EuroIntervention 2023;19:e832-e843 published online ahead of print September 2023 ■ published online e-edition December 2023

De-escalation from ticagrelor to clopidogrel in patients with acute myocardial infarction: the TALOS-AMI HBR substudy

Min Chul Kim[1], MD, PhD; Sung Gyun Ahn[2], MD, PhD; Kyung Hoon Cho[1], MD, PhD; Doo Sun Sim[1], MD, PhD; Young Joon Hong[1], MD, PhD; Ju Han Kim[1], MD, PhD; Myung Ho Jeong[1], MD, PhD; Jun-Won Lee[2], MD, PhD; Young-Jin Youn[2], MD, PhD; Hee-Yeol Kim[3], MD, PhD; Ki-Dong Yoo[4], MD, PhD; Doo-Soo Jeon[5], MD, PhD; Eun-Seok Shin[6], MD, PhD; Young-Hoon Jeong[7], MD, PhD; Kiyuk Chang[8], MD, PhD; Youngkeun Ahn[1]*, MD, PhD

1. Division of Cardiology, Department of Internal Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, South Korea; 2. Division of Cardiology, Department of Internal Medicine, Wonju Severance Christian Hospital, Wonju, South Korea; 3. Division of Cardiology, Department of Internal Medicine, Bucheon St Mary's Hospital, Bucheon, South Korea; 4. Division of Cardiology, Department of Internal Medicine, The Catholic University of Korea, St Vincent's Hospital, Suwon, South Korea; 5. Division of Cardiology, Department of Internal Medicine, Incheon St Mary's Hospital, Incheon, South Korea; 6. Division of Cardiology, Department of Internal Medicine, Ulsan University Hospital, Ulsan, South Korea; 7. Division of Cardiology, Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, South Korea; 8. Division of Cardiology, Department of Internal Medicine, The Catholic University of Korea, Seoul St Mary's Hospital, Seoul, South Korea

M.C. Kim and S.G. Ahn contributed equally to this work.

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00427

KEYWORDS

- adjunctive pharmacotherapy
- clinical trials
- NSTEMI
- STEMI

Abstract

Background: The benefits of de-escalation of $P2Y_{12}$ inhibition after percutaneous coronary intervention (PCI) may differ by high bleeding risk (HBR) status.

Aims: We investigated the efficacy and safety of de-escalation from ticagrelor to clopidogrel after PCI by HBR status.

Methods: This is a non-prespecified *post hoc* analysis of the TicAgrelor Versus CLOpidogrel in Stabilized Patients with Acute Myocardial Infarction (TALOS-AMI) trial. Net adverse clinical events (a composite of cardiovascular death, myocardial infarction, stroke, or Bleeding Academic Research Consortium [BARC] bleeding type 2, 3, or 5) at 1 year post-PCI were compared between the de-escalation (clopidogrel plus aspirin) and the active control (ticagrelor plus aspirin) groups by HBR status, as defined by the modification of the Academic Research Consortium (ARC) criteria.

Results: A total of 2,625 patients in the TALOS-AMI trial were analysed. Of these, 589 (22.4%) met the modified ARC-HBR criteria. The de-escalation group had lower primary endpoint rates than the control group in both HBR (hazard ratio [HR] 0.47, 95% confidence interval [CI]: 0.26-0.84) and non-HBR (HR 0.59, 95% CI: 0.41-0.84) patients. There were no differences in treatment effect for the primary endpoint regardless of HBR status (p for interaction=0.904). BARC bleeding type 3 or 5 was less common in the de-escalation than the control group among HBR patients only (HR 0.24, 95% CI: 0.07-0.84).

Conclusions: In stabilised acute myocardial infarction patients, unguided de-escalation from ticagrelor to clopidogrel was associated with a lower rate of net adverse clinical outcomes irrespective of HBR status. The effect of de-escalation of $P2Y_{12}$ inhibition on reducing haemorrhagic events was greater in patients with HBR.

**Corresponding author: Division of Cardiology, Department of Internal Medicine, Cardiovascular Center, Chonnam National University Hospital, Chonnam National University School of Medicine, 42 Jebong-ro, Dong-gu, Gwangju 61469, South Korea. E-mail: cecilyk@hanmail.net.*

SUBMITTED ON 29/05/2023 - REVISION RECEIVED ON 15/07/2023 - ACCEPTED ON 15/08/2023

DOI: 10.4244/EIJ-D-23-00427

Abbreviations

AMI	acute myocardial infarction
ARC	Academic Research Consortium
CKD	chronic kidney disease
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
HBR	high bleeding risk
MACCE	major adverse cardiac and cerebrovascular events
PCI	percutaneous coronary intervention
PRECISE-DAPT	PREdicting bleeding Complications In patients undergoing Stent Implantation and subsEquent Dual Anti Platelet Therapy
TALOS-AMI	TicAgrelor Versus CLOpidogrel in Stabilized Patients with Acute Myocardial Infarction

Introduction

Ticagrelor and prasugrel are potent $P2Y_{12}$ inhibitors and are preferable to clopidogrel in patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI), as revealed by pivotal randomised trials[1,2] and subsequent guideline updates[3,4]. However, clopidogrel is still recommended when the bleeding risk outweighs the thrombotic risk associated with potent $P2Y_{12}$ inhibitors[3,5]. As both thrombotic and haemorrhagic events are linked to poor clinical outcomes[6,7], various strategies − such as shortening the mandatory duration of dual antiplatelet therapy (DAPT)[8], switching from potent $P2Y_{12}$ inhibitors to clopidogrel[9], decreasing the doses of potent $P2Y_{12}$ inhibitors[10], and $P2Y_{12}$ inhibitor monotherapy (thus dropping aspirin)[11-14] − have sought to create trade-offs between thrombosis and haemorrhage.

As time elapses after PCI, both the thrombotic and bleeding risks diminish, and the bleeding risk becomes higher than the ischaemic risk after 1 month[15]. Thus, the recent TicAgrelor Versus CLOpidogrel in Stabilized Patients with Acute Myocardial Infarction (TALOS-AMI) trial evaluated uniform unguided de-escalation of $P2Y_{12}$ inhibition (from ticagrelor to clopidogrel) at 1 month in AMI patients with no thrombotic or haemorrhagic events[9]. This reduced the net adverse clinical outcomes (principally bleeding events) compared to those patients on standard ticagrelor-based 12-month DAPT. We hypothesised that the benefit of de-escalation might be more profound in patients with HBR than those with non-HBR. Therefore, using TALOS-AMI trial data, we explored the efficacy and safety of de-escalation in patients with HBR and those with non-HBR.

Editorial, see page 789

Methods

STUDY DESIGN AND POPULATION

This study is a non-prespecified *post hoc* analysis of the TALOS-AMI trial, which was an open-label, assessor-masked, multicentre, non-inferiority, randomised trial conducted at 32 centres in South Korea between February 2014 and December 2018[9,16]. The trial explored whether de-escalation from ticagrelor to clopidogrel 1 month after PCI using drug-eluting stents (DES) in stabilised AMI patients was non-inferior in terms of net ischaemic and bleeding outcomes from 1 to 12 months compared to the active control strategy (maintenance of ticagrelor for 12 months). All patients received aspirin and ticagrelor during the screening period (1 month after PCI), and those without any adverse clinical events were randomised in the outpatient department. The protocol was approved by the institutional review board or ethics committee of each participating centre, and all procedures adhered to the principles of the Declaration of Helsinki. All patients provided written informed consent.

STUDY DEFINITIONS AND ENDPOINTS

The current study investigates whether the benefits of the TALOS-AMI trial were maintained by patients both at HBR and non-HBR. HBR was defined as a modification of the Academic Research Consortium for High Bleeding Risk (ABC-HBR) criteria[5], because in the TALOS-AMI trial, i) many HBR patients were excluded at baseline and during the first month after index PCI[9,16] and ii) of 204 patients who were not screened in the first month, bleeding events occurred in 10 patients **(Supplementary Table 1)**. This was not unexpected given the original data (on 43 patients) in terms of the incidence of BARC bleeding type 3 or 5[9]. Also, hidden bleeding events could have occurred in patients who were not followed up during screening, given the high risk of major bleeding events associated with ticagrelor compared to clopidogrel in Korean patients[17]. Therefore, we modified the ARC-HBR criteria to include as many HBR patients as possible. **Supplementary Table 2** lists our major and minor HBR criteria and the differences from the ARC-HBR criteria. Nine major and two minor ARC-HBR criteria that served as exclusion criteria for the TALOS-AMI trial were, thus, not used to define HBR in the present work. Rather, two minor ARC-HBR criteria − age ≥75 years and moderate chronic kidney disease (CKD) − were transferred to the major HBR criteria in the current study, because these were associated with significant bleeding (BARC bleeding type 3 or 5 rates >4%) in several validation studies employing the ARC-HBR criteria[18,19]. Moreover, a combination of age ≥75 years and moderate CKD was associated with a higher incidence of BARC bleeding type 3 or 5 than all other ARC-HBR components combined[18]. Consequently, we defined HBR when 1 major or 2 minor modified HBR criteria were fulfilled **(Supplementary Table 2)**.

A detailed study protocol (including definitions and endpoints) has been previously published[9,16]. Briefly, the primary endpoint was a net adverse clinical event − a composite of cardiovascular death, myocardial infarction, stroke, or BARC bleeding type 2, 3, or 5 − from 1 to 12 months after the index PCI. The key secondary endpoint was BARC bleeding type 3 or 5. Other secondary endpoints included a major adverse cardiac and cerebrovascular event (MACCE; a composite of cardiovascular death, myocardial infarction, or stroke), BARC bleeding type 2, 3, or 5, a composite of MACCE and BARC bleeding type 3 or 5, all-cause death, cardiovascular death, myocardial infarction, stroke, ischaemia-driven revascularisation, and stent thrombosis from 1 to 12 months after the index PCI.

STATISTICAL ANALYSIS

Continuous variables are presented as means±standard deviations and were compared using the unpaired t-test. Categorical variables

are expressed as counts with percentages and were compared using Pearson's chi-square test or Fisher's exact test. We constructed Kaplan-Meier curves and used the log-rank test to compare the groups in terms of the primary and secondary endpoints (MACCE, BARC bleeding type 3 or 5, and a composite of MACCE and BARC bleeding type 3 or 5). Cox's proportional hazards models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazards assumption was evaluated using the log-minus-log plot and the Schoenfeld residual test; all Cox's proportional hazards models of clinical endpoints satisfied the proportional hazards assumption. A formal interaction test was performed to assess the consistency of the de-escalation effects (compared to those of active control) in patients at HBR and non-HBR.

The primary and secondary endpoints of the 2 groups were compared by HBR and non-HBR status. Sensitivity analysis employed the PREdicting bleeding Complications In patients undergoing Stent Implantation and subsEquent Dual Anti Platelet Therapy (PRECISE-DAPT) scores and the original ARC-HBR criteria[5,20]. Of the variables contributing to the PRECISE-DAPT score, previous bleeding, which was excluded in the TALOS-AMI trial, was ignored. Therefore, only 4 variables were used when calculating this score (www.precisedaptscore.com). All analyses were performed on an intention-to-treat principle, all were 2-tailed, and $p<0.05$ indicated statistical significance. All analyses were performed with the aid of Stata/MP version 16.0 software (StataCorp).

Results

ASSESSMENT OF MODIFIED HBR CRITERIA

Figure 1 shows the study flow. Between February 2014 and December 2018, 2,697 patients were enrolled in the TALOS-AMI trial, of whom 2,625 were analysed in the present study (using the modified HBR criteria) after excluding 72 patients for whom data on at least one of the modified criteria were missing **(Supplementary Table 2)**. Using the modified criteria, 589 patients (22.4%) were at HBR and the other 2,036 (77.6%) were at non-HBR. The prevalence of the modified HBR criteria in the HBR group are shown in **Supplementary Figure 1**. Age ≥75 years (53.0%) and moderate CKD (48.9%) were the most common major criteria. Of the minor criteria, the prevalence of mild anaemia was 39.6%, but the rate of ischaemic stroke was only 7.0%. The incidence of BARC bleeding type 3 or 5 between 1 and 12 months was ≥4% (major and minor criteria). However, the incidence of major bleeding was <4% in isolation (without other concomitant criteria). **Supplementary Figure 2** shows the clinical impacts of multiple HBR criteria. The proportions of multiple HBR criteria were 70.5% (1 criterion), 22.8% (2 criteria), 6.3% (3 criteria), and 0.5% (4 criteria; which included only 3 patients). Increased numbers of HBR criteria modestly predicted the clinical outcome (a composite of MACCE and BARC bleeding type 3 or 5) with incremental prognostic value, but the risk of BARC bleeding type 3 or 5 increased with the number of HBR criteria.

BASELINE CHARACTERISTICS AND CLINICAL OUTCOMES BETWEEN HBR AND NON-HBR BY MODIFIED ARC-HBR CRITERIA

Baseline characteristics and the procedural profiles are shown in **Supplementary Table 3**. The HBR group contained higher proportions of elderly and female patients. In terms of medical history, the HBR group featured more hypertensive and diabetic patients than the non-HBR group and also those with higher incidences of previous PCI and cerebrovascular accidents. However, the incidences of dyslipidaemia and current smokers were higher in the non-HBR group. In terms of laboratory findings, the creatinine clearance

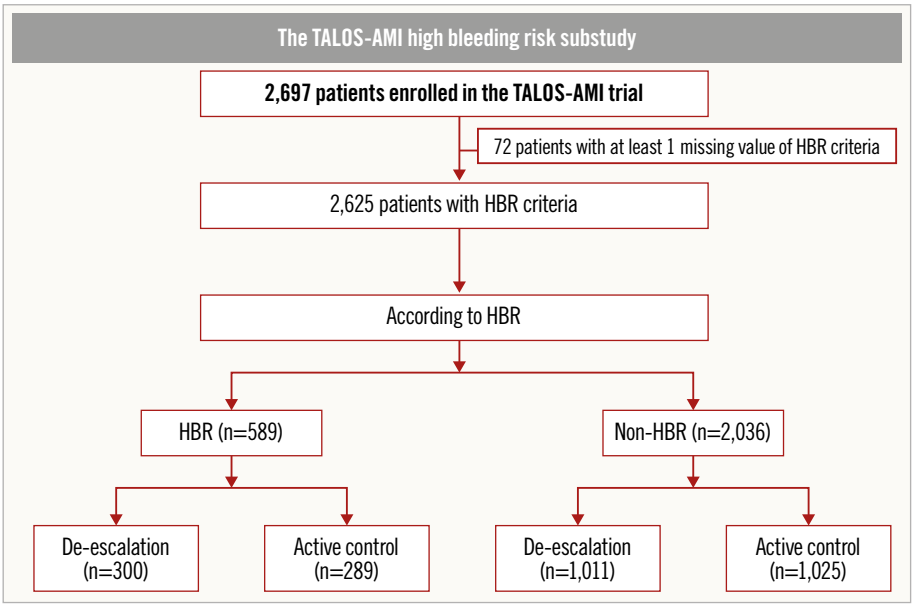


Figure 1. *Study flowchart. HBR: high bleeding risk; TALOS-AMI: TicAgrelor Versus CLOpidogrel in Stabilized Patients with Acute Myocardial Infarction*

rate, the haemoglobin and platelet levels, and the white blood cell count were lower in the HBR group. The rates of left ventricular ejection fraction <40% were 13.5% in the HBR group and 5.9% in the non-HBR group (p<0.001). There were no between-group differences in terms of clinical presentation or the access site. In both groups, the most frequently infarct-related artery was the left anterior descending artery. Multivessel treatment was performed more in the HBR group than the non-HBR group (33.3 vs 28.7%; p=0.034). The clinical outcomes are shown in **Supplementary Table 4** and **Figure 2**. The primary endpoint incidence was significantly higher in the HBR group (8.7 vs 5.2%, HR 1.75, 95% CI: 1.26-2.45; p=0.001). The key secondary endpoint, BARC bleeding type 3 or 5, was also more common in the HBR group (2.5 vs 1.3%, HR: 2.01, 95% CI: 1.07-3.78; p=0.030). The incidences of other secondary endpoints (MACCE, a composite of MACCE and BARC bleeding type 3 or 5, all-cause mortality, cardiovascular mortality, and spontaneous myocardial infarction) were all higher in the HBR group. There were no between-group differences in the incidences of stroke, ischaemia-driven revascularisation, or stent thrombosis.

BASELINE CHARACTERISTICS AND CLINICAL OUTCOMES ACCORDING TO HBR BY MODIFIED ARC-HBR CRITERIA AND TREATMENT ARM

For both the HBR and non-HBR groups, the characteristics and outcomes were investigated by the treatment arm **(Figure 1)**. Of the HBR group, 300 were allocated to the de-escalation group and 289 to the active control group. In the non-HBR group, 1,011 patients were in the de-escalation group and 1,025 in the active control group. The baseline and procedural characteristics were balanced

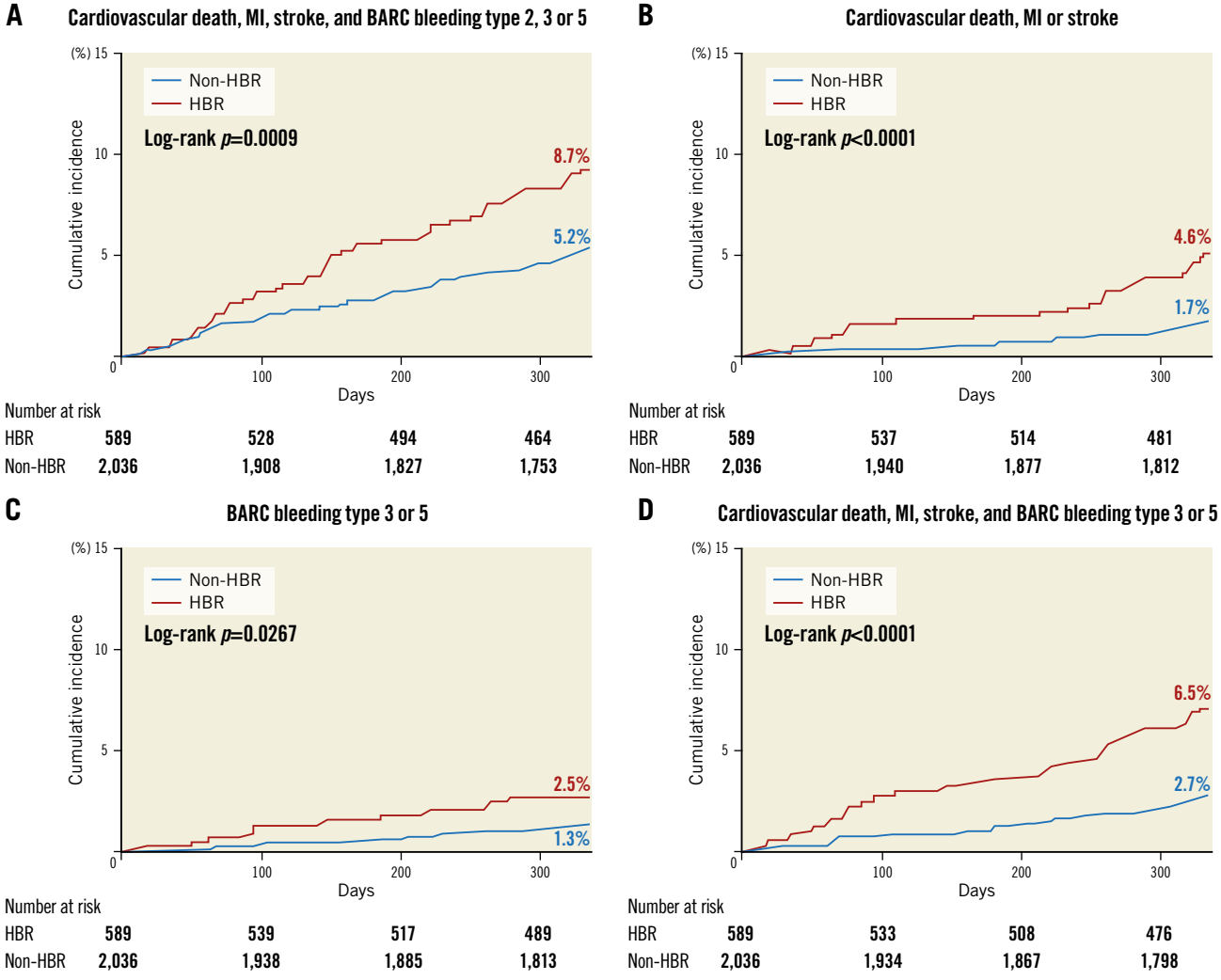


Figure 2. *Cumulative incidence of the primary and secondary outcomes by HBR. A) Primary endpoint: a composite of cardiovascular death, myocardial infarction, stroke, or BARC bleeding type 2, 3, or 5. B) Secondary endpoint: a major adverse cardiac and cerebrovascular event (MACCE; a composite of cardiovascular death, myocardial infarction, or stroke). C) Key secondary endpoint: BARC type 3 or 5 bleeding. D) Secondary endpoint: a composite of MACCE and BARC bleeding type 3 or 5. BARC: Bleeding Academic Research Consortium; HBR: high bleeding risk; MI: myocardial infarction*

between the de-escalation and active control groups for both HBR and non-HBR patients **(Table 1)**. Among the HBR patients, the primary endpoint occurred less frequently in the de-escalation group compared to the active control group (5.7 vs 11.8%, HR 0.47, 95% CI: 0.26-0.84; p=0.011) **(Table 2, Figure 3)**. The incidence of BARC bleeding type 3 or 5 (1.0 vs 4.2%, HR 0.24, 95% CI: 0.07-0.84; p=0.026) and a composite of MACCE and BARC bleeding type 3 or 5 (4.0. vs 9.0%, HR 0.43, 95% CI: 0.22-0.86; p=0.017)

Table 1. Baseline and procedural characteristics by HBR and treatment arm.

		HBR (n=589)			Non-HBR (n=2,036)		
		De-escalation (n=300)	Active control (n=289)	*p*-value	De-escalation (n=1,011)	Active control (n=1,025)	*p*-value
Demographics	Age, years	70.7±10.8	71.2±10.2	0.522	57.0±9.3	56.6±9.5	0.421
	Male	198 (66.0)	191 (66.1)	0.982	898 (88.8)	892 (87.0)	0.213
	Body mass index, kg/m^2	24.0±3.3	23.5±4.0	0.103	24.9±3.2	24.8±3.4	0.832
Medical history	Hypertension	191 (63.7)	190 (65.7)	0.598	443 (43.8)	453 (44.2)	0.864
	Diabetes	104 (34.7)	94 (32.5)	0.582	245 (24.2)	265 (25.9)	0.399
	Diabetes treated with insulin	10 (3.3)	10 (3.5)	0.932	16 (1.6)	18 (1.8)	0.760
	Dyslipidaemia	115 (38.3)	102 (35.3)	0.445	427 (42.2)	443 (43.2)	0.654
	Current smoker	92 (30.7)	79 (27.3)	0.373	557 (55.1)	576 (56.2)	0.617
	Impaired renal function*	160 (53.3)	144 (49.8)	0.395	–	–	–
Past medical history	Previous PCI	17 (5.7)	25 (8.7)	0.159	42 (4.2)	32 (3.1)	0.213
	Previous CABG	2 (0.7)	1 (0.3)	1.000	1 (0.1)	–	–
	Previous CVA	23 (7.7)	18 (6.2)	0.493	27 (2.7)	30 (2.9)	0.726
Clinical presentation							
STEMI		150 (50.0)	152 (52.6)	0.529	560 (55.4)	550 (53.7)	0.433
NSTEMI		150 (50.0)	137 (47.4)		451 (44.6)	475 (46.3)	
Laboratory findings	Creatinine clearance†, mL/min/1.73 m^2	68.2±25.1	68.6±26.6	0.859	91.8±20.7	94.1±22.9	0.016
	Haemoglobin, g/dL	13.3±1.9	13.1±1.9	0.248	15.0±1.3	14.9±1.4	0.301
	Platelet, 10^9/L	233.8±61.5	234.0±64.6	0.959	242.7±61.0	239.7±55.9	0.256
	White blood cell count, 10^9/L	9.8±3.4	9.6±3.4	0.348	10.4±3.4	10.6±3.5	0.162
	LVEF <40%	40/289 (13.8)	36/273 (13.2)	0.821	59/979 (6.0)	56/980 (5.7)	0.769
Access site							
Radial		136 (45.3)	123 (42.6)	0.427	482 (47.7)	514 (50.1)	0.528
Femoral		152 (50.7)	148 (51.2)		479 (47.4)	461 (45.0)	
Glycoprotein IIb/IIIa inhibitor		74 (24.7)	67 (23.2)	0.673	234 (23.1)	241 (23.5)	0.845
Infarct-related artery							
Left main coronary artery		7 (2.3)	10 (3.5)	0.766	14 (1.4)	14 (1.4)	0.044
Left anterior descending artery		134 (44.8)	120 (41.8)		524 (52.3)	495 (48.7)	
Left circumflex artery		38 (12.7)	40 (13.9)		160 (16.0)	212 (20.9)	
Right coronary artery		120 (40.1)	117 (40.8)		303 (30.3)	295 (29.0)	
Number of treated vessels		1.4±0.6	1.4±0.7	0.394	1.4±0.6	1.4±0.6	0.830
Multivessel treatment		98 (32.7)	98 (33.9)	0.749	287 (28.4)	298 (29.1)	0.733
Numbers of stents for infarct-related artery		1.2±0.4	1.2±0.4	0.765	1.2±0.5	1.2±0.4	0.584
Total stent length of infarct-related artery, mm		30.9±13.7	30.7±15.3	0.915	29.7±18.9	29.1±13.4	0.406
Stent diameter of infarct-related artery, mm		3.2±0.4	3.2±0.5	0.696	3.2±0.5	3.2±1.0	0.613
Intravascular imaging	Optical coherence tomography	9 (3.0)	10 (3.5)	0.752	38 (3.8)	25 (2.4)	0.086
	Intravascular ultrasonography	69 (23.0)	65 (22.5)	0.883	252 (24.9)	238 (23.2)	0.368

Values are expressed as mean±SD, n (%) or n/N (%). *Impaired renal function was defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 of body surface area at presentation. †Creatinine clearance was calculated by the MDRD (Modification of Diet in Renal Disease) formula: 186 *(serum creatinine)–1.154 *(age)–0.203 *0.742 (for women). CABG: coronary artery bypass graft; CVA: cerebrovascular accident; HBR: high bleeding risk; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction

Table 2. Primary and secondary outcomes by HBR and treatment arm.

		HBR (n=589)				Non-HBR (n=2,036)				*p*-value for interaction
		De-escalation (n=300)	Active control (n=289)	Hazard ratio (95% CI)	*p*-value	De-escalation (n=1,011)	Active control (n=1,025)	Hazard ratio (95% CI)	*p*-value	
Primary endpoint*		17 (5.7)	34 (11.8)	0.47 (0.26-0.84)	0.011	40 (4.0)	66 (6.4)	0.59 (0.40-0.88)	0.009	0.904
Secondary endpoints	BARC bleeding type 3 or 5	3 (1.0)	12 (4.2)	0.24 (0.07-0.84)	0.026	12 (1.2)	15 (1.5)	0.79 (0.37-1.69)	0.542	0.413
	MACCE†	11 (3.7)	16 (5.5)	0.65 (0.30-1.40)	0.269	14 (1.4)	20 (2.0)	0.69 (0.35-1.36)	0.285	0.088
	BARC bleeding type 2, 3 or 5	8 (2.7)	20 (6.9)	0.38 (0.17-0.85)	0.019	30 (3.0)	49 (4.8)	0.60 (0.38-0.95)	0.029	0.226
	BARC bleeding type 2	7 (2.3)	10 (3.5)	0.67 (0.26-1.76)	0.417	20 (2.0)	39 (3.8)	0.51 (0.30-0.87)	0.013	0.593
	BARC bleeding type 3	3 (1.0)	12 (4.2)	0.24 (0.07-0.84)	0.026	12 (1.2)	15 (1.5)	0.79 (0.37-1.69)	0.542	0.413
	BARC bleeding type 5	1 (0.3)	–	–	–	–	–	–	–	–
	MACCE and BARC bleeding type 3 or 5	12 (4.0)	26 (9.0)	0.43 (0.22-0.86)	0.017	22 (2.2)	32 (3.1)	0.68 (0.39-1.16)	0.157	0.553
	All-cause death	5 (1.7)	9 (3.1)	0.53 (0.18-1.58)	0.252	5 (0.5)	1 (0.1)	4.95 (0.58-42.37)	0.144	0.058
	Cardiovascular death	2 (0.7)	5 (1.7)	0.38 (0.07-1.96)	0.249	3 (0.3)	1 (0.1)	2.98 (0.31-28.61)	0.345	0.464
Myocardial infarction	Any myocardial infarction	5 (1.7)	8 (2.8)	0.59 (0.19-1.80)	0.354	7 (0.7)	11 (1.1)	0.63 (0.24-1.61)	0.332	0.376
	Spontaneous	5 (1.7)	6 (2.1)	0.79 (0.24-2.58)	0.692	4 (0.4)	7 (0.7)	0.56 (0.16-1.92)	0.358	0.092
	Periprocedural	–	2 (0.7)	–	–	3 (0.3)	4 (0.4)	0.74 (0.17-3.30)	0.692	–
	Target vessel myocardial infarction	1 (0.3)	2 (0.7)	0.47 (0.04-5.19)	0.538	6 (0.6)	6 (0.6)	0.98 (0.32-3.05)	0.975	0.588
Stroke		4 (1.3)	4 (1.4)	0.95 (0.24-3.79)	0.938	4 (0.4)	8 (0.8)	0.50 (0.15-1.65)	0.251	0.217
Ischaemia-driven revascularisation	Target lesion revascularisation	2 (0.7)	2 (0.7)	0.94 (0.13-6.66)	0.949	12 (1.2)	7 (0.7)	1.69 (0.67-4.29)	0.270	0.711
	Target vessel revascularisation	3 (1.0)	4 (1.4)	0.70 (0.16-3.14)	0.643	14 (1.4)	13 (1.3)	1.06 (0.50-2.25)	0.881	0.670
	Any revascularisation	8 (2.7)	12 (4.2)	0.63 (0.26-1.53)	0.305	24 (2.4)	26 (2.5)	0.91 (0.52-1.58)	0.728	0.927
Stent thrombosis		1 (0.3)	1 (0.3)	0.93 (0.06-14.86)	0.959	2 (0.2)	2 (0.2)	0.98 (0.14-6.99)	0.987	0.668

Values are expressed as n (%). *Composite of cardiovascular death, myocardial infarction, stroke, or BARC bleeding type 2, 3, or 5. †Composite of cardiovascular death, myocardial infarction, or stroke. BARC: Bleeding Academic Research Consortium; CI: confidence interval; HBR: high bleeding risk; MACCE: major adverse cardiac and cerebrovascular event

were also lower in the de-escalation group. The incidence rates of other secondary endpoints were similar between the groups. In the non-HBR group, the risks of the primary endpoint (4.0 vs 6.4%, HR 0.59, 95% CI: 0.40-0.88; p=0.009) and BARC bleeding type 2, 3, or 5 (HR 0.60, 95% CI: 0.38-0.95; p=0.029) were lower in the de-escalation group **(Table 2, Figure 4)**. However, the incidence of BARC bleeding type 3 or 5 did not differ between the groups (1.2 vs 1.5%, HR 0.79, 95% CI: 0.37-1.69; p=0.542). No interaction was evident between the de-escalation and active control groups for the primary endpoint or other secondary endpoints **(Table 2, Central illustration)**. The adherence rates, assessed by pill count adherence in the HBR subgroup of the intention-to-treat population at 6 months and 12 months after index PCI (5 and 11 months after randomisation), were 97.6% in the de-escalation group and 98.1% in the active control group at 6 months and 97.6% in the de-escalation group and 97.5% in the active control group at 12 months, respectively. The adherence rates in the non-HBR subgroup at 6 months and 12 months after index PCI were 98.7% in the de-escalation group and 97.6% in the active control group at 6 months and 98.7% in the de-escalation group and 97.2% in the active control group at 12 months, respectively. There were no significant differences in adherence.

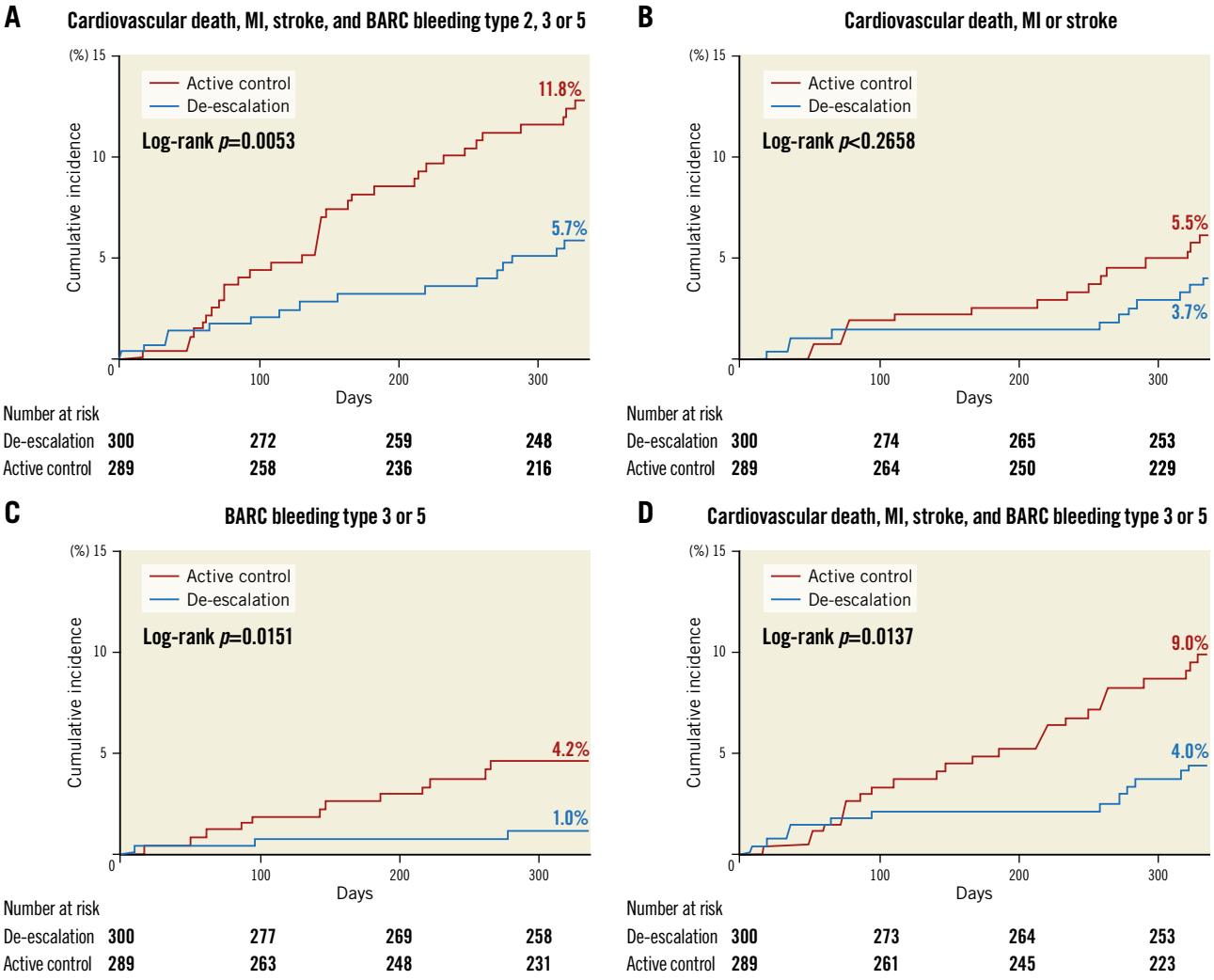


Figure 3. *Cumulative incidence of the primary and secondary outcomes by HBR and treatment arm. A) Primary endpoint: a composite of cardiovascular death, myocardial infarction, stroke, or BARC bleeding type 2, 3, or 5. B) Secondary endpoint: a major adverse cardiac and cerebrovascular event (MACCE; a composite of cardiovascular death, myocardial infarction, or stroke). C) Key secondary endpoint: BARC type 3 or 5 bleeding. D) Secondary endpoint: a composite of MACCE and BARC bleeding type 3 or 5. BARC: Bleeding Academic Research Consortium; HBR: high bleeding risk; MI: myocardial infarction*

VALIDATION BY THE PRECISE-DAPT SCORE AND ARC-HBR CRITERIA

The prevalence of HBR was 13.5% (355 patients) by the PRECISE-DAPT score and 11.5% (303 patients) by the ARC-HBR criteria **(Supplementary Figure 3, Supplementary Figure 4)**. The baseline characteristics and clinical outcomes of HBR and non-HBR patients identified via the PRECISE-DAPT score and ARC-HBR criteria were comparable to those of patients grouped using the modified HBR criteria **(Supplementary Table 5, Supplementary Table 6, Supplementary Figure 5, Supplementary Figure 6)**. The treatment arms according to the PRECISE-DAPT scores and ARC-HBR criteria are shown in **Supplementary Figure 3**. The baseline and procedural characteristics were well balanced between the de-escalation and active control groups for both HBR and non-HBR patients, as revealed by both the PRECISE-DAPT score and ARC-HBR criteria **(Supplementary Table 7, Supplementary Table 8)**. The PRECISE-DAPT analysis revealed that the incidence of the primary endpoint (HR 0.54, 95% CI: 0.38-0.78; p=0.001) and a composite of MACCE and BARC bleeding type 3 or 5 (HR 0.57, 95% CI: 0.35-0.95; p=0.035) were significantly lower in de-escalation only in the non-HBR group. In the HBR group, although de-escalation somewhat reduced the incidence rate of the primary endpoint (7.2 vs 12.1%, HR 0.59, 95% CI: 0.29-1.17) and BARC bleeding type 3 or 5 (2.2 vs 5.2%, HR 0.42, 95% CI: 0.13-1.38), statistical significance was lacking **(Supplementary Table 9, Supplementary Figure 7, Supplementary Figure 8)**. In the ARC-HBR analysis, the primary endpoint occurred less on de-escalation (compared to control) in both the HBR (6.2 vs 13.4%, HR 0.43, 95% CI: 0.20-0.95; p=0.036) and non-HBR (4.1 vs 6.8%, HR 0.59,

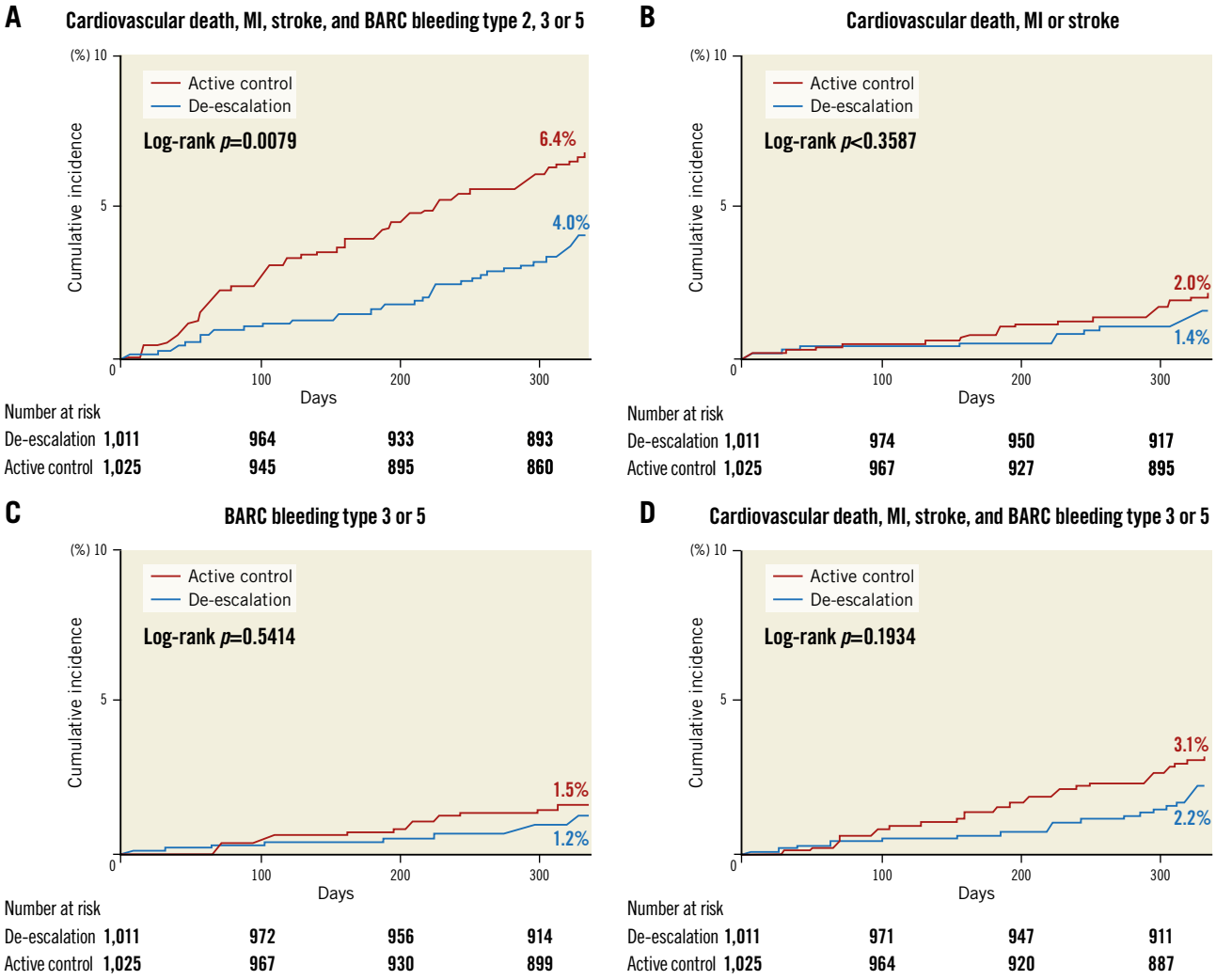


Figure 4. *Cumulative incidence of the primary and secondary outcomes by non-HBR and treatment arm. A) Primary endpoint: a composite of cardiovascular death, myocardial infarction, stroke, or BARC bleeding type 2, 3, or 5. B) Secondary endpoint: a major adverse cardiac and cerebrovascular event (MACCE; a composite of cardiovascular death, myocardial infarction, or stroke). C) Key secondary endpoint: BARC type 3 or 5 bleeding. D) Secondary endpoint: a composite of MACCE and BARC bleeding type 3 or 5. BARC: Bleeding Academic Research Consortium; HBR: high bleeding risk; MI: myocardial infarction*

95% CI: 0.41-0.84; p=0.004) groups. There was no significant difference in the incidence of BARC bleeding type 3 or 5 between the treatment arms of either the HBR group or non-HBR group **(Supplementary Table 10, Supplementary Figure 9, Supplementary Figure 10)**.

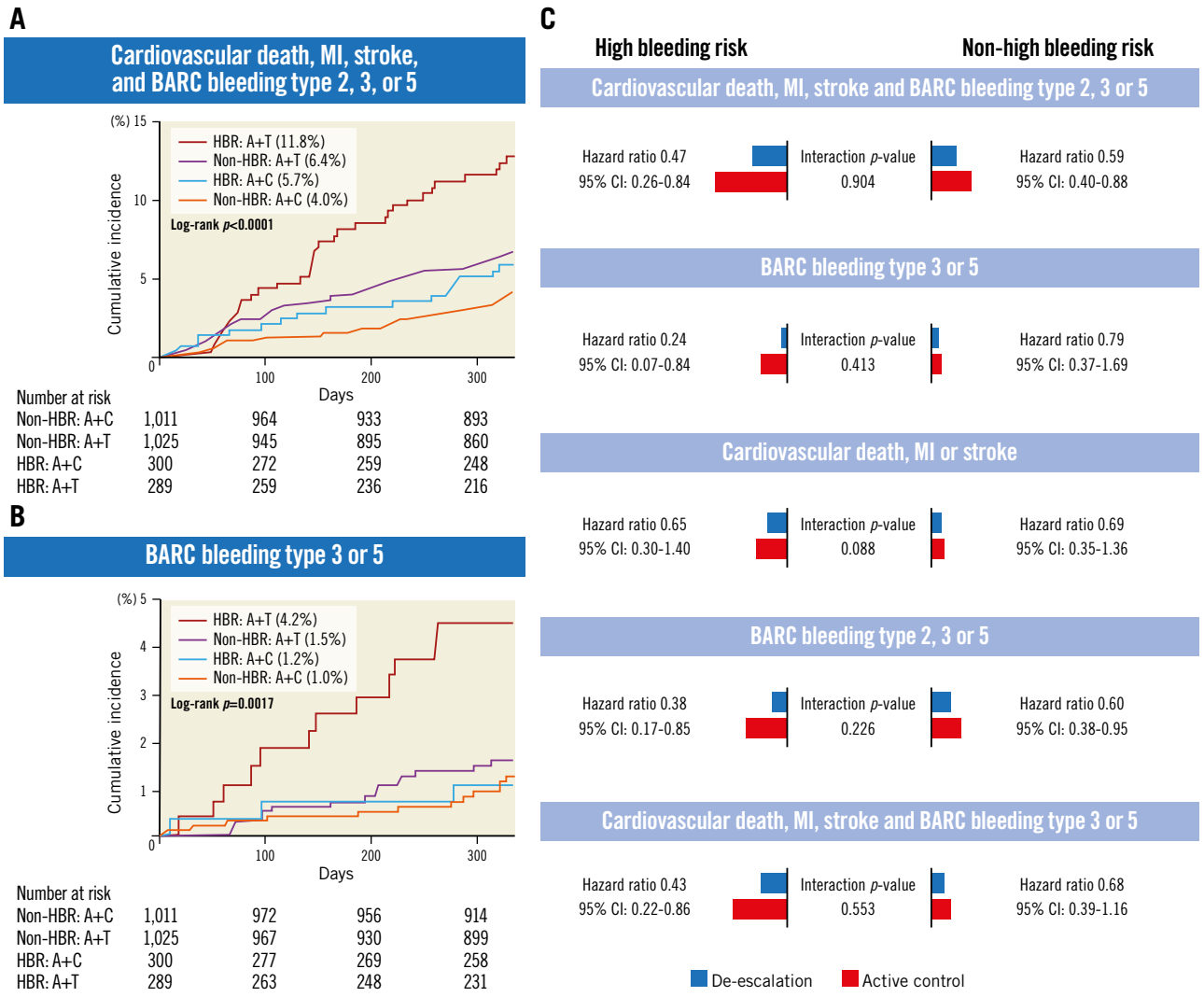
Discussion

We explored whether the benefit of uniform, unguided de-escalation of the $P2Y_{12}$ inhibitor from ticagrelor to clopidogrel 1 month after index PCI for AMI patients would be more noticeable in subjects at HBR, using the modified ARC-HBR criteria. The key findings are as follows: 1) de-escalation of DAPT from ticagrelor to clopidogrel reduced the net ischaemic and bleeding events both in patients at HBR and non-HBR, 2) the improved clinical outcomes were principally attributable to reduced haemorrhagic events but with maintenance of anti-ischaemic efficacy, and 3) BARC bleeding type 3 or 5 was less common in the de-escalation group than the ticagrelor-based standard 12-month DAPT group among patients with HBR alone; this was not the case for those with non-HBR.

UNFAVOURABLE PCI OUTCOMES IN AN HBR POPULATION

DAPT duration, the choice of $P2Y_{12}$ inhibitor (with aspirin as the bedrock), and a decision on aspirin or $P2Y_{12}$ monotherapy after DAPT are determined via the thorough assessment of individual thrombotic and bleeding risks, because post-PCI clinical outcomes are influenced by a complex interplay between the risks[4,21,22]. Bleeding *per se* is closely linked to increased thrombosis via multiple mechanisms such as discontinuation of antiplatelet agents, nitric oxide-depleted blood transfusions, and

CENTRAL ILLUSTRATION Effects of ticagrelor-based de-escalation in patients with AMI who are undergoing PCI using DES according to high bleeding risk.



A) Cumulative incidence of the primary endpoint (net clinical outcome) according to HBR and treatment arm. B) Cumulative incidence of BARC bleeding type 3 or 5 according to the HBR and treatment arm. C) Cumulative event rates between 1 and 12 months in patients with HBR and non-HBR. A: active control; AMI: acute myocardial infarction; BARC: Bleeding Academic Research Consortium; C: clopidogrel; CI: confidence interval; DES: drug-eluting stent; HBR: high bleeding risk; MI: myocardial infarction; PCI: percutaneous coronary intervention; T: ticagrelor; TALOS-AMI: TicAgrelor Versus CLOpidogrel in Stabilized Patients with Acute Myocardial Infarction

bleeding-induced enhancement of inflammation and thrombosis[22]. Patients aged ≥75 years (a minor ARC-HBR criterion) are associated with many cardiometabolic comorbidities such as diabetes, CKD, and extensive polyvascular disease, all of which increase thrombotic risk. Moreover, reduced creatinine clearance is both a high thrombotic and bleeding risk[3,5]. For these reasons, patients at HBR exhibited a poorer prognosis than those with non-HBR[7,23]. In the present study, we found that HBR status by the modified ARC-HBR criteria was linked to increased BARC bleeding type 3 or 5 and more ischaemic events.

DE-ESCALATION OF DAPT STRATEGIES IN AMI PATIENTS AT HBR

The current standard DAPT regimen for AMI patients undergoing PCI consists of aspirin and a $P2Y_{12}$ inhibitor, such as ticagrelor or prasugrel in preference to clopidogrel[3,4]. Recently, various modified strategies have emerged to create a trade-off between thrombosis and haemorrhage. Such strategies include a shortened DAPT period[8], a reduced dose (5 mg) of prasugrel[10], de-escalation of the $P2Y_{12}$ inhibitor from ticagrelor to clopidogrel[9], and $P2Y_{12}$ inhibitor monotherapy[11-14]. The benefits of these strategies were particularly

marked in patients at HBR[8,23]. Our results show that net adverse clinical outcomes occurred less frequently in the de-escalation group than in the active control group, regardless of the HBR status. However, the incidence of BARC bleeding type 3 or 5 events was lower in the de-escalation group among only HBR, not non-HBR, patients.

Notably, unguided DAPT de-escalation from ticagrelor to clopidogrel did not increase the incidence of thrombotic events even in AMI patients at high thrombotic risk, in line with the results of previous trials that alternated the standard DAPT[8-12,14,24,25]. Any benefit of prolonged DAPT in terms of decreasing ischaemic events is offset by more haemorrhagic events when a high thrombotic risk and an HBR coexist[26]. In such a situation, the HBR may dominate. Over time (approximately 1 month after an acute coronary syndrome), the bleeding risk surpasses the ischaemic risk[15]. Therefore, in AMI patients who are stabilised 1 month after PCI, de-escalation of the DAPT strategy from ticagrelor to clopidogrel, reducing the dose of prasugrel from 10 to 5 mg, or ticagrelor monotherapy (thus dropping aspirin) are viable alternatives to ticagrelor- or prasugrel-based 12-month DAPT, especially for those at HBR.

GUIDED AND UNGUIDED DE-ESCALATION DAPT STRATEGIES IN HBR PATIENTS

The current study is a *post hoc* analysis of the TALOS-AMI trial which evaluated an unguided ticagrelor-based de-escalation strategy in HBR patients; the POPular Genetics and TROPICAL-ACS trials evaluated guided de-escalation of DAPT strategy in this population[27,28]. In the individual patient-level meta-analysis, which included the 3 randomised trials mentioned above and the HOST REDUCE POLYTECH ACS trial, ischaemic and bleeding endpoints were significantly lower in the de-escalation strategy compared to the standard antiplatelet strategy[10,29]. Notably, bleeding endpoints were more reduced with unguided de-escalation than with the guided de-escalation strategy, and this was proved in another meta-analysis[30]. This prominent reduction of bleeding endpoints with the unguided de-escalation strategy might be associated with several factors, such as study population (the trials regarding unguided de-escalation strategy only enrolled Asian patients) or the timing of de-escalation. The current *post hoc* analysis of the TALOS-AMI trial shows the benefits of a ticagrelor-based de-escalation strategy in HBR patients. As far as we know, there are only a few studies which have investigated the efficacy and safety of guided de-escalation strategy in HBR patients.

In the ESC Guidelines for the management of acute coronary syndromes, DAPT de-escalation may be considered as an alternative treatment regimen based on whether it is guided or unguided by platelet function test or CYP2C19 genotyping (Class IIb, Level of Evidence A)[3]. However, this recommendation was based on the results of the POPular Genetics and TROPICAL-ACS trials, both of which evaluated guided de-escalation strategies[27,28]; the results of large trials which evaluated unguided de-escalation strategies (the TALOS-AMI and HOST REDUCE POLYTECH ACS trials) were only introduced after this. Therefore, the next guidelines (2023 ESC Guidelines for ACS) may reflect the evidence from these more recent trials, and de-escalation of DAPT strategy may be recommended more, especially in patients with HBR.

Limitations

Several limitations exist in the present study. First, this is a *post hoc* analysis using data from the TALOS-AMI trial. Our findings only generate hypotheses, and research validation is essential. Second, patients at HBR in our study do not reflect our daily PCI practice, as subjects with HBR and those having actual bleeding episodes or coagulopathy were excluded from the study at enrolment. Third, we arbitrarily modified the definition of ARC-HBR, because we lacked data on some ARC-HBR criteria. We considered that age ≥75 years and moderate CKD (an ARC-HBR minor criterion) were important in terms of the HBR. Both factors were individually associated with more bleeding episodes in the present study and in previous trials[18,19]. However, major bleeding only occurred in less than 4% of patients in isolation of major criteria and without any other coexisting criteria, and 70.5% of the distribution of HBR subgroups corresponds to only one HBR definition. Nevertheless, a sensitivity analysis using the original ARC-HBR definition and the PRECISE-DAPT scores yielded findings consistent with our principal results. Compared to the ticagrelor-based 12-month DAPT, the de-escalation strategy tended to lower the incidence of bleeding events in patients with HBR using the ARC-HBR definition and the PRECISE-DAPT score. Fourth, there were no data for CYP2C19 genotyping. However, the TALOS-AMI study aimed to evaluate the benefits of an unguided de-escalation of DAPT strategy. Fifth, we could not check the prescription rate of proton pump inhibitors (PPI), which have been associated with reduced gastrointestinal bleeding. In other trials regarding antiplatelet strategies performed in South Korea, the prescription rate for PPI was about 18%, and we think the rate of PPI prescription in this subgroup analysis may have been similar to that of the abovementioned trials[10]. Finally, the interaction p-values for all outcomes are >0.05, which indicates that there were no statistically significant differences in de-escalation treatment effects between the HBR and non-HBR groups despite large differences in the hazard ratios in some outcomes, such as major bleeding. This finding suggests that the current study had inadequate power; thus, the results should be interpreted cautiously.

Conclusions

Uniform unguided de-escalation of the $P2Y_{12}$ inhibitor from ticagrelor to clopidogrel 1 month after AMI was safe and efficacious in terms of decreasing the rate of net adverse clinical outcomes, regardless of HBR status by the modified ARC-HBR criteria. The effect of de-escalation of DAPT strategy on reductions in BARC bleeding type 3 or 5 was profound for patients at HBR. De-escalating DAPT from ticagrelor to clopidogrel might be a reasonable option in stabilised AMI patients with HBR.

Impact on daily practice

Compared to ongoing ticagrelor-based DAPT, for AMI patients undergoing PCI with DES, switching from ticagrelor to clopidogrel after 1 month reduced haemorrhage while maintaining protection against thrombotic events in both HBR and non-HBR patients. Future studies should investigate the impact of the de-escalation of DAPT strategy from ticagrelor to clopidogrel in AMI patients with HBR at earlier timepoints after PCI.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001-15.

2. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators; Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045-57.

3. 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.

4. Writing Committee Members; Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, Fremes SE, Gaudino MF, Goldberger ZD, Grant MC, Jaswal JB, Kurlansky PA, Mehran R, Metkus TS Jr, Nnacheta LC, Rao SV, Sellke FW, Sharma G, Yong CM, Zwischenberger BA. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79:e21-129.

5. 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. *Circulation.* 2019;140:240-61.

6. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD; ADAPT-DES Investigators. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet.* 2013;382:614-23.

7. Marquis-Gravel G, Dalgaard F, Jones AD, Lokhnygina Y, James SK, Harrington RA, Wallentin L, Steg PG, Lopes RD, Storey RF, Goodman SG, Mahaffey KW, Tricoci P, White HD, Armstrong PW, Ohman EM, Alexander JH, Roe MT. Post-Discharge Bleeding and Mortality Following Acute Coronary Syndromes With or Without PCI. *J Am Coll Cardiol.* 2020;76:162-71.

8. Valgimigli M, Frigoli E, Heg D, Tijssen J, Jüni P, Vranckx P, Ozaki Y, Morice MC, Chevalier B, Onuma Y, Windecker S, Tonino PAL, Roffi M, Lesiak M, Mahfoud F, Bartunek J, Hildick-Smith D, Colombo A, Stanković G, Iñiguez A, Schultz C, Kornowski R, Ong PJL, Alasnag M, Rodriguez AE, Moschovitis A, Laanmets P, Donahue M, Leonardi S, Smits PC; MASTER DAPT Investigators. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. *N Engl J Med.* 2021;385:1643-55.

9. Kim CJ, Park MW, Kim MC, Choo EH, Hwang BH, Lee KY, Choi YS, Kim HY, Yoo KD, Jeon DS, Shin ES, Jeong YH, Seung KB, Jeong MH, Yim HW, Ahn Y, Chang K; TALOS-AMI investigators. Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. *Lancet.* 2021;398:1305-16.

10. Kim HS, Kang J, Hwang D, Han JK, Yang HM, Kang HJ, Koo BK, Rhew JY, Chun KJ, Lim YH, Bong JM, Bae JW, Lee BK, Park KW; HOST-REDUCE-POLYTECH-ACS investigators. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet.* 2020;396:1079-89.

11. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, Džavík V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta SR, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han YL, Pocock S, Gibson CM. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med.* 2019;381:2032-42.

12. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, Yoo SY, Cho DK, Hong BK, Kwon H, Ahn CM, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y; TICO Investigators. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. *JAMA.* 2020;323:2407-16.

13. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, Im ES, Jeong JO, Cho BR, Oh SK, Yun KH, Cho DK, Lee JY, Koh YY, Bae JW, Choi JW, Lee WS, Yoon HJ, Lee SU, Cho JH, Choi WG, Rha SW, Lee JM, Park TK, Yang JH, Choi JH, Choi SH, Lee SH, Gwon HC; SMART-CHOICE Investigators. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. *JAMA.* 2019;321:2428-37.

14. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Möllmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S; GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet.* 2018;392:940-9.

15. Rodriguez F, Harrington RA. Management of Antithrombotic Therapy after Acute Coronary Syndromes. *N Engl J Med.* 2021;384:452-60.

16. Park MW, Kim CJ, Kim MC, Choo EH, Hwang BH, Park CS, Kim HY, Yoo KD, Jeon DS, Jeong MH, Seung KB, Ahn Y, Chang K. A prospective, multicentre, randomised, open-label trial to compare the efficacy and safety of clopidogrel versus ticagrelor in stabilised patients with acute myocardial infarction after percutaneous coronary intervention: rationale and design of the TALOS-AMI trial. *EuroIntervention.* 2021;16:1170-6.

17. You SC, Rho Y, Bikdeli B, Kim J, Siapos A, Weaver J, Londhe A, Cho J, Park J, Schuemie M, Suchard MA, Madigan D, Hripcsak G, Gupta A, Reich CG, Ryan PB, Park RW, Krumholz HM. Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. *JAMA.* 2020;324:1640-50.

18. Ueki Y, Bär S, Losdat S, Otsuka T, Zanchin C, Zanchin T, Gragnano F, Gargiulo G, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Heg D, Valgimigli M, Windecker S, Räber L. Validation of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores. *EuroIntervention.* 2020;16:371-9.

19. Silverio A, Di Maio M, Buccheri S, De Luca G, Esposito L, Sarno G, Vecchione C, Galasso G. Validation of the academic research consortium high bleeding risk criteria in patients undergoing percutaneous coronary intervention: A systematic review and meta-analysis of 10 studies and 67,862 patients. *Int J Cardiol.* 2022;347:8-15.

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

21. Cao D, Chandiramani R, Chiarito M, Claessen BE, Mehran R. Evolution of antithrombotic therapy in patients undergoing percutaneous coronary intervention: a 40-year journey. *Eur Heart J.* 2021;42:339-51.

22. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML. Antiplatelet therapy after percutaneous coronary intervention. *EuroIntervention.* 2022;17:e1371-96.

23. Escaned J, Cao D, Baber U, Nicolas J, Sartori S, Zhang Z, Dangas G, Angiolillo DJ, Briguori C, Cohen DJ, Collier T, Dudek D, Gibson M, Gil R, Huber K, Kaul U, Kornowski R, Krucoff MW, Kunadian V, Mehta S, Moliterno DJ, Ohman EM, Oldroyd KG, Sardella G, Sharma SK, Shlofmitz R, Weisz G, Witzenbichler B, Pocock S, Mehran R. Ticagrelor monotherapy in patients at high bleeding risk undergoing percutaneous coronary intervention: TWILIGHT-HBR. *Eur Heart J.* 2021;42:4624-34.

24. Dangas G, Baber U, Sharma S, Giustino G, Mehta S, Cohen DJ, Angiolillo DJ, Sartori S, Chandiramani R, Briguori C, Dudek D, Escaned J, Huber K, Collier T, Kornowski R, Kunadian V, Kaul U, Oldroyd K, Sardella G, Shlofmitz R, Witzenbichler B, Ya-Ling H, Pocock S, Gibson CM, Mehran R. Ticagrelor With or Without Aspirin After Complex PCI. *J Am Coll Cardiol.* 2020;75:2414-24.

25. Valgimigli M, Smits PC, Frigoli E, Bongiovanni D, Tijssen J, Hovasse T, Mafragi A, Ruifrok WT, Karageorgiev D, Aminian A, Garducci S, Merkely B, Routledge H, Ando K, Diaz Fernandez JF, Cuisset T, Nesa Malik FT, Halabi M, Belle L, Din J, Beygui F, Abhyankar A, Reczuch K, Pedrazzini G, Heg D, Vranckx P; MASTER DAPT Investigators. Duration of antiplatelet therapy after complex percutaneous coronary intervention in patients at high bleeding risk: a MASTER DAPT trial sub-analysis. *Eur Heart J.* 2022;43:3100-14.

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

27. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, Barbato E, Morisco C, Tjon Joe Gin RM, Asselbergs FW, Mosterd A, Herrman JR, Dewilde WJM, Janssen PWA, Kelder JC, Postma MJ, de Boer A, Boersma C, Deneer VHM, Ten Berg JM. A Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI. *N Engl J Med.* 2019;381:1621-31.

28. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Hadamitzky M, Merkely B, Kiss RG, Komócsi A, Dézsi CA, Holdt L, Felix SB, Parma R, Klopotowski M, Schwinger RHG, Rieber J, Huber K, Neumann FJ, Koltowski L, Mehilli J, Huczek Z, Massberg S; TROPICAL-ACS Investigators. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet.* 2017;390:1747-57.

29. Kang J, Rizas KD, Park KW, Chung J, van den Broek W, Claassens DMF, Choo EH, Aradi D, Massberg S, Hwang D, Han JK, Yang HM, Kang HJ, Chang K, Ten Berg JM, Sibbing D, Koo BK, Kim HS. Dual antiplatelet therapy de-escalation in acute coronary syndrome: an individual patient meta-analysis. *Eur Heart J.* 2023;44:1360-70.

30. Kuno T, Fujisaki T, Shoji S, Sahashi Y, Tsugawa Y, Iwagami M, Takagi H, Briasoulis A, Deharo P, Cuisset T, Latib A, Kohsaka S, Bhatt DL. Comparison of Unguided De-Escalation Versus Guided Selection of Dual Antiplatelet Therapy After Acute Coronary Syndrome: A Systematic Review and Network Meta-Analysis. *Circ Cardiovasc Interv.* 2022;15:e011990.

Supplementary data

Supplementary Table 1. Reasons for screening failure.

Supplementary Table 2. Study definitions for major and minor HBR criteria compared with the definitions from ARC-HBR criteria.

Supplementary Table 3. Baseline and procedural characteristics by HBR.

Supplementary Table 4. Primary and secondary outcomes by HBR.

Supplementary Table 5. Baseline and procedural characteristics by PRECISE-DAPT score-based HBR and ARC-HBR criteria.

Supplementary Table 6. Primary and secondary outcomes by PRECISE-DAPT score-based HBR and ARC-HBR criteria.

Supplementary Table 7. Baseline and procedural characteristics by PRECISE-DAPT score-based HBR and treatment arm.

Supplementary Table 8. Baseline and procedural characteristics by ARC-HBR criteria and treatment arm.

Supplementary Table 9. Primary and secondary outcomes by PRECISE-DAPT score-based HBR and treatment arm.

Supplementary Table 10. Primary and secondary outcomes by ARC-HBR criteria and treatment arm.

Supplementary Figure 1. Prevalence of HBR criteria within the HBR group and impact on major bleeding outcome.

Supplementary Figure 2. Clinical impact of multiple HBR criteria.

Supplementary Figure 3. Study flow according to PRECISE-DAPT score and ARC-HBR criteria.

Supplementary Figure 4. Distribution of study patients by PRECISE-DAPT score and ARC-HBR criteria.

Supplementary Figure 5. Cumulative incidences of primary and secondary outcomes by PRECISE-DAPT score-based HBR.

Supplementary Figure 6. Cumulative incidences of primary and secondary outcomes by ARC-HBR criteria.

Supplementary Figure 7. Cumulative incidences of primary and secondary outcomes by PRECISE-DAPT score-based HBR and treatment arm.

Supplementary Figure 8. Cumulative incidences of primary and secondary outcomes by PRECISE-DAPT score-based non-HBR and treatment arm.

Supplementary Figure 9. Cumulative incidences of primary and secondary outcomes by ARC-HBR criteria-based HBR and treatment arm.

Supplementary Figure 10. Cumulative incidences of primary and secondary outcomes by ARC-HBR criteria-based non-HBR and treatment arm.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00427

Supplementary data

Supplementary Table 1. Reasons for screening failure.

	Screening failure (n = 204)
Follow up loss	92 (45.1)
Fail to visit at randomization	85 (41.7)
Transfer to another institute (follow up loss)	7 (3.4)
Adverse events	14 (6.9)
Death before randomization	4 (2.0)
Stroke (intracranial aneurysm and intracranial bleeding)	4 (2.0)
GI or GU bleeding, or hemoptysis	5 (2.5)
Unspecified bleeding	1 (0.5)
Medication non-adherence	21 (10.3)
Non-compliance	2 (1.0)
Intolerance of study medications	9 (4.4)
Investigator directed	10 (4.9)
Inclusion and exclusion criteria violation	77 (37.7)
Incorrect diagnosis	3 (1.5)
DES not used for PCI	1 (0.5)
Cardiogenic shock	2 (1.0)
Anemia	4 (2.0)
History of intracranial bleeding	1 (0.5)
Concomitant anticoagulation, or NSAIDs	5 (2.5)
COPD	5 (2.5)
Renal replacement therapy, or ESRD	2 (1.0)
Enrolled in another clinical trial	1 (0.5)
Withdrawal of consent	34 (16.7)
Unsuitable for study by investigator	15 (7.4)
Nor certain	4 (2.0)

Values are expressed as n (%).

Abbreviations: COPD, chronic obstructive pulmonary disease; DES, drug-eluting stent; ESRD, end stage renal disease; GI, gastrointestinal; GU, genitourinary; NSAID, non-steroid anti-inflammatory drug; PCI, percutaneous coronary intervention.

Supplementary Table 2. Study definitions for major and minor HBR criteria compared with the definitions from ARC-HBR criteria.

	Study definition	ARC-HBR criteria
Major criteria		
Severe CKD	Severe CKD (eGFR < 30 mL/min)	Severe or end-stage CKD (eGFR < 30 mL/min)
Moderate anemia	10 g/dL ≤ Hemoglobin < 11 g/dL	Hemoglobin < 11 g/dL
Age ≥ 75	Transferred from minor criteria	Age ≥ 75 years
Moderate CKD	Transferred from minor criteria	Moderate CKD (eGFR 30-59 mL/min)
	NA	Moderate or severe baseline thrombocytopenia (platelet count < 100 x 10^9/L)
	NA	Anticipated use of long-term oral anticoagulation
	NA	Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or any time, if recurrent
	NA	Chronic bleeding diathesis
	NA	Liver cirrhosis with portal hypertension
	NA	Active malignancy (excluding nonmelanoma skin cancer) within the past 12 months
	NA	Previous spontaneous ICH (at any time) Previous traumatic ICH within the past 12 months Presence of a brain arteriovenous malformation Moderate to severe ischemic stroke within the past 6 months
	NA	Nondeferrable major surgery on DAPT

	NA	Recent major surgery or major trauma within 30 days before PCI
Minor criteria		
Mild anemia	No difference compared to ARC-HBR	Hemoglobin 11-12.9 g/dL for men and 11-11.9 g/dL for women
Any ischemic stroke	No difference compared to ARC-HBR	Any ischemic stroke at any time not meeting the major criterion
	Transfer to major criteria	Age ≥ 75 years
	Transfer to major criteria	Moderate CKD (eGFR 30-59 mL/min)
	NA	Spontaneous bleeding within the past 12 months not meeting the major criterion
	NA	Long-term use of oral NSAIDs or steroids

Abbreviations: ARC-HBR, Academic Research Consortium for High Bleeding Risk; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; GFR, glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial hemorrhage; NSAID, non-steroid anti-inflammatory drug.

Supplementary Table 3. Baseline and procedural characteristics by HBR.

	HBR (n = 589)	Non-HBR (n = 2,036)	p Value
Demographics			
Age, years	71.0 ± 10.5	56.8 ± 9.4	<0.001
Male	389 (66.0)	1,790 (87.9)	<0.001
Body mass index, kg/m^2	23.7 ± 3.6	24.9 ± 3.3	<0.001
Medical history			
Hypertension	381 (64.7)	896 (44.0)	<0.001
Diabetes	198 (33.6)	510 (25.0)	<0.001
Diabetes treated with insulin	20 (3.4)	34 (1.7)	0.009
Dyslipidemia	217 (36.8)	870 (42.7)	0.011
Current smoker	171 (29.0)	1,133 (55.6)	<0.001
Impaired renal function*	304 (51.6)	–	–
Past medical history			
Previous PCI	42 (7.1)	74 (3.6)	<0.001
Previous CABG	3 (0.5)	1 (0.0)	0.037
Previous CVA	41 (7.0)	57 (2.8)	<0.001
Clinical presentation			0.164
STEMI	302 (51.3)	1,110 (54.5)	
NSTEMI	287 (48.7)	926 (45.5)	
Laboratory findings			
Creatinine clearance†, mL/min/1.73 m^2	68.4 ± 25.8	92.9 ± 21.9	<0.001
Hemoglobin, g/dL	13.2 ± 1.9	15.0 ± 1.4	<0.001
Platelet, 10^9/L	233.9 ± 63.0	241.2 ± 58.5	0.012
White blood cell count, 10^9/L	9.7 ± 3.4	10.5 ± 3.5	<0.001
LVEF < 40%	76/562 (13.5)	115/1,959 (5.9)	<0.001
Access site			0.102
Radial	259 (44.0)	996 (48.9)	
Femoral	300 (50.9)	940 (46.2)	
Glycoprotein IIb/IIIa inhibitor	141 (23.9)	475 (23.3)	0.759
Infarct-related artery			<0.001
Left main coronary artery	17 (2.9)	28 (1.4)	
Left anterior descending artery	254 (43.3)	1,019 (50.5)	
Left circumflex artery	78 (13.3)	372 (18.4)	
Right coronary artery	237 (40.4)	598 (29.6)	
Number of treated vessels	1.4 ± 0.7	1.4 ± 0.6	0.042
Multivessel treatment	196 (33.3)	585 (28.7)	0.034

Numbers of stents for infarct-related artery	1.2 ± 0.4	1.2 ± 0.5	0.155
Total stent length of infarct-related artery, mm	30.8 ± 14.5	29.4 ± 16.4	0.067
Stent diameter of infarct-related artery, mm	3.2 ± 0.5	3.2 ± 0.8	0.218
Intravascular imaging			
Optical coherence tomography	19 (3.2)	63 (3.1)	0.872
Intravascular ultrasonography	134 (22.8)	490 (24.1)	0.509

Values are expressed as mean (SD) or n (%). *Impaired renal function was defined as an estimated glomerular filtration rate of less than 60 mL/ min/1.73 m^2 of body surface area at presentation. †Creatinine clearance was calculated by MDRD (Modification of Diet in Renal Disease) formula: 186 * (serum creatinine)$^{-1.154}$ * (age)$^{-0.203}$ * 0.742 (for women).

Abbreviations: CABG, coronary artery bypass graft; CVA, cerebrovascular accident; HBR, high bleeding risk; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Supplementary Table 4. Primary and secondary outcomes by HBR.

	HBR (n = 589)	Non-HBR (n = 2,036)	HR (95% CI)	p Value
Primary endpoint*	51 (8.7)	106 (5.2)	1.75 (1.26-2.45)	0.001
Secondary endpoints				
BARC bleeding type 3 or 5	15 (2.5)	27 (1.3)	2.01 (1.07-3.78)	0.030
MACCE†	27 (4.6)	34 (1.7)	2.89 (1.75-4.80)	<0.001
BARC bleeding type 2, 3 or 5	28 (4.8)	79 (3.9)	1.28 (0.83-1.97)	0.262
BARC bleeding type 2	17 (2.9)	59 (2.9)	1.03 (0.60-1.77)	0.903
BARC bleeding type 3	15 (2.5)	27 (1.3)	2.01 (1.07-3.78)	0.030
BARC bleeding type 5	1 (0.2)	0	–	–
MACCE, and BARC bleeding type 3 or 5	28 (6.5)	54 (2.7)	2.57 (1.70-3.90)	<0.001
All-cause death	14 (2.4)	6 (0.3)	8.42 (3.24-21.91)	<0.001
Cardiovascular death	7 (1.2)	4 (0.2)	6.32 (1.85-21.58)	0.003
Myocardial infarction				
Any myocardial infarction	13 (2.2)	18 (0.9)	2.63 (1.29-5.37)	0.008
Spontaneous	11 (1.9)	11 (0.5)	3.64 (1.58-8.39)	0.002
Periprocedural	2 (0.3)	7 (0.3)	1.04 (0.22-5.00)	0.962
Target vessel myocardial infarction	3 (0.5)	12 (0.6)	0.91 (0.26-3.22)	0.882
Stroke	8 (1.4)	12 (0.6)	2.41 (0.98-5.88)	0.055
Ischemia-driven revascularization				
Target lesion revascularization	4 (0.7)	19 (0.9)	0.77 (0.26-2.25)	0.628
Target vessel revascularization	7 (1.2)	27 (1.3)	0.94 (0.41-2.16)	0.888
Any revascularization	20 (3.4)	50 (2.5)	1.46 (0.87-2.45)	0.153
Stent thrombosis	2 (0.3)	4 (0.2)	1.83 (0.34-9.99)	0.486

Values are expressed as n (%). *Composite of cardiovascular death, myocardial infarction, stroke, and BARC bleeding type 2, 3, or 5. †Composite of cardiovascular death, myocardial infarction, or stroke.

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; HBR, high bleeding risk; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular event.

Supplementary Table 5. Baseline and procedural characteristics by PRECISE-DAPT score-based HBR and ARC-HBR criteria.

	PRECISE-DAPT			ARC-HBR		
	HBR (n = 355)	Non-HBR (n = 2,270)	p Value	HBR (n = 303)	Non-HBR (n = 2,322)	p Value
Demographics						
Age, years	72.8 ± 9.3	58.0 ± 10.3	<0.001	72.8 ± 9.4	58.3 ± 10.5	<0.001
Male	227 (63.9)	1,952 (86.0)	<0.001	180 (59.4)	1,999 (86.1)	<0.001
Body mass index, kg/m^2	23.5 ± 3.3	24.8 ± 3.4	<0.001	23.2 ± 3.1	24.8 ± 3.4	<0.001
Medical history						
Hypertension	243 (68.5)	1,034 (45.6)	<0.001	206 (68.0)	1,071 (46.1)	<0.001
Diabetes	140 (39.4)	568 (25.0)	<0.001	122 (40.3)	586 (25.2)	<0.001
Diabetes treated with insulin	13 (3.7)	41 (1.8)	0.022	14 (4.6)	40 (1.7)	0.001
Dyslipidemia	127 (35.8)	960 (42.3)	0.020	121 (39.9)	966 (41.6)	0.579
Current smoker	99 (27.9)	1,205 (53.1)	<0.001	76 (25.1)	1,228 (52.9)	<0.001
Impaired renal function*	208 (58.6)	97 (4.3)	<0.001	152 (50.2)	153 (6.6)	<0.001
Past medical history						
Previous PCI	21 (5.9)	95 (4.2)	0.140	25 (8.3)	91 (3.9)	0.001
Previous CABG	0	4 (0.2)	1.000	1 (0.3)	3 (0.1)	0.388
Previous CVA	24 (6.8)	74 (3.3)	0.001	41 (13.5)	57 (2.5)	<0.001
Clinical presentation			0.357			0.010
STEMI	199 (56.1)	1,213 (53.4)		142 (46.9)	1,270 (54.7)	
NSTEMI	156 (43.9)	1,057 (46.6)		161 (53.1)	1,052 (45.3)	
Laboratory findings						
Creatinine clearance†, mL/min/1.73 m^2	58.5 ± 17.6	91.9 ± 22.9	<0.001	67.7 ± 27.1	90.0 ± 23.5	<0.001

Hemoglobin, g/dL	13.1 ± 2.0	14.8 ± 1.5	<0.001	12.0 ± 1.5	14.9 ± 1.4	<0.001
Platelet, 10^9/L	239.8 ± 64.3	239.5 ± 58.9	0.947	232.4 ± 66.3	240.5 ± 58.6	0.027
White blood cell count, 10^9/L	11.8 ± 4.6	10.1 ± 3.2	<0.001	9.2 ± 3.2	10.4 ± 3.5	<0.001
LVEF < 40%	53/340 (15.6)	138/2,181 (6.3)	<0.001	47/292 (16.1)	144/2,229 (6.5)	<0.001
Access site			0.006			0.691
Radial	142 (40.0)	1,113 (49.0)		138 (45.5)	1,117 (48.1)	
Femoral	192 (54.1)	1,048 (46.2)		150 (49.5)	1,090 (46.9)	
Glycoprotein IIb/IIIa inhibitor	105 (29.6)	511 (22.5)	0.003	69 (22.8)	547 (23.6)	0.762
Infarct-related artery			<0.001			<0.001
Left main coronary artery	10 (2.8)	35 (1.6)		10 (3.3)	35 (1.5)	
Left anterior descending artery	148 (41.7)	1,125 (50.0)		131 (43.7)	1,142 (49.6)	
Left circumflex artery	41 (11.5)	409 (18.2)		36 (12.0)	414 (18.0)	
Right coronary artery	156 (43.9)	679 (30.2)		123 (41.0)	712 (30.9)	
Number of treated vessels	1.4 ± 0.6	1.4 ± 0.6	0.269	1.4 ± 0.6	1.4 ± 0.6	0.057
Multivessel treatment	124 (34.9)	657 (28.9)	0.022	110 (36.3)	671 (28.9)	0.008
Numbers of stents for infarct-related artery	1.2 ± 0.4	1.2 ± 0.5	0.432	1.2 ± 0.5	1.2 ± 0.5	0.115
Total stent length of infarct-related artery, mm	31.3 ± 14.6	29.5 ± 16.2	0.036	31.9 ± 15.1	29.5 ± 16.1	0.010
Stent diameter of infarct-related artery, mm	3.2 ± 0.5	3.2 ± 0.8	0.535	3.1 ± 0.4	3.2 ± 0.8	0.014
Intravascular imaging						
Optical coherence tomography	8 (2.3)	74 (3.3)	0.311	7 (2.3)	75 (3.2)	0.387
Intravascular ultrasonography	81 (22.8)	543 (23.9)	0.650	71 (23.4)	553 (23.8)	0.883

Values are expressed as mean (SD) or n (%). *Impaired renal function was defined as an estimated glomerular filtration rate of less than 60 mL/ min/1.73 m^2 of body surface area at presentation. †Creatinine clearance was calculated by MDRD (Modification of Diet in Renal Disease) formula: 186 * (serum creatinine)$^{-1.154}$ * (age)$^{-0.203}$ * 0.742 (for women).

Abbreviations: ARC-HBR, Academic Research Consortium for High Bleeding Risk; CABG, coronary artery bypass graft; CVA, cerebrovascular accident;

HBR, high bleeding risk; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; STEMI, ST-segment elevation myocardial infarction.

Supplementary Table 6. Primary and secondary outcomes by PRECISE-DAPT score-based HBR and ARC-HBR criteria.

	PRECISE-DAPT				ARC-HBR			
	HBR (n = 355)	Non-HBR (n = 2,270)	Hazard ratio (95% CI)	p Value	HBR (n = 303)	Non-HBR (n = 2,322)	Hazard ratio (95% CI)	p Value
Primary endpoint*	34 (9.6)	123 (5.4)	1.83 (1.26-2.68)	0.002	30 (9.9)	127 (80.9)	1.91 (1.29-2.85)	0.002
Secondary endpoints								
BARC bleeding type 3 or 5	13 (3.7)	29 (1.3)	2.96 (1.54-5.69)	0.001	10 (3.3)	32 (1.4)	2.54 (1.25-5.16)	0.012
MACCE†	17 (4.8)	44 (1.9)	2.58 (1.47-4.51)	0.001	18 (5.9)	43 (1.9)	3.41 (1.97-5.91)	<0.001
BARC bleeding type 2, 3 or 5	20 (5.6)	87 (3.8)	1.51 (0.93-2.45)	0.110	15 (5.0)	92 (4.0)	1.31 (0.76-2.26)	0.413
BARC bleeding type 2	10 (2.8)	66 (2.9)	0.99 (0.51-1.92)	0.925	9 (3.0)	67 (2.9)	1.07 (0.54-2.15)	0.934
BARC bleeding type 3	13 (3.7)	29 (1.3)	2.96 (1.54-5.69)	0.001	10 (3.3)	32 (1.4)	2.54 (1.25-5.16)	0.012
BARC bleeding type 5	1 (0.3)	–	–	–	1 (0.3)	–	–	–
MACCE, and BARC bleeding type 3 or 5	27 (7.6)	65 (2.9)	2.78 (1.77-4.35)	<0.001	25 (8.3)	67 (2.9)	3.06 (1.93-4.84)	<0.001
All-cause death	11 (3.1)	9 (0.4)	8.03 (3.33-19.37)	<0.001	10 (3.3)	10 (0.4)	8.07 (3.36-19.39)	<0.001
Cardiovascular death	5 (1.4)	6 (0.3)	5.48 (1.67-17.96)	0.010	5 (1.7)	6 (0.3)	6.73 (2.05-22.04)	0.005
Myocardial infarction								
Any myocardial infarction	9 (2.5)	22 (1.0)	2.73 (1.26-5.93)	0.011	9 (3.0)	22 (0.9)	3.34 (1.54-7.26)	0.002
Spontaneous	8 (2.3)	14 (0.6)	3.80 (1.60-9.07)	0.002	7 (2.3)	15 (0.6)	3.80 (1.55-9.33)	0.003
Periprocedural	1 (0.3)	8 (0.4)	0.83 (0.10-6.63)	1.000	2 (0.7)	7 (0.3)	2.33 (0.48-11.20)	0.279
Target vessel myocardial infarction	1 (0.3)	14 (0.6)	0.47 (0.06-3.60)	0.436	2 (0.7)	13 (0.6)	1.25 (0.28-5.56)	0.689
Stroke	4 (1.1)	16 (0.7)	1.65 (0.55-4.92)	0.395	5 (1.7)	15 (0.6)	2.69 (0.98-7.39)	0.072
Ischemia-driven revascularization								
Target lesion revascularization	2 (0.6)	21 (0.9)	0.63 (0.15-2.69)	0.759	3 (1.0)	20 (0.9)	1.23 (0.36-4.13)	0.821
Target vessel revascularization	4 (1.1)	30 (1.3)	0.88 (0.31-2.50)	1.000	4 (1.3)	30 (1.3)	1.09 (0.38-3.08)	1.000

Any revascularization	12 (3.4)	58 (2.6)	1.38 (0.74-2.57)	0.369	13 (4.3)	57 (2.5)	1.87 (1.02-3.41)	0.062
Stent thrombosis	1 (0.3)	5 (0.2)	1.33 (0.16-11.40)	0.582	1 (0.3)	5 (0.2)	1.64 (0.19-14.05)	0.521

Values are expressed as n (%). *Composite of cardiovascular death, myocardial infarction, stroke, and BARC bleeding type 2, 3, or 5. †Composite of cardiovascular death, myocardial infarction, or stroke.

Abbreviations: ARC-HBR, Academic Research Consortium for High Bleeding Risk; BARC, Bleeding Academic Research Consortium; CI, confidence interval; HBR, high bleeding risk; MACCE, major adverse cardiac and cerebrovascular event; PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.

Supplementary Table 7. Baseline and procedural characteristics by PRECISE-DAPT score-based HBR and treatment arm.

	HBR (n = 355)			Non-HBR (n = 2,270)		
	De-escalation (n = 181)	Active control (n = 174)	p Value	De-escalation (n = 1,130)	Active control (n = 1,140)	p Value
Demographics						
Age, years	73.2 ± 9.2	72.4 ± 9.3	0.428	58.0 ± 10.1	57.9 ± 10.5	0.845
Male	117 (64.6)	110 (63.2)	0.780	979 (86.6)	973 (85.4)	0.377
Body mass index, kg/m^2	23.8 ± 3.1	23.2 ± 3.4	0.127	24.8 ± 3.3	24.7 ± 3.5	0.620
Medical history						
Hypertension	118 (65.2)	125 (71.8)	0.178	516 (45.7)	518 (45.4)	0.914
Diabetes	73 (40.3)	67 (38.5)	0.725	276 (24.4)	292 (25.6)	0.513
Diabetes treated with insulin	7 (3.9)	6 (3.4)	0.834	19 (1.7)	22 (1.9)	0.657
Dyslipidemia	65 (35.9)	62 (35.6)	0.956	477 (42.2)	483 (42.4)	0.940
Current smoker	55 (30.4)	44 (25.3)	0.284	594 (52.6)	611 (53.6)	0.623
Impaired renal function*	103 (56.9)	105 (60.3)	0.511	57 (5.0)	40 (3.5)	0.071
Past medical history						
Previous PCI	9 (5.0)	12 (6.9)	0.442	50 (4.4)	45 (3.9)	0.570
Previous CABG	0	0	–	3 (0.3)	1 (0.1)	0.372
Previous CVA	11 (6.1)	13 (7.5)	0.601	39 (3.5)	35 (3.1)	0.609
Clinical presentation			0.598			0.546
STEMI	99 (54.7)	100 (57.5)		611 (54.1)	602 (52.8)	
NSTEMI	82 (45.3)	74 (42.5)		519 (45.9)	538 (47.2)	
Laboratory findings						
Creatinine clearance†, mL/min/1.73 m^2	59.4 ± 18.3	57.5 ± 16.9	0.294	90.7 ± 21.8	93.2 ± 23.8	0.008

Hemoglobin, g/dL	13.2 ± 2.0	13.0 ± 2.0	0.234	14.8 ± 1.5	14.8 ± 1.5	0.370
Platelet, 10^9/L	242.5 ± 62.5	236.9 ± 66.2	0.415	240.4 ± 61.0	238.7 ± 56.6	0.507
White blood cell count, 10^9/L	12.0 ± 4.8	11.6 ± 4.4	0.438	10.0 ± 3.1	10.2 ± 3.4	0.132
LVEF < 40%	32/173 (18.5)	21/167 (12.6)	0.132	67/1,095 (6.1)	71/1,086 (6.5)	0.688
Access site			0.953			0.614
Radial	71 (39.2)	71 (40.8)		547 (48.4)	566 (49.6)	
Femoral	99 (54.7)	93 (53.4)		532 (47.1)	516 (45.3)	
Glycoprotein IIb/IIIa inhibitor	52 (28.7)	53 (30.5)	0.721	256 (22.7)	255 (22.4)	0.870
Infarct-related artery			0.875			0.038
Left main coronary artery	6 (3.3)	4 (2.3)		15 (1.3)	20 (1.8)	
Left anterior descending artery	76 (42.0)	72 (41.4)		582 (52.0)	543 (48.1)	
Left circumflex artery	19 (10.5)	22 (12.6)		179 (16.0)	230 (20.4)	
Right coronary artery	80 (44.2)	76 (43.7)		343 (30.7)	336 (29.8)	
Number of treated vessels	1.4 ± 0.5	1.4 ± 0.6	0.285	1.4 ± 0.6	1.4 ± 0.6	0.877
Multivessel treatment	63 (34.8)	61 (35.1)	0.960	322 (28.5)	335 (29.4)	0.640
Numbers of stents for infarct-related artery	1.2 ± 0.4	1.2 ± 0.4	0.901	1.2 ± 0.5	1.2 ± 0.4	0.473
Total stent length of infarct-related artery, mm	30.6 ± 13.1	31.9 ± 16.0	0.405	29.9 ± 18.5	29.1 ± 13.5	0.251
Stent diameter of infarct-related artery, mm	3.2 ± 0.5	3.2 ± 0.5	0.192	3.2 ± 0.5	3.2 ± 1.0	0.491
Intravascular imaging						
Optical coherence tomography	5 (2.8)	3 (1.7)	0.724	42 (3.7)	32 (2.8)	0.222
Intravascular ultrasonography	49 (27.1)	32 (18.4)	0.051	272 (24.1)	271 (23.8)	0.867

Values are expressed as mean (SD) or n (%). *Impaired renal function was defined as an estimated glomerular filtration rate of less than 60 mL/ min/1.73 m^2 of body surface area at presentation. †Creatinine clearance was calculated by MDRD (Modification of Diet in Renal Disease) formula: 186 * (serum creatinine)$^{-1.154}$ * (age)$^{-0.203}$ * 0.742 (for women).

Abbreviations: CABG, coronary artery bypass graft; CVA, cerebrovascular accident; HBR, high bleeding risk; LVEF, left ventricular ejection fraction;

NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; STEMI, ST-segment elevation myocardial infarction.

Supplementary Table 8. Baseline and procedural characteristics by ARC-HBR criteria and treatment arm.

	HBR (n = 303)			Non-HBR (n = 2,322)		
	De-escalation (n = 146)	Active control (n = 157)	p Value	De-escalation (n = 1,165)	Active control (n = 1,157)	p Value
Demographics						
Age, years	73.0 ± 9.4	72.6 ± 9.5	0.734	58.5 ± 10.4	58.1 ± 10.5	0.380
Male	83 (56.8)	97 (61.8)	0.382	1,013 (87.0)	986 (85.2)	0.228
Body mass index, kg/m^2	23.4 ± 3.2	23.0 ± 3.0	0.215	24.8 ± 3.2	24.8 ± 3.6	0.622
Medical history						
Hypertension	101 (69.2)	105 (66.9)	0.668	533 (45.8)	538 (46.5)	0.718
Diabetes	62 (42.5)	60 (38.2)	0.451	287 (24.6)	299 (25.8)	0.503
Diabetes treated with insulin	8 (5.5)	6 (3.8)	0.492	18 (1.5)	22 (1.9)	0.509
Dyslipidemia	64 (43.8)	57 (36.3)	0.181	478 (41.0)	488 (42.2)	0.575
Current smoker	36 (24.7)	40 (25.5)	0.869	613 (52.6)	615 (53.2)	0.796
Impaired renal function*	75 (51.4)	77 (49.0)	0.686	85 (7.3)	68 (5.9)	0.168
Past medical history						
Previous PCI	7 (4.8)	18 (11.5)	0.035	52 (4.5)	39 (3.4)	0.175
Previous CABG	0	1 (0.6)	1.000	3 (0.3)	0	0.250
Previous CVA	23 (15.8)	18 (11.5)	0.276	27 (2.3)	30 (2.6)	0.668
Clinical presentation			0.139			0.367
STEMI	62 (42.5)	80 (51.0)		648 (55.6)	622 (53.8)	
NSTEMI	84 (57.5)	77 (49.0)		517 (44.4)	535 (46.2)	
Laboratory findings						
Creatinine clearance†, mL/min/1.73 m^2	67.3 ± 27.0	68.0 ± 27.2	0.832	88.7 ± 22.4	91.3 ± 24.6	0.010

Hemoglobin, g/dL	12.0 ± 1.6	12.0 ± 1.5	0.816	14.9 ± 1.3	14.9 ± 1.4	0.375
Platelet, 10^9/L	236.2 ± 66.0	229.0 ± 66.7	0.345	241.2 ± 60.6	239.8 ± 56.6	0.555
White blood cell count, 10^9/L	9.4 ± 3.1	9.0 ± 3.4	0.310	10.4 ± 3.5	10.5 ± 3.5	0.189
LVEF < 40%	24/141 (17.0)	23/151 (15.2)	0.678	75/1,127 (6.7)	69/1,102 (6.3)	0.706
Access site			0.508			0.822
Radial	63 (43.2)	75 (47.8)		555 (47.6)	562 (48.6)	
Femoral	77 (52.7)	73 (46.5)		554 (47.6)	536 (46.3)	
Glycoprotein IIb/IIIa inhibitor	34 (23.3)	35 (22.3)	0.837	274 (23.5)	273 (23.6)	0.965
Infarct-related artery			0.382			0.078
Left main coronary artery	3 (2.1)	7 (4.5)		18 (1.6)	17 (1.5)	
Left anterior descending artery	66 (45.5)	65 (41.9)		592 (51.3)	550 (47.9)	
Left circumflex artery	14 (9.7)	22 (14.2)		184 (15.9)	230 (20.0)	
Right coronary artery	62 (42.8)	62 (42.8)		361 (31.3)	351 (30.6)	
Number of treated vessels	1.4 ± 0.6	1.4 ± 0.6	0.761	1.4 ± 0.6	1.4 ± 0.6	0.924
Multivessel treatment	54 (37.0)	56 (35.7)	0.812	331 (28.4)	340 (29.4)	0.605
Numbers of stents for infarct-related artery	1.2 ± 0.5	1.2 ± 0.5	0.548	1.2 ± 0.5	1.2 ± 0.4	0.626
Total stent length of infarct-related artery, mm	33.0 ± 13.9	30.8 ± 16.1	0.189	29.6 ± 18.2	29.3 ± 13.5	0.653
Stent diameter of infarct-related artery, mm	3.2 ± 0.4	3.1 ± 0.4	0.615	3.2 ± 0.5	3.2 ± 1.0	0.612
Intravascular imaging						
Optical coherence tomography	2 (1.4)	5 (3.2)	0.450	45 (3.9)	30 (2.6)	0.084
Intravascular ultrasonography	35 (24.0)	36 (22.9)	0.830	286 (24.5)	267 (23.1)	0.405

Values are expressed as mean (SD) or n (%). *Impaired renal function was defined as an estimated glomerular filtration rate of less than 60 mL/ min/1.73 m^2 of body surface area at presentation. †Creatinine clearance was calculated by MDRD (Modification of Diet in Renal Disease) formula: 186 * (serum creatinine)$^{-1.154}$ * (age)$^{-0.203}$ * 0.742 (for women).

Abbreviations: ARC-HBR, Academic Research Consortium for High Bleeding Risk; CABG, coronary artery bypass graft; CVA, cerebrovascular accident;

HBR, high bleeding risk; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Supplementary Table 9. Primary and secondary outcomes by PRECISE-DAPT score-based HBR and treatment arm.

	HBR (n = 355)				Non-HBR (n = 2,270)			
	De-escalation (n = 181)	Active control (n = 174)	Hazard ratio (95% CI)	p Value	De-escalation (n = 1,130)	Active control (n = 1,140)	Hazard ratio (95% CI)	p Value
Primary endpoint*	13 (7.2)	21 (12.1)	0.59 (0.29-1.17)	0.118	44 (3.9)	79 (6.9)	0.54 (0.38-0.78)	0.001
Secondary endpoints								
BARC bleeding type 3 or 5	4 (2.2)	9 (5.2)	0.42 (0.13-1.38)	0.164	11 (1.0)	18 (1.6)	0.60 (0.28-1.27)	0.199
MACCE†	8 (4.4)	9 (5.2)	0.85 (0.33-2.20)	0.740	17 (1.5)	27 (2.4)	0.62 (0.34-1.13)	0.135
BARC bleeding type 2, 3 or 5	7 (3.9)	13 (7.5)	0.51 (0.20-1.28)	0.141	31 (2.7)	56 (4.9)	0.54 (0.35-0.84)	0.007
BARC bleeding type 2	4 (2.2)	6 (3.4)	0.64 (0.18-2.28)	0.536	23 (2.0)	43 (3.8)	0.53 (0.32-0.87)	0.014
BARC bleeding type 3	4 (2.2)	9 (5.2)	0.42 (0.13-1.38)	0.164	11 (1.0)	18 (1.6)	0.60 (0.28-1.27)	0.199
BARC bleeding type 5	1 (0.6)	–	–	–	–	–	–	–
MACCE, and BARC bleeding type 3 or 5	10 (5.5)	17 (9.8)	0.56 (0.26-1.22)	0.131	24 (2.1)	41 (3.6)	0.57 (0.35-0.95)	0.035
All-cause death	4 (2.2)	7 (4.0)	0.55 (0.16-1.87)	0.372	6 (0.5)	3 (0.3)	1.98 (0.49-7.90)	0.310
Cardiovascular death	2 (1.1)	3 (1.7)	0.64 (0.11-3.82)	0.680	3 (0.3)	3 (0.3)	0.99 (0.20-4.89)	1.000
Myocardial infarction								
Any myocardial infarction	4 (2.2)	5 (2.9)	0.76 (0.20-2.84)	0.746	8 (0.7)	14 (1.2)	0.56 (0.23-1.33)	0.206
Spontaneous	4 (2.2)	4 (2.3)	0.96 (0.24-3.82)	1.000	5 (0.4)	9 (0.8)	0.54 (0.18-1.62)	0.291
Periprocedural	–	1 (0.6)	–	–	3 (0.3)	5 (0.4)	0.59 (0.14-2.46)	0.487
Target vessel myocardial infarction	1 (0.6)	–	–	–	6 (0.5)	8 (0.7)	0.73 (0.25-2.11)	0.603
Stroke	2 (1.1)	2 (1.1)	0.96 (1.14-6.85)	1.000	6 (0.5)	10 (0.9)	0.59 (0.21-1.62)	0.324
Ischemia-driven revascularization								
Target lesion revascularization	2 (1.1)	–	–	–	12 (1.1)	9 (0.8)	1.31 (0.55-3.10)	0.498

Target vessel revascularization	2 (1.1)	2 (1.1)	0.94 (0.13-6.69)	1.000	15 (1.3)	15 (1.3)	0.98 (0.48-2.00)	0.981
Any revascularization	5 (2.8)	7 (4.0)	0.68 (0.22-2.13)	0.511	27 (2.4)	31 (2.7)	0.85 (0.51-1.42)	0.618
Stent thrombosis	1 (0.6)	–	–	–	2 (0.2)	3 (0.3)	0.65 (0.11-3.89)	1.000

Values are expressed as n (%). *Composite of cardiovascular death, myocardial infarction, stroke, and BARC bleeding type 2, 3, or 5. †Composite of cardiovascular death, myocardial infarction, or stroke.

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; HBR, high bleeding risk; MACCE, major adverse cardiac and cerebrovascular event; PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.

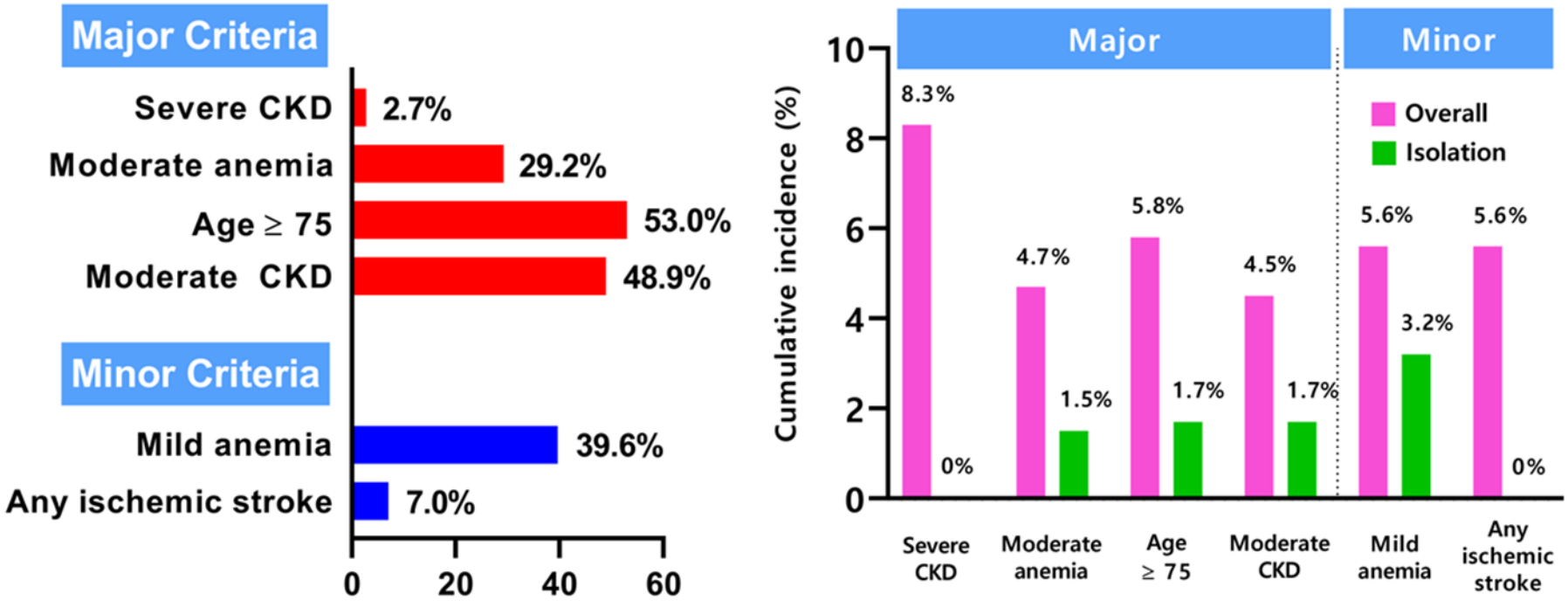
Supplementary Table 10. Primary and secondary outcomes by ARC-HBR criteria and treatment arm.

	HBR (n = 303)				Non-HBR (n = 2,322)			
	De-escalation (n = 146)	Active control (n = 157)	Hazard ratio (95% CI)	p Value	De-escalation (n = 1,165)	Active control (n = 1,157)	Hazard ratio (95% CI)	p Value
Primary endpoint*	9 (6.2)	21 (13.4)	0.43 (0.20-0.95)	0.036	48 (4.1)	79 (6.8)	0.59 (0.41-0.84)	0.004
Secondary endpoints								
BARC bleeding type 3 or 5	3 (2.1)	7 (4.5)	0.45 (0.12-1.74)	0.339	12 (1.0)	20 (1.7)	0.58 (0.29-1.19)	0.149
MACCE†	6 (4.1)	12 (7.6)	0.51 (0.19-1.35)	0.194	19 (1.6)	24 (2.1)	0.77 (0.42-1.40)	0.428
BARC bleeding type 2, 3 or 5	5 (3.4)	10 (6.4)	0.52 (0.18-1.52)	0.238	33 (2.8)	59 (5.1)	0.54 (0.35-0.83)	0.005
BARC bleeding type 2	4 (2.7)	5 (3.2)	0.85 (0.23-3.16)	1.000	23 (2.0)	44 (3.8)	0.51 (0.31-0.84)	0.008
BARC bleeding type 3	3 (2.1)	7 (4.5)	0.45 (0.12-1.74)	0.339	12 (1.0)	20 (1.7)	0.58 (0.29-1.19)	0.149
BARC bleeding type 5	1 (0.7)	–	–	–	–	–	–	–
MACCE, and BARC bleeding type 3 or 5	7 (4.8)	18 (11.5)	0.39 (0.17-0.94)	0.035	27 (2.3)	40 (3.5)	0.65 (0.40-1.07)	0.101
All-cause death	3 (2.1)	7 (4.5)	0.44 (0.11-1.71)	0.339	7 (0.6)	3 (0.3)	2.28 (0.59-8.82)	0.343
Cardiovascular death	1 (0.7)	4 (2.5)	0.26 (0.03-2.31)	0.373	4 (0.3)	2 (0.2)	1.96 (0.36-10.70)	0.687
Myocardial infarction								
Any myocardial infarction	3 (2.1)	6 (3.8)	0.51 (0.13-2.04)	0.504	9 (0.8)	13 (1.1)	0.67 (0.29-1.57)	0.383
Spontaneous	3 (2.1)	3 (2.5)	0.77 (0.17-3.42)	1.000	6 (0.5)	9 (0.8)	0.65 (0.23-1.82)	0.429
Periprocedural	–	2 (1.3)	–	–	3 (0.3)	4 (0.3)	0.73 (0.16-3.26)	0.725
Target vessel myocardial infarction	1 (0.7)	1 (0.6)	1.01 (0.06-16.20)	1.000	6 (0.5)	7 (0.6)	0.83 (0.28-2.47)	0.771
Stroke	2 (1.4)	3 (1.9)	0.68 (0.11-4.07)	1.000	6 (0.5)	9 (0.8)	0.65 (0.23-1.83)	0.429
Ischemia-driven revascularization								
Target lesion revascularization	2 (1.4)	1 (0.6)	2.02 (0.18-22.26)	0.611	12 (1.0)	8 (0.7)	1.46 (0.60-3.56)	0.377

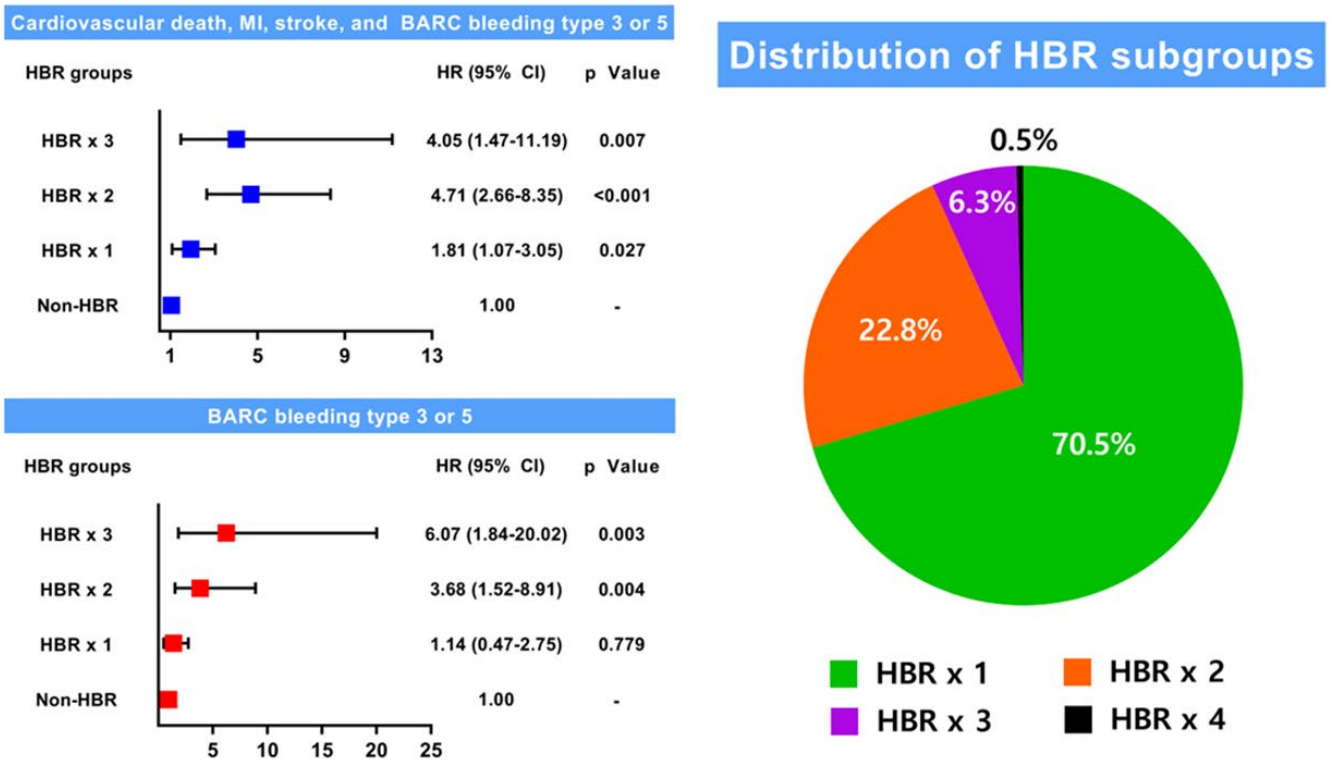
Target vessel revascularization	2 (1.4)	2 (1.3)	1.00 (0.14-7.10)	1.000	15 (1.3)	15 (1.3)	0.97 (0.47-1.98)	0.985
Any revascularization	4 (2.7)	9 (5.7)	0.45 (0.14-1.45)	0.261	28 (2.4)	29 (2.5)	0.94 (0.56-1.57)	0.873
Stent thrombosis	1 (0.7)	–	–	–	2 (0.2)	3 (0.3)	0.65 (0.11-3.87)	0.686

Values are expressed as n (%). *Composite of cardiovascular death, myocardial infarction, stroke, and BARC bleeding type 2, 3, or 5. †Composite of cardiovascular death, myocardial infarction, or stroke.

Abbreviations: ARC-HBR, Academic Research Consortium for High Bleeding Risk; BARC, Bleeding Academic Research Consortium; CI, confidence interval; HBR, high bleeding risk; MACCE, major adverse cardiac and cerebrovascular event.

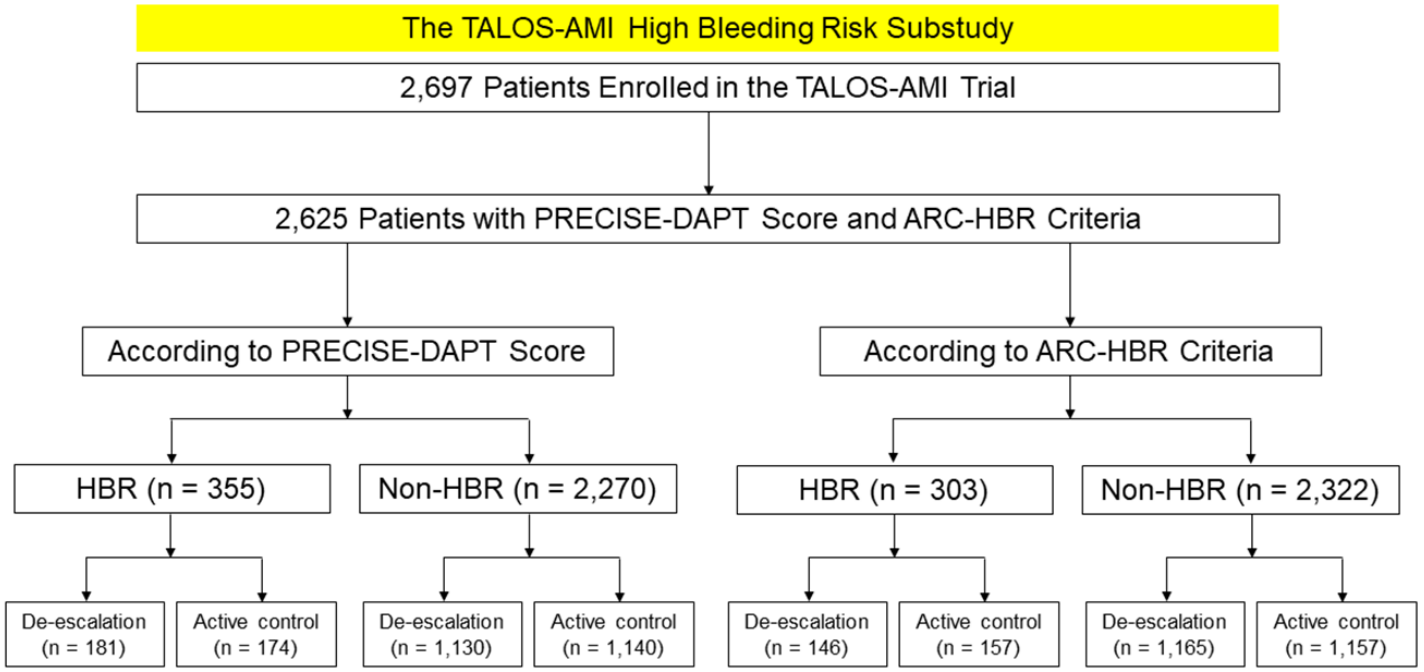


Supplementary Figure 1. Prevalence of HBR criteria within the HBR group and impact on major bleeding outcome.
(Left) Prevalence of HBR criteria within the HBR group. **(Right)** Cumulative incidence of BARC bleeding type 3 or 5 between 1 and 12 months in overall patients with a specific HBR criterion. CKD: chronic kidney disease; HBR: High Bleeding Risk



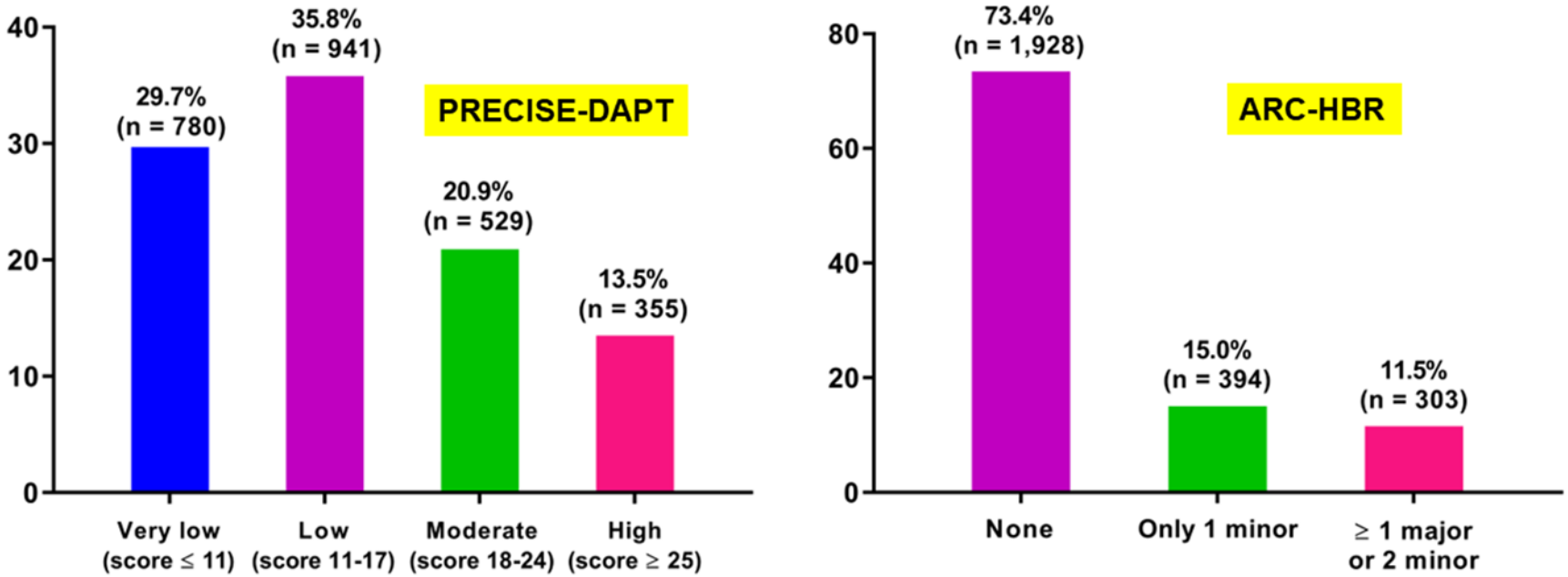
Supplementary Figure 2. Clinical impact of multiple HBR criteria.

(Top Left) Risk of composite MACCE and BARC bleeding type 3 or 5 according to the number of HBR criteria. **(Bottom Left)** Risk of BARC bleeding type 3 or 5 according to the number of HBR criteria. **(Right)** Distribution of HBR patients into subgroups. BARC: Bleeding Academic Research Consortium; CI: confidence interval; HBR: High Bleeding Risk; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular event; MI: myocardial infarction



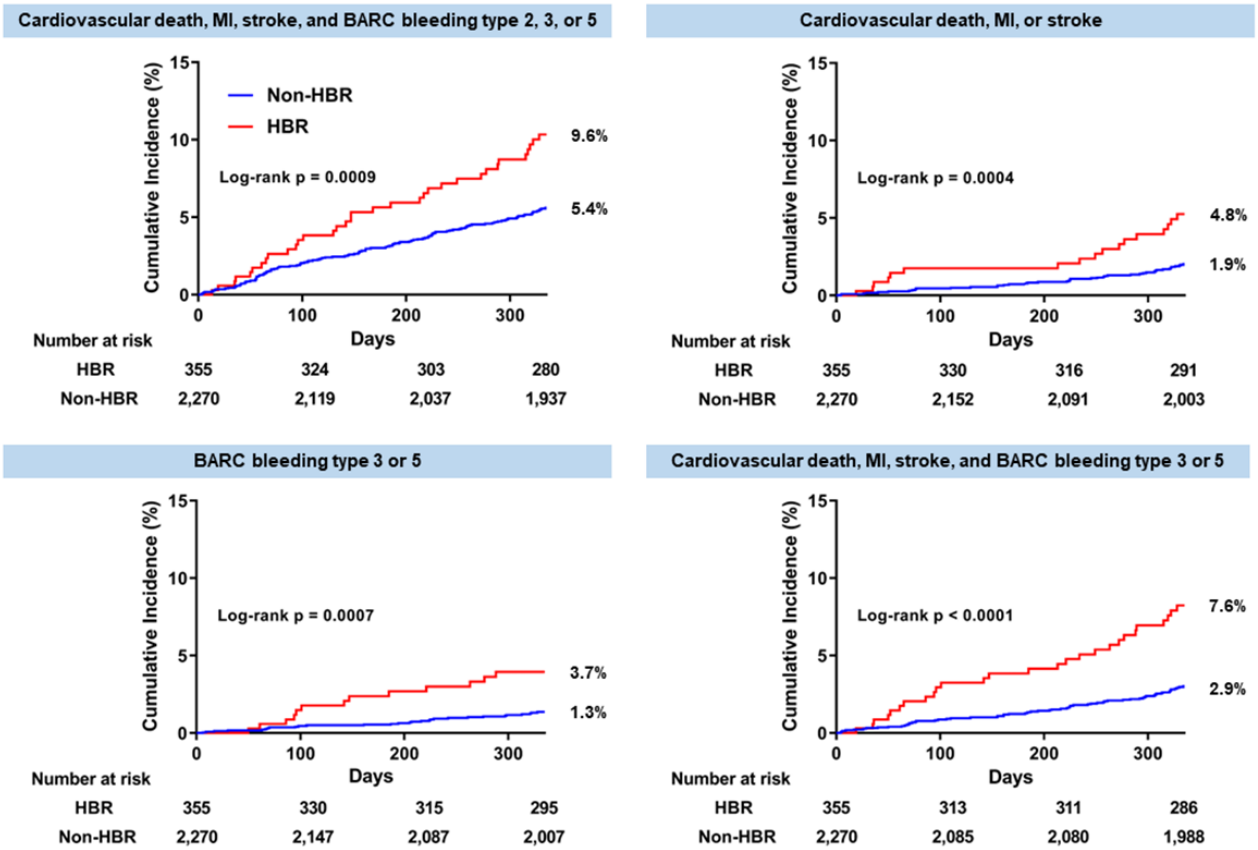
Supplementary Figure 3. Study flow according to PRECISE-DAPT score and ARC-HBR criteria.

ARC-HBR: Academic Research Consortium for High Bleeding Risk; HBR: High Bleeding Risk; PRECISE-DAPT: Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; TALOS-AMI: Ticagrelor versus Clopidogrel in Stabilized Patients with Acute Myocardial Infarction



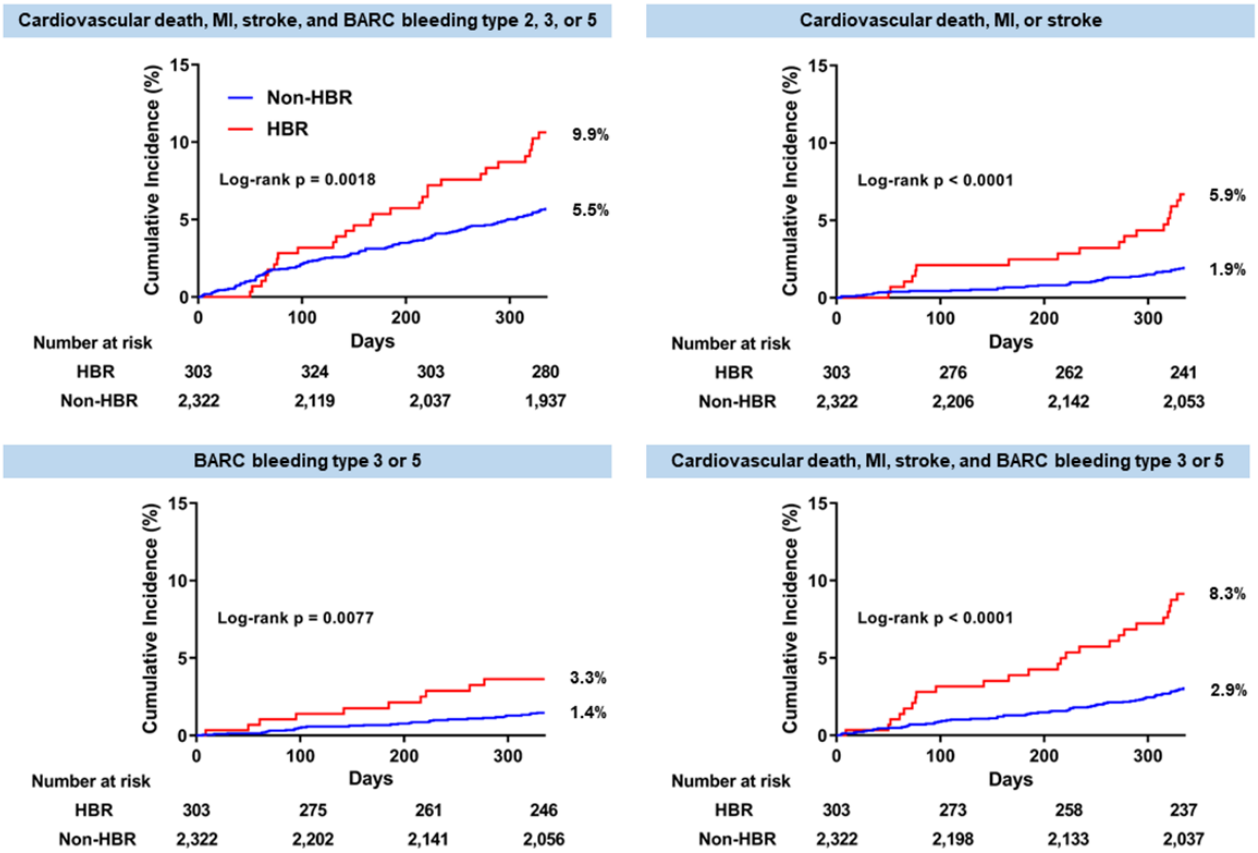
Supplementary Figure 4. Distribution of study patients by PRECISE-DAPT score and ARC-HBR criteria.

ARC-HBR: Academic Research Consortium for High Bleeding Risk; PRECISE-DAPT: Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy



Supplementary Figure 5. Cumulative incidences of primary and secondary outcomes by PRECISE-DAPT score-based HBR.

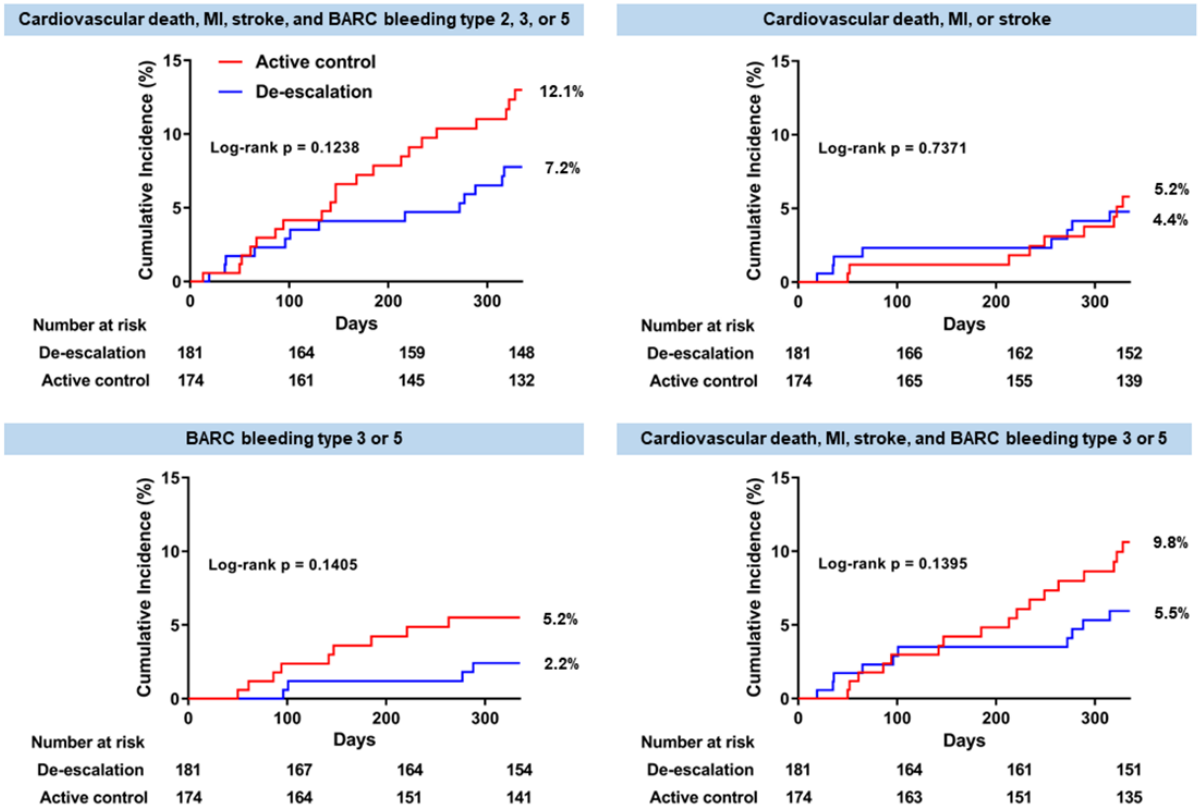
BARC: Bleeding Academic Research Consortium; HBR: high bleeding risk; MI: myocardial infarction; PRECISE-DAPT: Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy



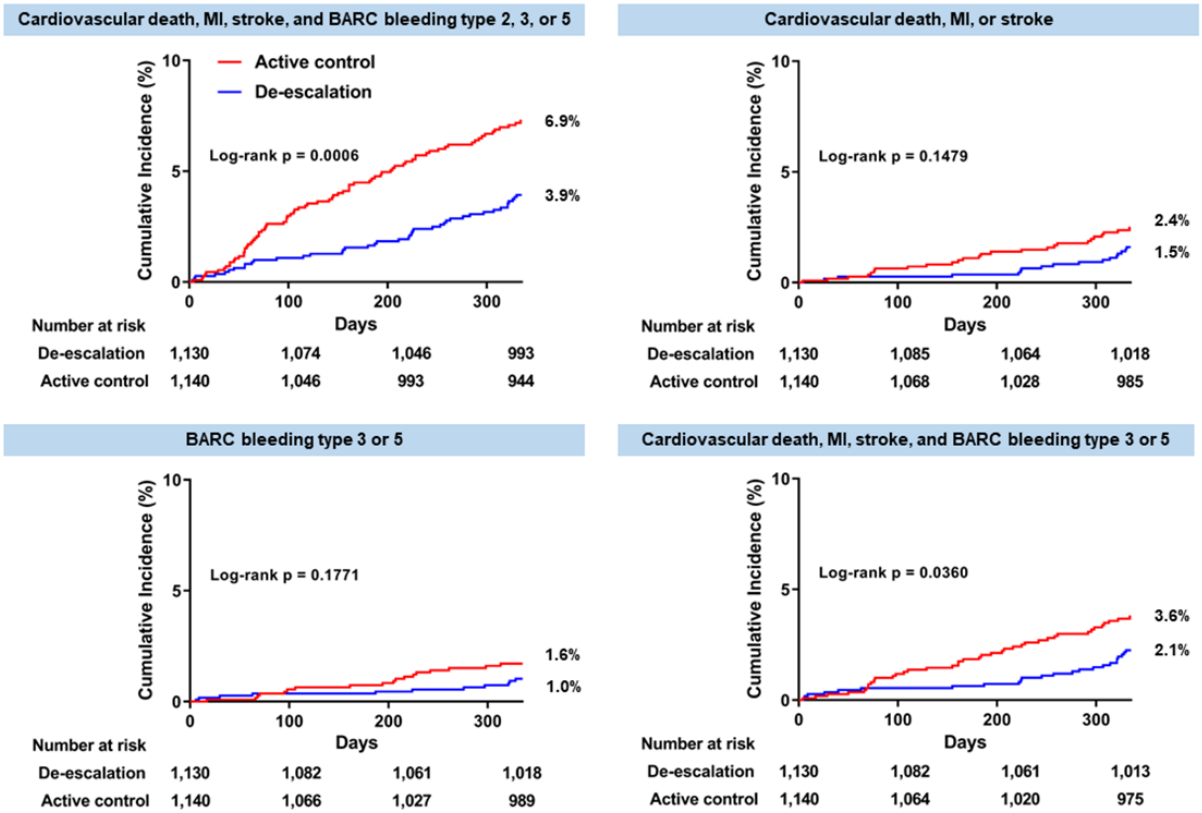
Supplementary Figure 6. Cumulative incidences of primary and secondary outcomes by ARC-HBR criteria.

ARC-HBR: Academic Research Consortium for High Bleeding Risk; BARC: Bleeding Academic Research Consortium; HBR: high bleeding risk; MI:

myocardial infarction

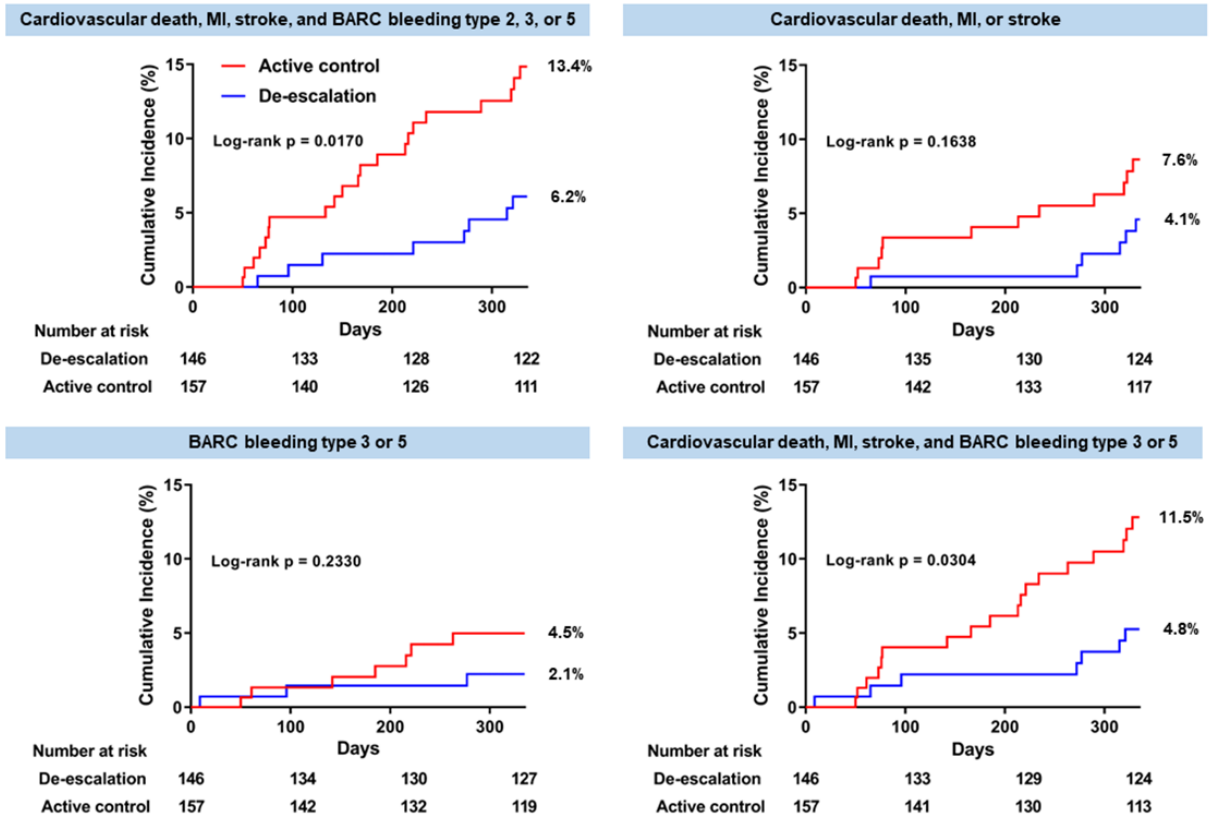


Supplementary Figure 7. Cumulative incidences of primary and secondary outcomes by PRECISE-DAPT score-based HBR and treatment arm.
BARC: Bleeding Academic Research Consortium; HBR: high bleeding risk; MI: myocardial infarction; PRECISE-DAPT: Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy



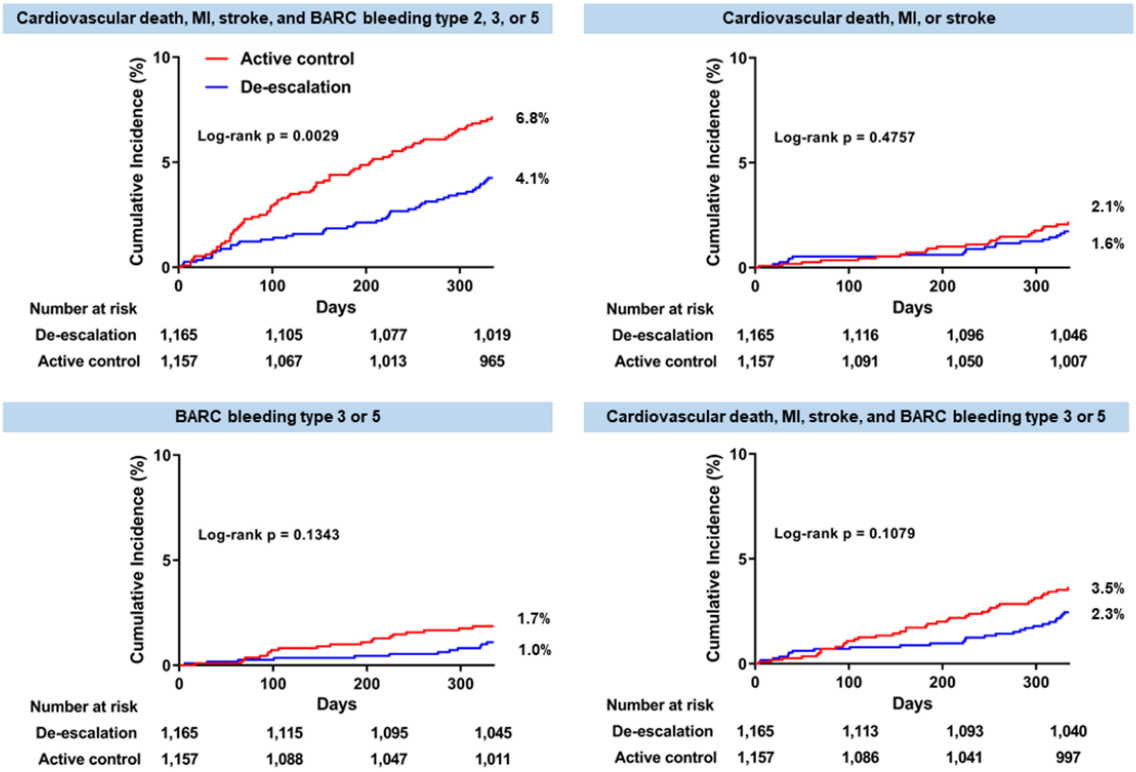
Supplementary Figure 8. Cumulative incidences of primary and secondary outcomes by PRECISE-DAPT score-based non-HBR and treatment arm.

BARC: Bleeding Academic Research Consortium; HBR: high bleeding risk; MI: myocardial infarction; PRECISE-DAPT: Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy



Supplementary Figure 9. Cumulative incidences of primary and secondary outcomes by ARC-HBR criteria-based HBR and treatment arm.

ARC-HBR: Academic Research Consortium for High Bleeding Risk; BARC: Bleeding Academic Research Consortium; HBR: high bleeding risk; MI: myocardial infarction



Supplementary Figure 10. Cumulative incidences of primary and secondary outcomes by ARC-HBR criteria-based non-HBR and treatment arm.

ARC-HBR: Academic Research Consortium for High Bleeding Risk; BARC: Bleeding Academic Research Consortium; HBR: high bleeding risk; MI: myocardial infarction