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CLINICAL RESEARCH
Ischaemic heart disease

Long-term outcomes of high bleeding risk patients undergoing percutaneous coronary intervention: a Korean nationwide registry

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Abstract

Background and Aims Patients with high bleeding risk (HBR) undergoing percutaneous coronary intervention (PCI) are at increased risk of not only bleeding, but also ischaemic events. This study aimed to determine the long-term relative risk of ischaemic and bleeding events in HBR patients.

Methods This study was a nationwide cohort study, based on the Korean National Health Insurance Review and Assessment Service database. Patients diagnosed with stable angina or acute coronary syndrome and those who underwent PCI in Korea between 2009 and 2018 were included in the analysis. According to the Academic Research Consortium HBR criteria, the total population was divided into HBR and non-HBR groups. The co-primary outcomes were major bleeding events and ischaemic (composite of cardiac death, myocardial infarction, and ischaemic stroke) events.

Results Among a total of 325 417 patients who underwent PCI, 66 426 patients (20.4%) had HBR. During the follow-up period, HBR patients had a higher risk for major bleeding events (23.9% vs. 8.9%, $P < .001$) and ischaemic events (33.8% vs. 14.4%, $P < .001$). However, the impact of HBR was significant for major bleeding events [hazard ratio (HR) 3.12, 95% confidence interval (CI) 3.04–3.21, $P < .001$] and for ischaemic events (HR 2.50, 95% CI 2.45–2.56, $P < .001$). The HBR group was also associated with a greater risk of all-cause mortality (HR 3.73, 95% CI 3.66–3.79, $P < .001$). The average annual rate of major bleeding events within the first year after PCI was 5.5% for a single major criterion, and 2.9% for a single minor criterion.

Conclusions Among patients undergoing PCI, those with HBR were at increased long-term risk for both bleeding and ischaemic events, with a greater risk of mortality compared to non-HBR patients.

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Structured Graphical Abstract

Key Question

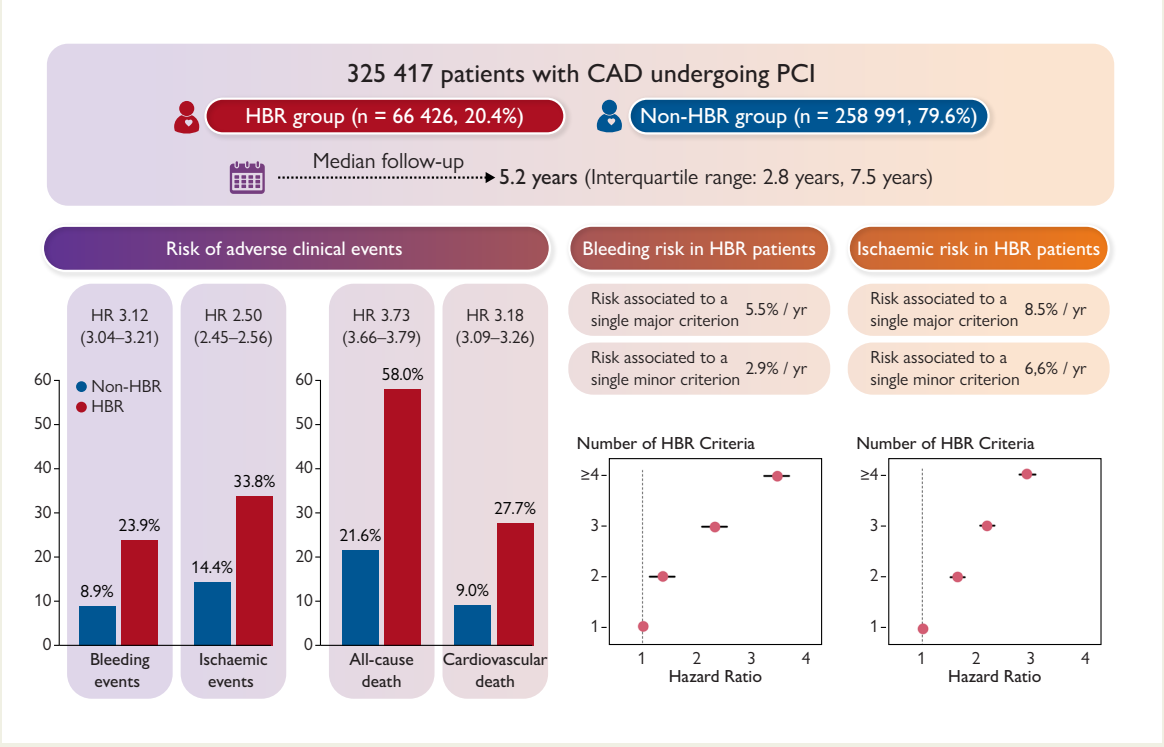
What is the clinical implication of the Academic Research Consortium-high bleeding risk (HBR) definition in regard to future bleeding and ischaemic adverse events in patients undergoing percutaneous coronary intervention (PCI)?

Key Finding

Patients with HBR had a higher risk for both bleeding and ischaemic events following PCI, associated to greater risk of mortality compared to those with non-HBR.

Take Home Message

In patients undergoing PCI, HBR is not only associated with future bleeding risk, but also with future ischaemic and mortality risk. HBR should be interpreted as an overall "risk burden", which needs to be carefully assessed to prevent adverse clinical events.



High bleeding risk (HBR) patients had higher bleeding and ischaemic risk compared with non-HBR patients. The relative impact of HBR was greater for major bleeding than ischaemic events. The risk is increasing along with the increase in HBR risk factors. CAD, coronary artery disease; HR, hazard ratio; PCI, percutaneous coronary intervention.

Keywords High bleeding risk • Percutaneous coronary intervention • Major bleeding • Ischaemic event • Mortality

Introduction

The major objective of post-percutaneous coronary intervention (PCI) medical therapy is to prevent recurrent ischaemic events. However, the importance of preventing bleeding events has recently gained attention especially for those with complex medical conditions and multiple co-morbidities. Previous studies have reported the detrimental impact of post-PCI bleeding, which had a similar impact on mortality as occurrence of ischaemic events.[1,2] A definition of patients at high bleeding risk (HBR) who receive PCI has been proposed by the Academic Research Consortium (ARC) HBR consensus.[3] Accordingly, current guidelines recommend individualized antiplatelet therapy according to HBR status.[4,5]

Moreover, it is recognized that HBR patients are not only at higher risk of bleeding, but also of ischaemic events.[6,7] This can be explained by the overlap between risk factors that augment ischaemic and bleeding risk.[3] Therefore, the optimal antithrombotic strategy in HBR patients should not only take into account the increased bleeding risk but also the increased ischaemic risk. However, the impact of HBR on long-term bleeding risk in a large all-comer PCI population and its effect on future ischaemic events has not been fully evaluated.

In the current study, we evaluated the distribution and prevalence of HBR in a large cohort of all-comer PCI over a decade from a nationwide database and validated the predictive value of the ARC-HBR criteria on both future ischaemic and bleeding adverse events.

Methods

Data sources

This study was performed on the National Health Claims Database established by the National Health Insurance Service (NHIS) of Korea. Korean NHIS is a mandatory health insurance service that covers 100% of the Korean residents, which was ~52 million people during the study period.[8] Based on the 13-digit resident identification code, a unique dataset is confirmed for each individual. Detailed medical information, including each patient's demographic information, procedures, and medical prescription records, is recorded, and the diagnoses are recorded using the International Classification of Diseases-10th Revision-Clinical Modification (ICD-10-CM) codes.[8,9] The study protocol was approved by the ethics committee and Institutional Review Board at Seoul National University Hospital Institutional Review Board (ID 1911-091-1079). Informed consent was not considered necessary because the patient records and information were anonymized and de-identified before analysis.

Study population

We identified patients who were diagnosed with coronary artery disease [stable angina or acute coronary syndrome (unstable angina, myocardial infarction); ICD-10-CM codes 20, 21, and 22] and received PCI during the identification period (from January 2009 to December 2018). We obtained patients' baseline characteristics, including age, sex, and comorbidities, such as hypertension, diabetes, dyslipidaemia, congestive heart failure, atrial fibrillation, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, history of PCI, coronary artery bypass surgery, pulmonary embolism, and deep vein thrombosis. To evaluate bleeding risk, information associated with ARC-HBR definitions was included. The detailed definitions of comorbidities are shown in Supplementary data online, *Table S1*. On the basis of ARC-HBR definition, patients were classified as HBR if they fulfilled at least one major or two minor criteria.[3] Those not meeting HBR definition were considered non-HBR.

Study outcomes

The co-primary outcomes of this study were bleeding events [defined as Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding] and ischaemic (defined as a composite of cardiac death, myocardial infarction, and ischaemic stroke) events during the follow-up period. Secondary endpoints included net adverse clinical events (a composite of ischaemic and bleeding events), all-cause death, cardiovascular death, myocardial infarction, ischaemic stroke, and any bleeding events (including major bleeding events). To assess the clinical outcomes, patients were followed up for at least 1 year and censored at the outcome events or at the end of the study period. All endpoints were defined by ICD-10-CM codes, and detailed definitions of the outcomes are described in Supplementary data online, *Table S2*.

Statistical analysis

Variables are expressed as mean ± standard deviation or median [25th and 75th percentiles (Q1–Q3)] for continuous variables, and as numbers (%) for categorical variables. The χ^2 test and Student's *t*-test were used to compare baseline and procedural characteristics, and the statistical significance was provided as *P*-values. The cumulative incidence of the co-primary endpoints during the follow-up period was assessed using the Kaplan–Meier method and compared between groups with the log-rank test. A Cox regression hazards model was used to evaluate the association between the presence of HBR and clinical outcomes. Because the occurrence of bleeding or ischaemic events could affect the occurrence of the other primary outcome, we defined bleeding events and ischaemic events as competing risk on each other and performed Fine and Gray's competing risk analysis. Also, for analysis of recurrent events, the Andersen–Gill (AG) model, which is an extension of the original Cox model, was used. The standard AG model, along with the modified model with a robust sandwich covariance matrix, was used to analyse recurrent events of the two co-primary outcomes and net adverse clinical events. Estimated risks were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). To determine the prognostic impact of non-fatal ischaemic events and bleeding events on mortality in both HBR and non-HBR patients, a 'look-back' approach was used where the risks of non-fatal ischaemic events and bleeding events were compared in patients with a mortality event. The discriminative ability of the ARC-HBR definition for the co-primary endpoints was assessed through the area under the receiver-operating characteristic curve (AUC). When performing receiver-operating characteristic (ROC) analysis, we assigned ARC-HBR definition of major criteria as 1 point and minor criteria as .5 points.[10] For sensitivity analysis, propensity score matching (PSM) analysis was conducted to balance the effect of various clinical risk factors (age, gender) and iatrogenic factors on the propensity to receive different post-PCI medical therapy between the HBR and non-HBR groups. Propensity score matching was conducted with a 1:2 ratio using greedy matching method, using a calliper with equal to .2 times the standard deviation of the logit of the propensity score. The covariates included non-modifiable clinical risk factors (age, gender) and iatrogenic factors that are not included in the HBR criteria (antiplatelet agent usage, including aspirin, clopidogrel, and potent $P2Y_{12}$ inhibitors). An inverse probability weighted (IPW) regression analysis was also performed using the propensity score. To explore a better criteria than the ARC-HBR, we performed feature selection using machine learning based least absolute shrinkage and selection operator (LASSO) Cox regression model. Detailed description is provided in the Supplementary Appendix. All *P*-values were two-sided, and $P < .05$ was considered statistically significant.

Results

Baseline characteristics

A total of 458 000 patients were diagnosed with coronary artery disease (stable angina, unstable angina, or acute myocardial infarction) and underwent PCI between January 2009 and December 2018. Among these, 1571 (.3%) patients were excluded due to inadequate demographic information, and 130 986 (28.6%) patients were excluded from the analysis because of a lack of laboratory information that precluded assessment of HBR status according to the ARC-HBR definition; 26 patients were excluded due to age under 19. Accordingly, 325 417 patients were included in the final analysis. According to the ARC-HBR criteria, 66 426 (20.4%) patients were categorized as HBR and 258 991 (79.6%) as non-HBR (*Figure 1*). The baseline characteristics and concomitant antithrombotic medications prescribed during the initial 3 months after index PCI are shown in *Table 1*. Clinical risk factors associated with coronary artery disease were significantly more common in the HBR group.

The prevalence of each HBR criteria is shown in *Table 2*. An anticipated use of long-term oral anticoagulant (OAC) and severe anaemia were the most common major criteria, while old age and mild anaemia were the most common minor criteria. The combination of major and minor criteria that qualified the patients as having HBR is shown in Supplementary data online, *Figure S1*. Old age with mild anaemia was the most common combination of HBR, which accounted for 16.1% of the HBR population, followed by an anticipated use of long-term OAC (8.2%) and severe anaemia (7.4%).

Clinical outcomes

The clinical outcomes during the total follow-up period (median follow-up 5.2 years, interquartile range, 2.8–7.5 years) are shown in *Table 3*.

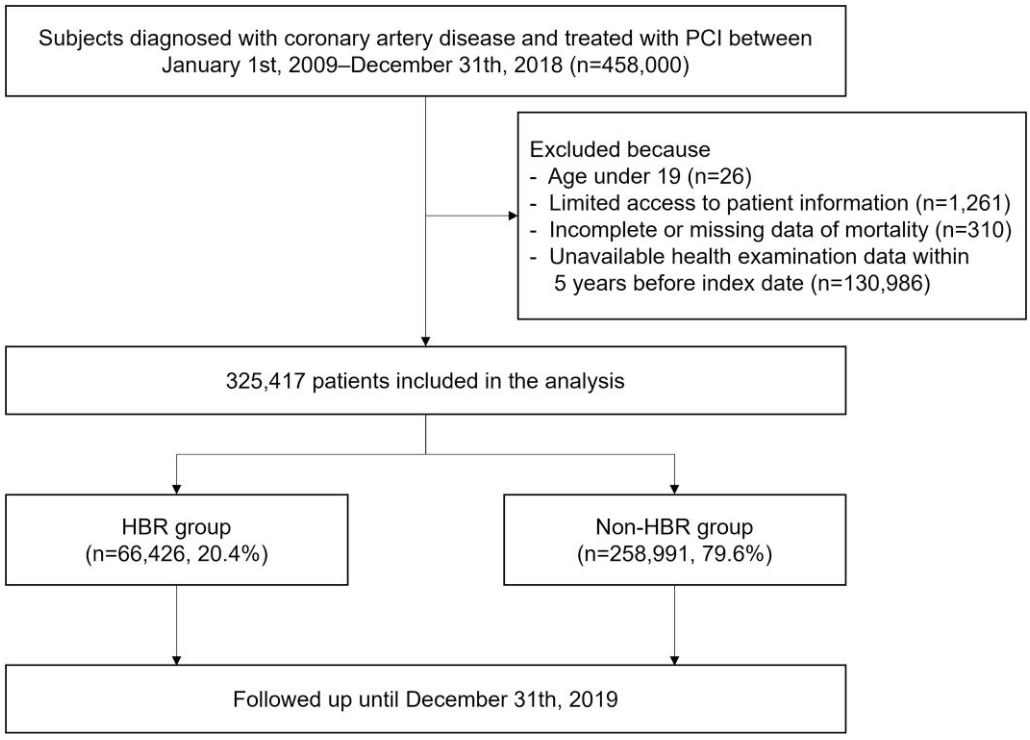


Figure 1 Flowchart of patient selection. HBR, high bleeding risk; PCI, percutaneous coronary intervention

For the co-primary endpoints, the bleeding composite outcome occurred in 23.9% in the HBR group and 8.9% in the non-HBR group (HR 3.12, 95% CI 3.04–3.21, $P < .001$), while the ischaemic composite outcome occurred in 33.8% in the HBR group and 14.4% in the non-HBR group (HR 2.50, 95% CI 2.45–2.56, $P < .001$). The HR of HBR on bleeding outcomes was numerically larger than that for ischaemic outcomes even after considering the competing risk (adjusted HR 2.84, 95% CI 2.77–2.92, $P < .001$ for bleeding events and HR 2.24, 95% CI 2.19–2.29, $P < .001$ for ischaemic events). *Figure 2* shows the 10-year cumulative event curves for bleeding and ischaemic outcomes in the HBR and non-HBR groups. Regarding secondary outcomes, the HBR group had a greater risk of net adverse clinical outcomes (HR 2.67, 95% CI 2.62–2.72, $P < .001$) and mortality, including both all-cause (HR 3.73, 95% CI 3.66–3.79, $P < .001$) and cardiovascular mortality (HR 3.18, 95% CI 3.09–3.26, $P < .001$) (see Supplementary data online, *Figure S2*). Additional analyses which took into account recurrent events also showed consistent results (see Supplementary data online, *Table S3*). Also, the prognostic impact of non-fatal ischaemic events (myocardial infarction and ischaemic stroke) and bleeding events (BARC 3 bleeding) on mortality is shown in Supplementary data online, *Table S4*. Both non-fatal ischaemic and bleeding events were associated with a higher risk of mortality, while the relative hazard of mortality was higher in patients who experienced a bleeding event vs. an ischaemic event.

For the propensity score analysis, the baseline characteristics and clinical outcomes of the 1:2 PSM patients and IPW population are shown in Supplementary data online, *Tables S5* and *S6*. In this population, the HBR group as compared with the non-HBR group was associated with a higher risk of clinical events, both bleeding and ischaemic, and mortality events.

Individual impact of each criteria and the combined risk of multiple criteria

The clinical event rate for each major and minor criterion is shown in *Table 4*. The average bleeding rate for HBR patients with one major criterion was 5.5% at 1 year and 21.1% at 10-year follow-up, while that for ischaemic events was 8.5% at 1 year and 27.7% at 10-year follow-up. For a single minor criterion, the average bleeding event rate was 2.9% at 1 year and 14.4% at 10-year follow-up, while that for ischaemic events was 6.6% at 1 year and 22.6% at 10-year follow-up. The relative impact on both bleeding and ischaemic events was greater for a major criterion compared to a minor criterion. Among HBR patients, 15 972 patients (24.0%) had a single risk factor, 34 149 patients (51.4%) had two risk factors, 11 662 patients (17.6%) had three risk factors, and 4643 patients (7.0%) had four or more risk factors. As the number of HBR risk factors increased, the risk of bleeding and ischaemic outcomes increased incrementally. However, the incremental risk increase from an additional risk factor was greater for bleeding events compared to ischaemic events, as shown in *Figure 3*. Compared with the reference (those with one HBR risk factor), those with ≥4 risk factors had a 3.56-fold increased risk for bleeding events and a 3.00-fold increased risk for ischaemic events.

Predictive value of the ARC-HBR criteria

Using the ROC analysis for the ARC-HBR criteria, the predictive value of the ARC-HBR criteria for bleeding events was greater than that for ischaemic events [AUC: .638 (95% CI .634–.642) for bleeding events vs. .625 (95% CI .622–.628) for ischaemic events, P for comparison < .001, Supplementary data online, *Figure S3*]. Other statistic numbers (i.e. sensitivity, specificity, positive predictive value, negative predictive value, and

Table 1 Baseline characteristics

	Total population ($n = 325\,417$)	Non-HBR ($n = 258\,991$)	HBR ($n = 66\,426$)
Age	65.2 ± 10.8	63.4 ± 10.3	72.2 ± 9.5
Male	228 974 (70.4)	190 346 (73.5)	38 628 (58.2)
Comorbidities			
Hypertension	196 785 (60.5)	145 607 (56.2)	51 178 (77.0)
Diabetes mellitus	94 987 (29.2)	68 403 (26.4)	26 584 (40.0)
Dyslipidaemia	212 700 (65.4)	163 536 (63.1)	49 164 (74.0)
Heart failure	37 358 (11.5)	22 294 (8.6)	15 064 (22.7)
Previous myocardial infarction	21 920 (6.7)	15 353 (5.9)	6567 (9.9)
Chronic pulmonary disease	51 001 (15.7)	35 044 (13.5)	15 957 (24.0)
Peripheral artery disease	53 472 (16.4)	37 144 (14.3)	16 328 (24.6)
Atrial fibrillation	11 050 (3.4)	1826 (.7)	9224 (13.9)
Previous pulmonary thromboembolism	991 (.3)	375 (.14)	616 (.93)
Previous deep vein thrombosis	533 (.16)	149 (.06)	384 (.58)
CHA_2DS_2-VASc score	2.0 ± 1.6	1.7 ± 1.5	3.3 ± 1.7
Clinical diagnosis at index PCI			
Stable angina	107 554 (33.1)	83 725 (32.3)	23 829 (35.9)
Acute coronary syndrome	217 863 (66.9%)	175 266 (67.7)	42 597 (64.1)
Unstable angina	105 392 (32.4%)	84 613 (32.7)	20 779 (31.3)
Myocardial infarction	112 471 (34.6%)	90 653 (35.0)	21 818 (32.8)
Antithrombotic medication at discharge			
Aspirin	241 957 (74.4)	196 967 (76.1)	44 990 (67.7)
Clopidogrel	218 345 (67.1)	175 013 (67.6)	43 332 (65.2)
Prasugrel or ticagrelor	35 905 (11.0)	31 854 (12.3)	4051 (6.1)
DAPT duration	734.1 ± 791.2	767.0 ± 807.8	605.7 ± 708.3
Warfarin	4500 (1.4)	0 (.0)	4500 (6.8)
NOAC	2825 (.87)	0 (.0)	2825 (4.3)

The data are presented as mean ± SD for continuous variables according to the normality and number (percentage) for categorical variables. $P < .001$ for all comparisons.
DAPT, dual antiplatelet therapy; HBR, high bleeding risk; NOAC, novel oral anticoagulant; PCI, percutaneous coronary intervention.

accuracy) are shown in Supplementary data online, *Table S7*. The overall accuracy of the ARC-HBR criteria was 81.0% (95% CI 80.8%–81.1%).

In a machine learning based LASSO regression model, we demonstrated the best predictive performance for major bleeding by selecting 12 features, as shown in Supplementary data online, *Figure S4* and Supplementary data online, *Table S7*. The AUC of the ROC curve was .640 (95% CI .636–.643), which showed a similar predictive value to that of the ARC-HBR criteria.

Discussion

To the best of our knowledge, this all-comer East-Asian nationwide cohort is the largest series validating the HBR-ARC definition and its impact on both bleeding and ischaemic outcomes. The main findings can be summarized as follows (*Structured Graphical Abstract*): (i) from a large cohort of patients ($n = 325\,417$) identified in a Korean national registry who underwent PCI and had adequate information to measure HBR status, 20.4% had HBR according to the ARC criteria; (ii) HBR patients were at higher risk for long-term adverse clinical events, including bleeding and ischaemic outcomes, and also mortality events; (iii) for each individual criteria of the ARC-HBR definition, a major criterion was associated with a bleeding event rate of 5.5% during the first year after PCI, while one minor criterion was associated with a bleeding event rate of 2.9%; (iv) within the HBR group, there was an incremental risk increase with the presence of additional HBR risk factors. The incremental risk added by additional risk factors was larger for bleeding events compared to ischaemic events; and (v) patients in the HBR group had a greater risk of all-cause and cardiovascular mortality.

The major consequence of coronary artery disease is myocardial ischaemia, which can be relieved or prevented through revascularization

Table 2 Baseline characteristics of ARC-HBR criteria

	Total population ($n = 325\,417$)	Non-HBR ($n = 258\,991$)	HBR ($n = 66\,426$)
Major criteria			
Anticipated use of long-term oral anticoagulation	14 746 (4.5)		14 746 (22.2)
Severe or end-stage CKD (eGFR < 30 mL/min)	6065 (1.9)		6065 (9.1)
Haemoglobin < 11 g/dL	16 101 (5.0)		16 101 (24.2)
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months	5794 (1.8)		5794 (8.7)
Chronic bleeding diathesis	7301 (2.2)		7301 (11.0)
Liver cirrhosis with portal hypertension	3858 (1.2)		3858 (5.8)
Active malignancy	3605 (1.1)		3605 (5.4)
Previous spontaneous ICH	788 (.2)		788 (1.2)
Recent major surgery or major trauma within 30 days before PCI	56 (.02)		56 (.08)
Minor criteria			
Age ≥ 75 years old	68 619 (21.1)	35 064 (13.5)	33 555 (50.5)
Moderate CKD (eGFR 30–59 mL/min)	10 785 (3.3)	3269 (1.3)	7516 (11.3)
Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women	48 784 (15.0)	20 801 (8.0)	27 983 (42.1)
Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months	2745 (.8)	574 (.2)	2171 (3.3)
Long-term use of oral NSAIDs or steroids	11 122 (3.4)	3683 (1.4)	7439 (11.2)
Any ischaemic stroke at any time	4380 (1.4)	2159 (.8)	2221 (3.3)

The data are presented as number (percentage). $P < .001$ for all comparisons in the minor criteria analysis.
ARC, Academic Research Consortium; CKD, chronic kidney disease; GFR, glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial haemorrhage; NSAIDs, non-steroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention.

with implantation of a bare metal stent, a foreign material which can sometimes itself be the source of future ischaemic complications.[11] Therefore, the main focus of treating these patients is to decrease the risk of ischaemic complications, mainly through antithrombotic therapy. However, recent insights have shed light to the significance of post-PCI bleeding complications and its association with mortality.[1,2,12] Furthermore, along with the expansion of PCI candidates, sicker patients with severe comorbidities who are vulnerable to bleeding events are receiving PCI more frequently than ever. Consequently, the ARC has proposed a standardized definition for HBR with the primary goal of advancing the consistency and quality of data collection and ultimately improving clinical outcomes.[3] Via this consensus, which is based on a combination of major and minor criteria, clinicians can identify patients with HBR who may benefit from a shorter duration of dual antiplatelet therapy (DAPT) or by a de-escalation of its intensity.[4,5,13,14]

However, this consensus was based on literature review and mostly expert opinions, and therefore needs validation from 'real-world' cohorts to promote its application to daily clinical practice. Previously, the ARC-HBR definition was validated in several registry studies.[6,7,10,15,16] These studies reported that 32.8%–44.5% of PCI candidates were identified as HBR patients. This is almost twice as high as what we found in the current study of 325 417 all-comers that received PCI for a decade. This might be explained by the different study populations. Previous registries did not include as many patients as the current study and were mostly from tertiary centres, which could lead to selection bias, where only higher risk patients are included. Our study was from a nationwide cohort of all-comers and included all identifiable patients undergoing PCI during the study period. Also, the higher prevalence of certain criteria could have led to higher proportion of HBR patients compared to our study. For example, the prevalence of atrial fibrillation, the main reason for OAC prescription, was higher in previous cohort studies compared to the general population.[16,17] Regarding moderate or severe chronic renal disease, the prevalence is very high in registry studies. Considering that these risk factors frequently co-exist, the prevalence of around 20% seems to be a more logical prevalence of HBR in the all-comer population.

As expected, the HBR group was associated with a significantly higher risk of bleeding events,[6,7,10] and the presence of multiple HBR criteria resulted in even higher risk. Although the ARC-HBR definition is binary, it should be noted that there is cumulative increment of bleeding events corresponding with the number of HBR criteria. We could demonstrate that those who had four or more HBR criteria had a 3.56-fold higher risk of bleeding compared to those who had only one HBR criteria. Interestingly, from our study, we could calculate the individual effect on bleeding events of each HBR criterion. According to the ARC-HBR initiative, a major criterion is expected to portend an incidence of major bleeding > 4% at 1 year, and <4% for a minor criterion.[3] This was clearly confirmed in our analysis. All single major criteria were associated with over 4% of bleeding events at 1 year. Single minor criteria were associated with under 4% of bleeding events at 1 year. As for the predictive value of the ARC-HBR criteria, the AUC results were

Table 3 Clinical outcomes of high bleeding risk and non-high bleeding risk patients

Variable	Non-HBR ($n = 258\,991$)	HBR ($n = 66\,426$)	Hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
Bleeding composite outcome	14 313 (8.9)	8921 (23.9)	3.12 (3.04–3.21)	2.84 (2.77–2.92)
BARC 3 bleeding	13 661 (8.4)	8397 (22.4)	3.07 (2.99–3.16)	
BARC 5 bleeding	652 (.4)	524 (1.7)	3.94 (3.51–4.42)	
Ischaemic composite outcome	23 697 (14.4)	12 427 (33.8)	2.50 (2.45–2.56)	2.24 (2.19–2.29)
Net adverse clinical events	34 933 (20.5)	18 815 (46.7)	2.67 (2.62–2.72)	
All-cause death	29 080 (21.6)	21 525 (58.0)	3.73 (3.66–3.79)	
Cardiovascular death	13 183 (9.0)	8795 (27.7)	3.18 (3.09–3.26)	
Myocardial infarction	6689 (4.0)	1962 (5.5)	1.41 (1.34–1.48)	
Stroke	7459 (4.4)	3867 (9.3)	2.49 (2.40–2.59)	
Ischaemic stroke	5883 (3.4)	3112 (7.4)	2.53 (2.42–2.64)	
Any bleeding	83 227 (46.6)	25 770 (60.1)	1.62 (1.59–1.64)	
Intracranial haemorrhage	1816 (1.1)	899 (2.2)	2.36 (2.18–2.55)	
Hospitalization for GI bleeding	8576 (4.8)	6268 (14.6)	3.52 (3.41–3.64)	
Intraocular bleeding	5606 (3.3)	2235 (5.5)	1.89 (1.80–1.99)	
Urogenital bleeding	32 856 (20.5)	9184 (26.2)	1.40 (1.37–1.43)	
Respiratory bleeding	21 590 (12.3)	6420 (16.5)	1.43 (1.39–1.47)	
Nasal bleeding	15 657 (8.9)	4223 (10.7)	1.28 (1.24–1.32)	
Intraarticular/intramuscular bleeding	1984 (1.3)	545 (1.6)	1.36 (1.23–1.49)	
Other bleeding	8222 (5.3)	4060 (11.4)	2.46 (2.37–2.56)	

Data are *n* (Kaplan–Meier estimate, %). $P < .001$ for all comparisons.
BARC, Bleeding Academic Research Consortium; CI, confidence interval; GI, gastrointestinal; HBR, high bleeding risk.
[a]Interaction between the two co-primary outcomes was considered a competing risk in Fine and Gray's competing risk regression model.

statistically significant, however, the values were around slightly higher than .6. This may be interpreted as a moderate predictive value at best, but we still believe that this criterion is valid due to the following reasons. The HBR criterion is a score that estimates patients who are at higher risk of bleeding, while the ROC curve is based on actual major bleeding events. Minor bleeding events, which are difficult to collect as events, were not analysed. Second, other than the AUC, many other statistic values should be taken into account when interpreting the true clinical value of a diagnostic test. As for the ARC-HBR criterion, we found that the specificity and negative predictive values were higher than 80%, suggesting that the absence of HBR is highly correlated with a low risk of bleeding events. Moreover, taking the disease prevalence (7.1%) into account, the accuracy, which can be interpreted as the overall probability that a patient is correctly classified, was also >80%. When comparing the predictive value of the ARC-HBR criteria between the bleeding endpoint and ischaemic endpoint, the values were similar, implying that HBR is a risk for endpoints of distinct identity.

High bleeding risk patients are also at high risk for ischaemic events along with bleeding events, with a 2.50-fold higher ischaemic risk in our study compared with non-HBR patients. The hazard of HBR compared with non-HBR on bleeding was numerically higher than that for ischaemia. However, it should be acknowledged that the clinical impact in terms of 'number needed to harm' was lower for ischaemic events suggesting a bigger clinical impact on ischaemia than bleeding. Since many risk factors for bleeding overlap with those associated with ischaemic risk, it is expected that HBR patients would have a higher risk of ischaemic events.[18,19] From our study, we could demonstrate that the relative impact of HBR on outcomes was greater for bleeding events than ischaemic events. Previous studies reported benefit of shortening DAPT duration without increasing ischaemia in HBR patients.[20–22] Costa *et al.*[23] reported HBR patients with complex PCI experienced significantly increased bleeding events from the use of long-term DAPT without any benefit in ischaemic events or mortality. Recently, an individual patient meta-analysis showed benefit of DAPT de-escalation strategy in patients undergoing PCI not only in bleeding endpoints but also in ischaemic endpoints.[13] Nevertheless, the clinical significance of bleeding events leads to a reasonable decision to shorten DAPT duration or de-escalate DAPT intensity even if the ischaemic risk may be high in HBR patients.

An important finding of our study was that HBR was associated with a higher risk of mortality, more than a three-fold increase in both all-cause mortality risk and cardiovascular mortality risk. This was also shown in previous studies,[6,16] and can be explained by a couple of manners. High bleeding risk itself is a risk for post-PCI bleeding complications, which are highly associated with short- and long-term mortality.[1,24] Also, patients with HBR carry multiple atherosclerotic risk factors that lead to higher frailty and an increased risk of mortality. Specifically, older age and comorbidities such as

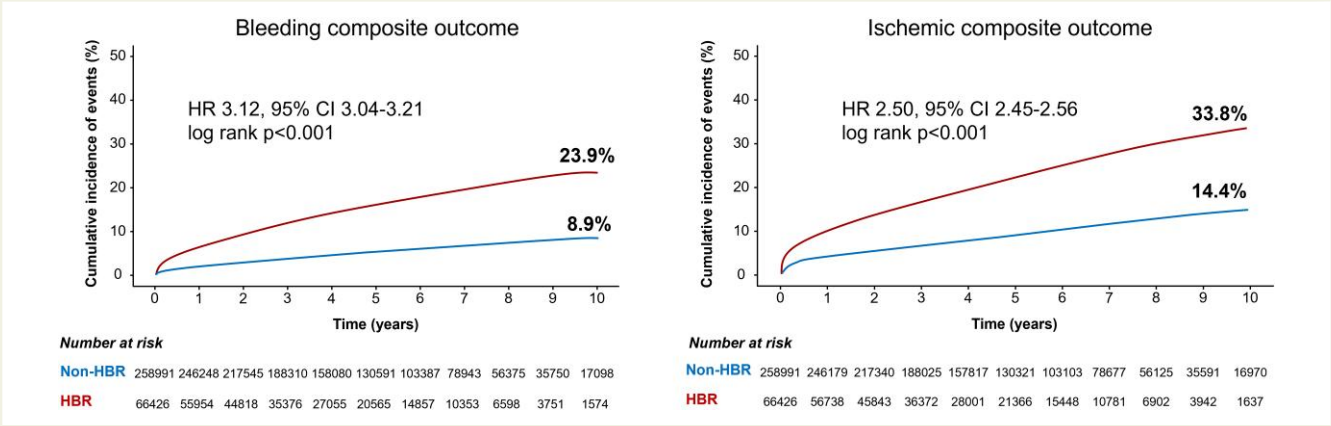
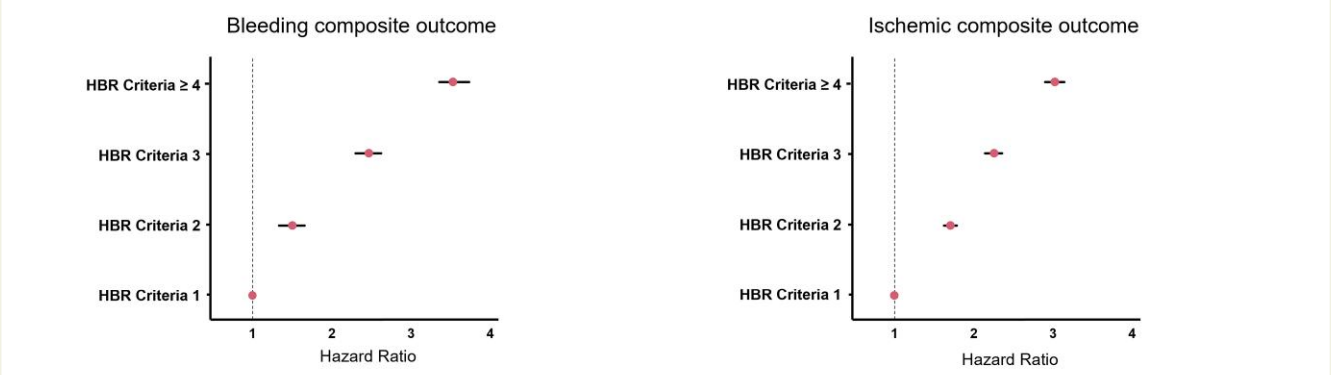


Figure 2 Cumulative incidence of the bleeding and ischaemic composite outcomes. Patients with HBR experienced more bleeding and ischaemic events compared to non-HBR patients. HBR, high bleeding risk

Table 4 Cumulative risk of bleeding and ischaemic composite outcome for each criterion

	Bleeding composite outcome		*Ischaemic composite outcome*	
	1 year	***10 years***	***1 year***	***10 years***
Total (n = 325 417)	8627 (2.7)	23 215 (11.2)	16 513 (5.1)	36 029 (16.6)
Major criteria[a]	1962 (5.5)	4610 (21.1)	3157 (8.5)	6455 (27.7)
Anticipated use of long-term oral anticoagulation (n = 14 746)	838 (5.9)	1707 (19.9)	1562 (10.7)	2964 (33.5)
Severe or end-stage CKD (eGFR < 30 mL/min) (n = 6065)	706 (12.8)	1371 (43.5)	726 (12.6)	1381 (46.2)
Haemoglobin < 11 g/dL (n = 16 101)	1220 (8.2)	2833 (29.7)	1597 (10.1)	3242 (31.9)
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months (n = 5794)	714 (14.0)	1267 (36.0)	783 (14.3)	1331 (38.0)
Chronic bleeding diathesis (n = 7301)	405 (5.8)	891 (21.4)	588 (8.2)	1191 (27.7)
Liver cirrhosis with portal hypertension (n = 3858)	235 (6.4)	536 (22.8)	253 (6.7)	513 (21.8)
Active malignancy (n = 3605)	228 (7.0)	412 (19.4)	193 (5.7)	360 (17.7)
Previous spontaneous ICH (n = 788)	115 (15.7)	153 (25.1)	119 (15.4)	176 (31.6)
Recent major surgery or major trauma within 30 days before PCI (n = 56)	14 (27.7)	19 (46.0)	6 (11.7)	10 (24.1)
Minor criteria[b]	1826 (2.9)	5533 (14.4)	4315 (6.6)	9443 (22.6)
Age ≥ 75 years old (n = 35 064)	1088 (3.3)	3015 (15.9)	3039 (8.7)	6268 (29.6)
Moderate CKD (eGFR 30–59 mL/min) (n = 3269)	85 (2.7)	268 (14.4)	135 (4.2)	368 (18.2)
Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women (n = 20 801)	493 (2.4)	1714 (12.4)	844 (4.1)	2118 (15.3)
Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months (n = 574)	13 (2.3)	63 (17.5)	28 (4.9)	65 (17.7)
Long-term use of oral NSAIDS or steroids (n = 3683)	104 (2.9)	326 (17.4)	173 (4.7)	404 (19.1)
Any ischaemic stroke at any time (n = 2159)	43 (2.0)	147 (10.9)	96 (4.5)	220 (15.1)

The data are presented as number (Kaplan–Meier estimate, %).
CKD, chronic kidney disease; GFR, glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial haemorrhage; NSAIDs, non-steroidal anti-inflammatory drug; PCI, percutaneous coronary intervention.
[a]Patients with only one major criterion were analysed.
[b]Patients with one minor criterion and no major criteria were analysed.



Bleeding composite outcome	HR (95% CI)	P-value	Total patients	Event number
HBR Criteria 1	REF		15972	1544
HBR Criteria 2	1.52 (1.44-1.62)	<0.001	34149	4371
HBR Criteria 3	2.43 (2.27-2.59)	<0.001	11662	2032
HBR Criteria ≥ 4	3.56 (3.28-3.86)	<0.001	4643	974

Ischemic composite outcome	HR (95% CI)	P-value	Total patients	Event number
HBR Criteria 1	REF		15972	1982
HBR Criteria 2	1.78 (1.69-1.87)	<0.001	34149	6663
HBR Criteria 3	2.31 (2.18-2.45)	<0.001	11662	2617
HBR Criteria ≥ 4	3.00 (2.79-3.23)	<0.001	4643	1165

Figure 3 Cumulative incremental bleeding and ischaemic risk in HBR patients corresponding to the number of HBR criteria. Along with the increase in HBR risk factors, the risk of bleeding and ischaemic outcomes increased with an incremental pattern. The extent of increasing risk is more significant in bleeding events. HBR, high bleeding risk

anaemia and renal failure, which are major components of HBR, are well-known risk factors of mortality after PCI. Therefore, HBR should not be solely interpreted as a risk for bleeding events, but an overall 'risk burden' that requires meticulous treatment. Additionally, we demonstrated that patients who experienced a clinical event, either ischaemic (myocardial infarction or ischaemic stroke) or bleeding event (BARC 3 bleeding), were at a higher risk of mortality. Interestingly, the mortality rate of HBR patients without events was similar to that of non-HBR patients with events. The relative risk of a clinical event on mortality was higher for a bleeding event, both in the HBR and non-HBR groups. Regarding the relative hazard of death in BARC 3 subcategories, the mortality risk was highest for BARC 3A events. Our results were distinct from a previous study by Valgimigli *et al.*[25] One explanation of this difference can be the operational definition of BARC 3 events, which is discussed in the limitation section.

In the current study, the validity of the ARC-HBR criteria was tested and confirmed in a huge all-comer East-Asian nationwide cohort. It has been reported that Asian patients may have slightly different ischaemia/bleeding trade-off due to a greater risk of bleeding.[26] Therefore, the external validity of our findings could be questioned from the fact that the study population of the current study was exclusively East-Asian. However, most of the studies that were referred to in developing the expert consensus on the ARC-HBR criteria were those that were performed in the USA and in Europe. Further, multiple smaller studies in non-Asian populations have reported the usefulness of these criteria in risk stratification of patients at increased risk of clinical events. Further, the risk factors of HBR are universal risk factors for bleeding events regardless of ethnicity, which were developed by a committee of worldwide experts.[3] We would welcome studies with large numbers of non-Asian patients to confirm our findings. Second, in the current era of potent $P2Y_{12}$ inhibitors, the bleeding risk is elevated while the ischaemic risk is decreased as compared to the clopidogrel era. Therefore, it can be argued that in those receiving more potent $P2Y_{12}$ inhibitors where the risk of bleeding would naturally be greater, the impact of HBR on major bleeding would be consistent if not accentuated.

Study limitations

This study has several limitations that should be discussed. First, from the total population, 28.6% were excluded from analysis, mainly due to lack of laboratory test results within 5 years of the index date. The exclusion was to accurately evaluate HBR, which included haemoglobin and creatinine levels. We can assume various causes of those without laboratory data, i.e. relatively more healthy patients, or patients with poor compliance. We assume that the excluded patients would not change the trend of our results, but we still acknowledge that this may be a limitation of our study. Second, an operational definition was used to define HBR and occurrence of adverse clinical events. Although the ICD-10-CM based diagnosis and baseline laboratory results of the total study population were fully available, some clinical outcomes (i.e. BARC bleeding individual subtype) that require additional data on intravenous medication may not have been accurately defined. However, utilizing an operational definition is commonly used when analysing health claims data. Additionally, one advantage of our analysis was that we had the full necessary data for operational definitions for all analysed patients. Third, moderate or severe baseline thrombocytopaenia, one of the major criteria in ARC-HBR definition, was not incorporated in the measurement of HBR status due to limited data. However, thrombocytopaenia accounts for the smallest percentage of <5% among major criteria in previous validation studies.[6,16] Fourth, some of the HBR criteria had to be partially modified from the original definition to fit the available data and this may potentially have led to underestimation of HBR patients. Fifth, the study cohort was a Korean population, which is not representative of other ethnicities with different ischaemic and bleeding risk profiles.[26,27] Therefore, extrapolation to other ethnicities should be performed with caution. Nevertheless, this study includes the largest number of patients for validation of the ARC-HBR definition and its impact on both bleeding and ischaemic outcomes.

Conclusions

Among all-comer patients receiving PCI, 20.4% of patients were identified as HBR according to the ARC-HBR definition. Those who met

the ARC-HBR criteria were at higher risk for both ischaemic and bleeding adverse events. The risk of HBR was greater for major bleeding than ischaemic outcomes. Moreover, HBR was associated with a greater risk of all-cause and cardiovascular mortality compared to non-HBR patients.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

K.W.P. declares that he has received consulting fees from Shockwave Medical and speaker's fees from Daiichi Sankyo, Daewoong Pharmaceutical, and InnoN Pharmaceutical, outside of the submitted work. K.W.P. is a board member of EzCaretech. H.-S.K. declares that he has received research grants or speaker's fees from Daiichi Sankyo, Boston Scientific, Terumo, Biotronik, and Dio, as well as Medtronic, Abbott Vascular, Edwards Life Science, AmGen, and Behringer Ingelheim. D.J.A. declares that he has received consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx Pharma, Pfizer, Sanofi, and Vectura, outside the present work; D.J.A. also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions, and Scott R. MacKenzie Foundation. All other authors declare no competing interests.

Data Availability

Data are not available due to personal information protection act. This analysis was done within a close system using the National Health Claims Database established by the National Health Insurance Service (NHIS) of Korea.

Funding

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Ethical Approval

The study protocol was approved by the ethics committee and Institutional Review Board at Seoul National University Hospital Institutional Review Board (ID 2008-172-1152).

Pre-registered Clinical Trial Number

None supplied.

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