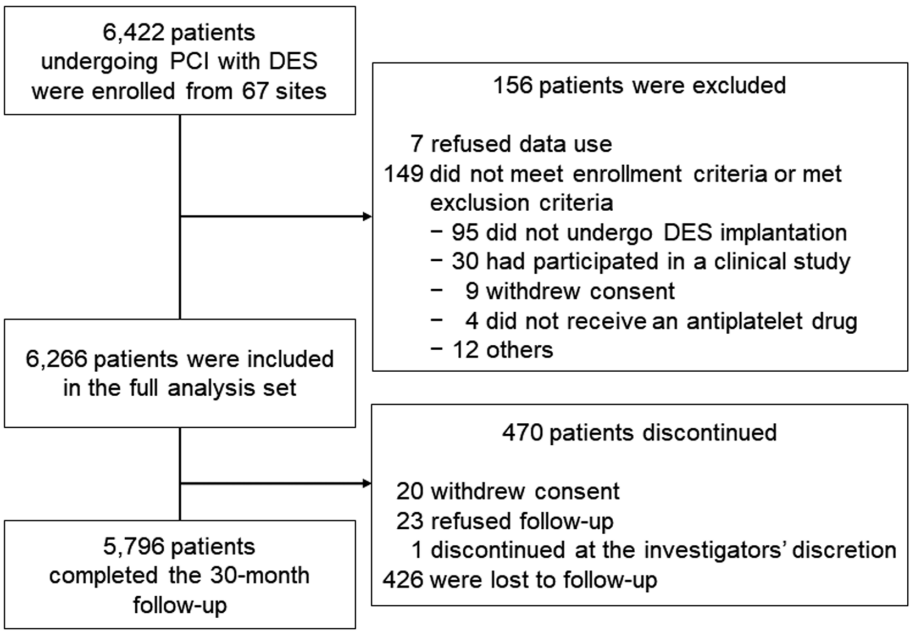

Figure 1. Study flowchart. DES, drug-eluting stent; PCI, percutaneous coronary intervention.

shorter durations of dual antiplatelet therapy (DAPT). However, real-world clinical practice includes high ischemic risk patients undergoing complex PCI and those at extremely high risk for atherosclerotic vascular disease. As these patients tend to be excluded from randomized trials, the DAPT period tends to be longer than that recommended in the guidelines due to concerns with thrombotic events, even though approximately half of the patients are supposed to be at high risk of bleeding.[3] Real-world data partly reflect treatment based on the concerns and preferences of treating physicians given the complex scenarios. A survey of the current situation will help determine the optimal DAPT period.

We conducted a large-scale registry study, the PENDULUM (Platelet rEactivity in patieNts with DrUg eLUting stent and balancing risk of bleeding and ischeMic event) registry,[4] between December 2015 and June 2017 in Japanese patients undergoing PCI. The PENDULUM registry enrolled 6,266 PCI patients from 67 sites across Japan. In clinical practice, 72% of patients underwent radial approach treatment, 94% underwent DES deployment with image guidance, and 84% were prescribed proton-pump inhibitors to improve the efficacy and safety of modern PCI. The PENDULUM registry suggested that measures of platelet aggregation ($P2Y_{12}$ reactive units [PRUs]) are associated with clinical outcomes such as stent thrombosis and serious adverse events (AEs) at 1 year.[4]

In this paper, we addressed the 30-month long-term follow up of the PENDULUM registry, analyzing the relationship between DAPT cessation and clinical events, and also evaluating the impact of high $P2Y_{12}$ reaction unit (HPR) at the time of PCI initiation on clinical outcomes to identify the optimal antiplatelet therapy. These findings may provide important information for determining antiplatelet strategies in clinical practice.

Methods

Study Design, Setting, and Participants

Details of the methods and study design of the prospective, multicenter PENDULUM registry have been published elsewhere.[4] This report focuses on the 30-month follow up and outcomes of patients enrolled in the PENDULUM registry.

The full inclusion and exclusion criteria have also been described previously.[4] Briefly, participants were Japanese patients aged ≥20 years who underwent PCI with second-generation DES and who were receiving antiplatelet drugs. To reduce potential bias, all patients who provided informed consent were registered consecutively.

Study Procedures

The treating physician selected the drug type, dosage, and duration of treatment according to the standard of care and based on the approved doses and indications of antiplatelet drugs in Japan. The approved dosage of aspirin is 100 mg once daily, which can be increased up to 300 mg once daily. For clopidogrel, the approved dosage is a 300-mg loading dose on the first day of treatment, followed by a maintenance dose of 75 mg once daily. The approved prasugrel dosage consists of a 20-mg loading dose, followed by a maintenance dose of 3.75 mg once daily. Treatment for complications was not limited and was prescribed according to the treating physician's judgment.

Outcomes were evaluated at enrollment and 1, 12, 24, and 30 months after PCI, with data for these evaluations being obtained from medical records. Patient follow up was conducted as part of routine clinical practice. In cases where the patient's medical records were incomplete, investigators attempted further data collection by either telephone calls, e-mails, or letters. Detailed data on drug

Table 1. Patient Background Characteristics

	Total (N=6,266)
Age (years)	70.0±10.7
≥75	2,325 (37.1)
Male sex	4,909 (78.3)
Body weight (kg)	64.0±12.6
≤50	794 (12.7)
Body mass index (kg/m^2)	24.2±3.6
PRU (n=5,907)	237.5±70.7
Non-HPR	3,678 (58.7)
HPR	2,229 (35.6)
Hypertension	5,188 (82.8)
Hyperlipidemia	4,926 (78.6)
Diabetes mellitus	2,771 (44.2)
Current cigarette smoking	1,327 (21.2)
Anemia	1,160 (18.5)
Heart failure	865 (13.8)
Peripheral arterial disease	438 (7.0)
AF	539 (8.6)
Malignancy	389 (6.2)
Previous MI	1,575 (25.1)
Previous PCI	2,566 (41.0)
Previous CABG	265 (4.2)
History of ischemic stroke	657 (10.5)
History of cerebral hemorrhage	124 (2.0)
History of renal insufficiency	1,114 (17.8)
Clinical presentation	
Non-ACS	4,251 (67.8)
ACS	2,015 (32.2)
Unstable angina	790 (12.6)
Non-STEMI	323 (5.2)
STEMI	908 (14.5)
Baseline laboratory parameters	
Hb (g/dL)	13.3±2.0
Creatinine clearance (mL/min)	68.2±35.5
White blood cell count (/μL)	6,944.2±2,815.6
Angiographic features	
No. of disease vessels	
1	3,165 (50.5)
2	1,864 (29.7)
3	1,151 (18.4)
Left main disease	349 (5.6)
LVEF (%)	56.7±12.9
Procedural data	
Puncture site	
Femoral access	1,631 (26.0)
Brachial access	269 (4.3)
Radial access	4,517 (72.1)
Imaging guided	5,918 (94.4)
PCI for chronic total occlusion	428 (6.8)
Second-generation DES	6,266 (100.0)
Medical status at discharge	
Aspirin	6,148 (98.1)
P2Y$_{12}$ inhibitor	6,209 (99.1)
Prasugrel	3,924 (62.6)
Clopidogrel	2,223 (35.5)
OAC	621 (9.9)
Proton pump inhibitor	5,302 (84.6)
NSAIDs	334 (5.3)
Steroids	249 (4.0)
Antihyperlipidemic agent	5,406 (86.3)
Modified ARC-HBR	
HBR patients	3,192 (50.9)

Data are presented as mean±standard deviation or n (%). ACS, acute coronary syndrome; AF, atrial fibrillation; ARC-HBR, Academic Research Consortium for High Bleeding Risk; CABG, coronary artery bypass; DES, drug-eluting stent; Hb, hemoglobin; HPR, high P2Y$_{12}$ reaction unit; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PRU, P2Y$_{12}$ reactivity units; STEMI, ST-elevation myocardial infarction.

(**Table 1** continued the next column.)

administration status and ischemic events, thrombotic events, bleeding events, and any other AE were collected at each time point. An independent assessment committee evaluated thrombotic and bleeding events.

Study Endpoints and Definitions

The primary endpoints were the cumulative incidences of major adverse cardiac and cerebrovascular events (MACCE) and major bleeding (Bleeding Academic Research Consortium [BARC] type 3 and 5) at 0–30 months after index PCI. The secondary endpoints were the cumulative incidences of each component of MACCE (i.e., all-cause death, non-fatal myocardial infarction, non-fatal stroke, and stent thrombosis) and major bleeding at 0–30 months after index PCI. Other secondary endpoints were the incidence of each component of MACCE, cardiovascular death, and bleeding events based on all categories of BARC criteria[5] and Thrombolysis in Myocardial Infarction criteria.[6] Additionally, the risks of the primary and secondary endpoints and time elapsed after PCI were assessed. The primary and secondary endpoints were also evaluated at 0–12 months and at 12–30 months after index PCI, as a landmark analysis. For the landmark analysis at 12–30 months, patients whose events occurred during the period from PCI to 12 months after PCI were treated as dropouts. As previously reported,[3] the definition of Academic Research Consortium for High Bleeding Risk (ARC-HBR) was partially modified based on the original ARC-HBR criteria.[7]

In addition, we explored outcomes in relation to PRU levels. These were measured 12–48 h after the first PCI, and used to divide patients into 2 groups, using a PRU cut-off value of 208, which is widely accepted as the gold standard (HPR: PRU >208).

Statistical Analysis

For baseline demographic and clinical characteristics, continuous variables are described using mean with standard deviation and categorical values using n (%). The proportion of patients who continued receiving DAPT

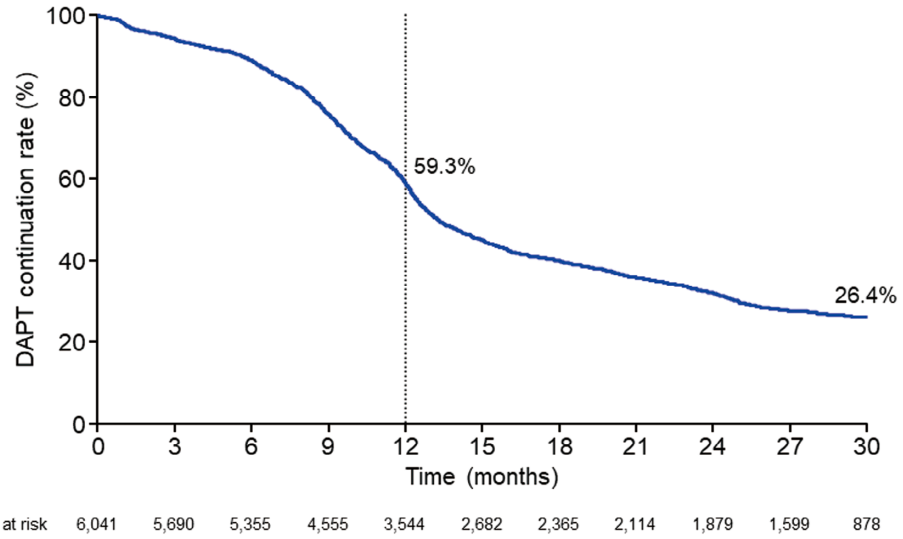

Figure 2. Proportion of patients who continued to receive dual antiplatelet therapy. Patients who were not treated with DAPT on the day of PCI were recorded as having 0 days of continuation. DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

during the 30-month follow up and the cumulative incidences of major bleeding and MACCE were evaluated by using the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) for endpoints were estimated with Cox proportional hazards models. The following clinically relevant factors were used for the adjustment of covariates: sex, age, body weight, hypertension, smoking, anemia, diabetes, acute coronary syndrome (ACS), platelet count, peripheral arterial disease (PAD), heart failure, malignant tumor, anticoagulant at discharge, gastrointestinal bleeding, chronic kidney disease (CKD), non-steroidal anti-inflammatory drug or steroid use at discharge, liver cirrhosis, history of cerebral infarction or intracranial hemorrhage and PRU levels at 12–48 h after index PCI were used for MACCE; and sex, age, body weight, diabetes, ACS, previous PCI, PAD, myocardial infarction, atrial fibrillation, history of cerebral infarction or intracranial hemorrhage, complex PCI, PRU levels at 12–48 h after index PCI, CKD, and anemia were used for major bleeding. The number of patients who discontinued either aspirin or $P2Y_{12}$ inhibitors were used to calculate the duration of DAPT continuation. Patients who restarted DAPT at a later time were excluded from the DAPT discontinuation analysis. All tests were 2-sided, with a level of significance of 5%. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical Approval

The study protocol was approved by the Ethics Committee at Toho University Ohashi Medical Center on 14 December 2015 (reference code: 15-71). The study conduct was in accordance with local laws and regulations and the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The trial was registered in the University hospital Medical Information Network (UMIN) Clinical Trial Registry under the identifier UMIN000020332.

Results

Patients

A total of 6,422 patients undergoing PCI with DES were enrolled (**Figure 1**). Overall, 156 patients were excluded, 6,266 patients were included in the full analysis set, and 5,796 patients completed the 30-month follow up.

Table 1 summarizes the main background characteristics of patients included in this study. Participants were elderly, with a mean age of 70.0±10.7 years, and 2,015 (32.2%) patients had ACS. A total of 5,918 (94.4%) patients were treated by an imaging-guided procedure (intravascular ultrasound or optical coherence tomography), complex PCI was conducted in 1,279 (20.4%) patients, and radial access was used in 4,517 (72.1%) patients. The proportion of patients who fulfilled the modified ARC-HBR criteria was 50.9%.

PRU was measured in 5,907 patients (94.3%); their mean PRU value was 237.5±70.7. According to their PRU status in relation to the cut-off value of 208, 3,678 (62.3%) were included in the non-HPR group and 2,229 (37.7%) were included in the HPR group. Patient background characteristics according to PRU status are shown in **Supplementary Table 1**.

Figure 2 shows the proportion of patients who continued receiving DAPT during the 30-month follow-up period by the Kaplan-Meier method (patients who were not treated with DAPT on the day of PCI were recorded as having 0 days of treatment continuation). Although DAPT was used in most patients immediately after PCI, the continuation rate of DAPT markedly decreased to 59.3% at 12 months. At 30 months, 26.4% of patients continued receiving DAPT.

Details of the treatment with antiplatelet drugs after PCI are shown in **Supplementary Table 2**. Aspirin was predominantly used as an antiplatelet monotherapy 30 months after PCI by 42.1% of patients in the non-HPR group and

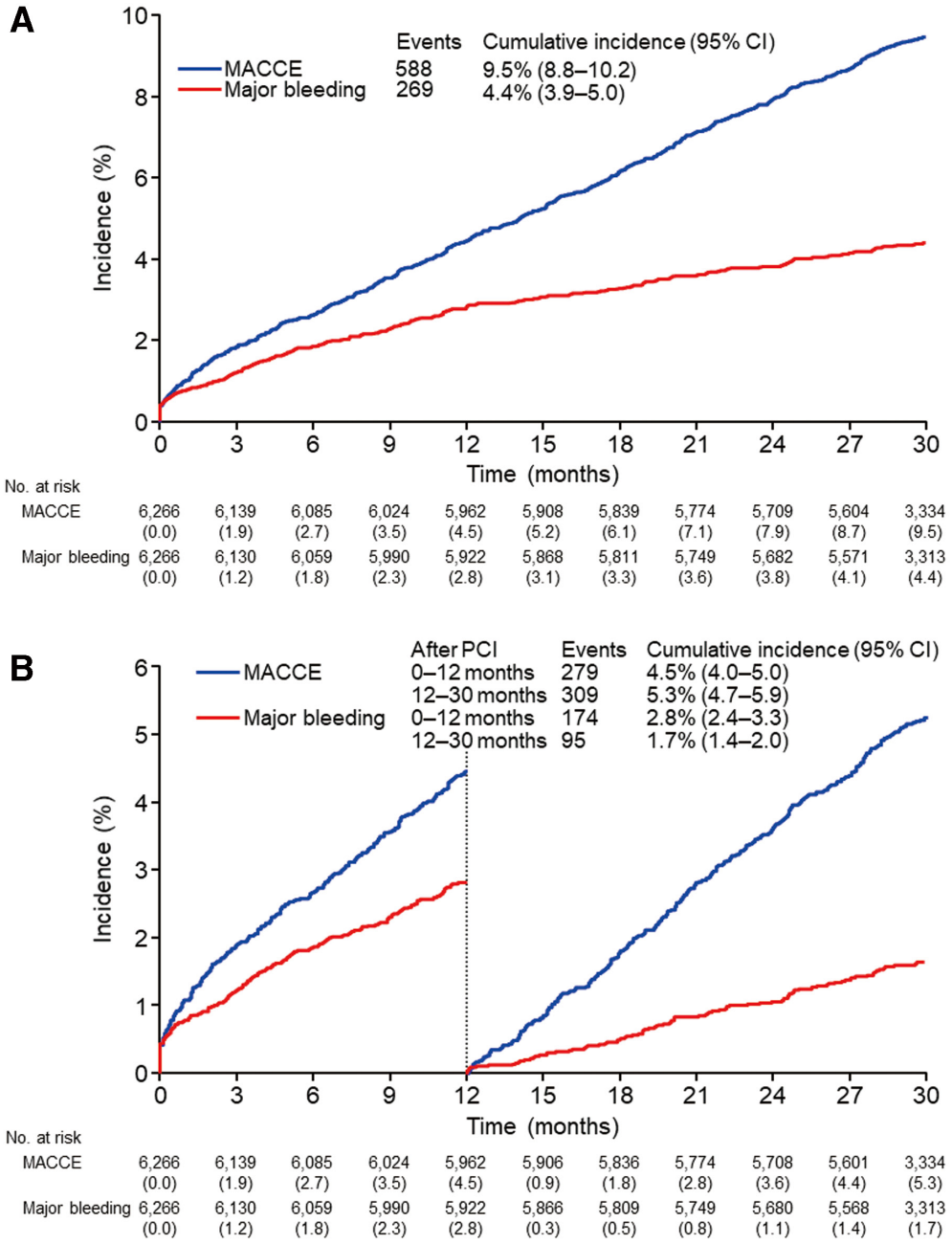

Figure 3. Cumulative incidences of MACCE and major bleeding events (**A**) at 30 months after PCI and (**B**) at 0–12 months and 12–30 months after PCI (landmark analysis). CI, confidence interval; MACCE, major adverse cardiovascular and cerebrovascular events; PCI, percutaneous coronary intervention.

36.7% in the HPR group.

Primary Endpoint

At 30 months after PCI, the cumulative incidence of MACCE was 9.5% (95% CI, 8.8–10.2), and that for major bleeding (i.e., BARC type 3 and 5) was 4.4% (95% CI, 3.9–5.0) (**Figure 3A**). Landmark analyses of MACCE and major bleeding at 0–12 months and 12–30 months are shown in **Figure 3B**. The cumulative incidence of MACCE was similar between the first year (4.5% at 0–12 months) and subsequent years (5.3% at 12–30 months). Major bleeding was observed more frequently in the first year after PCI. The cumulative incidence of major bleeding was 2.8% at 0–12 months and 1.7% at 12–30 months.

Secondary Endpoints

The estimated cumulative incidences of each component of MACCE and major bleeding from 0 to 30 months after PCI are shown in **Figure 4A** and **4B**. The cumulative incidence of all-cause death was 6.5% (95% CI, 5.9–7.2);

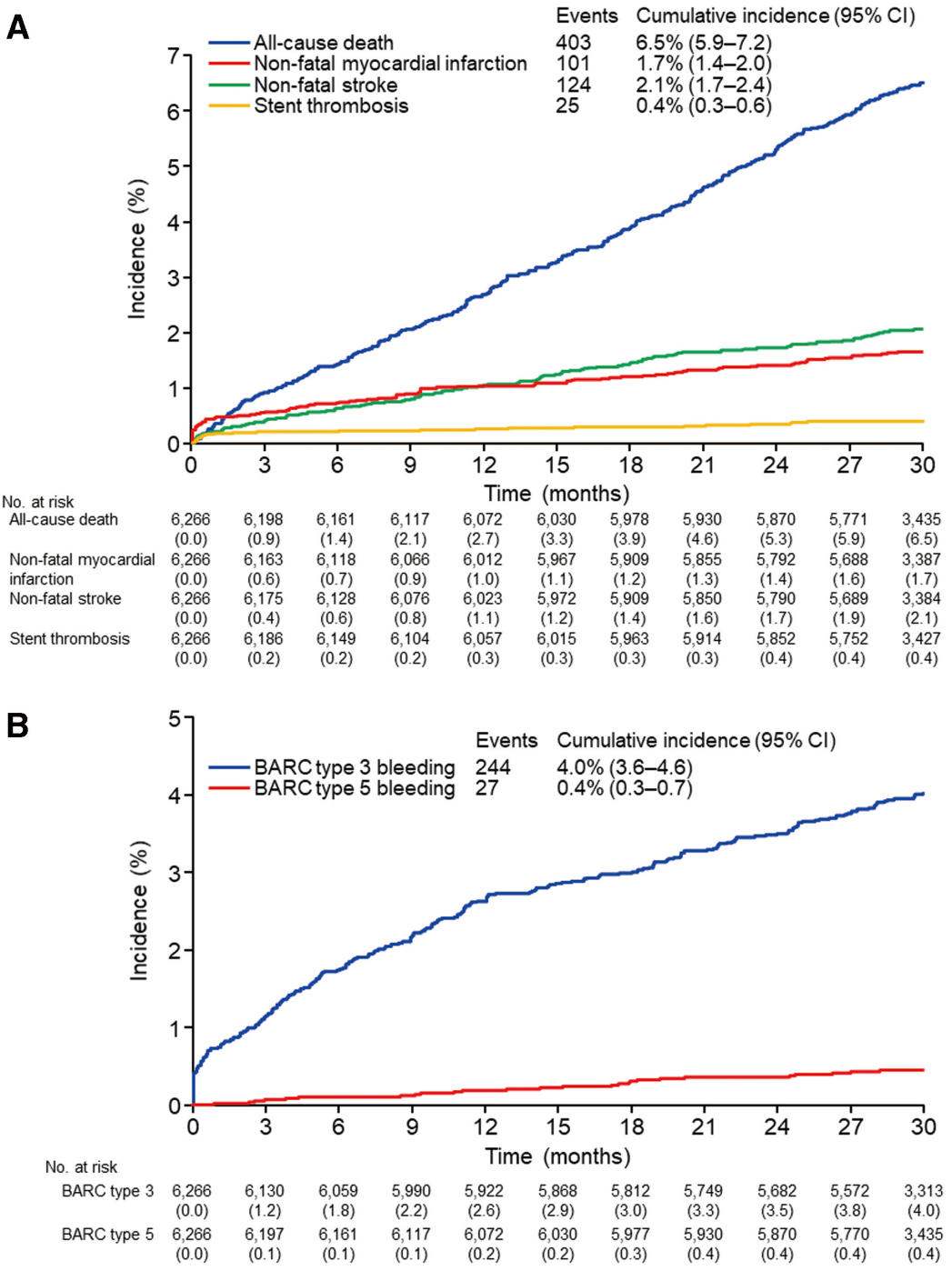

Figure 4. Cumulative incidences of each component of (**A**) MACCE and (**B**) major bleeding from 0 to 30 months after PCI. BARC, Bleeding Academic Research Consortium; CI, confidence interval; MACCE, major adverse cardiovascular and cerebrovascular events; PCI, percutaneous coronary intervention.

non-fatal myocardial infarction, 1.7% (95% CI, 1.4–2.0); non-fatal stroke, 2.1% (95% CI, 1.7–2.4), and stent thrombosis 0.4% (95% CI, 0.3–0.6). The cumulative incidence of BARC type 3 bleeding was 4.0% (95% CI, 3.6–4.6), and that of BARC type 5 bleeding was 0.4% (95% CI, 0.3–0.7). The event rates for MACCE and thrombotic events at 30 months after PCI are shown in **Supplementary Table 3**.

Primary and Secondary Endpoints Stratified by PRU Status

The cumulative incidences of MACCE and major bleeding at 30 months after PCI by PRU status are shown in

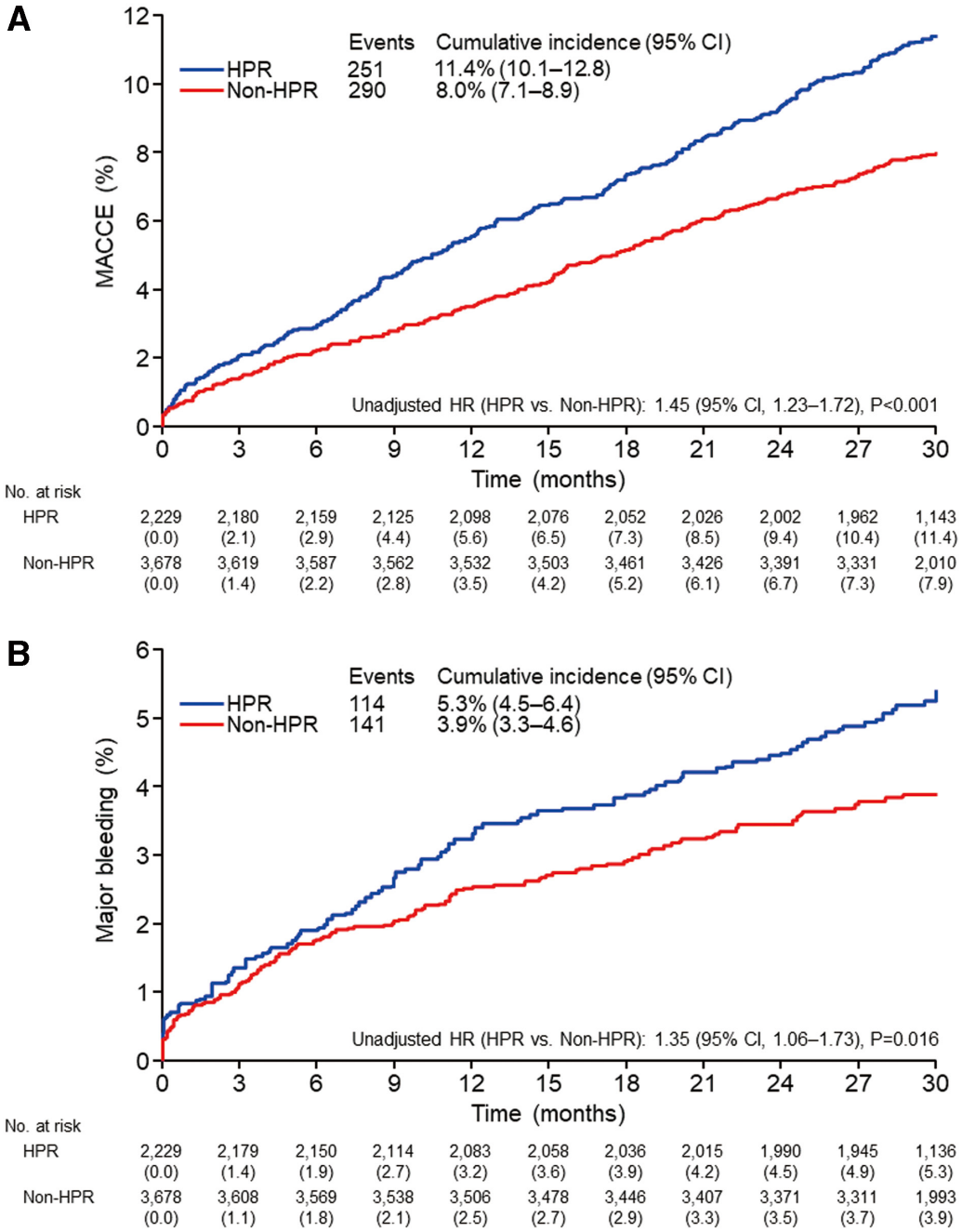

Figure 5. Cumulative incidences of (**A**) MACCE and (**B**) major bleeding events at 30 months after PCI by PRU status. CI, confidence interval; HPR, high $P2Y_{12}$ reaction unit; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular events; PCI, percutaneous coronary intervention; PRU, $P2Y_{12}$ reactivity unit.

Figure 5A and **5B**. The incidence of MACCE was significantly higher in the HPR group compared with the non-HPR group (11.4% vs. 8.0%; unadjusted HR, 1.45; 95% CI, 1.23–1.72; P<0.001). Compared with the non-HPR group, the incidence of major bleeding was also significantly higher in the HPR group (5.3% vs. 3.9%; unadjusted HR, 1.35; 95% CI, 1.06–1.73; P=0.016).

The cumulative incidences of each component of MACCE from 0 to 30 months after PCI by PRU status are shown in **Supplementary Figure A–D**.

Risk Factors for the Primary Endpoint

Multivariate Cox regression analyses of MACCE and major bleeding events are shown in **Tables 2** and **3**. Significant risk factors for MACCE at 0–30 months were male sex, age, body weight ≤50 kg, diabetes mellitus, ACS, PAD, history of cerebral infarction, CKD, and anemia. Body weight ≤50 kg, ACS, PAD, CKD, heart failure, malignancy,

Table 2. Multivariate Regression Analysis of MACCE From 1 to 30 Months After PCI

Variables	Events, n (%)	Multivariate HR (95% CI)	P value
Sex: male vs. female	461 (9.4) vs. 127 (9.4)	1.64 (1.27–2.11)	<0.001
Age: ≥75 vs. <75 years	294 (12.6) vs. 294 (7.5)	1.22 (1.00–1.48)	0.050
Weight: ≤50 vs. >50 kg	130 (16.4) vs. 443 (8.3)	1.94 (1.51–2.49)	<0.001
Diabetes: yes vs. no	324 (11.7) vs. 264 (7.6)	1.35 (1.12–1.63)	0.002
ACS: yes vs. no	203 (10.1) vs. 385 (9.1)	1.42 (1.17–1.73)	<0.001
Previous PCI: yes vs. no	264 (10.3) vs. 324 (8.8)	1.04 (0.84–1.29)	0.708
Peripheral artery disease: yes vs. no	94 (21.5) vs. 494 (8.5)	1.47 (1.13–1.92)	0.005
History of MI: yes vs. no	170 (10.8) vs. 413 (8.9)	1.17 (0.93–1.46)	0.19
History of AF: yes vs. no	71 (13.2) vs. 517 (9.0)	1.20 (0.90–1.59)	0.212
History of cerebral infarction or hemorrhage: yes vs. no	93 (15.0) vs. 465 (8.6)	1.49 (1.16–1.91)	0.002
Complex PCI: yes vs. no	128 (10.0) vs. 460 (9.2)	1.08 (0.87–1.34)	0.495
PRU value at 12–48 h after index PCI: >208 vs. ≤208	251 (11.3) vs. 290 (7.9)	1.06 (0.88–1.29)	0.536
CKD: eGFR <30 vs. ≥30 mL/min/1.73 m^2	161 (27.0) vs. 217 (6.3)	2.67 (2.04–3.50)	<0.001
Anemia: Hb <11 vs. ≥13 (male) / ≥12 g/dL (female)	154 (21.2) vs. 237 (6.0)	1.86 (1.41–2.45)	<0.001

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular events. Other abbreviations as in Table 1.

Table 3. Multivariate Regression Analysis of Major Bleeding From 1 to 30 Months After PCI

Variables	Events, n (%)	Multivariate HR (95% CI)	P value
Sex: male vs. female	208 (4.2) vs. 61 (4.5)	1.42 (0.96–2.09)	0.080
Age: ≥75 vs. <75 years	126 (5.4) vs. 143 (3.6)	0.83 (0.60–1.15)	0.251
Weight: ≤50 vs. >50 kg	62 (7.8) vs. 200 (3.8)	2.18 (1.47–3.22)	<0.001
Hypertension: yes vs. no	238 (4.6) vs. 31 (2.9)	1.20 (0.78–1.84)	0.416
Current smoking: yes vs. no	52 (3.1) vs. 183 (4.6)	0.74 (0.52–1.05)	0.093
Anemia: Hb <11 vs. ≥13 (male) / ≥12 g/dL (female)	71 (9.8) vs. 119 (3.0)	1.76 (1.15–2.69)	0.009
Diabetes: yes vs. no	116 (4.2) vs. 153 (4.4)	0.83 (0.61–1.11)	0.210
ACS: yes vs. no	88 (4.4) vs. 181 (4.3)	1.39 (1.03–1.89)	0.034
Platelet count: <10×10^4 vs. ≥10×10^4/μL	6 (7.6) vs. 251 (4.2)	1.46 (0.59–3.64)	0.414
Peripheral artery disease: yes vs. no	39 (8.9) vs. 230 (3.9)	1.76 (1.15–2.70)	0.009
Heart failure: yes vs. no	82 (9.5) vs. 187 (3.5)	1.79 (1.28–2.51)	<0.001
Malignant tumor: yes vs. no	27 (6.9) vs. 242 (4.1)	1.64 (1.02–2.64)	0.041
Anticoagulation at discharge: yes vs. no	65 (10.5) vs. 204 (3.6)	2.46 (1.75–3.47)	<0.001
History of GI bleeding: yes vs. no	15 (8.2) vs. 232 (4.0)	1.64 (0.90–2.96)	0.104
CKD: eGFR <30 vs. ≥30 mL/min/1.73 m^2	62 (10.4) vs. 98 (2.9)	1.95 (1.24–3.05)	0.004
NSAIDs or steroids at discharge: yes vs. no	3 (6.4) vs. 235 (4.1)	1.15 (0.71–1.85)	0.579
Liver cirrhosis: yes vs. no	2 (8.3) vs. 267 (4.3)	0.67 (0.09–5.01)	0.699
History of cerebral infarction or hemorrhage: yes vs. no	42 (5.7) vs. 210 (4.0)	1.03 (0.69–1.54)	0.875
PRU value at 12–48 h after index PCI: >208 vs. ≤208	114 (5.1) vs. 141 (3.8)	1.02 (0.76–1.38)	0.885

GI, gastrointestinal. Other abbreviations as in Tables 1,2.

anemia, and anticoagulation at discharge were found to be significant risk factors for major bleeding. We did not observe a significant relationship between PRU and MACCE or major bleeding.

Discussion

Herein, we report the 30-month outcomes of the PENDULUM registry, which is one of the largest registry studies to include East Asian patients in the modern era of PCI. To the best of our knowledge, this is the first report reflecting contemporary PCI practice, in which DAPT duration tends to be short after DES implantation. The main findings of the present study are as follows: (1) during the 30-month study period, MACCE increased constantly after 12 months, but the increase in major bleeding slowed down after 12 months; and (2) HPR was associated with both higher incidence of MACCE and bleeding events at 30 months. However, after adjustment, PRU measured immediately after index PCI was not an independent risk factor for MACCE or major bleeding at 30 months.

The 2018 Japanese guidelines in use during the follow-up period of the study recommended a DAPT period of 12 months for patients with ACS and 6 months for those with

stable coronary artery disease.[2] In addition, for patients with high bleeding risk (HBR), a much shorter DAPT period was recommended. In this study, the continuation rate of DAPT at 12 months was 59.3% and 26.4% at 30 months (median 385.0 days), and the majority of patients were treated with aspirin as single antiplatelet therapy (SAPT) at 30 months; therefore, it is likely that antiplatelet therapy was used for a longer period of time than that recommended by the guidelines. This preference for longer DAPT duration is consistent with that reported in a single-center study in which there was a 12-month DAPT continuation rate of 72.9% in 1,087 patients who were eligible but not-enrolled in STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2).[8] Both studies were conducted around the same period, which may suggest that DAPT duration tends to be longer in actual clinical practice. Although it is difficult to elucidate the exact reason, concerns and physician bias regarding antithrombotic events after PCI may tend to increase the length of DAPT in clinical practice.

In the present study, MACCE continued to increase at a consistent rate, even at >12 months after PCI. Conversely, the occurrence of major bleeding had a more gradual onset >12 months after PCI. This is in contrast to the 24-month follow-up results of the ADAPT-DES (Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents) study. In the ADAPT-DES study, the Kaplan-Meier curve for ischemic events gradually flattened, and the Kaplan-Meier curve for hemorrhagic events monotonically increased.[9] The predominant difference between our study and ADAPT-DES is the DAPT duration. The DAPT continuation rate at 12 months in the PENDULUM registry was ~20% lower than the 12-month DAPT continuation rate in ADAPT-DES (80.8%),[10] and the number of patients continuing DAPT decreased sharply after 12 months in the PENDULUM registry (26.4% in the PENDULUM registry at 30 months). In contrast, in the ADAPT-DES study, the DAPT continuation rate was >50% at 24 months, which is similar to the 12-month DAPT continuation rate of the PENDULUM registry. Indeed, the Kaplan-Meier curve for major bleeding had the inflection point at 12 months. However, we can speculate that ischemic events may not decrease because of the high DAPT discontinuation rate. Thus, one potential reason for the monotonic increase in ischemic events and decrease in bleeding events in this study may be the shortening of the DAPT period. Furthermore, this increase in events may also suggest the importance of using the antiplatelet agent of choice as a single agent. Indeed, the recent HOST-EXAM (Harmonizing Optimal Strategy for Treatment of coronary artery diseases-EXtended Antiplatelet Monotherapy) study clearly demonstrated that $P2Y_{12}$ inhibitors are more clinically useful than aspirin in patients when given >12 months after PCI.[11] It is possible that the use of aspirin monotherapy in the present study may have been related to event rates after 12 months. Taken together, it may be possible that bleeding events did not increase with the discontinuation of DAPT, but that MACCE attributable to patient background increased linearly. These data suggest that there is still room to improve cardiovascular death rates and the ischemic event rate, and may provide important information regarding the causal effect of DAPT cessation in a real-world setting.

We previously reported that the incidence of MACCE up to 12 months after PCI was associated with HPR immediately after PCI.[4] Conversely, in this study, although unadjusted analysis showed a significant relationship between MACCE at 30 months after PCI and HPR immediately after PCI, HPR was not found to be a significant independent risk factor for MACCE. It is clear that PRU immediately after PCI does not reflect the PRU after $P2Y_{12}$ inhibitor discontinuation or at the long-term follow-up period. Thus, it is reasonable to assume that PRU and MACCE were not associated because inhibitors were no longer administered; however, it is noteworthy that the dissociation of MACCE rates between HPR and non-HPR patients continued to increase after the rapid discontinuation of DAPT at 12 months. It may be reasonable to assume that the PRU values immediately after PCI reflect 2 different clinical implications. One is platelet reactivity, which could be directly related to the development of stent thrombosis, myocardial infarction, and outcomes of ACSs, especially in the early period after PCI. The other is a phenotype representing a high-risk subset of events, especially in the late phase after PCI. In fact, patients with HPR had a high rate of diabetes mellitus, anemia, renal failure, heart failure, PAD, and a history of revascularization (**Supplementary Table 1**). These patient background characteristics suggest a high risk for both ischemic and bleeding events. The ABCD-gene score has been reported as a predictor of HPR in Japanese patients undergoing PCI.[12] The ABCD-gene score factors of older age, weight, CKD, and diabetes mellitus were consistent with the patient demographics of the HPR group in the present study. Thus, it is reasonable to consider that HPR was associated with a higher MACCE rate and all-cause death. Similarly, the finding that HPR patients have more bleeding events than non-HPR patients can be explained by differences in the background of HPR patients. Patient characteristics that are independent risk factors for bleeding and ARC-HBR were more frequent among patients with HPR. In other words, HPR is a patient background characteristic that reflects HBR and translated to long-term bleeding events. Although this is contrary to the results of the ADAPT-DES study, which showed higher bleeding in non-HPR patients,[9] this may be related to the higher number of HBR cases among the patients with HPR in our study. These observations suggest the clinical importance and difficulty of antiplatelet therapy in patients with HPR who have a combined risk of bleeding and ischemia.

Components of MACCE

In the present long-term follow-up study, there was no association between adjusted HPR and all-cause death, myocardial infarction, or stroke, and the only association with PRU was stent thrombosis. In the ADAPT-DES study, myocardial infarction was associated with HPR, even with long-term observation,[9,10] but the main cause was stent thrombosis-related myocardial infarction. In this study, it is speculated that the low frequency of stent thrombosis events weakened the association between myocardial infarction and PRU.

Study Limitations

This study has several limitations. This was a prospective registry study with no mandated interventions and no prespecified treatment comparisons, so no causal relationships can be inferred. PRU was measured just once during the 12–48 h immediately after PCI, and the possibility of

measurement errors cannot be discounted. During the observation period, antiplatelet therapy changes were allowed at the physician's discretion, which may have affected both the outcome results and the duration of DAPT continuation. The study was conducted with Japanese patients only, which limits the generalizability of the findings. Finally, this study was initiated when aspirin was the primarily used antiplatelet monotherapy; therefore, aspirin was the most used antiplatelet monotherapy in our study. However, this is in contrast with the findings of the STOPDAPT-2 and HOST-EXAM studies, as well as the revised Japanese treatment guidelines (revised in 2020), which recommend $P2Y_{12}$ inhibitors over aspirin as antiplatelet monotherapy after discontinuing DAPT.[11,13,14]

Conclusions

Our results showed that MACCE consistently increased after 12 months post-PCI, whereas the increase in major bleeding events slowed down after 12 months in East Asian patients who underwent PCI in a real-world clinical setting. Stent thrombosis was the only event associated with HPR, and patients with HPR had a higher incidence of both ischemic and bleeding events. This suggests that HPR is a marker of both ischemic and bleeding events in the late phase after PCI as well as platelet function in the early phase.

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Disclosures

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Author Contributions

All authors provided substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; participated in drafting the work or revising it critically for important intellectual content; provided final approval of the version to be published; and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability

The deidentified participant data and related study documents will be shared on request for up to 36 months after the publication of this article. Requests should be made to the corresponding author and the requestor should include a methodologically sound proposal on how the data will be used; the proposal may be reviewed by the responsible personnel at Daiichi Sankyo Co., Ltd., and the data requestor will need to sign a data access agreement. Once approved, the data will be shared in an appropriate way depending on the type of data requested.

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Supplementary Files

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