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CORRIGENDUM

Single Antiplatelet Therapy With Prasugrel vs. Dual Antiplatelet Therapy in Japanese Percutaneous Coronary Intervention Patients With High Bleeding Risk

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The authors apologize for the written mistakes in the Discussion section and **Supplementary Table 4**. Corrections are shown below.

1. Page 791, right column, Lines 13–14

Incorrect:

Also, at 1 month after PCI, 21.5% and 11.4% in the PENDULUM mono…

Correct:

Also, at 1 month after PCI, 21.6% and 11.5% in the PENDULUM mono…

2. **Supplementary Table 4**

Incorrect:

	PENDULUM mono group					Historical control group				
	1 day after PCI	1 month after PCI	3 months after PCI	6 months after PCI	12 months after PCI	1 day after PCI	1 month after PCI	3 months after PCI	6 months after PCI	12 months after PCI
(…)	(…)	(…)	(…)	(…)	(…)	(…)	(…)	(…)	(…)	(…)
OAC use	239 (20.4)	250 (21.5)	237 (20.5)	229 (20.0)	221 (19.6)	243 (9.6)	288 (11.4)	273 (11.0)	260 (10.6)	251 (10.4)
Prasgrel + Aspirin + OAC	199 (17.0)	151 (13.0)	61 (5.3)	19 (1.7)	10 (0.9)	234 (9.2)	243 (9.7)	179 (7.2)	140 (5.7)	117 (4.8)
Prasgurel + OAC	40 (3.4)	96 (8.2)	166 (14.4)	194 (17.0)	191 (16.9)	1 (0.0)	9 (0.4)	21 (0.8)	25 (1.0)	28 (1.2)
OAC alone	0 (0)	0 (0)	2 (0.2)	6 (0.5)	10 (0.9)	0 (0.0)	2 (0.1)	7 (0.3)	14 (0.6)	19 (0.8)

Correct:

	PENDULUM mono group					Historical control group				
	1 day after PCI	1 month after PCI	3 months after PCI	6 months after PCI	12 months after PCI	1 day after PCI	1 month after PCI	3 months after PCI	6 months after PCI	12 months after PCI
(…)	(…)	(…)	(…)	(…)	(…)	(…)	(…)	(…)	(…)	(…)
OAC use	239 (20.4)	252 (21.6)	242 (21.0)	234 (20.5)	234 (20.7)	242 (9.5)	290 (11.5)	282 (11.3)	269 (10.9)	272 (11.2)
Prasgrel + Aspirin + OAC	199 (17.0)	152 (13.0)	63 (5.5)	19 (1.7)	10 (0.9)	233 (9.2)	244 (9.7)	183 (7.3)	144 (5.8)	129 (5.3)
Prasgurel + OAC	40 (3.4)	96 (8.2)	168 (14.6)	197 (17.2)	201 (17.8)	1 (0.0)	9 (0.4)	25 (1.0)	27 (1.1)	31 (1.3)
OAC alone	0 (0)	0 (0)	2 (0.2)	6 (0.5)	10 (0.9)	0 (0.0)	2 (0.1)	7 (0.3)	14 (0.6)	19 (0.8)

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ORIGINAL ARTICLE
Antithrombotic Therapy

Single Antiplatelet Therapy With Prasugrel vs. Dual Antiplatelet Therapy in Japanese Percutaneous Coronary Intervention Patients With High Bleeding Risk

Masato Nakamura, MD, PhD; Kazushige Kadota, MD, PhD; Koichi Nakao, MD, PhD; Yoshihisa Nakagawa, MD, PhD; Junya Shite, MD, PhD; Hiroyoshi Yokoi, MD, PhD; Ken Kozuma, MD, PhD; Kengo Tanabe, MD, PhD; Takashi Akasaka, MD, PhD; Toshiro Shinke, MD, PhD; Takafumi Ueno, MD, PhD; Atsushi Hirayama, MD, PhD; Shiro Uemura, MD, PhD; Atsushi Harada; Takeshi Kuroda, PhD; Atsushi Takita; Raisuke Iijima, MD, PhD; Yoshitaka Murakami, PhD; Shigeru Saito, MD, PhD

Background: Outcomes with prasugrel single antiplatelet therapy (SAPT) vs. dual antiplatelet therapy (DAPT) in Japanese percutaneous coronary intervention (PCI) patients with high bleeding risk (HBR) are currently unknown.

Methods and Results: Data from 1,173 SAPT and 2,535 DAPT patients from the PENDULUM mono and PENDULUM registry studies (respective median DAPT durations: 108 vs. 312 days) were compared. The adjusted cumulative incidence of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding from 1 to 12 months after PCI (primary endpoint) was 2.8% (95% confidence interval [CI], 1.9–4.2) and 4.1% (95% CI, 3.3–5.1), respectively (hazard ratio [HR], 0.69; 95% CI, 0.45–1.06; P=0.090). The adjusted cumulative incidences of BARC 2, 3, or 5 bleeding from 0 to 12 months after PCI (secondary endpoint) were 3.8% (95% CI, 2.7–5.3) and 5.6% (95% CI, 4.7–6.7), respectively (HR, 0.68; 95% CI, 0.47–0.98; P=0.039). There was no significant difference in major adverse cardiac and cerebrovascular events (MACCE) from 1 to 12 months after PCI (HR, 0.93; 95% CI, 0.63–1.37; P=0.696) and at 12 months after PCI (HR, 0.85; 95% CI, 0.61–1.19; P=0.348) between the groups.

Conclusions: Prasugrel SAPT may reduce BARC 2, 3, or 5 bleeding, without increasing MACCE, in Japanese patients with HBR.

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

Recent trials have highlighted the importance of optimal medical therapy (OMT) for the management of ischemic heart disease, irrespective of the revascularization strategy.[1] In addition to lifestyle modifications, good control of risk factors and optimal antithrombotic therapy are key components of OMT.[2] The beneficial effect of new-generation drug-eluting stents on the outcomes of patients with ischemic heart disease has led to substantial changes in the strategy of OMT after revascularization.

Editorial p 794

Dual antiplatelet therapy (DAPT) has been essential to

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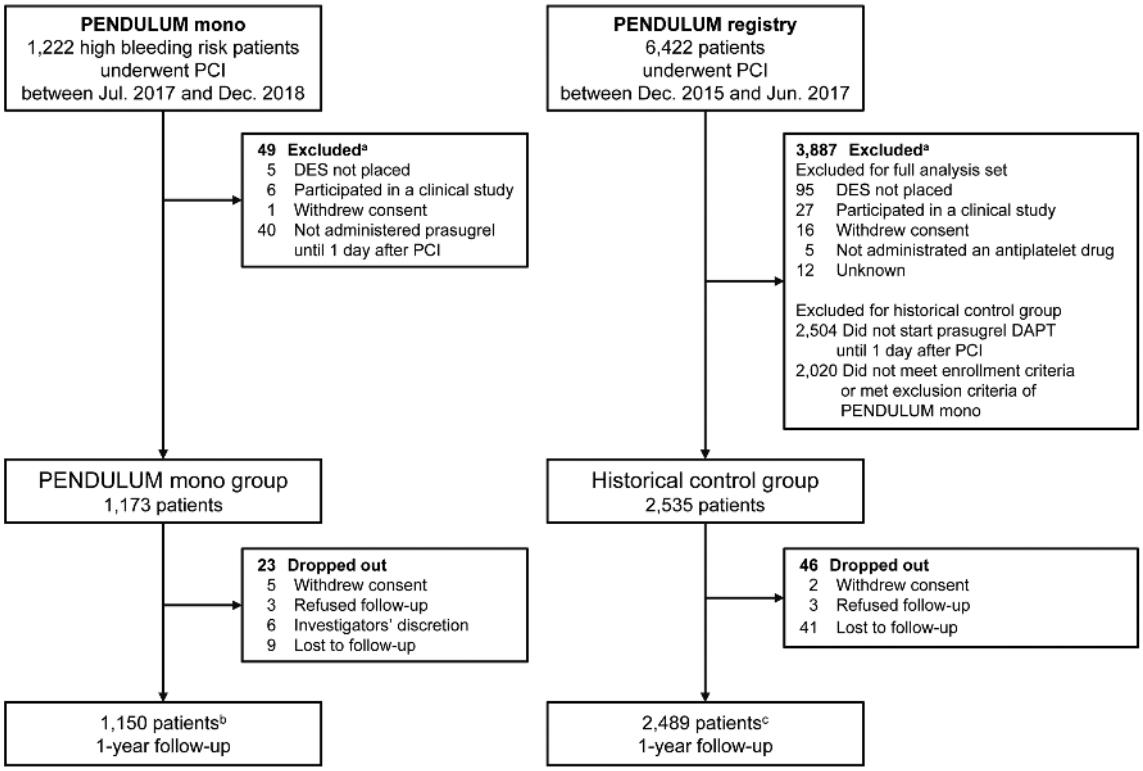

Figure 1. Patient characteristics. [a]Some patients met more than 1 exclusion criteria. [b]Includes 33 patients who died. [c]Includes 94 patients who died. DES, drug-eluting stent; PCI, percutaneous coronary intervention.

prevent stent thrombosis, but bleeding complications have been reported with long-term DAPT use.[3] A way to prevent bleeding complications is to shorten the DAPT duration after percutaneous coronary intervention (PCI). A recent network meta-analysis showed that both short- (<6 months) and mid-term (6 months) DAPT followed by aspirin monotherapy had a similar safety and effectiveness profile compared with 12-month DAPT, and a better safety profile compared with extended-term (>12 months) DAPT; however, these strategies had a higher risk of myocardial infarction (MI) and stent thrombosis compared with extended-term DAPT.[4] Therefore, the aspirin (acetylsalicylic acid [ASA])-off strategy is currently in the spotlight as a strategy to reduce bleeding complications without increasing ischemic risk. This strategy may have a big effect on daily practice, as the prevalence of high bleeding risk (HBR) in all PCI cases is reported to be at approximately 50%.[5]

Genetic polymorphisms of the cytochrome P450 2C19 (*CYP2C19*) gene are relatively common among Asians, including the Japanese population,[6] and could be a major concern for monotherapy with clopidogrel. Indeed, recent trials have been conducted with potent $P2Y_{12}$ inhibitors to address this concern.[7] Prasugrel is a $P2Y_{12}$ inhibitor with pharmacokinetics that are not affected by genetic polymorphisms, and thus, may be a suitable treatment option for Japanese patients.

In the PENDULUM mono study,[8] we showed the feasibility and applicability of SAPT with prasugrel in Japanese patients with HBR undergoing PCI; however, these results have not been verified in a comparative study.

The present study is a historical control study that aims to compare a SAPT cohort with prasugrel from PENDULUM mono vs. a DAPT cohort with HBR from the PENDULUM registry study as a historical control.[9]

Methods

Study Design

This study was a prespecified analysis of 2 previous multicenter, non-interventional, prospective registry studies (the PENDULUM mono[8] and PENDULUM registry[9] studies) (**Supplementary Table 1**). We adopted a historical control study design to compare SAPT with prasugrel vs. DAPT. Both studies were conducted by the same research organization (steering committee, event adjudication committee, and participating institutions).

The registration periods were July 2017 to December 2018 for PENDULUM mono, and December 2015 to June 2017 for PENDULUM registry. Evaluation time points for the current study were at discharge and at 1 month and 12 months after PCI. Throughout the study, patients who were considered unsuitable for continued treatment with prasugrel alone were allowed to change to other antiplatelet treatments as judged by the attending physician.

The study protocols were approved by the institutional review board or independent ethics committee at each participating center, and the studies were performed in

Table 1. Baseline Characteristics

Characteristics	PENDULUM mono (N=1,173)	Historical control (N=2,535)	SMD	SMD, after IPTW
Age, years, mean (SD)	76.3 (8.7)	73.4 (9.6)	0.311	0.053
≥75 years	801 (68.3)	1,324 (52.2)	0.333	0.002
Sex, male	825 (70.3)	1,827 (72.1)	−0.038	−0.022
Body weight, kg, mean (SD)	59.9 (11.5)	61.3 (12.5)	−0.115	−0.017
≤50 kg	248 (21.1)	478 (18.9)	0.057	−0.006
Body mass index, kg/m^2, mean (SD)	23.6 (3.6)	23.7 (3.6)	−0.040	0.030
Hypertension	989 (84.3)	2,111 (83.3)	0.028	0.016
Hyperlipidemia	876 (74.7)	1,897 (74.8)	−0.003	0.012
Diabetes mellitus	460 (39.2)	1,083 (42.7)	−0.071	−0.002
Smoking, current	168 (14.3)	452 (17.8)	−0.096	0.040
Heart failure	177 (15.1)	393 (15.5)	−0.011	−0.067
Peripheral artery disease	53 (4.5)	144 (5.7)	−0.053	−0.015
Atrial fibrillation	197 (16.8)	249 (9.8)	0.206	0.022
Malignancy	86 (7.3)	184 (7.3)	0.003	−0.028
History of myocardial infarction	207 (17.6)	595 (23.5)	−0.144	−0.160
History of percutaneous coronary intervention	436 (37.2)	923 (36.4)	0.016	0.023
History of coronary artery bypass grafting	37 (3.2)	109 (4.3)	−0.061	−0.106
History of ischemic stroke	114 (9.7)	235 (9.3)	0.015	−0.036
History of transient ischemic attack	17 (1.4)	30 (1.2)	0.023	−0.009
History of cerebral hemorrhage	33 (2.8)	66 (2.6)	0.013	0.032
History of gastrointestinal bleeding	77 (6.6)	88 (3.5)	0.142	−0.001
ARC-HBR	923 (78.7)	1,722 (67.9)	0.245	0.036
Non-ACS	792 (67.5)	1,563 (61.7)	0.123	−0.001
ACS	381 (32.5)	972 (38.3)	−0.123	0.001
Unstable angina	134 (11.4)	350 (13.8)	−0.072	0.007
Non-STEMI	87 (7.4)	168 (6.6)	0.031	0.059
STEMI	160 (13.6)	455 (17.9)	−0.118	−0.049
Medication at discharge				
Prasugrel	1,169 (99.7)	2459 (97.0)	0.208	0.229
Clopidogrel	0 (0)	54 (2.1)	−0.209	−0.223
Aspirin	1,103 (94.0)	2,508 (98.9)	−0.269	−0.197
Anticoagulant	257 (21.9)	297 (11.7)	0.275	0.001
DOAC	204 (17.4)	181 (7.1)	0.316	0.086
Warfarin	53 (4.5)	116 (4.6)	−0.003	−0.124
Proton pump inhibitor	1,036 (88.3)	2,182 (86.1)	0.067	0.062
Non-steroidal anti-inflammatory drugs except aspirin	75 (6.4)	188 (7.4)	−0.040	0.028
Steroids	41 (3.5)	129 (5.1)	−0.079	−0.039

Data are presented as n (%), unless otherwise indicated. ACS, acute coronary syndrome; ARC, Academic Research Consortium; DOAC, direct oral anticoagulants; HBR, high bleeding risk; IPTW, inverse probability of treatment weighting; SD, standard deviation; SMD, standardized mean difference; STEMI, ST-elevation myocardial infarction.

accordance with the principles of the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice Guidelines. All patients provided written informed consent. Both studies were registered in the UMIN-CTR Clinical Trial Registry: UMIN000028023 (PENDULUM mono) and UMIN000020332 (PENDULUM registry).

Study Population

The PENDULUM registry is an all-comers PCI registry, but PENDULUM mono (N=1,173) recruited PCI patients who were not considered appropriate for long-term DAPT with ASA because of their HBR status. The historical cohort in this analysis was extracted from patients who met the criteria for PENDULUM mono among those enrolled in the PENDULUM registry. Among 6,267 patients (full analysis set) enrolled in the PENDULUM registry, 2,535 patients who met the criteria for PENDULUM mono and received prasugrel within 1 day after PCI were selected as the historical cohort. Patient inclusion/exclusion criteria of the PENDULUM registry and PENDULUM mono studies are indicated in **Supplementary File 1**.

Outcomes

The primary endpoint was Bleeding Academic Research Consortium (BARC) 2, 3, and 5 bleeding[10] from 1 to 12 months after PCI. The secondary endpoints were BARC 2, 3, or 5 bleeding from PCI to 12 months; the cumulative incidence of BARC 3 or 5 bleeding from 1 to 12 months after PCI and from PCI to 12 months; cumulative incidence

Table 2. Proportion and Cumulative Incidence of Bleeding and Cardiovascular Events From 1 to 12 Months and for 12 Months After Percutaneous Coronary Intervention

	Unadjusted						Adjusted by IPTW			
	Event rate		Cumulative incidence (95% CI)		Hazard ratio (95% CI)	P value	Cumulative incidence (95% CI)		Hazard ratio (95% CI)	P value
	PENDULUM mono (N=1,173)	Historical control (N=2,535)	PENDULUM mono (N=1,173)	Historical control (N=2,535)			PENDULUM mono (N=1,173)	Historical control (N=2,535)		
Months 1–12, primary										
BARC 2, 3, or 5 bleeding (primary)	34 (3.0)	92 (3.7)	3.2% (2.3–4.5)	4.1% (3.3–5.0)	0.80 (0.54–1.18)	0.257	2.8% (1.9–4.2)	4.1% (3.3–5.1)	0.69 (0.45–1.06)	0.090
BARC 3 or 5 bleeding	28 (2.4)	61 (2.4)	2.6% (1.8–3.8)	2.6% (2.1–3.4)	0.99 (0.63–1.55)	0.961	2.3% (1.5–3.5)	2.6% (2.0–3.4)	0.85 (0.52–1.40)	0.527
MACCE[a]	42 (3.6)	105 (4.2)	3.8% (2.9–5.2)	4.6% (3.8–5.5)	0.87 (0.61–1.24)	0.426	3.8% (2.7–5.3)	4.3% (3.5–5.3)	0.93 (0.63–1.37)	0.696
All period (months 0–12)										
BARC 2, 3, or 5 bleeding	48 (4.1)	128 (5.0)	4.4% (3.3–5.8)	5.5% (4.6–6.5)	0.81 (0.58–1.13)	0.209	3.8% (2.7–5.3)	5.6% (4.7–6.7)	0.68 (0.47–0.98)	0.039
BARC 3 or 5 bleeding	36 (3.1)	88 (3.5)	3.3% (2.4–4.6)	3.7% (3.0–4.5)	0.88 (0.60–1.30)	0.523	2.8% (1.9–4.2)	3.8% (3.0–4.7)	0.72 (0.47–1.11)	0.137
MACCE[a]	54 (4.6)	141 (5.6)	4.8% (3.7–6.3)	5.9% (5.1–7.0)	0.83 (0.61–1.13)	0.237	4.6% (3.5–6.2)	5.6% (4.7–6.7)	0.85 (0.61–1.19)	0.348

Data are presented as n (%). [a]MACCE is a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and stent thrombosis. BARC, Bleeding Academic Research Consortium; CI, confidence interval; IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiac and cerebrovascular events.

of major adverse cardiac and cerebrovascular events (MACCE: all-cause death, non-fatal MI, non-fatal stroke, and stent thrombosis) and each component of the thrombotic events (all-cause death, cardiovascular death, non-fatal MI, and non-fatal stroke) recorded from 1 to 12 months after PCI and from PCI to 12 months.

The outcomes of this study were assessed by an independent event adjudication committee. The event assessment committee and the definitions of events were unified in the PENDULUM mono and PENDULUM registry studies.

Statistical Analysis

To reduce the effect of treatment selection bias and potential confounders, we applied a propensity score method to make a fair comparison between PENDULUM mono and historical control data. Propensity scores were calculated by using multivariate logistic regression including the following variables: age, body weight, estimated glomerular filtration rate, hemoglobin, oral anticoagulant (OAC) use at discharge, diabetes mellitus, acute coronary syndrome (ACS), platelet count, peripheral artery disease, gastrointestinal bleeding, non-steroidal anti-inflammatory drugs or steroid use at discharge, ischemic stroke or transient ischemic attack or intracerebral hemorrhage, and complex PCI. All variables included in the propensity score calculation were prespecified before the logistic model was constructed. The selection of these variables was made according to the Japanese Circulation Society 2020 guideline and previous reports.[2,11] During the model construction, gender was not mentioned as a risk factor for bleeding or thrombotic event and thus was not included as a factor for the propensity score calculation. The inverse probability of treatment weighting (IPTW) method was used for a fair comparison between the 2 groups, PENDULUM mono and historical control data. Standardized mean differences were calculated for baseline characteristics to check the confounders' balance between the 2 groups. We applied 3 approaches using propensity score methods (1-to-1 matching, multivariate adjustment, and stratified analysis). For time-to-event outcomes, the cumulative incidence and 95% confidence intervals (CIs) at 12 months were calculated by using the Kaplan-Meier method. Hazard ratios (HR) and 95% CIs were calculated by using the Cox regression model.

Patients who switched treatment from prasugrel to another $P2Y_{12}$ inhibitor during the observation period were recorded as having continued treatment with a $P2Y_{12}$ inhibitor. DAPT discontinuation was defined as the discontinuation of either ASA or $P2Y_{12}$. If a patient discontinued treatment with ASA or a $P2Y_{12}$ inhibitor and this patient restarted DAPT later, this patient was excluded from the analysis of the DAPT rate. A P value <0.05 was considered statistically significant. SAS Release 9.4 (SAS Institute, Cary, NC, USA) was used for the statistical analysis.

Results

Patient Characteristics

The patient characteristics are shown in **Figure 1**. The historical control consisted of 2,535 patients who met the criteria for PENDULUM mono and started prasugrel administration 1 day after PCI in the PENDULUM registry study. The characteristics of the extracted and the non-extracted populations are shown in **Supplementary Table 2**. Baseline characteristics of patients are shown in **Table 1**, **Supplementary Table 3**, and **Supplementary Figure 1**. The median duration of DAPT was 108 days in PENDULUM mono and 312 days in the historical control. A Kaplan-Meier curve for the discontinuation of DAPT in both groups is shown in **Supplementary Figure 2**. Details of the

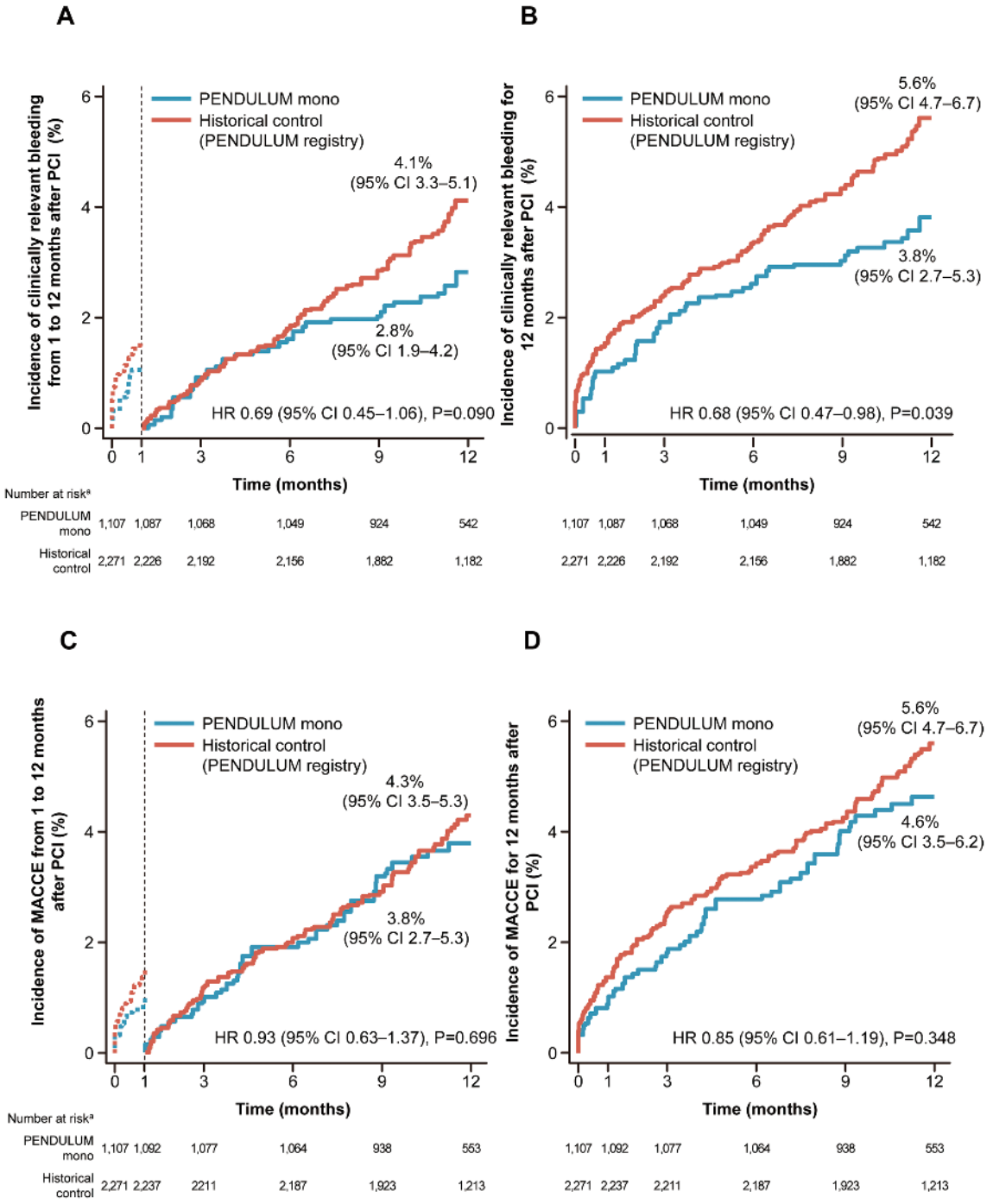

Figure 2. Time-to-event curves for BARC 2, 3, or 5 bleeding from 1 to 12 months after PCI (**A**, primary) and for 12 months after PCI (**B**) and MACCE (all-cause death, non-fatal MI, non-fatal stroke, and stent thrombosis) from 1 to 12 months after PCI (**C**) and for 12 months after PCI (**D**). [a]Patients who did not have the data necessary to calculate propensity scores were excluded from the analysis. BARC, Bleeding Academic Research Consortium; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

administration status of antiplatelet drugs are described in **Supplementary Table 4**.

Study Outcomes

Unadjusted Analysis The cumulative incidence of BARC 2, 3, or 5 bleeding from 1 to 12 months after PCI was 3.2% (95% CI, 2.3–4.5) in PENDULUM mono and 4.1% (95% CI, 3.3–5.0) in the historical control (**Table 2**). The cumulative incidence of BARC 2, 3, or 5 bleeding for 12 months after PCI was 4.4% (95% CI, 3.3–5.8) in PENDULUM

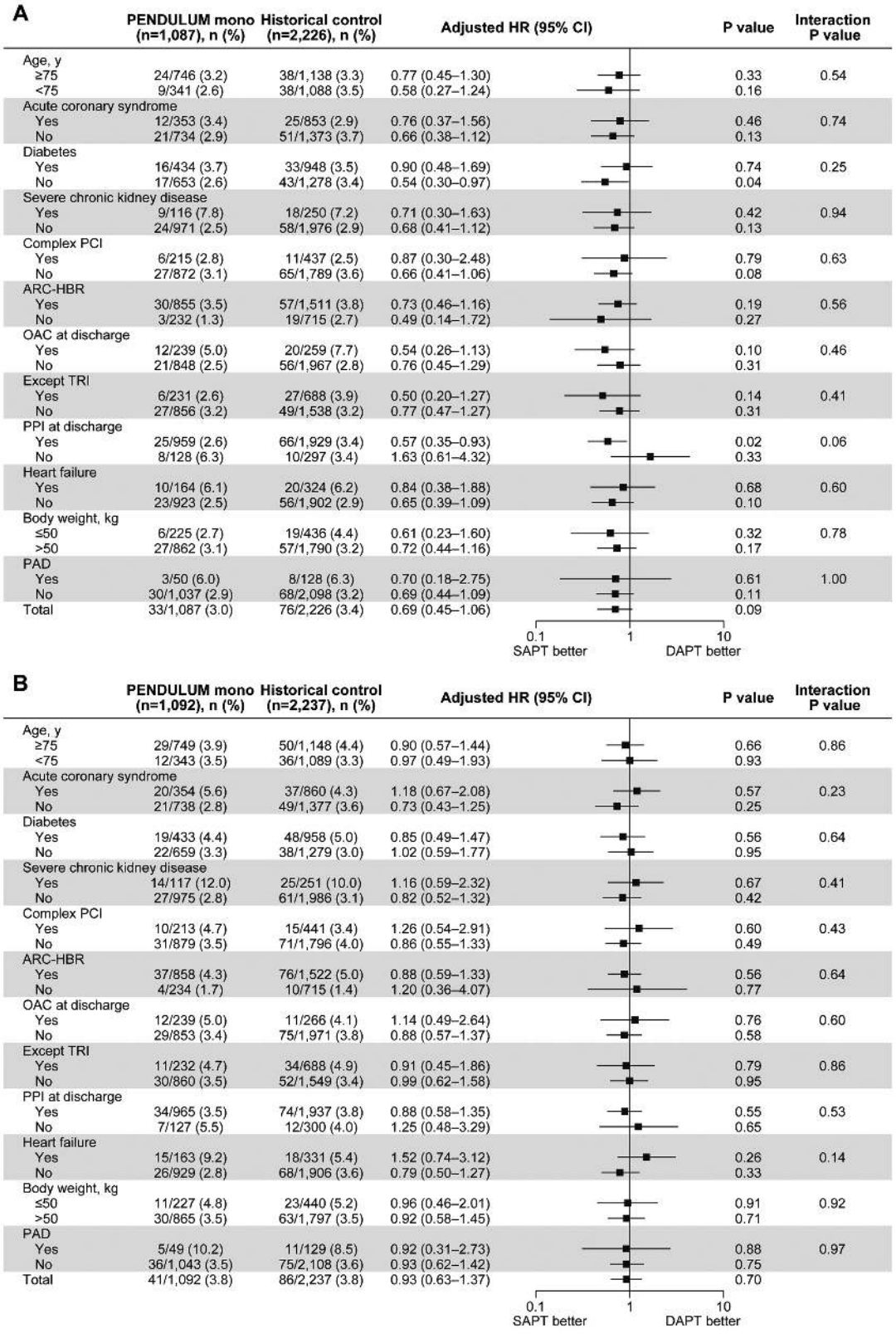

Figure 3. Subgroup analysis for the effect of prasugrel monotherapy on the primary endpoint (BARC 2, 3, or 5 bleeding from 1 to 12 months after PCI) (**A**) and MACCE (**B**). ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; CI, confidence interval; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; OAC, oral anticoagulant; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; SAPT, single antiplatelet therapy; TRI, transradial intervention.

mono and 5.5% (95% CI, 4.6–6.5) in the historical control. The cumulative incidence of MACCE from 1 to 12 months after PCI was 3.8% (95% CI, 2.9–5.2) in PENDULUM mono and 4.6% (95% CI, 3.8–5.5) in the historical control.

Adjusted Analysis With the IPTW method, the adjusted cumulative incidence of BARC 2, 3, or 5 bleeding from 1 to 12 months after PCI was 2.8% (95% CI, 1.9–4.2) in PENDULUM mono and 4.1% (95% CI, 3.3–5.1) in the historical control (**Table 2**, **Supplementary Table 5**). Although the primary endpoint did not reach statistical significance, it was numerically lower in PENDULUM mono vs. the historical control (HR, 0.69; 95% CI, 0.45–1.06; P=0.090) (**Figure 2A**). The adjusted cumulative incidence of BARC 2, 3, or 5 bleeding at 12 months after PCI was 3.8% (95% CI, 2.7–5.3) in PENDULUM mono and 5.6% (95% CI, 4.7–6.7) in the historical control. There was a significantly lower risk of bleeding in PENDULUM mono vs. the historical control (HR, 0.68; 95% CI, 0.47–0.98; P=0.039) (**Figure 2B**). The adjusted cumulative incidence of MACCE from 1 to 12 months after PCI was 3.8% (95% CI, 2.7–5.3) in PENDULUM mono and 4.3% (95% CI, 3.5–5.3) in the historical control. There was no significant difference in MACCE from 1 to 12 months after PCI (HR, 0.93; 95% CI, 0.63–1.37; P=0.696) and at 12 months after PCI (HR, 0.85; 95% CI, 0.61–1.19; P=0.348) between the 2 studies (**Figure 2C**,**D**). The adjusted cumulative incidence of BARC types 3 or 5 is shown in **Supplementary Figure 3**. Adjustments were made using 3 additional methods: 1:1 matching, stratification, and multivariate analysis, all of which showed similar trends (**Supplementary Figure 4**).

The results of the subgroup analysis are shown in **Figure 3A** and **3B**. Overall, the risk of BARC 2, 3, or 5 bleeding from 1 to 12 months after PCI tended to be lower in PENDULUM mono vs. the historical control. Among patients with proton-pump inhibitor (PPI) use at discharge, the risk of BARC 2, 3, or 5 bleeding from 1 to 12 months after PCI was significantly lower in PENDULUM mono vs. the historical control. In contrast, the risk of MACCE was not significantly different between PENDULUM mono vs. the historical control. The P value of the interaction was not significant for both major bleeding and MACCE.

Discussion

This historical control study found that: (1) the primary endpoint (BARC types 2, 3, and 5 from 1 to 12 months after PCI) was not significant, but numerically lower with prasugrel monotherapy vs. prasugrel DAPT (HR, 0.69; 95% CI, 0.45–1.06), whereas the incidence of BARC types 2, 3, and 5 at 12 months after PCI was significantly lower in the prasugrel monotherapy group (HR, 0.68; 95% CI, 0.47–0.98); (2) switching from prasugrel DAPT to SAPT did not increase the incidence of MACCE from 1 to 12 months after PCI; and (3) subgroup analyses showed that bleeding risks were generally lower with prasugrel monotherapy, and thrombotic events were less affected by prasugrel monotherapy or DAPT. These results suggest that for HBR patients not suitable for long-term ASA combination treatment, transitioning to prasugrel monotherapy after a short period of DAPT may reduce bleeding events without an increase in ischemic events between the perioperative to 12-month periods post-PCI.

We selected the primary endpoint to exclude initial bleeding up to 1 month after PCI to assess the effects of pure drug efficacy, excluding procedure-related bleeding. This study highlighted the benefit of switching to prasugrel SAPT on bleeding risk when perioperative bleeding events were added. Differences in BARC 2, 3, or 5 bleeding incidence between the 2 groups at the perioperative phase suggests a potentially significant effect of early interruption of ASA on bleeding for patients receiving triple antithrombotic drugs. In PENDULUM mono, 125 (10.7%) patients switched to prasugrel monotherapy within 1 month after PCI; the majority used concomitant OAC (96 patients, 8.2%). In the historical control group, 20 (0.8%) patients switched to prasugrel monotherapy within 1 month after PCI, and less than half of them (9 patients, 0.4%) used concomitant OAC. Also, at 1 month after PCI, 21.5% and 11.4% in the PENDULUM mono and historical control groups, respectively, used concomitant OACs. The difference in the incidence of bleeding events at 1 month after PCI and the larger difference in relatively minor bleeding confirm the usefulness of the ASA-off strategy for preventing bleeding in patients with atrial fibrillation, as demonstrated in the What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing (WOEST) trial.[12] After that, the bleeding events diverged at ~6 months after PCI when the switch to prasugrel monotherapy was mostly implemented. Therefore, it seems reasonable to speculate that P2Y12 inhibitor monotherapy after a shorter DAPT period may reach statistical significance because the observed DAPT duration of the PENDULUM mono registry was slightly longer than the recent randomized controlled trials with patients who used DAPT for 1–3 months.

Reportedly, HBR patients have a higher ischemic risk.[13,14] In general, risk factors for bleeding and ischemic events overlap with each other, meaning that early termination of DAPT may be associated with exacerbation of ischemic events. Notably, this study has shown the potential to reduce bleeding risk without increasing ischemic events, even in patients with high ischemic risk (e.g., ACS, complex PCI, or peripheral artery disease). In the PENDULUM registry sub-analysis, we reported that half of Japanese patients who underwent PCI were HBR patients.[5] Ueki et al and Cao et al also reported a high prevalence of HBR in daily practice from a PCI registry in Europe and the US, respectively,[13,14] suggesting HBR as a global challenge for improving PCI outcomes. Overall, our findings are in line with recent clinical trials testing the superiority of P2Y12 inhibitor monotherapy after short-term DAPT. In the ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study (STOPDAPT-2), Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT), and Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome (TICO) studies, monotherapy with clopidogrel or ticagrelor after 1–3 months of DAPT was consistently associated with a significantly lower incidence of bleeding vs. P2Y12 inhibitors plus ASA, with no apparent differences in ischemic risk.[15–17] However, clinical implications from these trials may differ, given the differences in the characteristics of patients enrolled in these trials. TWILIGHT included patients at high risk of ischemic or bleeding events.[16] TICO included ACS patients but excluded those with HBR.[17] In both trials, the observed event rates were lower than expected. Therefore, the generalizability of these findings requires careful consideration. In the STOPDAPT-2 trial, the efficacy of the ASA-off strategy was mainly observed in the

HBR subset.[15] Regarding bleeding events, it is likely that reduced exposure to antiplatelet therapy would be most beneficial in high-risk patients such as HBR patients. However, it remains to be determined whether $P2Y_{12}$ SAPT confers benefits for HBR patients. Compared with the A Randomized Clinical Evaluation of the BioFreedom™ Stent (LEADERS FREE)[18] and A Randomized Controlled Trial With Resolute Onyx in One Month Dual Antiplatelet Therapy (DAPT) for High-Bleeding Risk Patients (Onyx ONE)[19] trials in which HBR patients received mainly ASA monotherapy following 1 month of DAPT, the present study showed lower rates of bleeding and ischemic events. Additionally, the high rate of anticoagulant use in these trials and the lack of IIb/IIIa inhibitor use, along with the high rate of PPI use and the trans-radial approach in Japan, may have contributed to the overall reduction of bleeding events. In contrast, the high rate of imaging-guided PCI use may have contributed to the decline in ischemic events.

$P2Y_{12}$ inhibitor monotherapy is largely restricted to ticagrelor, but in Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome (ISAR-REACT 5),[20] prasugrel DAPT showed lower bleeding rates and similar ischemic event rates to ticagrelor DAPT after PCI. Therefore, it is reasonable to consider that prasugrel would be a good candidate for monotherapy, and findings from this study support the use of prasugrel monotherapy, especially for HBR patients.

In the subgroup analysis, prasugrel SAPT tended to reduce bleeding risk compared with long-term DAPT in patients who did not have risk factors for bleeding. However, for patients at risk, this trend differed for each risk factor, suggesting that bleeding management should be tailored accordingly. The observed lower bleeding risk in the monotherapy group among patients taking PPIs at discharge suggests that PPIs should be used concomitantly, even in patients receiving prasugrel SAPT. However, this warrants further investigation.

The present study has some limitations. First, this was a historical control-matching study, not a randomized controlled trial, and was limited by the possibility of unadjusted confounders. Thus, we cannot draw definite conclusions. Second, not all patients in PENDULUM mono received SAPT with prasugrel. Therefore, we were not able to thoroughly verify the benefits of SAPT with prasugrel due to the observational study design. Third, it was difficult to determine the optimal short duration of DAPT due to the observational study design. However, previous trials evaluating the use of DAPT for 1–3 months and subsequent $P2Y_{12}$ inhibitors demonstrated a more significant reduction in bleeding events compared with DAPT use for 12 months. Therefore, a shorter duration of DAPT than that in this study may be adequate. Fourth, the standard dose of prasugrel in Japan (3.75 mg) differs from that overseas; thus, the generalizability of our findings is limited to Japan. Fifth, the possibility of bias of event assessors cannot be denied. Although the adjudicators were the same, the event assessors could know whether the patient was in the SAPT group or the DAPT group due to the historical control study design. Therefore, findings from this study should be interpreted with caution. Finally, as the PENDULUM mono and PENDULUM registry studies were conducted in a routine clinical setting, there may be underreporting. However, both studies were designed prospectively, had similar study periods, and had overlapping of participating facilities. Therefore, both studies were considered appropriate for comparison.

In conclusion, the incidence of BARC 2, 3, or 5 bleeding tended to be lower with prasugrel SAPT vs. DAPT, although without reaching a statistically significant difference. Prasugrel SAPT may reduce BARC 2, 3, or 5 bleeding events without increasing MACCE in Japanese patients who were not considered appropriate for long-term combination treatment with ASA because of their HBR status and who were planned to receive SAPT with prasugrel. Our result should be confirmed in a randomized clinical trial.

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Author Contributions

Masato Nakamura contributed to drafting the manuscript and critically revising the draft for important intellectual content. All authors made substantial contributions to the concept and design of the study; acquisition, analysis, and interpretation of the data; and final approval of the manuscript for publication. All authors agree to be accountable for the accuracy and integrity of the data published.

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IRB Information

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

Data Availability

The deidentified participant data and the study protocol 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 researchers who make the request should include a methodologically sound proposal on how the data will be used. The proposal may be reviewed for approval by the responsible personnel at Daiichi Sankyo Co. Ltd., and the data requestors will need to sign a data access agreement. The data will be shared in an appropriate way to meet the type of data ordered.

Clinical Trial Registration

PENDULUM mono study URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_his_list.cgi?recptno=R000032055. Unique Identifier: UMIN000028023

PENDULUM registry study URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_his_list.cgi?recptno=R000023479. Unique Identifier: UMIN000020332.

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Supplementary Files

Please find supplementary file(s);
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