Journal of Cardiology 73 (2019) 479–487

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Performance of HAS-BLED, ORBIT, PRECISE-DAPT, and PARIS risk score for predicting long-term bleeding events in patients taking an oral anticoagulant undergoing percutaneous coronary intervention

Ruka Yoshida (MD)[a,b], Hideki Ishii (MD, PhD, FJCC)[c,*], Itsuro Morishima (MD, PhD)[b], Akihito Tanaka (MD, PhD)[a], Yasuhiro Morita (MD)[b], Kensuke Takagi (MD)[b], Naoki Yoshioka (MD)[b], Kenshi Hirayama (MD)[c], Naoki Iwakawa (MD)[c], Hiroshi Tashiro (MD)[a], Hiroki Kojima (MD)[a], Takayuki Mitsuda (MD)[a], Yusuke Hitora (MD)[c], Kenji Furusawa (MD)[a], Hideyuki Tsuboi (MD, PhD, FJCC)[b], Toyoaki Murohara (MD, PhD, FJCC)[c]

[a] *Department of Cardiology, Nagoya University Hospital, Nagoya, Japan*
[b] *Department of Cardiology, Ogaki Municipal Hospital, Ogaki, Japan*
[c] *Department of Cardiology, Nagoya University graduate school of medicine, Nagoya, Japan*

ARTICLE INFO

Article history:
Received 12 September 2018
Received in revised form 29 September 2018
Accepted 17 October 2018
Available online 28 December 2018

Keywords:
Antiplatelet therapy
Oral anticoagulant
Percutaneous coronary intervention
Bleeding risk score

ABSTRACT

Background: No standardized tool exists for weighting bleeding risk before selecting an antithrombotic regimen in patients undergoing percutaneous coronary intervention (PCI) who require both oral anticoagulant (OAC) and antiplatelet agents.
Methods: We performed PCI in 3718 consecutive patients between April 2011 and March 2017, 302 of whom were treated with both OAC and antiplatelet agents. We retrospectively evaluated the predictive performance of four major bleeding risk scores (HAS-BLED, ORBIT, PRECISE-DAPT, and PARIS score). Patients were followed for up to 3 years for bleeding events, defined as a composite of major and minor bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) criteria and the Bleeding Academic Research Consortium (BARC) criteria.
Results: TIMI significant bleedings (major, minor, and requiring medical attention) were seen in 90 patients (29.8%); whereas the BARC class ≥3 bleedings were seen in 53 patients (17.5%). Regarding TIMI significant bleedings, HAS-BLED, ORBIT, and PRECISE-DAPT scores equally categorized high-risk patients, but the PARIS score could not [high-risk versus non-high-risk: hazard ratio (HR), 1.74; 95% confidence interval (CI), 1.15–2.64; $p = 0.01$; HR, 1.63; 95% CI, 1.08–2.48; $p = 0.02$; HR, 1.62; 95% CI, 1.06–2.51; $p = 0.03$; HR, 1.05; 95% CI, 0.70–1.63; $p = 0.79$, respectively); regarding BARC class ≥3 bleeding, all four scores could stratify high-risk patients (high-risk versus non-high-risk: HR, 2.23; 95% CI, 1.30–3.88; $p = 0.004$; HR, 2.25; 95% CI, 1.31–3.96; $p = 0.003$; HR, 3.87; 95% CI, 2.06–7.91; $p < 0.0001$; HR, 1.85; 95% CI, 1.04–3.47; $p = 0.04$, respectively).
Conclusions: In patients taking an OAC undergoing PCI, HAS-BLED, ORBIT, and PRECISE-DAPT scores predicted TIMI significant bleeding events better than the PARIS score; whereas all four scores could predict BARC class ≥3 bleeding events.

* Corresponding author at: Department of Cardiology, Nagoya University Graduate School of Medicine, 6 Tsurumai-cho, Showa ward, Nagoya, 466-8560, Japan. Tel.: +81 527412111; fax: +81 527442785.
E-mail address: hkishii@med.nagoya-u.ac.jp (H. Ishii).

https://doi.org/10.1016/j.jjcc.2018.10.013
0914-5087/

Introduction

Long-term oral anticoagulant (OAC) use is necessary in patients with mechanical heart valves and most patients with atrial fibrillation (AF) [1,2]. In the clinical setting, approximately 5–10% of patients undergoing percutaneous coronary intervention (PCI) have concomitant AF [3]. In such patients, both antiplatelet therapy (APT) and OAC are indicated; however, great concern regarding bleeding complications has been raised [4–6].

International guidelines encourage weighting bleeding risk before selecting a treatment regimen in patients at high risk of bleeding who undergo PCI [7]. Prediction scores for bleeding events have been recently proposed for patients who are taking dual APT (DAPT) [8,9]. On the other hand, a prediction score (HAS-BLED and ORBIT score) was proposed for AF patients who are taking OAC or APT [10,11]. However, no standardized tool exists for this purpose in patients undergoing PCI who need both OAC and APT.

Therefore, we validated four different risk scores (PRECISE-DAPT, PARIS, HAS-BLED, and ORBIT scores) in our cohort of patients undergoing PCI who required both OAC and APT in order to assess their ability to predict bleeding events.

Materials and methods

Patient population

Among 3718 patients who underwent PCI at Ogaki Municipal Hospital from April 2011 to March 2017, patients with indications for long-term OAC treatment were enrolled. Exclusion criteria were as follows: history of intracranial bleeding, cardiogenic shock, patients who did not take APT, peptic ulcer in the previous 6 months, thrombocytopenia (platelet count, $<50 \times 10^9$/L), major bleeding [according to the Thrombolysis in Myocardial Infarction (TIMI) criteria] in the previous 12 months, and life expectancy of less than 12 months. The indication for PCI was based on established European, US, and Japanese guidelines. This study was approved by the research review board of Ogaki Municipal Hospital. Moreover, this study was conducted according to the Helsinki Declaration. All patients consented participation in this study.

Antithrombotic treatment

All patients received at least one antiplatelet agent [thienopyridine (200 mg ticlopidine, 75 mg clopidogrel, or 3.75 mg prasugrel daily) and/or 81–100 mg aspirin daily] and an OAC [vitamin K antagonist (VKA) or a direct OAC (DOAC)]. Although the standard antiplatelet regimen after PCI in the hospital was both thienopyridine and aspirin for at least 1 month even in patients who were taking an OAC, the type and timing of discontinuing antiplatelet agents were at the discretion of each attending physician. The selection of the OAC was also left to the discretion of the attending physician. To reduce the risk of bleeding, proton-pump inhibitors were administered and access-site-closure devices (when PCI was conducted through a femoral access site) were used in most patients. In the periprocedural period, OACs were continued whenever possible.

Assessments and follow-up

Demographic, angiographic, and procedural data were collected from hospital charts or hospital databases. Follow-up data were obtained from hospital charts or by contacting patients on the telephone for up to 3 years. All patient follow-up data were obtained by March 2018.

The endpoint of this study was TIMI significant bleeding (defined as a composite of TIMI major, minor, and requiring medical attention) [12,13] and occurring 7 days or later after the index PCI; bleeding occurring earlier was censored. We selected 7 days as a conservative timeframe based on the current trend in the length of hospital stay for patients with acute coronary syndrome and to exclude events related to the index PCI procedure. Bleeding events after 7 days were also assessed with the use of the Bleeding Academic Research Consortium (BARC) criteria [13]. The bleeding definitions used in the present study are shown in Online Table 1.

Anemia was classified as a hemoglobin level <12 g/dl in men and <11 g/dl in women [14]. Creatinine clearance was calculated using the Cockroft-Gault formula [15]. The estimated glomerular filtration rate (eGFR) was calculated using the following equation for Japanese patients recommended by the Japanese Society of Nephrology:

$$\text{eGFR}\ (\text{mL/min}/1.73\ \text{m}^2) = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}\ (\times\ 0.739 \text{ if female})$$ [16].

Study goal

The objective of this study was to compare the four bleeding scores (HASBLED [10], ORBIT [11], PRECISE-DAPT [9], and PARIS score [8]) regarding their ability to stratify bleeding risk within our cohort (those who took both OAC and APT). For this objective, the four scores were calculated and assigned to each patient. The primary endpoint for score validation was the occurrence of TIMI significant bleeding at 7 days or later after the index procedure and at the end of follow-up. The four bleeding scores were validated with the occurrence of BARC class $\geq$3 as well. We also estimated the 3-year cumulative incidence of bleeding by 1 minus the Kaplan–Meier estimate of bleeding-free survival at 3 years, to take into account loss to follow-up.

Statistical analysis

Continuous variables are summarized as mean and standard deviation (SD) or median and interquartile range (IQR), and categorical variables are shown as numbers and proportions. Continuous variables were compared using Student's t-test or the Wilcoxon rank-sum test based on their distributions. Categorical variables were compared using chi-squared tests.

Each patient in our cohort was assigned four bleeding risk scores: the HAS-BLED score, ORBIT score, PRECISE-DAPT score, and PARIS score. The distribution of each risk score was visualized graphically.

Time dependent receiver operating characteristic curve (ROC) analyses were carried out to examine the ability of the four scores to identify the patients with bleeding events [17]. Model discrimination was assessed using the C-statistic in our cohort.

Patients were then divided into two groups according to each score: HAS-BLED score, non-high (0–3) and high (4–6); ORBIT score, non-high (0–2) and high (3–7); PRECISE-DAPT, non-high (lowest three quartiles) and high (highest quartile); PARIS score, non-high (low and intermediate) and high (highest tertile). Bleeding event rates at 3 years were calculated in each risk grouping using the Kaplan–Meier method and compared using the log-rank test. As a measure of the strength of the association between each risk score and bleeding events, we calculated hazard ratio (HR) and 95% confidence interval (CI) using Cox proportional-hazards regression analysis.

All statistical analyses were performed using JMP software version 13.1 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics and bleeding events

Of 3718 patients who underwent PCI during the study period, we identified 302 eligible subjects who took both OAC and APT (Fig. 1). During the 3-year follow-up, the TIMI significant bleeding events occurred in 90 patients (29.8%), and BARC class ≥3 bleeding occurred in 53 patients (17.5%). The clinical characteristics of the recruited patients are summarized in Table 1. The over-all follow-up rate was 92.1%.

The median length of follow-up was 916 (IQR = 580–1080) days for the bleeding group and 1080 (IQR = 556–1080) days for the no-bleeding group. The mean age of the patients tended to be higher in the bleeding than in the no-bleeding group [73.5 (SD = 8.9) years and 71.6 (SD = 9.3) years, respectively; $p = 0.09$]. The mean HAS-BLED, ORBIT, and PRECISE-DAPT scores were significantly higher in the bleeding than in the no-bleeding group [HAS-BLED: bleeding group, 3.63 (SD = 1.16); no-bleeding group, 3.13 (SD = 1.04); $p = 0.001$; ORBIT: bleeding group, 2.92 (SD = 1.58); no-bleeding group, 2.35 (SD = 1.27); $p = 0.003$; PRECISE-DAPT: bleeding group, 32.4 (SD = 16.7); no-bleeding group, 26.9 (SD = 12.6); $p = 0.002$]; however, the mean value of the PARIS score was similar in the two groups [bleeding group, 8.3 (SD = 2.7); no bleeding group, 7.9 (SD = 2.5); $p = 0.26$].

The indications for OAC were similar in the two groups (Table 1). The most common indication was AF, accounting for approximately 70% of indications.

Table 2 shows the location of the worst bleeding site. Of 90 patients who experienced a bleeding event, 15 were major, including seven cases of intracranial bleeding. Gastrointestinal bleeding was the most frequent bleeding site. The median time to the first occurrence of TIMI significant bleeding was 228 (IQR = 89–513) days.

Distribution of each score

The overall distribution of each bleeding risk score is displayed in Fig. 2. As shown in Fig. 2A, the peak value of the HAS-BLED score distribution was 3, which differs widely from that of the original derivation and validation cohort of the HAS-BLED score [10], indicating our cohort had a much higher bleeding risk. The distribution of ORBIT score in our cohort was similar with that of original derivation and validation cohort, except there were no patient with score 0 [11] (Fig. 2B). Regarding the PRECISE-DAPT score, the numbers of patients categorized at very low (≤10), low (11–17), moderate (18–24), and high (≥25) bleeding risk were 16 (5.3%), 45 (14.9%), 80 (26.5%), and 161 (53.3%), respectively. Regarding the PARIS score, the number of patients categorized at low (0–3), intermediate (4–7), and high (≥8) bleeding risk were 11 (3.6%), 111 (36.8%), and 180 (59.6%), respectively. The histogram was shifted to the higher-risk group, compared with those of the original cohorts used to derive and validate the PRECISE-DAPT and PARIS scores [8,9] (Fig. 2C and D).

Predictive performance of each score

The time-dependent ROC curve analysis results are shown in Fig. 3. At 180 days, the diagnostic power of each bleeding score to distinguish patients with or without TIMI significant bleeding was similar among four scores, with an area under the curve (AUC) of approximately 0.58–0.60. However, the AUCs of the four scores gradually differed from each other during the 3 years of follow up, ending up at 0.62 for the HAS-BLED score, 0.61 for the ORBIT score, 0.60 for the PRECISE-DAPT score, and 0.52 for the PARIS score (HAS-BLED vs. PARIS, $p = 0.04$; ORBIT vs. PARIS, $p = 0.006$, PRECISE-DAPT vs. PARIS, $p = 0.02$) (Fig. 3A). On the other hand, ORBIT and PRECISE-DAPT score have kept the highest AUC of approximately 0.7 to stratify BARC class ≥3 bleeding events (Fig. 3B).

The C-statistic for bleeding events is summarized in Table 3. The C-statistic for TIMI significant bleeding was approximately 0.6 for the HAS-BLED, the ORBIT, and the PRECISE-DAPT score; however, it was 0.53 for the PARIS score. Regarding BARC class ≥3 bleeding events, the C-statistic of the ORBIT and the PRECISE-DAPT score was numerically highest among four bleeding risk scores.

Score performance was also consistent, including for TIMI significant bleeding occurring earlier than 7 days after PCI [C-statistic, 0.59 (95% CI, 0.53–0.65, $p < 0.001$); C-statistic, 0.59 (95% CI, 0.53–0.65, $p < 0.001$); C-statistic, 0.59 (95% CI, 0.53–0.65, $p < 0.001$); C-statistic, 0.54 (95% CI, 0.48–0.60, $p = 0.24$), respectively].

As TIMI significant bleeding, the Kaplan–Meier event-free survival analysis showed that the non-high bleeding risk group had a lower risk of adverse bleeding events than the high bleeding risk group stratified according to the HAS-BLED, ORBIT, and PRECISE-DAPT scores, but not when patients were stratified according to the PARIS score (Fig. 4); as BARC class ≥3 bleeding events, the Kaplan–Meier event-free survival analysis showed that the non-high

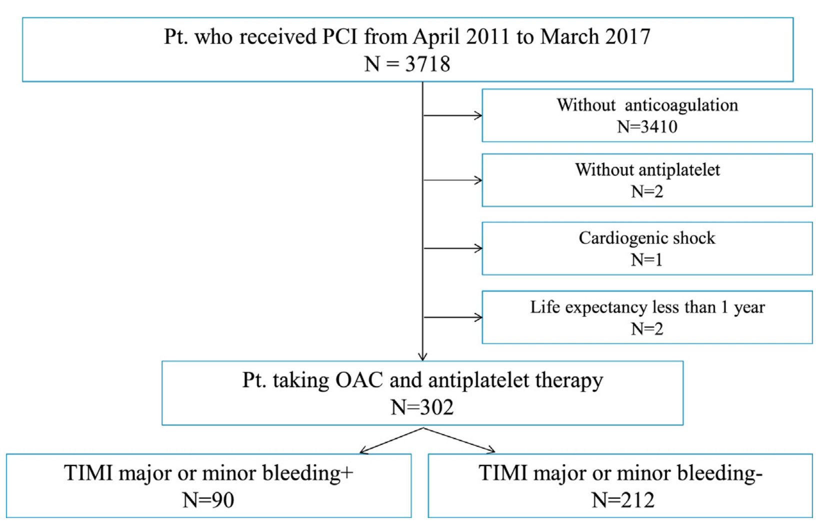

Fig. 1. Flowchart detailing the study design.
OAC, oral anticoagulant; PCI, percutaneous coronary intervention; Pt., patient; TIMI, Thrombolysis in Myocardial Infarction criteria.

Table 1
Patient's clinical characteristics, bleeding score, medication, and procedural characteristics at baseline.

Patients: *n*	All patients (*n* = 320)	TIMI bleeding			BARC ≥3 bleeding		
		+ (*n* = 90)	– (*n* = 212)	*p*-value	+ (*n* = 53)	– (*n* = 249)	*p*-value
Clinical baseline characteristics							
Mean (SD) age (years)	72.1 (9.2)	73.5 (8.9)	71.6 (9.3)	0.09	75.7 (8.7)	71.4 (9.2)	0.02
Male sex	235 (77.8%)	70 (77.8%)	165 (77.8%)	1.00	36 (67.9%)	199 (79.9%)	0.07
Mean (SD) BMI (kg/m^2)	23.4 (3.8)	23.2 (3.8)	23.5 (3.8)	0.53	22.4 (3.6)	23.6 (3.8)	0.03
Diabetes mellitus	137 (45.4%)	45 (50%)	92 (43.4%)	0.29	26 (49.1%)	111 (44.6%)	0.55
Hypertension	224 (74.1%)	67 (74.4%)	157 (74.1%)	0.94	38 (71.7%)	186 (74.7%)	0.65
Hypercholesterolemia	190 (62.9%)	59 (65.6%)	131 (61.8)	0.53	33 (62.3%)	157 (63.1%)	0.91
Smoking history	191 (63.2%)	60 (66.7%)	131 (61.8%)	0.42	31 (58.5%)	160 (64.3%)	0.43
Prior myocardial infarction	78 (25.8%)	16 (17.8%)	62 (29.3%)	0.03	7 (13.2%)	71 (28.5%)	0.01
Prior heart failure	141 (46.7%)	46 (51.1%)	95 (44.8%)	0.32	34 (64.2%)	107 (43.0%)	0.005
Prior stroke	42 (13.9%)	16 (17.8%)	26 (12.3%)	0.21	13 (24.5%)	29 (11.7%)	0.02
Prior PCI	116 (38.4%)	34 (37.8%)	82 (38.7%)	0.88	17 (32.1%)	99 (39.8%)	0.29
Prior CABG	58 (19.2%)	21 (23.3%)	37 (17.5%)	0.24	10 (18.9%)	48 (19.3%)	0.95
Ccr (ml/min)	60.1 (24.1)	55.3 (24.6)	62.1 (23.7)	0.03	50.4 (25.4)	62.1 (23.4)	0.001
HAS-BLED score	3.27 (1.09)	3.63 (1.16)	3.13 (1.04)	0.001	3.81 (1.24)	3.15 (1.03)	<0.0001
Hypertension	224 (74.1%)	67 (74.4%)	157 (74.1%)	0.94	38 (71.7%)	186 (74.7%)	0.65
Abnormal renal function	12 (4.0%)	7 (7.8%)	5 (2.36%)	0.04	6 (11.3%)	6 (2.4%)	0.01
Abnormal liver function	38 (9.3%)	9 (10.0%)	19 (9.0%)	0.79	6 (11.3%)	22 (8.9%)	0.59
Stroke	42 (13.9%)	16 (17.8%)	26 (12.3%)	0.21	13 (24.5%)	29 (11.7%)	0.02
Bleeding	52 (17.2%)	22 (24.4%)	30 (14.2%)	0.03	15 (28.3%)	37 (14.9%)	0.03
Labile INR	86 (28.4%)	36 (40.0%)	50 (23.6%)	0.05	22 (41.5%)	64 (25.7%)	0.02
Elderly	243 (80.4%)	77 (85.6%)	166 (78.3%)	0.14	49 (92.5%)	195 (77.9%)	0.01
Drugs	302 (100%)	90 (100%)	212 (100%)	-	53 (100%)	249 (100%)	-
Alcohol	9 (3.0%)	3 (3.3%)	6 (2.8%)	0.82	1 (1.9%)	8 (3.2%)	0.59
ORBIT score	2.52 (1.39)	2.92 (1.58)	2.35 (1.27)	0.003	3.36 (1.65)	2.35 (1.27)	<0.0001
Age ≥75 years	129 (42.7%)	42 (46.7%)	87 (41.0%)	0.37	33 (62.3%)	96 (38.6%)	0.002
Anemia	60 (19.9%)	26 (28.9%)	34 (16.0%)	0.01	21 (39.6%)	39 (15.7%)	0.0002
Bleeding history	36 (11.9%)	17 (18.9%)	19 (9.0%)	0.02	11 (20.8%)	25 (10.0%)	0.04
eGFR <60 ml/min/1.73 m^2	139 (46.0%)	45 (50.0%)	94 (44.3%)	0.37	28 (52.8%)	111 (44.6%)	0.27
Treatment with antiplatelets	302 (100%)	90 (100%)	212 (100%)	-	53 (100%)	249 (100%)	-
PRECISE-DAPT score	28.5 (14.2)	32.4 (16.7)	26.9 (12.6)	0.002	36.7 (17.3)	26.8 (12.8)	<0.0001
Hemoglobin (g/dl)	13.3 (1.9)	12.8 (2.0)	13.5 (1.9)	0.01	12.3 (2.1)	13.5 (1.8)	<0.0001
White-blood-cell count	6730 [5405,8910]	6205 [5070,8178]	6905 [5628,9148]	0.03	6170 [5010,7780]	6860 [5455,8950]	0.11
Mean (SD) age (years)	72.1 (9.2)	73.5 (8.9)	71.6 (9.3)	0.09	75.7 (8.7)	71.4 (9.2)	0.02
Ccr (ml/min)	60.1 (24.1)	55.3 (24.6)	62.1 (23.7)	0.03	50.4 (25.4)	62.1 (23.4)	0.001
Prior bleeding	36 (11.9%)	17 (18.9%)	19 (9.0%)	0.02	11 (20.8%)	25 (10.0%)	0.04
PARIS score	8.0 (2.6)	8.3 (2.7)	7.9 (2.5)	0.26	9.1 (2.6)	7.8 (2.5)	0.001
Age <50 years	6 (2.0%)	0 (0.0%)	6 (2.8%)	0.04	0 (0.0%)	6 (2.4%)	0.59
50–59	27 (5.6%)	6 (6.7%)	11 (5.2%)	0.62	3 (5.7%)	14 (5.6%)	0.99
60–69	87 (28.8%)	26 (28.9%)	61 (28.8%)	0.98	10 (18.9%)	77 (30.9%)	0.07
70–79	121 (40.1%)	31(34.4%)	90 (42.5%)	0.19	19 (35.9%)	102 (41.0%)	0.49
≥80 years	71 (23.5%)	27 (30.0%)	44 (21.0%)	0.09	21 (39.6%)	50 (20.1%)	0.004
BMI <25	214 (70.9%)	61 (67.8%)	153 (72.2%)	0.44	39 (73.6%)	175 (70.3%)	0.63
25–34.9	84 (27.8%)	29 (32.2%)	55 (25.9%)	0.27	14 (26.4%)	70 (28.1%)	0.80
≥35	4 (1.3%)	0 (0.0%)	4 (1.9%)	0.09	0 (0.0%)	4 (1.6%)	1.0
Current smoking	72 (23.8%)	13 (14.4%)	59 (27.8%)	0.01	9 (17.0%)	63 (25.3%)	0.18
Anemia	60 (19.9%)	26 (28.9%)	34 (16.0%)	0.01	21 (39.6%)	39 (15.7%)	0.0002
Ccr <60 ml/min	159 (52.6%)	55 (61.1%)	104 (49.1%)	0.05	34 (64.2%)	125 (50.2%)	0.06
Triple therapy	250 (82.7%)	74 (82.2%)	176 (83.0%)	0.87	45 (84.9%)	205 (82.3%)	0.64
Medication at discharge							
Aspirin	269 (89.1%)	81 (90.0%)	188 (88.7%)	0.73	48 (90.6%)	221 (88.8%)	0.70
Thienopyridine	281 (93.0%)	83 (92.2%)	198 (93.4%)	0.72	50 (94.3%)	231 (92.8%)	0.68
DAPT	250 (82.8%)	74 (82.2%)	176 (83.0%)	0.87	45 (84.9%)	205 (82.3%)	0.64
PPI	280 (92.7%)	82 (91.1%)	198 (93.4%)	0.49	49 (92.5%)	231 (92.8%)	0.94
Type of OAC				0.49			0.38
VKA	176 (58.3%)	55 (61.1%)	121 (57.1%)		31 (58.5%)	145 (58.2%)	
Rivaroxaban	52 (17.2%)	13 (14.4%)	39 (18.4%)		6 (11.3%)	46 (18.5%)	
Dabigatran	13 (4.3%)	3 (3.3%)	10 (4.7%)		2 (3.8%)	11 (4.4%)	
Apixaban	54 (17.9%)	15 (16.7%)	39 (18.4%)		11 (20.8%)	43 (17.3%)	
Edoxaban	7 (2.3%)	4 (4.4%)	3 (1.4%)		3 (5.7%)	4 (1.6%)	
Indication for OAC				0.83			0.16
Atrial fibrillation	208 (68.9%)	64 (71.1%)	144 (67.9%)		42 (79.3%)	166 (66.7%)	
Post cardiac surgery	49 (16.2%)	13 (14.4%)	36 (17.0%)		5 (9.4%)	44 (17.7%)	
Other (apical aneurysm, pulmonary embolism, PAD)	45 (14.9%)	13 (14.4%)	32 (15.1%)		6 (11.3%)	39 (15.7%)	
DAPT continuation (continue number/survivor, %)							
At 1 month	257/301 (85.4%)	72/89 (80.9%)	185/212 (87.3%)	0.15	42/50 (80.8%)	215/249 (86.3%)	0.41
At 3 months	194/297 (65.3%)	52/89 (58.4%)	142/208 (68.3%)	0.10	30/52 (57.7%)	164/245 (66.9%)	0.27
At 6 months	152/295 (51.5%)	36/89 (40.4%)	116/206 (56.3%)	0.01	21/52 (40.4%)	131/243 (53.9%)	0.11
At 12 months	99/283 (35.0%)	25/82 (30.5%)	74/201 (36.8%)	0.31	14/45 (31.1%)	85/238 (35.7%)	0.67

Table1 (*Continued*)

Patients: *n*	All patients (*n* = 320)	TIMI bleeding			BARC ≥3 bleeding		
		+ (*n* = 90)	– (*n* = 212)	*p*-value	+ (*n* = 53)	– (*n* = 249)	*p*-value
Procedural characteristics							
DES	207 (68.5%)	64 (71.1%)	143 (67.5%)	0.53	39 (73.6%)	168 (67.5%)	0.38
Indication of PCI				0.36			0.31
STEMI	93 (30.8%)	27 (30.0%)	66 (31.1%)		13 (24.5%)	80 (32.1%)	
NSTEMI	7 (2.3%)	2 (2.2%)	5 (2.4%)		2 (3.8%)	5 (2.0%)	
Unstable AP	32 (10.6%)	14 (15.6%)	18 (8.5%)		9 (17.0%)	23 (9.2%)	
Stable AP	170 (56.3%)	47 (52.2%)	123 (58.0%)		29 (54.7%9	141 (56.6%)	

Values are the mean ± standard deviation (SD), *n* (%), or median (interquartile range) as appropriate. BMI, body-mass index; PCI, pertcutaneous coronary intervention; CABG, coronary artery bypass graft; Ccr, creatinine clearance; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; PAD, peripheral arterial disease; DAPT, dual antiplatelet therapy; PPI, proton-pump inhibitor; OAC, oral anticoagulant; VKA, vitamin K antagonist; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; AP, angina pectoris; DES, drug-eluting stent.

bleeding risk group had a lower risk of bleeding events than the high bleeding risk group stratified according to all four risk scores (Fig. 5).

Kaplan–Meier 3-year estimates of TIMI significant bleeding events stratified according to the high vs. non-high category of each risk score were as follows: high-risk group, 44.3%; non-high-risk group, 27.5% (HR, 1.74; 95% CI, 1.15–2.64; $p = 0.01$) for the HAS-BLED, high-risk group, 41.8%; non-high-risk group, 28.0% (HR, 1.63; 95% CI, 1.08–2.48; $p = 0.02$) for the ORBIT, high, 40.8%; non-high, 26.3% (HR, 1.63; 95% CI, 1.07–2.53; $p = 0.02$) for the PRECISE-DAPT, high, 34.7%; non-high, 32.9% (HR, 1.07; 95% CI, 0.70–1.64; $p = 0.76$) for the PARIS. Kaplan–Meier 3-year estimates of BARC class ≥3 bleeding events stratified according to the high vs. non-high category of each risk score were as follows: high-risk group, 31.5%; non-high-risk group, 13.8% (HR, 2.23; 95% CI, 1.30–3.88; $p = 0.004$) for the HAS-BLED, high-risk group, 28.9%; non-high-risk group, 14.5% (HR, 2.25; 95% CI, 1.31–3.96; $p = 0.003$) for the ORBIT, high, 31.2%; non-high, 9.1% (HR, 3.87; 95% CI, 2.06–7.91; $p < 0.0001$) for the PRECISE-DAPT, high, 23.4%; non-high, 15.7% (HR, 1.85; 95% CI, 1.04–3.47; $p = 0.04$) for the PARIS.

Table 2
Location of worst bleeding event per patient.

Patients: *n*	All patients (*n* = 320)
TIMI criteria	
Major	15 (5.0%)
Minor	38 (12.6%)
Requiring medical attention	37 (12.3%)
BARC criteria	
5	5 (1.7%)
3c	7 (2.3%)
3b	12 (4.0%)
3a	29 (9.6%)
Location of worst bleeding event	
Intracranial	7 (2.3%)
Access site	8 (2.6%)
Retroperitneal	1 (0.3%)
Gastrointestinal	35 (11.5%)
Skin hematoma requiring medical attention	2 (0.6%)
Nose	9 (3.0%)
Urogenital	13 (4.3%)
Respiratory tract	4 (1.3%)
Mouth	6 (2.0%)
Muscle	3 (1.0%)
Others	4 (1.3%)

Values are *n* (%). TIMI, Thrombolysis in Myocardial Infarction; BARC, the Bleeding Academic Research Consortium.

Discussion

In this study, we compared four different bleeding risk scores in Japanese patients treated with PCI who required both OAC and APT. The main findings of the present study were as follows:

1) The distribution of all risk scores were much higher than those in the original articles among this study population.
2) During the 3-year follow-up, the incidence of TIMI significant bleeding was 29.8%, and that of BARC class ≥3 bleeding was 17.5%.
3) The HAS-BLED, ORBIT, and PRECISE-DAPT scores were better able to stratify TIMI significant bleeding risk than the PARIS score (the AUC was 0.62 for the HAS-BLED score, 0.61 for the ORBIT score, 0.60 for the PRECISE-DAPT score, and 0.52 for the PARIS score).
4) Although all four scores could predict BARC class ≥3 bleeding events, the PRECISE-DAPT score stratified the BARC class ≥3 bleeding events the most comprehensively.

Strategies to deal with bleeding complications after PCI include cessation of antithrombotic therapy and/or blood transfusion, both of which are associated with worse clinical outcomes [18]; therefore, prevention appears to be the most secure approach. When using antithrombotic agents, careful assessment of patient bleeding risk should be paid. From this point of view, the results of the present study are of clinical significance.

Contrary to the risk of an ischemic event, the risk of serious bleeding in Asians seemed greater compared than that of Western populations. Indeed, clinical experience with warfarin has raised the concern that Asians have a considerably higher risk of intracranial hemorrhage than Western populations [19]. Also, there are concerns about an increased incidence of bleeding complications in Asians not only in the peri-procedural period but also long-term [20–22]. In the J-RHYTHM registry, which enrolled 7937 Japanese patients with non-valvular AF, the distribution of the HAS-BLED score was higher than that of the original HAS-BLED cohort [10,23]. A recently published investigation by Yoshikawa et al., which validated the DAPT score in a Japanese population that underwent PCI, likewise revealed that the distribution of the DAPT score shifted one point lower than that of the original DAPT cohort, which meant that the Japanese PCI population was burdened with a bleeding risk rather than an ischemic event risk [24,25]. Until now, there have been limited investigations comparing the PRECISE-DAPT score and PARIS score in an Asian cohort. Therefore, it is unknown whether those scores are higher in all Asian patients undergoing PCI than in Western populations or only in those patients who required both OAC and APT after PCI.

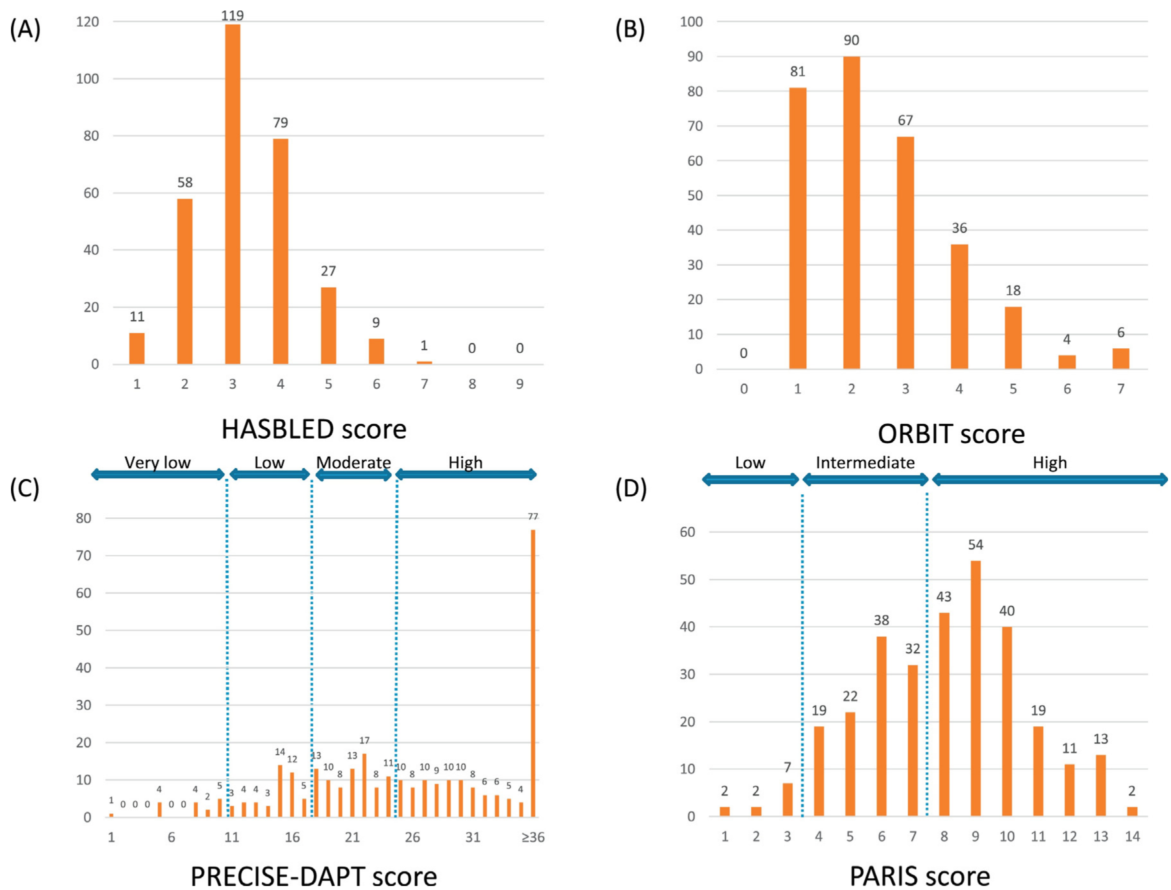

Fig. 2. Histograms displaying the distribution of bleeding risk scores. Panel A refers to the HAS-BLED score distribution in our cohort. Panel B refers to ORBIT score distribution. Panel C refers to PRECISE-DAPT score distribution. Patients were categorized into four quartiles: very low risk, score ≤10; low risk, score 11–17; moderate risk, score 18–24; and high risk, score ≥25. Panel D refers to PARIS score distribution. Patients were categorized into three tertiles: low risk, score ≤3; intermediate risk, score 4–7; and high risk, score ≥8.

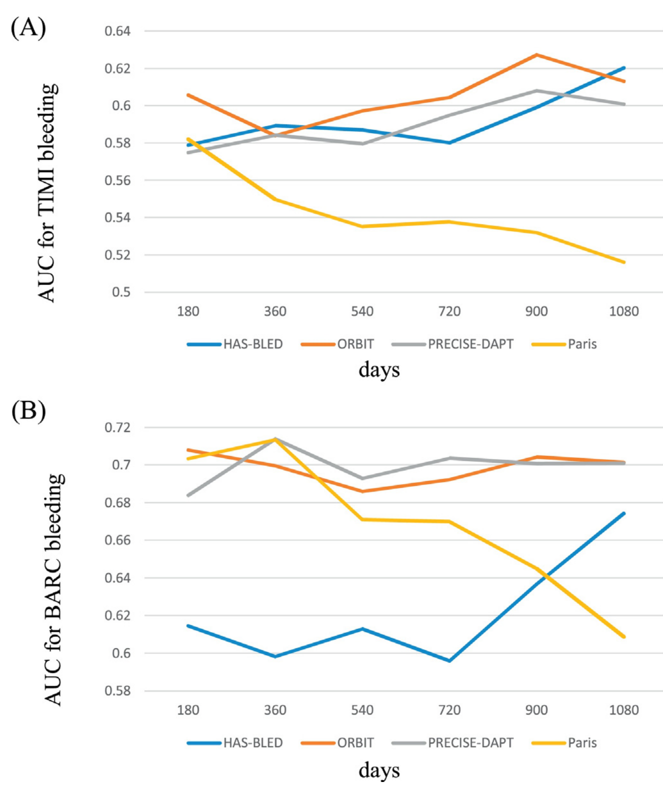

Fig. 3. Time-dependent receiver operating characteristic curve.
AUC, area under the curve; HAS-BLED, HAS-BLED score; ORBIT, ORBIT score; PRECISE-DAPT, PRECISE-DAPT score; PARIS, PARIS score; TIMI, Thrombolysis in Myocardial Infarction criteria; BARC, Bleeding Academic Research Consortium.

Table 3
Discrimination of each predictive model of adverse bleeding events (TIMI major or minor bleeding).

Variables	C-statistic	95% confidence interval	*p*-value
TIMI major or minor bleeding			
HAS-BLED	0.58	0.52–0.64	<0.0001
ORBIT	0.59	0.53–0.65	<0.0001
PRECISE-DAPT	0.58	0.51–0.64	0.001
PARIS	0.53	0.47–0.60	0.24
BARC class ≥3 bleeding			
HAS-BLED	0.62	0.54–0.70	0.0001
ORBIT	0.67	0.60–0.75	<0.0001
PRECISE-DAPT	0.67	0.59–0.75	<0.0001
PARIS	0.64	0.56–0.72	0.001

TIMI, Thrombolysis in Myocardial Infarction; BARC, the Bleeding Academic Research Consortium.

The distributions of the risk scores in our study, which deviated significantly upward, was inconsistent with those of the HAS-BLED, PRECISE-DAPT, and PARIS studies.

TIMI significant bleeding events occurred in about 30% of the enrolled subjects during the 3-year follow-up in this study. In the PRECISE-DAPT trial, the predicted bleeding risk in patients with the highest bleeding risk was 2% during 1 year; in PARIS trial, the observed rate of bleeding events in the high-risk group was 9.5% during 2 years; and in HAS-BLED trial, the rate of bleeding events at 1 year was 1.5% in all the patients. Although our study had a longer follow-up period than did previous studies, with follow-up period of 1 or 2 years [8–10], the incidence of bleeding events was much higher than that of previous studies. Even compared with the Japanese PCI population, which had a 3% rate bleeding event defined as a composite of moderate or severe bleeding according to GUSTO criteria [25], the incidence of bleeding events was much higher in this study population of patients using both an OAC and APT after PCI.

In the present study, major, minor, and bleeding requiring medical attention were evaluated as the primary endpoint. Various studies have suggested the clinical importance of minor bleeding [26]. Genereux et al. reported that not only major but minor bleeding events had a clinical impact on 2-year mortality of post-discharge after PCI [27]. Moreover, Rao et al. reported that all degrees of TIMI bleeding among acute coronary syndrome patients were associated with a similar risk of 30-day death or MI [28].

All risk scores which were validated in the present study had only a low to moderate predictive performance for TIMI significant bleeding events in our cohort. This can probably be ascribed to a higher bleeding risk in our cohort. The PRECISE-DAPT score slightly underestimated the bleeding risk in the PLATO PCI population, which was used as an external validation cohort [9,29]. We speculated that this resulted from a higher bleeding risk in the PLATO PCI population which consisted entirely of patients with acute coronary syndrome. The disproportionate distribution of risk scores in our cohort might have influenced the discrimination ability of the risk scores. The difference of bleeding definition used among the present study and the derivation studies might also have affected the relatively low predictive performance of bleeding risk scores. The definition of bleeding events in the PRECISE-DAPT trial was TIMI major or minor bleeding, and that in the PARIS study was BARC class 3 or 5 bleeding; whereas HAS-BLED used its own definition (any bleeding requiring hospitalization and/or causing a decrease in hemoglobin level of >2 g/L and/or requiring transfusion). We selected TIMI significant bleeding (major, minor, and

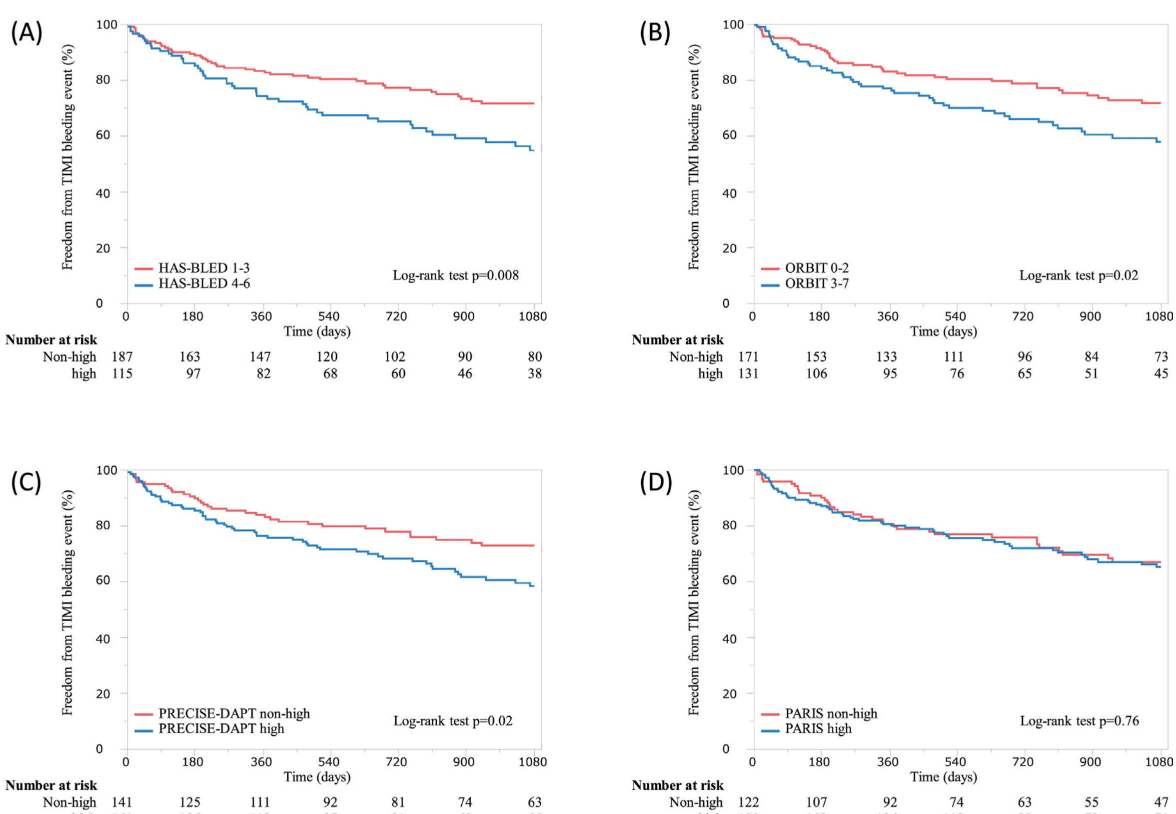

Fig. 4. Cumulative incidence of a composite of major bleeding, minor bleeding, and bleeding requiring medical attention according to Thrombolysis in Myocardial Infarction (TIMI) criteria. Panel A shows the freedom from adverse bleeding events in patients stratified by HAS-BLED score: non-high (1–3) and high (4–6). Panel B shows that in patients stratified by ORBIT score: non-high (1–2) and high (3–7). Panel C shows that in patients stratified by PRECISE-DAPT score: non-high (lowest three quartiles) and high (highest quartile). Panel D shows that in patients stratified by PARIS score: non-high (low and intermediate) and high (highest tertile).

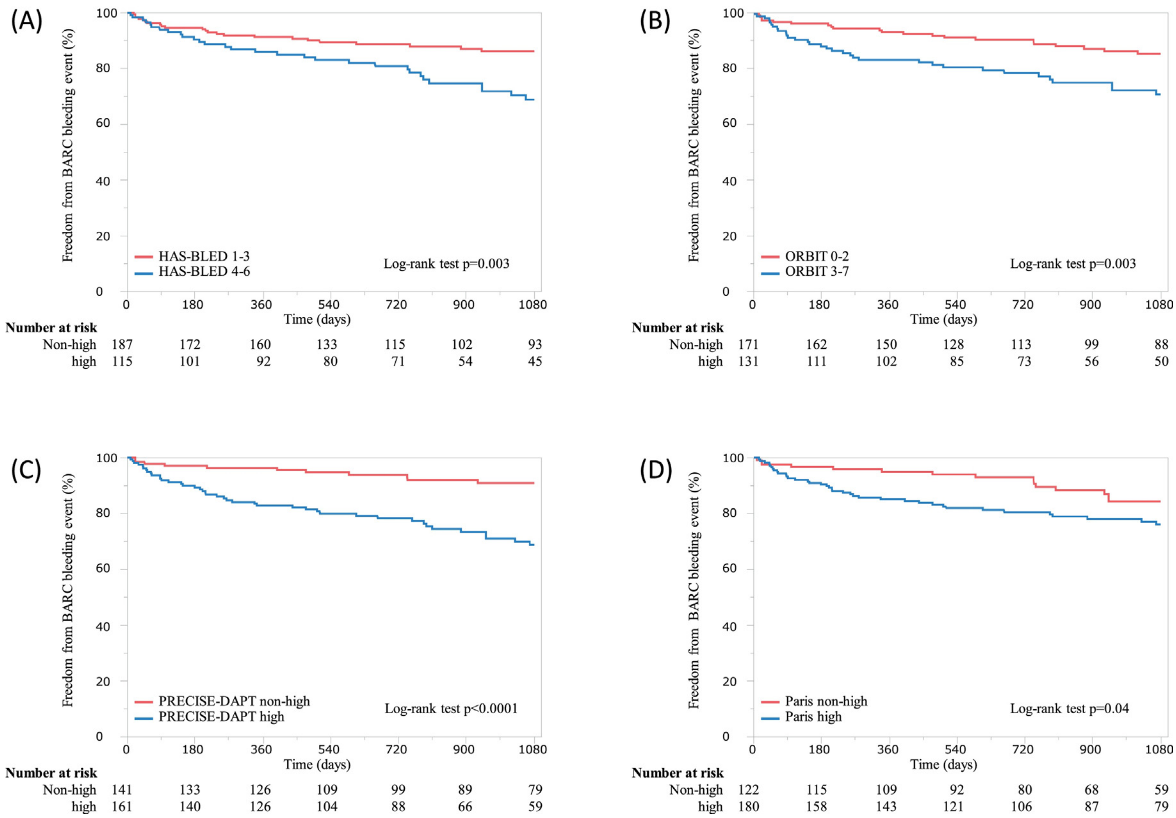

Fig. 5. Cumulative incidence of Bleeding Academic Research Consortium (BARC) class ≥3 bleeding. Panel A shows the freedom from adverse bleeding events in patients stratified by HAS-BLED score: non-high (1–3) and high (4–6). Panel B shows that in patients stratified by ORBIT score: non-high (1–2) and high (3–7). Panel C shows that in patients stratified by PRECISE-DAPT score: non-high (lowest three quartiles) and high (highest quartile). Panel D shows that in patients stratified by PARIS score: non-high (low and intermediate) and high (highest tertile).

bleeding requiring medical attention) as the primary endpoint for bleeding risk score validation, because this definition covers all the bleeding definitions used in the three validation studies. However, the heterogeneity of bleeding definition among validation trials has led to inconsistencies and uncertainties in assessing and reporting bleeding events even in the same patient population. Indeed, in the present study, the PARIS score was not able to stratify the risk of TIMI significant bleeding, but able to stratify the risk of BARC class ≥3 bleeding. Thus, a unified bleeding definition is particularly important.

The prevalence of AF and valvular heart disease substantially increases with aging [30], and the mean age of patients in our cohort was approximately 5 years older than that in previous studies [8–10]. It is also known that nutritional status is associated with bleeding and cardiovascular outcomes in elderly patients with stable angina pectoris [31,32]. Thus, it is an issue in the future to consider nutritional status combined with well-known risk factors or bleeding risk score in investigations of bleeding risk in patients taking an OAC and undergoing PCI.

Study limitations

This study had several limitations. First, it was performed at a single medical center and followed a non-randomized, retrospective study design. Accordingly, only a limited number of patients were enrolled. Moreover, by the nature of the retrospective observational design, regimens of antiplatelet therapy and the duration of the DAPT were at the discretion of the treating physicians. Second, we could not examine the compliance of each patient. Third, patients taking a DOAC tended to be included more in recent years. Therefore, DOACs were used more frequently in patients on single APT and OAC regimen, although this regimen was employed in fewer than one-sixth of the patients. Fourth, we did not evaluate the incidence of ischemic events. Furthermore, we could not construct a new risk score for patients taking an OAC and APT because of the limited number of patients. Additional studies with large sample sizes and long-term follow-up investigating bleeding risk scores for patients taking an OAC treated with PCI are needed.

Conclusion

In this retrospective study of patients receiving OAC and undergoing PCI, the HAS-BLED, ORBIT, and PRECISE-DAPT scores were better able to stratify the risk of TIMI significant bleeding than the PARIS score. Although all four scores could predict BARC class ≥3 bleeding events, the PRECISE-DAPT score could stratify the BARC class ≥3 bleeding events the best when analyzed comprehensively.

Additional prospective studies with large sample size evaluating those specific patients are necessary.

Research Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

H.I. received lecture fees from Astellas Pharma Inc., Bayer Pharmaceutical Co., Ltd., Daiichi-Sankyo Pharma Inc., and MSD K. K. T.M. received lecture fees from Bayer Pharmaceutical Co., Ltd.,

Daiichi-Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K. K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K. K., Pfizer Japan Inc., Sanofi-aventis K. K., and Takeda Pharmaceutical Co., Ltd. T.M. received unrestricted research grant for Department of Cardiology, Nagoya University Graduate School of Medicine from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K. K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K. K., Otsuka Pharma Ltd., Pfizer Japan Inc., Sanofi-aventis K. K., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd. Other authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.10.013.

References

[1] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin 3rd JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521–643.

[2] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.

[3] Perez-Gomez F, Alegria E, Berjon J, Iriarte JA, Zumalde J, Salvador A, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. J Am Coll Cardiol 2004;44:1557–66.

[4] Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Schjerning Olsen AM, Mikkelsen A, et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. J Am Coll Cardiol 2013;62:981–9.

[5] Yamashita Y, Uozumi R, Hamatani Y, Esato M, Chun YH, Tsuji H, et al. Current status and outcomes of direct oral anticoagulant use in real-world atrial fibrillation patients- Fushimi AF Registry. Circ J 2017;81:1278–85.

[6] Yoshida R, Morishima I, Takagi K, Morita Y, Tsuboi H, Murohara T. Comparison between long-term clinical outcomes of vitamin K antagonist and direct oral anticoagulants in patients with atrial fibrillation undergoing percutaneous coronary intervention. Circ J 2018;82:2016–24.

[7] Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082–115.

[8] Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. J Am Coll Cardiol 2016;67:2224–34.

[9] Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389:1025–34.

[10] Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093–100.

[11] O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. Eur Heart J 2015;36:3258–64.

[12] Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet 2009;374:29–38.

[13] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

[14] Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). Arch Intern Med 2002;162:1401–8.

[15] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.

[16] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–92.

[17] Chiang C-T, Hung H. Non-parametric estimation for time-dependent AUC. J Statist Plan Infer 2010;140:1162–74.

[18] Rao SV, Eikelboom JA, Granger CB, Harrington RA, Califf RM, Bassand JP. Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1193–204.

[19] Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol 2007;50:309–15.

[20] Kohsaka S, Miyata H, Ueda I, Masoudi FA, Peterson ED, Maekawa Y, et al. An international comparison of patients undergoing percutaneous coronary intervention: A collaborative study of the National Cardiovascular Data Registry (NCDR) and Japan Cardiovascular Database-Keio interhospital Cardiovascular Studies (JCD-KiCS). Am Heart J 2015;170:1077–85.

[21] Wang TY, Chen AY, Roe MT, Alexander KP, Newby LK, Smith Jr SC, et al. Comparison of baseline characteristics, treatment patterns, and in-hospital outcomes of Asian versus non-Asian white Americans with non-ST-segment elevation acute coronary syndromes from the CRUSADE quality improvement initiative. Am J Cardiol 2007;100:391–6.

[22] Mak KH, Bhatt DL, Shao M, Hankey GJ, Easton JD, Fox KA, et al. Ethnic variation in adverse cardiovascular outcomes and bleeding complications in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study. Am Heart J 2009;157:658–65.

[23] Okumura K, Inoue H, Atarashi H, Yamashita T, Tomita H, Origasa H, et al. Validation of CHA(2)DS(2)-VASc and HAS-BLED scores in Japanese patients with nonvalvular atrial fibrillation: an analysis of the J-RHYTHM Registry. Circ J 2014;78:1593–9.

[24] Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735–49.

[25] Yoshikawa Y, Shiomi H, Watanabe H, Natsuaki M, Kondo H, Tamura T, et al. Validating utility of dual antiplatelet therapy score in a large pooled cohort from 3 Japanese percutaneous coronary intervention studies. Circulation 2018;137:551–62.

[26] Nakamura M, Kougame N, Iijima R, Ono T, Ikeda N, Tokue M, et al. Individualized antiplatelet therapy after drug-eluting stent deployment: Implication of clinical trials of different durations of dual antiplatelet therapy. J Cardiol 2017;70:511–7.

[27] Genereux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, et al. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. J Am Coll Cardiol 2015;66:1036–45.

[28] Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Mahaffey KW, et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. J Am Coll Cardiol 2006;47:809–16.

[29] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.

[30] Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino Sr RB, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009;373:739–45.

[31] Tatami Y, Ishii H, Aoki T, Harada K, Hirayama K, Shibata Y, et al. Decreased serum albumin predicts bleeding events in patients on antiplatelet therapy after percutaneous coronary intervention. Circ J 2017;81:999–1005.

[32] Kunimura A, Ishii H, Uetani T, Aoki T, Harada K, Hirayama K, et al. Impact of Geriatric Nutritional Risk Index on cardiovascular outcomes in patients with stable coronary artery disease. J Cardiol 2017;69:383–8.