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CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk

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Aims To validate the set of clinical and biochemical criteria proposed by consensus by the Academic Research Consortium (ARC) for High Bleeding Risk (HBR) for the identification of HBR patients. These criteria were categorized into *major and minor*, if expected to carry in isolation, respectively, ≥4% and <4% Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding risk within 1-year after percutaneous coronary intervention (PCI). High bleeding risk patients are those meeting at least 1 major or 2 minor criteria.

Methods and results All patients undergoing PCI at Bern University Hospital, between February 2009 and September 2018 were prospectively entered into the Bern PCI Registry (NCT02241291). Age, haemoglobin, platelet count, creatinine, and use of oral anticoagulation were prospectively collected, while the remaining HBR criteria except for planned surgery were retrospectively adjudicated. A total of 16 580 participants with complete ARC-HBR criteria were included. After assigning 1 point to each major and 0.5 point to each minor criterion, we observed for every 0.5 score increase a step-wise augmentation of BARC 3 or 5 bleeding rates at 1 year ranging from 1.90% among patients fulfilling no criterion, through 4.01%, 5.98%, 7.42%, 8.60%, 12.21%, 12.29%, and 17.64%. All major and five out of six minor criteria, conferred in isolation a risk for BARC 3 or 5 bleeding at 1 year exceeding 4% at the upper limit of the 95% confidence intervals.

Conclusion All major and the majority of minor ARC-HBR criteria identify in isolation patients at HBR.

Keywords Academic Research Consortium • Bleeding • Percutaneous coronary intervention • Validation

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Introduction

Over the last four decades, percutaneous coronary intervention (PCI) has reduced the risk of cardiac adverse events and improved quality of life among patients with coronary artery disease.[1] Yet, this benefit has come at expenses of higher peri- and post-procedural bleeding rates.[2] Mounting evidence indicates that bleeding events, even if *minor*, impact quality of life,[3] health care costs,[4] and mortality.[5–7]

In response to the lack of a widely accepted outline for computing bleeding risk among patients undergoing PCI, the Academic Research Consortium (ARC) for High Bleeding Risk (HBR) has recently offered a new framework for the identification of patients at HBR.[8] A set of clinical and biochemical criteria, which were previously shown to confer heightened bleeding risk, have been proposed by consensus.[8] These criteria were further categorized into *major*, if expected to carry in isolation at least 4% Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding risk within 12 months after PCI, or *minor*, if expected to confer lower than major bleeding risks.[8] Patients at HBR were defined as those meeting at least 1 major or 2 minor criteria.[8] Recent data from the CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) registry cohort-2 indicate that ARC-HBR criteria identify an HBR population.[9] However, only a selected and sometimes modified set of criteria was investigated and no information is available on the contribution of each criterion on the incidence of BARC 3 or 5 bleeding at 1 year.[9] These criteria, generated in the context of a collaboration among leading research organizations, regulatory authorities, and physician–scientists from the USA, Asia, and Europe, are meant to inform patient selection for clinical practice or future clinical trials as well as the regulatory pathways for both drugs and devices.

We therefore sought to provide the first validation of the originally proposed ARC-HBR consensus definition in a large and unselected PCI cohort.

Methods

All consecutive patients undergoing PCI at Bern University Hospital, Switzerland, between February 2009 and September 2018 were prospectively entered into the CARDIOBASE Bern PCI Registry (ClinicalTrials.gov. Unique identifier: NCT02241291). The registry complied with the Declaration of Helsinki and was approved by the institutional ethics committee.[10] Dual antiplatelet therapy (DAPT) was initiated before, at the time, 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 received clopidogrel. The routinely recommended DAPT duration was 12 months for all acute or chronic coronary syndrome patients until August 2017, unless high bleeding risk features were deemed present, including concomitant oral anticoagulation, which mandated DAPT not to exceed a duration of 6 months. From August 2017, the routinely recommended DAPT duration for chronic coronary syndrome patients became 6 months. Patients were contacted post-discharge during any unscheduled hospital visit, during planned hospital visits (e.g. staged procedure), and finally at 1 year after index PCI. Survival data were obtained from hospital records and municipal civil registries. A health questionnaire was sent to all living patients with questions on rehospitalization and adverse events, including bleeding occurrences, followed by telephone contact in case of missing response. General practitioners and referring cardiologists were contacted as necessary for additional information.

Clinical endpoints and definitions

The primary bleeding endpoint was the composite of BARC type 3 or 5 from intervention to 1 year.[11] Pre-specified secondary endpoints and endpoint definitions are in the Supplementary material online, *Appendix*. A clinical event committee blinded to outcome data adjudicated all events using original source documents (Supplementary material online, *Appendix*).

Academic Research Consortium for High Bleeding Risk criteria

The fulfilment of one or more originally proposed ARC-HBR criterion/a without adaptations was screened for each included patient (Supplementary material online, *Table S1*). Age, haemoglobin, platelet count, creatinine value, and anticipated use of long-term oral anticoagulation were prospectively collected in the database. All other HBR criteria except for planned surgery on DAPT were assessed retrospectively from electronic clinical records by trained study personnel, at variance with a prior report applying only some and largely modified criteria in a smaller sample of the Bern-PCI database.[12] For the generation of the ARC-HBR score, we assigned 1 point to each adjudicated major criterion and 0.5 point to each adjudicated minor criterion. In a random sample of 597 patients, ARC-HBR criteria were independently re-adjudicated by a different observer which provided at least 98% consistency (Supplementary material online, *Table S2*).

Statistical analysis

Baseline and procedural characteristics, medications, and ARC-HBR criteria are shown with means and standard deviations (SD) or counts with percentages (*P*-values from *t*-tests, Fisher's tests or chi-square tests as appropriate, comparing ACR-HBR vs. non-ARC-HBR patients). Time-to-event analyses were used for clinical outcomes. Patients were censored at 1-year follow-up or at the time of last contact if they withdrew consent or were lost to follow-up after hospital discharge. Cox regression and Kaplan–Meier cumulative event curves were used to compare ARC-HBR vs. non-ARC-HBR patients and single criteria vs. reference categories (Wald chi-square tests). A landmark at 30 days of follow-up time was used to compare event rates within 30 days and from 31 days to 1 year. Two-sided Z-tests were used to assess whether the cumulative incidences of 1-year BARC 3 or 5 bleeding did not include the major criteria threshold of 4%. Adjustment for the other ARC-HBR criteria using multivariable Cox's regression models was implemented to test whether the single criteria remain predictive for 4% BARC 3 or 5 bleeding. Competing risk with all-cause death time-to-event analyses were also conducted as sensitivity analyses. A random subsample of patients was re-assessed for ARC-HBR criteria and the agreement with the first assessor shown with the Gwet's agreement coefficients. Supplementary analyses were conducted using the Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding criteria and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) moderate or severe bleeding criteria as the outcome. Analyses were done in Stata Release 16.1 (StataCorp LP, College Station, TX).

Results

Patient population

Between February 2009 and September 2018, 17 220 consecutive patients were included in the Bern PCI Registry and 16 580 participants had complete data for the ARC-HBR criteria and were included in the current analysis (Supplementary material online, *Table S3*). Mean age was 67.8 years (± 12.0), 74.5% were men and 9379 or 56.6% had an acute coronary syndrome at presentation (Supplementary material online, *Table S4*). The majority of patients received one or more drug-eluting stent at the time of intervention and 26.2% underwent multivessel PCI (Supplementary material online, *Table S5*). At discharge, DAPT, oral anticoagulation (OAC) plus a single antiplatelet agent or a combination of DAPT and OAC was implemented in 95.2%, 11.8%, and 10.0% of the patients, whereas at 1 year the corresponding figures were 65.4%, 13.7%, and 1.7%, respectively (Supplementary material online, *Table S6*). A total of 15 481 (93.4%) patients had 1-year complete information, whereas in the remaining 1099 patients, who refused further participation ($n = 524$ or 3.2%) or were lost to follow-up ($n = 575$ or 3.5%), the median follow-up was 2 (1–5) days.

Academic Research Consortium for High Bleeding Risk population

Altogether, 5752 (34.7%) patients were HBR as defined by ≥1 major ($n = 3876$ or 23.4%) or ≥2 ($n = 3109$ or 18.8%) minor criteria. Among the non-HBR population, 3364 (20.3%) and 7464 (45%) patients fulfilled a single minor or no criterion, respectively (Supplementary material online, *Table S1* and *Figure S1*).

High bleeding risk compared with non-HBR patients were on average 11 years older, less frequently males, had lower BMI and less frequently smokers, but more frequently history of hypertension, diabetes mellitus, myocardial infarction, PCI, and coronary artery bypass grafting and presented with lower left ventricular ejection fraction; they underwent more frequently intervention for left main or coronary artery bypass lesions and received more frequently intra-aortic balloon pump or left ventricular assist devices during PCI (Supplementary material online, *Tables S4* and *S5*).

Clinical outcomes

A total of 663 BARC 3 or 5 bleeding occurred, including 406 (7.9%) and 257 (2.5%) in HBR and non-HBR population, respectively (HR 3.18, 95%CI 2.72–3.72, $P < 0.001$), owing to higher rates of BARC 3 and BARC 5 instances in the former group (Supplementary material online, *Table S7*). At landmark analysis, a three-fold fold increase of BARC 3 or 5 bleeding rates was observed among HBR patients within 30 days (4.06% vs. 1.18%; HR 3.45, 95%CI 2.76–4.29, $P < 0.001$) and from 30 days to 1 year (3.96% vs. 1.36%; HR 2.95, 95%CI 2.36–3.68, $P < 0.001$) (Supplementary material online, *Table S7*). The rates of TIMI major or minor and GUSTO moderate to severe bleeding were also increased among HBR both within the first 30 days and thereafter up to 1 year (Supplementary material online, *Table S7*). Stratified analysis based on HBR category with respect to cardiovascular ischaemic or fatal endpoints provided consistent results (Supplementary material online, *Table S7*).

Academic Research Consortium for High Bleeding Risk score

The average ARC-HBR score was 0.66 (± 0.82) in the overall cohort, 1.61 (± 0.69) in the HBR and 0.16 (±0.23) in non-HBR populations.

There was a step-wise increase of BARC 3 or 5 bleeding rates as a function of the ARC-HBR score with event rates increasing from 1.90% at 1 year among patients fulfilling no criterion, through 4.01%, 5.98%, 7.42%, 8.60%, 12.21%, 12.29%, and 17.64% for every 0.5 increase (*Figures 1 and 2*), with an Harrell's C-index of 0.676 (95%CI 0.656–0.696). A consistent pattern was observed when only major criteria were cumulatively added (*Figure 1*). The rate of BARC 3 or 5 bleeding increased from 4.01% (95%CI 3.36–4.77) among patients with a single minor criterion to 6.16% (95%CI 4.95–7.65) among those with two minor criteria. These findings remained consistent when TIMI or GUSTO bleeding scales were appraised (Supplementary material online, *Figures S2* and *S3*).

Weight of major and minor criteria

BARC 3 or 5 bleeding

When assessed in isolation, all major and five out of six minor criteria, including advanced age, mild to moderate kidney dysfunction, mild anaemia, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) or steroids and remote stroke, conferred a BARC 3 or 5 bleeding risk which exceeded 4% at the upper limit of the 95% confidence intervals (*Take home figure*). The risk of BARC 3 or 5 bleeding was not computable for the minor category of remote prior bleeding. Results remained entirely consistent after exclusion of bleeding related to the access site (Supplementary material online, *Figure S4*). When each major or minor criteria was assessed at multivariable analysis, by adjusting for all ARC-HBR major or minor criteria but the one considered, all major and four minor criteria, including advanced age, mild to moderate kidney dysfunction, history of remote prior bleeding, and long-term use NSAIDs or steroids remained associated with a bleeding risk which included or exceeded 4% at the upper limit of the 95% confidence intervals (*Figure 3*). At competing risk modelling, all major and all minor criteria but prior bleeding—which was not computable—exceeded 4% at the upper limit of the 95% confidence intervals when tested in isolation (Supplementary material online, *Figure S5*). Finally, at competing risk model multivariable adjustment, the rates of BARC 3 exceeded 4% for all major and minor criteria (Supplementary material online, *Figure S6*). Results remained identical at a set of sensitivity analyses which only included 15 481 patients with 1-year complete information.

Discussion

The ARC-HBR initiative has provided a new framework for identifying HBR patients among those undergoing PCI on the basis of a literature review and clinical consensus.[8] The primary goal was advancing the consistency and quality of data collection and reporting, thereby supporting organizations tasked with making recommendations for clinical practice or regulatory decisions. The application of the 11 major and 6 minor proposed criteria requires an in-depth assessment of patient's medical history, which is not routinely collected among PCI databases. Therefore, only a selected and/or modified set of criteria has been so far analysed.[9,12] We provide the first

	Nr of patients N=16580	BARC 3 or 5 events	Cumulative incidence [95% CI]	p-value vs score 0	p-value vs 4%
Score 0	**n=7464**	**134**	**1.90 [1.61 - 2.25]**	**[Ref.]**	**<0.001**
score 0.5	n=3364	123	4.01 [3.36 - 4.77]	<0.001	0.988
score 1	n=2342	128	5.98 [5.05 - 7.08]	<0.001	<0.001
score 1.5	n=1479	98	7.42 [6.13 - 8.98]	<0.001	<0.001
score 2	n=996	74	8.60 [6.90 - 10.69]	<0.001	<0.001
score 2.5	n=506	54	12.21 [9.47 - 15.66]	<0.001	<0.001
score 3	n=260	28	12.29 [8.62 - 17.36]	<0.001	<0.001
score >3	n=169	24	17.64 [12.11 - 25.30]	<0.001	<0.001
Minor criteria					
only 1 minor	n=3364	123	4.01 [3.36 - 4.77]	<0.001	0.988
only 2 minor	n=1423	78	6.16 [4.95 - 7.65]	<0.001	0.002
only >2 minor	n=453	22	5.58 [3.70 - 8.36]	<0.001	0.174
Major criteria					
only 1 major	n=919	50	5.74 [4.38 - 7.50]	<0.001	0.028
only 2 major	n=208	16	9.21 [5.73 - 14.62]	<0.001	0.018
only 3 major	n=50	7	17.40 [8.52 - 33.63]	<0.001	0.029
only >3 major	n=7	2	31.43 [8.79 - 78.72]	<0.001	0.141
Major and Minor criteria					
1 major + 1 minor	n=1069	79	8.23 [6.65 - 10.17]	<0.001	<0.001
1 major + 2 minor	n=746	55	8.45 [6.55 - 10.87]	<0.001	<0.001
2 major + 1 minor	n=310	36	13.40 [9.83 - 18.13]	<0.001	<0.001
2 major + 2 minor	n=184	18	11.10 [7.11 - 17.10]	<0.001	0.004
2 major + 3 minor	n=42	9	26.64 [14.70 - 45.33]	<0.001	0.003
3 major + 1 minor	n=67	6	10.07 [4.62 - 21.21]	<0.001	0.123
3 major + 2 minor	n=30	3	14.78 [4.78 - 40.67]	0.001	0.190
3 major + 3 minor	n=6	1	20.00 [3.08 - 79.62]	0.016	0.371
>3 major + 1 minor	n=11	2	27.08 [7.46 - 72.36]	<0.001	0.162

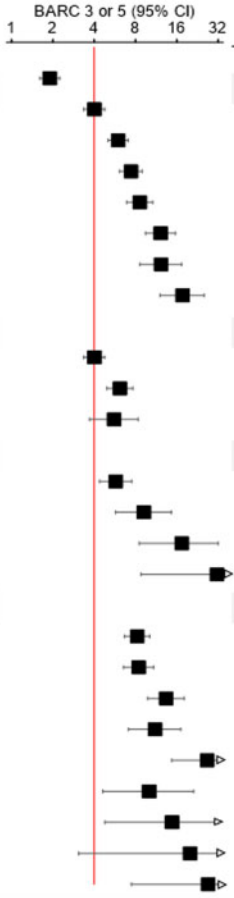

Figure 1 BARC 3 or 5 at 1 year according to ARC-HBR criteria (major = one point, minor = half point). BARC, bleeding academic research consortium; CI, confidence interval; Nr, number. The red line depicts 4% cut-point for a major criterion, corresponding to a score of 1.

comprehensive validation of the originally proposed ARC-HBR criteria and definition in the setting of a large all-comer PCI registry, based on prospectively adjudicated clinical endpoints.

Our key findings were as follows:

(1) Slightly more than one-third of an all-comer PCI population fulfilled HBR definition and incurred a three-fold greater risk of BARC 3 or 5 bleeding as a result of higher event rates within 30 days and from 30 days to 1 year after intervention. These observations were confirmed with TIMI or GUSTO bleeding scales.

(2) The risk of BARC 3 or 5 bleeding accrued progressively as a function of the number of major or minor criteria present with roughly a doubling of the risk for every single unit of ARC-HBR score increase.

(3) The 1-year BARC 3 or 5 bleeding risk exceeded 4% at the upper limit of the 95% confidence intervals for all major and five out of six minor criteria when assessed in isolation; for all major and four minor criteria, when assessed at multivariable analyses; for all major and five minor criteria, at competing risk modelling, and for all major and minor criteria at competing risk multivariable modelling.

Our results indicate that the ARC-HBR criteria identify a large population of PCI patients at high bleeding risk. There was also strong evidence that the risk of BARC 3 or 5 bleeding events was additive and increased linearly based on the number of fulfilled criteria. We, however, did not observe that the so-called *minor* criteria conferred lower bleeding risk than that provided by *major* criteria. Five or four out of six minor criteria conferred a BARC 3 or 5 bleeding risk exceeding the 4% cut-off at 1 year when analysed in isolation or at multivariable analysis, respectively. These findings were reinforced by the competing risk modelling, whereby either five, when assessed in isolation, or all six minor criteria, at multivariable analysis, were associated with ≥4% BARC 3 or 5 bleeding risks. Moreover, the BARC 3 or 5 bleeding risks associated with single major criteria were largely comparable with those observed among patients with single minor criteria. Minor criteria include advanced age, use of NSAIDs or steroids, conditions predisposing to bleeding which occurred more remotely from PCI than the major ones (e.g. a spontaneous bleeding requiring hospitalization or transfusion constitutes a major criterion if

occurred within 6 months before PCI but a minor criterion if occurred within 6–12 months prior), mild anaemia or mild to moderate renal dysfunction. While some of these criteria were relatively infrequent (<2% e.g. prior stroke or bleeding or use of NSAIDs or steroids), advanced age, mild anaemia, and mild to moderate renal dysfunction were observed in 16.7%, 6.5%, and 4.8% of the patients among the non-HBR population and, in isolation, identified three patient subsets in whom the highest absolute number of bleeding instances occurred, namely 75, 23, and 14, respectively, corresponding to 65% (112/173) of overall bleeding events which occurred in isolation with each minor or major criterion. Our results are in keeping with our preliminary observations made for a selected set of ARC-HBR criteria in a smaller subset of patients in the BERN PCI registry,[12] and with the findings from the CREDO-Kyoto registry.[9] The rates of GUSTO moderate to severe bleeding equalled or exceeded 4% at 1 year among patients with a single minor criterion such as advanced age, mild anaemia, or moderate renal dysfunction and, among these three patient subsets, a total of 129 bleeding occurred as compared with overall 49 among patients who met in isolation the 6 major appraised criteria.[9] Hence, targeted interventions addressing bleeding risks in these three populations have the highest probability of success to mitigate overall bleeding occurrences among PCI patients.

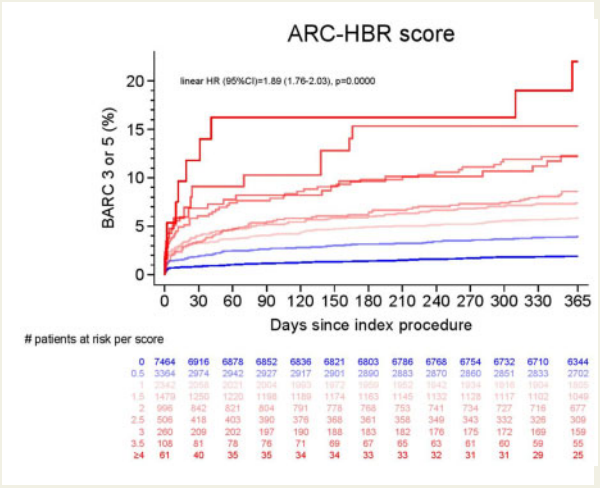

Figure 2 Kaplan-Meier curves for BARC 3 or 5 bleeding according to the ARC HBR score. ARC, academic research consortium; BARC, bleeding academic research consortium; CI, confidence interval; HBR, high bleeding risk; HR, hazard ratio.

Our results have important implications for practice, as question the originally proposed criteria qualification into major or minor. The belief that a single minor criterion would not confer similar bleeding risk as compared with a single major criterion could not be proven by our data. Moreover, at least some minor criteria were highly prevalent among PCI patients, allowing the identification of large groups of PCI patients at HBR. Hence, clinicians should value not only major but also minor criteria in isolation for the identification of HBR patients in view of implementing dedicated bleeding avoidance strategies.

Our results should be interpreted in view of several limitations. First, they arise from a single-centre albeit large cohort study and as such may suffer from limited generalizability. Yet, it is encouraging that our findings are consistent with a previous multicentre report among Asian patients.[9] Second, eight criteria needed retrospective adjudication which may have led to imprecision and underestimation of their true prevalence in our PCI population. However, in a random

Isolated risk factor present	Nr of patients N=16580	BARC 3 or 5 (%) events	Cumulative incidence [95% CI]	p-value vs score 0	p-value vs 4%
No criteria [score 0]	n=7464	134	1.90 [1.61 - 2.25]	[Ref.]	<0.001
Age ≥75 years [minor]	n=1804	75	4.53 [3.62 - 5.67]	<0.001	0.301
Oral anticoagulation [major]	n=452	11	2.52 [1.40 - 4.50]	0.344	0.048
Chronic kidney disease [minor]	n=522	14	3.10 [1.85 - 5.19]	0.081	0.272
Chronic kidney disease [major]	n=40	4	10.97 [4.25 - 26.74]	<0.001	0.180
Hemoglobin [minor]	n=708	23	3.53 [2.36 - 5.27]	0.006	0.517
Hemoglobin [major]	n=125	10	8.89 [4.88 - 15.92]	<0.001	0.069
Prior Bleeding [minor]	n=4	0			
Prior Bleeding [major]	n=26	1	3.85 [0.55 - 24.31]	0.468	0.967
Thrombocytopenia [major]	n=45	7	16.27 [8.09 - 31.19]	0.000	0.030
Chronic Bleeding Diathesis [major]	n=2	1	50.00 [8.96 - 99.40]	0.000	0.193
Liver Cirrhosis with portal hypertension [major]	n=5	1	20.00 [3.08 - 79.62]	0.018	0.371
Long-term use NSAIDs or Steroids [minor]	n=196	9	4.77 [2.51 - 8.97]	0.006	0.619
Active malignancy [major]	n=78	8	10.83 [5.57 - 20.50]	<0.001	0.059
Prior Stroke [minor]	n=130	2	1.65 [0.42 - 6.45]	0.832	0.043
Prior Stroke [major]	n=99	2	2.19 [0.55 - 8.46]	0.865	0.235
Surgery or Trauma within 30 days [major]	n=47	5	11.06 [4.75 - 24.61]	0.000	0.131

Take home figure

	Nr of patients N=16580	BARC 3 or 5 (%) events	Adjusted Cumulative incidence [95% CI]	Adj BARC 3 or 5 (95% CI) 1 2 4 8 16 32	Adjusted p-value vs absence of risk factor	Adjusted p-value vs 4%
No criteria [score 0]	n=7464	134	1.90 [1.61 - 2.25]			<0.001
Age ≥75 years [minor]	n=5288	309	3.62 [3.09 - 4.25]		<0.001	0.199
Oral anticoagulation [major]	n=1908	132	3.74 [3.03 - 4.63]		<0.001	0.524
Chronic kidney disease [minor]	n=2797	199	4.34 [3.56 - 5.30]		<0.001	0.436
Chronic kidney disease [major]	n=491	47	5.24 [3.76 - 7.31]		<0.001	0.164
Hemoglobin [minor]	n=2446	132	3.20 [2.59 - 3.95]		0.018	0.021
Hemoglobin [major]	n=1132	112	4.66 [3.63 - 5.99]		<0.001	0.267
Prior Bleeding [minor]	n=33	4	4.73 [1.72 - 13.02]		0.216	0.766
Prior Bleeding [major]	n=282	35	4.96 [3.41 - 7.23]		<0.001	0.312
Thrombocytopenia [major]	n=233	31	6.86 [4.68 - 10.05]		<0.001	0.032
Chronic Bleeding Diathesis [major]	n=13	2	3.89 [0.93 - 16.28]		0.545	0.970
Liver Cirrhosis with portal hypertension [major]	n=25	4	5.62 [2.07 - 15.31]		0.113	0.572
Long-term use NSAIDs or Steroids [minor]	n=724	51	3.53 [2.61 - 4.77]		0.021	0.388
Active malignancy [major]	n=381	31	4.13 [2.84 - 6.01]		0.008	0.871
Prior Stroke [minor]	n=550	26	2.20 [1.46 - 3.32]		0.526	<0.001
Prior Stroke [major]	n=308	18	2.82 [1.72 - 4.61]		0.636	0.095
Surgery or Trauma within 30 days [major]	n=224	23	5.05 [3.28 - 7.79]		0.001	0.346

Figure 3 Rates of BARC 3 or 5 bleeding at 1 year according to isolated ARC-HBR criteria. First BARC 3 or 5 counted per patient (% from lifetable estimate). Only the single risk factor was present in isolation. The definition of every single ARC-HBR criteria are reported in the supplementary appendix. BARC, bleeding academic research consortium; CI, confidence interval; HR, hazard ratio; Nr, Number; NSAIDs, nonsteroidal anti-inflammatory drugs. The red line depicts 4% cut-point for a major criterion, corresponding to a score of 1.

cohort of 598 patients, the interobserver variability was ≥98%, which provides reassurance over the consistency of the retrospective adjudication process. Third, a single major criterion, namely non-deferrable major surgery on DAPT was not assessed as this condition may not have been known at the time of PCI and requires prospective data collection. Finally, a total of 650 (3.8%) patients had to be excluded from the analysis because of incomplete ARC-HBR criteria.

In conclusion, the ARC-HBR criteria identified roughly a third of PCI patients in whom BARC 3 or 5 bleeding or ICH risk was increased compared with non-HBR patients. A graded increase of bleeding risk as a function of the number of fulfilled criteria was observed for BARC 3 or 5 occurrences. All major and the majority of minor criteria met the 1-year major criteria performance goal of ≥4% BARC 3 or 5 bleeding. Sixty-five per cent of overall bleeding events, which occurred in isolation with each criterion, were observed among patients fulfilling only 1 among 3 minor criteria, including advanced age, moderate renal dysfunction, and mild anaemia. Our analysis, further corroborated by findings from the CREDO-Kyoto registry, supports the extension of bleeding avoidance strategies and future HBR trials to patients with single minor criteria.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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