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ORIGINAL ARTICLE
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Comparison of Discriminative Ability of Bleeding Risk Criteria and Scores for Predicting Short- and Mid-Term Major Bleeding Events in Patients Undergoing Percutaneous Coronary Intervention

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Background: This study aimed to compare the discriminative ability of the Japanese Version of High Bleeding Risk (J-HBR), Academic Research Consortium for High Bleeding Risk (ARC-HBR), and Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) scores for predicting major bleeding events.

Methods and Results: Between January 2017 and December 2020, 646 consecutive patients who underwent successful percutaneous coronary intervention (PCI) were enrolled. We scored the ARC-HBR and J-HBR criteria by assigning 1 point to each major criterion and 0.5 point to each minor criterion. The primary outcome was major bleeding events, defined as Bleeding Academic Research Consortium type 3 or 5 bleeding events. According to the J-HBR, ARC-HBR, and PRECISE-DAPT scores, 428 (66.3%), 319 (49.4%), and 282 (43.7%) patients respectively had a high bleeding risk. During the follow-up period (median, 974 days), 44 patients experienced major bleeding events. The area under the curve (AUC) using the time-dependent receiver operating characteristic curve for major bleeding events was 0.84, 0.82, and 0.83 within 30 days and 0.86, 0.83, and 0.80 within 2 years for the J-HBR, ARC-HBR, and PRECISE-DAPT scores, respectively. The AUC values did not differ significantly among the 3 bleeding risk scores.

Conclusions: The J-HBR score had a discriminative ability similar to the ARC-HBR and PRECISE-DAPT scores for predicting short- and mid-term major bleeding events.

Key Words: High bleeding risk; Major bleeding event; Percutaneous coronary intervention

With recent advances in both the devices for percutaneous coronary intervention (PCI) and optimal medical therapy, including dual antiplatelet therapy (DAPT), the incidence of ischemic events such as stent thrombosis and myocardial infarction (MI) in patients with coronary artery disease (CAD) has decreased.[1,2] In contrast, the long-term use of DAPT can increase the risk of bleeding events after PCI.[3,4] East Asian patients, including Japanese, have a higher risk of bleeding events than patients in Western countries,[5] and major bleeding events after PCI are associated with poorer clinical outcomes.[6] Bleeding Academic Research Consortium (BARC) type 3b bleeding and MI are similarly associated with mortality risk in patients with acute coronary syndrome after PCI.[7] Therefore, it is important to identify patients with a high bleeding risk (HBR), for whom DAPT should be prescribed for a shorter duration to prevent major bleeding events. Various bleeding risk scores have been developed and used in clinical practice. The Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score is a standard risk assessment score for bleeding reported in 2017.[8] The 2018 Japanese Circulation Society (JCS) Guideline on diagnosis and treatment of acute coronary syndrome

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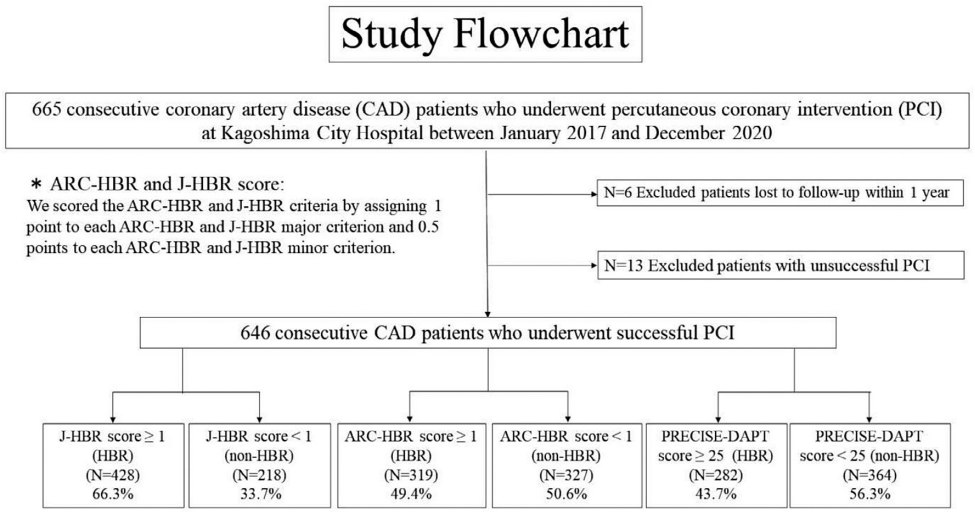


Figure 1. Study flowchart showing patient selection. ARC-HBR, Academic Research Consortium for High Bleeding Risk; HBR, high bleeding risk; J-HBR, Japanese version of the High Bleeding Risk; PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.

and the JCS 2018 Guideline on revascularization of stable coronary artery disease cited the PRECISE-DAPT score to assess bleeding risk.[9,10] The Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria, reported in 2019, were developed to establish a standard definition for identifying HBR patients undergoing PCI.[11] The ARC-HBR criteria have been validated in several studies and are applicable for Japanese patients.[12,13] Furthermore, low body weight, frailty, heart failure, chronic kidney disease requiring dialysis, and peripheral vascular disease (PVD) are independent predictors of bleeding events in Japanese patients,[14–16] and so a Japanese version of the HBR (J-HBR) criteria has been developed. The 2020 JCS guideline in the Focused Update on antithrombotic therapy in patients with coronary artery disease recommends that an antithrombotic regimen should be determined based on the J-HBR criteria.[17] However, because it has not been clarified whether the ARC-HBR and J-HBR criteria have better discriminative ability for major bleeding events than other risk scores, we designed a comparative study. In the current JCS guidelines, the PRECISE-DAPT score revealed a similar or better discriminative ability than the Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) and Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) bleeding risk scores.[17] Furthermore, few studies have analyzed the discriminatory ability of bleeding risk scores for predicting major bleeding events after PCI using a time-dependent receiver operating characteristic (ROC) curve analysis. Most major bleeding events tend to occur in the early phase of the post-PCI period, and the incidence gradually decreases because of de-escalation of DAPT.[12,18,19] Therefore, non-time-dependent ROC curve analysis, which only analyzes the binary value of the presence or absence of an event, may not accurately predict the risk, because it does not consider the time of event onset. Thus, in this study we aimed to compare the discriminative abilities of the J-HBR, ARC-HBR, and PRECISE-DAPT scores for predicting major bleeding events using a time-dependent ROC curve analysis.

Methods

Study Design and Settings

In this single-center retrospective observational study, we reviewed 665 consecutive patients with CAD who underwent PCI at Kagoshima City Hospital between January 1, 2017, and December 31, 2020, with an observation period until December 31, 2022. We excluded 13 patients with unsuccessful PCI and 6 patients who were lost to follow-up within 1 year. Thus, 646 consecutive patients with CAD who underwent successful PCI were included and categorized into 2 groups (HBR and non-HBR) according to the J-HBR, ARC-HBR, and PRECISE-DAPT scores (**Figure 1**). All participants underwent successful PCI for the causative lesions using standard intracoronary imaging (intravascular ultrasound or optical coherence tomography), mainly using a new-generation drug-eluting stent (DES) or a drug-coated balloon (DCB). Participants who were hospitalized more than once during the study period were not considered twice; only data from the first hospitalization were used for analysis.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kagoshima City Hospital (registration number 2021-37, 38). Written informed consent was given by each patient who underwent PCI as an opt-out procedure.

Definitions

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or taking antihypertensive medication currently. Diabetes mellitus was defined as the use of antihyperglycemic medication, previous diagnosis of diabetes mellitus, or glycated hemoglobin level ≥6.5% (National Glycohemoglobin Standardization Program). Dyslipidemia was defined as low-density lipo-

Table 1. Baseline Clinical Characteristics

	All (N=646)	J-HBR score		P value
		HBR (N=428)	Non-HBR (N=218)	
Age	68.8±11.4	72.5±10.5	61.7±9.5	<0.001
Male sex	496 (76.8%)	302 (70.6%)	194 (89.0%)	<0.001
BMI (kg/m^2)	23.8 (21.5–26.1)	22.9 (20.7–25.3)	25.1 (23.5–27.0)	<0.001
Coronary risk factors				
Hypertension	468 (72.5%)	313 (73.1%)	155 (71.1%)	0.642
Diabetes mellitus	271 (42.0%)	193 (45.1%)	78 (35.8%)	0.028
Dyslipidemia	436 (67.5%)	274 (64.0%)	162 (74.3%)	0.010
Current smoker	190 (29.4%)	110 (25.7%)	80 (36.7%)	0.005
Family history of CAD	74 (11.5%)	41 (9.6%)	33 (15.1%)	0.049
Previous stroke	86 (13.3%)	77 (18.0%)	9 (4.1%)	<0.001
Previous MI	137 (21.2%)	102 (23.8%)	35 (16.1%)	0.025
Previous PCI or CABG	140 (21.7%)	95 (22.2%)	45 (20.6%)	0.687
Heart failure	165 (25.5%)	165 (38.6%)	0 (0.0%)	<0.001
Atrial fibrillation	62 (9.6%)	59 (13.8%)	3 (1.4%)	<0.001
Hemodialysis	34 (5.3%)	34 (7.9%)	0 (0.0%)	<0.001
COPD	40 (6.2%)	35 (8.2%)	5 (2.3%)	0.003
Peripheral vascular disease	76 (11.8%)	76 (17.8%)	0 (0.0%)	<0.001
Diagnosis				0.116
ACS	337 (52.2%)	211 (49.3%)	126 (57.8%)	
STEMI	262 (40.6%)	165 (38.6%)	97 (44.5%)	
NSTEMI/UAP	75 (11.6%)	46 (10.7%)	29 (13.3%)	
Stable CAD	309 (47.8%)	217 (50.7%)	92 (42.2%)	
Lesion location				0.214
LMCA	16 (2.5%)	12 (2.8%)	4 (1.8%)	
LAD	303 (46.9%)	203 (47.4%)	100 (45.9%)	
LCX	104 (16.1%)	61 (14.3%)	43 (19.7%)	
RCA	222 (34.3%)	152 (35.5%)	70 (32.1%)	
Graft	1 (0.2%)	0 (0.0%)	1 (0.5%)	
Laboratory data				
LDL-C (mg/dL)	100 (75–128)	93 (73–118)	113 (88–142)	<0.001
HDL-C (mg/dL)	45 (37–54)	46 (37–55)	45 (38–52)	0.645
TG (mg/dL)	111 (78–171)	104 (74–153)	133 (93–206)	<0.001
HbA1c (%)	6.1 (5.6–7.1)	6.1 (5.6–7.2)	6.0 (5.7–6.9)	0.672
eGFR (mL/min/1.73 m^2)	64 (50–77)	57 (44–71)	72 (64–83)	<0.001
Hb (g/dL)	13.6 (12.2–14.9)	12.8 (11.6–14.2)	14.6 (13.6–15.6)	<0.001
Platelet count (×10^4/mL)	20.3 (17.1–24.3)	19.9 (15.9–24.1)	21.3 (18.1–24.6)	0.001
Echocardiography finding				
LVEF	63 (51–70)	60 (48–69)	65 (58–71)	<0.001
LVEF <40%	62 (9.6%)	59 (13.8%)	3 (1.4%)	<0.001
Lesion characteristics				
AHA/ACC Type B2/C	421 (65.2%)	291 (68.0%)	130 (59.6%)	0.037
No. of diseased vessels	1.6±0.8	1.7±0.8	1.6±0.7	0.070
Multivessel disease	298 (46.1%)	206 (48.1%)	92 (42.2%)	0.157
Access site				<0.001
Radial	425 (65.8%)	259 (60.5%)	166 (76.1%)	
Femoral	181 (28.0%)	138 (32.3%)	43 (19.7%)	
Brachial	40 (6.2%)	31 (7.2%)	9 (4.2%)	
Mechanical support				
IABP	51 (7.9%)	45 (10.5%)	6 (2.8%)	<0.001
V-A ECMO	18 (2.8%)	17 (4.0%)	1 (0.5%)	0.010
PCI procedure				0.006
DES	577 (89.3%)	377 (88.1%)	200 (91.8%)	
DCB	32 (5.0%)	18 (4.2%)	14 (6.4%)	
Other	37 (5.7%)	33 (7.7%)	4 (1.8%)	

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

	All (N=646)	J-HBR score		P value
		HBR (N=428)	Non-HBR (N=218)	
Medication at discharge				
ACE-I or ARB	456 (70.6%)	297 (69.4%)	159 (72.9%)	0.363
β-blocker	339 (52.5%)	222 (51.9%)	117 (53.7%)	0.678
Calcium-channel blocker	260 (40.3%)	173 (40.4%)	87 (39.9%)	0.932
Statin	589 (91.2%)	374 (87.4%)	215 (98.6%)	<0.001
Insulin	51 (7.9%)	42 (9.8%)	9 (4.1%)	0.013
Aspirin	635 (98.3%)	417 (97.4%)	218 (100%)	0.019
Clopidogrel	210 (32.5%)	162 (37.9%)	48 (22.0%)	<0.001
Prasugrel	420 (65.0%)	253 (59.1%)	167 (76.6%)	<0.001
Oral anticoagulant	74 (11.5%)	74 (17.3%)	0 (0.0%)	<0.001
Proton-pump inhibitor	608 (94.1%)	406 (94.9%)	202 (92.7%)	0.290

Data are shown as mean±standard deviation or median with interquartile range, and n (%). ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AHA/ACC, American Heart Association/American College of Cardiology; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DCB, drug-coated balloon; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, glycated hemoglobin; HBR, high bleeding risk; HDL-C, high-density lipoprotein-cholesterol; IABP, intra-aortic balloon pumping; J-HBR, Japanese version of the High Bleeding Risk; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein-cholesterol; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction; TG, triglyceride; UAP, unstable angina pectoris; V-A ECMO, veno-arterial extracorporeal membrane oxygenation.

protein-cholesterol level ≥140 mg/ dL, high-density lipoprotein-cholesterol level <40 mg/dL, triglyceride level ≥150 mg/dL, or taking lipid-lowering medication currently. A current smoker was defined as having a smoking habit at the time of admission. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. Heart failure was defined based on the Framingham criteria.[20] PVD was defined as the abdominal aorta, renal arteries, and/or lower extremity arteries requiring surgical or endovascular treatment, or an ankle-brachial index ≤0.9 for the lower extremity arteries.[21]

J-HBR, ARC-HBR, and PRECISE-DAPT Scores

Baseline data pertaining to the 5 variables (age, hemoglobin level, white blood cell count, creatinine clearance, and previous spontaneous bleeding) of the PRECISE-DAPT score, the 17 major and minor criteria of the ARC-HBR score, and the 3 specific criteria (low body weight or frailty, heart failure, and PVD) of the J-HBR score were obtained from the medical records, by telephone interview with the patient or relatives, or from the primary physician. As previously reported,[12,18,19] the ARC-HBR and J-HBR scores are calculated by assigning 1 point to each of their major criteria and 0.5 point to each of their minor criteria, with ARC-HBR score ≥1 and J-HBR score ≥1 defined as HBR. The PRECISE-DAPT score was calculated using an online calculator (http://www.precisedaptscore.com/predapt/webcalculator.html), with a score ≥25 defined as HBR. In principle, DAPT duration was 1–3 months for patients with anticoagulation and 6–12 months for patients without anticoagulation, in accordance with the JCS guidelines in the study period.[9,10]

Data Collection and Clinical Outcome Measures

Clinical and follow-up data were retrospectively obtained from the medical records at the time of outpatient visits, by telephone interviews with the patient or relatives, or from the primary physician. The primary outcome measure was the cumulative incidence of major bleeding events defined as BARC type 3 or 5 bleeding events. The secondary outcome measures were the cumulative incidence of all-cause death and ischemic events (defined as MI and ischemic stroke), and 3-point major adverse cardiovascular event (MACE) defined as all-cause death, MI, and stroke.

Statistical Analysis

Categorical variables are presented as frequency and percentage. Normally distributed continuous variables are presented as mean±standard deviation, and non-normally distributed continuous variables are presented as median and interquartile range. Categorical variables were compared using the chi-square test. Continuous variables were compared using the Mann-Whitney U test or Student's t-test, as appropriate. Cumulative event curves were derived using the Kaplan-Meier method and compared between groups using the log-rank test. To examine whether the incidence of major bleeding events increased in a stepwise manner as the bleeding risk score increased, the bleeding risk score was stratified into 3 or 4 categories. The PRECISE-DAPT score was classified into 3 categories (0–17, 18–24, ≥25), the ARC-HBR score was classified into three categories (0–0.5, 1–1.5, ≥2), and the J-HBR score was classified into four categories (0–0.5, 1–1.5, 2–2.5, ≥3).[8,19,22] Landmark analysis at 30 days was performed to distinguish between early and late events after PCI. Those patients who had individual endpoint events before 30 days were excluded from each landmark analysis beyond 30 days. To investigate the discriminative ability of the J-HBR, ARC-HBR, and PRECISE-DAPT scores for predicting major bleeding events, a time-dependent ROC curve analysis was performed based on the primary outcomes, and the area under the curve (AUC) for each bleeding risk score was calculated. The time-dependent AUCs for each bleeding risk score were compared with the null hypothesis that "the AUCs of both scores are equal at the time 't'".[23] As a subanalysis, the ROC curve was used to calculate the AUC for the primary endpoint according to each bleeding risk score, and each AUC was compared using the Delong

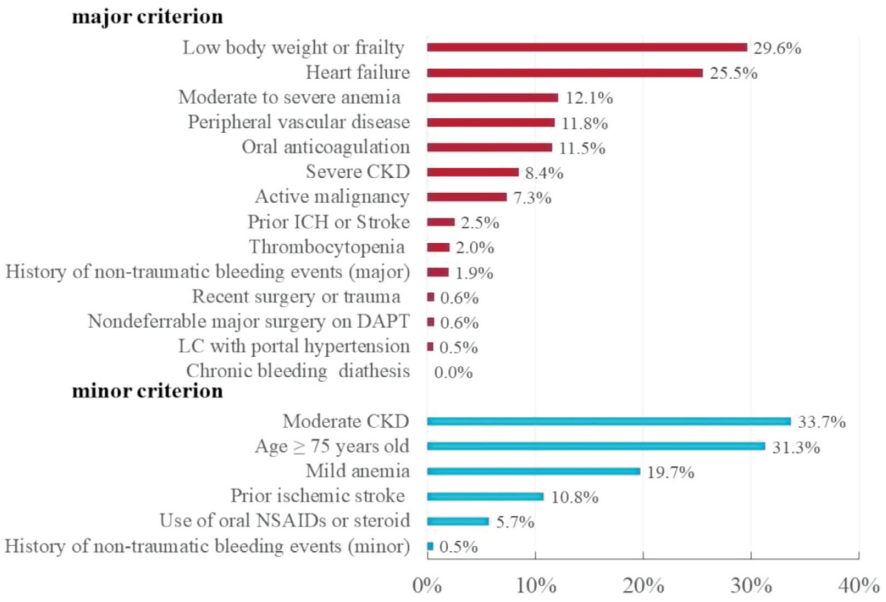


Figure 2. Prevalence of each criterion included in the ARC-HBR and J-HBR scores. ARC-HBR, Academic Research Consortium for High Bleeding Risk; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; ICH, intracranial hemorrhage; J-HBR, Japanese version of the High Bleeding Risk; LC, liver cirrhosis; NSAID, nonsteroidal anti-inflammatory drug.

test. Bonferroni adjustment was used to address concerns regarding multiple comparisons that arose from paired comparisons (resulting in a significance threshold of 0.017). Statistical significance was set at $P<0.05$. All statistical analyses were performed using JMP Pro (version 16.0; SAS Institute Inc., Cary, NC, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html; Kanda, 2012), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 4.1.2). It is a modified version of the R commander (version 2.7-1) designed to add statistical functions that are frequently used in biostatistics.[24]

Results

Clinical Characteristics

Based on the J-HBR, ARC-HBR, and PRECISE-DAPT scores, 428 (66.3%), 319 (49.4%), and 282 (43.7%) patients, respectively, were classified into the HBR group. The baseline clinical, lesion, and procedural characteristics of patients with CAD in the HBR and non-HBR groups according to the J-HBR score are shown in **Table 1**. Patients in the HBR group were older, were more frequently of the female sex, had a lower body mass index, and a higher prevalence of diabetes mellitus, previous stroke, previous MI, heart failure, atrial fibrillation, and hemodialysis than those in the non-HBR group. eGFR, serum hemoglobin level, and platelet count were lower in the HBR group than in the non-HBR group. Further, left ventricular ejection fraction was lower, occurrence of complex lesions was higher, and proportion of use of the transradial approach was lower in the HBR group. The use of mechanical support was higher and the use of DES and DCB was lower in the HBR group than in the non-HBR group. In terms of medication at discharge, patients in the HBR group received clopidogrel and oral anticoagulants more frequently and statins, prasugrel, and aspirin less frequently than those in the non-HBR group. The prevalence of all individual risk criteria in the J-HBR and ARC-HBR definitions is shown in **Figure 2**. The common major criteria for the J-HBR and ARC-HBR were low body weight or frailty, heart failure, moderate-to-severe anemia, PVD, oral anticoagulant use, severe CKD, and active malignancy; the prevalence of other criteria was less than 5%. The most common minor criteria were moderate CKD, advanced age, mild anemia, and history of ischemic stroke.

Clinical Outcomes According to Each Bleeding Risk Score

During the median follow-up period of 974 (730–1,319) days, 44 patients experienced major bleeding events, 21 experienced ischemic events, and 98 died. The frequency of persistent discontinuation of DAPT was not significantly different between the HBR and non-HBR groups according to the J-HBR and PRECISE-DAPT scores, whereas it was significantly higher in the HBR group than in the non-HBR group according to the ARC-HBR score (**Supplementary Figure 1**). Investigation of the association between major bleeding events and antithrombotic medication status revealed that 70% of the patients received DAPT at the time of major bleeding events (**Supplementary Table**). Kaplan-Meier curves revealed a higher incidence of the primary outcome in the HBR group than in the non-HBR group according to each bleeding risk score (**Figure 3A–C**, **Table 2**). In the evaluation of each component of major bleeding events, approximately 40% were gastrointestinal bleeding events, whereas intracranial bleeding and other bleeding events accounted for approximately 20% (**Table 2**). In the 30-day landmark analysis, the cumulative incidence of major bleeding events was significantly higher in each HBR group than in each non-HBR group within and

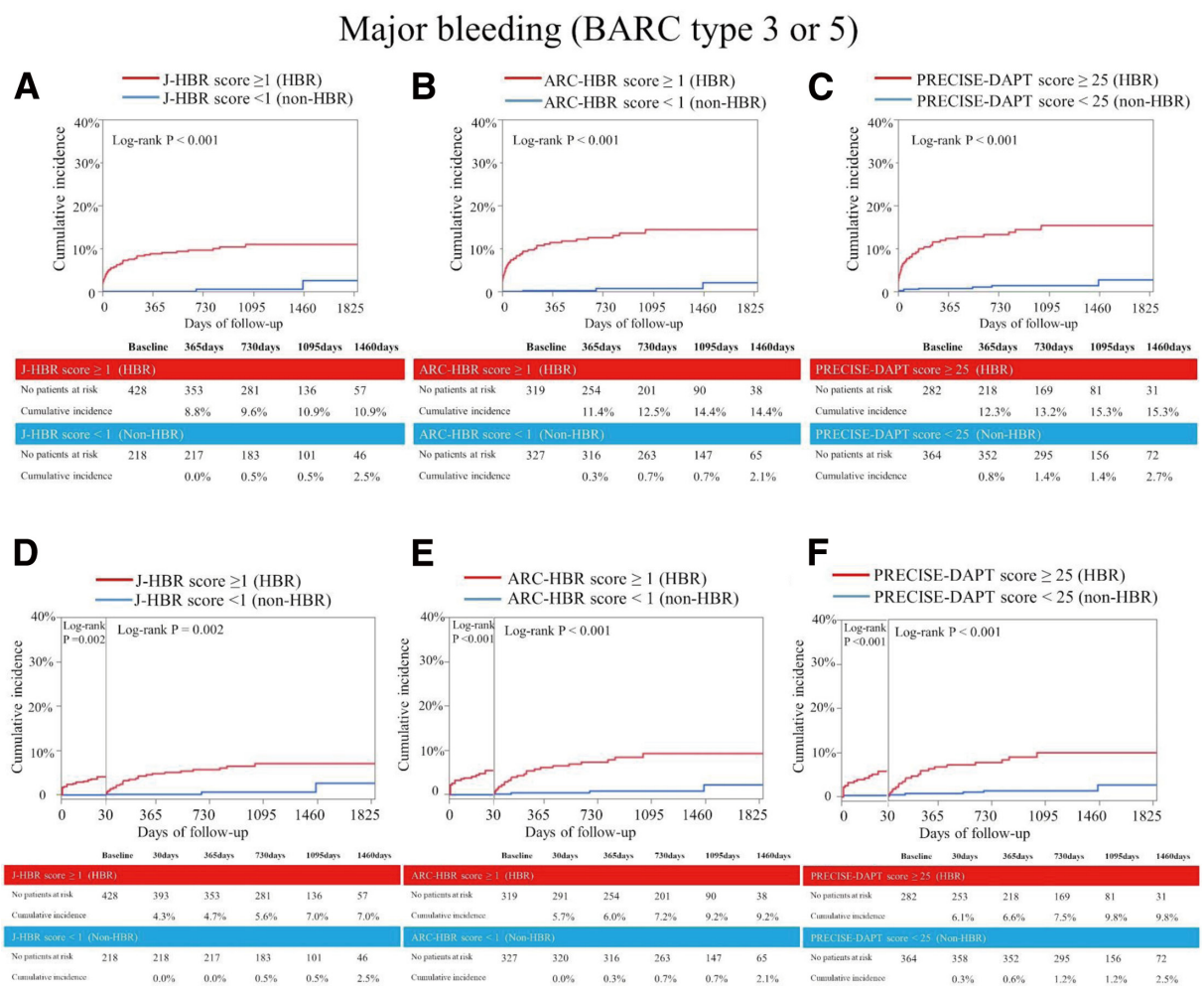


Figure 3. Kaplan-Meier analysis for the cumulative incidence of the primary outcome measure. (**A**) Kaplan-Meier analysis for major bleeding events between HBR and non-HBR groups according to J-HBR scores. (**B**) Kaplan-Meier analysis for major bleeding events between HBR and non-HBR groups according to ARC-HBR scores. (**C**) Kaplan-Meier analysis for major bleeding events between HBR and non-HBR groups according to PRECISE-DAPT score. (**D**) Landmark analysis within and beyond 30 days for major bleeding events between HBR and non-HBR groups according to J-HBR scores. (**E**) Landmark analysis within and beyond 30 days for major bleeding events between HBR and non-HBR groups according to ARC-HBR scores. (**F**) Landmark analysis within and beyond 30 days for major bleeding events between HBR and non-HBR groups according to PRECISE-DAPT scores. ARC-HBR, Academic Research Consortium for High Bleeding Risk; BARC, Bleeding Academic Research Consortium; HBR, high bleeding risk; J-HBR, Japanese version of the High Bleeding Risk; PRECISE-DAPT, Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.

beyond 30 days (**Figure 3D–F**, **Table 3**). As each bleeding risk score increased, the cumulative incidence of major bleeding events increased stepwise (**Figure 4A–C**). In the 30-day landmark analysis, the cumulative incidence of major bleeding events increased in a stepwise manner as each bleeding risk score increased within and beyond 30 days (**Figure 4D–F**). Kaplan-Meier analysis for the secondary ischemic outcome measure revealed that the HBR group according to the ARC-HBR and PRECISE-DAPT scores had a significantly higher incidence of ischemic stroke than the non-HBR group, and the cumulative incidence of MI did not differ significantly between HBR and non-HBR groups. The cumulative incidence of ischemic stroke and MI did not differ significantly between the HBR and non-HBR groups according to the J-HBR score (**Table 2**). The cumulative incidence of all-cause death (cardiovascular and non-cardiovascular) and 3-point MACE was significantly higher in each HBR group than in each non-HBR group (**Table 2**). The same trend persisted in the landmark analysis of the secondary outcome measures (3-point MACE, and all-cause death) within and beyond 30 days. In contrast, ischemic events did not differ significantly within 30 days between each HBR and non-HBR group and HBR group according to the ARC-HBR score and PRECISE-DAPT score had a significantly higher incidence of ischemic events (only ischemic stroke) beyond 30 days (**Table 3**).

ROC Curve Analysis for Primary Outcome Measure

The time-dependent ROC curve analysis showed the AUC for major bleeding events of 0.84, 0.82, and 0.83 within 30

Table 2. Clinical Outcomes Between HBR and Non-HBR Groups According to Each Bleeding Risk Score

	No. patients with events (cumulative 2-year incidence: %)				
	All (N=646)	J-HBR (HBR) (N=428)	J-HBR (Non-HBR) (N=218)	P value	ARC-HBR (HBR) (N=319)
Major bleeding event (BARC type 3 or 5 bleeding)	44 (6.5%)	42 (9.6%)	2 (0.5%)	<0.001	41 (12.5%)
Gastrointestinal bleeding	19 (2.8%)	18 (4.3%)	1 (0.0%)	0.004	17 (5.5%)
Access site bleeding	6 (0.9%)	6 (1.4%)	0 (0.0%)	0.076	6 (1.9%)
Intracranial bleeding	9 (1.3%)	9 (2.1%)	0 (0.0%)	0.022	9 (2.8%)
Other	10 (1.5%)	9 (2.1%)	1 (0.5%)	0.078	9 (2.9%)
Ischemic event (MI and ischemic stroke)	21 (2.5%)	15 (2.8%)	6 (1.9%)	0.402	14 (3.4%)
MI	12 (1.5%)	7 (1.5%)	5 (1.4%)	0.750	6 (1.8%)
Ischemic stroke	9 (1.0%)	8 (1.3%)	1 (0.5%)	0.102	8 (1.7%)
All-cause death	98 (12.1%)	94 (17.5%)	4 (1.4%)	<0.001	82 (20.7%)
Cardiovascular death	56 (7.9%)	53 (11.2%)	3 (1.4%)	<0.001	43 (12.6%)
Non-cardiovascular death	42 (4.6%)	41 (7.1%)	1 (0.0%)	<0.001	39 (9.3%)
3-point MACE (death, MI, stroke)	116 (14.1%)	106 (19.6%)	10 (3.3%)	<0.001	94 (23.4%)

The number of patients with events counted during the entire follow-up period. The cumulative 2-year incidence was estimated using the Kaplan-Meier method. ARC-HBR, Academic Research Consortium for High Bleeding Risk; BARC, Bleeding Academic Research Consortium; MACE, major adverse cardiovascular event; PRECISE-DAPT, Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy. Other abbreviations as in Table 1.

(**Table 2** continued the next page.)

Table 3. Clinical Outcomes Between HBR and Non-HBR Groups According to Each Bleeding Risk Score Within and Beyond 30 Days

	No. patients with events (cumulative 2-year incidence; %)				
	All (N=646)	J-HBR (HBR) (N=428)	J-HBR (Non-HBR) (N=218)	P value	ARC-HBR (HBR) (N=319)
Within 30 days					
Major bleeding event (BARC type 3 or 5 bleeding)	18 (2.8%)	18 (4.3%)	0 (0.0%)	0.002	18 (5.7%)
Gastrointestinal bleeding	7 (1.1%)	7 (1.7%)	0 (0.0%)	0.054	7 (2.3%)
Access site bleeding	5 (0.8%)	5 (1.2%)	0 (0.0%)	0.108	5 (1.6%)
Intracranial bleeding	3 (0.5%)	3 (0.7%)	0 (0.0%)	0.211	3 (1.0%)
Others	3 (0.5%)	3 (0.7%)	0 (0.0%)	0.205	3 (1.0%)
Ischemic event (MI and ischemic stroke)	3 (0.5%)	3 (0.7%)	0 (0.0%)	0.206	2 (0.7%)
MI	2 (0.3%)	2 (0.5%)	0 (0.0%)	0.303	1 (0.3%)
Ischemic stroke	1 (0.2%)	1 (0.3%)	0 (0.0%)	0.464	1 (0.3%)
All-cause death	22 (3.4%)	22 (5.1%)	0 (0.0%)	<0.001	15 (4.7%)
Cardiovascular death	20 (3.1%)	20 (4.7%)	0 (0.0%)	0.001	14 (4.4%)
Non-cardiovascular death	2 (0.3%)	2 (0.5%)	0 (0.0%)	0.303	1 (0.3%)
3-point MACE (death, MI, stroke)	24 (3.7%)	24 (5.6%)	0 (0.0%)	<0.001	17 (5.3%)
Beyond 30 days					
Major bleeding event (BARC type 3 or 5 bleeding)	26/611 (3.7%)	24/393 (5.6%)	2/218 (0.5%)	0.002	23/291 (7.2%)
Gastrointestinal bleeding	12/611 (1.7%)	11/393 (2.7%)	1/218 (0.0%)	0.034	10/291 (3.3%)
Access site bleeding	1/611 (0.2%)	1/393 (0.3%)	0/218 (0.0%)	0.452	1/291 (0.4%)
Intracranial bleeding	6/611 (0.9%)	6/393 (1.4%)	0/218 (0.0%)	0.056	6/291 (1.9%)
Others	7/611 (1.1%)	6/393 (1.4%)	1/218 (0.5%)	0.201	6/291 (1.9%)
Ischemic event (MI and ischemic stroke)	18/623 (2.0%)	12/405 (2.1%)	6/218 (1.9%)	0.686	12/303 (2.8%)
MI	10/623 (1.2%)	5/405 (1.1%)	5/218 (1.4%)	0.435	5/303 (1.5%)
Ischemic stroke	8/623 (0.8%)	7/405 (1.0%)	1/218 (0.5%)	0.139	7/303 (1.4%)
All-cause death	76/624 (9.0%)	72/406 (13.1%)	4/218 (1.4%)	<0.001	67/304 (16.8%)
Cardiovascular death	36/624 (5.0%)	33/406 (6.9%)	3/218 (1.4%)	<0.001	29/304 (8.6%)
Non-cardiovascular death	40/624 (4.3%)	39/406 (6.7%)	1/218 (0.0%)	<0.001	38/304 (9.0%)
3-point MACE (death, MI, stroke)	92/622 (10.8%)	82/404 (14.8%)	10/218 (3.3%)	<0.001	77/302 (19.1%)

In the landmark analysis beyond 30 days, the number of patients who had an event during the 30 days to entire follow-up period was counted, whereas the cumulative incidence between 30 days and 2 years was estimated by the Kaplan-Meier method. Abbreviations as in Tables 1,2.

(**Table 3** continued the next page.)

	No. patients with events (cumulative 2-year incidence: %)				
	ARC-HBR (Non-HBR) (N=327)	P value	PRECISE-DAPT (HBR) (N=282)	PRECISE-DAPT (Non-HBR) (N=364)	P value
Major bleeding event (BARC type 3 or 5 bleeding)	3 (0.7%)	<0.001	38 (13.2%)	6 (1.4%)	<0.001
Gastrointestinal bleeding	2 (0.3%)	<0.001	16 (5.9%)	3 (0.6%)	<0.001
Access site bleeding	0 (0.0%)	0.012	6 (2.2%)	0 (0.0%)	0.005
Intracranial bleeding	0 (0.0%)	0.001	7 (2.4%)	2 (0.6%)	0.021
Other	1 (0.4%)	0.005	9 (3.3%)	1 (0.3%)	0.001
Ischemic event (MI and ischemic stroke)	7 (1.6%)	0.048	13 (3.5%)	8 (1.7%)	0.031
MI	6 (1.3%)	0.763	5 (1.6%)	7 (1.4%)	0.867
Ischemic stroke	1 (0.3%)	0.008	8 (2.0%)	1 (0.3%)	0.002
All-cause death	16 (3.7%)	<0.001	78 (21.9%)	20 (4.5%)	<0.001
Cardiovascular death	13 (3.4%)	<0.001	47 (14.9%)	9 (2.5%)	<0.001
Non-cardiovascular death	3 (0.3%)	<0.001	31 (8.3%)	11 (2.0%)	<0.001
3-point MACE (death, MI, stroke)	22 (5.0%)	<0.001	89 (24.7%)	27 (5.9%)	<0.001

	No. patients with events (cumulative 2-year incidence; %)				
	ARC-HBR (Non-HBR) (N=327)	P value	PRECISE-DAPT (HBR) (N=282)	PRECISE-DAPT (Non-HBR) (N=364)	P value
Within 30 days					
Major bleeding event (BARC type 3 or 5 bleeding)	0 (0.0%)	<0.001	17 (6.1%)	1 (0.3%)	<0.001
Gastrointestinal bleeding	0 (0.0%)	0.006	6 (2.2%)	1 (0.3%)	0.021
Access site bleeding	0 (0.0%)	0.023	5 (1.8%)	0 (0.0%)	0.010
Intracranial bleeding	0 (0.0%)	0.076	3 (1.1%)	0 (0.0%)	0.046
Others	0 (0.0%)	0.073	3 (1.1%)	0 (0.0%)	0.043
Ischemic event (MI and ischemic stroke)	1 (0.3%)	0.532	3 (1.1%)	0 (0.0%)	0.044
MI	1 (0.3%)	0.969	2 (0.7%)	0 (0.0%)	0.101
Ischemic stroke	0 (0.0%)	0.305	1 (0.4%)	0 (0.0%)	0.245
All-cause death	7 (2.1%)	0.071	17 (6.0%)	5 (1.4%)	0.001
Cardiovascular death	6 (1.8%)	0.060	16 (5.7%)	4 (1.1%)	0.001
Non-cardiovascular death	1 (0.3%)	0.970	1 (0.4%)	1 (0.3%)	0.833
3-point MACE (death, MI, stroke)	7 (2.1%)	0.032	19 (6.7%)	5 (1.4%)	<0.001
Beyond 30 days					
Major bleeding event (BARC type 3 or 5 bleeding)	3/320 (0.7%)	<0.001	21/253 (7.5%)	5/358 (1.2%)	<0.001
Gastrointestinal bleeding	2/320 (0.3%)	0.007	10/253 (3.8%)	2/358 (0.3%)	0.001
Access site bleeding	0/320 (0.0%)	0.289	1/253 (0.4%)	0/358 (0.0%)	0.226
Intracranial bleeding	0/320 (0.0%)	0.007	4/253 (1.3%)	2/358 (0.6%)	0.156
Others	1/320 (0.4%)	0.031	6/253 (2.2%)	1/358 (0.3%)	0.011
Ischemic event (MI and ischemic stroke)	6/320 (1.3%)	0.059	10/264 (2.4%)	8/359 (1.7%)	0.130
MI	5/320 (1.0%)	0.732	3/264 (0.8%)	7/359 (1.5%)	0.591
Ischemic stroke	1/320 (0.3%)	0.014	7/264 (1.6%)	1/359 (0.3%)	0.004
All-cause death	9/320 (1.6%)	<0.001	61/265 (16.9%)	15/359 (3.2%)	<0.001
Cardiovascular death	7/320 (1.6%)	<0.001	31/265 (9.8%)	5/359 (1.5%)	<0.001
Non-cardiovascular death	2/320 (0.0%)	<0.001	30/265 (7.9%)	10/359 (1.7%)	<0.001
3-point MACE (death, MI, stroke)	15/320 (2.9%)	<0.001	70/263 (19.3%)	22/359 (4.6%)	<0.001

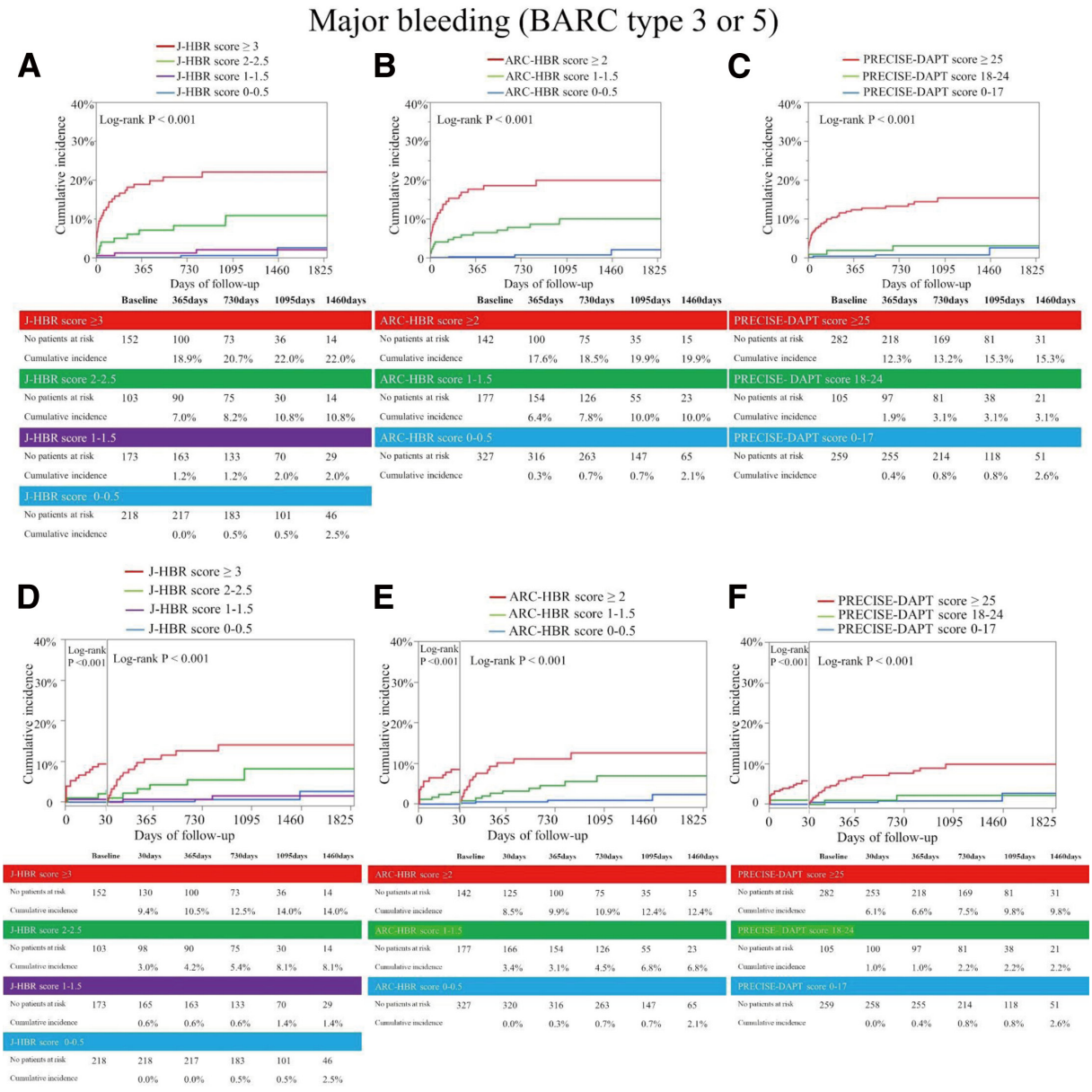
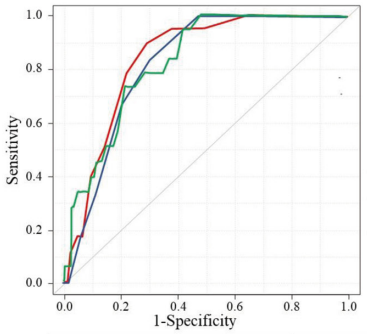


Figure 4. Kaplan-Meier analysis for the cumulative incidence of major bleeding events stratified by each bleeding risk score. (**A**) Kaplan-Meier analysis for major bleeding events among J-HBR scores 0–0.5, 1–1.5, 2–2.5, and ≥3. (**B**) Kaplan-Meier analysis for major bleeding events among ARC-HBR scores 0–0.5, 1–1.5, and ≥2. (**C**) Kaplan-Meier analysis for the major bleeding events among PRECISE-DAPT scores 0–17, 18–24, and ≥ 25. (**D**) Landmark analysis within and beyond 30 days for major bleeding events among J-HBR scores 0–0.5, 1–1.5, 2–2.5, and ≥3. (**E**) Landmark analysis within and beyond 30 days for major bleeding events among ARC-HBR scores 0–0.5, 1–1.5, and ≥2. (**F**) Landmark analysis within and beyond 30 days for major bleeding events among PRECISE-DAPT scores 0–17, 18–24, and ≥25. ARC-HBR, Academic Research Consortium for High Bleeding Risk; J-HBR, Japanese version of the High Bleeding Risk; PRECISE-DAPT, Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.

days, 0.86, 0.83, and 0.80 within 2 years, 0.85, 0.82, and 0.77 between 30 days and 2 years according to the J-HBR, ARC-HBR, and PRECISE-DAPT scores, respectively. The predictability of the J-HBR score for major bleeding events was similar to that of the ARC-HBR and PRECISE-DAPT scores within 30 days, within 2 years, and between 30 days and 2 years (**Figure 5**). As a subanalysis, major bleeding events were analyzed using a (non-time-dependent) ROC curve, as shown in **Supplementary Figure 2**. The AUC of the ROC curves for predicting major bleeding events within 30 days, within 2 years, and between 30 days and 2 years according to the J-HBR, ARC-HBR, and PRECISE-DAPT scores did not differ significantly. The J-HBR score had a higher sensitivity and lower specificity for predicting major bleeding events within 30 days, within 2 years, and between 30 days and 2 years than the other 2 risk scores.

A Time-dependent ROC curve analysis for predicting major bleeding events within 30 days

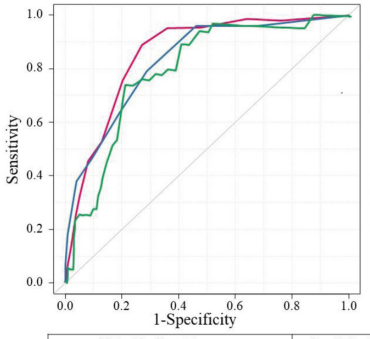


	Area under the curve
J-HBR score	0.84
ARC-HBR score	0.82
PRECISE-DAPT score	0.83

	P for the difference
J-HBR score vs ARC-HBR score	1.00
J-HBR score vs PRECISE-DAPT score	1.00
ARC-HBR score vs PRECISE-DAPT score	1.00

Major bleeding at 30 days	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
J-HBR score (≥1)	94.2%	51.9%	5.1%	99.7%
ARC-HBR score (≥1)	82.4%	69.6%	6.9%	99.3%
PRECISE-DAPT score (≥25)	82.3%	60.9%	5.4%	99.2%

B Time-dependent ROC curve analysis for predicting major bleeding events within two year

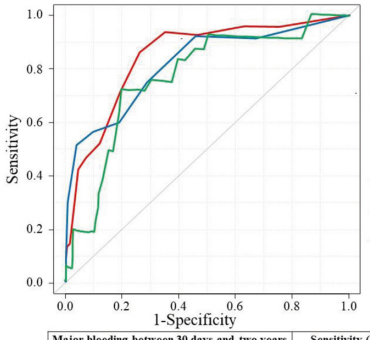


	Area under the curve
J-HBR score	0.86
ARC-HBR score	0.83
PRECISE-DAPT score	0.80

	P for the difference
J-HBR score vs ARC-HBR score	0.25
J-HBR score vs PRECISE-DAPT score	0.38
ARC-HBR score vs PRECISE-DAPT score	1.00

Major bleeding at two years	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
J-HBR score (≥1)	92.1%	57.1%	12.9%	99.1%
ARC-HBR score (≥1)	77.0%	74.9%	17.5%	97.9%
PRECISE-DAPT score (≥25)	77.0%	65.8%	13.4%	97.6%

C Time-dependent ROC curve analysis for predicting major bleeding events between 30 days to two year



	Area under the curve
J-HBR score	0.85
ARC-HBR score	0.82
PRECISE-DAPT score	0.77

	P for the difference
J-HBR score vs ARC-HBR score	0.42
J-HBR score vs PRECISE-DAPT score	0.47
ARC-HBR score vs PRECISE-DAPT score	1.00

Major bleeding between 30 days and two years	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
J-HBR score (≥1)	90.2%	56.9%	7.5%	99.3%
ARC-HBR score (≥1)	72.0%	75.0%	10.1%	98.6%
PRECISE-DAPT score (≥25)	72.2%	65.9%	7.6%	98.4%

Figure 5. Time-dependent receiver operating characteristic (ROC) curve analysis for predicting major bleeding events (BARC type 3 or 5 bleeding) according to the J-HBR, ARC-HBR, and PRECISE-DAPT scores. (**A**) Time-dependent ROC curve analysis for predicting major bleeding events within 30 days. (**B**) Time-dependent ROC curve analysis for predicting major bleeding events within 2 years. (**C**) Time-dependent ROC curve analysis for predicting major bleeding events between 30 days and 2 years. ARC-HBR, Academic Research Consortium for High Bleeding Risk; BARC, Bleeding Academic Research Consortium; J-HBR, Japanese version of the High Bleeding Risk; PRECISE-DAPT, Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; PPV, positive predictive value; NPV, negative predictive value.

Discussion

This study investigated the predictive abilities of the J-HBR, ARC-HBR, and PRECISE-DAPT scores for short- and mid-term major bleeding events after PCI. There were 2 main findings. (1) The J-HBR scores had a discriminative ability similar to the ARC-HBR and PRECISE-DAPT scores for predicting major bleeding events within 30 days, within 2 years, and between 30 days and 2 years after PCI in patients with CAD. (2) The incidence of major bleeding events increased stepwise as the bleeding risk scores increased within and beyond 30 days.

Association Between Major Bleeding Events and Each Bleeding Risk Score

Major bleeding events are a significant complication after PCI and associated with a poor prognosis.[6] Although the use of risk scores to predict bleeding events is important, it has not been clarified whether the ARC-HBR and J-HBR criteria have better discriminative ability for major bleeding events than other risk scores. The discriminative abilities of the J-HBR, ARC-HBR, and PRECISE-DAPT scores for predicting major bleeding events within 1 year or more are comparable,[19,25,26] and the results of our study also showed no significant differences in the discriminative

ability for predicting major bleeding events among the J-HBR, ARC-HBR, and PRECISE-DAPT scores in the time-dependent ROC curve analysis. In contrast to previous studies,[19,25–28] the AUC values in the present study for the J-HBR, ARC-HBR, and PRECISE-DAPT scores were higher (0.77–0.86 vs. 0.61–0.75 in previous studies).[19,25–28] We observed few major bleeding events in the non-HBR group according to the J-HBR and ARC-HBR scores, which may have contributed to the higher discriminative ability of those scores. The reason for fewer major bleeding events in our study could be the limited use of the transfemoral approach (28% vs. 58–76% in previous studies)[19,25–27] and the smaller incidence of acute coronary syndrome (52.2% vs. 100% in a previous study).[28] In the CREDO-Kyoto registry cohort 3,[29] the cumulative incidence of major bleeding events in the HBR group according to the J-HBR criteria within 1 year was higher than in our study (14.0% vs. 8.8% within 1 year, respectively), regardless of whether the proportion of patients with HBR was similar (64% vs. 66.3%, respectively). This was partly attributable to the increased use of the transfemoral approach in the CREDO-Kyoto registry cohort 3 than in our study (53% vs. 28%, respectively) and advances in PCI devices that have allowed for shorter DAPT duration. In line with a previous study,[30] 70% of the patients who experienced major bleeding events received DAPT at the time of major bleeding events in the present study.

Considering the effect of DAPT on major bleeding events, early de-escalation of DAPT may reduce their incidence. Another reason for the fewer major bleeding events in our study may be the retrospective collection of the clinical data on bleeding events, leading to the possibility of missing some bleeding events. In the present study, analysis of the time-dependent ROC curves showed that the discriminative ability of the J-HBR and ARC-HBR scores to predict major bleeding events did not decrease beyond 30 days compared with the PRECISE-DAPT score. This may be because the ARC-HBR and J-HBR scores include many stable factors related to long-term bleeding events (e.g., advanced age, prior stroke, anemia, and renal dysfunction).

The J-HBR score comprises more risk factors than the other risk scores and identified a greater proportion of patients with HBR. In line with previous studies,[19,26,27,28] the J-HBR score was more sensitive than other bleeding risk scores in the present study and may be a highly effective screening tool for patients with HBR. Thus, patients identified as non-HBR according to the J-HBR score could be considered to have a low risk of bleeding. Furthermore, in line with previous studies,[19,29] in the present study the bleeding risk increased stepwise as the J-HBR score increased. The J-HBR score may more precisely identify patients with non-HBR, and further stratify patients with HBR from intermediate bleeding risk to extremely high bleeding risk. Efforts should be made to reduce major bleeding events, especially in patients with an extremely high bleeding risk (e.g., those with higher J-HBR scores), by using the radial artery approach and shortening the DAPT duration. For patients with higher J-HBR scores, a simple PCI procedure (e.g., avoiding a 2-stent strategy in bifurcation lesions and longer stenting in diffuse lesions) may be recommended to enable a shorter DAPT duration.

Association Between Ischemic and Mortality Risks and Each Bleeding Risk Score

Bleeding risk (e.g., CKD, PVD, atrial fibrillation, and heart failure) generally overlaps with ischemic risk,[14] and patients with HBR according to the J-HBR, ARC-HBR, and PRECISE-DAPT scores show increased occurrence of bleeding and ischemic events.[18,19,26,29] In the present study, patients with HBR according to the ARC-HBR and PRECISE-DAPT scores had a higher cumulative incidence of ischemic events than patients with non-HBR; however, patients with HBR according to the J-HBR score had an incidence of ischemic events similar to those of patients with non-HBR, which suggests that the J-HBR score may be able to identify patients with HBR without increased ischemic risk. The possible explanations for this phenomenon are as follows. (1) The number of ischemic events was smaller than that of major bleeding events, which made it difficult to achieve significant statistical results for ischemic events. (2) More patients were classified as having HBR according to the J-HBR score than according to the ARC-HBR and PRECISE-DAPT scores, thus reducing the cumulative incidence of ischemic events. In the present study, the cumulative incidence of all-cause death was significantly higher in the HBR group than in the non-HBR group, regardless of the bleeding risk score. Generally, regardless of the type of bleeding risk score, patients with HBR not only have an increased risk of major bleeding events but also an increased risk of ischemic events, and thus may be at a higher mortality risk than patients with non-HBR. Therefore, attention should be paid to ischemic and bleeding events in patients with HBR after PCI. Close follow-up and systemic management, including optimal medical therapy, may be important for improving clinical outcomes.

Study Limitations

There are several to note. First, this was a retrospective, single-center study with a small number of participants. Second, selection bias regarding PCI procedures and medications is possible, which may have affected the clinical outcomes. Third, we retrospectively investigated all J-HBR, ARC-HBR, and PRECISE-DAPT scores, although the prevalence of each criterion or score may have been underestimated. Fourth, the 3 bleeding risk scores were calculated only once before PCI, and changes over time were not evaluated during the follow-up period. Therefore, these bleeding risk scores may have changed over time. Fifth, because the number of major bleeding events was insufficient, multivariate analysis could not be performed to investigate whether each component of the J-HBR, ARC-HBR, or PRECISE-DAPT score was individually associated with major bleeding events.

Conclusions

The J-HBR, ARC-HBR, and PRECISE-DAPT scores may be useful tools for stratifying bleeding risk in patients with CAD after PCI. The J-HBR score had a discriminative ability similar to other bleeding scores for predicting short- and mid-term major bleeding events.

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Disclosures

The authors declare that there are no conflicts of interest. M.O. is a member of *Circulation Reports*' Editorial Team.

IRB Information

This study was approved by the Institutional Review Board of Kagoshima City Hospital (registration number 2021-37, 38).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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