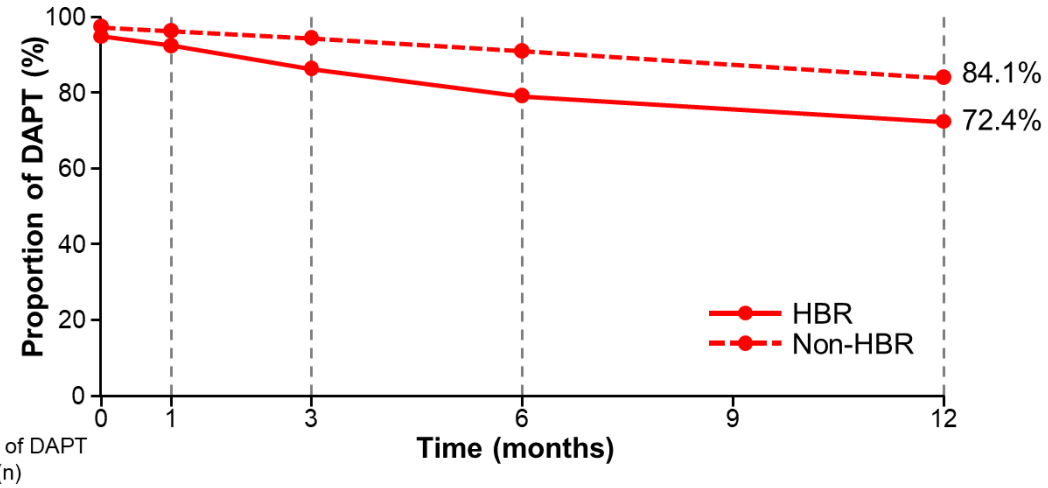
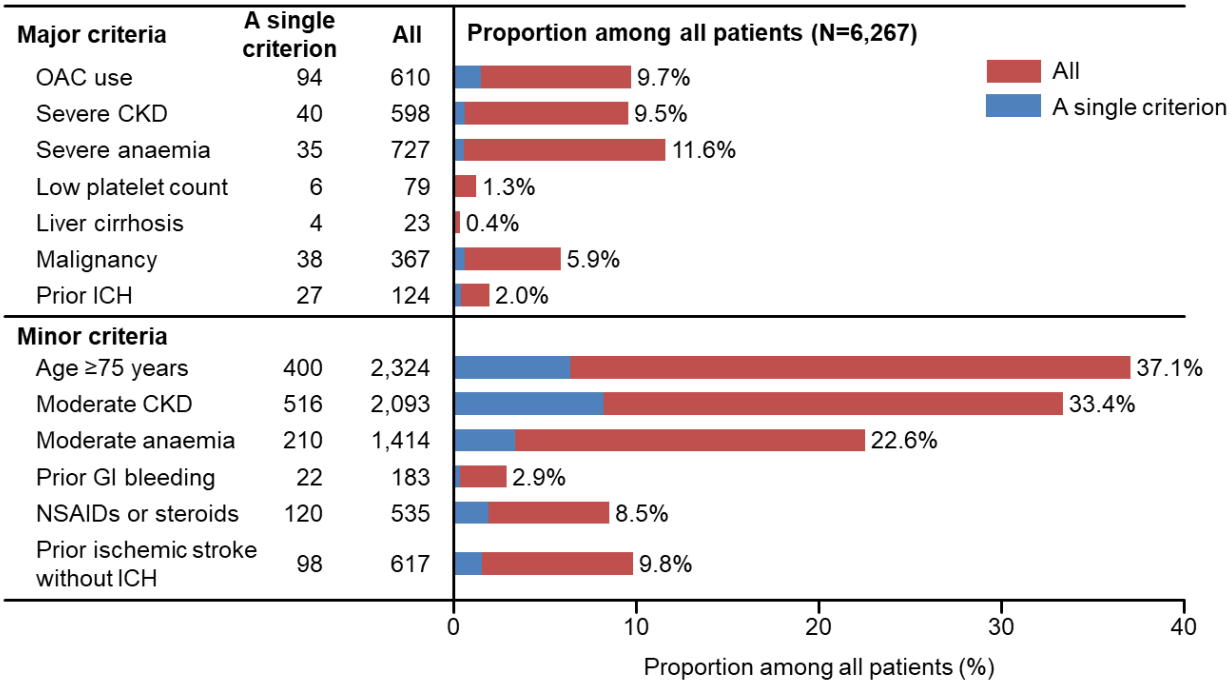
Supplementary data



Proportion of DAPT % (n)					
All (6267)	96.0 (6018)	94.4 (5887)	90.4 (5594)	85.0 (5206)	78.3 (4727)
HBR (3185)	94.8 (3019)	92.4 (2919)	86.3 (2692)	79.3 (2435)	72.4 (2186)
Non-HBR (3082)	97.3 (2999)	96.4 (2968)	94.5 (2902)	90.8 (2771)	84.1 (2541)
p value	<0.001	<0.001	<0.001	<0.001	<0.001

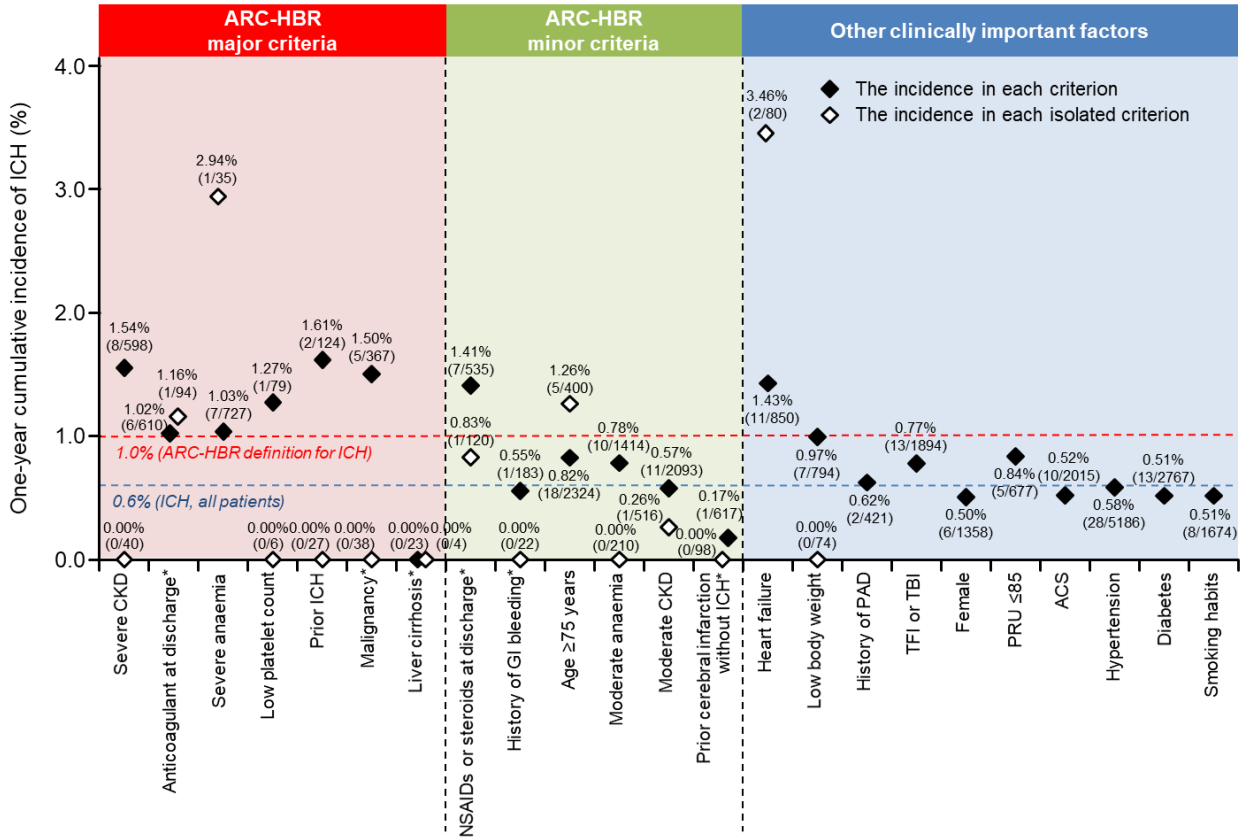
Supplementary Figure 1. Proportion of patients who continued to receive DAPT over time.

DAPT: dual antiplatelet therapy; HBR: high bleeding risk



Supplementary Figure 2. Proportion of patients who fulfilled each ARC-HBR criterion.

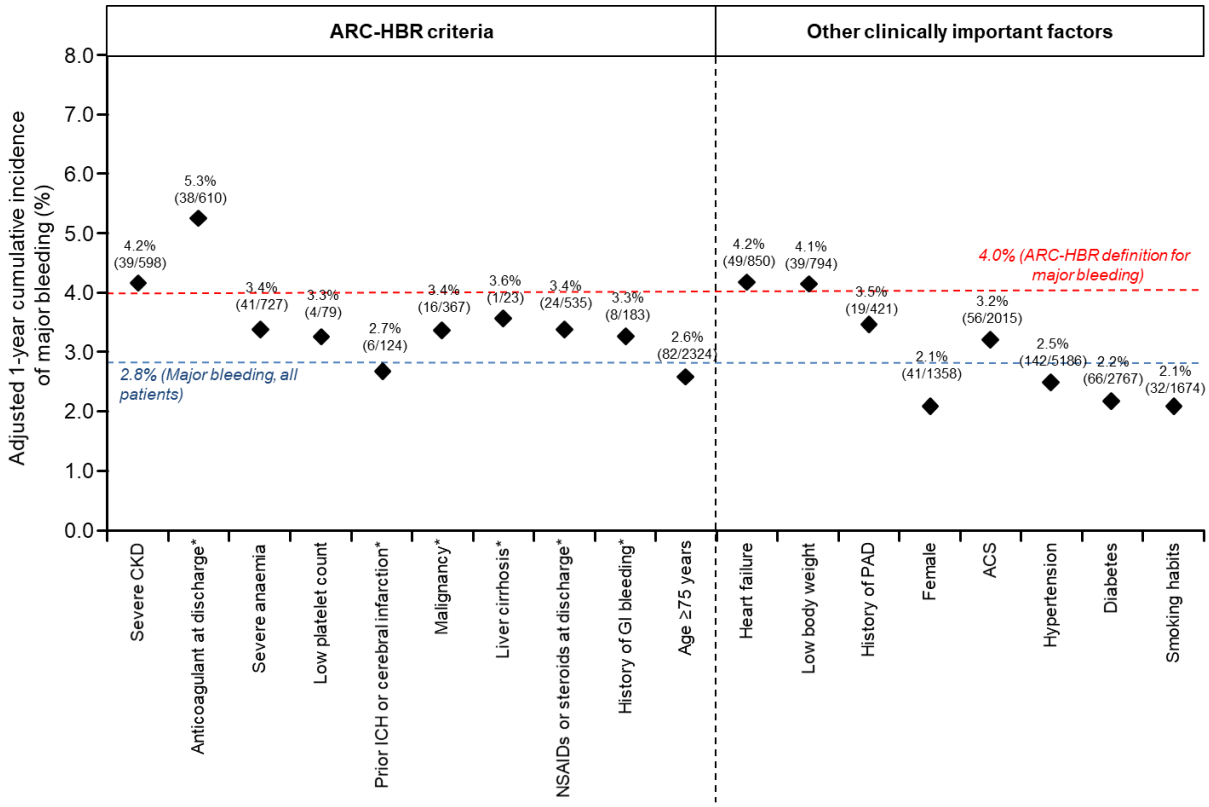
ARC: Academic Research Consortium; CKD: chronic kidney disease; GI: gastrointestinal; ICH: intracranial haemorrhage; NSAIDs: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulant



Supplementary Figure 3. Cumulative incidence of ICH stratified by ARC-HBR criteria and other clinically important factors.

*Modified from the original ARC-HBR criteria.

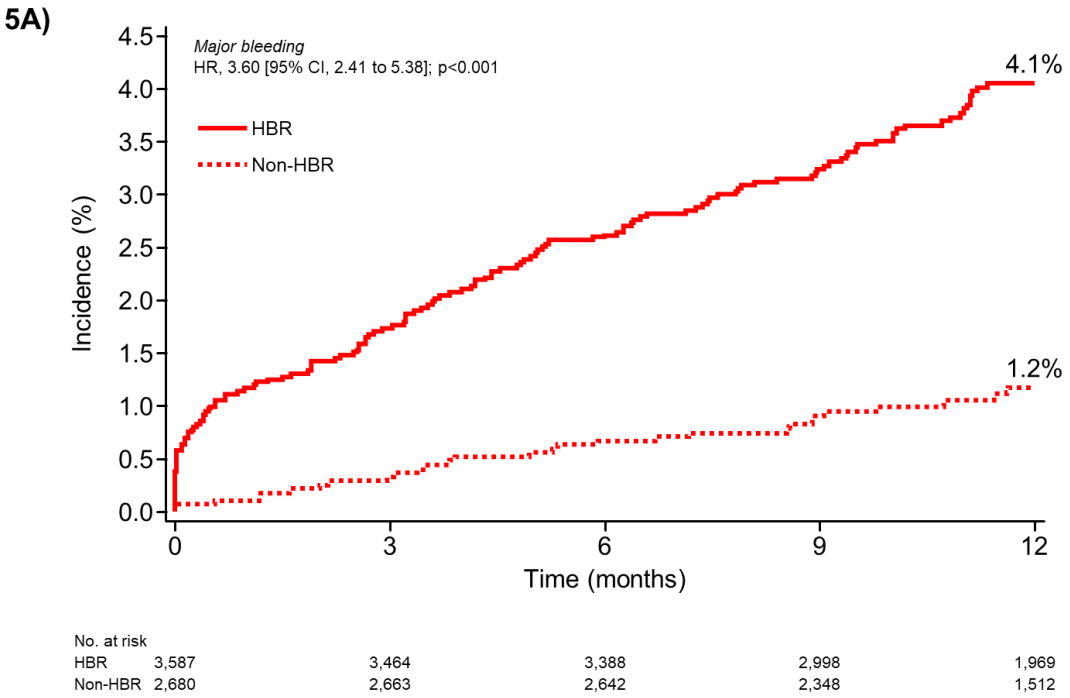
ACS: acute coronary syndrome; ARC: Academic Research Consortium; CKD: chronic kidney disease; GI: gastrointestinal; HBR: high bleeding risk; ICH: intracranial haemorrhage; PAD: peripheral arterial disease; PRU: platelet reactivity unit; TBI: transbrachial intervention; TFI: transfemoral intervention.

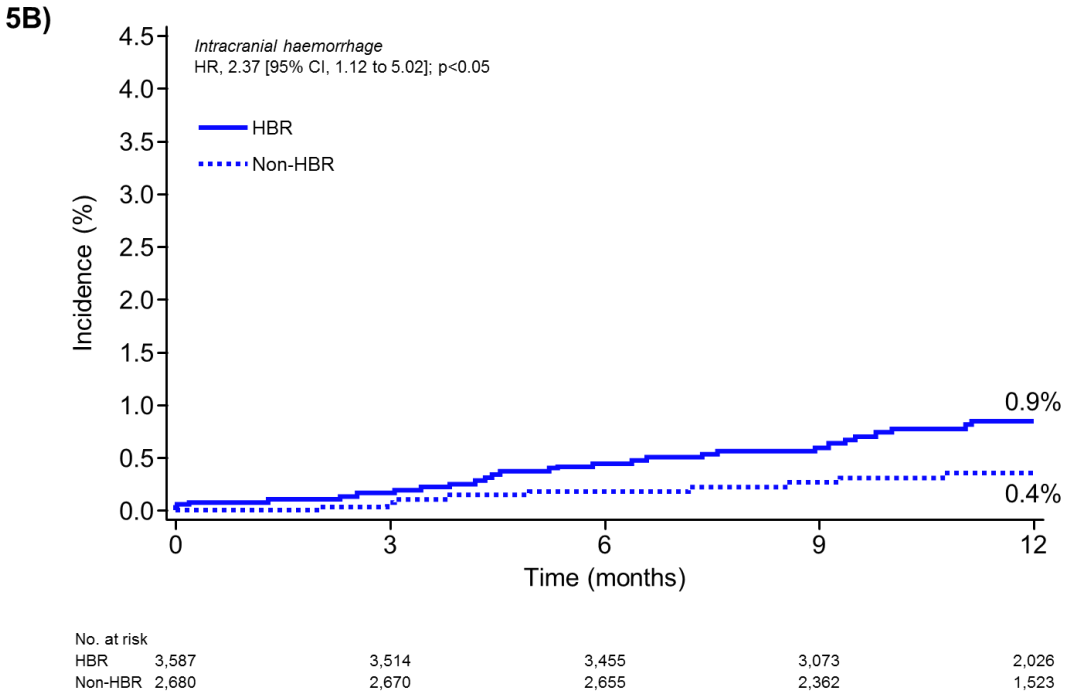


Supplementary Figure 4. Adjusted cumulative incidence of major bleeding stratified by ARC-HBR criteria and other clinically important factors.

*Modified from the original ARC-HBR criteria.

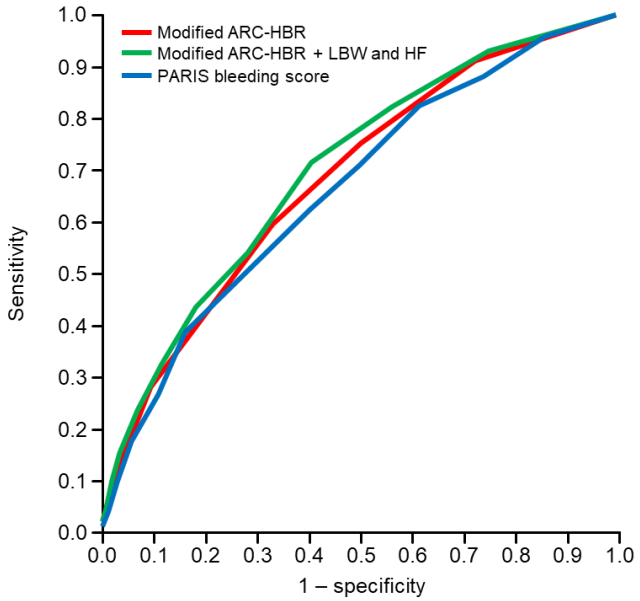
ACS: acute coronary syndrome; ARC: Academic Research Consortium; CKD: chronic kidney disease; GI: gastrointestinal; HBR: high bleeding risk; ICH: intracranial haemorrhage; PAD: peripheral arterial disease





Supplementary Figure 5. Cumulative incidence of major bleeding (A) and intracranial haemorrhage (B) by ARC-HBR criteria plus low body weight and heart failure.
ARC: Academic Research Consortium; CI: confidence interval; HBR: high bleeding risk; HR: hazard ratio

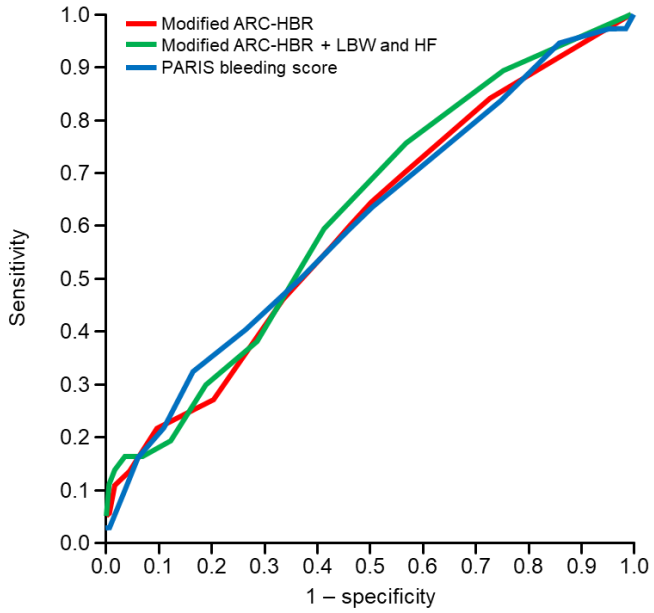
6A)



Risk score (N=6,267)	C-index (95% CI)	Cut-off
Modified ARC-HBR	0.681 (0.641 – 0.722)	1.5
Modified ARC-HBR + LBW and HF	0.700 (0.660 – 0.740)	1.5
PARIS major bleeding score	0.662 (0.620 – 0.704)	9

Criteria	HBR, n	Non-HBR, n	Sensitivity, %	Specificity, %
Modified ARC-HBR (≥1)	3,185	3,082	75.2	49.8
Modified ARC-HBR + LBW and HF (≥1)	3,587	2,680	82.4	43.4
PARIS major bleeding score (≥8)	1,692	4,575	48.5	73.6

6B)



Risk score (N=6,267)	C-index (95% CI)	Cut-off
Modified ARC-HBR	0.597 (0.505 – 0.689)	1.0
Modified ARC-HBR + LBW and HF	0.620 (0.533 – 0.708)	1.0
PARIS major bleeding score	0.602 (0.508 – 0.697)	9

Criteria	HBR, n	Non-HBR, n	Sensitivity, %	Specificity, %
Modified ARC-HBR (≥1)	3,185	3,082	64.9	49.3
Modified ARC-HBR + LBW and HF (≥1)	3,587	2,680	75.7	42.9
PARIS major bleeding score (≥8)	1,692	4,575	40.5	73.1

Supplementary Figure 6. Receiver operating characteristic curve analysis of major bleeding (A) and intracranial haemorrhage (B) for each bleeding risk criterion category.

ARC: Academic Research Consortium; CI: confidence interval; HBR: high bleeding risk; HF: heart failure; LBW: low body weight

Supplementary Table 1. Full methodological details of the PENDULUM (Platelet rEactivity in patieNts with DrUg eLUting stent and balancing risk of bleeding and ischeMic event) registry study[7].

Item	Details
Study design	A prospective, multicentre study of Japanese patients who underwent PCI
Enrolment period	Between December 2015 and June 2017
Setting	67 Japanese institutions, nationwide. Patients were followed up as part of routine clinical practice. Patients were expected to visit the hospital whenever possible, but could be questioned by telephone or letter if visits were difficult.
Inclusion criteria	Age ≥20 years Indicated for PCI with drug-eluting stents Administered antiplatelet drugs
Exclusion criteria	Enrolment, or planned enrolment, in another clinical study before completion of the observation period
DAPT details	DAPT was based on the standard of care; drug type, dosage, and treatment duration were selected at the discretion of the attending physician The standard duration of DAPT according to Japanese treatment guidelines is a minimum of 6 months for non-ACS patients and a minimum of 12 months for patients with ACS
Approved dosages	Aspirin, 100 mg administered once daily; the dosage can be increased up to 300 mg once daily Clopidogrel, 300 mg administered once as a loading dose on the treatment start day, followed by 75 mg once daily as a maintenance dosage Prasugrel, 20 mg administered once as a loading dose, followed by 3.75 mg once daily as a maintenance dosage
Primary endpoints	The incidence of first MACCE event[a] and first major bleeding event[b] 12 months after index PCI Thrombotic and haemorrhagic events were evaluated by independent assessment committees
Sample size	The required sample size for the registry was calculated based on both the incidence of MACCE and major bleeding at 12 months after index PCI Published data suggested that in the Japanese population the incidence of MACCE was 3% and the incidence of major bleeding was 4% Using this information, the incidence of the primary endpoints was set at 3% with a precision of ±0.5% within the range of the 95% CI Allowing for a withdrawal rate of 10% during the first 12 months of the study, the required number of patients was calculated as 4,969 (rounded up to 5,000 patients)

[a]Defined as all-cause death, non-fatal myocardial infarction, non-fatal stroke, and stent thrombosis.

[b]Defined as Bleeding Academic Research Consortium types 3 and 5.

ACS: acute coronary syndrome; CI: confidence interval; DAPT: dual antiplatelet therapy; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention

Supplementary Table 2. High bleeding risk definitions[a].

ARC-HBR criteria[1]	This study	Category	Comments
Age ≥75 years	Age ≥75 years	Minor	Identical
Anticipated use of long-term oral anticoagulation[b]	Use of oral anticoagulation at discharge	Major	Modified
Severe or end-stage chronic kidney disease (eGFR <30 mL/min)	eGFR <30 mL/min/1.73 m^2	Major	Identical
Moderate chronic kidney disease (eGFR 30–59 mL/min)	eGFR 30–<60 mL/min/1.73 m^2	Minor	Identical
Haemoglobin <11 g/dL	Haemoglobin <11 g/dL	Major	Identical
Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women	Haemoglobin 11–<13 g/dL for men and 11–<12g/dL for women	Minor	Identical
Spontaneous bleeding requiring hospitalisation or transfusion in the past 6 months or at any time, if recurrent		Major	Not applicable[f]
Spontaneous bleeding requiring hospitalisation or transfusion within the past 12 months not meeting the major criterion	Prior gastrointestinal bleeding at any time	Minor	Modified
Moderate or severe baseline thrombocytopaenia[c] (platelet count <100×10^9/L)	Platelet count <100×10^9/L	Major	Identical
Chronic bleeding diathesis		Major	Not applicable
Liver cirrhosis with portal hypertension	Liver cirrhosis	Major	Modified
Long-term use of oral NSAIDs or steroids	Use of NSAIDs or steroids at discharge	Minor	Modified
Active malignancy[d] (excluding non-melanoma skin cancer) within the past 12 months	Malignancy at baseline (undergoing or planning treatment)	Major	Modified

Previous spontaneous intracranial haemorrhage (at any time) Previous traumatic intracranial haemorrhage within the past 12 months Presence of a brain arteriovenous malformation Moderate or severe ischaemic stroke[e] within the past 6 months	History of intracranial haemorrhage at any time	Major	Modified
Any ischaemic stroke at any time not meeting the major criterion	History of ischaemic stroke[g] without intracranial haemorrhage at any time	Minor	Identical
Non-deferrable major surgery on dual antiplatelet therapy		Major	Not applicable
Recent major surgery or major trauma within 30 days before PCI		Major	Not applicable

[a]Definition of ARC-HBR: meets at least one of the major criteria or at least two of the minor criteria. The major and minor criteria were defined differently for the original article and the current analysis, as shown.

[b]This excludes vascular protection doses.

[c]Baseline thrombocytopaenia is defined as thrombocytopaenia before PCI.

[d]Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

[e]National Institutes of Health Stroke Scale score ≥5.

[f]For the present analysis, "Spontaneous bleeding requiring hospitalisation or transfusion within the past 12 months not meeting the major criterion" was combined with "Spontaneous bleeding requiring hospitalisation or transfusion in the past 6 months or at any time, if recurrent", to form the major criterion "Composite of prior bleeding".

[g]For the present analysis, "Any ischaemic stroke at any time not meeting the major criterion" was combined with "Moderate or severe ischaemic stroke within the past 6 months", to form the major criterion "History of ischaemic stroke".

ARC: Academic Research Consortium; eGFR: estimated glomerular filtration rate; HBR: high bleeding risk; NSAIDs: non-steroidal anti-inflammatory drugs; PCI: percutaneous coronary intervention

Supplementary Table 3. Baseline laboratory parameters.

Characteristics	Total (N=6,267)	ARC-HBR (n=3,185)	Non-ARC-HBR (n=3,082)	*p*-value (ARC-HBR vs non-ARC-HBR)
Haemoglobin, g/dL	N=6,087	N=3,108	N=2,979	
Mean (SD)	13.3 (2.0)	12.3 (1.9)	14.4 (1.6)	<0.001
<11	727 (11.6)	727 (22.8)	0 (0.0)	<0.001
Male: ≥11 to <13; Female: ≥11 to <12	1,414 (22.6)	1,204 (37.8)	210 (6.8)	<0.001
eGFR, mL/min/1.73 m^2	N=6,122	N=3,133	N=2,989	
Mean (SD)	61.2 (27.6)	49.6 (23.5)	73.4 (26.3)	<0.001
<30	598 (9.5)	598 (18.8)	0 (0.0)	<0.001
≥30 to <60	2,093 (33.4)	1,577 (49.5)	516 (16.7)	
White blood cell count, $\times 10^3/\mu L$	N=6,086	N=3,108	N=2,978	
Mean (SD)	6.94 (2.82)	6.70 (2.51)	7.19 (3.09)	<0.001
Platelet count, $\times 10^4/\mu L$	N=6,084	N=3,107	N=2,977	
Mean (SD)	21.4 (6.6)	20.6 (6.9)	22.1 (6.3)	<0.001
<10	79 (1.3)	79 (2.5)	0 (0.0)	<0.001
No. of diseased vessels				
1	3,165 (50.5)	1,476 (46.3)	1,689 (54.8)	<0.001
2	1,865 (29.8)	987 (31.0)	878 (28.5)	<0.05
3	1,151 (18.4)	680 (21.4)	471 (15.3)	<0.001
Left main coronary trunk	349 (5.6)	202 (6.3)	147 (4.8)	<0.05
Procedural data				
Puncture site				
Femoral	1,632 (26.0)	986 (31.0)	646 (21.0)	<0.001
Brachial	270 (4.3)	177 (5.6)	93 (3.0)	<0.001
Radial	4,516 (72.1)	2,082 (65.4)	2,434 (79.0)	<0.001
Imaging guided				

IVUS or OCT/OFDI	5,918 (94.4)	2,999 (94.2)	2,919 (94.7)	0.342
Complex PCI				
All	1,712 (27.3)	676 (21.2)	604 (19.6)	0.110
≥3 stents	435 (6.9)	247 (7.8)	188 (6.1)	<0.05
Number of treatment lesions ≥3	577 (9.2)	311 (9.8)	266 (8.6)	0.121
Bifurcation with 2 stents	112 (1.8)	49 (1.5)	63 (2.0)	0.131
Total stent length >60 mm	725 (11.6)	401 (12.6)	324 (10.5)	<0.05
Chronic total occlusion lesion	429 (6.8)	202 (6.3)	227 (7.4)	0.109

Data are presented as n (%) or mean (SD).

ARC: Academic Research Consortium; eGFR: estimated glomerular filtration rate; HBR: high bleeding risk; IVUS: intravascular ultrasound; OCT: optical coherence tomography; OFDI: optical frequency domain imaging; PCI: percutaneous coronary intervention; SD: standard deviation

Supplementary Table 4. The proportion of events in each combination of criteria.

Criteria	Patients with criteria	Events	
		Major bleeding	ICH
Total	6,267	165 (2.6)	37 (0.6)
1 minor criterion (point: 0.5)			
History of GI bleeding	22	0 (0.0)	0 (0.0)
Moderate anaemia	210	4 (1.9)	0 (0.0)
Moderate CKD	516	8 (1.6)	1 (0.2)
NSAIDs or steroids	120	2 (1.7)	1 (0.8)
≥75 years	400	12 (3.0)	5 (1.3)
History of ischaemic stroke without ICH	98	0 (0.0)	0 (0.0)
1 major criterion (point: 1)			
Severe anaemia	35	2 (5.7)	1 (2.9)
Low platelet count	6	0 (0.0)	0 (0.0)
Severe CKD	40	0 (0.0)	0 (0.0)
OAC use	94	7 (7.4)	1 (1.1)
Liver cirrhosis	4	0 (0.0)	0 (0.0)
Malignancy	38	1 (2.6)	0 (0.0)
History of ICH	27	0 (0.0)	0 (0.0)
Combination of 2 minor criteria (point: 1)			
History of GI bleeding + moderate anaemia	5	0 (0.0)	0 (0.0)
History of GI bleeding + moderate CKD	10	1 (10.0)	0 (0.0)
History of GI bleeding + NSAIDs or steroids	2	0 (0.0)	0 (0.0)
History of GI bleeding + ≥75 years	8	0 (0.0)	0 (0.0)
History of GI bleeding + history of ischaemic stroke without ICH	1	0 (0.0)	0 (0.0)
Moderate anaemia + moderate CKD	130	6 (4.6)	2 (1.5)
Moderate anaemia + NSAIDs or steroids	16	1 (6.3)	0 (0.0)
Moderate anaemia + ≥75 years	159	2 (1.3)	0 (0.0)
Moderate anaemia + history of ischaemic stroke without ICH	22	0 (0.0)	0 (0.0)
Moderate CKD + NSAIDs or steroids	35	2 (5.7)	1 (2.9)
Moderate CKD + ≥75 years	304	2 (0.7)	2 (0.7)
Moderate CKD + history of ischaemic stroke without ICH	38	1 (2.6)	0 (0.0)
NSAIDs or steroids + ≥75 years	38	0 (0.0)	0 (0.0)

NSAIDs or steroids + history of ischaemic stroke without ICH	8	1 (12.5)	0 (0.0)
≥75 years + history of ischaemic stroke without ICH	51	0 (0.0)	0 (0.0)
Combination of 3 minor criteria (point: 1.5)			
History of GI bleeding + moderate anaemia + moderate CKD	9	0 (0.0)	0 (0.0)
History of GI bleeding + moderate anaemia + NSAIDs or steroids	2	0 (0.0)	0 (0.0)
History of GI bleeding + moderate anaemia + ≥75 years	9	1 (11.1)	0 (0.0)
History of GI bleeding + moderate anaemia + history of ischaemic stroke without ICH	0	—	—
History of GI bleeding + moderate CKD + NSAIDs or steroids	0	—	—
History of GI bleeding + moderate CKD + ≥75 years	2	0 (0.0)	0 (0.0)
History of GI bleeding + moderate CKD + history of ischaemic stroke without ICH	0	—	—
History of GI bleeding + NSAIDs or steroids + ≥75 years	2	0 (0.0)	0 (0.0)
History of GI bleeding + NSAIDs or steroids + history of ischaemic stroke without ICH	0	—	—
History of GI bleeding + ≥75 years + history of ischaemic stroke without ICH	2	0 (0.0)	0 (0.0)
Moderate anaemia + moderate CKD + NSAIDs or steroids	17	2 (11.8)	0 (0.0)
Moderate anaemia + moderate CKD + ≥75 years	193	7 (3.6)	2 (1.0)
Moderate anaemia + moderate CKD + history of ischaemic stroke without ICH	22	0 (0.0)	0 (0.0)
Moderate anaemia + NSAIDs or steroids + ≥75 years	14	1 (7.1)	1 (7.1)
Moderate anaemia + NSAIDs or steroids + history of ischaemic stroke without ICH	1	0 (0.0)	0 (0.0)
Moderate anaemia + ≥75 years + history of ischaemic stroke without ICH	21	0 (0.0)	0 (0.0)
Moderate CKD + NSAIDs or steroids + ≥75 years	30	1 (3.3)	0 (0.0)
Moderate CKD + NSAIDs or steroids + history of ischaemic stroke without ICH	1	0 (0.0)	0 (0.0)

Moderate CKD + ≥75 years + history of ischaemic stroke without ICH	33	0 (0.0)	0 (0.0)
NSAIDs or steroids + ≥75 years + history of ischaemic stroke without ICH	4	0 (0.0)	0 (0.0)
Combination of 1 major and 1 minor criteria (point: 1.5)			
Severe anaemia + history of GI bleeding	5	0 (0.0)	0 (0.0)
Severe anaemia + moderate anaemia	0	—	—
Severe anaemia + moderate CKD	37	1 (2.7)	0 (0.0)
Severe anaemia + NSAIDs or steroids	10	0 (0.0)	0 (0.0)
Severe anaemia + ≥75 years	43	1 (2.3)	0 (0.0)
Severe anaemia + history of ischaemic stroke without ICH	2	0 (0.0)	0 (0.0)
Low platelet count + history of GI bleeding	0	—	—
Low platelet count + moderate anaemia	3	0 (0.0)	0 (0.0)
Low platelet count + moderate CKD	3	0 (0.0)	0 (0.0)
Low platelet count + NSAIDs or steroids	0	—	—
Low platelet count + ≥75 years	2	0 (0.0)	0 (0.0)
Low platelet count + history of ischaemic stroke without ICH	1	0 (0.0)	0 (0.0)
Severe CKD + history of GI bleeding	1	0 (0.0)	0 (0.0)
Severe CKD + moderate anaemia	81	5 (6.2)	3 (3.7)
Severe CKD + moderate CKD	0	—	—
Severe CKD + NSAIDs or steroids	9	0 (0.0)	0 (0.0)
Severe CKD + ≥75 years	23	3 (13.0)	0 (0.0)
Severe CKD + history of ischaemic stroke without ICH	5	0 (0.0)	0 (0.0)
OAC use + history of GI bleeding	3	0 (0.0)	0 (0.0)
OAC use + moderate anaemia	28	2 (7.1)	0 (0.0)
OAC use + moderate CKD	53	2 (3.8)	0 (0.0)
OAC use + NSAIDs or steroids	8	0 (0.0)	0 (0.0)
OAC use + ≥75 years	39	2 (5.1)	0 (0.0)
OAC use + history of ischaemic stroke without ICH	15	1 (6.7)	1 (6.7)
Liver cirrhosis + history of GI bleeding	0	—	—
Liver cirrhosis + moderate anaemia	1	0 (0.0)	0 (0.0)
Liver cirrhosis + moderate CKD	0	—	—
Liver cirrhosis + NSAIDs or steroids	0	—	—
Liver cirrhosis + ≥75 years	0	—	—

Liver cirrhosis + history of ischaemic stroke without ICH	0	—	—
Malignancy + history of GI bleeding	1	0 (0.0)	0 (0.0)
Malignancy + moderate anaemia	17	0 (0.0)	0 (0.0)
Malignancy + moderate CKD	19	0 (0.0)	0 (0.0)
Malignancy + NSAIDs or steroids	4	0 (0.0)	0 (0.0)
Malignancy + ≥75 years	35	0 (0.0)	0 (0.0)
Malignancy + history of ischaemic stroke without ICH	2	0 (0.0)	0 (0.0)
History of ICH + history of GI bleeding	0	—	—
History of ICH + moderate anaemia	9	0 (0.0)	0 (0.0)
History of ICH + moderate CKD	8	0 (0.0)	0 (0.0)
History of ICH + NSAIDs or steroids	0	—	—
History of ICH + ≥75 years	5	0 (0.0)	0 (0.0)
History of ICH + history of ischaemic stroke without ICH	0	—	—
1 major criterion (point: 1) * East Asian-specific HBR only			
Body weight ≤50 kg	74	0 (0.0)	0 (0.0)
Heart failure	80	2 (2.5)	2 (2.5)

Data are presented as n (%).

CKD: chronic kidney disease; GI: gastrointestinal; HBR: high bleeding risk; ICH: intracranial haemorrhage; NSAIDs: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulant