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Validation of the Academic Research Consortium High Bleeding Risk Definition in Contemporary PCI Patients

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ABSTRACT

BACKGROUND Bleeding following percutaneous coronary intervention has important prognostic implications. The Academic Research Consortium (ARC) recently proposed a list of clinical criteria to define patients at high bleeding risk (HBR).

OBJECTIVES This study sought to validate the ARC definition for HBR patients in a contemporary real-world cohort.

METHODS Patients undergoing coronary stenting between 2014 and 2017 at a tertiary-care center were defined as HBR if they met at least 1 major or 2 minor ARC-HBR criteria. To account for the presence of multiple criteria, patients were further stratified by the number of times they fulfilled the ARC-HBR definition. The primary endpoint was a composite of peri-procedural in-hospital or post-discharge bleeding at 1 year. Secondary endpoints included individual components of the primary bleeding endpoint, myocardial infarction, and all-cause mortality.

RESULTS Among 9,623 patients, 4,278 (44.4%) qualified as HBR. Moderate or severe anemia was the most common major criterion (33.2%); age ≥75 years was the most frequent minor criterion and the most common overall (46.8%). The rate of the primary bleeding endpoint at 1 year was 9.1% in HBR patients compared with 3.2% in non-HBR patients ($p < 0.001$), with a stepwise increase in bleeding risk corresponding to the number of times the ARC-HBR definition was fulfilled. HBR patients also experienced significantly higher rates of all secondary endpoints.

CONCLUSIONS This study validates the ARC-HBR definition in a contemporary group of patients who underwent percutaneous coronary intervention. The ARC-HBR definition identified patients at increased risk not only for bleeding but also for thrombotic events, including all-cause mortality. Coexistence of multiple ARC-HBR criteria showed additive prognostic value. (J Am Coll Cardiol 2020;75:2711–22) © 2020 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ARC = Academic Research Consortium

ARC-HBR = Academic Research Consortium for High Bleeding Risk

AUC = area under the curve

BARC = Bleeding Academic Research Consortium

CKD = chronic kidney disease

DAPT = dual antiplatelet therapy

HBR = high bleeding risk

MI = myocardial infarction

PCI = percutaneous coronary intervention

ROC = receiver-operating characteristic

Advancement in device technology and continuous technical refinements have allowed expanding the spectrum of patients treated with percutaneous coronary intervention (PCI) to several complex clinical settings, including patients with severe comorbid conditions. In such patients, however, the benefit of coronary revascularization is jeopardized by the increased risk of bleeding events potentially

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arising from peri-procedural vascular complications or long-term antithrombotic therapy. Several studies have found the detrimental impact of post-PCI bleeding on survival to be similar to, if not greater than, that of thrombotic events (1–4). To facilitate risk stratification of patients, multiple scoring systems have been developed, albeit using heterogeneous cohorts and different definitions (5–10). As a result, ambiguity about how to effectively identify patients at high bleeding risk (HBR) remains, and it is reflected in the varying inclusion criteria adopted by the completed and ongoing trials in such patients (11–15).

Recently, the Academic Research Consortium for High Bleeding Risk (ARC-HBR) provided a consensus document with a list of clinical criteria classified as either major or minor to identify patients at HBR among those undergoing PCI (16). The presence of HBR, according to the ARC-HBR initiative, is expected to portend an incidence of Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding ≥4% at 1 year. This definition of HBR is arbitrarily binary, and its primary goals are to provide practical guidance for clinical decision making and to promote a standardized approach for future research. Nonetheless, since the ARC-HBR criteria were developed, their prevalence and prognostic association with clinical outcomes are yet to be established. Hence, the objectives of our analysis were to evaluate the following: 1) the prevalence and distribution of the ARC-HBR criteria in a contemporary real-world group of patients undergoing PCI; 2) bleeding complications and other adverse events associated with the ARC-HBR definition; 3) the incremental prognostic value of multiple coexisting ARC-HBR criteria; and 4) the relative contribution of each ARC-HBR criterion to the occurrence of bleeding at 1 year.

METHODS

STUDY DESIGN AND DATA COLLECTION. The study group consisted of all consecutive patients who underwent PCI with stent implantation at a large-volume tertiary-care center (Mount Sinai Hospital, New York) between January 2014 and December 2017. All data were prospectively collected in the institutional database after obtaining informed consent

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from the participating patients. Treatment modalities and antithrombotic management were at the physician's discretion and according to local standard of care at the time of intervention. Baseline and procedural characteristics, including the available ARC-HBR criteria, were systematically obtained using standardized forms at the time of index hospitalization for PCI. Dedicated research personnel were responsible for collecting follow-up information by telephone calls and medical record review up to 1 year after PCI. Complete information on in-hospital events was available for all patients. After hospital discharge, median time of follow-up was 350 days (interquartile range: 94 to 365 days).

Supplemental Table 1 illustrates the list of major and minor ARC-HBR criteria and their respective definitions adapted to the current study database. In line with the ARC-HBR document, patients were defined as HBR if they fulfilled at least 1 major or 2 minor criteria. Conversely, those not meeting any ARC-HBR criterion or patients with only 1 minor criterion were considered non-HBR. To evaluate the incremental prognostic value of multiple coexisting criteria while accounting for the binary nature of the ARC-HBR definition, patients were stratified according to the number of times they formally fulfilled the ARC-HBR definition: 1 (1 × HBR), 2 (2 × HBR), 3 (3 × HBR), 4 times or more (4 × HBR) (Supplemental Figure 1). Patients with missing data on any of the 11 ARC-HBR criteria evaluated in the present analysis were excluded.

ENDPOINT DEFINITIONS. The primary endpoint of the study was the rate of major bleeding at 1 year, defined as the composite of peri-procedural in-hospital bleeding or post-discharge bleeding. Peri-procedural in-hospital bleeding was identified according to the data definitions of the National Cardiovascular Data Registry CathPCI Registry (version 4.4) as any bleeding occurring during hospitalization for the index PCI associated with a hemoglobin drop ≥3 g/dl, blood transfusion, or requiring procedural intervention or surgery at the bleeding site (17). Post-discharge bleeding was defined as a bleeding event requiring either hospitalization or blood transfusion. A detailed comparison between the study endpoint definition and the BARC classification for type 3 to 5 bleeding is provided in Supplemental Table 2.

Secondary endpoints were the individual components of the primary bleeding endpoint represented by peri-procedural in-hospital and post-discharge bleeding, as well as all-cause mortality and post-discharge myocardial infarction (MI; defined according to the Third Universal Definition). An independent clinical events committee adjudicated all the in-hospital and post-discharge events leading to readmission at our institution; all other events were patient reported.

TABLE 1 Baseline Clinical Characteristics and Therapy at Discharge

	Non-HBR (n = 5,345)	HBR (n = 4,278)	p Value
Demographics			
Age, yrs	61.8 ± 9.7	71.7 ± 11.00	<0.001
Female	1,149 (21.5)	1,495 (34.9)	<0.001
Body mass index, kg/m^2	29.0 ± 5.5	28.5 ± 5.9	<0.001
African American	461 (8.6)	514 (12.0)	<0.001
Asian	1,276 (23.9)	624 (14.6)	<0.001
Medical history			
Hyperlipidemia	4,821 (90.2)	3,904 (91.3)	0.08
Hypertension	4,766 (89.2)	4,056 (94.8)	<0.001
Current smoker	961 (18.0)	366 (8.6)	<0.001
Diabetes mellitus	2,329 (43.6)	2,315 (54.1)	<0.001
Peripheral artery disease	338 (6.3)	609 (14.2)	<0.001
Previous MI	1,152 (21.6)	1,106 (25.9)	<0.001
Previous CABG	707 (13.2)	945 (22.1)	<0.001
Atrial fibrillation	108 (2.0)	734 (17.2)	<0.001
Clinical presentation			
Asymptomatic	215 (4.0)	215 (5.0)	0.02
Stable angina	2,667 (49.9)	2010 (47.0)	0.005
Unstable angina	1,724 (32.3)	1,401 (32.7)	0.61
NSTEMI	538 (10.1)	554 (12.9)	<0.001
STEMI	201 (3.8)	98 (2.3)	<0.001
Antiplatelet therapy at discharge			
DAPT	5,258 (98.4)	3,968 (92.8)	<0.001
Aspirin	5,265 (98.5)	3,970 (92.8)	<0.001
Clopidogrel	3,557 (66.5)	3,553 (83.1)	<0.001
Prasugrel	515 (9.6)	182 (4.3)	<0.001
Ticagrelor	1,262 (23.6)	511 (11.9)	<0.001
Oral anticoagulant therapy at discharge			
Warfarin	–	369 (8.6)	–
Dabigatran	–	48 (1.1)	–
Rivaroxaban	–	220 (5.1)	–
Apixaban	–	153 (3.6)	–

Values are mean ± SD or n (%).

CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; HBR = high bleeding risk; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

STATISTICAL ANALYSIS. Variables are expressed as mean ± SD if continuous and as numbers (frequencies) if categorical. The chi-square test and Student's *t*-test were used to compare baseline and procedural characteristics, as appropriate. Cumulative incidence of the primary and secondary endpoints at 1 year were assessed using the Kaplan-Meier method and compared between groups with the log-rank test for the time to the first event.

Proportional hazards Cox regression was used to evaluate the association between the presence of HBR

TABLE 2 Angiographic and Procedural Characteristics

	Non-HBR (n = 5,345)	HBR (n = 4,278)	p Value
Angiographic characteristics			
Multivessel disease	3,330 (62.3)	2,955 (69.1)	<0.001
Lesion location			
Left main	178 (3.3)	271 (6.3)	<0.001
Left anterior descending	2,580 (48.3)	1,962 (45.9)	0.02
Left circumflex	1,741 (32.6)	1,447 (33.8)	0.19
Right coronary artery	1,588 (29.7)	1,280 (29.9)	0.82
Saphenous vein graft	160 (3.0)	230 (5.4)	<0.001
Lesion complexity			
Bifurcation	1,153 (21.6)	814 (19.0)	0.002
Severe calcification	627 (11.7)	897 (21.0)	<0.001
In-stent restenosis	707 (13.2)	630 (14.7)	0.03
Chronic total occlusion	467 (8.7)	244 (5.7)	<0.001
Syntax score	12.5 ± 9.0	14.1 ± 11.0	<0.001
Procedural characteristics			
Arterial access site			
Femoral	4,170 (78.0)	3,561 (83.2)	<0.001
Radial	1,072 (20.1)	615 (14.4)	<0.001
Number of stents	1 (1–2)	1 (1–2)	0.97
Type of stent			
Bare-metal stent	58 (1.1)	186 (4.3)	<0.001
Drug-eluting stent	5,292 (99.0)	4,093 (95.7)	<0.001
Maximum stent diameter, mm	3.14 ± 0.48	3.19 ± 0.50	<0.001
Total stent length, mm	33.1 ± 20.7	32.7 ± 20.9	0.27
Rotational atherectomy	678 (12.7)	905 (21.2)	<0.001
Contrast volume, ml	149.4 ± 60.8	143.5 ± 63.4	<0.001
Glycoprotein IIb/IIIa inhibitors	456 (8.5)	204 (4.8)	<0.001

Values are n (%), mean ± SD, or median (interquartile range).
HBR = high bleeding risk.

and clinical outcomes at 1 year. A multivariable model including all the ARC-HBR criteria was performed to assess their relative contributions to the occurrence of bleeding complications. Estimated risks are expressed as hazard ratios and 95% confidence intervals (CIs). Odds ratios for peri-procedural in-hospital events were computed using a logistic regression model.

An UpSet plot was generated for quantitative visualization of the most frequent (up to 80) combinations (i.e., exclusive intersections) of major and minor criteria that qualified patients in the HBR group (18).

The discriminative ability of the ARC-HBR definition for the primary bleeding endpoint was assessed through the receiver-operating characteristic (ROC) area under the curve (AUC) on the entire study group. We built unadjusted ROC curves by using the ARC-HBR definition both as a binary classifier for identification of the overall group of HBR patients and as a continuous variable by adding multiple criteria. To generate a continuous variable, we assigned 0.5 and 1 point to minor and major criteria, respectively, given their relative weight to define HBR. Thus, only patients with 1 or more points were classified as HBR. This approach enabled us to simulate a point-based risk score, which is more appropriate for comparing the ARC-HBR discriminative ability with that of other contemporary bleeding risk scores.

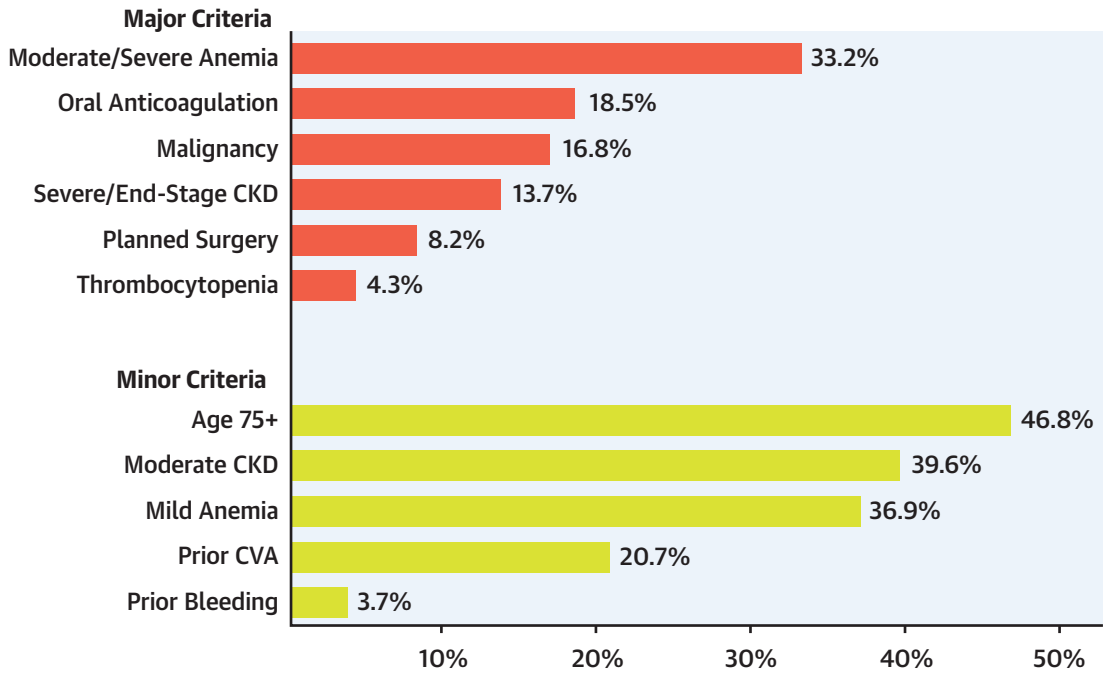
All probability testing was 2-sided, and statistical significance was declared for p values <0.05. The analyses were performed with STATA software version 15.1 (StataCorp, College Station, Texas) and R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

BASELINE CHARACTERISTICS. Of the 9,623 patients included in the analysis, 4,278 (44.4%) were considered to be at HBR according to the ARC-HBR definition (Supplemental Figure 2). Differences in baseline clinical, angiographic, and procedural characteristics between HBR and non-HBR groups are summarized in Tables 1 and 2. Compared with non-HBR, patients in the HBR group were older, more commonly female, and had a greater burden of comorbidities such as hypertension, diabetes, and peripheral artery disease. They presented more often with history of prior MI and coronary artery bypass grafting. HBR patients were also more likely to have more complex coronary artery disease, including a higher prevalence of multivessel disease, left main disease, and severely calcified lesions. Although the overall rate of bare-metal stent use was low, it was 4 times higher in the HBR group than in non-HBR. With regard to antiplatelet therapy, HBR patients were less frequently discharged on dual antiplatelet therapy (DAPT), aspirin, and potent $P2Y_{12}$ inhibitors, whereas rates of clopidogrel use were higher. Among HBR patients taking oral anticoagulant agents, more than one-half (53%) were discharged with a direct oral anticoagulant.

PREVALENCE AND DISTRIBUTION OF ARC-HBR CRITERIA. The prevalence of each major and minor criterion within the HBR group is shown in Figure 1, and the overlap between major and minor criteria and their most frequent combinations are summarized in Figures 2A and 2B. Most HBR patients exhibited both major and minor criteria (47.3%). Conversely, patients with at least 1 major criterion but no minor criteria were the least represented (22.1%). In the non-HBR group, 38.9% of patients had 1 minor criterion and therefore did not meet the ARC-HBR definition.

FIGURE 1 Prevalence of the ARC-HBR Criteria Within the HBR Group



Bars indicate the overall prevalence of each major and minor criterion among patients qualified as being at high bleeding risk (HBR). ARC-HBR = Academic Research Consortium for High Bleeding Risk; CKD = chronic kidney disease; CVA = cerebrovascular accident.

Age ≥75 years, although minor, was the most prevalent criterion overall (46.8%). Moderate or severe anemia was not only the most frequent major criterion (33.2%) but also the most common HBR-qualifying condition when occurring in isolation (i.e., without other coexisting criteria). Combinations of at least 2 minor criteria among age ≥75 years, mild anemia, and moderate chronic kidney disease (CKD) were the next most common HBR-qualifying conditions. Thrombocytopenia and prior bleeding were the least prevalent major and minor criteria, respectively.

Within the HBR group, 61.6% of patients fulfilled the ARC-HBR definition only once (1 × HBR), 29.1% twice (2 × HBR), 7.9% thrice (3 × HBR), and 1.4% 4 times or more (4 × HBR). The prevalence of the ARC-HBR criteria and their combinations in each HBR subgroup are illustrated in Supplemental Figures 3A to 3D.

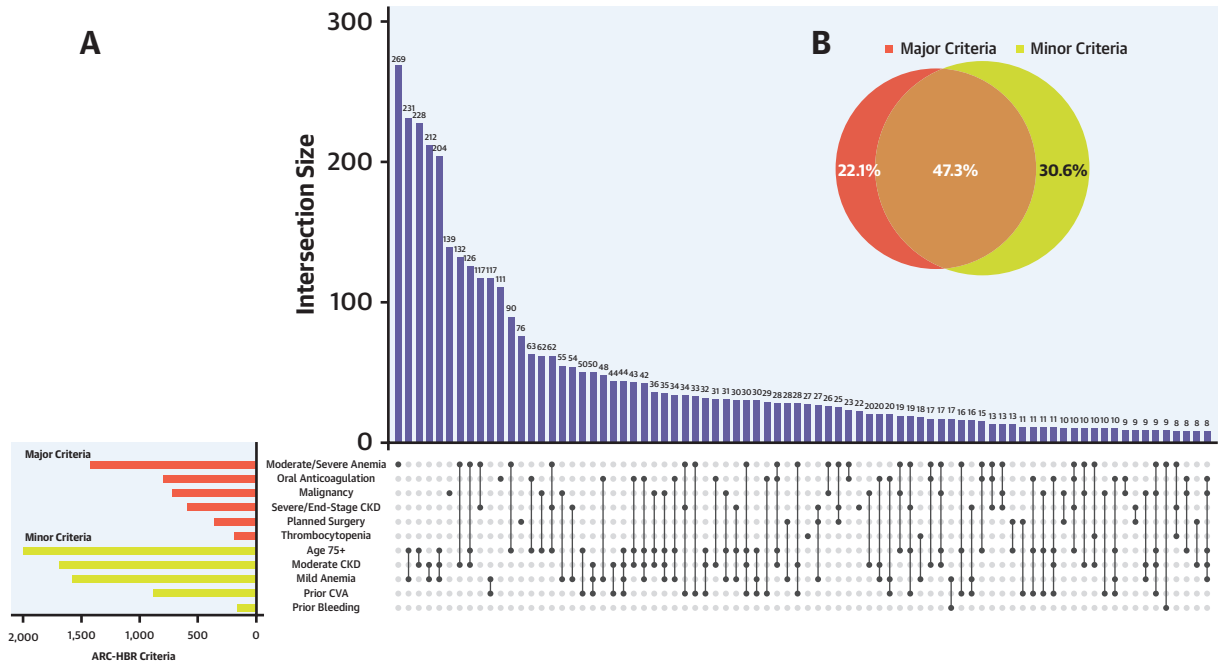
CLINICAL OUTCOMES. The primary bleeding endpoint occurred in 9.1% of patients in the HBR group and in 3.2% of the non-HBR group ($p < 0.001$) (**Figure 3**). This finding was reflected in higher rates of both peri-procedural in-hospital bleeding (4.8% vs. 1.4%; $p < 0.001$) and post-discharge bleeding (4.6% vs. 1.8%; $p < 0.001$) in the HBR group (**Figures 4A and 4B**). Patients at HBR also experienced higher all-cause mortality (4.7% vs. 0.6%; $p < 0.001$) and MI (4.2% vs. 2.0%; $p < 0.001$) at 1 year compared with non-HBR (**Figures 5A and 5B**).

Within the non-HBR group, the rates of the primary bleeding endpoint (3.6% vs. 2.9%; $p = 0.09$), peri-procedural in-hospital bleeding (1.8% vs. 1.2%; $p = 0.08$) and post-discharge bleeding (1.9% vs. 1.7%; $p = 0.53$) were not significantly different between patients who met 1 minor criterion and those who did not (Supplemental Figures 4, 5A, and 5B).

The ROC AUC for the ARC-HBR definition, when used as binary variable (HBR vs. non-HBR) to predict the primary bleeding endpoint in the overall group, was 0.64 (95% CI: 0.61 to 0.66) (Supplemental Figure 6A).

ADDITIVE PROGNOSTIC VALUE OF ARC-HBR CRITERIA. Among patients with multiple ARC-HBR criteria, the risk of bleeding at 1 year increased in a stepwise fashion, corresponding to the number of times the ARC-HBR definition was fulfilled (**Central Illustration**). Comparable trends were observed with respect to secondary bleeding endpoints, all-cause mortality, and MI (Supplemental Figures 7A, 7B, 8A, and 8B).

FIGURE 2 Combinations of Major and Minor Criteria in the HBR Group



(A) UpSet plot showing the 80 most common combinations of Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria in the high bleeding risk (HBR) group. **Black dots** indicate the presence of a criterion. **Black lines** connecting the dots represent a combination of criteria. **Vertical bars above** correspond to the number of patients with a particular combination. **Horizontal bars on the left** correspond to the total number of patients with each specific criterion. **(B)** Venn diagram showing the prevalence of all major criteria **(red circle)** and all minor criteria **(yellow circle)** in the high bleeding risk group. The **overlapping area between the 2 circles** represents patients with both major and minor criteria. CKD = chronic kidney disease; CVA = cerebrovascular accident.

With the ROC curve generated using the ARC-HBR definition as a continuous variable and progressively adding multiple minor and major criteria, the AUC for the primary bleeding endpoint increased to 0.68 (95% CI: 0.65 to 0.71) (Supplemental Figure 6B).

ASSESSMENT OF INDIVIDUAL ARC-HBR CRITERIA. The 1-year rates of the primary bleeding endpoint associated with each of the ARC-HBR criteria are presented in **Figure 6**. When occurring in isolation, all major criteria, except for malignancy, were associated with an incidence of bleeding ≥4% at 1 year. Among minor criteria, prior cerebrovascular accident, age ≥75 years, and moderate CKD were also associated, in isolation, with a bleeding rate ≥4%.

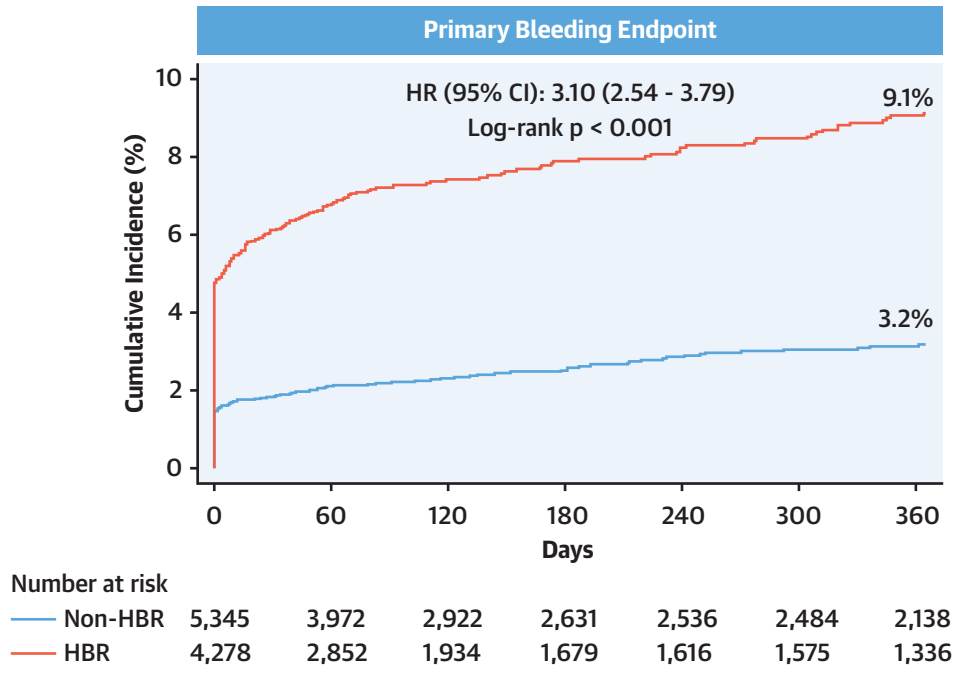
Results of the multivariable analysis (Supplemental Table 3) showed that every major criterion, with the exception of planned surgery, had a stronger impact on bleeding risk than each of the minor criteria. Moderate or severe anemia was the ARC-HBR criterion associated with the highest risk of bleeding complications at 1 year.

DISCUSSION

The main findings of this study on the validation of the ARC-HBR definition in a contemporary group of patients undergoing PCI can be summarized as follows: 1) in a real-world cohort, 44% of patients undergoing coronary stent implantation met the ARC-HBR definition; 2) the rate of the primary bleeding endpoint at 1 year in patients at HBR was higher than the 4% cutoff assumed by ARC-HBR consensus and nearly 3 times higher than in non-HBR patients; 3) HBR patients also experienced significantly higher rates of MI and all-cause mortality; and 4) the prognostic value of the ARC-HBR definition was further increased when the presence of multiple coexisting criteria was taken into account.

Most of the available data on bleeding complications after coronary stenting are derived from clinical trials of antiplatelet therapy. Despite different endpoint definitions, the overall incidence of major bleeding has been consistently reported to be <3% at 1-year follow-up, with particularly low event rates in

FIGURE 3 Cumulative Incidence of the Primary Bleeding Endpoint at 1 Year



Kaplan-Meier curves showing rates of the primary bleeding endpoint at 1 year according to presence or absence of high bleeding risk (HBR) in patients undergoing percutaneous coronary intervention. CI = confidence interval; HR = hazard ratio.

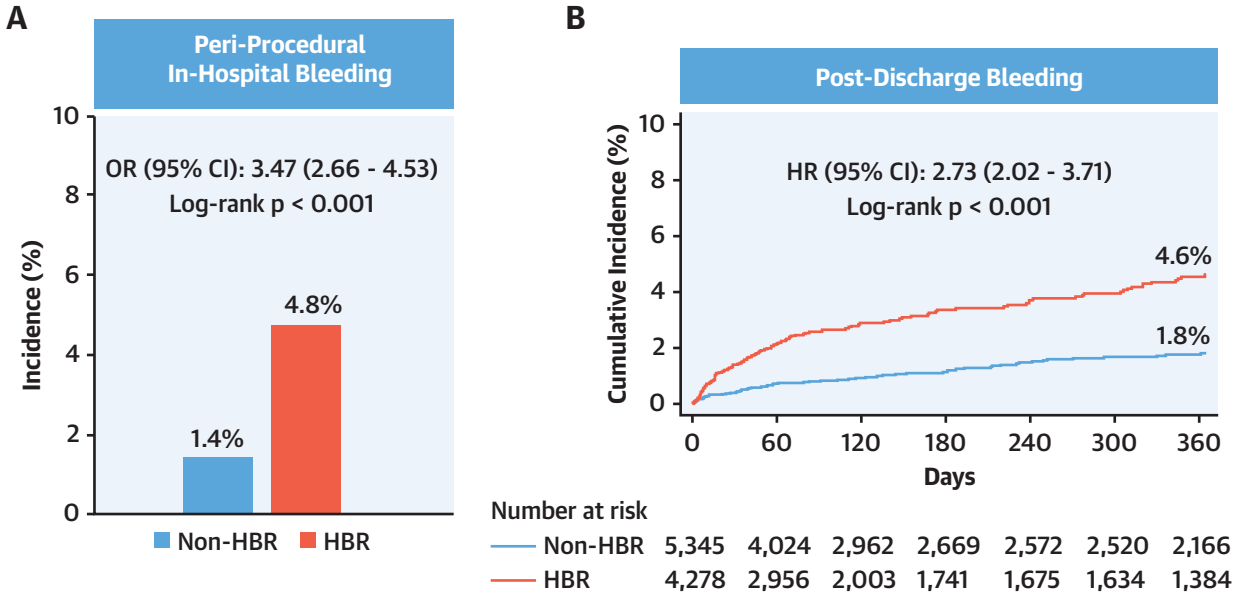
studies on low-risk patients (16). Recently, concerns regarding the limited generalizability and clinical implications of such trials have been raised, with growing attention towards a more individualized risk-based approach to patients undergoing PCI.

There is compelling evidence in favor of a strong association between post-PCI bleeding complications and the risk of short- and long-term mortality (19–23). Data from the U.S. National Cardiovascular Data Registry consisting of more than 3 million PCI procedures showed that peri-procedural bleeding, as defined in the present study, is responsible for approximately 12% of in-hospital mortality (24). Consequently, the need for bleeding avoidance strategies involving optimized peri-procedural management and tailored antithrombotic therapy has been emphasized, with guidelines endorsing the use of algorithms to predict the patient's bleeding risk and inform decision making (25,26). However, risk scores are intrinsically influenced by the characteristics of the studies used for their development, and this limits their prognostic value when applied to a diverse real-world group of patients (27). The ARC-HBR definition, which is based on expert consensus after extensive review of published reports, promotes a more pragmatic approach to assessment of bleeding risk in PCI-treated patients (16). Hence, our findings are essential to support the validity of this newly introduced definition of HBR and encourage its future application in clinical settings.

In this study, almost 1 in 2 patients undergoing PCI was at HBR according to the ARC-HBR criteria. This high prevalence is in contrast with that observed in 2 validation cohorts for the PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score, where only 23% of patients were classified as HBR (5). Similarly, another recent randomized trial of antiplatelet therapy reported that approximately 20% of the enrolled study group was at HBR according to the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients) score (28). These discrepancies may be explained either by the inclusion of an unselected real-world group in our study or by the nature of the ARC-HBR definition itself, which is perhaps more sensitive, albeit less specific, than numerical risk scores in capturing this patient group.

Consistent with previous HBR trials, advanced age (≥75 years) was the most frequent criterion in our

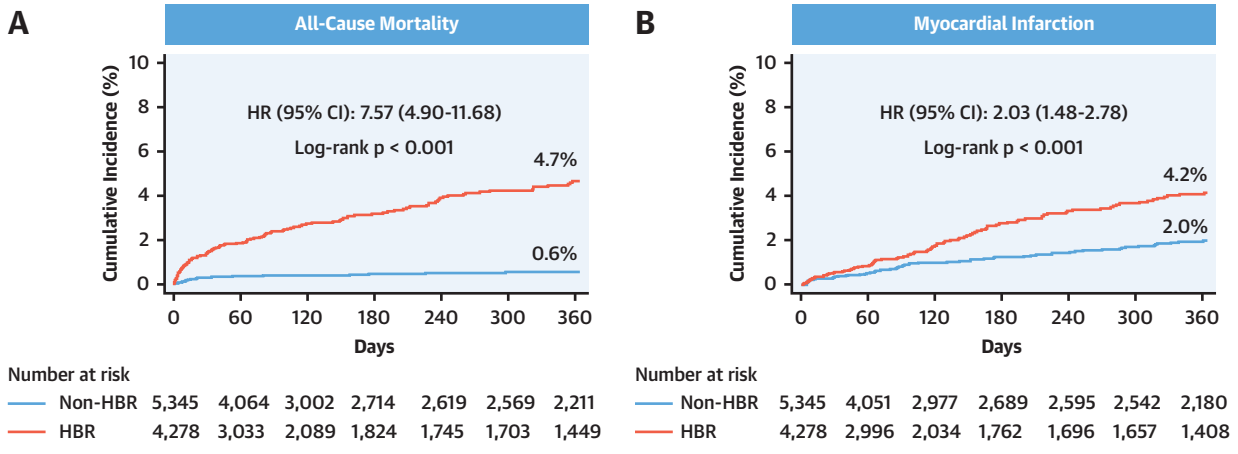
FIGURE 4 Cumulative Incidence of Peri-Procedural In-Hospital Bleeding and Post-Discharge Bleeding



(A) Peri-procedural in-hospital bleeding consisting of bleeding associated with a hemoglobin drop ≥3 g/dl, blood transfusion, or procedural intervention or surgery at the bleeding site, the individual rates of which were 1.4% versus 1.2% ($p = 0.36$), 3.6% versus 0.3% ($p < 0.001$), and 1.5% versus 0.3% ($p < 0.001$) in high bleeding risk (HBR) versus non-high bleeding risk (non-HBR) patients, respectively. **(B)** Post-discharge bleeding. CI = confidence interval; HR = hazard ratio; OR = odds ratio.

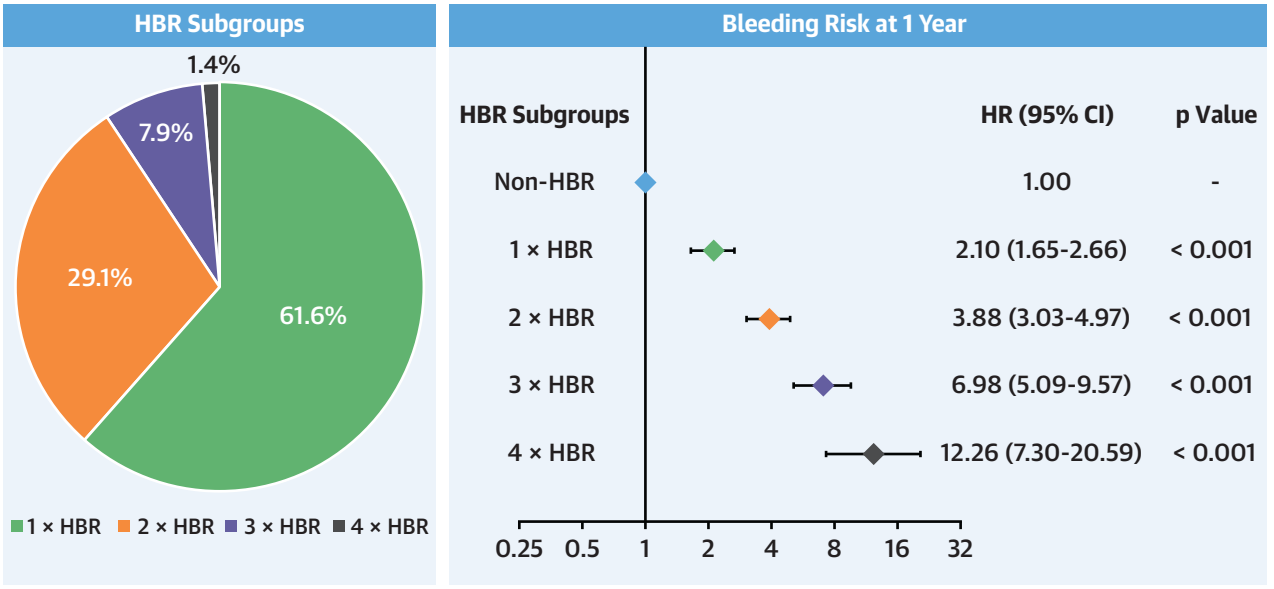
study, whereas the prevalence of other disease-specific and clinically meaningful criteria differed. Moderate or severe anemia, representing the most common major criterion in our study (33%), was present in only about 15% of patients in both the LEADERS FREE (Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk) and ONYX ONE (Randomized Controlled Trial With Resolute Onyx in One Month

FIGURE 5 Cumulative Incidence of All-Cause Mortality and Myocardial Infarction



Kaplan-Meier curves showing rates of the secondary endpoints at 1 year according to presence or absence of high bleeding risk (HBR) in patients undergoing percutaneous coronary intervention. **(A)** All-cause mortality. **(B)** Myocardial infarction. CI = confidence interval; HR = hazard ratio.

CENTRAL ILLUSTRATION **Additive Effect of Multiple Academic Research Consortium for High Bleeding Risk Criteria**



Cao, D. et al. J Am Coll Cardiol. 2020;75(21):2711–22.

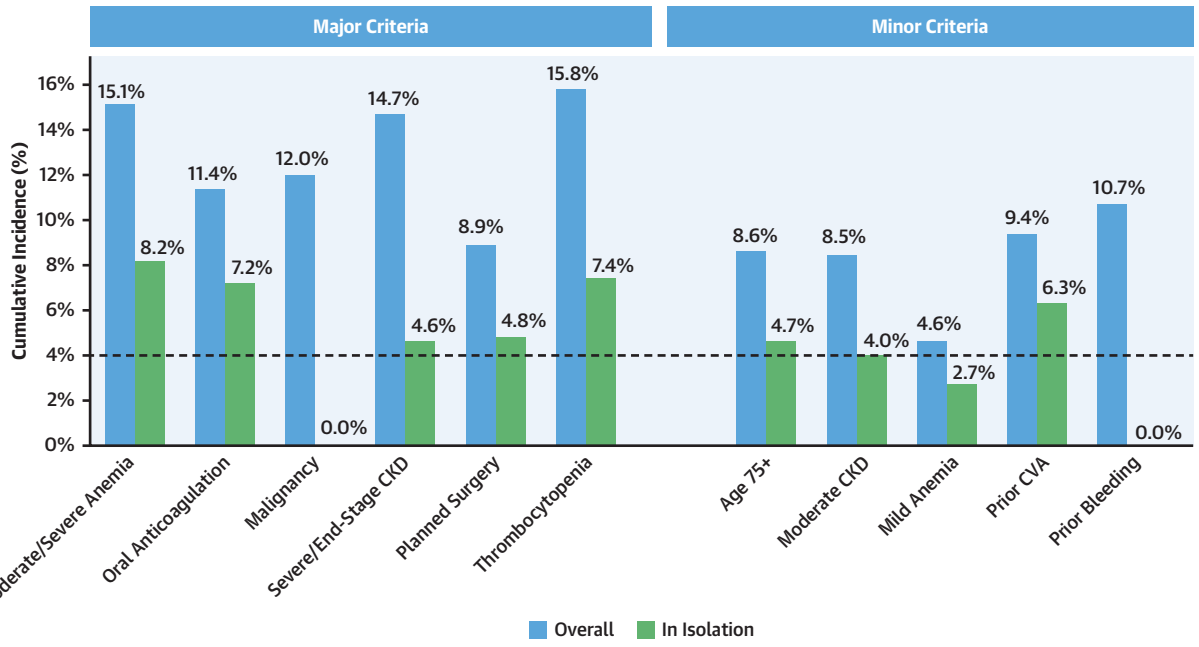
(Left) The sum of major and minor criteria satisfied by each patient was used to stratify patients according to the number of times they fulfilled the Academic Research Consortium for High Bleeding Risk definition. The **pie chart** shows the distribution of high bleeding risk (HBR) patients into subgroups with increasing numbers of multiple coexisting criteria (1 × HBR to 4 × HBR). **(Right)** Risk of the primary bleeding endpoint at 1 year for each high bleeding risk subgroup; the reference group is non-HBR patients. There are stepwise increments in bleeding risk corresponding to the number of times the Academic Research Consortium for High Bleeding Risk definition is fulfilled. CI = confidence interval; HR = hazard ratio.

DAPT for High-Bleeding Risk Patients) trials. Conversely, the percentages of patients with an indication for oral anticoagulation were 37% and 39% in LEADERS FREE and ONYX ONE, respectively, but only 18% in our study (11,13). The preferential enrollment of patients receiving oral anticoagulant agents in clinical trials mandating a shortened DAPT regimen may account for these differences.

In the present study, more than one-third of the HBR patients met multiple criteria, with the result that they fulfilled the ARC-HBR definition 2 or more times. Interestingly, within the lower-risk subgroup (1 × HBR), most patients qualified as HBR because of a combination of minor criteria, among which advanced age, mild anemia, and moderate CKD were the most common. By contrast, patients in the higher-risk subgroups showed an increasing prevalence of major criteria, such as oral anticoagulation, severe or end-stage CKD, and malignant disease.

The ARC-HBR definition successfully identified patients from an all-comers group of participants who were at a higher risk for bleeding complications at 1 year. The 9.1% rate of the primary bleeding endpoint observed in our HBR cohort far exceeded the pre-specified 4% cutoff and may reflect the large prevalence of very high-risk subjects with multiple HBR-qualifying conditions encountered in contemporary practice. According to the ARC-HBR document, the presence of at least 1 major criterion confers a 1-year risk of major bleeding ≥4%. Conversely, each minor criterion, in isolation, is associated with a bleeding risk <4%. In the present study, we report the bleeding rates specific to each of the ARC-HBR criteria and their relative contributions to the risk of bleeding complications at 1 year. Our results should be interpreted in light of the readapted definitions for some of the variables, as well as the very low prevalence of certain criteria, especially when considered in isolation. These limitations notwithstanding, our findings highlight the drawbacks of a binary definition that does not account for the relative weight of the different criteria used to

FIGURE 6 Cumulative Incidence of the Primary Bleeding Endpoint at 1 Year Associated With Each of the ARC-HBR Criteria



Bars and percentages representing Kaplan-Meier estimates of the primary bleeding endpoint in patients presenting with a specific Academic Research Consortium for High Bleeding Risk (ARC-HBR) criterion. CKD = chronic kidney disease; CVA = cerebrovascular accident.

identify HBR patients, and anticipate the need for their future recalibration. Furthermore, the observed AUC value of <0.7 indicates a modest discriminative capability of the ARC-HBR criteria to distinguish between patients with or without a future event. Yet, most of the validated and widely accepted risk assessment tools for bleeding have shown comparable discrimination, which, on the whole, points toward the shortcomings of basing clinical judgment only on a limited number of risk parameters (16).

Patients at HBR also carried a higher burden of atherosclerotic disease leading to an increased risk of MI compared with non-HBR patients. The dual impact of certain clinical conditions such as age and CKD on both thrombotic and bleeding risk is well established. Moreover, prescription of less intensive antiplatelet regimens and DAPT disruption from bleeding in HBR patients may amplify their risk of adverse cardiac events (29). Despite the accumulating evidence on the superiority of new-generation drug-eluting stents over bare-metal stents even with a short DAPT course (11,12,14), our findings suggest that physicians still exercise caution in using drug-eluting stents in HBR patients. Eventually, additional unmeasured conditions such as frailty and therapy nonadherence, presumably more frequent among older and more severely diseased patients, may have contributed to the >7-fold risk of mortality observed in the HBR cohort.

Although the ARC-HBR consensus acknowledges the lack of sufficient data to generate a numerical score accounting for the relative weight of each criterion, it recognizes that the presence of multiple criteria portends a higher bleeding risk (16). The present study provides robust evidence in support of this assumption. We reported highly significant stepwise increments in the risk of bleeding complications closely reflecting the increasing number of coexisting HBR-qualifying conditions. As such, our findings also demonstrate the additive prognostic value of the ARC-HBR criteria and their potential use for data analysis and clinical assessment.

STUDY LIMITATIONS. First, not all 20 ARC-HBR criteria were present in our analysis; inclusion of those missed criteria would potentially lead to improved event rate estimation and enhanced discriminative ability. In addition, for some of the criteria, our definitions partially differed from the original ones of the ARC-HBR document. However, although detailed ARC-HBR criteria are intended primarily for prospective application, in cohort studies it is common practice to adapt variable

definitions to the available records for optimizing data capture. Second, the ARC initiative defines HBR as a risk of major bleeding ≥4% at 1 year according to the BARC scale, which was not available for this study. Nonetheless, our bleeding endpoint definition shares many elements with BARC type 3 to 5 (Supplemental Table 2), and it likely provides a reliable estimate of major bleeding events. Although we cannot exclude numerically different event rates if actual BARC endpoints were used, the strength and consistency of our findings in a usual-care cohort enhance the generalizability of the ARC-HBR criteria, even when using an alternative definition of bleeding. Third, despite being a single-center study from an urban, high-volume, tertiary care hospital, we have shown that HBR patients, even if widely under-represented in most clinical trials, compose more than 40% of our real-world practice. Moreover, the high rates of use of potent $P2Y_{12}$ inhibitors, direct oral anticoagulants, and drug-eluting stents, among others, make this large cohort representative of a contemporary PCI population. Finally, we did not have follow-up data on adherence to antiplatelet medications after discharge, and future research on HBR patients is needed to help understand how bleeding risk varies according to their antithrombotic management.

CONCLUSIONS

The present study validates the ARC-HBR definition in a contemporary real-world group of patients undergoing PCI with stent implantation. The ARC-HBR definition successfully identified patients experiencing higher rates of bleeding complications and adverse thrombotic events, including all-cause mortality, up to 1 year after PCI. The prognostic value of the ARC-HBR definition was further increased when the presence of multiple coexisting criteria was taken into account.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The ARC-HBR criteria identify a heterogeneous group of patients at increased risk of bleeding complications following PCI who may also face an elevated risk of thrombotic events.

TRANSLATIONAL OUTLOOK: While the ARC-HBR criteria may require recalibration as evidence accrues, additional studies are needed to understand the interplay between bleeding and thrombotic risks.

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KEY WORDS bleeding, coronary artery disease, HBR, percutaneous coronary intervention

APPENDIX For supplemental figures and tables, please see the online version of this paper.