Prevalence of the Academic Research Consortium for High Bleeding Risk Criteria and Prognostic Value of a Simplified Definition

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Background: The Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria have been suggested as the standard definition of HBR. However, the prevalence of individual criteria and their prognostic value for long-term bleeding events after percutaneous coronary intervention are scarcely studied.

Methods and Results: The study population comprised 1,193 patients treated with everolimus-eluting stents between 2010 and 2011. Data on all 17 major and minor criteria of the ARC-HBR definition were retrospectively collected, and applied to this study population. Major bleeding was defined as the occurrence of a BARC type 3 or 5 bleeding event. A simplified definition was developed by excluding the low-frequency criterion, and the prognostic value was assessed by a receiver-operating characteristic curve. Mean follow-up was $2,996 \pm 433$ days and there were 656 HBR patients (55.0%). The cumulative incidence of major bleeding was significantly higher in the HBR group than in the non-HBR group (16.2% vs. 5.7% at 8 years, $P < 0.001$). The frequencies of 6 of the 17 criteria were less than 1%. The prognostic value of the simplified definition made by excluding these 6 criteria for major bleeding was comparable to that of the original (c -statistic=0.598 and 0.600, $P=0.08$).

Conclusions: Some risk criteria of the ARC-HBR definition are observed infrequently. Our simplified definition identified patients with long-term bleeding risk as successfully as the original definition.

Key Words: Bleeding; Coronary artery disease; Percutaneous coronary intervention

Prolonged dual antiplatelet therapy (DAPT) reduces the risk of thrombotic events, but is associated with higher risk of bleeding events.^{1–4} The current guidelines recommend assessment of each patient on the basis of the risk score to minimize bleeding complications in patients with high bleeding risk (HBR).^{5–7} However, HBR patients are not well defined and the definition of HBR has varied among studies.^{8–12} Recently, the Academic Research Consortium (ARC) for HBR proposed a new definition consisting of 17 major and minor criteria to standardize HBR. Natsuaki et al¹³ reported the generality of the ARC-HBR definition in a real-world setting. In their study, however, some data for the ARC-HBR criteria were not available and a bleeding event was defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria. To date, the prevalence and influence of all the ARC-HBR criteria has not been fully elucidated. Therefore, we aimed to investigate the prevalence of all the risk criteria and the

prognostic ability of the ARC-HBR criteria for long-term bleeding events based on the Bleeding Academic Research Consortium (BARC) after percutaneous coronary intervention (PCI). We also sought to develop a user-friendly version to easily apply the HBR definition in daily practice.

Methods

Study Population

This study was a retrospective single-center study. Between January 2010 and December 2011, 2,426 patients were underwent PCI using a drug-eluting stent, and of them a total of 1,787 consecutive patients undergoing everolimus-eluting stent (EES; Xience V, Abbott Vascular, Santa Clara, CA, USA) implantation between January 2010 and December 2011 were enrolled.¹⁴ After excluding patients with repeat EES implantation ($n=288$), combined use of EES and other types of stent ($n=280$), and in-hospital events (in-hospital death: $n=17$, in-hospital definite stent

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thrombosis [ST]: n=1, in-hospital ischemic stroke: n=2, in-hospital major bleeding: n=6), we analyzed 1,193 patients (**Figure 1**). The procedures were in accordance with the Declaration of Helsinki. Informed consent was given by all patients for both the procedure and subsequent data collection and analysis for research purposes, and the study was approved by the institutional ethics committee.

Study Definitions and Outcomes

Primary bleeding endpoint was defined as a BARC type 3 or 5 bleeding event.¹⁵ Primary ischemic endpoint was defined as a composite of ST, myocardial infarction (MI) or ischemic stroke. The endpoints of this study were all-cause death, cardiac death, MI, definite or probable ST, target lesion revascularization, and ischemic stroke. ST and MI were defined according to the ARC definitions.¹⁶

Follow-up and Data Collection

Serial angiographic follow-up was routinely scheduled at 8 and 20 months after PCI. Baseline data of all 17 major and minor criteria of the ARC-HBR definition and the clinical follow-up information were obtained at the time of the office visit, by telephone survey, or by mail to the primary care physician or patient. The study population was divided into 2 groups according to the ARC-HBR definition, which has been described previously (**Supplementary Table 1**).¹⁷

Antiplatelet Therapy

All the patients were pretreated with aspirin (100 mg daily) and ticlopidine (200 mg daily)/clopidogrel (75 mg daily). DAPT for at least 8 months after the index procedure was recommended, but the duration of antiplatelet therapy was left to the discretion of each physician. The status of antiplatelet therapy was evaluated throughout the follow-up period, and persistent discontinuation of DAPT was

defined as withdrawal of aspirin or thienopyridine for at least 2 office visits or telephone inquiries.

Statistical Analysis

Categorical variables were compared using the chi-square test. Continuous variables are expressed as mean $\pm$ SD and compared using Student's t-test or the Wilcoxon rank-sum test based on the distribution. The cumulative incidence was estimated using the Kaplan-Meier method, and differences were assessed using the log-rank test. Cox proportional hazard model was used to estimate the effects of the HBR group relative to the non-HBR group for clinical events, which was expressed as hazard ratios and their 95% confidence intervals (CIs). We did not make any statistical adjustment models because the ARC-HBR definition should be considered as indicator variables for future events and summarized the relevant confounders. The cumulative incidence of the primary bleeding endpoint was assessed on the basis of the presence or absence of the individual ARC-HBR criterion, and according to the number of ARC-HBR criteria. The cumulative incidence of the primary bleeding endpoint was also assessed according to the number of ARC-HBR major and minor criteria. Patients with ARC-HBR major criteria were included in the ≥ 2 majors, or 1 major group according to the number of major criteria regardless of the number of overlapping minor criteria. Patients with ≥ 2 ARC-HBR minor criteria without major criteria were included in the ≥ 2 minors without major group. A simplified definition was generated from the ARC-HBR definition by excluding the criteria with frequencies $<1\%$. The discrimination performance of the original and simplified definitions was assessed by calculating the area under the receiver-operating characteristic curve and expressed as the c-statistic. All P-values <0.05 were considered to be significant. Statistical analyses were performed using JMP 9.0 (SAS Institute, Cary, NC,

Figure 2. Prevalence of individual criteria of the Academic Research Consortium for High Bleeding Risk definition (ARC-HBR). CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; HBR, high risk bleeding; LC, liver cirrhosis; NSAIDs, nonsteroidal anti-inflammatory drugs.

USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Prevalence of HBR

There were 656 patients (55%) meeting the ARC-HBR criteria in the present study population. The numbers and prevalence of the individual ARC-HBR criteria are summarized in **Figure 2**.

Baseline Characteristics

Baseline patient, lesion, and procedural characteristics of the overall patient population, HBR group, and non-HBR group are indicated in **Table 1**. Patients in the HBR group were much older and had significantly higher rates of hypertension, diabetes, heart failure, and peripheral artery disease than those in the non-HBR group.

Clinical Outcomes

Mean follow-up period of the survivors was $2,996 \pm 433$ days. The cumulative incidences of clinical events at 8 years are indicated in **Table 2**. The cumulative incidences of major bleeding, intracranial bleeding, gastrointestinal bleeding were much higher in the HBR group (16.2% vs. 5.7%, $P < 0.0001$; 7.2% vs. 3.0%, $P = 0.002$ and 7.2% vs.

1.8%, $P = 0.001$, respectively). Bleeding events occurred at a relatively constant rate up to 8 years, and the annual rate of major bleeding in the HBR group was 2.0% during the 8 years. The rate of DAPT discontinuation was not significantly different during the follow-up period (**Supplementary Figure**). The cumulative incidence of primary ischemic events was also higher in the HBR group (12.7% vs. 8.3%, $P = 0.001$).

Prevalence and Influence of Individual Risk Criteria

Prevalence of all individual risk criteria of the ARC-HBR definition are indicated in **Figure 2**. In this study population, patients with chronic bleeding diathesis and nondeferrable major surgery on DAPT were not identified. Furthermore, the rate of patients with prior spontaneous bleeding requiring hospitalization or transfusion, liver cirrhosis with portal hypertension, prior trauma or major surgery within 30 days was less than 1%. Among the major criteria, the use of oral anticoagulation, severe chronic kidney disease, severe anemia, and thrombocytopenia were associated with major primary bleeding events during the follow-up (**Figure 3, Supplementary Table 2**). Among the minor criteria, the cumulative rate of major bleeding in patients with moderate chronic kidney disease was significantly higher than in that of those without. The cumulative incidence of major bleeding tend to be higher as the

Table 1. Baseline Characteristics of Study Patients Undergoing PCI

	Overall	HBR	Non-HBR	P value
n	1,193	656	537	
Age, years	70.1±11.2	74.9±9.8	64.3±9.9	<0.0001
Male	861 (72.2)	427 (65.1)	434 (80.8)	<0.0001
BMI, kg/m ²	24.3±3.5	23.7±3.6	25.0±3.5	<0.0001
Hypertension	848 (71.1)	495 (75.5)	353 (65.7)	0.0002
Diabetes mellitus	467 (39.2)	284 (43.3)	183 (34.1)	0.001
Insulin therapy	130 (10.9)	98 (14.9)	32 (6.0)	<0.0001
Dyslipidemia	745 (62.4)	380 (57.9)	365 (68.0)	0.004
Current smoking	166 (13.9)	52 (7.9)	114 (21.2)	<0.0001
eGFR, mL/min/1.73m ²	60.9±25.7	49.1±24.7	75.3±18.7	<0.0001
Ccr, mL/min	67.3±36.9	47.7±29.2	91.2±30.8	<0.0001
Hemodialysis	68 (5.8)	68 (10.4)	0 (0)	<0.0001
Severe CKD	135 (11.3)	135 (20.6)	0 (0)	<0.0001
Clinical diagnosis				0.02
STEMI	208 (17.4)	102 (15.6)	106 (19.7)	
NSTEMI/UAP	245 (20.5)	124 (18.9)	121 (22.5)	
Stable angina	740 (62.0)	430 (65.6)	310 (57.7)	
Previous MI	418 (35.0)	245 (37.4)	173 (32.2)	0.06
Previous stroke	114 (9.7)	95 (14.5)	19 (3.5)	<0.0001
Peripheral artery disease	82 (6.9)	61 (9.3)	2 (3.9)	0.0003
Previous PCI	532 (44.6)	298 (45.4)	234 (43.6)	0.52
Previous CABG	45 (3.8)	28 (4.3)	17 (3.2)	0.32
Multivessel disease	361 (30.3)	209 (31.9)	152 (28.3)	0.18
Heart failure	128 (10.7)	101 (15.4)	27 (5.0)	<0.0001
Anemia (Hb <11 g/dL)	196 (16.4)	196 (29.9)	0 (0)	<0.0001
Platelet count <10 ⁵ /uL	29 (2.4)	29 (4.4)	0 (0)	<0.0001
Malignancy	79 (6.6)	18 (2.7)	0 (0)	0.0001
Medications at hospital discharge				
Antiplatelet therapy				
Thienopyridine	1,190 (99.7)	654 (99.7)	536 (99.8)	0.98
Aspirin	1,186 (99.4)	652 (99.4)	534 (99.4)	0.88
Warfarin	152 (12.7)	152 (23.2)	0 (0)	<0.0001
Statin	943 (79.5)	471 (71.8)	472 (87.9)	<0.0001
β -blocker	425 (35.6)	249 (38.0)	176 (32.8)	0.06
ACEI/ARB	848 (71.1)	444 (67.7)	404 (75.2)	0.004
Calcium-channel blocker	482 (40.4)	275 (41.9)	207 (38.6)	0.24
Proton pump inhibitor	675 (56.6)	387 (56.0)	288 (53.6)	0.06
H ₂ -blocker	230 (19.3)	111 (16.9)	119 (22.2)	0.02
Lesion location				
Left main trunk	94 (7.9)	55 (8.4)	39 (7.3)	0.47
Left anterior descending	668 (56.0)	367 (56.0)	301 (56.1)	0.97
Left circumflex	347 (29.2)	190 (29.0)	157 (29.2)	0.92
Right coronary artery	530 (44.4)	297 (45.3)	233 (43.4)	0.51
Chronic total occlusion	174 (14.6)	90 (13.7)	84 (15.6)	0.35
In-stent restenosis	193 (16.2)	108 (16.5)	85 (15.8)	0.77
Bifurcation	526 (44.1)	270 (41.2)	256 (47.7)	0.02
Ostial lesion	227 (19.0)	124 (18.9)	103 (19.2)	0.9
AHA/ACC B2/C	907 (76.0)	507 (77.3)	400 (74.5)	0.26
Minimal stent diameter, mm	2.75±0.35	2.75±0.35	2.75±0.35	0.80
Total stent number	2.2±1.4	2.1±1.4	2.3±1.5	0.20
Total stent length, mm	47.1±34.5	45.9±32.4	48.5±36.9	0.18

Values are mean±SD or n (%), unless otherwise specified. ACC, American College of Cardiology; AHA, American Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; Ccr, Creatinine clearance; CKD, chronic kidney disease; CTE, coronary thrombotic event; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UAP, unstable angina.

Table 2. Cumulative Incidence of Clinical Outcomes

	HBR	Non-HBR	HR (95% CI)	P value
	No. of patients with events (cumulative 8-year incidence)	No. of patients with events (cumulative 8-year incidence)	HBR relative to Non-HBR	
n	656	537		
Major bleeding	70 (16.2)	27 (5.7)	2.76 (1.80–4.38)	<0.0001
Intracranial bleeding	31 (7.2)	13 (3.0)	2.68 (1.44–5.29)	0.002
Gastrointestinal bleeding	31 (7.2)	9 (1.8)	1.75 (1.25–2.49)	0.001
MI/ST/ischemic stroke	60 (12.7)	31 (8.3)	2.01 (1.32–3.10)	0.001
MI	34 (7.1)	17 (4.5)	1.93 (1.11–3.47)	0.02
Definite/probable ST	2 (0.4)	3 (0.6)	0.65 (0.09–3.97)	0.64
Definite ST	1 (0.2)	3 (0.6)	0.32 (0.02–2.57)	0.30
Ischemic stroke	28 (6.4)	14 (3.6)	2.22 (1.19–4.34)	0.01
All-cause death	263 (42.7)	53 (10.4)	5.08 (3.82–6.88)	<0.0001
Cardiac death	84 (16.6)	17 (3.6)	5.12 (3.12–8.92)	<0.0001
Any TLR	93 (16.8)	72 (14.6)	1.21 (0.90–1.66)	0.20
Clinically indicated TLR	59 (11.5)	42 (9.7)	1.38 (0.93–2.06)	0.10

Data are presented as number of patients with event (cumulative incidence). Event rates estimated using Kaplan-Meier analysis. HR with 95% CI was estimated by univariate Cox proportional hazard model. CI, confidence interval; HBR, high bleeding risk; HR, hazard ratio; MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion revascularization.

Figure 3. Cumulative incidences of primary bleeding endpoints according to the presence or absence of the individual criteria of Academic Research Consortium for High Bleeding Risk definition (ARC-HBR). CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; HBR, high risk bleeding; LC, liver cirrhosis; NSAIDs, nonsteroidal anti-inflammatory drugs.

number of ARC-HBR major or minor criteria increased (≥ 2 majors: 24.3%, 1 major: 17.0%, ≥ 2 minors: 11.7%, non-HBR: 5.7%, $P < 0.0001$).

Simplified Definition

Among all the risk criteria, prevalences of prior bleeding and transfusion defined in both major and minor criteria, chronic bleeding diathesis, liver cirrhosis with portal hypertension, nondeferrable major surgery on DAPT, and prior trauma or surgery within 30 days were less than 1%. We generated a simplified ARC-HBR definition consisting of 11 criteria with frequencies $\geq 1\%$; 3 patients in the HBR group under the original definition were reclassified into the non-HBR group under the simplified definition. On the basis of the simplified definition, the cumulative incidence of major bleeding was significantly higher in the HBR group (16.2% vs. 5.7% at 8 years, $P < 0.001$; **Figure 4**). The area under curve of the original and simplified definitions was comparable (0.598 [95% CI 0.55–0.64] and 0.600 [95% CI 0.55–0.64], $P = 0.08$). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the original and simplified definitions, respectively, for major bleeding were 73.0%, 53.3%, 11.1%, 95.0%, and 48.8% and 73.0%, 53.1%, 11.2%, 95.0% and 49.1%, respectively.

Discussion

The main findings of this study were as follows. (1) After a retrospective investigation of all the criteria of the ARC-HBR definition, 55% of the patients met the ARC-HBR definition. (2) The frequencies of 6 of 17 criteria were observed infrequently in the real-world setting. (3) The ARC-HBR criteria were associated with long-term bleeding

events up to 8 years. (4) The simplified definition generated by excluding low-frequency criteria from the original definition identified patients with long-term bleeding risk as successfully as the original definition.

In the consensus document from the ARC-HBR, HBR was arbitrarily defined as a risk of BARC 3 or 5 bleeding $> 4\%$ at 1 year or that of an intracranial hemorrhage $\geq 1\%$ at 1 year.¹⁸ Natsuaki et al¹³ reported the clinical application of selected ARC-HBR criteria, and Sorrentino et al introduced modified ARC-HBR criteria to identify HBR patients because of the limited availability of retrospective data collection.¹⁹ This study is the first to investigate the prevalence of all of the criteria of the ARC-HBR definition and of the incidence of major bleeding defined by the BARC criteria. In addition, we extended the generality of the ARC-HBR criteria by providing an 8-year incidence of major bleeding in HBR and non-HBR patients. The frequency of HBR was reported to be 33–43% in all-comer registries in the USA, Switzerland, China, India and Japan if selected ARC-HBR criteria were investigated.^{13,19,20} In this study, in which all ARC-HBR risk criteria were investigated, HBR patients reached 55%, suggesting the frequency of HBR patients might be underestimated in previous reports using selected criteria, and that the rate of HBR patients is not low in daily practice. For such HBR patients, the optimal intensity and duration of DAPT represent a remarkable challenge.^{21–24} Nevertheless, the rate of DAPT discontinuation was relatively lower compared with that recommended in the current guideline and not different between the HBR and non-HBR groups during the long follow-up period. This tendency was in line with that in a large multicenter trial in Japan and it may be explained the fear of ST in the first-generation DES era, which lasted

until this study period, may have discouraged physicians from discontinuing DAPT.²⁵ In addition, patients meeting the ARC-HBR definition might not have been sufficiently taken into account during the study period.

Prevalence of Individual Criteria and Effect on Bleeding Events

Prior bleeding and transfusion were infrequently observed in this study, probably because elective PCI was avoided in daily practice during this period. The prevalence and effect on bleeding events of active malignancy defined in the ARC-HBR have not yet reported. Although active malignancy was not associated with long-term bleeding events, the cumulative rate of all-cause death was much higher in patients with active malignancy than in those without, which might have affected the rate of long-term bleeding events.

It has been reported that up to 17% patients undergo an invasive or therapeutic procedure within 1 year after PCI; however, the prevalence of elective major surgery was infrequent in the present study. Either elective major surgery was avoided during the proposed DAPT duration in the guidelines at that time or DAPT duration was shortened in these patients, and urgent major surgery was not performed in the study population.

Simplified Definition

The original ARC-HBR definition consists of 17 criteria, but some criteria of them were observed infrequently in this study. We proposed a simplified definition, and its discrimination ability was comparable to that of the original definition. This simple definition may be useful for easily identifying HBR patients in daily practice, and may help facilitate subsequent clinical decision making surrounding the treatment strategy and optimal duration of DAPT.

Study Limitations

First, although we investigated all ARC-HBR criteria by a retrospective method, the prevalence of each criteria may have been potentially underestimated. In addition, the number of patients meeting some criteria was relatively small, especially for the infrequent criteria excluded from the simplified definition. The prevalence and prognostic value of those criteria should be confirmed in large-scale studies. Second, DAPT duration of this study was different from current practice. Third, the bleeding risk in the Japanese population was different from those in USA and European populations. Actually, ethnicity itself has been reported as a risk factor of bleeding events.^{26,27} Therefore, some caution is required to extrapolate the results of this study outside Japan. Finally, our simplified definition was not validated. Further validation studies of this definition are required.

Conclusions

In our study population, some risk criteria of ARC-HBR definition were observed infrequently. Our simplified definition identified patients with long-term bleeding risk as successfully as the original definition.

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Data Availability

The deidentified participant data that underlie the results reported in this article will be shared upon request to the corresponding author, as Excel or csv files via E-mail, or URL link for individual participant data meta-analysis by investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose, beginning 9 months and ending 36 months after article publication. The study protocol will also be available.

Funding / Disclosures

None.

IRB Information

The institutional review board of Kurashiki Central Hospital (Ref. No: 3327).

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Supplementary Files

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-20-0395>