Impact of clinical presentation on bleeding risk after percutaneous coronary intervention and implications for the ARC-HBR definition

Felice Gragnano[1,2], MD; Alessandro Spirito[1], MD; Noé Corpataux[1,3], MD; Lukas Vaisnora[1], MD; Roberto Galea[1], MD; Giuseppe Gargiulo[4], MD, PhD; George C.M. Siontis[1], MD, PhD; Fabien Praz[1], MD; Jonas Lanz[1], MD; Michael Billinger[1], MD; Lukas Hunziker[1], MD; Stefan Stortecky[1], MD; Thomas Pilgrim[1], MD; Sarah Bär[1], MD; Yasushi Ueki[1], MD; Davide Capodanno[5], MD, PhD; Philip Urban[6], MD; Stuart Pocock[7], PhD; Roxana Mehran[8], MD; Dik Heg[9], PhD; Stephan Windecker[1], MD; Lorenz Räber[1], MD, PhD; Marco Valgimigli[1,10]*, MD, PhD

1. Department of Cardiology, Inselspital, Bern University Hospital, Bern, Switzerland; 2. Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Caserta, Italy; 3. University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany; 4. Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy; 5. Cardio-Thoracic-Vascular Department, Centro Alte Specialità e Trapianti, Catania, and Azienda Ospedaliero Universitaria Policlinico "G. Rodolico – San Marco", University of Catania, Catania, Italy; 6. La Tour Hospital, Geneva, Switzerland; 7. London School of Hygiene and Tropical Medicine, London, United Kingdom; 8. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 9. Clinical Trials Unit (CTU) Bern, University of Bern, Bern, Switzerland; 10. Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Lugano, Switzerland

GUEST EDITOR: Franz-Josef Neumann, MD; *Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany*

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00181

KEYWORDS

- ACS/NSTE-ACS
- bleeding
- clinical research
- NSTEMI
- stable angina
- STEMI

Abstract

Background: The identification of bleeding risk factors in patients undergoing percutaneous coronary intervention (PCI) is essential to inform subsequent management. Whether clinical presentation *per se* affects bleeding risk after PCI remains unclear.

Aims: We aimed to assess whether clinical presentation *per se* predisposes to bleeding in patients undergoing PCI and if the Academic Research Consortium (ARC) High Bleeding Risk (HBR) criteria perform consistently in acute (ACS) and chronic (CCS) coronary syndrome patients.

Methods: Consecutive patients undergoing PCI from the Bern PCI Registry were stratified by clinical presentation. Bleeding events at one year were compared in ACS versus CCS patients, and the originally defined ARC-HBR criteria were assessed.

Results: Among 16,821 patients, 9,503 (56.5%) presented with ACS. At one year, BARC 3 or 5 bleeding occurred in 4.97% and 3.60% of patients with ACS and CCS, respectively. After adjustment, ACS remained associated with higher BARC 3 or 5 bleeding risk (adjusted HR 1.21, 95% CI: 1.01-1.43; p=0.034), owing to non-access site-related occurrences, which accrued mainly within the first 30 days after PCI. The ARC-HBR score had lower discrimination among ACS compared with CCS patients, and its performance slightly improved when ACS was computed as a minor criterion.

Conclusions: ACS presentation *per se* predicts one-year major bleeding risk after PCI. The ARC-HBR score discrimination appeared lower in ACS than CCS, and its overall performance improved numerically when ACS was computed as an additional minor risk criterion.

**Corresponding author: Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Via Tesserete 48, 6900 Lugano, Switzerland. E-mail: marco.valgimigli@cardiocentro.org*

Abbreviations

ACS	acute coronary syndrome
ARC-HBR	Academic Research Consortium High Bleeding Risk
BARC	Bleeding Academic Research Consortium
CCS	chronic coronary syndrome
CI	confidence interval(s)
CKD	chronic kidney disease
DAPT	dual antiplatelet therapy
GUSTO	Global Use of Strategies to Open Occluded Arteries
HR	hazard ratio
NSAIDs	non-steroidal anti-inflammatory drugs
NSTEMI	non-ST-segment elevation myocardial infarction
OAC	oral anticoagulation
PCI	percutaneous coronary intervention
PH	portal hypertension
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction

Introduction

Patients undergoing percutaneous coronary intervention (PCI) for either acute (ACS) or chronic (CCS) coronary syndrome are at risk for haemorrhagic complications due to the invasive nature of the procedure and mandated use of antithrombotic therapy[1,2]. As bleeding events adversely affect patient outcomes, the identification of factors predisposing to heightened bleeding risk after PCI is essential for appropriate treatment selection[3,4].

The bleeding risk might differ according to the clinical presentation. Patients undergoing PCI for ACS are known to experience a higher crude incidence of bleeding complications compared with CCS[5,6]. However, whether ACS presentation *per se* – rather than differences in clinical and procedural characteristics and antithrombotic medications – is associated with an excess of bleeding remains controversial[1]. The higher bleeding risk in ACS patients might be due to a pro-inflammatory state causing a transient impairment of haemostasis[7], but may also result from differences in patient management and pharmacotherapy[2,8]. While some studies suggested that acute presentation might be independently associated with bleeding[5,6,9,10], this association has not been confirmed in other reports[11,12]. On this basis, international guidelines recommend relying on clinical presentation for ischaemic but not bleeding risk stratification purposes[2,8]. Also, the recent framework proposed by the Academic Research Consortium (ARC) for High Bleeding Risk (HBR) did not assign incremental bleeding risk to ACS patients under the premise that the more aggressive antithrombotic therapy prescribed more than the acute presentation *per se* might explain previous findings[1]. To date, no validation of the ARC-HBR criteria in separately appraised ACS and CCS patients exists.

We therefore investigated – in a large cohort of contemporary all-comer PCI patients – whether ACS presentation *per se* is associated with higher bleeding risk and whether the ARC-HBR criteria provide a consistent risk stratification framework in patients presenting with or without ACS.

Editorial, see page 867

Methods

STUDY DESIGN AND PARTICIPANTS

All consecutive patients undergoing PCI at Bern University Hospital between February 2009 and December 2018 were prospectively entered in the Bern PCI Registry (NCT02241291). No exclusion criteria were applied. Participants provided written informed consent. Clinical characteristics and outcomes up to one year were collected prospectively. The prescription of dual antiplatelet therapy (DAPT) followed the recommendations of international guidelines. Detailed information on data collection is available in **Supplementary Appendix 1**. The study complied with the Declaration of Helsinki and was approved by the institutional ethics committee.

ASSESSMENT OF ARC-HBR CRITERIA

The fulfilment of each ARC-HBR criterion was assessed systematically according to the originally proposed definition **(Supplementary Table 1)**. Age, haemoglobin, creatinine, platelet count, and anticipated use of long-term oral anticoagulation were collected prospectively. All other ARC-HBR criteria but non-deferrable major surgery on DAPT were evaluated retrospectively from electronic clinical records by trained investigators blinded to clinical outcomes. The ARC-HBR score was calculated by assigning one point to each adjudicated major criterion and 0.5 point to each adjudicated minor criterion. The inter-observer variability among different readers, as previously reported, indicated an excellent agreement for ARC-HBR criteria adjudication[4].

CLINICAL ENDPOINTS

The primary study endpoint was Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding, which was further stratified by (i) bleeding location (i.e., access site and non-access site-related), (ii) time of onset (i.e., early and late events with landmark at 30 days), and (iii) presence (i.e., CCS vs ACS) and type of ACS (unstable angina, non-ST-segment elevation myocardial infarction [NSTEMI], and ST-elevation myocardial infarction [STEMI]). Secondary endpoints included BARC 2, 3 or 5, Thrombolysis In Myocardial Infarction (TIMI)-defined, and Global Use of Strategies to Open Occluded Arteries (GUSTO)-defined bleeding. A clinical events committee adjudicated endpoint events against original source documents. Outcomes were defined in accordance with standardised definitions of the Academic Research Consortium.

STATISTICAL ANALYSIS

Baseline characteristics are reported as means (standard deviations) or counts and percentages. For the ACS versus CCS comparison, p-values were obtained using a t-test, Fisher's test or chi-square test, as appropriate. Time-to-event analyses and Kaplan-Meier event curves were used for outcomes. Analyses were performed at one year and with landmark analysis at 30 days. Univariate and multivariate Cox regression was carried out to investigate the association of clinical presentation and other clinical and treatment characteristics with bleeding. A p-value <0.2 was used to select variables for

the multivariable model. We assessed the unadjusted incidence of BARC 3 or 5 events at one year associated with each ARC-HBR criterion in ACS and CCS, and the incidence for each ARC-HBR criterion adjusted for the absence of all other criteria. Harrell's C-index was computed to evaluate the performance of the ARC-HBR criteria to predict BARC 3 or 5 bleeding. The discrimination of the ARC-HBR score after including ACS as an additional minor risk criterion was assessed. All analyses were performed using Stata Release 16.1 (StataCorp LP, College Station, TX, USA).

Results

POPULATION CHARACTERISTICS

A total of 17,339 consecutive patients were prospectively entered into the Bern PCI Registry. Overall, 518 participants were excluded because of incomplete haemoglobin (n=459) or creatinine (n=59) values, with a final study population of 16,821 patients, of whom 9,503 (56.5%) presented with ACS and 7,318 (43.5%) with CCS.

Compared with CCS, ACS patients were on average three years younger (66.5±12.8 vs 69.6±10.5 years), were more often active smokers, presented less frequently with cardiovascular risk factors such as hypertension and diabetes, and were less likely to have a history of myocardial infarction, coronary revascularisation, peripheral artery disease, and atrial fibrillation **(Table 1)**. ACS patients more frequently underwent femoral access, invasive haemodynamic support, and staged PCI, but less often left main, bypass graft, or multivessel intervention **(Supplementary Table 2)**. The ACS cohort was more likely to receive potent $P2Y_{12}$ inhibitors, glycoprotein IIb/IIIa antagonists, and proton pump inhibitors, but less likely to receive oral anticoagulants or triple antithrombotic therapy **(Supplementary Table 3)**.

CLINICAL OUTCOMES AT ONE-YEAR FOLLOW-UP

At one year, BARC 3 or 5 bleeding occurred in 427 (4.97%) patients with ACS and 248 (3.60%) patients with CCS (unadjusted hazard ratio [HR] 1.41, 95% confidence interval [CI]: 1.20-1.64; p<0.001) **(Table 2, Figure 1)**. At multivariable analysis, after adjusting for clinical, procedural, and treatment imbalances, ACS presentation remained independently associated with a higher risk of BARC 3 or 5 bleeding at one year (adjusted HR [adjHR] 1.21, 95% CI: 1.01-1.43; p=0.034) **(Table 2)**.

BARC 2, 3 or 5 bleeding events at one year occurred in 657 (7.65%) ACS and 363 (5.28%) CCS patients (unadjusted HR 1.49, 95% CI: 1.31-1.69; p<0.001), and were independently predicted by ACS presentation after adjustment (adjHR 1.25, 95% CI: 1.08-1.44; p=0.003) **(Table 2)**.

At sensitivity analyses, performed by adding "years of PCI" (i.e., 2009, 2010, etc.) as covariate in the multivariable model to explore a possible time effect on outcomes, the results remained largely consistent for both BARC type 3 or 5 (adjHR 1.27, 95% CI: 1.07-1.51; p=0.007) and type 2, 3 or 5 bleeding events (adjHR 1.22, 95% CI: 1.02-1.45; p=0.016).

ACS patients bled more than CCS patients also when the TIMI and the GUSTO scales were assessed **(Supplementary Table 4)**. The incidence of intracranial or fatal bleeding did not differ. The rates of death, ischaemic, and composite outcomes are reported in **Supplementary Table 4**. Other bleeding risk factors at univariate and multivariate analyses are shown in **Supplementary Table 5-Supplementary Table 8**.

BLEEDING EVENTS STRATIFIED BY LOCATION, TIME OF ONSET, AND ACS SUBTYPES

The one-year incidence of access site and non-access site-related BARC 3 or 5 bleeding was 0.62% and 4.40% in the ACS group and 0.49% and 3.18% in the CCS group, respectively **(Table 2)**. The corresponding figures for BARC 2, 3 or 5 bleeding were 0.73%, 7.02%, 0.52%, and 4.83%, respectively. After adjustment, ACS presentation remained independently associated with greater non-access site-related type 2, 3 or 5 bleeding (adjHR 1.23, 95% CI: 1.07-1.43; p=0.005), but with limited and inconclusive evidence for non-access site-related type 3 or 5 occurrences (adjHR 1.19, 95% CI: 0.99-1.43; p=0.063). Clinical presentation did not emerge as an independent predictor of access site-related bleeding **(Table 2)**.

At landmark analysis, the excess of BARC bleeding among ACS patients occurred mainly within the first 30 days after PCI, but not thereafter, and was largely driven by a twofold higher risk of non-access site-related events **(Table 3)**.

After adjustment, we found a gradient of BARC 3 or 5 bleeding risks across ACS subtypes, being the highest among STEMI patients (adjHR 1.92, 95% CI: 1.59-2.31; p<0.001), intermediate among NSTEMI patients (adjHR 1.26, 95% CI: 1.04-1.53; p=0.019), and negligible in unstable angina patients (adjHR 1.10, 95% CI: 0.74-1.66; p=0.63) **(Figure 2)**. A similar graded-risk profile was noted for BARC 2, 3 or 5 bleeding. Clinical characteristics, procedural factors, and medications in patients presenting with unstable angina, NSTEMI, and STEMI are detailed in **Supplementary Table 9-Supplementary Table 11**.

ARC-HBR CRITERIA IN PATIENTS WITH ACS AND CCS

Thirty-one percent (n=3,020) of ACS and 39% (n=2,869) of CCS patients qualified as HBR defined by the presence of at least one major or two minor ARC-HBR criteria. The risk of BARC-defined bleeding was significantly higher in patients who fulfilled versus those who did not fulfil the ARC-HBR definition for both ACS and CCS groups **(Figure 1)**.

Severe anaemia, thrombocytopaenia, and recent surgery or trauma were more frequently met criteria among ACS patients, whereas advanced age, oral anticoagulants, chronic kidney disease (CKD), mild anaemia, prior stroke, and use of non-steroidal inflammatory drugs or corticosteroids were more common in CCS patients **(Supplementary Figure 1A)**.

The unadjusted risks of BARC 3 or 5 bleeding for each ARC-HBR criterion by clinical presentation are displayed in **Supplementary Figure 2**. At multivariate analysis, after adjusting for each ARC-HBR criterion but the one considered, greater BARC 3 or 5 bleeding risk was found among ACS compared with

Table 1. Baseline characteristics stratified by clinical presentation.

	All patients (n=16,821)	ACS (n=9,503)	CCS (n=7,318)	*p*-value
Age, years	67.8±12.0	66.5±12.8	69.6±10.5	<0.001
Females	4,307 (25.6%)	2,415 (25.4%)	1,892 (25.9%)	0.52
BMI, kg/m²	27.3±4.7	27.2±4.6	27.6±4.7	<0.001
Current smoker	4,488 (27.1%)	3,104 (33.4%)	1,384 (19.0%)	<0.001
Hypertension	11,577 (69.3%)	5,869 (62.4%)	5,708 (78.3%)	<0.001
Diabetes mellitus	3,893 (23.2%)	1,892 (20.0%)	2,001 (27.4%)	<0.001
Hypercholesterolaemia	10,741 (64.5%)	5,144 (54.9%)	5,597 (76.8%)	<0.001
Family history of CAD	4,323 (25.9%)	2,147 (22.8%)	2,176 (29.9%)	<0.001
Previous myocardial infarction	2,976 (17.8%)	1,348 (14.3%)	1,628 (22.3%)	<0.001
Previous PCI	3,989 (23.8%)	1,553 (16.5%)	2,436 (33.4%)	<0.001
Previous CABG	1,701 (10.1%)	643 (6.8%)	1,058 (14.5%)	<0.001
Previous TIA or stroke	1,237 (7.4%)	545 (5.8%)	692 (9.5%)	<0.001
Peripheral artery disease	1,448 (8.7%)	636 (6.7%)	812 (11.1%)	<0.001
History of malignancy	1,810 (10.8%)	907 (9.6%)	903 (12.4%)	<0.001
Renal failure	3,329 (20.7%)	1,811 (20.4%)	1,518 (21.1%)	0.26
Renal failure on dialysis	193 (1.2%)	94 (1.0%)	99 (1.4%)	0.034
History of atrial fibrillation/flutter	1,450 (12.2%)	564 (8.3%)	886 (17.4%)	<0.001
Chronic obstructive lung disease	1,113 (6.6%)	545 (5.8%)	568 (7.8%)	<0.001
History of spontaneous bleeding	729 (4.3%)	377 (4.0%)	352 (4.8%)	0.008
Left ventricular function, %	52.3±13.7	49.0±13.4	57.1±12.5	<0.001
Haemoglobin before PCI, g/L	136.5±18.1	136.8±19.4	136.2±16.5	0.036
Haemoglobin nadir, g/L	127.0±20.6	124.3±20.6	131.5±19.9	<0.001
Leukocytes before PCI, g/L	8.9±4.3	10.3±4.8	7.5±3.2	<0.001
Thrombocytes before PCI, g/L	228.4±72.3	235.4±77.6	220.7±65.0	<0.001
ARC-HBR score	0.66±0.83	0.61±0.81	0.73±0.84	<0.001
Clinical indication for PCI	n=16,821	n=9,503	n=7,318	–
CCS	7,318 (43.5%)	0 (0.0%)	7,318 (100.0%)	
Unstable angina	783 (4.7%)	783 (8.2%)	0 (0.0%)	
NSTEMI	4,218 (25.1%)	4,218 (44.4%)	0 (0.0%)	
STEMI	4,502 (26.8%)	4,502 (47.4%)	0 (0.0%)	
Killip class	n=16,780	n=9,477	n=7,303	<0.001
Killip I	13,936 (83.1%)	7,334 (77.4%)	6,602 (90.4%)	
Killip II	1,668 (9.9%)	1,091 (11.5%)	577 (7.9%)	
Killip III	496 (3.0%)	398 (4.2%)	98 (1.3%)	
Killip IV	680 (4.1%)	654 (6.9%)	26 (0.4%)	

ACS: acute coronary syndrome; ARC-HBR: Academic Research Consortium for High Bleeding Risk; BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCS: chronic coronary syndrome; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TIA: transient ischaemic attack

CCS patients with no ARC-HBR criterion as well as those with moderate CKD, or recent spontaneous bleeding and also trended higher in patients with advanced age **(Figure 3)**.

ARC-HBR SCORE IN PATIENTS WITH ACS AND CCS

Mean ARC-HBR score was lower among ACS than CCS patients (0.61±0.81 vs 0.73±0.84; p<0.001), and distributed differently between study groups **(Supplementary Figure 1B)**. For each 0.5-point increase in the ARC-HBR score from 0 to ≥2.5 points, a stepwise increase in the risk of one-year BARC 3 or 5 events was observed in both groups **(Figure 4, Supplementary Figure 3)**. Compared with CCS, the incidence of BARC 3 or 5 events was higher among ACS patients with a score ≤1, but not for higher score values **(Figure 4)**.

The discrimination of the ARC-HBR score was lower among ACS compared with CCS patients with respect to BARC 3 or 5 bleeding (C-indices: 0.666 [95% CI: 0.641-0.691] vs 0.716 [95% CI: 0.685-0.747]; p=0.014). In the overall study population, the ARC-HBR score showed moderate discrimination to predict BARC 3 or 5 events (C-index: 0.679 [95% CI: 0.659-0.698]), which

Table 2. Adjudicated bleeding outcomes at one year stratified by clinical presentation.

	ACS (n=9,503)	CCS (n=7,318)	Unadjusted hazard ratio (95% CI)	*p*-value	Adjusted hazard ratio (95% CI)	*p*-value
BARC type 3 or 5						
Overall	427 (4.97%)	248 (3.60%)	1.41 (1.20-1.64)	<0.001	1.21 (1.01-1.43)	0.034
Access-site	56 (0.62%)	35 (0.49%)	1.25 (0.82-1.91)	0.29	1.12 (0.69-1.81)	0.65
Non-access-site	375 (4.40%)	218 (3.18%)	1.41 (1.19-1.67)	<0.001	1.19 (0.99-1.43)	0.063
BARC type 2, 3 or 5						
Overall	657 (7.65%)	363 (5.28%)	1.49 (1.31-1.69)	<0.001	1.25 (1.08-1.44)	0.003
Access-site	67 (0.73%)	37 (0.52%)	1.42 (0.95-2.12)	0.090	1.19 (0.78-1.82)	0.42
Non-access-site	599 (7.02%)	331 (4.83%)	1.49 (1.31-1.71)	<0.001	1.23 (1.07-1.43)	0.005

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome

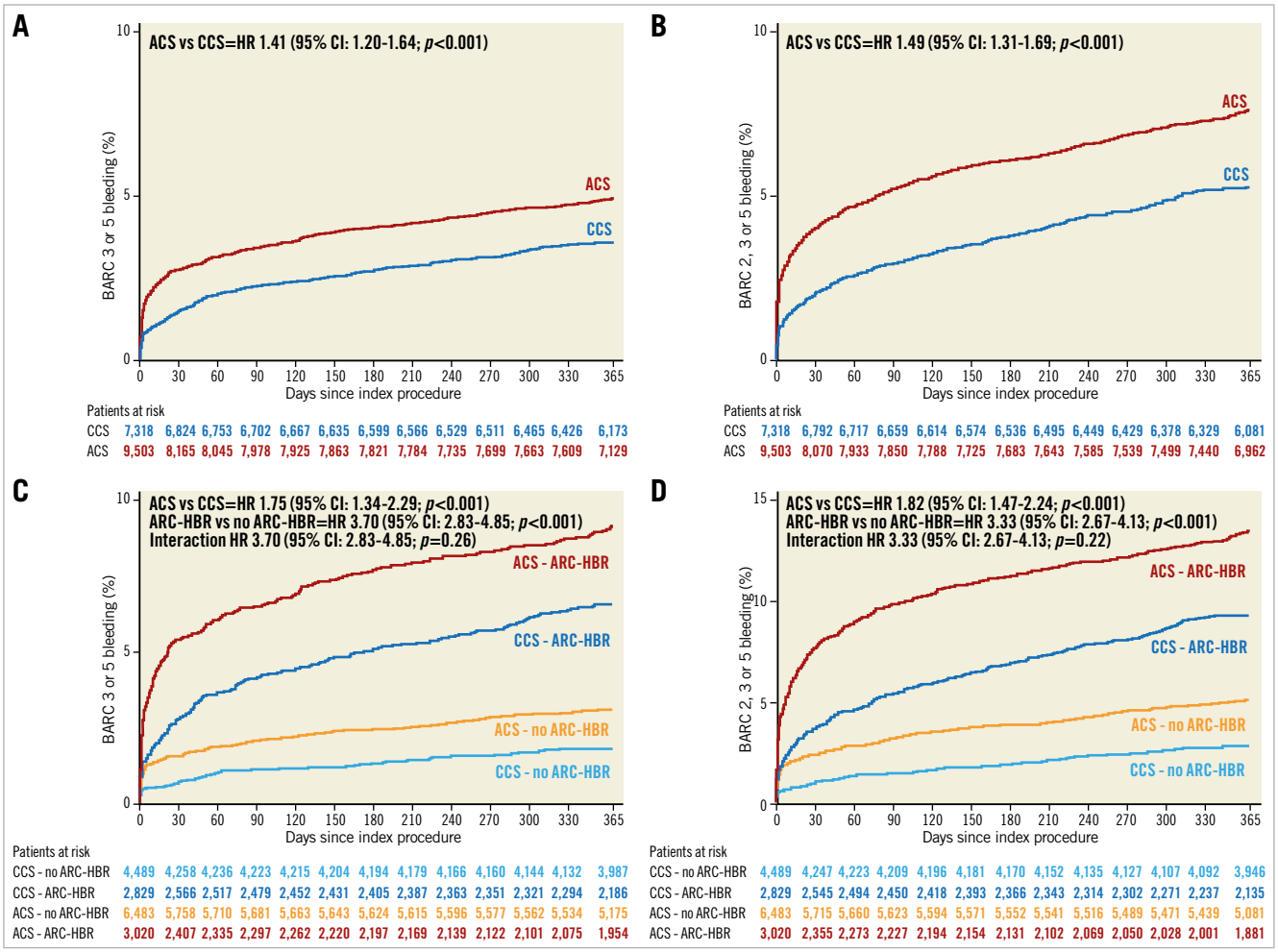


Figure 1. *Kaplan-Meier event curves for BARC-defined bleeding at one year by clinical presentation. BARC 3 or 5 and BARC 2, 3 or 5 events in ACS (red) versus CCS (blue) (A & B), and further stratified by the ARC-HBR definition (C & D). ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; HR: hazard ratio*

slightly increased when ACS was included as an additional minor risk criterion (C-index: 0.692 [95% CI: 0.673-0.711]) **(Figure 4)**. On the other hand, the ARC-HBR score performance significantly diminished when the originally proposed binary ARC-HBR definition was adopted (C-index: 0.639 [95% CI: 0.621-0.658]).

Discussion

We investigated the impact of clinical presentation on centrally adjudicated and prospectively collected bleeding events at one year and the ARC-HBR stratified performance in bleeding risk prediction in a large and unselected population of 16,821 PCI

Table 3. Adjudicated bleeding outcomes at 30 days and with landmark analysis from 30 days to one-year follow-up in ACS and CCS patients.

		ACS (n=9,503)	CCS (n=7,318)	Adjusted hazard ratio (95% CI)	*p*-value	*p*-interaction
BARC type 3 or 5	At 30 days	249 (2.77%)	106 (1.50%)	1.87 (1.49-2.34)	<0.001	<0.001
	From 31 days to 1 year	178 (2.26%)	142 (2.14%)	1.06 (0.85-1.32)	0.63	
Non-access-site BARC 3 or 5	At 30 days	201 (2.25%)	77 (1.09%)	2.08 (1.60-2.70)	<0.001	<0.001
	From 31 days to 1 year	174 (2.20%)	141 (2.11%)	1.04 (0.83-1.30)	0.74	
Access-site BARC 3 or 5	At 30 days	51 (0.55%)	32 (0.45%)	1.25 (0.81-1.95)	0.31	0.88
	From 31 days to 1 year	5 (0.06%)	3 (0.04%)	1.39 (0.33-5.82)	0.65	
BARC 2, 3 or 5	At 30 days	361 (4.02%)	143 (2.02%)	2.02 (1.66-2.45)	<0.001	<0.001
	From 31 days to 1 year	296 (3.78%)	220 (3.32%)	1.14 (0.96-1.36)	0.13	
Non-access-site BARC 2, 3 or 5	At 30 days	305 (3.42%)	113 (1.60%)	2.16 (1.74-2.68)	<0.001	<0.001
	From 31 days to 1 year	294 (3.73%)	218 (3.28%)	1.14 (0.96-1.36)	0.13	
Access-site BARC 2, 3 or 5	At 30 days	62 (0.67%)	33 (0.46%)	1.48 (0.97-2.25)	0.070	0.63
	From 31 days to 1 year	5 (0.06%)	4 (0.06%)	1.04 (0.28-3.89)	0.94	

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; HR: hazard ratio

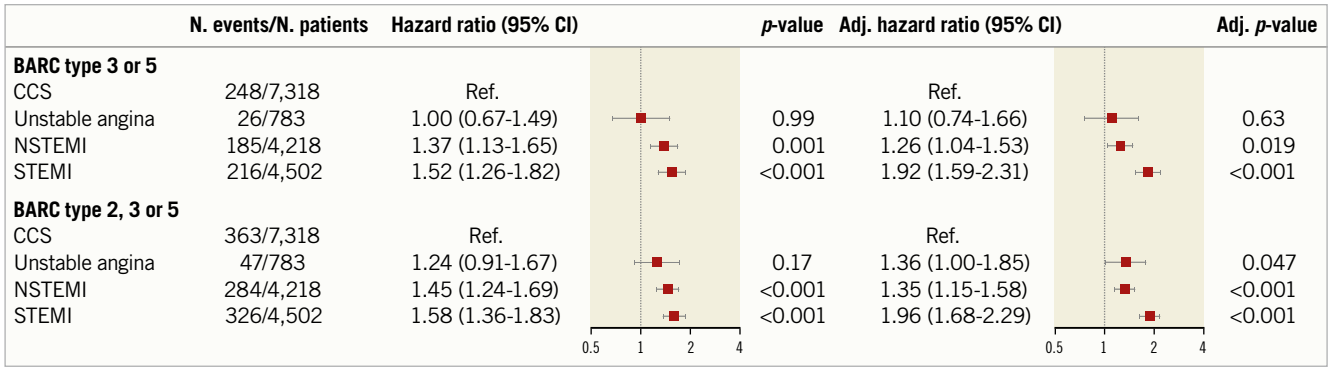


Figure 2. *Adjudicated BARC-defined bleeding at one year by ACS subtype. Unadjusted (left) and adjusted (right) hazard ratio for BARC 3 or 5 and BARC 2, 3 or 5 bleeding. CCS is the reference. BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction*

patients. The main findings can be summarised as follows **(Central illustration)**:

1) ACS presentation *per se*, after extensive multivariable adjustment, remained associated with greater BARC type 3 or 5 and type 2, 3 or 5 bleeding risks.
2) The excess of bleeding among ACS patients was driven by non-access site-related events, which accrued mainly within the first 30 days and was highest among STEMI patients, intermediate among NSTEMI, and minimal for unstable angina patients.
3) Compared with CCS, ACS patients were less likely to qualify as high bleeding risk according to the ARC-HBR definition and presented lower ARC-HBR scores, mainly due to less frequent fulfilment of the advanced age and oral anticoagulation criteria.
4) ACS patients bled more than CCS patients across multiple ARC-HBR criteria. After multivariate adjustment, based on all ARC-HBR criteria but the one considered, ACS patients continued to show higher BARC 3 or 5 bleeding risk if they fulfilled none, moderate CKD or recent bleeding criteria among the ARC-HBR criteria as well as if their ARC-HBR score was ≤1.
5) The ARC-HBR score discrimination was lower among ACS compared with CCS patients. The inclusion of ACS as an additional minor risk criterion slightly improved the performance of the score in the overall study cohort.

Clinical presentation is deemed critical to guide ischaemic risk stratification by international guidelines in view of the higher risk of coronary events following ACS and the potential benefit accrued with intensified and prolonged antithrombotic therapy compared with CCS[2,8]. However, whether it should also inform bleeding risk assessment and encourage the adoption of bleeding avoidance strategies remains unclear.

Our analysis from a large contemporary cohort of consecutive PCI patients provides evidence that ACS presentation *per se* carries enhanced major and actionable bleeding risks within one year

Clinical presentation	ARC-HBR criteria	N. patients	BARC 3 or 5 events	Cumulative incidence (%) (95% CI)	Adj. BARC 3 or 5 (95% CI)	ACS vs CCS Adj. *p*-value
ACS	No ARC-HBR criteria	4,581	104	2.93 (2.57-3.33)		<0.001
CCS	No ARC-HBR criteria	2,964	33	1.94 (1.65-2.29)		
ACS	ARC-HBR Age ≥75 years (minor)	2,842	176	4.21 (3.56-4.98)		0.054
CCS	ARC-HBR Age ≥75 years (minor)	2,534	137	2.80 (2.31-3.38)		
ACS	ARC-HBR OAC (major)	811	57	4.70 (3.76-5.86)		0.81
CCS	ARC-HBR OAC (major)	1,132	79	3.12 (2.49-3.91)		
ACS	ARC-HBR CKD (minor)	1,547	124	5.21 (4.25-6.38)		0.006
CCS	ARC-HBR CKD (minor)	1,290	81	3.46 (2.77-4.32)		
ACS	ARC-HBR CKD (major)	275	30	6.01 (4.29-8.41)		0.078
CCS	ARC-HBR CKD (major)	236	17	3.99 (2.83-5.64)		
ACS	ARC-HBR Anaemia (minor)	1,253	68	3.79 (3.05-4.72)		0.40
CCS	ARC-HBR Anaemia (minor)	1,238	66	2.52 (2.00-3.18)		
ACS	ARC-HBR Anaemia (major)	716	74	5.24 (4.07-6.74)		0.15
CCS	ARC-HBR Anaemia (major)	440	40	3.48 (2.64-4.59)		
ACS	ARC-HBR Previous bleeding (minor)	18	2	5.52 (2.00-15.26)		–
CCS	ARC-HBR Previous bleeding (minor)	15	2	3.67 (1.32-10.19)		
ACS	ARC-HBR Previous bleeding (major)	152	25	5.68 (3.89-8.31)		0.023
CCS	ARC-HBR Previous bleeding (major)	134	10	3.78 (2.56-5.58)		
ACS	ARC-HBR Thrombocytopaenia (major)	155	23	7.89 (5.40-11.52)		0.45
CCS	ARC-HBR Thrombocytopaenia (major)	80	9	5.25 (3.53-7.80)		
ACS	ARC-HBR Chronic bleeding diathesis (major)	4	1	5.46 (1.31-22.87)		>0.99
CCS	ARC-HBR Chronic bleeding diathesis (major)	9	1	3.63 (0.87-15.15)		
ACS	ARC-HBR Liver cirrhosis with PH (major)	14	4	6.25 (2.29-17.07)		–
CCS	ARC-HBR Liver cirrhosis with PH (major)	12	0	–		
ACS	ARC-HBR Long-term use NSAIDs or steroids (minor)	367	27	4.28 (3.16-5.79)		0.60
CCS	ARC-HBR Long-term use NSAIDs or steroids (minor)	377	26	2.85 (2.08-3.89)		
ACS	ARC-HBR Active malignancy (major)	207	16	4.87 (3.35-7.08)		0.77
CCS	ARC-HBR Active malignancy (major)	179	16	3.24 (2.20-4.76)		
ACS	ARC-HBR History of stroke (minor)	255	14	2.55 (1.68-3.85)		0.43
CCS	ARC-HBR History of stroke (minor)	303	12	1.69 (1.11-2.59)		
ACS	ARC-HBR History of stroke (major)	141	9	3.30 (2.01-5.43)		0.38
CCS	ARC-HBR History of stroke (major)	173	9	2.19 (1.33-3.63)		
ACS	ARC-HBR Recent surgery or trauma (major)	176	18	5.81 (3.82-8.81)		0.56
CCS	ARC-HBR Recent surgery or trauma (major)	53	7	3.86 (2.49-5.98)		

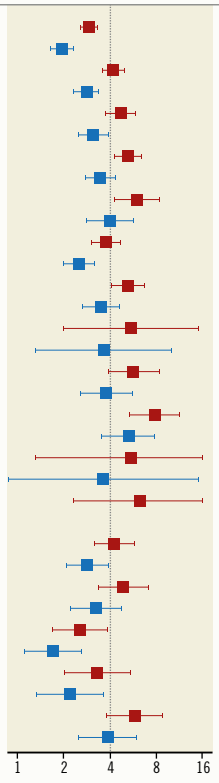


Figure 3. *Adjusted incidence of BARC 3 or 5 bleeding at one year for minor and major ARC-HBR criteria in ACS (red) and CCS (blue). The estimates of the main effects model, adjusted cumulative incidence in case all other criteria are set to absent. Dotted line: 4% bleeding incidence expected in the presence of a major ARC-HBR criterion. ACS: acute coronary syndrome; Adj: adjusted; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; CKD: chronic kidney disease; NSAIDs: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulation; PH: portal hypertension*

after PCI. The higher hazard associated with ACS was largely due to bleeding events unrelated to vascular access. As shown here, and consistent with many previous observations, non-access site-related bleeding events are much more prevalent than access site-related occurrences after PCI and have been associated with a roughly twofold greater mortality risk compared with access-site bleeding[13]. Therefore, our novel findings carry major implications for clinical practice.

Previous studies of PCI populations consistently reported a higher crude rate of bleeding complications – ranging from twofold to fourfold – in ACS versus CCS patients[5,6,9-12,14]. However, when potential confounders were adjusted for, ACS presentation emerged as an independent predictor of bleeding in some studies[5,6,9,10] but not in others[11,12]. This apparent inconsistency might be due to relevant differences among studies in terms of patient characteristics, follow-up duration (i.e., in-hospital, 30-day, or long-term), antithrombotic regimen (i.e., extensive versus selective use of glycoprotein IIb/IIIa antagonists), as well as bleeding definition, location, and severity[5,6,9-12]. The relatively low number of patients and/or events in some studies may have hampered extensive multivariable adjustment.

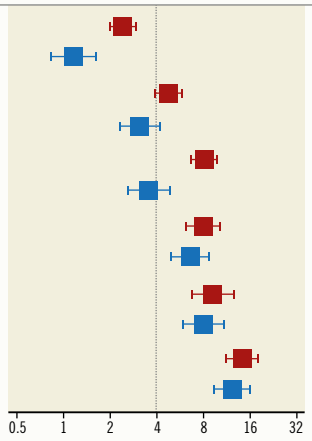
Our analysis of a large, unselected, and contemporary PCI cohort shows that ACS presentation *per se* represents an independent determinant of spontaneous bleeding. Compared with CCS patients, the bleeding hazard in ACS was driven by an excess of events occurring in the first 30 days after the intervention. This observation might partly explain why clinical presentation emerged as an independent predictor of events in scores modelling short-term bleeding risk after PCI (i.e., REPLACE-2/ACUITY/HORIZONS, NCDR-CathPCI Registry 1, NCDR-CathPCI Registry 2)[6,9] but not in those focusing on long-term occurrences (i.e., PARIS, PRECISE-DAPT)[15,16].

Our analysis also suggests the existence of a graded risk across ACS subtypes. Compared with CCS, the risk of bleeding was not different in patients presenting with unstable angina, whereas an NSTEMI or STEMI presentation conferred a 26% and 92% increase in the adjusted hazard, respectively. These findings are consistent with previous algorithms including cardiac biomarkers and/or ST-segment changes as independent predictors of post-PCI bleeding[3,5,6,9,17,18].

Acute presentation is a well-established determinant of ischaemic risk after PCI[2,8]. Our data add to this evidence that patients

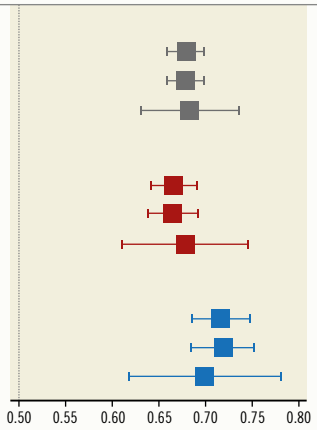
A

Clinical presentation	ARC-HBR score	N. patients	BARC 3 or 5 events (95% CI)	Cumulative incidence (%)	*p*-value
ACS	Score 0	4,581	104	2.43 (2.01-2.93)	<0.001
CCS	Score 0	2,964	33	1.16 (0.83-1.63)	
ACS	Score 0.5	1,902	82	4.80 (3.88-5.93)	0.011
CCS	Score 0.5	1,525	44	3.10 (2.31-4.17)	
ACS	Score 1	1,250	90	8.12 (6.64-9.92)	<0.001
CCS	Score 1	1,125	38	3.56 (2.60-4.86)	
ACS	Score 1.5	796	55	8.00 (6.19-10.31)	0.31
CCS	Score 1.5	703	43	6.61 (4.94-8.81)	
ACS	Score 2	485	37	9.26 (6.79-12.58)	0.49
CCS	Score 2	533	39	8.07 (5.96-10.89)	
ACS	Score ≥2.5	489	59	14.36 (11.28-18.18)	0.31
CCS	Score ≥2.5	468	51	12.30 (9.47-15.90)	



B

Outcomes at 1-year follow-up	Harrell's C-index (95% CI)	*p*-value (vs C-index 0.5)
All patients		
BARC type 3 or 5 overall	0.679 (0.659-0.698)	<0.001
BARC type 3 or 5 non-access site	0.678 (0.657-0.699)	<0.001
BARC type 3 or 5 access site	0.683 (0.631-0.735)	<0.001
ACS		
BARC type 3 or 5 overall	0.666 (0.641-0.691)	<0.001
BARC type 3 or 5 non-access site	0.664 (0.638-0.691)	<0.001
BARC type 3 or 5 access site	0.678 (0.610-0.746)	<0.001
CCS		
BARC type 3 or 5 overall	0.716 (0.685-0.747)	<0.001
BARC type 3 or 5 non-access site	0.718 (0.684-0.752)	<0.001
BARC type 3 or 5 access site	0.699 (0.618-0.780)	<0.001



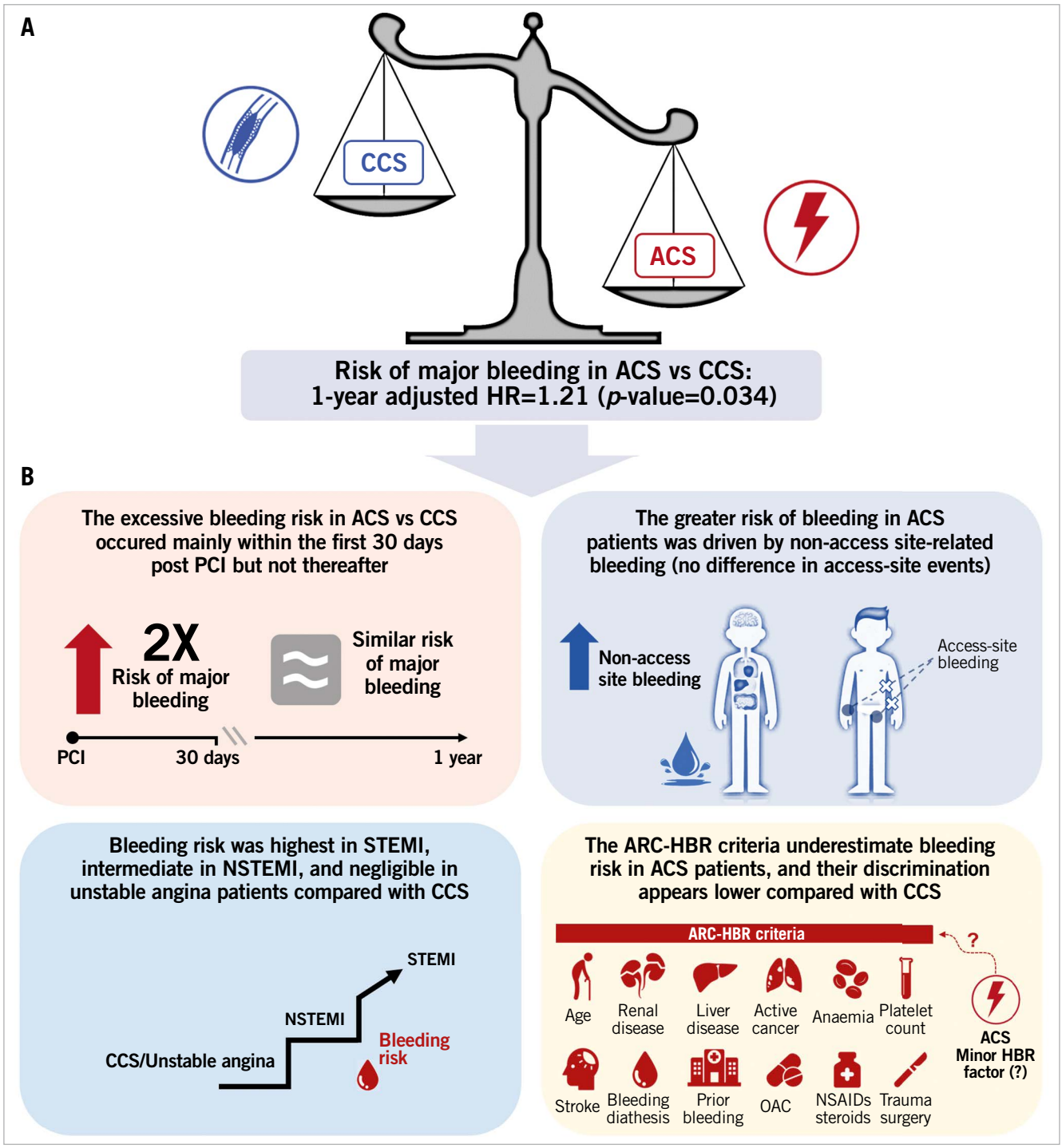
BARC 3 or 5 overall – ACS vs CCS: C-index, *p*=0.014
BARC 3 or 5 non-access site – ACS vs CCS: C-index, *p*=0.013
BARC 3 or 5 access site – ACS vs CCS: C-index, *p*=0.68

Figure 4. *Adjudicated BARC 3 or 5 bleeding at one year by ARC-HBR score. Incidence of BARC 3 or 5 bleeding for score values from 0 to ≥2.5 in ACS (red) and CCS (blue) patients. The dotted line indicates a 4% incidence of bleeding, expected in the presence of one major or two minor ARC-HBR criteria (A). Harrell's C-index of the ARC-HBR score for the prediction of BARC 3 or 5 bleeding (B). ACS: acute coronary syndrome; AUC: area under the curve; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; CI: confidence interval*

with ACS are also more prone to bleed and should therefore be carefully screened and managed to mitigate the concomitant high risk of ischaemic and bleeding complications. Given that the use of potent antithrombotic therapies is essential in ACS to prevent recurrent coronary events[2], every effort should be made to identify and act promptly on modifiable bleeding risk factors (i.e., anaemia, falls/trauma, use of NSAIDs or corticosteroids) in the acute setting – particularly within the first 30 days after STEMI.

This is the first study validating the ARC-HBR criteria in ACS and CCS patients separately. The ARC-HBR consensus did not include the acute presentation among the HBR criteria because the increased bleeding risk associated with ACS was deemed to be related to the more aggressive antiplatelet therapy and inconsistent evidence from the literature. Our analysis suggests that the ARC-HBR score discrimination was lower in ACS compared with CCS, mainly because of an underestimation of the bleeding risk among patients at a lower score. After extensive adjustment, including type and duration of antithrombotic therapy, ACS presentation appears to affect bleeding risk independently by acting somewhat as a minor HBR criterion. This consideration derives from the observation that the risk of bleeding is higher in ACS than CCS patients but still below the proposed 4% risk threshold for one-year major bleeding when assessed in isolation. Of note, this effect seems to be dissipated at scores ≥1.5, when the presence of multiple HBR criteria might prevail on the risks associated with ACS *per se*.

Our previous analysis showed that most of the so-called minor criteria identify in isolation patients at HBR and should be regarded



Central illustration. *Clinical presentation and bleeding risk after PCI. ACS presentation per se predisposes to excessive bleeding risk compared with CCS (A) that is driven largely by non-access-site complications occurring mainly in the first 30 days. The bleeding risk was highest among STEMI, intermediate among NSTEMI, and minimal in unstable angina. ACS per se might qualify as a minor criterion in future iterations of the ARC-HBR framework (B). ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; HR: hazard ratio; NSTEMI: non-ST-segment elevation myocardial infarction; OAC: oral anticoagulation; STEMI: ST-segment elevation myocardial infarction*

as major more than minor criteria[4]. Our current analysis adds to the previous one by suggesting that ACS might qualify as a truly minor criterion in future iterations of the proposed ARC-HBR nomenclature. This consideration is further supported by the observation that the discrimination ability of the ARC-HBR score slightly increases when ACS is included as an additional minor risk criterion.

The causes underlying a higher bleeding risk in ACS patients can only be speculated upon. Inflammation and haemostasis are

known to be tightly intertwined as platelets, leukocytes, and interleukins are involved in both mechanisms[7,19]. The development of a pro-inflammatory state in ACS patients might lead to a pro-haemorrhagic state, which could partly explain the excess in bleeding complications – the so-called inflammatory bleeding[7]. This hypothesis potentially matches our findings which show a more pronounced effect in the early post-PCI phase and in STEMIs – both featuring a more prominent inflammatory response[19]. The possible role of inflammation is also supported by prior studies reporting an independent association between white blood cell count and bleeding risk after PCI[16,20]. Differences in patient management may also partly account (despite multivariable adjustments) for bleeding predisposition in ACS. As prompt mechanical reperfusion is critical in ACS[2,8], bleeding risk assessment is usually incomplete before or shortly after the intervention (i.e., laboratory values not yet available). In addition, even if bleeding risk factors are known upfront, a timely PCI remains mandatory in ACS, giving little or no chance to address concomitant risk conditions adequately. Conversely, in CCS patients, careful assessment of bleeding risk is feasible, and PCI can be postponed pending the correction of modifiable factors predisposing to bleeding. Our analysis supports these considerations, showing that severe anaemia and history of recent trauma/surgery were less prevalent in the CCS than in the ACS cohort.

Altogether, our findings lend support to the concept that clinical presentation might integrate the bleeding risk stratification in addition to other validated risk factors such as those included in the ARC-HBR document, yet carrying a truly minor impact on risk prediction.

Limitations

Our results have several limitations. First, this is a single-centre study and may suffer from limited generalisability. However, the clinical characteristics of our study groups and the incidence of bleeding are consistent with those reported in multicentre cohorts[3,6,9,12]. Despite extensive adjustment, which was made possible by the large number of bleeding events accrued, we cannot exclude the effect of residual confounders, including more intense antithrombotic therapies in ACS than in CCS patients. Therefore, replication of our findings in other data sets remains desirable. Proton pump inhibitors were prescribed in about 40% of patients in our cohort. However, the prescription rate is overall consistent with other large contemporary registries of patients treated with DAPT for coronary artery disease[21]. Among the ARC-HBR criteria, eight were adjudicated retrospectively, which may potentially have resulted in an underestimation of their prevalence. Finally, one single major ARC-HBR criterion, planned post-PCI surgery, was not evaluated.

Conclusions

ACS presentation *per se* confers higher bleeding risk compared with CCS, largely owing to non-access-site complications that occur mainly in the first 30 days and seem more pronounced among STEMI patients. The ARC-HBR framework performed less well among ACS patients due to bleeding risk underestimation among those with no, one, or two minor criteria or a single major criterion. However, ACS presentation did not confer in isolation an HBR status and might therefore qualify as a minor criterion in future iterations of the ARC-HBR framework.

Impact on daily practice

Acute coronary syndrome presentation *per se* predisposes to excessive bleeding risk after PCI compared with chronic coronary syndrome, even after adjusting for clinical and procedural factors. The higher risk of bleeding in acute coronary syndrome patients is largely due to non-access-site complications occurring mainly in the first 30 days, which seems more pronounced in the setting of STEMI. Clinical presentation can affect the risk of bleeding events after PCI and should therefore inform risk stratification and clinical decision making in daily practice.

Guest Editor

This paper was guest edited by Franz-Josef Neumann, MD; Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany.

Funding

This study was supported by the Department of Cardiology at Bern University Hospital, Bern, Switzerland.

Conflict of interest statement

S. Stortecky reports grants from Edwards Lifesciences, Medtronic, Abbott Vascular, and Boston Scientific, and personal fees from Boston Scientific/BTG, and Teleflex, outside the submitted work. T. Pilgrim reports grants and personal fees from Biotronik, and Boston Scientific, personal fees from HighLife SAS, and other from Medtronic, outside the submitted work. D. Capodanno reports personal fees from AstraZeneca, Bayer, Sanofi, Boehringer, Daiichi Sankyo, and Biosensors, outside the submitted work. P. Urban reports other from CERC (CRO in Massy, France), during the conduct of the study, other from MedAlliance, and personal fees from Edwards Lifesciences, and Biosensors, outside the submitted work. L. Räber reports research grants to the institution by Abbott, Biotronik, Boston Scientific, Medis, Sanofi, and Regeneron, and speaker/consultation from Abbott, Amgen, AstraZeneca, Canon, Sanofi, and Vifor. S. Windecker reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, and Sinomed. S. Windecker serves as unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sinomed, V-Wave and Xeltis, but has not received personal payments from pharmaceutical companies or device manufacturers. He is also member of the steering/executive

committee group of several investigator-initiated trials that receive funding from industry without impact on his personal remuneration. S. Windecker is an unpaid member of the Pfizer Research Award selection committee in Switzerland. M. Valgimigli reports personal fees from AstraZeneca, grants and personal fees from Terumo, personal fees from Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Opsens, Bayer, CoreFLOW, Idorsia Pharmaceuticals Ltd, Universität Basel | Dept. Klinische Forschung, Vifor, Bristol Myers Squibb SA, iVascular, and Medscape, outside the submitted work. The Guest Editor reports lecture fees paid to his institution from Amgen, Bayer Healthcare, Biotronik, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Edwards Lifesciences, Ferrer, Pfizer, and Novartis, consultancy fees paid to his institution from Boehringer Ingelheim, and grant support from Bayer Healthcare, Boston Scientific, Biotronik, Edwards Lifesciences, GlaxoSmithKline, Medtronic, and Pfizer. The other authors have no conflicts of interest to declare.

References

1. 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.

2. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni 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.

3. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, Ohman ME, Witzenbichler B, Guagliumi G, Lansky AJ, Stone GW. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol.* 2010;55:2556-66.

4. Corpataux N, Spirito A, Gragnano F, Vaisnora L, Galea R, Svab S, Gargiulo G, Zanchin T, Zanchin C, Siontis G, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Räber L, Capodanno D, Urban P, Pocock S, Heg D, Windecker S, Valgimigli M. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. *Eur Heart J.* 2020;41:3743-9.

5. Loh JP, Pendyala LK, Torguson R, Chen F, Satler LF, Pichard AA, Waksman R. Incidence and correlates of major bleeding after percutaneous coronary intervention across different clinical presentations. *Am Heart J.* 2014;168:248-55.

6. Mehran R, Pocock S, Nikolsky E, Dangas GD, Clayton T, Claessen BE, Caixeta A, Feit F, Manoukian SV, White H, Bertrand M, Ohman EM, Parise H, Lansky AJ, Lincoff AM, Stone GW. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. *JACC Cardiovasc Interv.* 2011;4:654-64.

7. Ho-Tin-Noé B, Boulaftali Y, Camerer E. Platelets and vascular integrity: how platelets prevent bleeding in inflammation. *Blood.* 2018;131:277-88.

8. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42:1289-367.

9. Mehta SK, Frutkin AD, Lindsey JB, House JA, Spertus JA, Rao SV, Ou FS, Roe MT, Peterson ED, Marso SP; National Cardiovascular Data Registry. Bleeding in patients undergoing percutaneous coronary intervention; the development of a clinical risk algorithm from the National Cardiovascular Data Registry. *Circ Cardiovasc Interv.* 2009;2:222-9.

10. Patel NJ, Pau D, Nalluri N, Bhatt P, Thakkar B, Kanotra R, Agnihotri K, Ainani N, Patel N, Patel N, Shah S, Kadavath S, Arora S, Sheikh A, Badheka AO, Lafferty J, Alfonso C, Cohen M. Temporal Trends, Predictors, and Outcomes of In-Hospital Gastrointestinal Bleeding Associated With Percutaneous Coronary Intervention. *Am J Cardiol.* 2016;118:1150-7.

11. Ko DT, Yun L, Wijeysundera HC, Jackevicius CA, Rao SV, Austin PC, Marquis JF, Tu JV. Incidence, predictors, and prognostic implications of hospitalization for late bleeding after percutaneous coronary intervention for patients older than 65 years. *Circ Cardiovasc Interv.* 2010;3:140-7.

12. Feit F, Voeltz MD, Attubato MJ, Lincoff AM, Chew DP, Bittl JA, Topol EJ, Manoukian SV. Predictors and Impact of Major Hemorrhage on Mortality Following Percutaneous Coronary Intervention from the REPLACE-2 Trial. *Am J Cardiol.* 2007;100:1364-9.

13. Verheugt FW, Steinhubl SR, Hamon M, Darius H, Steg PG, Valgimigli M, Marso SP, Rao SV, Gershlick AH, Lincoff AM, Mehran R, Stone GW. Incidence, prognostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2011;4:191-7.

14. Subherwal S, Peterson ED, Dai D, Thomas L, Messenger JC, Xian Y, Brindis RG, Feldman DN, Senter S, Klein LW, Marso SP, Roe MT, Rao SV. Temporal trends in and factors associated with bleeding complications among patients undergoing percutaneous coronary intervention; a report from the National Cardiovascular Data CathPCI Registry. *J Am Coll Cardiol.* 2012;59:1861-9.

15. 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.

16. Gragnano F, Heg D, Franzone A, McFadden EP, Leonardi S, Piccolo R, Vranckx P, Branca M, Serruys PW, Benit E, Liebetrau C, Janssens L, Ferrario M, Zurakowski A, Diletti R, Dominici M, Huber K, Slagboom T, Buszman P, Bolognese L, Tumscitz C, Bryniarski K, Aminian A, Vrolix M, Petrov I, Garg S, Naber C, Prokopczuk J, Hamm C, Steg PG, Jüni P, Windecker S, Valgimigli M; GLASSY Investigators. PRECISE-DAPT score for bleeding risk prediction in patients on dual or single antiplatelet regimens: insights from the GLOBAL LEADERS and GLASSY. *Eur Heart J Cardiovasc Pharmacother.* 2020 Sep 17. [Epub ahead of print].

17. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, Dangas GD, Lincoff AM, White HD, Moses JW, King SB 3rd, Ohman EM, Stone GW. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes; an analysis from the ACUITY Trial. *J Am Coll Cardiol.* 2007;49:1362-8.

18. Mathews R, Peterson ED, Chen AY, Wang TY, Chin CT, Fonarow GC, Cannon CP, Rumsfeld JS, Roe MT, Alexander KP. In-hospital major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and validation of a model from the ACTION Registry®-GWTGTM. *Am J Cardiol.* 2011;107:1136-43.

19. Crea F, Libby P. Acute Coronary Syndromes: The Way Forward From Mechanisms to Precision Treatment. *Circulation.* 2017;136:1155-66.

20. Palmerini T, Généreux P, Mehran R, Dangas G, Caixeta A, Della Riva D, Mariani A, Xu K, Stone GW. Association among leukocyte count, mortality, and bleeding in patients with non–ST-segment elevation acute coronary syndromes (from the Acute Catheterization and Urgent Intervention Triage StrategY [ACUITY] Trial). *Am J Cardiol.* 2013;111:1237-45.

21. Sehested TSG, Carlson N, Hansen PW, Gerds TA, Charlot MG, Torp-Pedersen C, Køber L, Gislason GH, Hlatky MA, Fosbøl EL. Reduced risk of gastrointestinal bleeding associated with proton pump inhibitor therapy in patients treated with dual antiplatelet therapy after myocardial infarction. *Eur Heart J.* 2019;40:1963-70.

Supplementary data

Supplementary Appendix 1. Methods: data collection during follow-up and DAPT duration.

Supplementary Table 1. Definition of the High Bleeding Risk (HBR) criteria according to the Academic Research Consortium (ARC) consensus.

Supplementary Table 2. Procedural characteristics according to clinical presentation.

Supplementary Table 3. Medications according to clinical presentation.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00181

Supplementary data

Supplementary Appendix 1. Methods

Data collection during follow-up

Throughout one year after index PCI, patients were systematically contacted after discharge in case of any unscheduled hospital visit (i.e., due to bleeding complications or ischaemic events) and during planned hospital visits (i.e., staged coronary procedures). All participants were finally evaluated at one-year follow-up. Detailed information regarding adverse events and concomitant medications were recorded by trained study personnel. Bleeding events were categorised as access-site and non-access-site-related. Access-site bleeding included bleeding events complicating vascular access used to perform the PCI procedure and/or other invasive procedures (for example, intra-aortic balloon pump or left ventricular assist device insertion). At one year after index PCI, a health questionnaire was sent to all living patients with questions on re-hospitalisation and any adverse event (including bleeding and ischaemic occurrences), followed by phone contact in case of missing response. General practitioners, referring cardiologists, and other medical institutions were reached as necessary in order to collect discharge letters, coronary angiography documentation, or any other relevant medical records. A clinical events committee adjudicated all events using original source documents. Survival data were obtained from hospital records and municipal civil registries.

DAPT duration

Dual antiplatelet therapy (DAPT) consisting of aspirin and a $P2Y_{12}$ inhibitor was initiated before, at the time of, or immediately after the procedure. Prasugrel was introduced from September 2009, and ticagrelor from November 2011. The majority of patients with chronic coronary syndrome (CCS) 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 six-month duration. From August 2017, the routinely recommended DAPT duration for CCS patients became six months, in agreement with existing European and American guidelines.

Supplementary Table 1. Definition of the high bleeding risk (HBR) criteria according to the Academic Research Consortium (ARC) consensus.

	Major criteria	Minor criteria
Advanced age		Age ≥75 years
Oral anticoagulation	Anticipated use of long-term oral anticoagulation	
Chronic kidney disease	Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/ min)
Anaemia	Haemoglobin <11 g/dL	Haemoglobin 11–12.9 g/dL for men, and 11–11.9 g/dL for women
Prior bleeding	Spontaneous bleeding requiring hospitalisation or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalisation or transfusion within the past 12 months not meeting the major criterion
Thrombocytopaenia	Moderate or severe baseline thrombocytopaenia (platelet count <100 $\times 10^9$/L)	
Chronic bleeding diathesis	Inherited or acquired conditions known to be associated with increased bleeding risk such as platelet dysfunction, von Willebrand disease, inherited or acquired clotting factor deficiencies (including factors VII, VIII [haemophilia A], IX [haemophilia B], and XI), or acquired antibodies to clotting factors, among others	
Liver cirrhosis	Liver cirrhosis with portal hypertension	
NSAIDs or steroids		Long-term use of oral NSAIDs or steroids
Active malignancy	Diagnosis within the previous 12 months or ongoing active treatment, excluding non-melanoma skin cancer	
Prior stroke	Previous spontaneous ICH (at any time) Previous traumatic ICH within the past 12 months Presence of a brain arteriovenous malformation Moderate or severe ischaemic stroke within the past 6 months	Any ischaemic stroke at any time not meeting the major criterion
Planned surgery	Non-deferrable major surgery on dual antiplatelet therapy*	
Prior surgery or trauma	Recent major surgery or major trauma within 30 days before PCI	

* Not adjudicated in the current analysis.
CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ICH: intracranial haemorrhage; NSAIDs: non-steroidal anti-inflammatory drugs; PCI: percutaneous coronary intervention

Supplementary Table 2. Procedural characteristics according to clinical presentation.

	All patients (n=16,821)	ACS (n=9,503)	CCS (n=7,318)	*p*-value
Access site	n=11,879	n=6,792	n=5,087	<0.001
Radial	3,964 (33.4%)	2,137 (31.5%)	1,827 (35.9%)	<0.001
Femoral	7,912 (66.6%)	4,653 (68.5%)	3,259 (64.1%)	<0.001
Brachial	3 (0.0%)	2 (0.0%)	1 (0.0%)	>0.99
Coronary arteries treated				
Left main artery	809 (4.8%)	424 (4.5%)	385 (5.3%)	0.018
Left anterior descending artery	8,677 (51.6%)	4,881 (51.4%)	3,796 (51.9%)	0.51
Left circumflex artery	5,354 (31.8%)	2,952 (31.1%)	2,402 (32.8%)	0.015
Right coronary artery	6,104 (36.3%)	3,479 (36.6%)	2,625 (35.9%)	0.32
Bypass graft	556 (3.3%)	251 (2.6%)	305 (4.2%)	<0.001
Number of lesions	n=16,821	n=9,503	n=7,318	0.38
1	9,767 (58.1%)	5,560 (58.5%)	4,207 (57.5%)	0.18
2	4,702 (28.0%)	2,621 (27.6%)	2,081 (28.4%)	0.22
≥3	2,352 (14.0%)	1,322 (13.9%)	1,030 (14.1%)	0.77
Multivessel treatment (2-3 vessels)	4,398 (26.1%)	2,310 (24.3%)	2,088 (28.5%)	<0.001
IABP (prior to or during PCI)	210 (1.2%)	190 (2.0%)	20 (0.3%)	<0.001
Percutaneous left ventricular assist device	128 (0.8%)	104 (1.2%)	24 (0.4%)	<0.001
Staged PCI	2,714 (16.1%)	2,013 (21.2%)	701 (9.6%)	<0.001
Access site of first staged PCI	n=2,147	n=1,538	n=609	0.59
Radial	975 (45.4%)	704 (45.8%)	271 (44.5%)	
Femoral	1,172 (54.6%)	834 (54.2%)	338 (55.5%)	
Number of lesions treated	n=27,085	n=15,245	n=11,840	
Lesion type				
Restenotic lesion	1,576 (5.8%)	709 (4.7%)	867 (7.3%)	<0.001
Evidence of thrombus	3,883 (14.4%)	3,803 (25.0%)	80 (0.7%)	<0.001
Chronic total occlusion	830 (3.1%)	305 (2.0%)	525 (4.4%)	<0.001
Stent type				
Any DES	23,887 (95.2%)	13,610 (95.2%)	10,277 (95.1%)	0.66
Any bare metal stent	1,064 (4.2%)	610 (4.3%)	454 (4.2%)	0.84

Any absorbable scaffold*	79 (0.3%)	36 (0.3%)	43 (0.4%)	0.066
Mix of types of stent	42 (0.2%)	30 (0.2%)	12 (0.1%)	0.052
Only DES used per patient	24,959 (92.2%)	14,113 (92.6%)	10,846 (91.6%)	0.003
Total number of stents implanted in this lesion	1.32±0.61	1.35±0.63	1.28±0.58	<0.001
Total stent length, mm	27.76±17.36	29.14±17.92	25.93±16.41	<0.001
Mean stent diameter, mm	2.94±0.59	2.96±0.63	2.93±0.52	<0.001
Treatment of a bifurcation	3,750 (13.9%)	2,311 (15.2%)	1,439 (12.2%)	<0.001
Baseline TIMI flow	n=26,607	n=15,066	n=11,541	<0.001
0 or 1	6,239 (23.4%)	5,194 (34.5%)	1,045 (9.1%)	
2	4,210 (15.8%)	2,603 (17.3%)	1,607 (13.9%)	
3	16,157 (60.7%)	7,268 (48.2%)	8,889 (77.0%)	
Post-PCI TIMI flow	n=26,727	n=15,112	n=11,615	<0.001
0 or 1	184 (0.7%)	138 (0.9%)	46 (0.4%)	
2	387 (1.4%)	329 (2.2%)	58 (0.5%)	
3	26,156 (97.9%)	14,645 (96.9%)	11,511 (99.1%)	

* Polymer or metal absorbable.
Data of index PCI shown.
ACS: acute coronary syndrome; CCS: chronic coronary syndrome; DES: drug-eluting stent; IABP: intra-aortic balloon pump; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 3. Medications according to clinical presentation.

	All patients (n=16,821)	ACS (n=9,503)	CCS (n=7,318)	*p*-value
Procedure medications				
No loading dose	1,387 (8.2%)	544 (5.7%)	843 (11.5%)	<0.001
Only loading clopidogrel	8,060 (47.9%)	3,046 (32.1%)	5,014 (68.5%)	<0.001
Only loading prasugrel	1,908 (11.3%)	1,341 (14.1%)	567 (7.7%)	<0.001
Only loading ticagrelor	4,605 (27.4%)	3,720 (39.1%)	885 (12.1%)	<0.001
Loading clopidogrel and prasugrel	681 (4.0%)	676 (7.1%)	5 (0.1%)	<0.001
Loading clopidogrel and ticagrelor	154 (0.9%)	151 (1.6%)	3 (0.0%)	<0.001
Loading prasugrel and ticagrelor	26 (0.2%)	25 (0.3%)	1 (0.0%)	<0.001
Unfractionated heparin	16,452 (97.9%)	9,373 (98.7%)	7,079 (96.9%)	<0.001
Fondaparinux	1,685 (10.9%)	1,604 (18.2%)	81 (1.2%)	<0.001
LMWH	307 (1.8%)	238 (2.5%)	69 (0.9%)	<0.001
Bivalirudin	302 (1.8%)	103 (1.1%)	199 (2.7%)	<0.001
Glycoprotein IIb/IIIa inhibitors	1,497 (8.9%)	1,297 (13.7%)	200 (2.7%)	<0.001
Thrombolytic therapy	48 (0.3%)	32 (0.4%)	16 (0.2%)	0.19
Discharge medications				
Aspirin	15,881 (96.7%)	8,991 (98.4%)	6,890 (94.7%)	<0.001
Clopidogrel	8,850 (53.9%)	3,311 (36.2%)	5,539 (76.1%)	<0.001
Prasugrel	2,721 (16.6%)	2,090 (22.9%)	631 (8.7%)	<0.001
Ticagrelor	4,539 (27.7%)	3,615 (39.5%)	924 (12.7%)	<0.001
Any DAPT	15,623 (95.2%)	8,890 (97.3%)	6,733 (92.6%)	<0.001
Any OAC	1,943 (11.8%)	811 (8.9%)	1,132 (15.6%)	<0.001
Novel oral anticoagulants	689 (5.9%)	319 (4.9%)	370 (7.3%)	<0.001
Any DAPT and OAC/NOAC	1,655 (10.1%)	694 (7.6%)	961(13.2%)	<0.001
Statin	14,924 (90.9%)	8,513 (93.2%)	6,411 (88.1%)	<0.001
PPI	5,036 (40.5%)	3,082 (41.9%)	1,954 (38.6%)	<0.001
One-year follow-up medications				
Aspirin*	12,898 (89.9%)	7,233 (92.3%)	5,665 (86.9%)	<0.001
Clopidogrel*	5,378 (37.5%)	2,153 (27.5%)	3,225 (49.4%)	<0.001
Prasugrel*	2,069 (14.4%)	1,603 (20.5%)	466 (7.1%)	<0.001

Ticagrelor*	2,951 (20.6%)	2,353 (30.0%)	598 (9.2%)	<0.001
Any DAPT*	9,365 (65.2%)	5,685 (72.6%)	3,680 (56.4%)	<0.001
Any OAC	1,971 (13.7%)	900 (11.5%)	1,071 (16.4%)	<0.001
Novel oral anticoagulants	836 (7.4%)	413 (6.5%)	423 (8.5%)	<0.001
Any DAPT and OAC/NOAC	250 (1.7%)	132 (1.7%)	118 (1.8%)	0.60
Statin	12,042 (84.0%)	6,797 (87.0%)	5,245 (80.4%)	<0.001
PPI	3,993 (34.0%)	2,330 (34.6%)	1,663 (33.2%)	0.12

* Not stopped before 350 days since index PCI considered compliant.
ACS: acute coronary syndrome; CCS: chronic coronary syndrome; DAPT: dual antiplatelet therapy; LMWH: low molecular weight heparin; NOAC: new oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor

Supplementary Table 4. Adjudicated outcome events at one year according to clinical presentation.

	ACS (n=9,503)	CCS (n=7,318)	Hazard ratio (95% CI)	*p*-value
BARC type 2	279 (3.30%)	138 (2.03%)	1.67 (1.36-2.04)	<0.001
Access-site	11 (0.12%)	2 (0.03%)	4.29 (0.95-19.34)	0.058
Non-access-site	270 (3.20%)	136 (2.00%)	1.64 (1.33-2.01)	<0.001
BARC type 3	397 (4.62%)	226 (3.29%)	1.43 (1.22-1.69)	<0.001
Access-site	55 (0.60%)	35 (0.49%)	1.23 (0.80-1.88)	0.34
Non-access-site	346 (4.06%)	195 (2.85%)	1.46 (1.22-1.74)	<0.001
BARC type 3a	171 (2.01%)	112 (1.63%)	1.24 (0.98-1.58)	0.073
Access-site	27 (0.30%)	18 (0.25%)	1.17 (0.64-2.12)	0.60
Non-access-site	146 (1.74%)	97 (1.42%)	1.24 (0.96-1.60)	0.10
BARC type 3b	212 (2.46%)	96 (1.39%)	1.79 (1.41-2.28)	<0.001
Access-site	28 (0.31%)	17 (0.24%)	1.29 (0.70-2.35)	0.41
Non-access-site	185 (2.16%)	80 (1.16%)	1.89 (1.45-2.45)	<0.001
BARC type 3c	42 (0.50%)	26 (0.40%)	1.32 (0.81-2.15)	0.26
BARC type 4	27 (0.31%)	3 (0.04%)	7.26 (2.20-23.94)	0.001
BARC type 5	30 (0.36%)	24 (0.35%)	1.02 (0.59-1.74)	0.95
Access-site	1 (0.01%)	0 (0.00%)	2.31 (0.09-56.70)	>0.99
Non-access-site	29 (0.35%)	24 (0.35%)	0.98 (0.57-1.69)	0.94
TIMI minimal	309 (3.66%)	167 (2.46%)	1.52 (1.26-1.84)	<0.001
Access-site	14 (0.15%)	5 (0.07%)	2.18 (0.79-6.06)	0.13
Non-access-site	296 (3.52%)	162 (2.39%)	1.51 (1.24-1.83)	<0.001
TIMI minor	179 (2.10%)	99 (1.43%)	1.47 (1.15-1.88)	0.002
Access-site	28 (0.31%)	24 (0.34%)	0.92 (0.53-1.58)	0.75
Non-access-site	154 (1.82%)	77 (1.12%)	1.64 (1.25-2.15)	<0.001
TIMI major	261 (3.02%)	120 (1.74%)	1.77 (1.43-2.20)	<0.001
Access-site	27 (0.30%)	8 (0.11%)	2.62 (1.19-5.77)	0.017
Non-access-site	236 (2.75%)	114 (1.66%)	1.69 (1.35-2.12)	<0.001
TIMI major or minor	418 (4.84%)	218 (3.15%)	1.57 (1.33-1.84)	<0.001
Access-site	55 (0.60%)	32 (0.45%)	1.34 (0.87-2.08)	0.18
Non-access-site	369 (4.31%)	190 (2.76%)	1.59 (1.34-1.90)	<0.001
GUSTO mild	326 (3.83%)	169 (2.47%)	1.59 (1.32-1.91)	<0.001
Access-site	26 (0.29%)	8 (0.11%)	2.54 (1.15-5.61)	0.021

Non-access-site	304 (3.59%)	161 (2.36%)	1.56 (1.28-1.88)	<0.001
GUSTO moderate	198 (2.34%)	110 (1.60%)	1.47 (1.17-1.86)	0.001
Access-site	27 (0.30%)	20 (0.28%)	1.06 (0.59-1.89)	0.84
Non-access-site	171 (2.05%)	92 (1.35%)	1.53 (1.19-1.98)	<0.001
GUSTO severe	226 (2.62%)	119 (1.74%)	1.54 (1.23-1.93)	<0.001
Access-site	16 (0.17%)	10 (0.14%)	1.24 (0.56-2.74)	0.59
Non-access-site	211 (2.46%)	111 (1.63%)	1.55 (1.23-1.95)	<0.001
GUSTO severe or moderate	401 (4.68%)	221 (3.21%)	1.48 (1.26-1.75)	<0.001
Access-site	43 (0.47%)	30 (0.42%)	1.12 (0.70-1.79)	0.63
Non-access-site	362 (4.25%)	195 (2.85%)	1.52 (1.28-1.81)	<0.001
Death	862 (9.61%)	333 (4.82%)	2.11 (1.86-2.39)	<0.001
Cardiac death	655 (7.32%)	190 (2.79%)	2.79 (2.38-3.28)	<0.001
Vascular death	54 (0.64%)	35 (0.51%)	1.26 (0.82-1.93)	0.28
Non-cardiovascular death	153 (1.85%)	108 (1.59%)	1.18 (0.92-1.51)	0.19
Myocardial infarction	340 (3.99%)	361 (5.11%)	0.74 (0.64-0.86)	<0.001
Target vessel myocardial infarction	214 (2.48%)	305 (4.29%)	0.55 (0.46-0.65)	<0.001
Any revascularisation	696 (8.33%)	496 (7.32%)	1.17 (1.04-1.31)	0.008
Target lesion revascularisation	352 (4.20%)	266 (3.92%)	1.09 (0.93-1.28)	0.29
Target vessel revascularisation	497 (5.93%)	379 (5.58%)	1.08 (0.95-1.24)	0.23
Definite stent thrombosis	131 (1.49%)	64 (0.91%)	1.64 (1.21-2.21)	0.001
Stroke or TIA	198 (2.34%)	105 (1.54%)	1.54 (1.22-1.95)	<0.001
Stroke	164 (1.94%)	84 (1.23%)	1.59 (1.22-2.07)	<0.001
Ischaemic stroke	124 (1.45%)	58 (0.84%)	1.74 (1.27-2.38)	<0.001
Intracerebral haemorrhage	32 (0.40%)	27 (0.41%)	0.97 (0.58-1.62)	0.90
Unclear stroke	7 (0.08%)	0 (0.00%)	11.55 (0.66-202.20)	0.021
TIA	35 (0.42%)	21 (0.30%)	1.37 (0.80-2.35)	0.25
Death, myocardial infarction, or stroke	1237 (13.78%)	696 (9.91%)	1.42 (1.29-1.56)	<0.001
NACCE (death, myocardial infarction, stroke, BARC 3 or 5)	1494 (16.61%)	843 (11.99%)	1.42 (1.31-1.55)	<0.001

First event per (sub)event type counted per patient (% from lifetable estimate).
Crude risk difference assumes no event in patients alive and censored before 365 days.
ACS: acute coronary syndrome; CCS: chronic coronary syndrome; CI: confidence interval; GUSTO: Global Strategies for Opening Occluded Coronary Arteries; NACCE: net adverse cardiac and cerebrovascular events; TIA: transient ischaemic attack; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 5. Univariate analysis for overall, non-access-site, and access-site BARC type 3 or 5 bleeding at one year.

	Overall BARC 3 or 5		Non-access-site BARC 3 or 5		Access-site BARC 3 or 5	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Acute coronary syndrome*	1.41 (1.20-1.64)	<0.001	1.41 (1.19-1.67)	<0.001	1.25 (0.82-1.91)	0.29
Age (per 10 years)	1.38 (1.29-1.48)	<0.001	1.37 (1.28-1.48)	<0.001	1.47 (1.22-1.78)	<0.001
BMI	0.95 (0.93-0.97)	<0.001	0.95 (0.93-0.97)	<0.001	0.96 (0.91-1.00)	0.074
Current smoker	0.77 (0.64-0.92)	0.004	0.83 (0.69-1.00)	0.054	0.34 (0.17-0.65)	0.001
Diabetes mellitus	1.12 (0.94-1.33)	0.19	1.12 (0.94-1.34)	0.21	1.10 (0.69-1.77)	0.68
Hypertension	1.23 (1.04-1.45)	0.017	1.26 (1.05-1.50)	0.013	1.08 (0.68-1.70)	0.75
Hypercholesterolaemia	0.84 (0.72-0.97)	0.021	0.84 (0.71-0.98)	0.029	0.78 (0.52-1.19)	0.25
Family history of coronary artery disease	0.80 (0.67-0.96)	0.016	0.78 (0.65-0.95)	0.011	0.89 (0.55-1.44)	0.63
Previous myocardial infarction	1.02 (0.84-1.23)	0.85	1.03 (0.84-1.26)	0.75	0.81 (0.46-1.43)	0.47
Previous PCI	0.88 (0.73-1.05)	0.14	0.91 (0.75-1.09)	0.30	0.60 (0.34-1.04)	0.070
Previous CABG	1.00 (0.78-1.27)	0.99	1.10 (0.85-1.41)	0.46	0.30 (0.09-0.93)	0.038
History of cerebrovascular accident	1.57 (1.24-1.99)	<0.001	1.51 (1.17-1.95)	0.001	1.72 (0.92-3.24)	0.090
Peripheral artery disease	1.44 (1.15-1.81)	0.002	1.52 (1.20-1.93)	<0.001	1.15 (0.58-2.29)	0.68
History of malignancy	1.62 (1.33-1.98)	<0.001	1.70 (1.38-2.10)	<0.001	0.91 (0.46-1.80)	0.77
Renal failure	2.59 (2.22-3.02)	<0.001	2.63 (2.24-3.09)	<0.001	2.33 (1.52-3.58)	<0.001
History of atrial fibrillation/flutter	2.17 (1.80-2.61)	<0.001	2.20 (1.80-2.69)	<0.001	1.89 (1.10-3.22)	0.021
Chronic obstructive lung disease	1.52 (1.19-1.95)	<0.001	1.59 (1.23-2.06)	<0.001	1.33 (0.64-2.74)	0.44
History of spontaneous bleeding	2.61 (2.05-3.33)	<0.001	2.63 (2.04-3.40)	<0.001	2.43 (1.22-4.83)	0.011
Left ventricular function (%)	0.98 (0.97-0.98)	<0.001	0.98 (0.97-0.98)	<0.001	0.98 (0.96-0.99)	0.001
Killip II, III or IV	2.85 (2.43-3.33)	<0.001	2.93 (2.48-3.46)	<0.001	2.54 (1.64-3.94)	<0.001
Femoral access	1.85 (1.59-2.15)	<0.001	1.92 (1.64-2.26)	<0.001	1.56 (1.03-2.35)	0.035
IABP	2.82 (1.81-4.40)	<0.001	2.54 (1.55-4.17)	<0.001	4.22 (1.55-11.51)	0.005
Percutaneous left ventricular assist device	8.80 (6.19-12.53)	<0.001	7.90 (5.36-11.65)	<0.001	12.46 (5.76-26.96)	<0.001
Staged PCI	0.90 (0.73-1.11)	0.34	0.89 (0.71-1.11)	0.35	0.89 (0.50-1.61)	0.70
Femoral access at staged PCI	1.25 (0.95-1.63)	0.10	1.21 (0.91-1.62)	0.19	1.35 (0.65-2.78)	0.42
Triple therapy at discharge	1.45 (1.19-1.77)	<0.001	1.43 (1.16-1.77)	<0.001	1.70 (1.02-2.85)	0.043
Any OAC at discharge	1.60 (1.33-1.92)	<0.001	1.58 (1.30-1.92)	<0.001	1.93 (1.19-3.11)	0.007
Any DAPT at discharge	0.58 (0.43-0.77)	<0.001	0.60 (0.44-0.82)	0.001	0.45 (0.22-0.92)	0.029

DAPT with potent $P2Y_{12}$ inhibitor at discharge	0.83 (0.71-0.97)	0.018	0.83 (0.71-0.98)	0.027	0.77 (0.50-1.18)	0.23
PPI at discharge (not at follow-up)	2.05 (1.73-2.44)	<0.001	2.09 (1.74-2.51)	<0.001	1.91 (1.17-3.11)	0.009
PPI at follow-up (not at discharge)**	2.14 (1.75-2.63)	<0.001	2.36 (1.91-2.91)	<0.001	0.81 (0.35-1.85)	0.61
PPI at discharge and follow-up**	1.39 (1.16-1.66)	<0.001	1.39 (1.15-1.69)	<0.001	1.38 (0.84-2.27)	0.20
Haemoglobin before PCI (g/L)	0.97 (0.97-0.98)	<0.001	0.97 (0.97-0.98)	<0.001	0.97 (0.96-0.98)	<0.001
Number of lesions	1.02 (0.94-1.11)	0.57	0.99 (0.91-1.09)	0.91	1.23 (1.00-1.51)	0.046
Total stent length (mm)***	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.02)	0.10
Left anterior descending artery	0.85 (0.74-0.99)	0.037	0.82 (0.70-0.96)	0.013	1.34 (0.89-2.03)	0.16
Restenotic lesion	0.90 (0.68-1.19)	0.45	0.97 (0.72-1.29)	0.80	0.42 (0.13-1.29)	0.12
Thrombotic lesion	1.28 (1.08-1.52)	0.005	1.33 (1.11-1.59)	0.002	0.89 (0.53-1.51)	0.66
Chronic total occlusion	1.09 (0.78-1.52)	0.61	1.14 (0.80-1.61)	0.47	0.92 (0.34-2.52)	0.87
Currently on SAPT¶	0.52 (0.43-0.62)	<0.001	0.57 (0.47-0.70)	<0.001	0.22 (0.11-0.44)	<0.001
Currently on DAPT¶	1.90 (1.58-2.29)	<0.001	1.72 (1.41-2.09)	<0.001	4.13 (2.14-7.97)	<0.001
Leukocytes (10^3 cells per µL)	1.03 (1.02-1.04)	<0.001	1.03 (1.02-1.04)	<0.001	1.02 (1.00-1.05)	0.08
Thrombocytes (100×10^9/L)	1.00 (1.00-1.00)	0.023	1.00 (1.00-1.00)	0.006	1.00 (1.00-1.00)	0.54
Multivessel treatment	1.12 (0.95-1.32)	0.19	1.10 (0.93-1.31)	0.27	1.28 (0.82-2.00)	0.26
Minimum stent diameter (mm)	1.04 (0.90-1.20)	0.60	1.02 (0.87-1.19)	0.78	1.14 (0.76-1.70)	0.53
Bifurcation treatment	1.33 (1.11-1.58)	0.002	1.35 (1.12-1.63)	0.001	1.31 (0.81-2.14)	0.27
Fondaparinux	0.88 (0.67-1.14)	0.32	0.81 (0.60-1.08)	0.14	1.40 (0.76-2.56)	0.28
Low-molecular-weight heparin	1.61 (1.03-2.50)	0.037	1.63 (1.02-2.61)	0.041	1.24 (0.30-5.02)	0.76
Bivalirudin	0.84 (0.45-1.56)	0.57	0.85 (0.44-1.64)	0.63	0.64 (0.09-4.61)	0.66
Glycoprotein IIb/IIIa inhibitors	1.55 (1.24-1.93)	<0.001	1.42 (1.11-1.81)	0.005	2.25 (1.31-3.86)	0.003

Renal failure: <60 eGFR mL/min per 1.73 m², using the Modification of Diet in Renal Disease (MDRD) formula. OAC and DAPT at discharge, if deceased in hospital: as used at procedure.
* Chronic coronary syndrome (CCS) patients are the reference category.
**No PPI is the reference category.
***Stent length zero for ballooning only.
¶ Time-at-risk is split into sequences of no APT, on SAPT, and on DAPT. Currently not on any APT: reference group. BARC 3 or 5 events are counted per sequence and patient separately.
Estimates derived from 20 multiple imputed data sets, combined using Rubin's rule.

APT: antiplatelet therapy; BARC: Bleeding Academic Research Consortium; BMI: body mass index; CABG: coronary artery bypass graft; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; IABP: intra-aortic balloon pump; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; SAPT: single antiplatelet therapy

Supplementary Table 6. Multivariate analysis for overall, non-access-site, and access-site BARC type 3 or 5 bleeding at one year.

	Overall BARC 3 or 5		**Non-access-site BARC 3 or 5**		**Access-site BARC 3 or 5**	
	Adjusted HR (95% CI)	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**
Acute coronary syndrome*	1.21 (1.01-1.43)	0.034	1.19 (0.99-1.43)	0.063	1.12 (0.69-1.81)	0.65
Age (per 10 years)	1.13 (1.05-1.22)	<0.001	1.11 (1.03-1.20)	0.006	-	-
BMI	0.97 (0.95-0.98)	<0.001	0.96 (0.95-0.98)	<0.001	-	-
Current smoker	-	-	-	-	0.35 (0.18-0.68)	0.002
Prior CABG	-	-	-	-	0.23 (0.07-0.72)	0.012
Renal failure	1.40 (1.18-1.66)	<0.001	1.43 (1.19-1.72)	<0.001	1.46 (0.90-2.36)	0.12
History of atrial fibrillation	1.54 (1.25-1.89)	<0.001	1.53 (1.23-1.91)	<0.001	-	-
Chronic obstructive lung disease	1.19 (0.92-1.53)	0.18	1.22 (0.94-1.59)	0.14	-	-
History of spontaneous bleeding	1.45 (1.13-1.87)	0.004	1.44 (1.10-1.89)	0.008	1.77 (0.86-3.62)	0.11
Left ventricular ejection fraction	-	-	-	-	0.99 (0.97-1.00)	0.088
Haemoglobin before PCI, g/L	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	<0.001	0.98 (0.97-0.99)	<0.001
Leukocytes (10^3 cells per µL)	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	<0.001	-	-
Killip class II, III or IV	1.57 (1.32-1.86)	<0.001	1.62 (1.35-1.94)	<0.001	-	-
Femoral access site	1.22 (1.04-1.44)	0.017	1.26 (1.06-1.50)	0.009	-	-
Percutaneous left ventricular assist device	5.11 (3.53-7.40)	<0.001	4.53 (3.01-6.81)	<0.001	6.27 (2.67-14.69)	<0.001
Staged PCI	0.74 (0.54-1.01)	0.057	0.75 (0.54-1.04)	0.081	-	-
Femoral access site at staged PCI	1.35 (0.91-2.01)	0.13	1.28 (0.84-1.95)	0.25	-	-
Number of lesions	-	-	-	-	1.19 (0.95-1.49)	0.14
Restenotic lesion	-	-	-	-	0.44 (0.14-1.37)	0.15
Thrombotic lesion	-	-	-	-	0.59 (0.32-1.11)	0.10
Total stent length, mm**	1.01 (1.00-1.01)	0.001	1.01 (1.00-1.01)	<0.001	-	-
Minimum stent diameter, mm	-	-	-	-	1.45 (0.94-2.24)	0.096
Low-molecular-weight heparin	-	-	-	-	1.47 (0.92-2.36)	0.10
Fondaparinux	-	-	-	-	1.49 (0.79-2.82)	0.21
Glycoprotein IIb/IIIa inhibitors	1.58 (1.25-2.00)	<0.001	1.42 (1.10-1.83)	0.008	2.59 (1.42-4.72)	0.002
Any DAPT at discharge	0.29 (0.20-0.41)	<0.001	0.33 (0.23-0.48)	<0.001	-	-

DAPT with potent $P2Y_{12}$ inhibitor at discharge	0.83 (0.69-1.00)	0.055	0.84 (0.69-1.02)	0.072	-	-
Currently on SAPT¶	1.59 (0.68-3.73)	0.28	1.62 (0.63-4.11)	0.31	0.25 (0.03-2.02)	0.19
Currently on DAPT¶	4.32 (1.79-10.44)	0.001	3.83 (1.46-10.00)	0.006	1.10 (0.15-7.99)	0.92
PPI at discharge (not at follow-up)	1.87 (1.53-2.28)	<0.001	1.94 (1.57-2.41)	<0.001	-	-
PPI at follow-up (not at discharge)* **	2.55 (2.03-3.19)	<0.001	2.84 (2.25-3.58)	<0.001	-	-
PPI at discharge and follow-up* **	1.48 (1.21-1.82)	<0.001	1.52 (1.22-1.90)	<0.001	-	-

A p-value <0.2 was used to select variables to include in the multivariable model.
Renal failure: <60 eGFR mL/min per 1.73 m^2, using the Modification of Diet in Renal Disease (MDRD) formula.

OAC and DAPT at discharge, if deceased in hospital: as used at procedure.
*Chronic coronary syndrome patients are the reference category.
**Stent length zero for ballooning only.
***No PPI is the reference category.
¶Time-at-risk is split into sequences on no APT, on SAPT and on DAPT. Currently not on any APT is the reference category. Note that stop dates of aspirin were not available and $P2Y_{12}$ inhibitors stop dates were approximated if unclear. BARC 3 or 5 bleeding events are counted per sequence and patient separately. Since most access-site bleedings occur in-hospital under the current APT treatment, the discharge prescriptions were dropped from the model as they have a high degree of redundancy with current APT.
Estimates derived from 20 multiple imputed data sets, combined using Rubin's rule.

APT: antiplatelet therapy; BARC: Bleeding Academic Research Consortium; BMI: body mass index; CABG: coronary artery bypass graft; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; SAPT: single antiplatelet therapy

Supplementary Table 7. Univariate analysis for overall, non-access-site, and access-site BARC type 2, 3 or 5 bleeding at one year.

	Overall BARC 2, 3 or 5		Non-access-site BARC 2, 3 or 5		Access-site BARC 2, 3 or 5	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Acute coronary syndrome*	1.49 (1.31-1.69)	<0.001	1.49 (1.31-1.71)	<0.001	1.42 (0.95-2.12)	0.090
Age (per 10 years)	1.38 (1.31-1.46)	<0.001	1.37 (1.29-1.45)	<0.001	1.48 (1.24-1.77)	<0.001
BMI	0.97 (0.95-0.98)	<0.001	0.97 (0.95-0.98)	<0.001	0.95 (0.91-1.00)	0.037
Current smoker	0.76 (0.66-0.88)	<0.001	0.80 (0.69-0.93)	0.004	0.39 (0.22-0.69)	0.001
Diabetes mellitus	1.16 (1.01-1.33)	0.030	1.16 (1.01-1.34)	0.039	1.13 (0.73-1.75)	0.58
Hypertension	1.21 (1.05-1.38)	0.007	1.23 (1.06-1.41)	0.005	1.03 (0.68-1.56)	0.89
Hypercholesterolaemia	0.82 (0.72-0.92)	0.001	0.81 (0.72-0.92)	0.001	0.74 (0.50-1.10)	0.13
Family history of coronary artery disease	0.71 (0.61-0.82)	<0.001	0.69 (0.59-0.80)	<0.001	0.83 (0.53-1.31)	0.41
Previous myocardial infarction	1.05 (0.90-1.22)	0.53	1.07 (0.92-1.26)	0.38	0.74 (0.43-1.29)	0.29
Previous PCI	0.93 (0.81-1.07)	0.29	0.93 (0.80-1.08)	0.33	0.76 (0.47-1.23)	0.26
Previous CABG	0.97 (0.79-1.18)	0.76	1.03 (0.84-1.26)	0.78	0.34 (0.13-0.93)	0.036
History of cerebrovascular accident	1.47 (1.21-1.79)	<0.001	1.45 (1.18-1.78)	<0.001	1.47 (0.79-2.74)	0.22
Peripheral artery disease	1.41 (1.17-1.70)	<0.001	1.48 (1.22-1.80)	<0.001	0.98 (0.50-1.95)	0.96
History of malignancy	1.68 (1.43-1.97)	<0.001	1.74 (1.48-2.06)	<0.001	0.97 (0.52-1.81)	0.91
Renal failure	2.31 (2.04-2.62)	<0.001	2.34 (2.06-2.67)	<0.001	2.32 (1.55-3.46)	<0.001
History of atrial fibrillation/flutter	1.92 (1.64-2.25)	<0.001	1.93 (1.64-2.28)	<0.001	1.85 (1.12-3.07)	0.017
Chronic obstructive lung disease	1.58 (1.29-1.92)	<0.001	1.62 (1.32-1.99)	<0.001	1.29 (0.65-2.56)	0.45
History of spontaneous bleeding	2.52 (2.07-3.08)	<0.001	2.58 (2.10-3.18)	<0.001	2.08 (1.05-4.11)	0.036
Left ventricular function (%)	0.98 (0.97-0.98)	<0.001	0.98 (0.97-0.98)	<0.001	0.98 (0.97-0.99)	0.001
Killip II, III or IV	2.53 (2.22-2.88)	<0.001	2.56 (2.24-2.93)	<0.001	2.49 (1.65-3.76)	<0.001
Femoral access	1.87 (1.66-2.11)	<0.001	1.93 (1.70-2.19)	<0.001	1.56 (1.06-2.29)	0.023
IABP	2.41 (1.63-3.55)	<0.001	2.31 (1.53-3.50)	<0.001	3.64 (1.34-9.88)	0.011
Percutaneous left ventricular assist device	6.97 (5.06-9.58)	<0.001	6.57 (4.67-9.23)	<0.001	10.67 (4.95-23.00)	<0.001
Staged PCI	1.11 (0.95-1.30)	0.198	1.11 (0.94-1.31)	0.20	0.97 (0.57-1.64)	0.90
Femoral access at staged PCI	1.45 (1.18-1.78)	<0.001	1.44 (1.16-1.78)	<0.001	1.31 (0.66-2.60)	0.43
Triple therapy at discharge	1.48 (1.26-1.73)	<0.001	1.47 (1.24-1.73)	<0.001	1.62 (1.00-2.64)	0.051
Any OAC at discharge	1.56 (1.34-1.81)	<0.001	1.54 (1.32-1.81)	<0.001	1.79 (1.14-2.83)	0.012
Any DAPT at discharge	0.76 (0.59-0.99)	0.043	0.80 (0.61-1.06)	0.12	0.52 (0.25-1.07)	0.076

DAPT with potent $P2Y_{12}$ inhibitor at discharge	0.98 (0.87-1.11)	0.77	0.99 (0.87-1.12)	0.82	0.88 (0.59-1.30)	0.52
PPI at discharge (not at follow-up)	2.05 (1.78-2.36)	<0.001	2.09 (1.81-2.42)	<0.001	1.79 (1.13-2.84)	0.013
PPI at follow-up (not at discharge)**	1.97 (1.66-2.33)	<0.001	2.04 (1.71-2.43)	<0.001	1.34 (0.72-2.50)	0.35
PPI at discharge and follow-up**	1.51 (1.31-1.74)	<0.001	1.53 (1.32-1.77)	<0.001	1.46 (0.92-2.30)	0.10
Haemoglobin before PCI (g/L)	0.98 (0.97-0.98)	<0.001	0.98 (0.97-0.98)	<0.001	0.97 (0.96-0.98)	<0.001
Number of lesions	1.00 (0.93-1.07)	0.96	0.97 (0.90-1.05)	0.49	1.26 (1.04-1.52)	0.017
Total stent length (mm)***	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.02)	0.071
Left anterior descending artery	0.88 (0.78-0.99)	0.033	0.85 (0.75-0.97)	0.013	1.33 (0.90-1.96)	0.14
Restenotic lesion	0.97 (0.78-1.21)	0.77	1.00 (0.80-1.25)	0.99	0.58 (0.24-1.42)	0.23
Thrombotic lesion	1.32 (1.15-1.52)	<0.001	1.33 (1.15-1.54)	<0.001	1.15 (0.73-1.81)	0.54
Chronic total occlusion	1.25 (0.97-1.61)	0.091	1.28 (0.98-1.67)	0.069	1.01 (0.41-2.47)	0.98
Currently on SAPT¶	0.50 (0.43-0.58)	<0.001	0.54 (0.46-0.63)	<0.001	0.21 (0.11-0.41)	<0.001
Currently on DAPT¶	1.99 (1.71-2.32)	<0.001	1.85 (1.58-2.17)	<0.001	4.37 (2.34-8.16)	<0.001
Leukocytes (10^3 cells per µL)	1.03 (1.02-1.03)	<0.001	1.03 (1.02-1.04)	<0.001	1.02 (1.00-1.05)	0.049
Thrombocytes (100×10^9/L)	1.00 (1.00-1.00)	0.007	1.00 (1.00-1.00)	0.007	1.00 (1.00-1.00)	0.75
Multivessel treatment	1.11 (0.97-1.27)	0.13	1.09 (0.95-1.25)	0.23	1.39 (0.92-2.09)	0.11
Minimum stent diameter (mm)	1.06 (0.94-1.19)	0.31	1.06 (0.93-1.20)	0.37	1.02 (0.70-1.50)	0.91
Bifurcation treatment	1.41 (1.22-1.62)	<0.001	1.43 (1.24-1.65)	<0.001	1.37 (0.87-2.14)	0.17
Fondaparinux	1.02 (0.83-1.24)	0.85	0.94 (0.75-1.16)	0.54	1.78 (1.06-2.99)	0.029
Low-molecular-weight heparin	1.43 (0.97-2.09)	0.069	1.44 (0.97-2.14)	0.074	1.62 (0.52-5.12)	0.40
Bivalirudin	0.76 (0.45-1.29)	0.31	0.77 (0.45-1.34)	0.35	0.56 (0.08-3.99)	0.56
Glycoprotein IIb/IIIa inhibitors	1.67 (1.40-1.99)	<0.001	1.57 (1.30-1.89)	<0.001	2.64 (1.64-4.26)	<0.001

Renal failure: <60 eGFR mL/min per 1.73 m², using the Modification of Diet in Renal Disease (MDRD) formula. OAC and DAPT at discharge, if deceased in hospital: as used at procedure.
*Chronic coronary syndrome (CCS) patients are the reference category.
**No PPI is the reference category.
***Stent length zero for ballooning only.
¶Time-at-risk is split into sequences of no APT, on SAPT, and on DAPT. Currently not on any APT: reference group. BARC 3 or 5 events are counted per sequence and patient separately.
Estimates derived from 20 multiple imputed data sets, combined using Rubin's rule.

APT: antiplatelet therapy; BARC: Bleeding Academic Research Consortium; BMI: body mass index; CABG: coronary artery bypass graft; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; IABP: intra-aortic balloon pump; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; SAPT: single antiplatelet therapy

Supplementary Table 8. Multivariate analysis for BARC type 2, 3 or 5 bleeding at one year.

	Overall BARC 2, 3 or 5		Non-access-site BARC 2, 3 or 5		Access-site BARC 2, 3 or 5	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Acute coronary syndrome*	1.25 (1.08-1.44)	0.003	1.23 (1.07-1.43)	0.005	1.19 (0.78-1.82)	0.42
Age (per 10 years)	1.19 (1.12-1.26)	<0.001	1.19 (1.11-1.26)	<0.001	1.35 (1.12-1.63)	0.001
BMI	0.98 (0.97-0.99)	0.004	0.98 (0.97-0.99)	0.006	-	-
Previous CABG	0.69 (0.56-0.85)	<0.001	0.74 (0.60-0.92)	0.007	0.28 (0.10-0.75)	0.012
History of malignancy	1.21 (1.03-1.43)	0.022	1.27 (1.07-1.51)	0.007	-	-
Renal failure	1.31 (1.13-1.51)	<0.001	1.32 (1.14-1.53)	<0.001	-	-
History of atrial fibrillation/flutter	1.46 (1.23-1.73)	<0.001	1.46 (1.22-1.74)	<0.001	1.64 (0.96-2.82)	0.072
Chronic obstructive lung disease	1.23 (1.00-1.50)	0.049	1.25 (1.02-1.55)	0.034	-	-
History of spontaneous bleeding	1.53 (1.24-1.89)	<0.001	1.54 (1.24-1.91)	<0.001	-	-
Haemoglobin before PCI (g/L)	0.99 (0.98-0.99)	<0.001	0.99 (0.99-0.99)	<0.001	0.98 (0.97-0.99)	<0.001
Leukocytes (10^3 cells per µL)	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	<0.001	-	-
Left ventricular function (%)	0.99 (0.99-1.00)	0.026	0.99 (0.99-1.00)	0.009	-	-
Killip II, III or IV	1.34 (1.15-1.57)	<0.001	1.35 (1.15-1.59)	<0.001	1.42 (0.91-2.21)	0.11
Femoral access site	1.35 (1.18-1.54)	<0.001	1.34 (1.17-1.53)	<0.001	-	-
Percutaneous left ventricular assist device	4.10 (2.93-5.74)	<0.001	3.66 (2.55-5.24)	<0.001	7.23 (3.23-16.16)	<0.001
Number of lesions	-	-	0.93 (0.86-1.01)	0.080	-	-
Left anterior descending artery	0.87 (0.77-0.99)	0.041	0.87 (0.76-0.99)	0.040	-	-
Chronic total occlusion	1.28 (0.98-1.67)	0.065	1.31 (0.99-1.72)	0.055	-	-
Bifurcation treatment	1.20 (1.03-1.39)	0.017	1.23 (1.05-1.43)	0.009	-	-
Total stent length (mm)**	1.00 (1.00-1.01)	0.004	1.01 (1.00-1.01)	0.001	-	-
Minimum stent diameter (mm)	1.20 (1.06-1.36)	0.005	1.15 (1.00-1.32)	0.056	-	-
Glycoprotein IIb/IIIa inhibitors	1.64 (1.36-1.97)	<0.001	1.48 (1.21-1.80)	<0.001	2.89 (1.74-4.77)	<0.001
DAPT with potent $P2Y_{12}$ inhibitor at discharge	0.87 (0.75-1.00)	0.056	0.42 (0.30-0.59)	<0.001	-	-
Currently on SAPT¶	0.77 (0.36-1.64)	0.49	1.70 (0.73-4.00)	0.22	0.26 (0.03-2.02)	0.19
Currently on DAPT¶	1.67 (0.79-3.53)	0.17	3.94 (1.65-9.41)	0.002	1.24 (0.17-8.98)	0.83
PPI at discharge (not at follow-up)	1.88 (1.59-2.21)	<0.001	1.91 (1.61-2.27)	<0.001	1.52 (0.92-2.53)	0.10
PPI at follow-up (not at discharge)***	2.31 (1.91-2.78)	<0.001	2.43 (2.00-2.95)	<0.001	1.50 (0.78-2.90)	0.22
PPI at discharge and follow-up***	1.57 (1.33-1.85)	<0.001	1.58 (1.33-1.87)	<0.001	1.44 (0.88-2.37)	0.14

A p-value <0.2 was used to select variables to include in the multivariable model.
Renal failure: <60 eGFR mL/min per 1.73 m², using the Modification of Diet in Renal Disease (MDRD) formula. OAC and DAPT at discharge, if deceased in hospital: as used at procedure.

*Chronic coronary syndrome (CCS) patients are the reference category.
**Stent length zero for ballooning only.
***No PPI is the reference category.
¶Time-at-risk is split into sequences of no APT, on SAPT, and on DAPT. Currently not on any APT: reference group. BARC 3 or 5 events are counted per sequence and patient separately.
Estimates derived from 20 multiple imputed data sets, combined using Rubin's rule

APT: antiplatelet therapy; BARC: Bleeding Academic Research Consortium; BMI: body mass index; CABG: coronary artery bypass graft; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; IABP: intra-aortic balloon pump; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; SAPT: single antiplatelet therapy

Supplementary Table 9. Baseline characteristics stratified by type of ACS.

	Unstable angina (n=783)	NSTEMI (n=4,218)	STEMI (n=4,502)	*p*-value
Age, years	67.91±11.24	68.49±12.58	64.32±13.00	<0.001
Females	207 (26.4%)	1,162 (27.5%)	1,046 (23.2%)	<0.001
BMI, kg/m²	27.08±4.41	27.34±4.88	27.01±4.43	0.004
Current smoker	184 (23.5%)	1,191 (28.7%)	1,729 (39.6%)	<0.001
Hypertension	602 (76.9%)	2,925 (69.9%)	2,342 (52.8%)	<0.001
Diabetes mellitus	185 (23.6%)	1,049 (24.9%)	658 (14.8%)	<0.001
Hypercholesterolaemia	547 (69.9%)	2,522 (60.3%)	2,075 (47.0%)	<0.001
Family history of CAD	252 (32.3%)	936 (22.4%)	959 (21.6%)	<0.001
Previous myocardial infarction	189 (24.1%)	792 (18.9%)	367 (8.2%)	<0.001
Previous PCI	285 (36.4%)	840 (20.0%)	428 (9.6%)	<0.001
Previous CABG	106 (13.5%)	420 (10.0%)	117 (2.6%)	<0.001
Previous TIA or stroke	52 (6.6%)	322 (7.7%)	171 (3.8%)	<0.001
Peripheral artery disease	61 (7.8%)	405 (9.6%)	170 (3.8%)	<0.001
History of malignancy	96 (12.3%)	488 (11.6%)	323 (7.3%)	<0.001
Renal failure	116 (15.7%)	968 (24.0%)	727 (17.6%)	<0.001
Renal failure on dialysis	7 (0.9%)	67 (1.6%)	20 (0.4%)	<0.001
History of atrial fibrillation/flutter	55 (10.0%)	347 (11.4%)	162 (5.1%)	<0.001
Chronic obstructive lung disease	52 (6.6%)	326 (7.8%)	167 (3.7%)	<0.001
History of spontaneous bleeding	49 (6.3%)	214 (5.1%)	114 (2.5%)	<0.001
Left ventricular function, %	57.80±12.31	52.05±13.57	44.80±11.92	<0.001
Haemoglobin before PCI, g/L	137.05±16.99	133.31±20.19	140.80±18.26	<0.001
Haemoglobin nadir, g/L	130.16±19.69	123.41±21.31	124.31±19.94	<0.001
Leukocytes before PCI, g/L	7.89±2.93	9.55±4.84	11.71±4.61	<0.001
Thrombocytes before PCI, g/L	222.70±63.81	231.89±79.04	242.04±78.02	<0.001
ARC-HBR score	0.58±0.76	0.78±0.91	0.46±0.68	<0.001
Killip class	n=782	n=4,209	n=4,486	<0.001
Killip I	731 (93.5%)	3,404 (80.9%)	3,199 (71.3%)	
Killip II	42 (5.4%)	450 (10.7%)	599 (13.4%)	

Killip III	6 (0.8%)	200 (4.8%)	192 (4.3%)	
Killip IV	3 (0.4%)	155 (3.7%)	496 (11.1%)	

ACS: acute coronary syndrome; ARC-HBR: Academic Research Consortium for High Bleeding Risk; BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCS: chronic coronary syndrome; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TIA: transient ischaemic attack

Supplementary Table 10. Procedural characteristics according to the type of ACS.

	Unstable angina (n=783)	NSTEMI (n=4,218)	STEMI (n=4,502)	*p*-value
Access site	n=551	n=3,054	n=3,187	<0.001
Radial	208 (37.7%)	1,137 (37.2%)	792 (24.9%)	<0.001
Femoral	343 (62.3%)	1,915 (62.7%)	2,395 (75.1%)	<0.001
Brachial	0 (0.0%)	2 (0.1%)	0 (0.0%)	0.29
Coronary arteries treated				
Left main artery	32 (4.1%)	216 (5.1%)	176 (3.9%)	0.02
Left anterior descending artery	414 (52.9%)	2,158 (51.2%)	2,309 (51.3%)	0.67
Left circumflex artery	238 (30.4%)	1,693 (40.1%)	1,021 (22.7%)	<0.001
Right coronary artery	284 (36.3%)	1,334 (31.6%)	1,861 (41.3%)	<0.001
Bypass graft	41 (5.2%)	168 (4.0%)	42 (0.9%)	<0.001
Number of lesions	n=783	n=4,218	n=4,502	<0.001
1	453 (57.9%)	2,279 (54.0%)	2,828 (62.8%)	<0.001
2	217 (27.7%)	1,251 (29.7%)	1,153 (25.6%)	<0.001
≥3	113 (14.4%)	688 (16.3%)	521 (11.6%)	<0.001
Multivessel treatment (2-3 vessels)	214 (27.3%)	1,263 (29.9%)	833 (18.5%)	<0.001
IABP (prior or during PCI)	3 (0.4%)	49 (1.2%)	138 (3.1%)	<0.001
Percutaneous left ventricular assist device	4 (0.6%)	35 (0.9%)	65 (1.6%)	0.006
Staged PCI	90 (11.5%)	751 (17.8%)	1,172 (26.0%)	<0.001
Access site of first staged PCI	n=72	n=631	n=835	0.78
Radial	32 (44.4%)	283 (44.8%)	389 (46.6%)	
Femoral	40 (55.6%)	348 (55.2%)	446 (53.4%)	
Number of lesions treated	n=1,256	n=7,094	n=6,895	
Lesion type				
Restenotic lesion	119 (9.5%)	338 (4.8%)	252 (3.7%)	<0.001
Evidence of thrombus	23 (1.9%)	789 (11.1%)	2,991 (43.4%)	<0.001
Chronic total occlusion	28 (2.2%)	195 (2.7%)	82 (1.2%)	<0.001
Stent type				
Any DES	1,115 (96.2%)	6,390 (96.4%)	6,105 (94.0%)	<0.001
Any bare metal stent	33 (2.8%)	220 (3.3%)	357 (5.5%)	<0.001

Any absorbable scaffold*	10 (0.9%)	8 (0.1%)	18 (0.3%)	0.001
Mix of types of stent	1 (0.1%)	11 (0.2%)	18 (0.3%)	0.24
Only DES used per patient	1,162 (92.5%)	6,646 (93.7%)	6,305 (91.4%)	<0.001
Total number of stents implanted in this lesion	1.30±0.58	1.31±0.60	1.40±0.67	<0.001
Total stent length, mm	26.42±16.29	27.70±17.06	31.09±18.83	<0.001
Mean stent diameter, mm	2.93±0.48	2.91±0.75	3.01±0.51	<0.001
Treatment of a bifurcation	184 (14.7%)	1,090 (15.4%)	1,037 (15.0%)	0.64
Baseline TIMI flow	n=1,232	n=7,005	n=6,829	<0.001
0 or 1	121 (9.8%)	1,392 (19.9%)	3,681 (53.9%)	
2	210 (17.0%)	1,351 (19.3%)	1,042 (15.3%)	
3	901 (73.1%)	4,262 (60.8%)	2,105 (30.8%)	
Post-PCI TIMI flow	n=1,240	n=7,032	n=6,840	<0.001
0 or 1	6 (0.5%)	50 (0.7%)	82 (1.2%)	
2	6 (0.5%)	99 (1.4%)	224 (3.3%)	
3	1,228 (99.0%)	6,883 (97.9%)	6,534 (95.5%)	

Renal failure: <60 eGFR mL/min per 1.73 m², using the Modification of Diet in Renal Disease (MDRD) formula. OAC and DAPT at discharge, if deceased in hospital: as used at procedure.
* Chronic coronary syndrome (CCS) patients are the reference category.
**No PPI is the reference category.
***Stent length zero for ballooning only.
¶Time-at-risk is split into sequences of no APT, on SAPT, and on DAPT. Currently not on any APT: reference group. BARC 3 or 5 events are counted per sequence and patient separately.
Estimates derived from 20 multiple imputed data sets, combined using Rubin's rule.

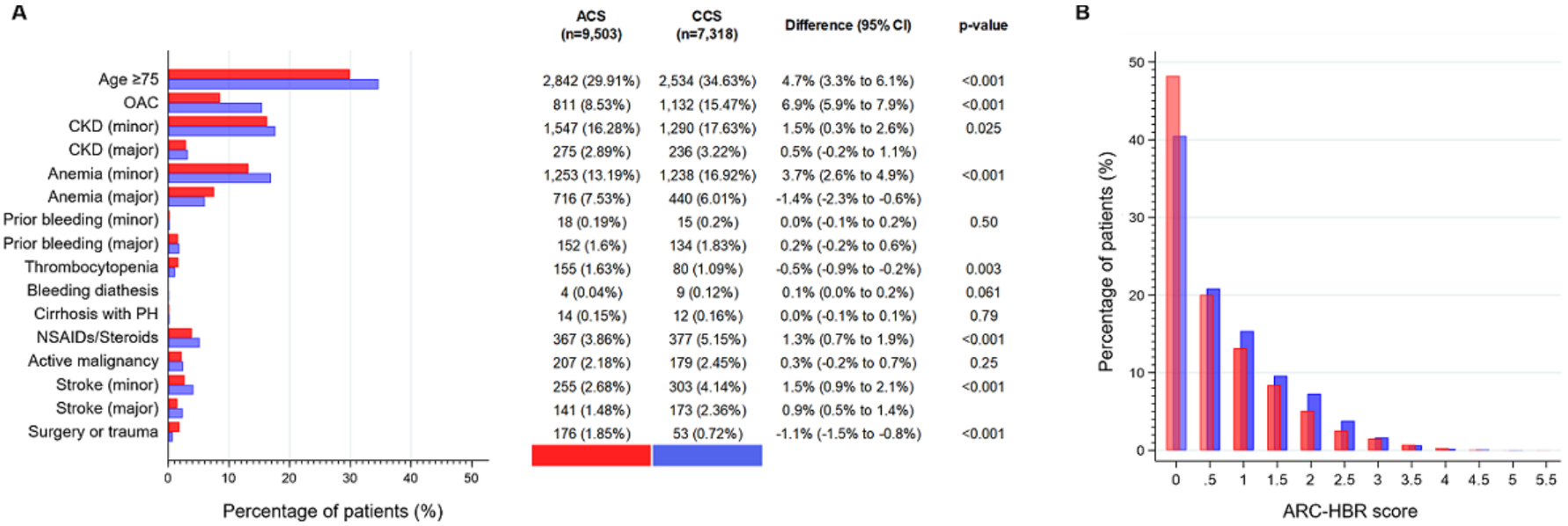
APT: antiplatelet therapy; BARC: Bleeding Academic Research Consortium; BMI: body mass index; CABG: coronary artery bypass graft; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; IABP: intra-aortic balloon pump; NSTEMI: non-ST-elevation myocardial infarction; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; SAPT: single antiplatelet therapy; STEMI: ST-elevation myocardial infarction

Supplementary Table 11. Medications according to the type of ACS.

	Unstable angina (n=783)	NSTEMI (n=4,218)	STEMI (n=4,502)	*p*-value
Procedure medications	n=783	n=4,218	n=4,502	<0.001
No loading dose	91 (11.6%)	362 (8.6%)	91 (2.0%)	<0.001
Only loading clopidogrel	383 (48.9%)	1,643 (39.0%)	1,020 (22.7%)	<0.001
Only loading prasugrel	48 (6.1%)	160 (3.8%)	1,133 (25.2%)	<0.001
Only loading ticagrelor	252 (32.2%)	1,888 (44.8%)	1,580 (35.1%)	<0.001
Loading clopidogrel and prasugrel	2 (0.3%)	79 (1.9%)	595 (13.2%)	<0.001
Loading clopidogrel and ticagrelor	6 (0.8%)	76 (1.8%)	69 (1.5%)	0.095
Loading prasugrel and ticagrelor	1 (0.1%)	10 (0.2%)	14 (0.3%)	0.59
Unfractionated heparin	765 (97.7%)	4,152 (98.5%)	4,456 (99.0%)	0.003
Fondaparinux	48 (6.8%)	700 (17.8%)	856 (20.5%)	<0.001
LMWH	20 (2.6%)	131 (3.1%)	87 (1.9%)	0.002
Bivalirudin	21 (2.7%)	56 (1.3%)	26 (0.6%)	<0.001
Glycoprotein IIb/IIIa inhibitors	29 (3.7%)	266 (6.3%)	1,002 (22.3%)	<0.001
Thrombolytic therapy	2 (0.3%)	5 (0.1%)	25 (0.6%)	0.002
Discharge medications				
Aspirin	763 (98.2%)	4,022 (98.0%)	4,206 (98.8%)	0.019
Clopidogrel	453 (58.3%)	1,881 (45.8%)	977 (22.9%)	<0.001
Prasugrel	51 (6.6%)	268 (6.5%)	1,771 (41.6%)	<0.001
Ticagrelor	259 (33.3%)	1,903 (46.4%)	1,453 (34.1%)	<0.001
Any DAPT	752 (96.8%)	3,978 (96.9%)	4,160 (97.7%)	0.069
Any OAC	73 (9.4%)	471 (11.5%)	267 (6.3%)	<0.001
Novel oral anticoagulants	26 (4.7%)	175 (5.9%)	118 (3.9%)	0.002
Any DAPT and OAC/NOAC	64 (8.2%)	403 (9.8%)	227 (5.3%)	<0.001
Statin	729 (93.8%)	3,767 (91.8%)	4,017 (94.3%)	<0.001
PPI	252 (43.8%)	1,425 (43.9%)	1,405 (39.7%)	0.001
One-year follow-up medications				
Aspirin*	632 (91.3%)	3,129 (90.7%)	3,472 (94.1%)	<0.001
Clopidogrel*	303 (43.8%)	1,124 (32.6%)	726 (19.7%)	<0.001
Prasugrel*	46 (6.6%)	241 (7.0%)	1,316 (35.7%)	<0.001

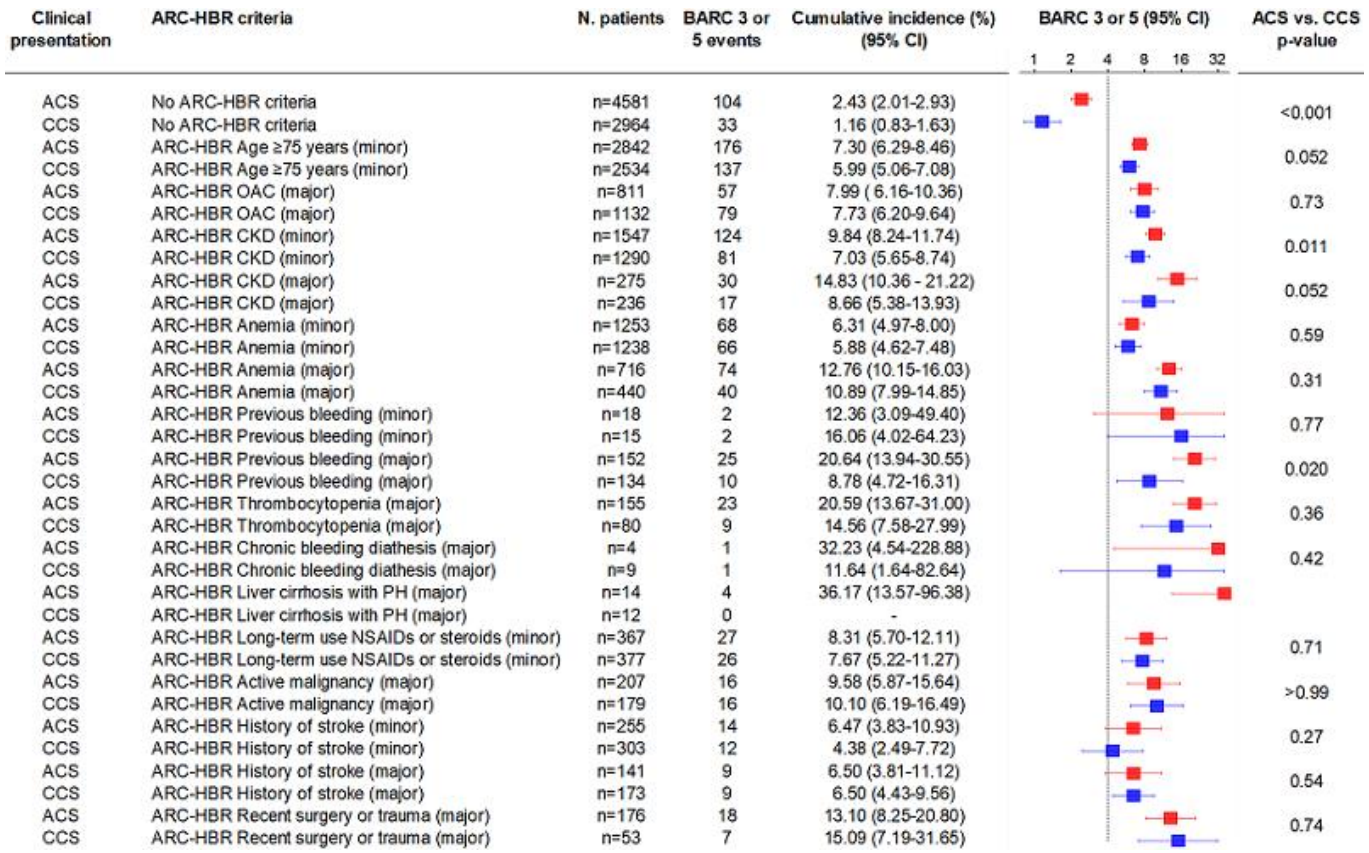
Ticagrelor*	171 (24.7%)	1,229 (35.6%)	953 (25.8%)	<0.001
Any DAPT*	472 (68.2%)	2,381 (69.0%)	2,832 (76.7%)	<0.001
Any OAC	72 (10.4%)	472 (13.7%)	356 (9.7%)	<0.001
Novel oral anticoagulants	30 (5.5%)	216 (7.6%)	167 (5.7%)	0.007
Any DAPT and OAC/NOAC	8 (1.2%)	57 (1.7%)	67 (1.8%)	0.45
Statin	570 (82.5%)	2,921 (84.8%)	3,306 (89.8%)	<0.001
PPI	213 (38.4%)	1,071 (36.4%)	1,046 (32.3%)	<0.001

*Not stopped before 350 days since index PCI considered compliant.
ACS: acute coronary syndrome; CCS: chronic coronary syndrome; DAPT: dual antiplatelet therapy; LMWH: low molecular weight heparin; NOAC: new oral anticoagulant; NSTEMI: non-ST-elevation myocardial infarction; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction



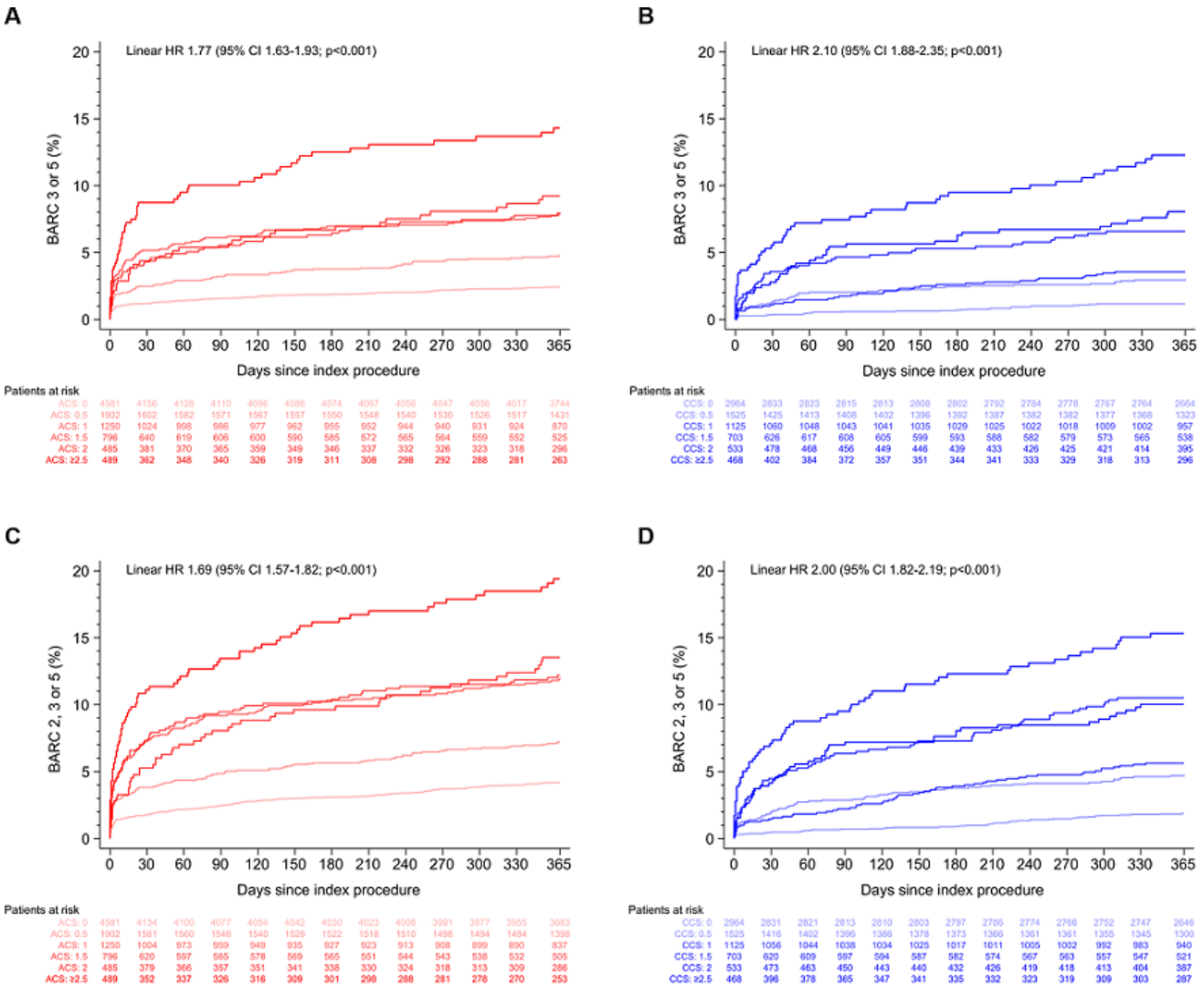
Supplementary Figure 1. Prevalence of minor and major ARC-HBR criteria (A) and ARC-HBR score distribution (B) in ACS (red) and CCS (blue) patients.

ACS: acute coronary syndrome; ARC-HBR: Academic Research Consortium for High Bleeding Risk; CCS: chronic coronary syndrome; CI: confidence interval; CKD: chronic kidney disease; NSAIDs: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulation; PH: portal hypertension



Supplementary Figure 2. Unadjusted rate of BARC 3 or 5 events at one year for minor and major ARC-HBR criteria in ACS (red) and CCS (blue).

Depicted are the estimates of the main effects model, adjusted cumulative incidence in case all other risk factors are set to absent.
Large values for the upper confidence intervals cut in the graph for clarity.
ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; CI: confidence interval; CKD: chronic kidney disease; NSAIDs: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulation; PH: portal hypertension.



Supplementary Figure 3. Kaplan-Meier event curves for BARC-defined bleeding at one year in patients stratified by clinical presentation and ARC-HBR score. BARC 3 or 5 in ACS (red) and CCS (blue) by ARC-HBR score (A & B). BARC 2, 3 or 5 in ACS and CCS by ARC-HBR score (C & D).

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; CI: confidence interval; HR: hazard ratio