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High bleeding risk and clinical outcomes in East Asian patients undergoing percutaneous coronary intervention: the PENDULUM registry

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KEYWORDS

- ACS/NSTE-ACS
- bleeding
- clinical research
- risk stratification
- stable angina

Abstract

Aims: We aimed to evaluate the validity of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria for East Asian patients undergoing contemporary percutaneous coronary intervention (PCI) from the PENDULUM registry.

Methods and results: This *post hoc* analysis included 6,267 Japanese patients undergoing PCI between December 2015 and June 2017 enrolled in PENDULUM. The primary endpoint was the incidence of major bleeding at 12 months post index PCI. In total, 3,185 (50.8%) and 3,082 (49.2%) patients were stratified to the ARC-HBR and non-ARC-HBR groups, respectively, and almost all patients had overlapping criteria. Incidence of major bleeding was 4.2% versus 1.4% in the ARC-HBR group versus the non-ARC-HBR group (hazard ratio 3.00 [95% confidence interval: 2.11-4.27]; p<0.001). As the number of overlapping ARC-HBR criteria increased, the incidence of major bleeding also increased. In contrast, the incidence of major bleeding was 4.2% for one major criterion, 2.1% for two minor criteria. Multivariate analysis suggested that severe CKD, anticoagulant use, acute coronary syndrome, low body weight and heart failure were independent predictors of major bleeding.

Conclusions: Half of the Japanese patients who underwent PCI in the PENDULUM registry met the ARC-HBR criteria, and many patients had overlapping criteria. ARC-HBR criteria are applicable to Japanese patients undergoing contemporary PCI.

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Abbreviations

ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
CI	confidence interval
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
HBR	high bleeding risk
HR	hazard ratio
ICH	intracranial haemorrhage
PCI	percutaneous coronary intervention
PPI	proton pump inhibitor

Introduction

Advances in percutaneous coronary intervention (PCI)-related technologies have allowed patients with increasingly complex medical conditions to be treated with PCI, resulting in more challenging post-PCI management[1]. As appropriate antiplatelet therapy is a cornerstone of PCI management, assessment of thrombotic and bleeding risk is essential[2,3]. The Academic Research Consortium for High Bleeding Risk (ARC-HBR) initiative aimed to define HBR in patients undergoing PCI through literature review and clinical consensus, thus enabling more consistent and higher quality clinical study data collection and reporting, and facilitating appropriate clinical practice recommendations or regulatory decisions[1,4]. Although not fully validated, the ARC-HBR criteria are a convenient tool for use in clinical practice because they do not require scores to be calculated and include factors that are not traditionally considered as risk factors.

Previous studies in East Asian patients have reported different risk profiles for thrombosis and bleeding compared with Western patients[5]. A lower dose of antiplatelet therapy was recommended for patients in Asian countries, owing to concerns with respect to a greater risk of bleeding[6]. However, the ARC consensus document suggests that there is a paucity of data in East Asians, stating that more research is required to elucidate the applicability of the ARC definition of HBR to Asian populations[1].

The PENDULUM (Platelet rEactivity in patieNts with DrUg eLUting stent and balancing risk of bleeding and ischeMic event) registry represents contemporary PCI practice, implementing a transradial approach and proton pump inhibitors (PPIs) in daily clinical practice[7]. The objective of this analysis was to evaluate the applicability of ARC-HBR criteria for Japanese patients participating in the PENDULUM registry, and to explore criteria related to HBR in Japanese patients.

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Methods

STUDY DESIGN AND PATIENT POPULATION

The PENDULUM registry (UMIN 000020332) was a prospective, multicentre study of Japanese patients who underwent PCI in a real-world setting. The study protocol was approved by the appropriate ethics panel at each participating centre, and the study was performed in accordance with the principles of the Declaration of Helsinki and applicable Japanese guidelines. All patients provided written informed consent.

Full details of the PENDULUM registry have been described previously[7] and are also provided in **Supplementary Table 1**. In brief, inclusion criteria were age ≥20 years, an indication for PCI with a second-generation drug-eluting stent (DES), and receipt of an antiplatelet treatment. The type and dose of antiplatelet drug administered to patients were at the investigator's discretion. There were no limitations placed on the treatment of any complications arising during follow-up.

ENDPOINTS

The primary endpoint for this analysis was the cumulative incidence of major bleeding at 12 months post index PCI. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) types 3 and 5[8]. The secondary endpoint was the cumulative incidence of intracranial haemorrhage (ICH). ICH was defined as a non-ischaemic stroke (e.g., cerebral haemorrhage, subarachnoid haemorrhage) with neurologic symptoms or with newly developed signs, and where the culprit lesion was detected by computed tomography or magnetic resonance imaging scans. Bleeding events were evaluated by independent assessment committees.

ANALYSIS GROUPS AND DEFINITIONS

The PENDULUM registry[7] was a prospective registry that was initiated in 2015, prior to the publication of the ARC-HBR criteria in 2019[1]. Therefore, we have integrated the prospectively collected PENDULUM data into a *post hoc* retrospective criterion analysis; no additional data were collected for this *post hoc* analysis.

For the *post hoc* criterion analysis, enrolled patients were retrospectively stratified into HBR and non-HBR groups according to ARC-HBR criteria. However, because the PENDULUM registry was initiated prior to the ARC-HBR publication, it did not collect data on all the specified ARC-HBR criteria. Thus, for our *post hoc* analysis, the HBR categories were modified **(Supplementary Table 2)**. Scores were calculated by allocating one point for each major criterion and 0.5 points for each minor criterion. The cumulative incidence of major bleeding was calculated for each ARC-HBR criterion. In addition, for patients with a score of 0.5 to 1.5, the cumulative incidence of major bleeding was calculated for each combination of criteria.

STATISTICAL ANALYSIS

For individual ARC-HBR criteria and clinically relevant variables, the one-year cumulative incidence of major bleeding and ICH was estimated using the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) were generated with Cox proportional hazards regression models. Univariate and multivariate Cox proportional hazards regression models were used to identify independent predictors of major bleeding. Covariates included in the multivariate model were the ARC-HBR criteria, criteria which were considered to be clinically important, and the criteria that showed ≥4% cumulative incidence in the stratified

analysis, which were not procedure-related but were clinically important. Discrimination of the bleeding risk score was assessed by C-statistics. The area under the curve as well as predictive BARC 3 or 5 bleeding probabilities were compared. All tests were two-sided with a 5% level of significance. Statistical analyses were performed using SAS, Release 9.4 (SAS Institute, Cary, NC, USA).

Results

PATIENT POPULATION

A total of 6,267 patients were enrolled in the PENDULUM registry, of whom 3,185 (50.8%) were in the HBR group and 3,082 (49.2%) were in the non-HBR group **(Figure 1A, Table 1)**. The overall mean age was 70 years, and 37.1% were ≥75 years old. The HBR group included more patients who were older (≥75 years), had diabetes, and did not present with acute coronary syndrome **(Figure 1B, Table 1)**. Baseline laboratory parameters are described in **Supplementary Table 3**. Dual antiplatelet therapy (DAPT) was continued for 12 months after index PCI in 72.4% of HBR patients and in 84.1% of non-HBR patients (p<0.001). Details of DAPT adherence over time are provided in **Supplementary Figure 1**. Except for some factors (age ≥75 years, moderate anaemia, and moderate chronic kidney disease), the proportion of patients with a single ARC-HBR criterion was only approximately 10% for each criterion; almost all patients had overlapping ARC-HBR criteria **(Supplementary Figure 2)**.

CLINICAL OUTCOME AT 12 MONTHS

The cumulative incidence of major bleeding at 12 months post PCI was significantly higher in HBR patients than non-HBR patients (4.2% vs 1.4%; HR 3.00 [95% CI: 2.11 to 4.27]; p<0.001) **(Figure 2A)**, as was the incidence of ICH (0.8% vs 0.5%; HR 1.82 [95% CI: 0.93 to 3.57]; p=0.083) **(Figure 2B)**. As the number of overlapping ARC-HBR criteria increased, the cumulative incidence of major bleeding also increased. In contrast, the incidence of major bleeding was 4.2% for one major criterion, 2.1% for two minor criteria **(Figure 3)**.

When the cumulative incidence of major bleeding was stratified by ARC-HBR criteria **(Figure 4)**, all of the ARC-HBR major criteria were associated with an incidence of major bleeding of ≥4%; however, among patients who fulfilled a single criterion, the incidence of major bleeding was >4% with anticoagulant use or severe anaemia (major criteria), <4% in those with any of the other major criteria, and <4% for each minor criterion **(Figure 4, Supplementary Table 4)**. The cumulative incidence of ICH stratified by ARC-HBR criteria is shown in **Supplementary Figure 3**. The adjusted cumulative incidences of major bleeding stratified by ARC-HBR criteria and other clinically important factors are shown in **Supplementary Figure 4**.

REGRESSION ANALYSIS TO IDENTIFY INDEPENDENT PREDICTORS OF MAJOR BLEEDING EVENTS

Based on the data indicating that, in addition to the ARC-HBR criteria, low body weight, heart failure, peripheral arterial disease, and non-radial approach were also associated with an incidence of major bleeding of ≥4%, univariate and multivariate analyses were used to calculate statistically significant independent predictors of major bleeding events **(Table 2)**.

The addition of low body weight and heart failure to the ARC-HBR criteria increased the prevalence of HBR to 57.2% overall. The group of patients who met ARC-HBR criteria and had low body weight or heart failure had a significantly higher cumulative incidence of bleeding events compared with the other patient group (for major bleeding: 4.1% vs 1.2%, HR 3.60 [95% CI: 2.41

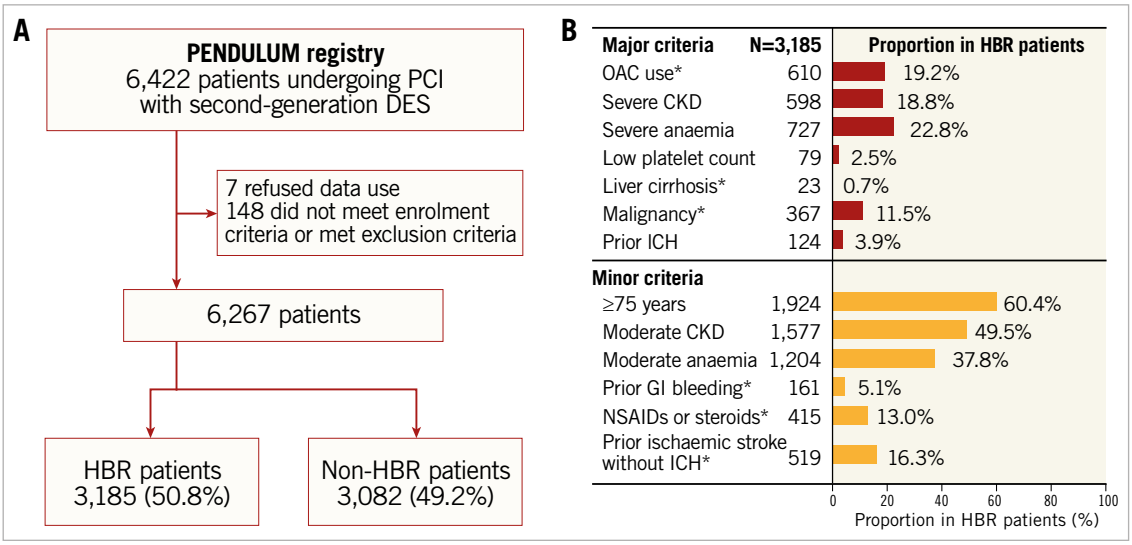

Figure 1. *Patient disposition (A) and proportion of HBR patients by each ARC-HBR criterion (B). *Modified from the original ARC-HBR criteria. ARC: Academic Research Consortium; CKD: chronic kidney disease; DES: drug-eluting stent; HBR: high bleeding risk; NSAID: non-steroidal anti-inflammatory drug; OAC: oral anticoagulant; PCI: percutaneous coronary intervention*

Table 1. Baseline demographic and clinical characteristics.

Characteristics		Total (N=6,267)	ARC-HBR (n=3,185)	Non-ARC-HBR (n=3,082)	*p*-value (ARC-HBR vs non-ARC-HBR)
Age, years		70.0 (10.7)	74.9 (9.2)	65.0 (9.9)	<0.001
≥75		2,324 (37.1)	1,924 (60.4)	400 (13.0)	<0.001
Sex, male		4,909 (78.3)	2,332 (73.2)	2,577 (83.6)	<0.001
Body weight, kg		64.0 (12.6)	60.8 (12.0)	67.2 (12.4)	<0.001
≤50		794 (12.7)	583 (18.3)	211 (6.8)	<0.001
Body mass index, kg/m²		24.2 (3.6)	23.7 (3.6)	24.8 (3.6)	<0.001
Hypertension		5,186 (82.8)	2,773 (87.1)	2,413 (78.3)	<0.001
Hyperlipidaemia		4,919 (78.5)	2,402 (75.4)	2,517 (81.7)	<0.001
Diabetes mellitus		2,767 (44.2)	1,515 (47.6)	1,252 (40.6)	<0.001
Current smoker		1,327 (21.2)	449 (14.1)	878 (28.5)	<0.001
Heart failure[a]		850 (13.6)	642 (20.2)	208 (6.7)	0.056
Peripheral artery disease		421 (6.7)	324 (10.2)	97 (3.1)	<0.001
Atrial fibrillation		538 (8.6)	477 (15.0)	61 (2.0)	<0.001
Malignancy		367 (5.9)	367 (11.5)	0 (0.0)	<0.001
History of myocardial infarction		1,575 (25.1)	825 (25.9)	750 (24.3)	0.128
History of PCI		2,567 (41.0)	1,361 (42.7)	1,206 (39.1)	<0.05
History of coronary artery bypass grafting		265 (4.2)	179 (5.6)	86 (2.8)	<0.001
History of ischaemic stroke		655 (10.5)	557 (17.5)	98 (3.2)	<0.001
History of transient ischaemic attack		80 (1.3)	55 (1.7)	25 (0.8)	<0.001
History of ICH		124 (2.0)	124 (3.9)	0 (0.0)	<0.001
History of gastrointestinal bleeding		183 (2.9)	161 (5.1)	22 (0.7)	<0.001
Clinical presentation	Non-ACS	4,252 (67.8)	2,262 (71.0)	1,990 (64.6)	<0.001
	ACS	2,015 (32.2)	923 (29.0)	1,092 (35.4)	
	Unstable angina	790 (12.6)	387 (12.2)	403 (13.1)	0.270
	Non-STEMI	323 (5.2)	165 (5.2)	158 (5.1)	<0.05
	STEMI	908 (14.5)	373 (11.7)	535 (17.4)	
Medication at discharge	Thienopyridine	6,195 (98.9)	3,129 (98.2)	3,066 (99.5)	<0.001
	Clopidogrel	2,213 (35.3)	1,333 (41.9)	880 (28.6)	<0.001
	Prasugrel	3,921 (62.6)	1,756 (55.1)	2,165 (70.2)	
	Aspirin	6,143 (98.0)	3,092 (97.1)	3,051 (99.0)	<0.001
	OAC	610 (9.7)	610 (19.2)	0 (0.0)	<0.001
	Proton pump inhibitor	5,295 (84.5)	2,679 (84.1)	2,616 (84.9)	0.402
	NSAIDs except aspirin	334 (5.3)	259 (8.1)	75 (2.4)	<0.001
	Steroids	250 (4.0)	198 (6.2)	52 (1.7)	<0.001

Data are presented as n (%) or mean (SD). [a]Heart failure was defined as either hospitalisation or having a treatment history. ACS: acute coronary syndrome; ARC: Academic Research Consortium; HBR: high bleeding risk; ICH: intracranial haemorrhage; NSAIDs: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-elevation myocardial infarction

to 5.38], p<0.001; for ICH: 0.9% vs 0.4%, HR 2.37 [95% CI: 1.12 to 5.02], p<0.05) **(Supplementary Figure 5)**. The C-indices did not improve when low body weight and heart failure were added into the ARC-HBR criteria; however, both ARC-HBR and ARC-HBR with low body weight and heart failure had higher sensitivity (but lower specificity) in estimating the occurrence of major bleeding. The PARIS major bleeding score had higher specificity than sensitivity **(Supplementary Figure 6)**.

Discussion

This study was the first to investigate the suitability of ARC-HBR in >6,000 Japanese patients receiving second-generation DES and enrolled in the PENDULUM real-world registry. The main findings of this study are the following: (i) approximately 50% of the Japanese patients who underwent PCI were classified as ARC-HBR patients, and the majority of HBR patients had overlapping criteria; (ii) the ARC-HBR criteria were suitable for Japanese patients in the contemporary PCI era, where patients are commonly managed with strategies such as lower doses of antiplatelet drugs[6], a transradial PCI approach[9], and use of PPIs; (iii) the multivariate regression analysis suggested that low body weight and heart failure are predictive factors for high bleeding risk but C-indices were not improved.

Ueki et al recently reported that approximately 40% of patients from the Bern Registry fulfilled the ARC-HBR criteria[10]. In the present study, 50.8% of patients (3,185/6,267) were found to have

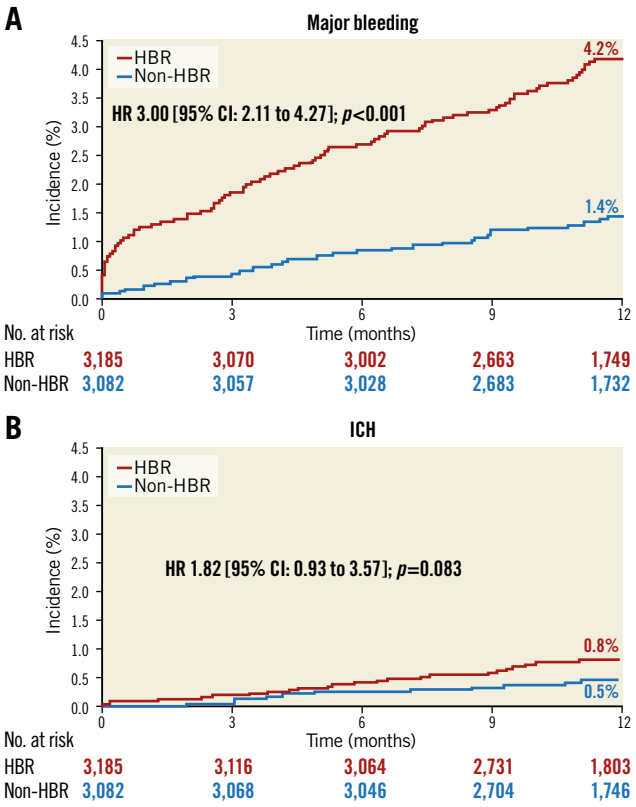

Figure 2. *Cumulative incidence of major bleeding (A) and ICH (B) by ARC-HBR status. CI: confidence interval; HBR: high bleeding risk; HR: hazard ratio; ICH: intracranial haemorrhage*

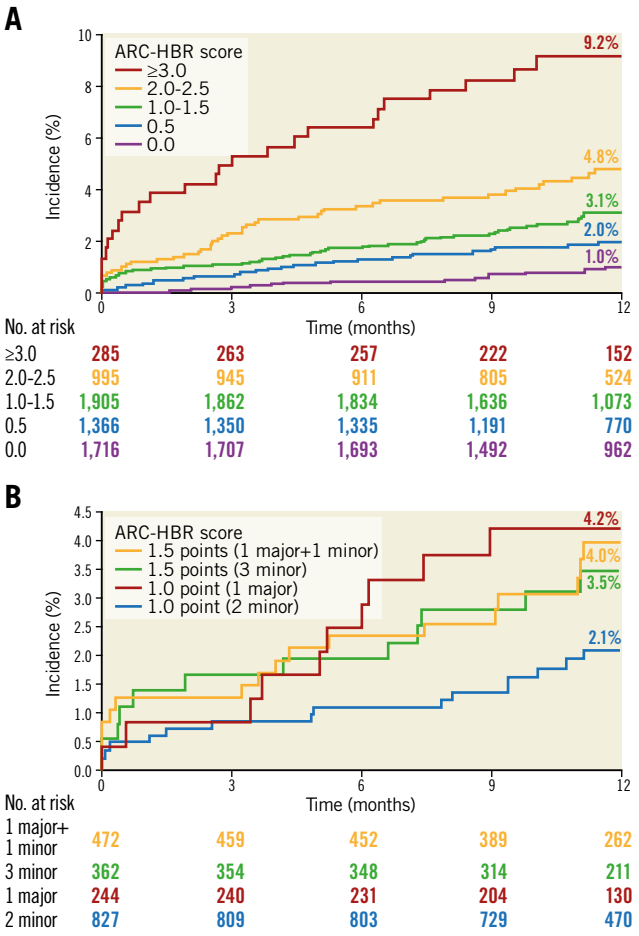

Figure 3. *Cumulative incidence of major bleeding by ARC-HBR score categories; 0 to ≥3.0 points (A), and 1 to 1.5 points (B). ARC: Academic Research Consortium; HBR: high bleeding risk*

HBR. In previous reports, the proportion of HBR patients in Japan has been reported to be 43%[11]. Taken together, it can be assumed that the incidence of HBR is approximately 50% in Japanese daily practice. Patient characteristics were similar between our study and those in the Bern Registry; however, the proportion of patients with overlapping bleeding risk criteria was higher in our study than in the Bern Registry. Only 244 (3.9%) patients had a single major ARC-HBR criterion even though the prevalence of HBR was 51% in this study. Of 4,781 HBR patients, 799 (16.7%) had a single major ARC-HBR criterion in the Bern Registry[10]. This may suggest that Japanese patients are more likely to have overlapping risk factors. The elucidation of the real impact of each minor criterion warrants further study.

The incidence of major bleeding in our study was lower than that in previous studies. In the Bern Registry, the risk of BARC 3 or 5 bleeding was 6.4% in the HBR group and 1.9% in the non-HBR group[10], and in the CREDO-Kyoto registry cohort-2[11] the risk of major bleeding was 10.4% versus 3.4%, respectively. There are several explanations as to why these differences might be possible. Firstly, the difference in patient demographics should be considered. It is well known that the incidence of major bleeding is higher in acute coronary syndrome patients. In the present study, the proportion of acute coronary syndrome patients was limited to almost 30% compared with almost 50% in the Bern Registry study. In addition, IIb/IIIa antagonist treatment is not available in Japan and the approved doses of antiplatelet regimens in Japan differ from those in other countries. Secondly, technical advances coupled with the improvement of medical management might contribute to the reduction of bleeding risk. It should be noted that the CREDO-Kyoto registry cohort-2 is almost 10 years old, and the procedures and medications used[11,12] were different from those used in the present study. Additionally, the hazard risk of bleeding in HBR patients compared to non-HBR patients (three times higher) was in line with the CREDO-Kyoto registry cohort-2 and the Bern Registry.

All of the ARC-HBR major criteria were found to be associated with an incidence of major bleeding ≥4% at one year. The same observation was made in patients who met isolated major criteria of anticoagulant use at discharge or severe anaemia. In our analysis, the incidence of major bleeding in patients with ARC-HBR scores of 1-1.5 was 3.1% (i.e., lower than 4%). Our results showed that, as the number of overlapping ARC-HBR criteria increased, the cumulative incidence of major bleeding also increased in East Asian patients, which was in line with the recent findings reported by Cao et al[13]. The incidence of major bleeding in patients with only one major criterion was 4.2%, while that in those with two

Table 2. Univariate and multivariate regression analysis of major bleeding at one year.

Variable		Events (%)	Univariate		Multivariate	
			HR	95% CI	HR	95% CI
Age, years; ≥75		82 (3.5) vs 83 (2.1)	1.714	1.263-2.325	0.991	0.656-1.497
Sex; male		124 (2.5) vs 41 (3.0)	0.828	0.581-1.178	1.292	0.793-2.102
Body weight, kg; ≤50		39 (4.9) vs 120 (2.3)	2.260	1.574-3.243	1.849	1.125-3.039
Hypertension		142 (2.7) vs 23 (2.1)	1.272	0.819-1.976	0.980	0.586-1.639
Diabetes mellitus		66 (2.4) vs 99 (2.8)	0.846	0.620-1.155	0.772	0.526-1.135
Current smoker		32 (1.9) vs 109 (2.8)	0.694	0.468-1.029	0.756	0.478-1.193
Heart failure		49 (5.8) vs 116 (2.1)	2.813	2.014-3.928	1.871	1.219-2.872
Peripheral arterial disease		19 (4.5) vs 146 (2.5)	1.824	1.131-2.943	1.437	0.806-2.560
Malignancy		16 (4.4) vs 149 (2.5)	1.787	1.067-2.992	1.338	0.690-2.595
Liver cirrhosis		1 (4.3) vs 164 (2.6)	1.734	0.243-12.384	1.388	0.183-10.548
History of ischaemic stroke without ICH		19 (3.1) vs 135 (2.5)	1.247	0.772-2.016	–	–
History of ICH		6 (4.8) vs 148 (2.5)	1.950	0.862-4.410	–	–
History of ischaemic stroke or ICH		25 (3.4) vs 129 (2.4)	1.399	0.912-2.147	1.059	0.639-1.753
History of gastrointestinal bleeding		8 (4.4) vs 142 (2.5)	1.802	0.884-3.674	1.228	0.535-2.818
ACS		56 (2.8) vs 109 (2.6)	1.105	0.800-1.525	1.480	1.010-2.169
Haemoglobin[a], g/dL	<11	41 (5.6) vs 69 (1.7)	3.388	2.302-4.986	1.756	1.022-3.017
	Male: ≥11 to <13; Female: ≥11 to <12	49 (3.5) vs 69 (1.7)	2.017	1.398-2.909	1.529	0.984-2.377
eGFR[b], mL/min/1.73 m^2	<30	39 (6.5) vs 59 (1.7)	3.991	2.663-5.981	1.999	1.131-3.534
	≥30 to <60	65 (3.1) vs 59 (1.7)	1.823	1.282-2.594	1.274	0.827-1.961
Platelet count, ×10^4/μL; <10		4 (5.1) vs 154 (2.6)	2.129	0.789-5.740	1.339	0.412-4.354
PRU value for 12-48 hours after initial PCI	>208	66 (3.0) vs 88 (2.4)	1.250	0.908-1.719	–	–
	>85	135 (2.6) vs 19 (2.8)	0.918	0.568-1.484	–	–
Puncture site; except radial		72 (3.8) vs 93 (2.1)	1.825	1.342-2.482	–	–
Complex PCI		40 (3.1) vs 125 (2.5)	1.262	0.884-1.802	–	–
Anticoagulant at discharge		38 (6.2) vs 127 (2.2)	2.834	1.973-4.072	2.506	1.619-3.879
NSAIDs or steroids at discharge		24 (4.5) vs 141 (2.5)	1.825	1.184-2.813	1.381	0.772-2.471

[a]Hazard ratio was calculated using ≥13 g/dL for male and ≥12 g/dL for female as the reference standard. [b]Hazard ratio was calculated using ≥60 mL/min/1.73 m^2 as the reference standard. ACS: acute coronary syndrome; CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; ICH: intracranial haemorrhage; NSAIDs: non-steroidal anti-inflammatory drugs; PCI: percutaneous coronary intervention; PRU: platelet reactivity unit

minor criteria was 2.1%, suggesting that the contribution of minor criteria to bleeding risk can be considered. The incidence of major bleeding was 7.6% and 6.0% in patients who met a single criterion of "use of anticoagulant at discharge" and "severe anaemia", respectively. Owing to the overlap of multiple HBR criteria in this cohort, the study is underpowered to evaluate the incidence of major bleeding in patients who met each criterion alone. To adjust the confounders, Cox regression analysis was performed. Severe chronic kidney disease, anticoagulant use at discharge, acute coronary syndrome, low body weight (≤50 kg), and heart failure were found to be independent risk factors.

A history of heart failure has been reported as an independent predictor of bleeding in the PENDULUM registry and CREDO-Kyoto registry cohort-2[7,11]. This is likely to be related to the higher mean ages of enrolled patients in the PENDULUM registry and in the CREDO-Kyoto registry cohort-2 (70.0 and 68.2 years, respectively)[7,11], compared with other registries discussed in the original ARC-HBR paper[1]. However, as our results are based on a *post hoc* analysis, the findings should be interpreted with caution. Indeed, most cases that met an isolated criterion did not demonstrate an incidence of major bleeding >4% and the cumulative incidence of major bleeding was similar. Furthermore, C-statistics did not improve with the addition of these factors. Further studies are warranted to assess the clinical impact of these factors in predicting major bleeding.

When comparing the HBR and non-HBR groups, there was a statistically significant difference in DAPT duration. Whether antiplatelet drug de-escalation is effective in reducing bleeding would require hypothetical testing. Even in patients with HBR, DAPT was used in 70% of patients after 12 months, and bleeding events were observed frequently. This strongly suggests that there is room for improvement.

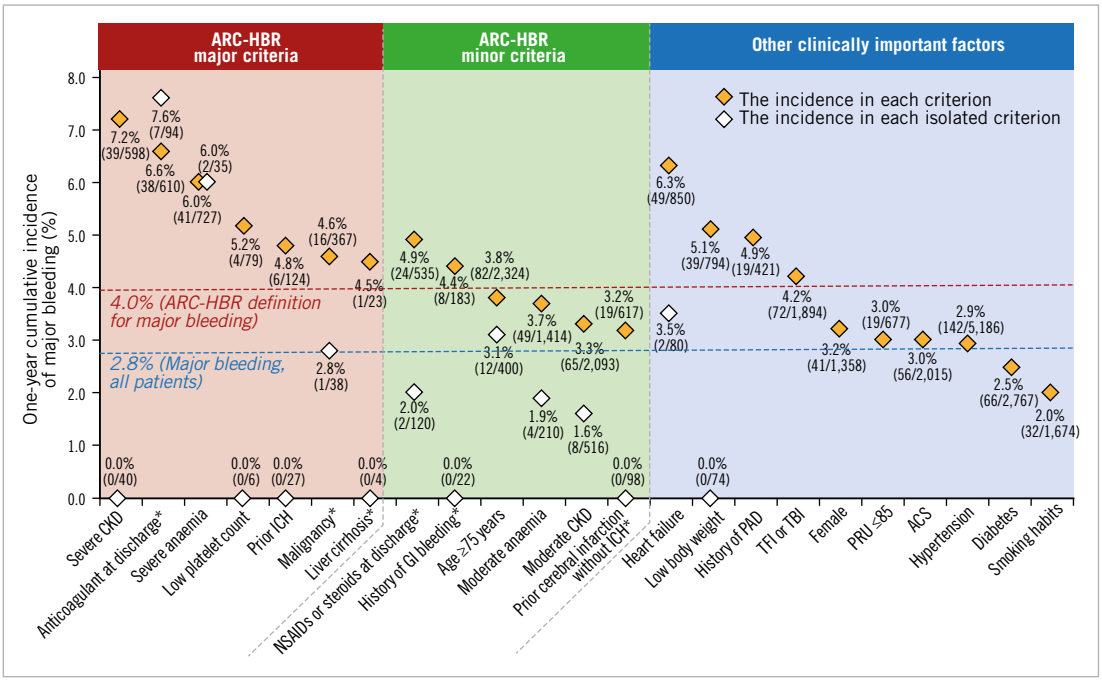

Figure 4. *Cumulative incidence of major bleeding by each ARC-HBR criterion and other clinically important factors. *Modified from the original ARC-HBR criteria. ACS: acute coronary syndrome; ARC: Academic Research Consortium; CKD: chronic kidney disease; GI: gastrointestinal; HBR: high bleeding risk; ICH: intracranial haemorrhage; PAD: peripheral arterial disease; PRU: platelet reactivity unit; TBI: transbrachial intervention; TFI: transfemoral intervention*

Limitations

This analysis has some limitations. First, the *post hoc* nature of the analysis means that not all variables from the original ARC-HBR definitions were collected, and we were unable to address some criteria (e.g., chronic bleeding diathesis and recent major surgery or major trauma within 30 days prior to PCI). The differences in the original ARC-HBR criteria and the modified version used in our analysis mean that the data from our study may not be directly comparable to other publications assessing HBR, limiting their clinical utility. Importantly, many of the ARC-HBR criteria were not available or were markedly modified, including our definition of gastrointestinal bleeding, which did not include hospitalisations or transfusion treatment. The incidence of bleeding was >4% in patients with prior gastrointestinal bleeding; therefore, it was included as a minor criterion in our study. Second, selection bias was inevitable, because this study was an observational study and not all patients undergoing PCI at each institution could be enrolled. Third, ARC-HBR defined major bleeding incidence as ≥4%; however, because East Asian and Western patients are reported to have different risk profiles for bleeding and thrombosis[5], 4% may not be a suitable cut-off for Japanese patients. This requires further study. Fourth, all patients enrolled in this study were Japanese and, thus, the results may not be completely generalisable to other East Asian populations. Fifth, we did not use a quantitative description for heart failure in our study (e.g., ejection fraction). Instead, we defined heart failure based on hospitalisation or having a treatment history. Finally, the present study focused on the risk of bleeding in Japanese patients and did not assess the risk of cardiovascular events or mortality, although we can assume that such risks are also increased in patients with HBR. Further analysis is needed to understand and manage these additional clinical risks in HBR patients.

Conclusions

In conclusion, this analysis showed that half of the Japanese patients who underwent PCI in the PENDULUM registry met ARC-HBR criteria, and many had overlapping criteria. The ARC-HBR criteria are applicable to Japanese patients undergoing contemporary PCI.

Impact on daily practice

Appropriate management strategies for patients with high bleeding risk (HBR) requiring dual antiplatelet therapy after percutaneous coronary intervention have not been fully established, particularly in East Asian patients, who have a different risk profile to Western patients. This analysis showed that the Academic Research Consortium (ARC) for HBR criteria are appropriate for estimation of bleeding risk in Japanese patients. Half of the Japanese patients who underwent PCI in the PENDULUM registry met the ARC-HBR criteria, and many patients had overlapping criteria.

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Conflict of interest statement

M. Nakamura has received grants from Daiichi Sankyo Co., Ltd., Sanofi K.K., and Bayer K.K., and other fees from Daiichi Sankyo Co., Ltd., Sanofi K.K., Terumo Corporation, and Bristol Myers Squibb K.K. K. Kadota has received personal fees from Daiichi Sankyo Co., Ltd., and Sanofi K.K. K. Nakao has received personal fees from Daiichi Sankyo Co., Ltd. Y. Nakagawa has received personal fees from Bristol Myers Squibb K.K. and Kowa Pharmaceutical Co., Ltd., and grants and personal fees from Daiichi Sankyo Co., Ltd., Bayer Yakuhin, Ltd., Sanofi K.K., Boston Scientific Corporation, and Abbott Vascular Japan Co., Ltd. J. Shite has received personal fees from Daiichi Sankyo Co., Ltd., Nipro, Abbott, and Terumo Corporation. H. Yokoi has received personal fees from Daiichi Sankyo Co., Ltd., Bayer K.K., and Sanofi K.K. K. Kozuma has received grants and personal fees from Daiichi Sankyo Co., Ltd. K. Tanabe has received personal fees from Daiichi Sankyo Co., Ltd., Sanofi K.K., AstraZeneca, Abbott Vascular Japan, Co., Ltd., Boston Scientific Corporation, and Terumo Corporation. R. Iijima has received personal fees from Daiichi Sankyo Co., Ltd. A. Harada and T. Kuroda are employees of Daiichi Sankyo Co., Ltd. Y. Murakami has received personal fees from Daiichi Sankyo Co., Ltd., SRD Co., Ltd., and Sanofi K.K.

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Supplementary data

Supplementary Figure 1. Proportion of patients who continued to receive DAPT over time.

Supplementary Figure 2. Proportion of patients who fulfilled each ARC-HBR criterion.

Supplementary Figure 3. Cumulative incidence of ICH stratified by ARC-HBR criteria and other clinically important factors.

Supplementary Figure 4. Adjusted cumulative incidence of major bleeding stratified by ARC-HBR criteria and other clinically important factors.

Supplementary Figure 5. Cumulative incidence of major bleeding (A) and intracranial haemorrhage (B) by ARC-HBR criteria plus low body weight and heart failure.

Supplementary Figure 6. Receiver operating characteristic curve analysis of major bleeding (A) and intracranial haemorrhage (B) for each bleeding risk criteria category.

Supplementary Table 1. Full methodological details of the PENDULUM (Platelet rEactivity in patieNts with DrUg eLUting stent and balancing risk of bleeding and ischeMic event) registry study[7].

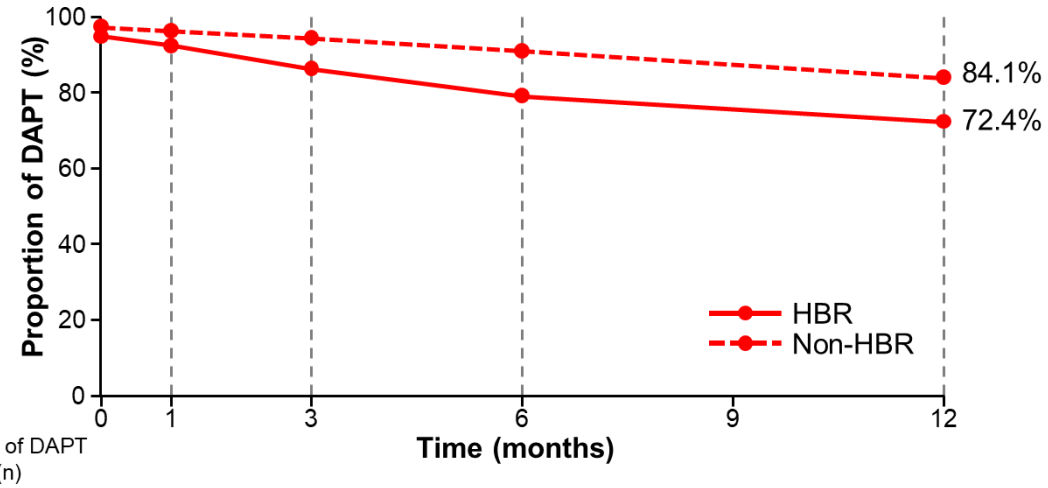
Supplementary Table 2. High bleeding risk definitions.

Supplementary Table 3. Baseline laboratory parameters.

Supplementary Table 4. The proportion of events in each combination of criteria.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00345

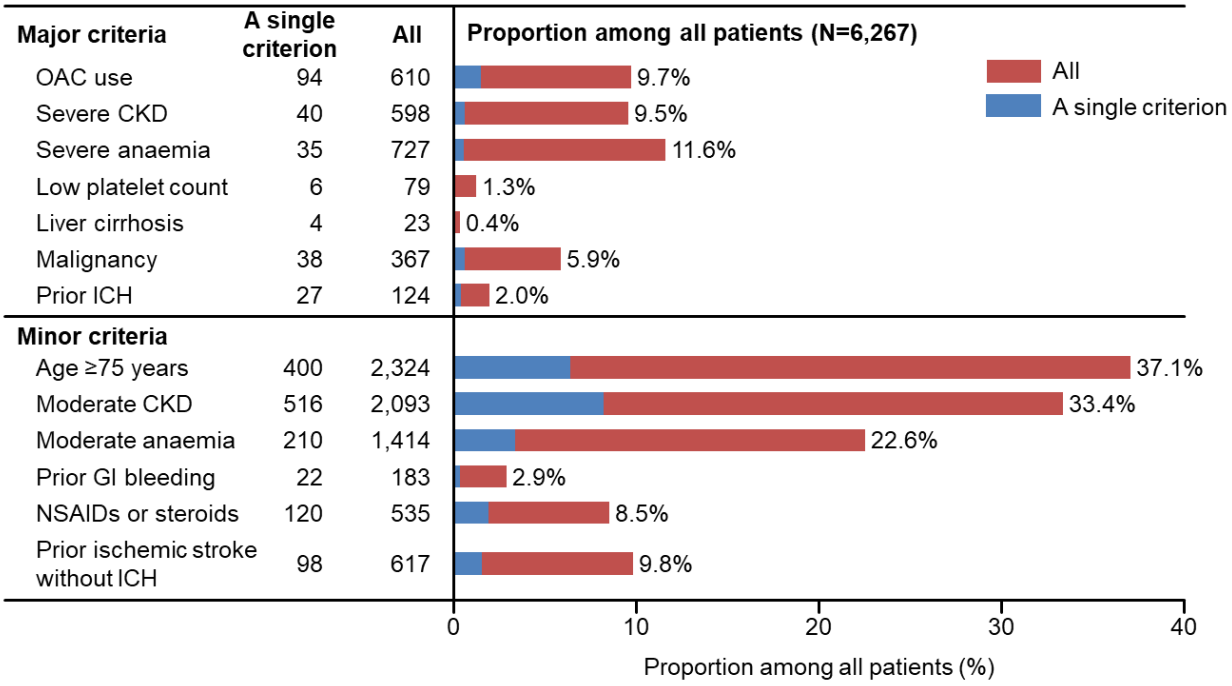
Supplementary data



Proportion of DAPT % (n)					
All (6267)	96.0 (6018)	94.4 (5887)	90.4 (5594)	85.0 (5206)	78.3 (4727)
HBR (3185)	94.8 (3019)	92.4 (2919)	86.3 (2692)	79.3 (2435)	72.4 (2186)
Non-HBR (3082)	97.3 (2999)	96.4 (2968)	94.5 (2902)	90.8 (2771)	84.1 (2541)
p value	<0.001	<0.001	<0.001	<0.001	<0.001

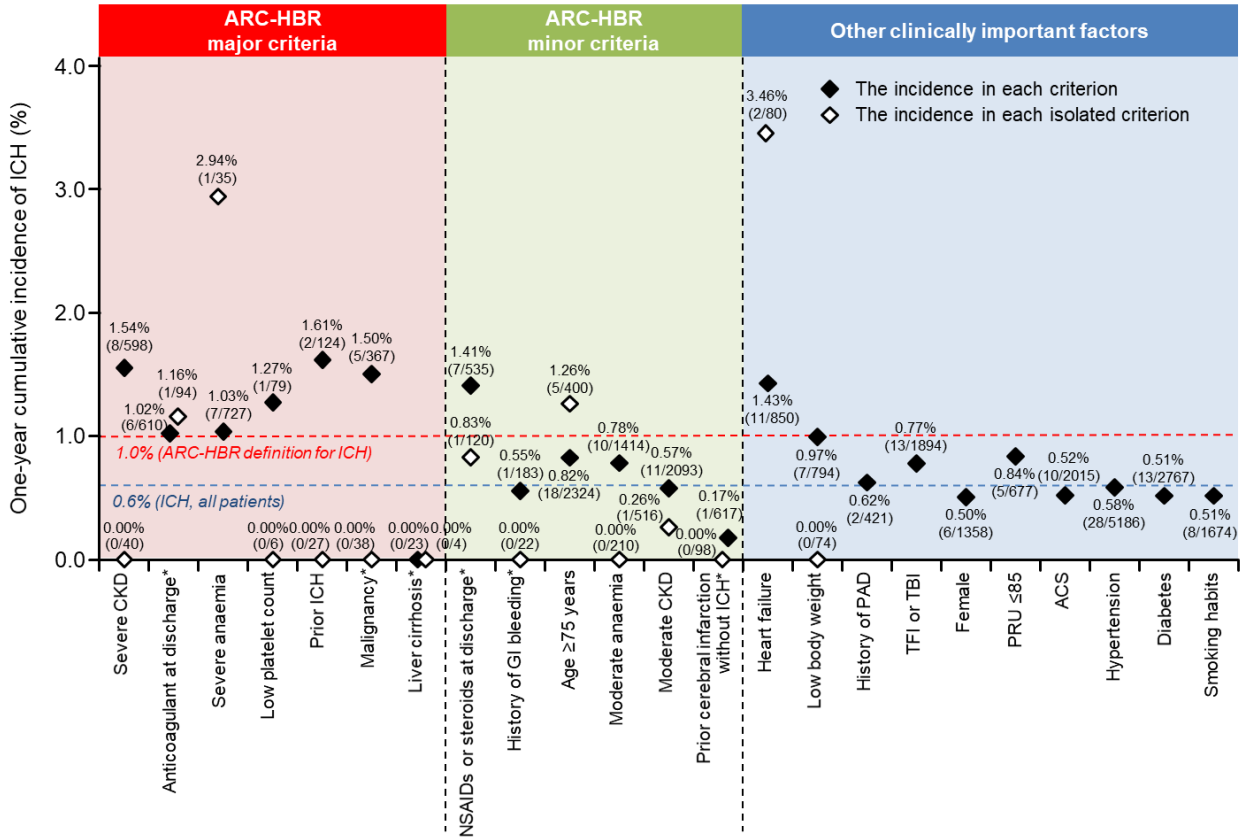
Supplementary Figure 1. Proportion of patients who continued to receive DAPT over time.

DAPT: dual antiplatelet therapy; HBR: high bleeding risk



Supplementary Figure 2. Proportion of patients who fulfilled each ARC-HBR criterion.

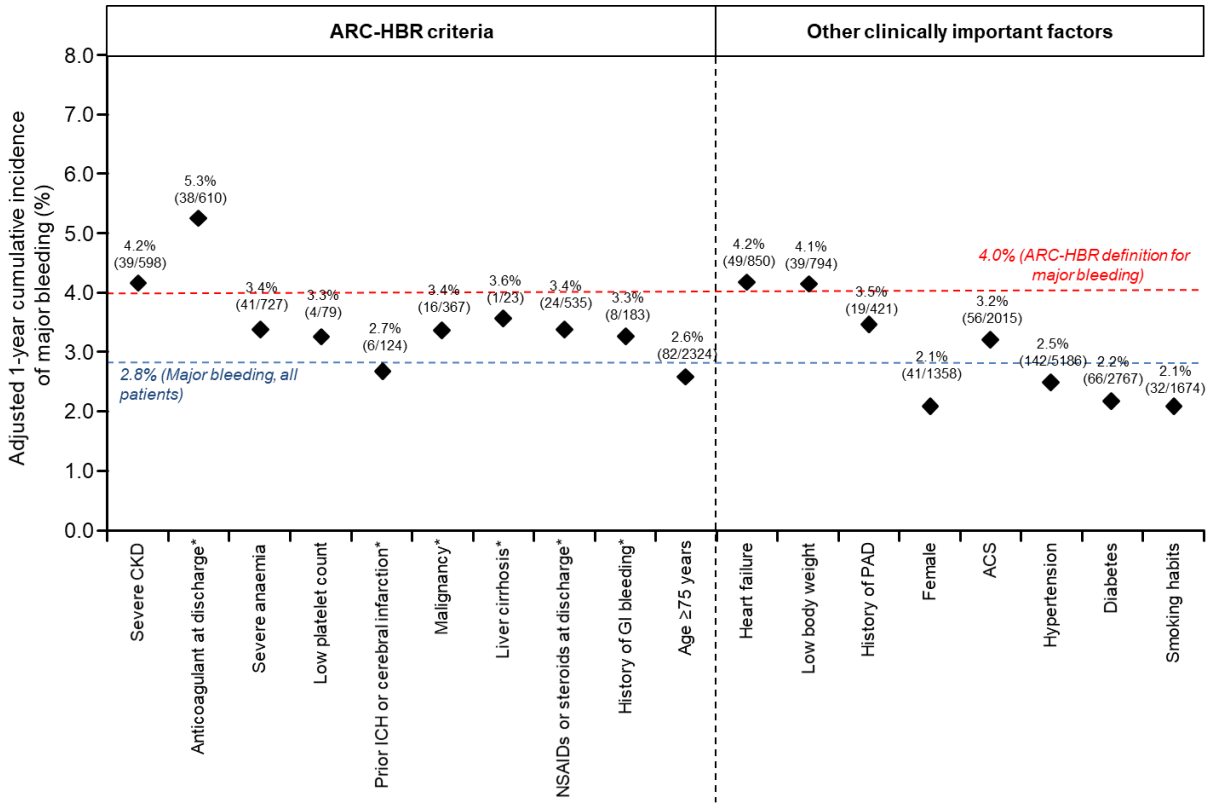
ARC: Academic Research Consortium; CKD: chronic kidney disease; GI: gastrointestinal; ICH: intracranial haemorrhage; NSAIDs: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulant



Supplementary Figure 3. Cumulative incidence of ICH stratified by ARC-HBR criteria and other clinically important factors.

*Modified from the original ARC-HBR criteria.

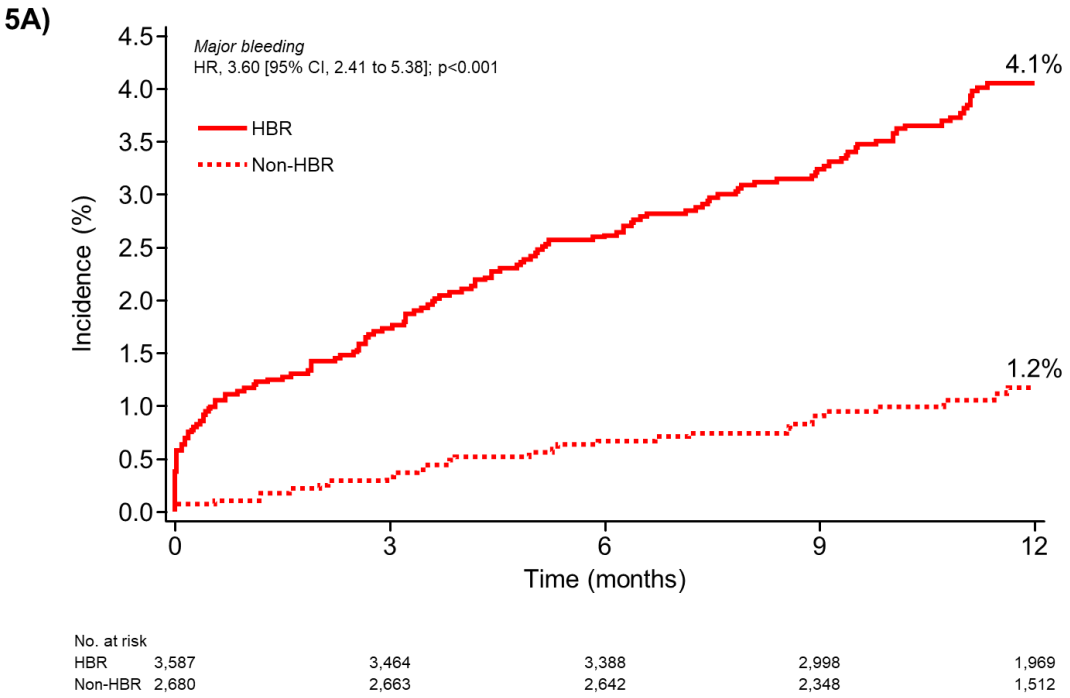
ACS: acute coronary syndrome; ARC: Academic Research Consortium; CKD: chronic kidney disease; GI: gastrointestinal; HBR: high bleeding risk; ICH: intracranial haemorrhage; PAD: peripheral arterial disease; PRU: platelet reactivity unit; TBI: transbrachial intervention; TFI: transfemoral intervention.

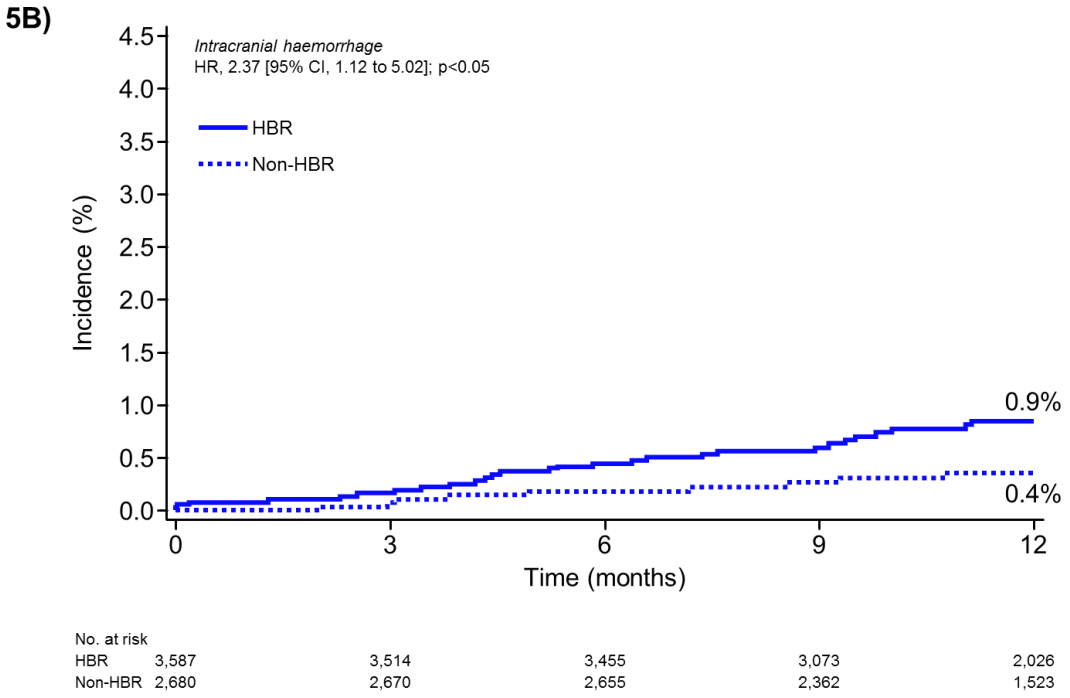


Supplementary Figure 4. Adjusted cumulative incidence of major bleeding stratified by ARC-HBR criteria and other clinically important factors.

*Modified from the original ARC-HBR criteria.

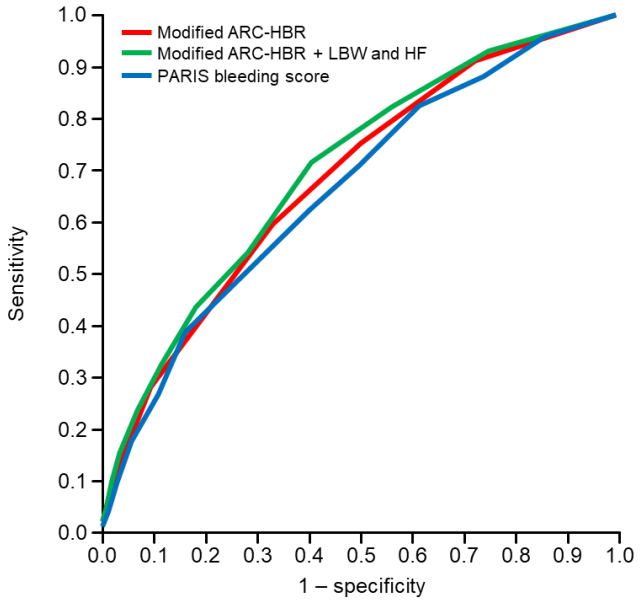
ACS: acute coronary syndrome; ARC: Academic Research Consortium; CKD: chronic kidney disease; GI: gastrointestinal; HBR: high bleeding risk; ICH: intracranial haemorrhage; PAD: peripheral arterial disease





Supplementary Figure 5. Cumulative incidence of major bleeding (A) and intracranial haemorrhage (B) by ARC-HBR criteria plus low body weight and heart failure.
ARC: Academic Research Consortium; CI: confidence interval; HBR: high bleeding risk; HR: hazard ratio

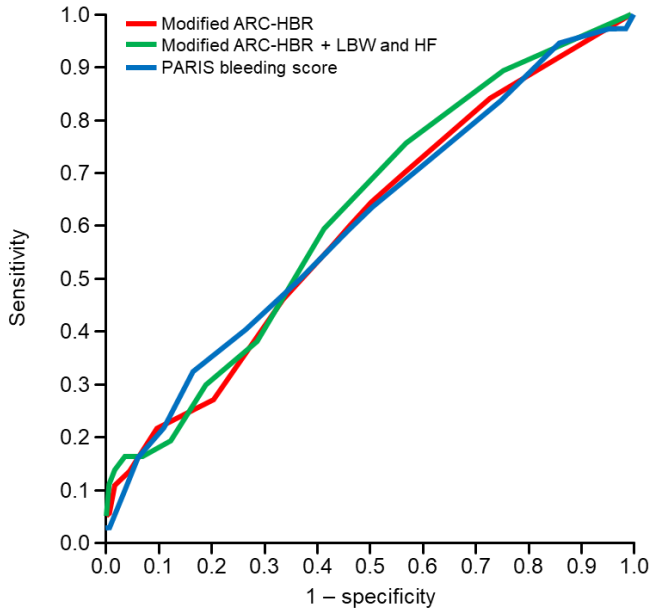
6A)



Risk score (N=6,267)	C-index (95% CI)	Cut-off
Modified ARC-HBR	0.681 (0.641 – 0.722)	1.5
Modified ARC-HBR + LBW and HF	0.700 (0.660 – 0.740)	1.5
PARIS major bleeding score	0.662 (0.620 – 0.704)	9

Criteria	HBR, n	Non-HBR, n	Sensitivity, %	Specificity, %
Modified ARC-HBR (≥1)	3,185	3,082	75.2	49.8
Modified ARC-HBR + LBW and HF (≥1)	3,587	2,680	82.4	43.4
PARIS major bleeding score (≥8)	1,692	4,575	48.5	73.6

6B)



Risk score (N=6,267)	C-index (95% CI)	Cut-off
Modified ARC-HBR	0.597 (0.505 – 0.689)	1.0
Modified ARC-HBR + LBW and HF	0.620 (0.533 – 0.708)	1.0
PARIS major bleeding score	0.602 (0.508 – 0.697)	9

Criteria	HBR, n	Non-HBR, n	Sensitivity, %	Specificity, %
Modified ARC-HBR (≥1)	3,185	3,082	64.9	49.3
Modified ARC-HBR + LBW and HF (≥1)	3,587	2,680	75.7	42.9
PARIS major bleeding score (≥8)	1,692	4,575	40.5	73.1

Supplementary Figure 6. Receiver operating characteristic curve analysis of major bleeding (A) and intracranial haemorrhage (B) for each bleeding risk criterion category.

ARC: Academic Research Consortium; CI: confidence interval; HBR: high bleeding risk; HF: heart failure; LBW: low body weight

Supplementary Table 1. Full methodological details of the PENDULUM (Platelet rEactivity in patieNts with DrUg eLUting stent and balancing risk of bleeding and ischeMic event) registry study[7].

Item	Details
Study design	A prospective, multicentre study of Japanese patients who underwent PCI
Enrolment period	Between December 2015 and June 2017
Setting	67 Japanese institutions, nationwide. Patients were followed up as part of routine clinical practice. Patients were expected to visit the hospital whenever possible, but could be questioned by telephone or letter if visits were difficult.
Inclusion criteria	Age ≥20 years Indicated for PCI with drug-eluting stents Administered antiplatelet drugs
Exclusion criteria	Enrolment, or planned enrolment, in another clinical study before completion of the observation period
DAPT details	DAPT was based on the standard of care; drug type, dosage, and treatment duration were selected at the discretion of the attending physician The standard duration of DAPT according to Japanese treatment guidelines is a minimum of 6 months for non-ACS patients and a minimum of 12 months for patients with ACS
Approved dosages	Aspirin, 100 mg administered once daily; the dosage can be increased up to 300 mg once daily Clopidogrel, 300 mg administered once as a loading dose on the treatment start day, followed by 75 mg once daily as a maintenance dosage Prasugrel, 20 mg administered once as a loading dose, followed by 3.75 mg once daily as a maintenance dosage
Primary endpoints	The incidence of first MACCE event[a] and first major bleeding event[b] 12 months after index PCI Thrombotic and haemorrhagic events were evaluated by independent assessment committees
Sample size	The required sample size for the registry was calculated based on both the incidence of MACCE and major bleeding at 12 months after index PCI Published data suggested that in the Japanese population the incidence of MACCE was 3% and the incidence of major bleeding was 4% Using this information, the incidence of the primary endpoints was set at 3% with a precision of ±0.5% within the range of the 95% CI Allowing for a withdrawal rate of 10% during the first 12 months of the study, the required number of patients was calculated as 4,969 (rounded up to 5,000 patients)

[a]Defined as all-cause death, non-fatal myocardial infarction, non-fatal stroke, and stent thrombosis.

[b]Defined as Bleeding Academic Research Consortium types 3 and 5.

ACS: acute coronary syndrome; CI: confidence interval; DAPT: dual antiplatelet therapy; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention

Supplementary Table 2. High bleeding risk definitions[a].

ARC-HBR criteria[1]	This study	Category	Comments
Age ≥75 years	Age ≥75 years	Minor	Identical
Anticipated use of long-term oral anticoagulation[b]	Use of oral anticoagulation at discharge	Major	Modified
Severe or end-stage chronic kidney disease (eGFR <30 mL/min)	eGFR <30 mL/min/1.73 m^2	Major	Identical
Moderate chronic kidney disease (eGFR 30–59 mL/min)	eGFR 30–<60 mL/min/1.73 m^2	Minor	Identical
Haemoglobin <11 g/dL	Haemoglobin <11 g/dL	Major	Identical
Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women	Haemoglobin 11–<13 g/dL for men and 11–<12g/dL for women	Minor	Identical
Spontaneous bleeding requiring hospitalisation or transfusion in the past 6 months or at any time, if recurrent		Major	Not applicable[f]
Spontaneous bleeding requiring hospitalisation or transfusion within the past 12 months not meeting the major criterion	Prior gastrointestinal bleeding at any time	Minor	Modified
Moderate or severe baseline thrombocytopaenia[c] (platelet count <100×10^9/L)	Platelet count <100×10^9/L	Major	Identical
Chronic bleeding diathesis		Major	Not applicable
Liver cirrhosis with portal hypertension	Liver cirrhosis	Major	Modified
Long-term use of oral NSAIDs or steroids	Use of NSAIDs or steroids at discharge	Minor	Modified
Active malignancy[d] (excluding non-melanoma skin cancer) within the past 12 months	Malignancy at baseline (undergoing or planning treatment)	Major	Modified

Previous spontaneous intracranial haemorrhage (at any time) Previous traumatic intracranial haemorrhage within the past 12 months Presence of a brain arteriovenous malformation Moderate or severe ischaemic stroke[e] within the past 6 months	History of intracranial haemorrhage at any time	Major	Modified
Any ischaemic stroke at any time not meeting the major criterion	History of ischaemic stroke[g] without intracranial haemorrhage at any time	Minor	Identical
Non-deferrable major surgery on dual antiplatelet therapy		Major	Not applicable
Recent major surgery or major trauma within 30 days before PCI		Major	Not applicable

[a]Definition of ARC-HBR: meets at least one of the major criteria or at least two of the minor criteria. The major and minor criteria were defined differently for the original article and the current analysis, as shown.

[b]This excludes vascular protection doses.

[c]Baseline thrombocytopaenia is defined as thrombocytopaenia before PCI.

[d]Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

[e]National Institutes of Health Stroke Scale score ≥5.

[f]For the present analysis, "Spontaneous bleeding requiring hospitalisation or transfusion within the past 12 months not meeting the major criterion" was combined with "Spontaneous bleeding requiring hospitalisation or transfusion in the past 6 months or at any time, if recurrent", to form the major criterion "Composite of prior bleeding".

[g]For the present analysis, "Any ischaemic stroke at any time not meeting the major criterion" was combined with "Moderate or severe ischaemic stroke within the past 6 months", to form the major criterion "History of ischaemic stroke".

ARC: Academic Research Consortium; eGFR: estimated glomerular filtration rate; HBR: high bleeding risk; NSAIDs: non-steroidal anti-inflammatory drugs; PCI: percutaneous coronary intervention

Supplementary Table 3. Baseline laboratory parameters.

Characteristics	Total (N=6,267)	ARC-HBR (n=3,185)	Non-ARC-HBR (n=3,082)	*p*-value (ARC-HBR vs non-ARC-HBR)
Haemoglobin, g/dL	N=6,087	N=3,108	N=2,979	
Mean (SD)	13.3 (2.0)	12.3 (1.9)	14.4 (1.6)	<0.001
<11	727 (11.6)	727 (22.8)	0 (0.0)	<0.001
Male: ≥11 to <13; Female: ≥11 to <12	1,414 (22.6)	1,204 (37.8)	210 (6.8)	<0.001
eGFR, mL/min/1.73 m^2	N=6,122	N=3,133	N=2,989	
Mean (SD)	61.2 (27.6)	49.6 (23.5)	73.4 (26.3)	<0.001
<30	598 (9.5)	598 (18.8)	0 (0.0)	<0.001
≥30 to <60	2,093 (33.4)	1,577 (49.5)	516 (16.7)	
White blood cell count, $\times 10^3/\mu L$	N=6,086	N=3,108	N=2,978	
Mean (SD)	6.94 (2.82)	6.70 (2.51)	7.19 (3.09)	<0.001
Platelet count, $\times 10^4/\mu L$	N=6,084	N=3,107	N=2,977	
Mean (SD)	21.4 (6.6)	20.6 (6.9)	22.1 (6.3)	<0.001
<10	79 (1.3)	79 (2.5)	0 (0.0)	<0.001
No. of diseased vessels				
1	3,165 (50.5)	1,476 (46.3)	1,689 (54.8)	<0.001
2	1,865 (29.8)	987 (31.0)	878 (28.5)	<0.05
3	1,151 (18.4)	680 (21.4)	471 (15.3)	<0.001
Left main coronary trunk	349 (5.6)	202 (6.3)	147 (4.8)	<0.05
Procedural data				
Puncture site				
Femoral	1,632 (26.0)	986 (31.0)	646 (21.0)	<0.001
Brachial	270 (4.3)	177 (5.6)	93 (3.0)	<0.001
Radial	4,516 (72.1)	2,082 (65.4)	2,434 (79.0)	<0.001
Imaging guided				

IVUS or OCT/OFDI	5,918 (94.4)	2,999 (94.2)	2,919 (94.7)	0.342
Complex PCI				
All	1,712 (27.3)	676 (21.2)	604 (19.6)	0.110
≥3 stents	435 (6.9)	247 (7.8)	188 (6.1)	<0.05
Number of treatment lesions ≥3	577 (9.2)	311 (9.8)	266 (8.6)	0.121
Bifurcation with 2 stents	112 (1.8)	49 (1.5)	63 (2.0)	0.131
Total stent length >60 mm	725 (11.6)	401 (12.6)	324 (10.5)	<0.05
Chronic total occlusion lesion	429 (6.8)	202 (6.3)	227 (7.4)	0.109

Data are presented as n (%) or mean (SD).

ARC: Academic Research Consortium; eGFR: estimated glomerular filtration rate; HBR: high bleeding risk; IVUS: intravascular ultrasound; OCT: optical coherence tomography; OFDI: optical frequency domain imaging; PCI: percutaneous coronary intervention; SD: standard deviation

Supplementary Table 4. The proportion of events in each combination of criteria.

Criteria	Patients with criteria	Events	
		Major bleeding	ICH
Total	6,267	165 (2.6)	37 (0.6)
1 minor criterion (point: 0.5)			
History of GI bleeding	22	0 (0.0)	0 (0.0)
Moderate anaemia	210	4 (1.9)	0 (0.0)
Moderate CKD	516	8 (1.6)	1 (0.2)
NSAIDs or steroids	120	2 (1.7)	1 (0.8)
≥75 years	400	12 (3.0)	5 (1.3)
History of ischaemic stroke without ICH	98	0 (0.0)	0 (0.0)
1 major criterion (point: 1)			
Severe anaemia	35	2 (5.7)	1 (2.9)
Low platelet count	6	0 (0.0)	0 (0.0)
Severe CKD	40	0 (0.0)	0 (0.0)
OAC use	94	7 (7.4)	1 (1.1)
Liver cirrhosis	4	0 (0.0)	0 (0.0)
Malignancy	38	1 (2.6)	0 (0.0)
History of ICH	27	0 (0.0)	0 (0.0)
Combination of 2 minor criteria (point: 1)			
History of GI bleeding + moderate anaemia	5	0 (0.0)	0 (0.0)
History of GI bleeding + moderate CKD	10	1 (10.0)	0 (0.0)
History of GI bleeding + NSAIDs or steroids	2	0 (0.0)	0 (0.0)
History of GI bleeding + ≥75 years	8	0 (0.0)	0 (0.0)
History of GI bleeding + history of ischaemic stroke without ICH	1	0 (0.0)	0 (0.0)
Moderate anaemia + moderate CKD	130	6 (4.6)	2 (1.5)
Moderate anaemia + NSAIDs or steroids	16	1 (6.3)	0 (0.0)
Moderate anaemia + ≥75 years	159	2 (1.3)	0 (0.0)
Moderate anaemia + history of ischaemic stroke without ICH	22	0 (0.0)	0 (0.0)
Moderate CKD + NSAIDs or steroids	35	2 (5.7)	1 (2.9)
Moderate CKD + ≥75 years	304	2 (0.7)	2 (0.7)
Moderate CKD + history of ischaemic stroke without ICH	38	1 (2.6)	0 (0.0)
NSAIDs or steroids + ≥75 years	38	0 (0.0)	0 (0.0)

NSAIDs or steroids + history of ischaemic stroke without ICH	8	1 (12.5)	0 (0.0)
≥75 years + history of ischaemic stroke without ICH	51	0 (0.0)	0 (0.0)
Combination of 3 minor criteria (point: 1.5)			
History of GI bleeding + moderate anaemia + moderate CKD	9	0 (0.0)	0 (0.0)
History of GI bleeding + moderate anaemia + NSAIDs or steroids	2	0 (0.0)	0 (0.0)
History of GI bleeding + moderate anaemia + ≥75 years	9	1 (11.1)	0 (0.0)
History of GI bleeding + moderate anaemia + history of ischaemic stroke without ICH	0	—	—
History of GI bleeding + moderate CKD + NSAIDs or steroids	0	—	—
History of GI bleeding + moderate CKD + ≥75 years	2	0 (0.0)	0 (0.0)
History of GI bleeding + moderate CKD + history of ischaemic stroke without ICH	0	—	—
History of GI bleeding + NSAIDs or steroids + ≥75 years	2	0 (0.0)	0 (0.0)
History of GI bleeding + NSAIDs or steroids + history of ischaemic stroke without ICH	0	—	—
History of GI bleeding + ≥75 years + history of ischaemic stroke without ICH	2	0 (0.0)	0 (0.0)
Moderate anaemia + moderate CKD + NSAIDs or steroids	17	2 (11.8)	0 (0.0)
Moderate anaemia + moderate CKD + ≥75 years	193	7 (3.6)	2 (1.0)
Moderate anaemia + moderate CKD + history of ischaemic stroke without ICH	22	0 (0.0)	0 (0.0)
Moderate anaemia + NSAIDs or steroids + ≥75 years	14	1 (7.1)	1 (7.1)
Moderate anaemia + NSAIDs or steroids + history of ischaemic stroke without ICH	1	0 (0.0)	0 (0.0)
Moderate anaemia + ≥75 years + history of ischaemic stroke without ICH	21	0 (0.0)	0 (0.0)
Moderate CKD + NSAIDs or steroids + ≥75 years	30	1 (3.3)	0 (0.0)
Moderate CKD + NSAIDs or steroids + history of ischaemic stroke without ICH	1	0 (0.0)	0 (0.0)

Moderate CKD + ≥75 years + history of ischaemic stroke without ICH	33	0 (0.0)	0 (0.0)
NSAIDs or steroids + ≥75 years + history of ischaemic stroke without ICH	4	0 (0.0)	0 (0.0)
Combination of 1 major and 1 minor criteria (point: 1.5)			
Severe anaemia + history of GI bleeding	5	0 (0.0)	0 (0.0)
Severe anaemia + moderate anaemia	0	—	—
Severe anaemia + moderate CKD	37	1 (2.7)	0 (0.0)
Severe anaemia + NSAIDs or steroids	10	0 (0.0)	0 (0.0)
Severe anaemia + ≥75 years	43	1 (2.3)	0 (0.0)
Severe anaemia + history of ischaemic stroke without ICH	2	0 (0.0)	0 (0.0)
Low platelet count + history of GI bleeding	0	—	—
Low platelet count + moderate anaemia	3	0 (0.0)	0 (0.0)
Low platelet count + moderate CKD	3	0 (0.0)	0 (0.0)
Low platelet count + NSAIDs or steroids	0	—	—
Low platelet count + ≥75 years	2	0 (0.0)	0 (0.0)
Low platelet count + history of ischaemic stroke without ICH	1	0 (0.0)	0 (0.0)
Severe CKD + history of GI bleeding	1	0 (0.0)	0 (0.0)
Severe CKD + moderate anaemia	81	5 (6.2)	3 (3.7)
Severe CKD + moderate CKD	0	—	—
Severe CKD + NSAIDs or steroids	9	0 (0.0)	0 (0.0)
Severe CKD + ≥75 years	23	3 (13.0)	0 (0.0)
Severe CKD + history of ischaemic stroke without ICH	5	0 (0.0)	0 (0.0)
OAC use + history of GI bleeding	3	0 (0.0)	0 (0.0)
OAC use + moderate anaemia	28	2 (7.1)	0 (0.0)
OAC use + moderate CKD	53	2 (3.8)	0 (0.0)
OAC use + NSAIDs or steroids	8	0 (0.0)	0 (0.0)
OAC use + ≥75 years	39	2 (5.1)	0 (0.0)
OAC use + history of ischaemic stroke without ICH	15	1 (6.7)	1 (6.7)
Liver cirrhosis + history of GI bleeding	0	—	—
Liver cirrhosis + moderate anaemia	1	0 (0.0)	0 (0.0)
Liver cirrhosis + moderate CKD	0	—	—
Liver cirrhosis + NSAIDs or steroids	0	—	—
Liver cirrhosis + ≥75 years	0	—	—

Liver cirrhosis + history of ischaemic stroke without ICH	0	—	—
Malignancy + history of GI bleeding	1	0 (0.0)	0 (0.0)
Malignancy + moderate anaemia	17	0 (0.0)	0 (0.0)
Malignancy + moderate CKD	19	0 (0.0)	0 (0.0)
Malignancy + NSAIDs or steroids	4	0 (0.0)	0 (0.0)
Malignancy + ≥75 years	35	0 (0.0)	0 (0.0)
Malignancy + history of ischaemic stroke without ICH	2	0 (0.0)	0 (0.0)
History of ICH + history of GI bleeding	0	—	—
History of ICH + moderate anaemia	9	0 (0.0)	0 (0.0)
History of ICH + moderate CKD	8	0 (0.0)	0 (0.0)
History of ICH + NSAIDs or steroids	0	—	—
History of ICH + ≥75 years	5	0 (0.0)	0 (0.0)
History of ICH + history of ischaemic stroke without ICH	0	—	—
1 major criterion (point: 1) * East Asian-specific HBR only			
Body weight ≤50 kg	74	0 (0.0)	0 (0.0)
Heart failure	80	2 (2.5)	2 (2.5)

Data are presented as n (%).

CKD: chronic kidney disease; GI: gastrointestinal; HBR: high bleeding risk; ICH: intracranial haemorrhage; NSAIDs: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulant