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ORIGINAL ARTICLE
Coronary Intervention

Early P2Y12 Inhibitor Single Antiplatelet Therapy for High-Bleeding Risk Patients After Stenting
— PENDULUM Mono 24-Month Analysis —

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Background: In PENDULUM mono, Japanese patients with high bleeding risk (HBR) received short-term dual antiplatelet therapy (DAPT) followed by single antiplatelet therapy (SAPT) with prasugrel after percutaneous coronary intervention (PCI). One-year data from PENDULUM mono showed better outcomes with prasugrel monotherapy after short-term DAPT compared with matched patients in the PENDULUM registry with longer DAPT durations according to guidelines at that time. This study presents 2-year results.

Methods and Results: We compared 24-month data from PENDULUM mono (n=1,107; de-escalation strategy group) and the PENDULUM registry (n=2,273; conventional strategy group); both were multicenter, non-interventional, prospective registry studies, using the inverse probability of treatment weighting (IPTW) method. In the PENDULUM mono group, the cumulative incidence of clinically relevant bleeding (CRB) at 24 months post-PCI (primary endpoint) was 6.8%, and that of major adverse cardiac and cerebrovascular events (MACCE) was 8.9%. After IPTW adjustment, the cumulative incidence of CRB was 5.8% and 7.2% in PENDULUM mono and the PENDULUM registry, respectively (hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.57–1.04; P=0.086), and that of MACCE was 8.0% and 9.5%, respectively (HR 0.77; 95% CI 0.59–1.01; P=0.061).

Conclusions: Japanese PCI patients with HBR prescribed prasugrel SAPT after short-term DAPT had a lower ischemic event risk than those prescribed long-term DAPT, and this was particularly relevant for ischemic events after 1 year.

Key Words: Bleeding risk; Japan; Percutaneous coronary intervention; Prasugrel; Single antiplatelet therapy

Dual antiplatelet therapy (DAPT) is known to prevent stent thrombosis and ischemic events after percutaneous coronary intervention (PCI).[1,2] However, prolonged DAPT increases the risk of bleeding events and death due to bleeding.[3,4] Therefore, according to risk-based stratification, it is reasonable to conduct a predictive assessment of bleeding and thrombotic risk in

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individual patients and select the most appropriate antithrombotic therapy, including DAPT duration.

The Japanese Circulation Society 2020 guidelines recommend short-term DAPT followed by single antiplatelet therapy (SAPT) with a P2Y12 inhibitor, such as prasugrel, for PCI patients with high bleeding risk (HBR).[5] The safety and efficacy of monotherapy with a P2Y12 inhibitor after further shortening of DAPT were evaluated in previous trials and showed favorable results.[6,7] However, these findings are based on clinical trial data rather than real-world data.

Of note, East Asians, including Japanese patients, are believed to have a higher risk of bleeding and a lower risk of ischemia than non-East Asians.[8–11] Whether these outcomes driven by randomized controlled trials hold true even in real-world settings is of particular interest because patients with a high risk of bleeding or ischemia are generally excluded from trials.

The PENDULUM mono study was a prospective non-interventional cohort study that evaluated bleeding and cardiovascular events associated with prasugrel SAPT after short-term DAPT in Japanese HBR patients following PCI. The comparison of 12-month outcomes in matched patients from PENDULUM mono and the PENDULUM registry showed that most patients in the PENDULUM registry treated with conventional therapy received DAPT, and most patients in PENDULUM mono undergoing de-escalation treatment received short-term DAPT followed by prasugrel SAPT until 12 months post-PCI.[12] The PENDULUM mono study found that the de-escalation treatment reduced bleeding events without increasing ischemic events.[13] Therefore, the benefits of prasugrel monotherapy after short-term DAPT in this patient population in a real-world setting were similar to those shown in previous clinical trials.[6,7] However, whether this benefit is maintained over a longer period in actual clinical practice is worth investigating. Because the risk of ischemic and hemorrhagic events tends to decrease over time, a longer follow-up is needed to determine the optimal antithrombotic therapy for patients with HBR.

Therefore, we present the latest results from PENDULUM mono (24-month results) in which Japanese HBR patients received short-term DAPT followed by SAPT with a P2Y12 inhibitor after PCI. We also compare these results with the 24-month data from the PENDULUM registry[14] to examine the effects of these treatment strategies on the long-term prognosis of PCI patients with HBR receiving a conventional antithrombotic therapy at that time.

Methods

Study Design

The present study compared 24-month data from PENDULUM mono and the PENDULUM registry (historical control), both of which were multicenter, non-interventional, prospective registry studies.[13,14] In PENDULUM mono, patients were registered from July 2017 to December 2018, whereas in the PENDULUM registry patients were registered from December 2015 to June 2017. The research period for the present study was from July 2017 to December 2020, and the follow-up period was 24 months. In the present report, we compare data from patients who received short-term DAPT followed by SAPT with prasugrel (cohort from PENDULUM mono; referred to as the de-escalation strategy group) to data from patients who received a conventional DAPT duration (cohort from PENDULUM registry used as the historical control/conventional strategy group) after PCI. Both studies were conducted before the Academic Research Consortium for High Bleeding Risk (ARC-HBR) report was published.

For the duration of the PENDULUM mono study, patients who were judged unable to continue prasugrel monotherapy were allowed to change to other antiplatelet treatments at the discretion of the attending physician. All clinical cases were collected by electronic data capture, and the events were assessed by independent event evaluation committees.

The study protocols of both registry studies were approved by the institutional review board or independent ethics committee at each participating center. Both studies were performed in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines.[15] Both PENDULUM mono and the PENDULUM registry were registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (IDs UMIN000028023 and UMIN000020332, respectively). All patients provided written informed consent before participation. To reduce potential bias, all patients who provided informed consent were registered consecutively.

Patients

The inclusion and exclusion criteria for PENDULUM mono and the PENDULUM registry have been published previously.[13,14] Briefly, PENDULUM mono included PCI patients who were not considered appropriate candidates for long-term DAPT with aspirin due to their HBR status, whereas the PENDULUM registry was an all-comers PCI registry.

To compare data from PENDULUM mono to those of the PENDULUM registry, patients enrolled in the PENDULUM registry who fulfilled the criteria for PENDULUM mono and received prasugrel within 1 day after PCI were used as historical controls. The inclusion and exclusion criteria for PENDULUM mono are provided in the **Supplementary Text**.

Outcomes

The primary safety endpoint was the cumulative incidence of clinically relevant bleeding (CRB), defined as Bleeding Academic Research Consortium (BARC) Types 2, 3, and 5, at 24 months after PCI and the efficacy endpoint was major adverse cardiac and cerebrovascular events (MACCE), defined as all cause death, non-fatal myocardial infarction (MI), non-fatal stroke, and stent thrombosis. Secondary endpoints were as follows: (1) the cumulative incidence of major bleeding (BARC Types 3 and 5), MACCE, and net adverse clinical and cerebral events; (2) the proportion of patients with each bleeding event (each BARC criterion and Thrombolysis in Myocardial Infarction major/minor bleeding criteria); and (3) the proportion of patients with cardiovascular events (all-cause death, cardiovascular death, non-fatal MI, non-fatal stroke, non-fatal cerebral infarction, and stent thrombosis) at 24 months after PCI. In the present study, the evaluation time points were at discharge, at the start of prasugrel SAPT, and at 1, 12, and 24 months after PCI.

Statistical Analysis

The sample size calculation has been reported previously.[13] The inverse probability of treatment weighting (IPTW) method was used to compare the 24-month data from

Table 1. Patient Characteristics

	De-escalation strategy group (n=1,107)	Conventional strategy group (n=2,273)	After IPTW, SMD
Age (years)	76.4±8.6	73.3±9.5	0.053
≥75 years	762 (68.8)	1,169 (51.4)	0.002
Male sex	778 (70.3)	1,644 (72.3)	−0.021
Body weight (kg)	60.0±11.5	61.2±12.4	−0.015
≤50 kg	234 (21.1)	448 (19.7)	−0.007
Body mass index (kg/m^2)	23.57±3.58	23.63±3.56	0.031
Hypertension	933 (84.3)	1,897 (83.5)	0.015
Hyperlipidemia	826 (74.6)	1,688 (74.3)	0.013
Diabetes	440 (39.7)	972 (42.8)	−0.003
Current smoker	163 (14.7)	406 (17.9)	0.039
Heart failure	169 (15.3)	346 (15.2)	−0.064
Peripheral artery disease	54 (4.9)	138 (6.1)	−0.009
Atrial fibrillation	189 (17.1)	222 (9.8)	0.029
Malignancy	81 (7.3)	173 (7.6)	−0.048
History of MI	189 (17.1)	519 (22.8)	−0.161
History of PCI	412 (37.2)	806 (35.5)	0.023
History of CABG	32 (2.9)	103 (4.5)	−0.106
History of ischemic stroke	105 (9.5)	208 (9.2)	−0.037
History of TIA	16 (1.4)	28 (1.2)	−0.008
History of cerebral hemorrhage	31 (2.8)	58 (2.6)	0.032
History of GI bleeding	71 (6.4)	81 (3.6)	−0.001
ARC-HBR	928 (83.8)	1,746 (76.8)	0.005
Non-ACS	749 (67.7)	1,389 (61.1)	−0.002
ACS	358 (32.3)	884 (38.9)	0.002
Unstable angina	127 (11.5)	317 (13.9)	0.005
Non-STEMI	85 (7.7)	161 (7.1)	0.060
STEMI	146 (13.2)	407 (17.9)	−0.047
Medication at discharge			
Prasugrel	1,103 (99.6)	2,203 (96.9)	0.226
As single antiplatelet therapy	63 (5.7)	5 (0.2)	0.262
Clopidogrel	0 (0.0)	51 (2.2)	−0.227
As single antiplatelet therapy	0 (0.0)	4 (0.2)	−0.061
Aspirin	1,041 (94.0)	2,249 (98.9)	−0.202
As single antiplatelet therapy	1 (0.1)	3 (0.1)	−0.029
Anticoagulant	243 (22.0)	274 (12.1)	0.001
DOAC	192 (17.3)	168 (7.4)	0.085
Warfarin	51 (4.6)	106 (4.7)	−0.123
Proton pump inhibitor	977 (88.3)	1,960 (86.2)	0.062
NSAIDs except aspirin	72 (6.5)	160 (7.0)	0.027
Steroids	39 (3.5)	106 (4.7)	−0.038
Medication at 24 months after PCI (Days 600–720)			
Prasugrel	818 (78.8)	860 (40.3)	0.909
As single antiplatelet therapy	752 (72.4)	148 (6.9)	1.827
Clopidogrel	30 (2.9)	173 (8.1)	−0.242
As single antiplatelet therapy	26 (2.5)	104 (4.9)	−0.153
Aspirin	141 (13.6)	1,714 (80.3)	−1.716
As single antiplatelet therapy	71 (6.8)	933 (43.7)	−0.935
Anticoagulants	199 (19.2)	258 (12.1)	−0.015

Unless stated otherwise, data are presented as the mean±SD or n (%). ACS, acute coronary syndrome; ARC-HBR, Academic Research Consortium for High Bleeding Risk; CABG, coronary artery bypass grafting; DOAC, direct oral anticoagulant; GI, gastrointestinal; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; SMD, standardized mean difference; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack.

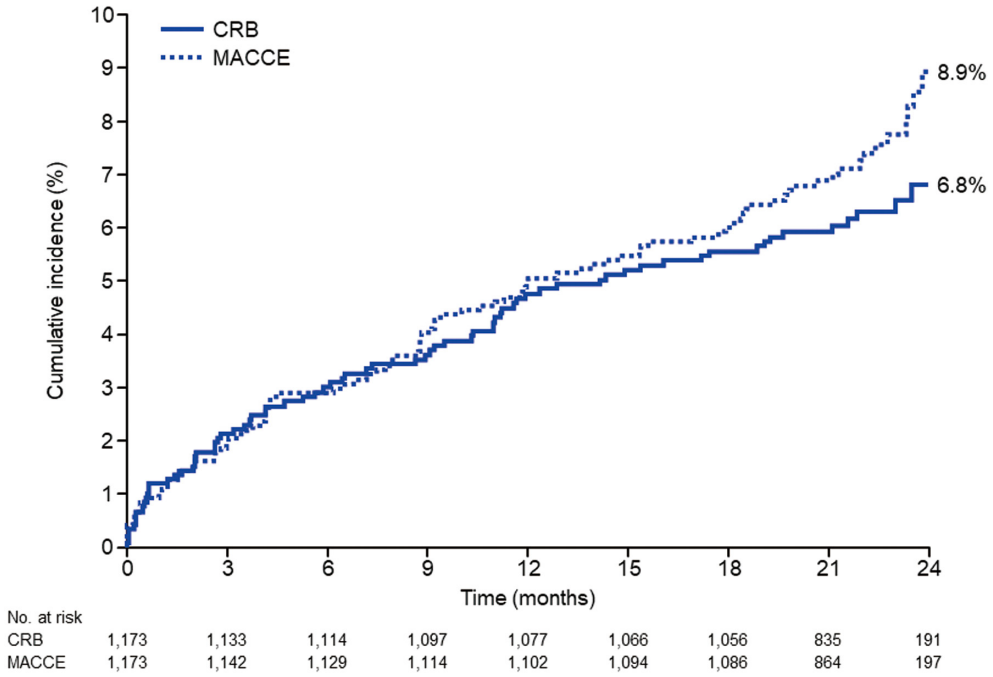

Figure 1. Cumulative incidence of clinically relevant bleeding (CRB) and major adverse cardiac and cerebrovascular events (MACCE).

PENDULUM mono and PENDULUM registry. Details of the IPTW method used have also been reported previously.[12]

For time-to-event outcomes, the Kaplan-Meier method was used to calculate the cumulative incidences and 95% confidence intervals (CIs) at 24 months. The Cox regression model was used to calculate hazard ratios (HRs) and 95% CIs, and univariate analysis was used to identify variables for the multivariate analysis. The duration of DAPT continuation was calculated using patients who discontinued either aspirin or $P2Y_{12}$ inhibitor. If these patients restarted DAPT at a later time, they were excluded from the analysis of DAPT continuation. The administration rates were calculated as the proportion of actual prescriptions with the total number of patients at baseline as the denominator. In addition, the end of treatment was defined as the last observation of treatment. A histogram was made for categorical variables, and summary statistics were used for continuous variables. Two-sided $P<0.05$ was considered statistically significant. All statistical analyses were performed using SAS Release 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

Of the 1,222 patients enrolled in PENDULUM mono, 49 were excluded, resulting in 1,173 patients being evaluated. Of those patients, 1,124 (95.8%) underwent a 24-month evaluation. The mean±SD duration of follow-up was 21.6±3.9 months. Of the 1,173 patients evaluated, a comparison with the historical control was made in 1,107 patients for whom a propensity score could be calculated.

Of the 6,267 patients enrolled in PENDULUM registry, 2,539 met the criteria for PENDULUM mono and received prasugrel within 1 day after PCI (historical cohort). Of the 2,539 patients included in the historical cohort, propensity scores were calculated in 2,273 patients, and these were compared with the patients from PENDULUM mono.

Patient demographic and clinical characteristics are summarized in **Table 1**. Patient background characteristics between the de-escalation and conventional strategy groups differed significantly. Therefore, the prespecified bleeding and ischemic risk factors of age, low body weight, severe chronic kidney disease, anemia, use of anticoagulants at discharge, diabetes, acute coronary syndrome (ACS), low platelet count, peripheral artery disease, history of gastrointestinal bleeding, the use of non-steroidal anti-inflammatory drugs or steroids at discharge, a history of stroke, and complex PCI were adjusted for by the IPTW method.

After adjustment by the IPTW method, more radial approaches and dyslipidemia medications at discharge were used in the de-escalation strategy group. Previous coronary artery bypass graft, previous MI, and 3-vessel disease were more common in the conventional compared with de-escalation strategy group. Low-density lipoprotein cholesterol levels and white blood cell counts were higher in the conventional than de-escalation strategy group. In the de-escalation strategy group (n=1,038), the administration rate of SAPT at 24 months (Days 600–720) was 81.8% (prasugrel, 72.4%; clopidogrel, 2.5%; aspirin, 6.8%) and that of DAPT was 6.7%; in the conventional strategy group (n=2,134), the administration rate of SAPT at 24 months was 55.5% (prasugrel, 6.9%; clopidogrel, 4.9%; aspirin, 43.7%)

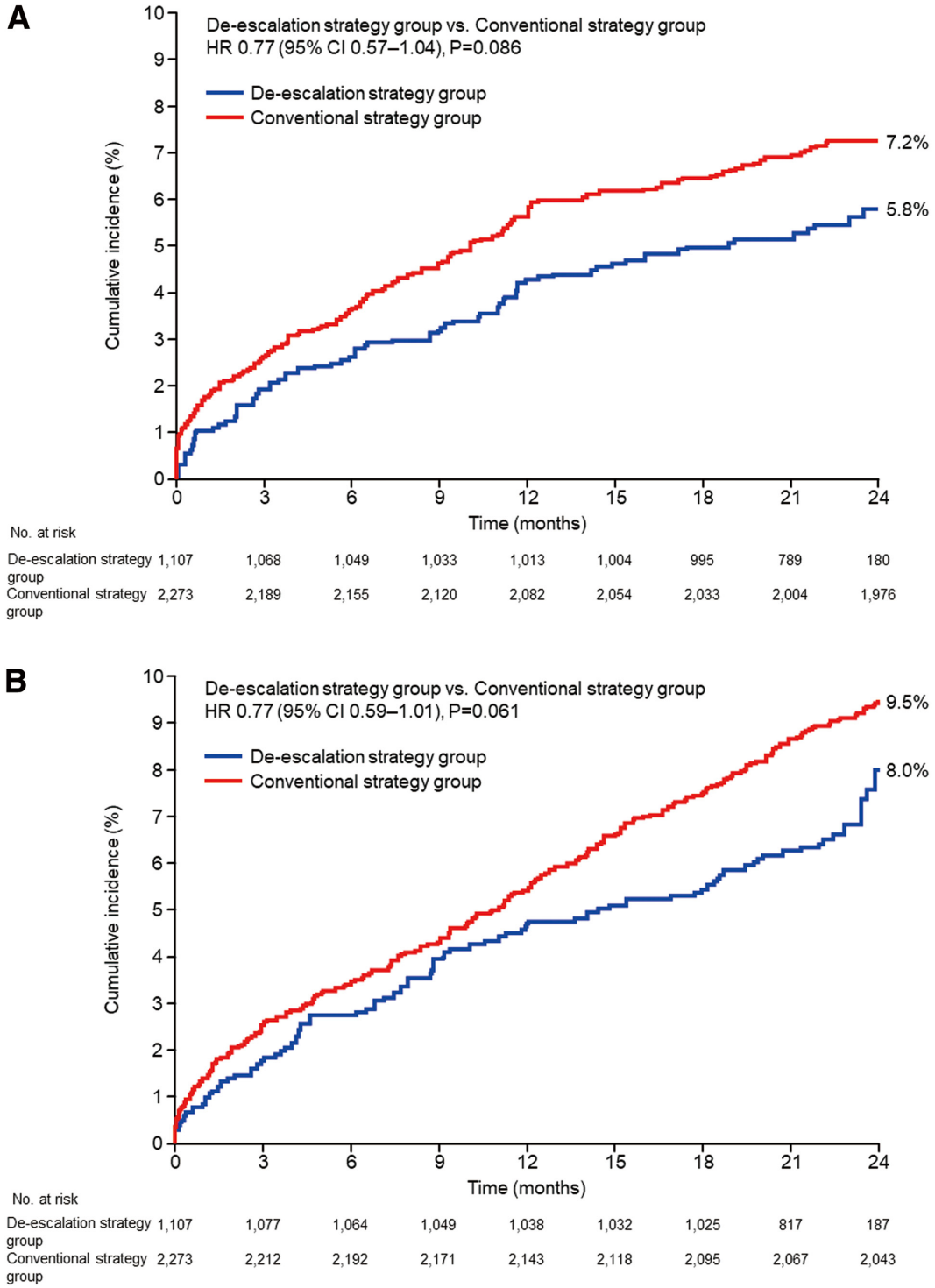

Figure 2. Cumulative incidence of (**A**) clinically relevant bleeding and (**B**) major adverse cardiac and cerebrovascular events adjusted using the inverse probability of treatment weighting method. CI, confidence interval; HR, hazard ratio.

and that of DAPT was 36.6% (**Supplementary Figure**). Among the patients who were followed up at 24 months, the median duration of DAPT continuation was 113.0 days in the de-escalation strategy group and 371.0 days in the conventional strategy group.

Outcomes

Among the 1,173 patients in the de-escalation strategy group, the cumulative incidence of CRB at 24 months after PCI was 6.8%, and that of MACCE was 8.9% (**Figure 1**).

After adjustment by the IPTW method, the adjusted

Table 2. Composite Endpoints at 24 Months

	De-escalation strategy group (n=1,107)	Conventional strategy group (n=2,273)	After IPTW	
			HR (95% CI)	P value
CRB (BARC Types 2, 3, and 5)	69 (6.2)	149 (6.6)	0.767 (0.567–1.038)	0.086
All bleeding events	126 (11.4)	226 (9.9)	0.980 (0.778–1.236)	0.867
BARC Type 1	69 (6.2)	89 (3.9)	1.451 (1.040–2.023)	0.028
BARC Type 2	23 (2.1)	57 (2.5)	0.642 (0.385–1.072)	0.090
BARC Type 3	47 (4.2)	94 (4.1)	0.843 (0.581–1.223)	0.369
BARC Type 4	0 (0.0)	0 (0.0)	–	
BARC Type 5	4 (0.4)	9 (0.4)	0.632 (0.189–2.113)	0.456
TIMI major bleeding	32 (2.9)	62 (2.7)	0.848 (0.540–1.332)	0.475
TIMI minor bleeding	15 (1.4)	32 (1.4)	0.715 (0.373–1.372)	0.314
CV events	182 (16.4)	429 (18.9)	0.906 (0.754–1.090)	0.295
All-cause death	59 (5.3)	157 (6.9)	0.726 (0.523–1.008)	0.056
CV death	28 (2.5)	86 (3.8)	0.652 (0.407–1.042)	0.074
Non-fatal MI	12 (1.1)	30 (1.3)	0.881 (0.436–1.779)	0.724
Non-fatal stroke	20 (1.8)	44 (1.9)	0.869 (0.504–1.501)	0.615
Non-fatal cerebral infarction	14 (1.3)	32 (1.4)	0.889 (0.464–1.704)	0.723
Stent thrombosis	1 (0.1)	5 (0.2)	0.672 (0.078–5.750)	0.716
Major bleeding (BARC Types 3 and 5)	51 (4.6)	102 (4.5)	0.831 (0.582–1.187)	0.308
MACCE	85 (7.7)	215 (9.5)	0.773 (0.591–1.012)	0.061
NACCE	123 (11.1)	286 (12.6)	0.801 (0.639–1.004)	0.055

BARC, Bleeding Academic Research Consortium; CI, confidence interval; CRB, clinically relevant bleeding; CV, cardiovascular; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NACCE, net adverse clinical and cerebral events; TIMI, Thrombolysis in Myocardial Infarction.

cumulative incidence of CRB and MACCE at 24 months after PCI was numerically lower (but not significantly) in the de-escalation than conventional strategy group (CRB incidence, 5.8% and 7.2%, respectively [HR 0.77; 95% CI 0.57–1.04; P=0.086]; and MACCE incidence, 8.0% and 9.5%, respectively [HR 0.77; 95% CI 0.59–1.01; P=0.061]; **Figure 2**).

The results of all composite endpoints at 24 months are presented in **Table 2**. The incidence of stent thrombosis was 0.1% in the de-escalation strategy group and 0.2% in the conventional strategy group (HR 0.672; 95% CI 0.078–5.750). The frequency of all-cause death in the de-escalation and conventional strategy groups was 5.3% and 6.9%, respectively (HR 0.726; 95% CI 0.523–1.008), and that of cardiovascular death was 2.5% and 3.8%, respectively (HR 0.652; 95% CI 0.407–1.042).

In patients with a history of ACS, the incidence of CRB was significantly lower in the de-escalation than conventional strategy group (HR 0.54; 95% CI 0.31–0.92; P=0.025; **Figure 3A**); however, the incidence of MACCE was similar in both groups (HR 0.75; 95% CI 0.49–1.14; P=0.170; **Figure 3B**). The de-escalation strategy group had a significantly lower risk of MACCE than the conventional strategy group for patients aged <75 years (HR 0.54; 95% CI 0.32–0.92; P=0.023), patients without complex PCI (HR 0.67; 95% CI 0.49–0.91; P=0.011), patients without concomitant oral anticoagulant use at discharge (HR 0.69; 95% CI 0.51–0.95; P=0.022), and patients without heart failure (HR 0.72; 95% CI 0.53–1.00; P=0.049; **Figure 3B**). For both CRB and MACCE, there was no significant interaction between the 2 registries for any of the risk factors evaluated (**Figure 3**).

Discussion

The main finding of this study is that a change in the early $P2Y_{12}$ inhibitor SAPT strategy in clinical practice may reduce ischemic and bleeding events. Two previous randomized controlled trials reported that short-term DAPT (1–3 months) followed by SAPT with $P2Y_{12}$ inhibitors reduces bleeding complications without increasing thrombotic events compared with 12 months of DAPT.[6,7] This bleeding prevention effect was particularly pronounced among HBR patients.

Although there seems to be a consensus among these randomized controlled trials on the benefit of an early SAPT strategy for HBR patients, it is not known whether this benefit can be obtained similarly in the real world. At the time of the PENDULUM registry study, DAPT was administered up to 12 months to more than half the patients and, after DAPT, these patients gradually transitioned to mainly aspirin SAPT.[16] Among HBR patients in the de-escalation strategy group, in whom the early $P2Y_{12}$ inhibitor SAPT strategy was applied, DAPT was interrupted at a median of 113.0 days. At 12 months after PCI, 85% of patients were receiving SAPT mainly with prasugrel, and SAPT rates remained unchanged (82%) until the end of the observation. Thus, it is reasonable to assume that the effects of shortening the duration of DAPT appeared in the first half of the study, and the effects of the difference in SAPT drug used appeared in the second half of the study when these 2 registries[13,14] were compared.

It is of note that the inclusion criteria of the PENDULUM mono study differed because that study was initiated before the publication of the ARC-HBR criteria, and the patients included were judged by their physicians to have HBR. However, the characteristics of the patients included were

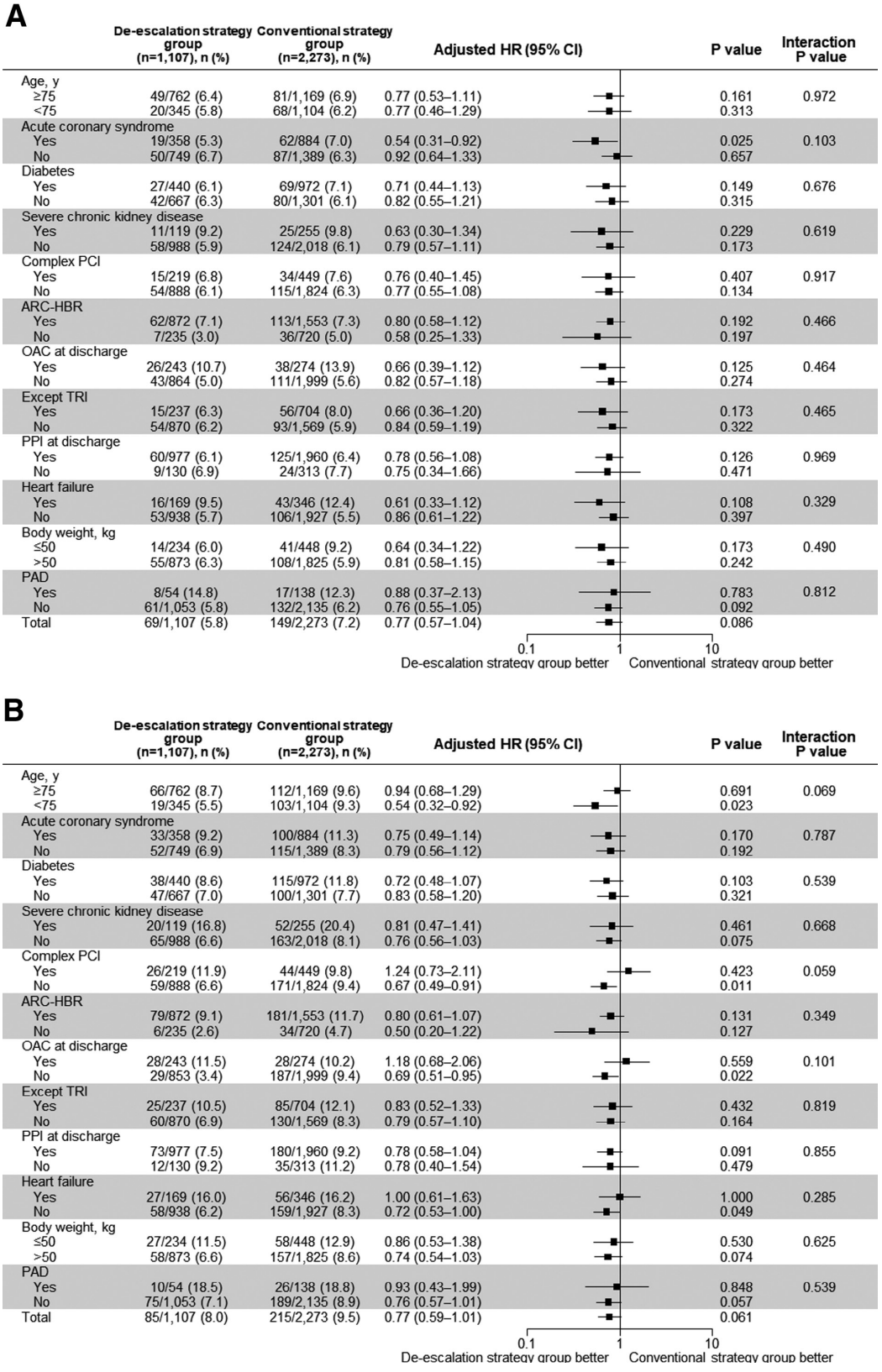

Figure 3. Forest plot for (**A**) clinically relevant bleeding and (**B**) major adverse cardiac and cerebrovascular events adjusted using the inverse probability of treatment weighting method. ARC-HBR, Academic Research Consortium for High Bleeding Risk; CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; OAC, oral anticoagulant; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; SAPT, single antiplatelet therapy; TRI, transradial intervention.

in good agreement with the HBR criteria of the Japanese Circulation Society guideline (83.8% in the de-escalation strategy group and 76.8% in the conventional therapy group).[5]

Notably, the present study was a comparison between registries[13,14] with a complicated distribution of drugs (e.g., number of drugs, duration of treatment, and drug combinations), which is expected because this study used data from a real-world setting, and this may have reduced the difference between the 2 registries. However, although statistical significance was not reached, our findings show that the early P2Y12 inhibitor SAPT strategy tended to reduce both CRB events and MACCE compared with the conventional strategy. This may reflect physicians' bias towards medication, making comparisons more complex than in randomized controlled trials. Notably, prescriptions represent the result of adjustments made by physicians. In randomized controlled trials, patient groups are set so that there are statistically significant differences between groups. However, in a registry conducted in a real-world clinical setting, treatment is tailored to each patient, and so a lack of a statistically significant difference between groups is more likely. Indeed, the PARIS registry clearly showed that physicians' decision to stop DAPT is the most reliable way to prevent ischemic complications.[17]

In our previous 12-month analysis, the reduction in CRB events in PENDULUM mono vs. the PENDULUM registry was found to be statistically significant (HR 0.68; 95% CI 0.47–0.98; P=0.039).[12] This suggests that a short DAPT duration contributes to the reduction in bleeding and is consistent with the findings of previous randomized controlled trials that showed that short DAPT duration reduced bleeding complications.[6,7] In the present long-term analysis at 24 months, the Kaplan-Meier curves for CRB separated early in the observation period and then shifted in parallel. The non-significant reduction in CRB at 24 months suggests that the comparison of prasugrel alone and aspirin alone in the latter part of the study may have counterbalanced the benefits that were present by 12 months. Another possible explanation for the lack of an increase in CRB in the conventional strategy group could be the relatively low risk of bleeding in patients who had no bleeding episodes within 1 year while continuing DAPT.

Regarding the possibility of an increased incidence of MACCE in the conventional strategy group, the occurrence of thrombotic events due to repeated bleeding with continued DAPT has been discussed previously in the AFIRE post hoc analysis.[18] As to whether there was repeated bleeding, only the first CRB event is reflected on the Kaplan-Meier curve, so even if there were repeated bleeding episodes, these are not reflected in this analysis. As a result, bleeding episodes at 2 years may be underestimated. DAPT accounted for approximately half the bleeding events in the conventional group at 24 months, whereas bleeding did not increase the difference between the 2 groups of events. In the present study, the early P2Y12 inhibitor SAPT strategy did not increase the incidence of stent thrombosis and tended to reduce the frequency of all-cause death and cardiovascular death. Because the Kaplan-Meier curves for MACCE separated in the latter half (after 12 months), this suggests that the early P2Y12 inhibitor SAPT strategy in which a P2Y12 inhibitor was chosen as the agent after SAPT may have contributed to the inhibition of ischemic events compared with conventional treatment, in which single-agent treatment with aspirin was administered. This seems to be in line with the results of the recent HOST-EXAM study, which showed that clopidogrel is superior to aspirin in chronic monotherapy after PCI.[19]

Although the observed findings were consistent across subgroups and showed no interaction, it is worth noting that there was a difference in the incidence of CRB in patients with ACS. The significant difference in CRB incidence in ACS patients (5.3% in the de-escalation strategy group vs. 7.0% in the conventional strategy group; P=0.025) raises concerns that conventional treatment with long-term DAPT, in terms of preventing a repeat ischemic event in ACS patients, resulted in increased bleeding. There was no significant difference in the incidence of MACCE in ACS patients among those in the de-escalation and conventional strategy groups, suggesting that the early P2Y12 inhibitor SAPT strategy may be beneficial for ACS patients. The median DAPT duration was 113.0 days in the de-escalation group and 371.0 days in the conventional strategy group. However, some studies of shorter duration have been reported in recent years.[6,20] The optimal DAPT duration still needs to be clarified.

In the subgroups of patients aged <75 years, without complex PCI, no concomitant oral anticoagulant use, and without heart failure, lower incidences of MACCE were observed in the de-escalation compared with conventional strategy group. These subgroups are all low-ischemic-risk subgroups, and the physician's dosing may have been biased, with DAPT preferentially selected for patients at high risk of ischemia and aspirin SAPT selected for those at low risk of ischemia. As a result, these subgroups may have shown greater efficacy with prasugrel SAPT.

Study Limitations

The limitations of this study are as reported for the 12-month analysis.[12] Briefly, definite conclusions cannot be drawn because this was not a randomized controlled trial, and unadjusted confounders may have affected our results. The possibility of underreporting cannot be ruled out because both registry studies were conducted in a routine clinical setting. The difference in patient backgrounds between the studies and the complex distribution of drugs may have contributed to the lack of significant differences between the 2 groups evaluated. The benefits of SAPT with prasugrel were not confirmed because the PENDULUM mono study was observational, and not all patients received SAPT with prasugrel. In addition, due to the observational study design, the optimal short duration of DAPT could not be determined, and DAPT with a shorter duration than that in the present study may be beneficial. In the PARIS registry, which assessed the impact of DAPT interruption on outcomes, patients who discontinued DAPT at the physician's discretion (not at the patient's discretion) had better outcomes.[17] The results of the present study should be interpreted with caution, because physician-judged discontinuation of DAPT may have biased the outcome in a positive direction. Finally, because this study was conducted in Japan, where the standard dose of prasugrel differs from that in other countries, the generalizability of our findings cannot be extrapolated to other countries.

Conclusions

Japanese PCI patients with HBR who were prescribed prasugrel SAPT after short-term DAPT tended to have

lower bleeding or ischemic event risk than patients prescribed long-term DAPT.

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IRB Information

The study protocols and associated documents of both registry studies were approved by the Ethics Committee at Toho University Ohashi Medical Center on 14 December 2015 (Reference code: 15-71) for the PENDULUM registry (UMIN000020332) and on 31 May 2017 (Reference code: H17006) for the PENDULUM mono (UMIN000028023).

Data Availability

The deidentified participant data and study protocol will be shared on a request basis for up to 36 months after the publication of this article. Researchers who make the request 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 requestors will need to sign a data access agreement. Please contact the corresponding author directly to request data sharing.

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Supplementary Files

Please find supplementary file(s);
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