EuroIntervention 2020;16:371-379 published online jaa February 2020

Validation of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores

Yasushi Ueki[1], MD; Sarah Bär[1], MD; Sylvain Losdat[2], PhD; Tatsuhiko Otsuka[1], MD; Christian Zanchin[1], MD; Thomas Zanchin[1], MD; Felice Gragnano[1], MD; Giuseppe Gargiulo[1], MD; George C.M. Siontis[1], MD, PhD; Fabien Praz[1], MD; Jonas Lanz[1], MD; Lukas Hunziker[1], MD; Stefan Stortecky[1], MD; Thomas Pilgrim[1], MD; Dik Heg[2], PhD; Marco Valgimigli[1], MD, PhD; Stephan Windecker[1], MD; Lorenz Räber[1]*, MD, PhD

1. Department of Cardiology, Bern University Hospital, Bern, Switzerland; 2. Institute of Social and Preventive Medicine and Clinical Trials Unit, University of Bern, Bern, Switzerland

Y. Ueki and S. Bär contributed equally to this study.

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00052

KEYWORDS

- ACS/NSTE-ACS
- bleeding
- coronary artery disease
- stable angina

Abstract

Aims: The Academic Research Consortium for High Bleeding Risk (ARC-HBR) defined consensus-based criteria for patients at high bleeding risk (HBR) undergoing percutaneous coronary intervention (PCI). We aimed to validate the ARC-HBR criteria for the bleeding outcomes using a large cohort of patients undergoing PCI.

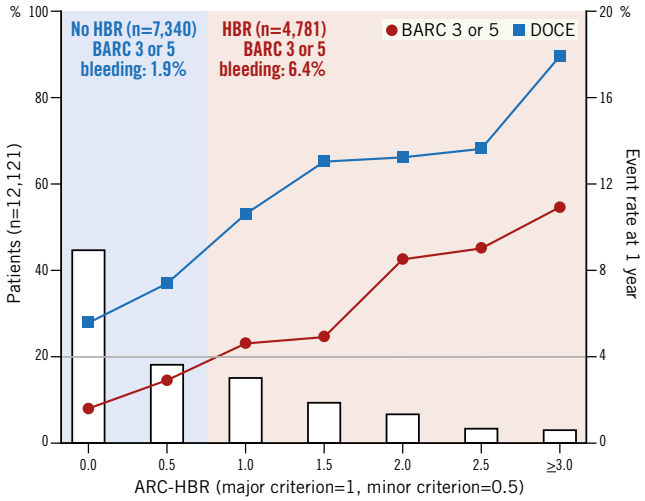
Methods and results: Between 2009 and 2016, patients undergoing PCI were prospectively included in the Bern PCI Registry. Patients were considered to be at HBR if at least one major criterion or two minor criteria were met. The primary endpoint was Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding at one year; ischaemic outcomes were assessed using the device-oriented composite endpoints (DOCE) of cardiac death, target vessel myocardial infarction, and target lesion revascularisation. Among 12,121 patients, those at HBR (n=4,781, 39.4%) had an increased risk of BARC 3 or 5 bleeding (6.4% vs 1.9%; p<0.001) and DOCE (12.5% vs 6.1%; p<0.001) compared with those without HBR. The degree of risk and prognostic value were related to the risk factors composing the criteria. The ARC-HBR criteria had higher sensitivity than the PRECISE-DAPT score and the PARIS bleeding risk score (63.8%, 53.1%, 31.9%), but lower specificity (62.7%, 71.3%, 86.5%) for BARC 3 or 5 bleeding.

Conclusions: Patients at HBR defined by the ARC-HBR criteria had a higher risk of BARC 3 or 5 bleeding as well as DOCE. The bleeding risk was related to its individual components. The ARC-HBR criteria were more sensitive for identifying patients with future bleedings than other contemporary risk scores at the cost of specificity. ClinicalTrials.gov Identifier: NCT02241291

**Corresponding author: Department of Cardiology, Bern University Hospital Inselspital, University of Bern, Freiburgstrasse 18, 3010 Bern, Switzerland. E-mail: lorenz.raeber@insel.ch*

SUBMITTED ON 09/01/2020 - REVISION RECEIVED ON 27/01/2020 - ACCEPTED ON 14/02/2020

DOI: 10.4244/EIJ-D-20-00052



Visual summary. *According to the ARC-HBR criteria, 40% of patients undergoing PCI were at HBR. Compared with patients without HBR, those at HBR had an increased risk of BARC 3 or 5 bleeding (6.4% vs 1.9%, p<0.001). There was a gradual risk increase for BARC 3 or 5 bleeding and DOCE as a function of the ARC-HBR score. BARC: Bleeding Academic Research Consortium; DOCE: device-oriented composite endpoints; HBR: high bleeding risk.*

Abbreviations

ARC-HBR	Academic Research Consortium for High Bleeding Risk
BARC	Bleeding Academic Research Consortium
CCS	chronic coronary syndrome
CKD	chronic kidney disease
DAPT	dual antiplatelet therapy
DOCE	device-oriented composite endpoints
eGFR	estimated glomerular filtration rate
HBR	high bleeding risk
ICH	intracranial haemorrhage
MI	myocardial infarction
NACE	net adverse composite endpoints
OAC	oral anticoagulant
PCI	percutaneous coronary intervention
ST	stent thrombosis
TLR	target lesion revascularisation
TVR	target vessel revascularisation

Introduction

Following percutaneous coronary intervention (PCI), the impact of major bleeding on prognosis is at least as pronounced as that of myocardial infarction[1,2]. Dual antiplatelet therapy (DAPT) reduces the risk of stent- and non-stent-related ischaemic adverse events in patients undergoing PCI; however, this benefit is offset (at least in part) in patients at high bleeding risk (HBR) and is directly related to the duration of DAPT. A recent study demonstrated that patients at HBR did not gain benefit from long-term DAPT irrespective of the underlying ischaemic risk, suggesting that the characterisation of bleeding risk outweighs ischaemic risk (i.e., PCI complexity) in terms of optimal DAPT duration[3].

Although several bleeding prediction scores are currently available and received a Class IIb (level A) recommendation in the 2017 European Society of Cardiology Focused Update on DAPT to characterise patients undergoing PCI[4], they afford a modest discrimination ability with an average C-statistic of approximately 0.7 to predict bleeding[5,6]. In the clinical trial setting, heterogeneous definitions of HBR have been applied across numerous studies, which may limit the interpretation and generalisability of reported data[7-9]. Against this background, the Academic Research Consortium for High Bleeding Risk (ARC-HBR), a collaboration among leading research organisations, regulatory authorities, and physician-scientists from the USA, Asia, and Europe focusing on PCI-related bleeding, developed a consensus-based definition of patients at HBR in May 2019[10]. HBR was arbitrarily defined as one-year risk of ≥4% for a Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding or ≥1% for intracranial haemorrhage (ICH). To date, data on the applicability of the ARC-HBR criteria in the real-world setting are scarce. Therefore, we validated the ARC-HBR criteria to predict bleeding outcomes using prospective data from a large cohort of unselected, consecutive patients undergoing PCI.

Editorial, see page 357

Methods

PATIENT POPULATION

All consecutive patients undergoing PCI at Bern University Hospital, Switzerland, were prospectively enrolled into the Bern PCI Registry (NCT02241291) between January 2009 and December 2016. For the present study, patients undergoing balloon angioplasty alone or implantation of bioresorbable scaffolds and those in whom ARC-HBR criteria could not be completely ascertained were excluded. The registry was approved by the institutional ethics committee. All patients provided written informed consent.

ARC-HBR CRITERIA

Some of the ARC-HBR criteria needed to be modified or were not available due to the data availability in the registry, as summarised in **Supplementary Table 1**. Major and minor ARC-HBR criteria applied in the current study are as follows: age ≥75 years (minor); oral anticoagulant or novel oral anticoagulant at discharge (major); estimated glomerular filtration rate (eGFR) <30 ml/min (major) and eGFR ≥30, <60 ml/min (minor); baseline haemoglobin <11 g/dL (major), and 11-12.9 g/dL for men and 11-11.9 g/dL for women (minor); spontaneous non-intracranial bleeding requiring hospitalisation or transfusion (major); thrombocytes at index PCI <100×10^9/L (major); non-steroidal anti-inflammatory drugs (NSAIDS) at discharge (minor); cancer history within one year prior to index PCI and/or ongoing treatment, excluding non-melanoma skin cancer (major); previous intracranial bleeding or previous stroke (major); any ischaemic stroke at any time not meeting the major criterion (minor). Definitions of the ARC-HBR criteria are provided in **Supplementary Appendix 1**. Patients were considered to be at HBR if at least one major criterion or two minor criteria were met[10]. The ARC-HBR score was calculated by adding 1 point for any major criterion and 0.5 for any minor criterion.

PROCEDURE

PCI was performed according to current guidelines[11]. Heparin (at least 5,000 IU or an initial bolus of 100 IU per kg body weight) was used for procedural anticoagulation with the aim of maintaining an activated clotting time >250 msec. The periprocedural use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. DAPT consisting of acetylsalicylic acid and a $P2Y_{12}$ inhibitor was initiated before, at the time of, or immediately after the procedure. Prasugrel was introduced as of September 2009, and ticagrelor as of November 2011. The majority of patients with chronic coronary syndrome (CCS) received clopidogrel. The routinely recommended DAPT duration was 12 months[12].

CLINICAL ENDPOINTS

The primary bleeding endpoint was bleeding defined as Bleeding Academic Research Consortium (BARC) 3 or 5[13]. Secondary endpoints, definitions, and patient follow-up are provided in **Supplementary Appendix 2**.

STATISTICAL ANALYSIS

Continuous variables were summarised as mean±standard deviation or median and interquartile range, and compared with the Student's t-test or the Mann-Whitney U test. Binary and categorical variables were calculated as frequencies (percentages) and were compared with the chi-square test or Fisher's exact test. Kaplan-Meier cumulative event curves were constructed for time-to-event variables and compared using the log-rank test. Subhazard ratio was obtained from a competing risk survival regression based on Fine and Gray's proportional subhazard model. Discrimination of the bleeding risk score was assessed by the C-statistic. Calibration was assessed by comparing predicted probabilities with the observed frequency of BARC 3 or 5 bleeding. Cox regression analysis was performed to test the prognostic significance of each component of the ARC-HBR criteria for BARC 3 or 5 bleeding and device-oriented composite endpoints (DOCE). Each component of the ARC-HBR criteria was adjusted by all components of the ARC-HBR criteria and clinically important variables reported by previous studies. For BARC 3 or 5 bleeding, female gender, body mass index, current smoker, hypertension, peripheral artery disease, acute coronary syndrome, and potent $P2Y_{12}$ at discharge, and for DOCE, age, female gender, current smoker, hypertension, peripheral artery disease, previous myocardial infarction, previous revascularisation (PCI and/or coronary artery bypass graft [CABG]), left ventricular ejection fraction, stent type (bare metal stent, first-generation drug-eluting stent), were entered into a multivariate model[5,6,14,15]. P-values were two-tailed and a value under 0.05 was considered statistically significant in all analyses. Statistical analyses were performed with R, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

PATIENTS

Of 13,748 patients enrolled into the Bern PCI Registry between January 2009 and December 2016, 12,121 patients were analysed for the present study with complete follow-up available in 11,314 (93.3%) patients at one year. Patients were excluded in case of balloon angioplasty without stent implantation (n=496), implantation of bioresorbable scaffolds (n=60), or if not all of the ARC-HBR criteria were assessable (n=1,071: missing haemoglobin [n=437], missing eGFR [n=710], missing thrombocytes [n=564], missing data on NSAIDs [n=152]).

BASELINE CHARACTERISTICS

Clinical and procedural characteristics and medication status are summarised in **Table 1**, **Supplementary Table 2** and **Supplementary Table 3**. Patients at HBR (n=4,781, 39.4%) were older and more commonly female, had more risk factors for atherosclerotic cardiovascular disease, comorbidities, CCS as an indication for PCI, and had higher PRECISE-DAPT scores compared with those without. Among HBR patients, PCI was more frequently performed in the anatomical setting of the left main and saphenous vein bypass grafts. New-generation drug-eluting stents were used in 93.4% of all patients with a lower frequency in patients at HBR. The use of potent $P2Y_{12}$ inhibitors was less frequent in patients at HBR.

ARC-HBR CRITERIA

The prevalence of ARC-HBR criteria is summarised in **Figure 1**. Age ≥75 years (31.9%), anaemia (26.4%), chronic kidney disease (CKD) (25.5%), oral anticoagulation (10.5%), and previous ICH or stroke (8.0%) were the leading ARC-HBR criteria in decreasing order. Prior spontaneous non-ICH bleeding (2.8%), thrombocytopaenia (1.3%), NSAIDS (1.7%), and active malignancy (1.9%) were rarely observed. Major CKD, major anaemia, and spontaneous non-ICH bleeding frequently overlapped with other criteria, as illustrated in **Supplementary Figure 1**. The ARC-HBR score had a C-statistic of 0.69 (95% CI: 0.66-0.71) for BARC 3 or 5 bleeding and showed

Table 1. Patient characteristics.

		HBR (n=4,781)	Non-HBR (n=7,340)	*p*-value
Age, years		75.5±10.0	62.8±10.4	<0.001
Age ≥75 years		3,026 (63.3%)	843 (11.5%)	<0.001
Female		1,644 (34.4%)	1,505 (20.5%)	<0.001
Body mass index, kg/m^2		26.7±4.9	27.8±4.5	<0.001
Current smoker		765 (16.0%)	2,502 (34.1%)	<0.001
Hypertension		3,780 (79.1%)	4,607 (62.8%)	<0.001
Diabetes mellitus		1,347 (28.2%)	1,430 (19.5%)	<0.001
Dyslipidaemia		3,125 (65.4%)	4,700 (64.0%)	0.060
Family history of coronary artery disease		972 (20.3%)	2,199 (30.0%)	<0.001
Previous myocardial infarction		932 (19.5%)	1,028 (14.0%)	<0.001
Previous PCI		1,127 (23.6%)	1,418 (19.3%)	<0.001
Previous CABG		677 (14.2%)	518 (7.1%)	<0.001
Peripheral artery disease		609 (12.7%)	361 (4.9%)	<0.001
Prior spontaneous non-ICH bleeding requiring hospitalisation or transfusion		338 (7.1%)	0 (0%)	<0.001
Active malignancy (excluding non-melanoma skin cancer) within past 12 months		234 (4.9%)	0 (0%)	<0.001
Previous ICH or previous stroke		146 (3.2%)	0 (0%)	<0.001
Any ischaemic stroke at any time not meeting the major criterion		965 (20.2%)	0 (0%)	<0.001
Left ventricular ejection fraction, %		50.6±14.9	54.2±12.3	<0.001
eGFR, ml/min/1.73 m^2		62.4±30.1	101±32.3	<0.001
eGFR ≥30, <60 ml/min/1.73 m^2		2,344 (49.0%)	314 (4.3%)	<0.001
eGFR <30 ml/min/1.73 m^2		434 (9.1%)	0 (0%)	<0.001
Haemoglobin, g/dL		12.5±2.0	14.3±1.3	<0.001
Haemoglobin 11.0-12.9 g/dL (males) or 11.0-11.9 g/dL (females)		1,362 (28.5%)	739 (10.1%)	<0.001
Haemoglobin ≤11.0 g/dL		1,095 (22.9%)	0 (0%)	<0.001
Thrombocytes × 10^9/L		226±84.8	228±63.1	<0.001
Thrombocytes <100×10^9/L		155 (3.2%)	0 (0%)	<0.001
Clinical indication for PCI				
Chronic coronary syndrome		2,356 (49.3%)	2,995 (40.8%)	<0.001
Acute coronary syndrome	Unstable angina	209 (4.4%)	380 (5.2%)	<0.001
	Non-ST-elevation myocardial infarction	1,286 (26.9%)	1,731 (23.6%)	
	ST-elevation myocardial infarction	930 (19.5%)	2,234 (30.4%)	
PRECISE-DAPT score		27.6 (11.4)	13.7 (7.4)	<0.001
Medication at discharge				
Aspirin		4,466 (93.4%)	7,187 (97.9%)	<0.001
Clopidogrel		3,449 (72.1%)	3,417 (46.6%)	<0.001
Potent P2Y$_{12}$ (prasugrel or ticagrelor)		1,180 (24.7%)	3,857 (52.5%)	<0.001
Any DAPT		4,413 (92.3%)	7,155 (97.5%)	<0.001
OAC or NOAC		1,271 (26.6%)	0 (0%)	<0.001
Any DAPT and OAC/NOAC		1,079 (22.6%)	0 (0%)	<0.001
NSAIDS		117 (2.5%)	86 (1.2%)	<0.001

Values are n (%) or mean±SD. CABG: coronary artery bypass graft; DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; HBR: high bleeding risk; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention

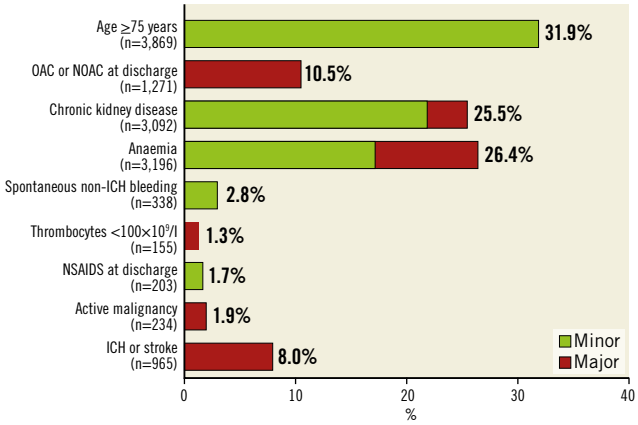
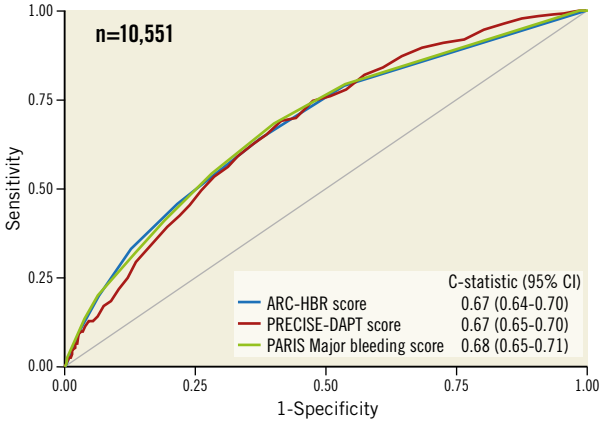


Figure 1. *Distribution of the ARC-HBR criteria. DAPT: dual antiplatelet therapy; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention*

accurate calibration **(Supplementary Figure 2)**. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the ARC-HBR score ≥1 (i.e., equivalent to one major or two minor ARC-HBR criteria) for BARC 3 or 5 bleeding at one year were 68.5%, 61.7%, 6.4%, 98.1%, and 61.9%, respectively. As an explanatory analysis, we compared the diagnostic ability and C-statistics among the ARC-HBR score, PRECISE-DAPT score, and PARIS bleeding score in patients in whom all three scores were available (n=10,551) **(Figure 2)**. The ARC-HBR criteria had higher sensitivity compared with other bleeding risk scores at the cost of lower specificity.



%	Sn	Sp	PPV	NPV	Accuracy
ARC-HBR score (≥1)	63.8	62.7	5.6	98.0	62.8
PRECISE-DAPT score (≥25)	53.1	71.3	6.0	97.8	70.7
PARIS Major bleeding score (≥8)	31.9	86.5	7.6	97.3	84.7

Figure 2. *ROC curves and diagnostic ability of bleeding prediction systems for one-year BARC 3 or 5 bleeding. BARC: Bleeding Academic Research Consortium; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; ROC: receiver operating characteristic; Sn: sensitivity; Sp: specificity*

CLINICAL OUTCOMES

Clinical outcomes at one year are summarised in **Table 2**. Compared to patients without HBR, those at HBR had an increased risk of BARC 3 or 5 bleeding (6.4% vs 1.9%, p<0.001) and DOCE (12.5% vs 6.1%, p<0.001) as well as other secondary endpoints including net adverse composite endpoints, all-cause death, cardiac death, myocardial infarction, target lesion revascularisation, definite stent thrombosis, stroke, and each BARC component. Patients at HBR had an increased risk of BARC 3 or 5 bleeding after considering all-cause death as a competing risk (hazard ratio 3.44, 95% CI: 2.80 to 4.17; p<0.001). There was a gradual risk increase for BARC 3 or 5 bleeding (0, 0.5: 1.9%, 1: 4.6%, and ≥1.5: 7.6%, p<0.001) and DOCE (0, 0.5: 6.1%, 1: 10.6%, and ≥1.5: 13.9%, p<0.001) as a function of the ARC-HBR score **(Figure 3)**. The frequency of BARC 3 or 5 bleeding and DOCE for each ARC-HBR score was: 0: 1.6% and 5.6%, 0.5: 2.9% and 7.4%, 1: 4.6% and 10.6%, 1.5: 4.9% and

Table 2. Event rates at one year.

	HBR (n=4,781)	Non-HBR (n=7,340)	*p*-value
Primary endpoint			
BARC 3 or 5 bleeding	304 (6.4%)	140 (1.9%)	<0.001
Secondary endpoints			
DOCE (cardiac death, TV-MI, TLR)	600 (12.5%)	446 (6.1%)	<0.001
NACE (cardiac death, TV-MI, TLR, BARC 3 or 5 bleeding)	923 (19.3%)	642 (8.8%)	<0.001
All-cause death	529 (11.1%)	120 (1.6%)	<0.001
Cardiac death	330 (6.9%)	92 (1.3%)	<0.001
Myocardial infarction	288 (6.0%)	270 (3.7%)	<0.001
Target vessel myocardial infarction	209 (4.4%)	210 (2.9%)	<0.001
Spontaneous myocardial infarction	156 (3.3%)	126 (1.7%)	<0.001
Any revascularisation	339 (7.1%)	522 (7.1%)	0.497
Target lesion revascularisation	191 (4.0%)	228 (3.1%)	0.002
Target vessel revascularisation	247 (5.2%)	365 (5.0%)	0.272
Non-target vessel revascularisation	148 (3.1%)	272 (3.7%)	0.209

	HBR (n=4,781)	Non-HBR (n=7,340)	*p*-value
Secondary endpoints			
Stent thrombosis (definite)	68 (1.4%)	67 (0.9%)	0.007
Acute (≤24 hours)	27 (0.6%)	29 (0.4%)	0.181
Subacute (>24 hours to 30 days)	20 (0.4%)	25 (0.3%)	0.460
Late (>30 days to 1 year)	21 (0.4%)	13 (0.2%)	0.006
Stroke	105 (2.2%)	50 (0.7%)	<0.001
Any bleeding	413 (8.6%)	229 (3.1%)	<0.001
BARC (2, 3, 5) bleeding	409 (8.6%)	219 (3.0%)	<0.001
BARC (2) bleeding	138 (3.0%)	93 (1.3%)	<0.001
BARC (3) bleeding	285 (6.2%)	135 (1.8%)	<0.001
BARC (4) bleeding	6 (0.1%)	12 (0.2%)	0.646
BARC (5) bleeding	19 (0.4%)	5 (0.1%)	<0.001

Values are n (%). BARC: Bleeding Academic Research Consortium; DOCE: device-oriented composite endpoints; NACE: net adverse composite endpoints; TLR: target lesion revascularisation; TV-MI: target vessel myocardial infarction

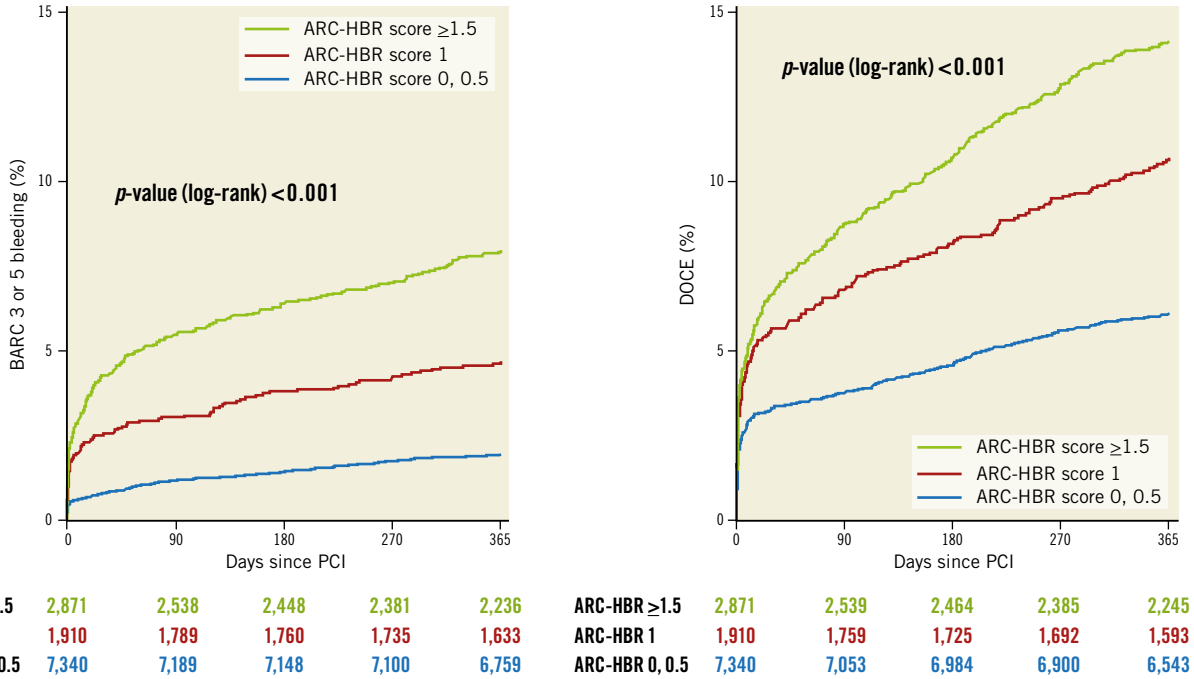


Figure 3. *Kaplan-Meier cumulative event curves for BARC 3 or 5 bleeding and DOCE at one year stratified by the ARC-HBR score. BARC: Bleeding Academic Research Consortium; DOCE: device-oriented composite endpoints; PCI: percutaneous coronary intervention*

13.0%, 2: 8.5% and 13.2%, 2.5: 9.0% and 13.6%, ≥3: 10.9% and 17.9%, respectively **(Figure 4)**. Each ARC-HBR criterion except for NSAIDS at discharge was associated with a BARC 3 or 5 bleeding risk of ≥4% **(Figure 5)**, while the bleeding risk associated with an ARC-HBR score of 0.5 or 1 was dependent on the individual criteria of the score **(Table 3)**.

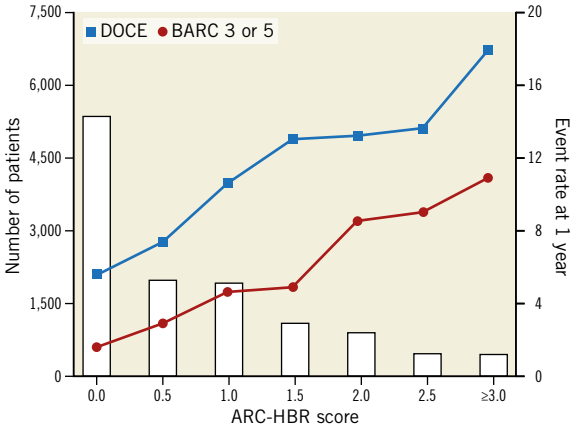


Figure 4. *Event rates according to the ARC-HBR score. BARC: Bleeding Academic Research Consortium; DOCE: device-oriented composite endpoints*

Table 3. BARC 3 or 5 bleeding rates in patients with an ARC-HBR score 1 and 0.5.

Criteria		BARC 3 or 5 bleeding
ARC-HBR score=1 (n=1,910)		
Major criteria	OAC or NOAC at discharge (n=284)	7 (2.5%)
	CKD (major) (n=13)	2 (15.4%)
	Anaemia (major) (n=151)	12 (8.0%)
	Spontaneous non-ICH bleeding (n=52)	1 (1.9%)
	Thrombocytes <100×10^9/l (n=16)	3 (18.8%)
	Active malignancy within past 12 months (n=40)	3 (7.5%)
	ICH or stroke (n=243)	7 (2.9%)
Combination of minor criteria	Age ≥75 years+CKD (minor) (n=750)	38 (5.1%)
	Age ≥75 years+anaemia (minor) (n=213)	8 (3.8%)
	Age ≥75 years+NSAIDS at discharge (n=15)	0 (0%)
	CKD (minor)+anaemia (minor) (n=106)	6 (5.7%)
	CKD (minor)+NSAIDS at discharge (n=6)	0 (0%)
	Anaemia (minor)+NSAIDS at discharge (n=21)	0 (0%)
ARC-HBR score=0.5 (n=1,982)		
Minor criteria	Age ≥75 years (n=843)	27 (3.2%)
	CKD (minor) (n=314)	15 (4.8%)
	Anaemia (minor) (n=739)	15 (2.0%)
	NSAIDS at discharge (n=86)	0 (0%)

Values are n (%). BARC: Bleeding Academic Research Consortium; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; DOCE: device-oriented composite endpoints; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention

COX REGRESSION ANALYSIS

The unadjusted and adjusted risks of individual components of the ARC-HBR criteria for BARC 3 or 5 bleeding and DOCE at one year are presented in **Table 4** and **Supplementary Table 4**, respectively. An oral anticoagulant (OAC) or novel oral anticoagulant (NOAC) at discharge and prior spontaneous non-ICH bleeding emerged as independent predictors for BARC 3 or 5 bleeding at one year, while CKD and anaemia were associated with both BARC 3 or 5 bleeding and DOCE.

Discussion

The implementation of bleeding avoidance strategies is considered relevant as bleeding contributes substantially to adverse outcomes including mortality[1,2]. Guidelines support the use of bleeding risk scores (class IIb, level A) to predict bleeding and potentially tailor antithrombotic therapies. However, these scores depend on the characteristics of patients included in the derivation cohort and are not necessarily applicable to routine clinical practice. The ARC-HBR criteria represent a new and pragmatic consensus-based approach to predict bleeding. Our study aimed to evaluate in detail the ARC-HBR criteria using an unselected PCI population consecutively enrolled at a large tertiary care centre.

Patients at HBR according to the ARC-HBR criteria were frequent (≈40%). The criteria including age ≥75 years, CKD, anaemia, oral anticoagulation, and previous ICH or stroke were frequently observed in the real-world PCI population, in line with inclusion criteria applied in previous HBR studies[7,9], while prior spontaneous non-ICH bleeding, thrombocytopaenia, NSAIDS, and active malignancy were relatively rare.

Patients at HBR had a higher risk (6.4%) of bleeding at one year as defined by BARC 3 or 5, exceeding the anticipated threshold of 4.0%. The rate of BARC 3 or 5 bleeding of 1.9% at one year in patients without HBR was comparable with results obtained from previous DAPT trials (i.e., <3.0%) with systematic exclusion of HBR patients[10]. It is noteworthy that patients fulfilling one minor criterion carried a twofold higher bleeding risk as compared with patients without HBR (2.9% vs 1.6%). Further studies should investigate whether "intermediate-risk" patients (i.e., one minor criterion) and "truly low-risk" (i.e., no criterion) should be treated equally in terms of DAPT intensity and duration.

Although the bleeding risk increased proportionally with increasing number of ARC-HBR criteria, importantly the degree of risk and prognostic value varied considerably among the ARC-HBR criteria. In the ARC-HBR consensus document, a major criterion is defined as any criterion that, in isolation, confers a BARC 3 or 5 bleeding risk of ≥4% at one year, and a minor criterion is defined as any criterion that, in isolation, confers increased bleeding risk with a BARC 3 or 5 bleeding rate of <4% at one year[10]. Although this analysis includes only a limited number of patients with each criterion being present in isolation, not all criteria met the expectation of predicting a BARC 3 or 5 bleeding risk ≥4% (major) or <4% (minor). Patients who fulfilled only "anticipated long-term use of an oral anticoagulant" (major criterion) had a BARC 3 or 5 bleeding rate of 2.5%,

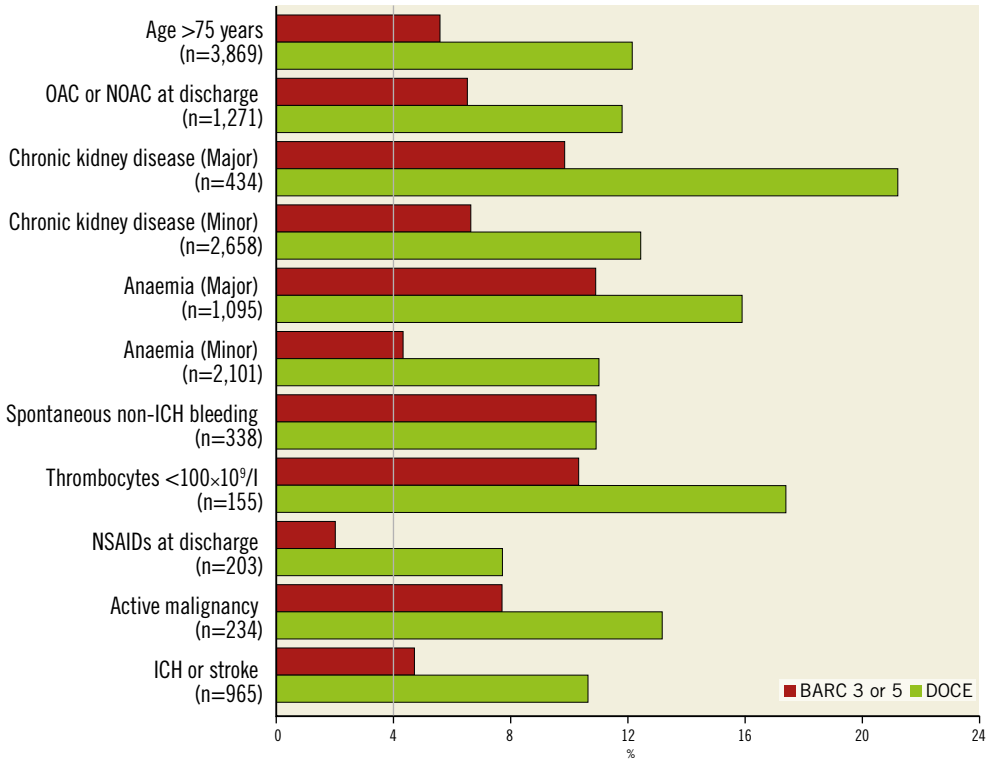


Figure 5. *Event rates at one year according to ARC-HBR criteria. BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; DOCE: device-oriented composite endpoints; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention*

while patients with "eGFR ≥30, <60 ml/min/1.73 m²" (minor criterion) had a bleeding risk of 4.8% at one year. Our data suggest that the bleeding risk associated with an ARC-HBR score 0.5 or 1 was dependent on the individual criteria composing the score. Physicians should note that an individualised approach based on the applied criteria may be needed in patients with an ARC-HBR score 0.5 or 1.

Table 4. Cox analysis for BARC 3 or 5 bleeding.

		Univariate		Multivariate model 1		Multivariate model 2	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age ≥75 years		2.15 (1.79-2.59)	<0.001	1.82 (1.47-2.26)	<0.001	1.20 (0.95-1.53)	0.125
OAC or NOAC at discharge		2.06 (1.62-2.61)	<0.001	2.14 (1.65-2.77)	<0.001	1.87 (1.44-2.43)	<0.001
Chronic kidney disease	eGFR ≥60 ml/min/1.73 m²	reference		reference		reference	
	eGFR ≥30, <60 ml/min/1.73 m²	2.80 (2.29-3.40)	<0.001	2.52 (2.01-3.17)	<0.001	1.82 (1.41-2.36)	<0.001
	eGFR <30 ml/min/1.73 m²	4.47 (3.22-6.19)	<0.001	3.88 (2.70-5.59)	<0.001	1.98 (1.33-2.95)	0.001
Anaemia	≥13.0 g/dL (males) or 12.0 g/dL (females)	reference		reference		reference	
	11.0-12.9 g/dL (males) or 11.0-11.9 g/dL (females)	1.69 (1.33-2.16)	<0.001	1.58 (1.23-2.04)	<0.001	1.32 (1.02-1.71)	0.036
	≤11.0 g/dL	4.60 (3.69-5.74)	<0.001	3.89 (3.04-4.97)	<0.001	2.64 (2.01-3.47)	<0.001
Spontaneous non-ICH bleeding		3.33 (2.38-4.66)	<0.001	2.94 (2.07-4.19)	<0.001	1.89 (1.31-2.73)	0.001
Thrombocytes <100×10⁹/l		3.30 (2.00-5.43)	<0.001	2.62 (1.47-4.66)	0.001	1.53 (0.85-2.75)	0.154
NSAIDS at discharge		0.53 (0.20-1.41)	0.202	0.42 (0.14-1.31)	0.136	0.47 (0.15-1.47)	0.197
Active malignancy within past 12 months		2.31 (1.44-3.70)	0.001	2.20 (1.35-3.59)	0.001	1.49 (0.90-2.42)	0.127
ICH or stroke		1.32 (0.97-1.80)	0.074	1.16 (0.83-1.61)	0.382	0.96 (0.69-1.33)	0.785

Of the study patients, 96.4% (11,689/12,121) were entered into the multivariable model for BARC 3 or 5 bleeding. In model 1, each criterion was adjusted by the following variables. In model 2, each criterion was adjusted by the following variables and all components of the ARC-HBR criteria. Variables: female gender, body mass index, current smoker, hypertension, peripheral artery disease, acute coronary syndrome, potent $P2Y_{12}$ at discharge. BARC: Bleeding Academic Research Consortium; CI: confidence interval; DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; HR: hazard ratio; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention

Consistent with previous analyses[16], HBR patients incurred an increased risk not only of bleeding but also of multiple ischaemic events including cardiac death, myocardial infarction and stent thrombosis. HBR patients had more frequent risk factors correlating with atherosclerotic disease burden such as diabetes mellitus and previous revascularisation, explaining in part the excess in ischaemic events. The dilemmatic dual impact of certain clinical characteristics such as renal failure was consistent with one of our previous analyses on the same cohort[16] as well as previous studies[6,17]. Although many operators are still reluctant to use newer-generation DES in HBR patients, there was only a small difference between groups in this cohort (92.0% vs 94.3%), which may not be applied as an explanation for an increased risk of ischaemic events. Patients categorised as HBR may represent a frailer population, a characteristic that was not specifically assessed in the Bern PCI Registry, i.e., a notion supported by a higher frequency of non-cardiac mortality (4.2% vs 0.3%).

The ARC-HBR criteria categorised approximately 40% of an unselected PCI population as HBR, while fewer patients were identified as HBR by other bleeding risk scores. Specifically, 26.9% of patients fulfilled the PRECISE-DAPT score ≥25 and 14.5% fulfilled the PARIS bleeding score ≥8. Accordingly, the ARC-HBR criteria were more sensitive than others (ARC-HBR score ≥1: 63.8% vs PRECISE-DAPT score ≥25: 53.1% vs PARIS bleeding score ≥8: 31.9%) at the cost of specificity (62.7% vs 71.3% vs 86.5%). The C-statistics were comparable among the three bleeding prediction systems. In contrast to the consistently high negative predictive value, a limited positive predictive value represents a common limitation of clinical bleeding prediction tools, although an impact of a relatively low rate of bleeding events on positive predictive value needs to be considered. In light of a limited performance of bleeding prediction systems and the large overlap with ischaemic events in HBR patients, it remains of the utmost importance to conduct randomised controlled trials (RCTs) investigating the impact of score-based treatment strategies.

To date, only one study has attempted to validate the ARC-HBR criteria: it suggested that patients at HBR had a higher bleeding rate and that each individual ARC-HBR criterion was associated with a major bleeding risk >4% at one year[18]. However, the analysis did not include BARC bleeding as endpoints and was carried out in an Asian (Japanese) population. In the present study, we confirmed consistent results with the BARC bleeding definition using a large PCI data set of an European population.

Limitations

First, the single-centre design of this study may limit the generalisability of our findings. Second, four ARC-HBR criteria were not applicable and three needed to be substantially modified due to the data availability in the registry, which might hinder a complete review of criteria and precise estimates of the bleeding risk for each HBR criterion in isolation as well as potential cumulative effects, although missing criteria in the present study appear to be rare. Lastly, DAPT duration and intensity cannot be considered due to the nature of the observational study design. The results need to be interpreted against the background of a routine 12-month DAPT duration determined by operator's discretion in most patients, while bleeding risk associated with oral anticoagulation might be underestimated due to the shortened duration of DAPT in patients with triple therapy (i.e., DAPT and OACs).

Conclusions

Patients at HBR defined by the ARC-HBR criteria were as frequent as 40% and had a higher risk not only of BARC 3 or 5 bleeding but also of ischaemic events. The bleeding risk was proportional to the risk score and related to its individual components. The low positive predictive value of the ARC-HBR criteria for BARC 3 or 5 bleeding remains a notable limitation.

Impact on daily practice

The application of the ARC-HBR criteria to identify BARC 3 or 5 bleeding at one year in patients undergoing PCI carries a high negative but low positive predictive value. The bleeding risk was related to its individual components. Physicians should note that an individualised approach may be needed based on the applied criteria.

Conflict of interest statement

Y. Ueki reports personal fees from Infraredex, outside the submitted work. S. Bär reports grants from Medis medical imaging systems, outside the submitted work. S. Stortecky reports grants from Edwards Lifesciences, Medtronic and Abbott Vascular, grants and personal fees from Boston Scientific, and personal fees from BTG, outside the submitted work. T. Pilgrim reports grants and personal fees from Biotronik and Symetis/Boston Scientific, and grants from Edwards Lifesciences, outside the submitted work. M. Valgimigli reports grants and personal fees from Terumo, Abbott and AstraZeneca, grants from Medicure, personal fees from Chiesi, Bayer, Daiichi Sankyo, Amgen, Alvimedica, and Biosensors, outside the submitted work. S. Windecker reports grants from Abbott, Amgen, Bayer, Boston Scientific, Biotronik, BMS, Edwards Lifesciences, Medtronic, Sinomed, and Polares, outside the submitted work. L. Räber reports grants and personal fees from Abbott Vascular, Biotronik, Sanofi and Regeneron, personal fees from Amgen, AstraZeneca, Bayer, CSL Behring and Occlutech, and grants from HeartFlow, outside the submitted work. The other authors have no conflicts of interest to declare.

References

1. Généreux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Yadav M, Francese DP, Palmerini T, Kirtane AJ, Litherland C, Mehran R, Stone GW. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2015;66:1036-45.

2. Baber U, Dangas G, Chandrasekhar J, Sartori S, Steg PG, Cohen DJ, Giustino G, Ariti C, Witzenbichler B, Henry TD, Kini AS, Krucoff MW, Gibson CM, Chieffo A, Moliterno DJ, Weisz G, Colombo A, Pocock S, Mehran R. Time-Dependent Associations Between Actionable Bleeding,

Coronary Thrombotic Events, and Mortality Following Percutaneous Coronary Intervention: Results From the PARIS Registry. *JACC Cardiovasc Interv.* 2016; 9:1349-57.

3. Costa F, Van Klaveren D, Feres F, James S, Raber L, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M; PRECISE-DAPT Study Investigators. Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. *J Am Coll Cardiol.* 2019;73:741-54.

4. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2018;39:213-60.

5. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet.* 2017;389:1025-34.

6. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, Krucoff MW, Moliterno DJ, Kirtane AJ, Stone GW, Colombo A, Chieffo A, Kini AS, Witzenbichler B, Weisz G, Steg PG, Pocock S. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. *J Am Coll Cardiol.* 2016;67: 2224-34.

7. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, Lipiecki J, Richardt G, Iniguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC; LEADERS FREE Investigators. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *N Engl J Med.* 2015;373:2038-47.

8. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrié D, Hovasse T, Garot P, El Mahmoud R, Spaulding C, Helft G, Diaz Fernandez JF, Brugaletta S, Pinar-Bermudez E, Mauri Ferre J, Commeau P, Teiger E, Bogaerts K, Sabate M, Morice MC, Sinnaeve PR; SENIOR investigators. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet.* 2018;391:41-50.

9. Ariotti S, Adamo M, Costa F, Patialiakas A, Briguori C, Thury A, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Ferlini M, Vranckx P, Valgimigli M; ZEUS Investigators. Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?: A Pre-Specified Analysis From the ZEUS Trial. *JACC Cardiovasc Interv.* 2016;9:426-36.

10. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Laschinger J, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock S, Price MJ, Rao SV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RW, Krucoff MW, Morice MC. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J.* 2019;40:2632-53.

11. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541-619.

12. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J.* 2010;31:2501-55.

13. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011; 123:2736-47.

14. Yeh RW, Kereiakes DJ, Steg PG, Cutlip DE, Croce KJ, Massaro JM, Mauri L; DAPT Study Investigators. Lesion Complexity and Outcomes of Extended Dual Antiplatelet Therapy After Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2017;70:2213-23.

15. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, Pencina MJ, Piccini JP, Peterson ED. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J.* 2015;36:3258-64.

16. Ueki Y, Karagiannis A, Zanchin C, Zanchin T, Stortecky S, Koskinas KC, Siontis GCM, Praz F, Otsuka T, Hunziker L, Heg D, Moschovitis A, Seiler C, Billinger M, Pilgrim T, Valgimigli M, Windecker S, Räber L. Validation of High-Risk Features for Stent-Related Ischemic Events as Endorsed by the 2017 DAPT Guidelines. *JACC Cardiovasc Interv.* 2019;12:820-30.

17. Kwok CS, Tiong D, Pradhan A, Andreou AY, Nolan J, Bertrand OF, Curzen N, Urban P, Myint PK, Zaman AG, Loke YK, Mamas MA. Meta-Analysis of the Prognostic Impact of Anemia in Patients Undergoing Percutaneous Coronary Intervention. *Am J Cardiol.* 2016;118:610-20.

18. Natsuaki M, Morimoto T, Shiomi H, Yamaji K, Watanabe H, Shizuta S, Kato T, Ando K, Nakagawa Y, Furukawa Y, Tada T, Nagao K, Kadota K, Toyofuku M, Kimura T. Application of the Academic Research Consortium High Bleeding Risk Criteria in an All-Comers Registry of Percutaneous Coronary Intervention. *Circ Cardiovasc Interv.* 2019;12:e008307.

Supplementary data

Supplementary Appendix 1. Clinical endpoints and definitions.

Supplementary Appendix 2. Patient follow-up.

Supplementary Figure 1. Overlap of ARC-HBR criteria.

Supplementary Figure 2. Calibration plot of the ARC-HBR score for BARC 3 or 5 bleeding at one year.

Supplementary Table 1. Comparison of definitions between the ARC-HBR criteria and the present study.

Supplementary Table 2. Procedural characteristics.

Supplementary Table 3. Medication at one year.

Supplementary Table 4. Cox analysis for DOCE.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00052

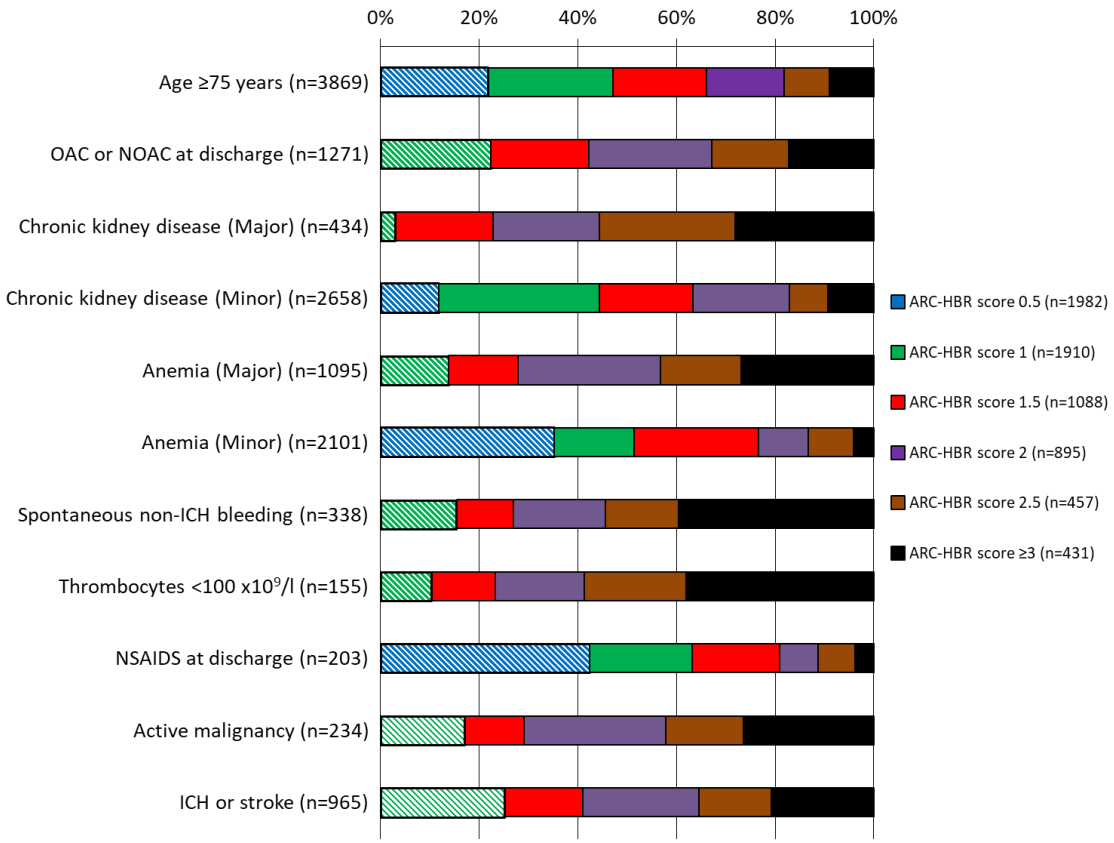
Supplementary data

Supplementary Appendix 1. Clinical endpoints and definitions

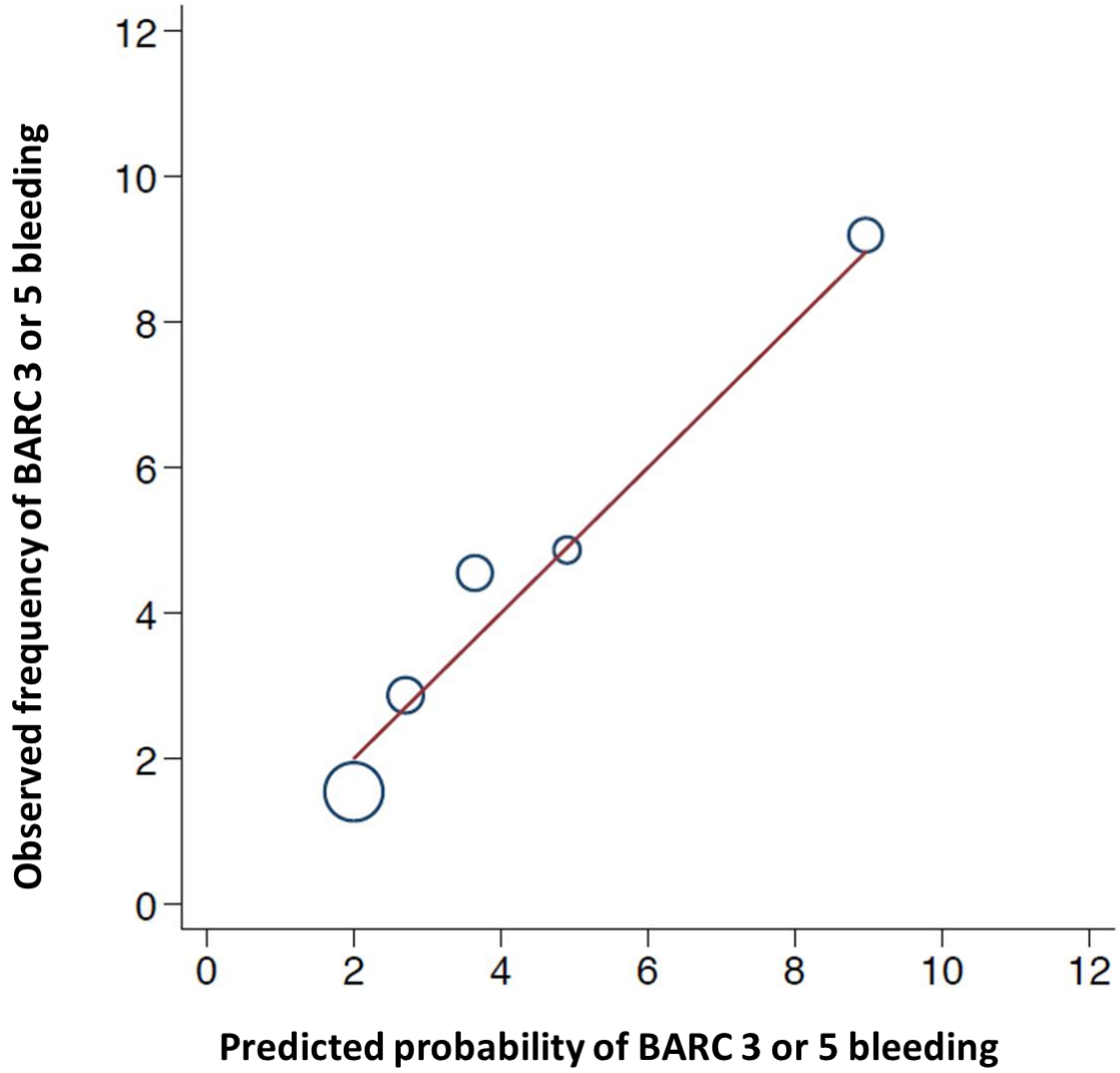
A clinical events committee consisting of two cardiologists (and a third referee in case of disagreement) adjudicated all events against the original source documents. Secondary endpoints were: the device-oriented composite endpoints (DOCE), defined as a composite of cardiac death, target vessel myocardial infarction (TV-MI), and target lesion revascularisation (TLR); the net adverse composite endpoints (NACE), defined as cardiac death, TV-MI, TLR, and BARC 3 or 5 bleeding; all-cause death; cardiac death; any myocardial infarction (MI); TV-MI; any repeat revascularisation; TLR; target vessel revascularisation (TVR); non-TVR; definite stent thrombosis (ST); stroke; any bleeding; and BARC 2, 3, or 5 bleeding. Cardiac death was defined as any death caused by an immediate cardiac cause, procedure-related mortality, and death of unknown cause. MI was defined according to the modified historical definition. ST was classified according to the Academic Research Consortium criteria. Stroke was defined as rapid development of clinical signs of focal or global disturbance of cerebral function lasting >24 hours with imaging evidence of acute, clinically relevant ischaemic brain lesion. Ischaemic cerebral infarctions with conversion to haemorrhage were categorised as stroke. Intracerebral haemorrhages were defined as rapid development of clinical signs of focal or global disturbance of cerebral function and imaging evidence of clinically relevant intracerebral bleeding. Spontaneous bleeding was defined as a history of previous clinically significant bleeding requiring medical attention [5]. Ongoing treatment of cancer was defined as planning for surgery or currently undergoing oncological systemic therapy (i.e., chemotherapy, hormone, and biological therapy) and/or radiation at index PCI.

Supplementary Appendix 2. Patient follow-up

Patients were systematically and prospectively followed throughout one year to assess death, myocardial infarction (MI), cerebrovascular accidents, revascularisation, stent thrombosis (ST), bleeding complications, re-hospitalisation and medical treatment. A health questionnaire was sent to all living patients with questions on re-hospitalisation and adverse events, followed by telephone contact in case of missing response. General practitioners and referring cardiologists were contacted as necessary for additional information. For patients treated for adverse events at other medical institutions, external medical records, discharge letters, and coronary angiography documentation were systematically collected and reviewed.



Supplementary Figure 1. Overlap of ARC-HBR criteria.
Diagonal line depicts patients fulfilling each criterion in isolation.
DAPT: dual antiplatelet therapy; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention



Supplementary Figure 2. Calibration plot of the ARC-HBR score for BARC 3 or 5 bleeding at one year.

Calibration was examined by dividing patients into quintiles according to their predicted risk. The mean predicted risk per quintile group was subsequently plotted against the observed risk per quintile group. Size of the circle depicts the sample size of each quintile group.

BARC: Bleeding Academic Research Consortium

Supplementary Table 1. Comparison of definitions between the ARC-HBR criteria and the present study.

ARC-HBR criteria	Present study	Category	Comments
Age ≥75	Age ≥75 years	Minor	Identical
Anticipated use of long-term oral anticoagulation	Oral anticoagulant or novel oral anticoagulant at discharge	Major	Modified
Severe or end-stage CKD (eGFR <30 mL/min)	eGFR <30 ml/min or haemodialysis	Major	Modified
Moderate CKD (eGFR 30–59 mL/min)	eGFR ≥30, <60 ml/min	Minor	Identical
Haemoglobin <11 g/dL	Haemoglobin at index PCI <11g/dL	Major	Identical
Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women	Haemoglobin at index PCI 11–12.9 g/dL for men and 11–11.9 g/dL for women	Minor	Identical
Spontaneous non-intracranial bleeding requiring hospitalisation or transfusion in the past 6 months or at any time, if recurrent	Spontaneous non-intracranial bleeding requiring hospitalisation or transfusion	Major	Modified
Spontaneous non-intracranial bleeding requiring hospitalisation or transfusion within the past 12 months not meeting the major criterion		Minor	Not available
Moderate or severe baseline thrombocytopaenia (platelet count <100 $\times 10^9$/L)	Thrombocytes at index PCI <100 $\times 10^9$/L	Major	Identical
Chronic bleeding diathesis		Major	Not available
Liver cirrhosis with portal hypertension		Major	Not available
Long-term use of oral NSAIDs or steroids	NSAIDS at discharge	Minor	Modified
Active malignancy (excluding non-melanoma skin cancer) within the past 12 months	Cancer history within 1 year prior to index PCI or ongoing treatment, excluding non-melanoma skin cancer	Major	Identical
Previous spontaneous ICH (at any time) Previous traumatic ICH within the past 12 months Presence of a bAVM	Previous stroke or previous ICH	Major	Modified

Moderate or severe ischaemic stroke within the past 6 months			
Any ischaemic stroke at any time not meeting the major criterion		Minor	Not available
Planned non-deferrable non-cardiac major surgery on DAPT		Major	Not available
Recent major surgery or major trauma within 30 days before PCI		Major	Not available

bAVM: brain arteriovenous malformation; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; ICH: intracranial haemorrhage; PCI: percutaneous coronary intervention

Supplementary Table 2. Procedural characteristics.

	HBR (n=4,781)	Non-HBR (n=7,340)	*p*-value
Target lesion coronary artery			
Left main artery	328 (6.9%)	203 (2.8%)	<0.001
Left anterior descending artery	2,440 (51.0%)	3,957 (53.9%)	0.002
Left circumflex artery	1,545 (32.3%)	2,377 (32.4%)	0.940
Right coronary artery	1,777 (37.2%)	2,697 (36.7%)	0.640
Bypass graft	234 (4.9%)	165 (2.3%)	<0.001
Number of lesions			0.160
1	2,596 (54.3%)	4,095 (55.8%)	
2	1,409 (29.5%)	2,136 (29.1%)	
≥3	776 (16.2%)	1,109 (15.1%)	
Lesion type			
In-stent restenosis	238 (5.0%)	354 (4.8%)	0.700
Thrombus	630 (13.2%)	1,807 (24.6%)	<0.001
Chronic total occlusion	161 (3.4%)	300 (4.1%)	0.041
Number of stents			0.160
1	1,995 (41.7%)	3,045 (41.5%)	
2	1,385 (29.0%)	2,235 (30.4%)	
≥3	1,401 (29.3%)	2,060 (28.1%)	
Stent type			<0.001
New-generation DES	4,397 (92.0%)	6,918 (94.3%)	
First-generation DES	25 (0.5%)	34 (0.5%)	
Bare metal stent	359 (7.5%)	388 (5.3%)	
Total device length (mm)	42.5±28.6	41.6±27.4	0.060
Mean stent diameter (mm)	3.0±0.6	3.0±0.4	0.250
Bifurcation with two stents implanted	283 (5.9%)	437 (6.0%)	0.940

Values are n (%) or mean±SD.

DES: drug-eluting stents; HBR: high bleeding risk

Supplementary Table 3. Medication at one year.

	HBR (n=4,781)	Non-HBR (n=7,340)	*p*-value
Aspirin	3,282 (68.6%)	6,294 (85.7%)	<0.001
Clopidogrel	1,084 (22.7%)	1,456 (19.8%)	<0.001
Potent $P2Y_{12}$ (prasugrel or ticagrelor)	425 (8.9%)	1,946 (26.5%)	<0.001
Any DAPT	1,233 (25.8%)	3,086 (42.0%)	<0.001
OAC or NOAC	1,061 (22.2%)	219 (3.0%)	<0.001
Any DAPT and OAC/NOAC	52 (1.1%)	8 (0.1%)	<0.001

Values are n (%).

DAPT: dual antiplatelet therapy; HBR: high bleeding risk; NOAC: novel oral anticoagulant; OAC: oral anticoagulant

Supplementary Table 4. Cox analysis for DOCE.

	Univariate		Multivariate model 1		Multivariate model 2	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age ≥75 years	1.79 (1.58-2.02)	<0.001	1.48 (1.27-1.72)	<0.001	1.23 (1.03-1.46)	0.020
OAC or NOAC at discharge	1.46 (1.23-1.73)	<0.001	1.06 (0.84-1.33)	0.626	1.06 (0.85-1.33)	0.602
Chronic kidney disease						
eGFR ≥60 ml/min/1.73 m^2	reference		reference		reference	
eGFR ≥30, <60 ml/min/1.73 m^2	1.85 (1.62-2.12)	<0.001	1.33 (1.11-1.60)	0.002	1.32 (1.10-1.59)	0.003
eGFR <30 ml/min/1.73 m^2	3.39 (2.72-4.22)	<0.001	2.30 (1.69-3.14)	<0.001	2.06 (1.50-2.84)	<0.001
Anaemia						
≥13.0 g/dL (males) or 12.0 g/dL (females)	reference		reference		reference	
11.0-12.9 g/dL (males) or 11.0-11.9 g/dL (females)	1.57 (1.35-1.82)	<0.001	1.37 (1.15-1.63)	<0.001	1.32 (1.10-1.57)	0.002
≤11.0 g/dL	2.38 (2.01-2.82)	<0.001	1.73 (1.39-2.15)	<0.001	1.57 (1.25-1.99)	<0.001
Spontaneous non-ICH bleeding	1.30 (0.93-1.80)	0.121	0.76 (0.48-1.21)	0.246	0.63 (0.40-1.00)	0.052
Thrombocytes <100 x10^9/l	2.25 (1.53-3.29)	<0.001	1.60 (0.97-2.63)	0.065	1.29 (0.78-2.14)	0.320
NSAIDS at discharge	0.80 (0.47-1.35)	0.396	0.74 (0.40-1.38)	0.342	0.74 (0.40-1.38)	0.345
Active malignancy within past 12 months	1.65 (1.15-2.36)	0.006	1.49 (0.99-2.25)	0.054	1.33 (0.88-2.02)	0.174
ICH or stroke	1.26 (1.03-1.55)	0.026	0.91 (0.70-1.18)	0.480	0.90 (0.70-1.17)	0.451

Of the study patients, 89.6% (10,856/12,121) were entered into the multivariable model for DOCE.

In model 1, each criterion was adjusted by the following variables. In model 2, each criterion was adjusted by the following variables and all components of the ARC-HBR criteria. Variables: age, female gender, current smoker, hypertension, peripheral artery disease, previous myocardial infarction, previous revascularisation (percutaneous coronary intervention and/or coronary artery bypass graft), left ventricular ejection fraction, stent type (bare metal stent, first-generation drug-eluting stent).

BARC: Bleeding Academic Research Consortium; CI: confidence interval; DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; NOAC: novel oral anticoagulant; HR: hazard ratio; ICH: intracranial haemorrhage; OAC: oral anticoagulant; PCI: percutaneous coronary intervention