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Prognostic and Practical Validation of ESC/EACTS High Ischemic Risk Definition on Long-Term Thrombotic and Bleeding Events in Contemporary PCI Patients

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Aims: The ESC/EACTS myocardial revascularization guidelines recently standardized the definition of patients at high ischemic risk (HIR). However, the ability of ESC/EACTS–HIR criteria to stratify ischemic and bleeding risk in a contemporary real-world East Asian cohort remains unexplored.

Methods: A total of 10,167 consecutive patients undergoing PCI from prospective Fuwai PCI Registry (January 2013 to December 2013) were reviewed. ESC/EACTS–HIR features was defined as having at least one of the eight clinical and angiographic characteristics. The primary ischemic endpoint was target vessel failure (cardiac death, target vessel myocardial infarction [MI], or target vessel revascularization [TVR]); bleeding outcome was assessed using the BARC type 2, 3, or 5 bleeding. Median follow-up was 29 months.

Results: Compared with non-HIR patients, HIR patients (n=5,149, 50.6%) were associated with increased risk for target vessel failure (adjusted hazard ratio [HR_{adjust}]: 1.48 [1.25–1.74]) and patient-oriented composite outcome (HR_{adjust}: 1.44 [1.28–1.63]), as well as cardiac death, MI, and TVR. By contrast, the risk of clinically relevant bleeding was not significantly different between the two groups. (HR_{adjust}: 0.84 [0.66–1.06]). Greater than or equal to three implanted stents and diabetic patients with diffuse multivessel coronary disease emerged as independent predictors for long-term adverse outcomes. There was no significant interaction between high bleeding risk (HBR) status and clinical outcomes associated with ESC/EACTS–HIR criteria (all $P_{interaction} > 0.05$).

Conclusion: The ESC/EACTS–HIR features identified patients at increased risk of thrombotic events, including cardiac death, but not for clinically relevant bleeding. Importantly, HBR did not modify cardiovascular risk subsequent to patients with ESC/EACTS–HIR features, suggesting its potential clinical applicability in tailoring antithrombotic therapy.

Key words: High ischemic risk, Guidelines, Risk stratification, High bleeding risk, Percutaneous coronary intervention

Introduction

Advances in interventional cardiology techniques and the advent of newer drugs and devices have allowed expanding the use of percutaneous coronary intervention (PCI) to several complex clinical

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scenarios, including patients with complex, multivessel coronary artery disease (CAD)[1]. Several studies linked PCI procedural complexity features with a higher risk of subsequent adverse clinical events[2-5]. To facilitate risk stratification after PCI, the concept of complex PCI has been developed in the setting of using heterogeneous cohorts and different definitions, resulting in a variety of clinical outcome results[6-12]. Therefore, ambiguity about how to effectively identify patients at high ischemic risk (HIR) remains, and it is reflected in the varying inclusion criteria adopted by clinical trials in such patients, which may limit the interpretation, generalizability, and pooling of reported data[13, 14].

In this regard, the 2018 ESC/EACTS guidelines on myocardial revascularization have been proposed to develop criteria for defining HIR patients undergoing PCI, with a list of clinical (diffuse multivessel disease in diabetic patients, chronic kidney disease [CKD], history of ST-elevation myocardial infarction (STEMI), and prior stent thrombosis on adequate antiplatelet therapy) and procedural characteristics (≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, treatment of chronic total occlusion (CTO), or stenting of the last remaining coronary artery)[15]. The primary goals of ESC/EACTS–HIR criteria are to inform optimal decision-making on antithrombotic therapy after PCI and to encourage a standardized method for future research. To date, since the ESC/EACTS–HIR criteria were introduced, their prevalence and prognostic association with clinical outcomes are yet to be established in the real-world PCI practice. Meanwhile, characterization of high bleeding risk (HBR) is increasingly important in patients who underwent complex percutaneous coronary revascularization[16]. Appropriate identification and clinical management of HBR patients is complex since HBR features are routinely listed as exclusion criteria in major randomized controlled trials of drug-eluting stents (DES) and antiplatelet therapies[17-20]. Recently, the PRECISE-DAPT score was developed and widely used for prediction of out-of-hospital bleeding in patients who receive dual antiplatelet therapy (DAPT) after stent implantation and was able to identify patients at HBR (score ≥ 25)[21-23]. Importantly, patients at HBR constitute a unique clinical conundrum given their predisposition to developing ischemic and bleeding complications after PCI[24, 25]. However, whether HBR assessed by PRECISE-DAPT score moderates the risk of adverse events for patients at ESC/EACTS-endorsed HIR features is unclear.

Therefore, the purpose of this study was to (1) characterize the prevalence and distribution of the ESC/EACTS–HIR criteria in a large prospective cohort of real-world group of patients undergoing PCI with DES implantation, (2) assess the long-term ischemic and bleeding outcomes in patients with ESC/EACTS guideline-endorsed HIR features receiving PCI compared with non-HIR patients, and (3) evaluate the influence of the underlying risk of HBR on the association between ESC–HIR features and clinical outcomes.

Materials and Methods

Patient Population

From January 2013 to December 2013, Fuwai PCI Registry has prospectively included data from a total of 10,724 consecutive patients who have undergone PCI in Fuwai Hospital (National Center for Cardiovascular Diseases, Beijing, China). For the present study, exclusion criteria were treatment by balloon angioplasty alone without stent placement, implantation of bioresorbable scaffolds or bare-metal stents, and unavailability of guideline-endorsed high-risk features for ischemic events at index PCI. Finally, 10,167 patients were selected for this analysis. This prospective PCI registry complied with the Declaration of Helsinki, and its protocol was approved by the hospital's ethical review board (Fuwai Hospital & National Center for Cardiovascular Diseases, Beijing, China). All patients provided written informed consent for prospective follow-up before the intervention.

Procedures and Patient Follow-Up

PCI was performed in accordance with current clinical practice guidelines[26]. Detailed information on procedures is provided in the supplementary material online. After PCI, patients were treated with aspirin indefinitely, and clopidogrel was recommended for at least 1 year (with longer duration of use at the discretion of the physician). The routinely recommended DAPT duration was 1 year, and the decision to discontinue or remain on DAPT after 1 year was made at the discretion of the patient's physician (and possibly influenced by the patient). Demographic features and cardiovascular risk factors were collected using patient interviews or review of medical records. During hospitalization, findings of coronary angiography and detailed procedural characteristics of PCI were collected. The coronary angiographic results were objectively assessed by a blinded independent core laboratory.

After discharge, the recommended clinical follow-up was at 1 month, 6 months, 1 year, and annually thereafter. The follow-up period was

extended to January 31, 2016 to ensure that all patients had the opportunity for at least 2-year follow-up evaluation. Follow-up data were collected through medical records, telephone communications, or face-to-face interviews after hospital discharge by trained clinical research coordinators who were blind to the purpose of the present study, until death occurred or up to the last day of the follow-up period. Patients were advised to return for coronary angiography if indications of ischemic events occurred. For patients treated for adverse events at other medical institutions, external medical records, discharge letters, and coronary angiography documentation were systematically collected and reviewed. The median duration of follow-up for the study patients was 29 months (interquartile range [IQR]: 26.5–31.1 months). The 24-month follow-up rate for the patients was 98.8%.

HIR and HBR Assessment

Patients were defined as HIR if they met at least one of the following characteristics according to 2018 ESC/EACTS myocardial revascularization guidelines: ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, treatment of CTO, diffuse (lesion length ≥ 20 mm) multivessel disease in diabetic patients, CKD (estimated glomerular filtration rate <60 ml/min/1.73 m^2), or history of STEMI[15]. The modified version of ESC/EACTS guideline-endorsed HIR features was made because study enrollment and data collection predate the publication of the ESC/EACTS–HIR criteria, and information on prior stent thrombosis on adequate antiplatelet therapy and stenting of the last remaining coronary artery was not available in the current database.

The PRECISE-DAPT score was calculated as previously described based on age, white blood cell count, creatinine clearance, hemoglobin, and previous history of bleeding. Patients were considered at HBR for PRECISE-DAPT score ≥ 25 and non-HBR for score <25 [27]. The sensitivity analysis that categorized patients into HBR was based on PARIS bleeding risk score (HBR: score ≥ 8 vs. non-HBR: score <8)[28]. Association, predictive performances, discriminative capacity and calibration statistics of the PRECISE-DAPT score and the PARIS bleeding score for predicting clinically relevant bleeding in the Fuwai PCI cohort are shown in Supplementary Method, **Supplementary Table 1-4**, and **Supplementary Fig. 1-2**.

Clinical Outcomes

For any clinical event, all original source documents were reviewed and adjudicated by a clinical event committee consisting of two cardiologists (and a third in case of disagreement) who were blinded to outcome data. The primary ischemic endpoint of target vessel failure (TVF) comprised cardiac death, target vessel (TV) myocardial infarction (MI), or TV revascularization (TVR). The primary bleeding endpoint was clinically relevant bleeding defined as the Bleeding Academic Research Consortium (BARC) type 2, 3 or 5 bleeding[29]. Secondary endpoints included patient-oriented composite outcome (POCO), consisting of all-cause death, any MI, or any coronary revascularization; a composite endpoint of target lesion failure (TLF), consisting of cardiac death, TVMI, or target lesion revascularization (TLR); and all-cause death, cardiac death, MI, definite/probable stent thrombosis, any coronary revascularization, TVR, TLR, stroke, or any bleeding events. All deaths were considered cardiac unless obvious noncardiac causes could be established. MI was defined as elevated cardiac troponin or myocardial band fraction of creatinine kinase (CK-MB) greater than the upper reference limit with concomitant ischemic symptoms or electrocardiography findings indicative of myocardial ischemia. Periprocedural MI (within 72 h) after PCI was defined according to the SCAI definition[30]. All MIs were considered to be TVMI unless there was clear evidence that they were attributable to a nontarget vessel. TVR was defined as angina or ischemia referable to the target vessel requiring repeat PCI or CABG. TLR was defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. Stent thrombosis was adjudicated according to the Academic Research Consortium definition[31]. Stroke was defined as any nonconvulsive focal or global neurological deficit of abrupt onset lasting >24 hour or leading to death, which was caused by ischemia or hemorrhage within the brain. Ischemic stroke was defined as an episode of neurological dysfunction attributable to ischemia within the brain. The definition of the bleeding event used in this study was adapted from BARC definition. Detailed information on the BARC classification for type 2, 3, or 5 bleeding is provided in Supplementary Method.

Statistical Analysis

Continuous variables were reported as mean ± SD or median (25th and 75th percentiles) and compared using Student's *t*-test or Wilcoxon rank-sum test. Categorical data were reported as proportions and compared by χ^2 test or Fisher's exact test. Kaplan–Meier estimates represent time-to-event incidences

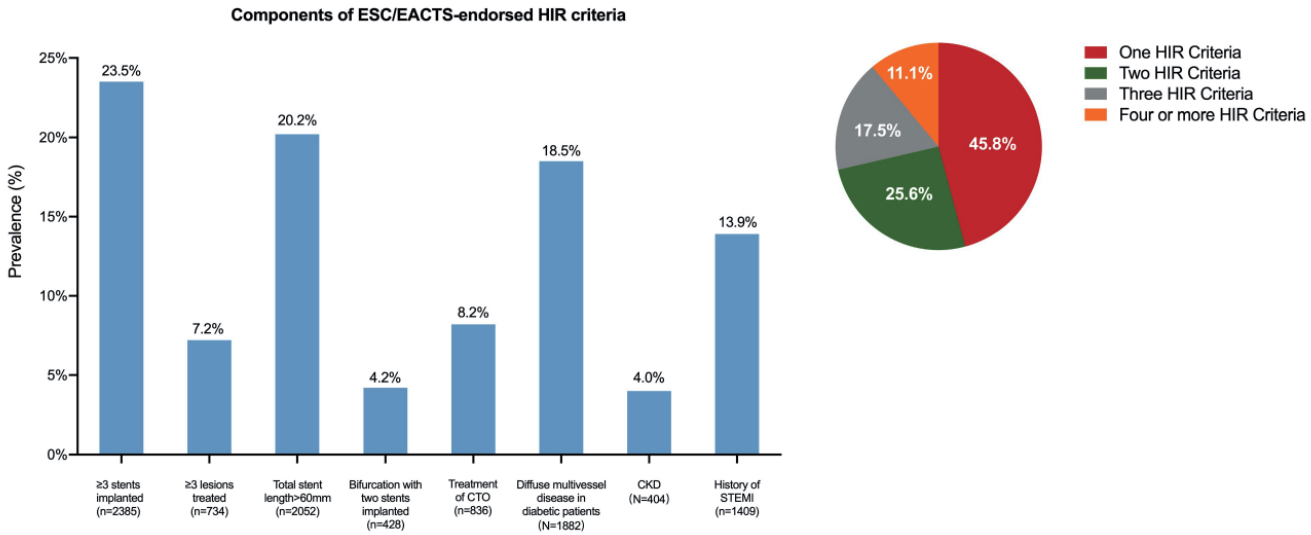

Fig. 1. Prevalence of the ESC/EACTS-endorsed HIR criteria components in the overall population
HIR = high ischemic risk

and were compared using the log-rank test among those with and without HIR features and after substratifying all participants by HIR and HBR. The impact of ESC/EACTS-endorsed HIR features on clinical outcomes was assessed using univariate and multivariable Cox proportional hazards regression. Covariates in the multivariable model were selected if they were clinically important variables reported by previous studies or because of significant differences between groups. For ischemic endpoints, they were age, sex, body mass index, hypertension, current smoking, left ventricular ejection fraction, peripheral artery disease, prior revascularization (PCI and/or coronary artery bypass graft [CABG]), acute coronary syndrome (ACS), mean stent diameter, type of DES implanted, and DAPT duration (as a time-adjusted covariate); for bleeding endpoints, they were age, sex, body mass index, hypertension, prior major bleeding event, anemia, oral anticoagulation use at discharge, and DAPT duration (as a time-adjusted covariate). A Cox regression analysis was also performed to test the prognostic significance of each component of the ESC/EACTS–HIR criteria for target vessel failure, patient-oriented composite outcome, and clinically relevant bleeding. A test for interaction was performed between the main effects of HIR criteria and HBR (PRECISE-DAPT score ≥ 25 points) on both ischemic and bleeding outcomes. Multiple sensitivity analyses were performed to evaluate the consistency of our overall findings. Using PRECISE-DAPT score to assign patients into four bleeding risk strata (very low: ≤ 10, low: 11–17, moderate: 18–24, and high: ≥ 25 points), we also tested interaction between bleeding status and adverse events for ESC/EACTS–HIR criteria. Additionally, we repeated all analyses using a different threshold to define HBR (PARIS bleeding risk score ≥ 8 points) or stratifying patients into three bleeding risk strata (PARIS bleeding risk score; low: ≤ 3, moderate: 4–7, and high: ≥ 8 points) to the consistency of the effect of HIR criteria. All P values are two-tailed, and we deemed $P<0.05$ to be statistically significant for all analyses. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Baseline and Procedural Characteristics

Among 10,167 patients (mean age: 58.3 ± 10.3 years) enrolled in the Fuwai PCI Registry, 5,149 (50.6%) had at least 1 ESC/EACTS-endorsed HIR criteria. The remaining 5,018 patients (49.4%) who did not fulfill any HIR criteria were grouped in the non-HIR category. The prevalence of each component of the ESC/EACTS-endorsed HIR definition is reported in **Fig. 1**. The most common ESC–HIR criterion was ≥ 3 stents implanted (23.5%), followed by total stent length >60 mm (20.2%), diffuse multivessel disease in diabetic patients (18.5%), and history of STEMI (13.9%). Within the HIR group, 45.8% of patients fulfilled one HIR criterion, 25.6% fulfilled two HIR criteria, 17.5% fulfilled three HIR criteria, and 11.1% patients fulfilled ≥ 4 HIR criteria.

In brief, patients with ESC/EACTS-endorsed HIR criteria were slightly older; had more comorbidities such as hypertension, diabetes,

dyslipidemia, and peripheral artery disease; and had higher PRECISE-DAPT scores compared with non-HIR patients **(Table 1)**. Patients with a history of cardiovascular disease, including prior MI, previous revascularization by PCI or CABG, or stroke, were more likely to be at HIR. Looking at the procedural characteristics, patients at HIR features had more frequent diseased vessels; had more in-stent restenosis, heavy calcified lesions, and B2/C lesions; and were more likely to be treated with glycoprotein IIb/IIIa inhibitors and intravascular ultrasound. Among HIR patients, PCI was more frequently performed in the anatomical setting of the left main, left circumflex, and right coronary artery.

Impact of ESC/EACTS–HIR Features on Clinical Events

Long-term clinical outcome for patients with ESC/EACTS–HIR features are detailed in **Table 2 and Fig. 2**. Compared with non-HIR patients, patients at HIR had higher crude rates of target vessel failure (6.9% vs. 4.4%; $P<0.001$) **(Fig. 2A)** and higher rates of patient-oriented composite outcome (13.1% vs. 9.0%; $P<0.001$) **(Fig. 2B)**, cardiac death, MI, definite/probable stent thrombosis, and TVR **(Fig. 2, C–F)**. There were no significant differences in the incidence of clinically relevant bleeding between the two groups (2.5% vs. 3.0%; $P=0.180$) **(Fig. 2G)**. The rates of target vessel failure (0: 4.4%, 1–2: 6.9%, and ≥ 3: 7.0%, $P<0.001$) and patient-oriented composite outcome (0: 9.0%, 1–2: 12.8%, and ≥ 3: 13.9%, $P<0.001$) both increased in a stepwise fashion according to the number of ESC/EACTS-endorsed features involved **(Supplementary Figs. 3A and 3B)**. Conversely, there was no gradual risk increase for clinically relevant bleeding (0: 2.9%, 1–2: 2.6%, and ≥ 3: 2.2%, $P=0.158$) as a function of the number of HIR criteria **(Supplementary Fig. 3C)**.

Unadjusted and adjusted clinical outcomes by HIR criteria are reported in **Table 2**. HIR criteria were associated with increased risk of target vessel failure (univariate hazard ratio [HR]: 1.62; 95% confidence interval [CI]: 1.37–1.91; $P<0.001$); this association persisted following multivariable adjustment (adjusted HR: 1.48; 95% CI: 1.25–1.74; $P<0.001$). In addition, the risks of a patient-oriented composite outcome, target lesion failure, cardiac death, MI, stent thrombosis, any revascularization, TVR, and stroke were significantly higher in the group with HIR than in the non-HIR group after adjustment for possible baseline confounders (adjusted HR for POCO, 1.44 [95% CI, 1.28–1.63]; HR for TLF, 1.52 [95% CI, 1.26–1.85]; adjusted HR for cardiac death, 1.95 [95% CI, 1.16–3.29]; adjusted HR for MI, 2.07 [95% CI, 1.51–2.83]; adjusted HR for TVR, 1.45 [95% CI: 1.20–1.74]). Contrarily, with respect to bleeding outcomes, no statistically significant differences were seen in the risk of clinically relevant bleeding by HIR features (univariate HR: 0.85 [95% CI, 0.67–1.08]; $P=0.181$; adjusted HR: 0.84 [95% CI, 0.66–1.06], $P=0.143$). By including ESC/EACTS-endorsed HIR criteria as a continuous variable (per number of HIR features) within the same multivariable models, the risk of adverse ischemic events tended to be greater as the number of HIR characteristics increased (per increase of the number of HIR criteria variables: for TVF, adjusted HR: 1.12, 95% CI: 1.05–1.19; $P_{trend}<0.001$; for POCO, adjusted HR: 1.14, 95% CI: 1.09–1.18; $P_{trend}<0.001$), whereas there were no significant adjusted associations between higher HIR criteria and clinically relevant bleeding (adjusted HR: 0.92, 95% CI: 0.84–1.02; $P_{trend}=0.114$).

The adjusted risks of individual components of the ESC/EACTS–HIR criteria for target vessel failure, patient-oriented composite outcome, and clinically relevant bleeding are presented in **Fig. 3**. Greater than or equal to three implanted stents and diffuse multivessel disease in diabetic patients emerged as independent predictors for target vessel failure and patient-oriented composite outcome, whereas each component of the HIR feature was not related to an increased risk of clinically relevant bleeding ($P>0.05$ for all).

Impact of ESC/EACTS–HIR Features on Clinical Events by HBR Status

Clinical outcomes according to the presence of ESC/EACTS–HIR features in patients with and without HBR are reported in **Fig. 4 and Table 3**. Rates of target vessel failure, patient-oriented composite outcome, cardiac death, MI, and definite/probable stent thrombosis were highest in patients with both HIR and HBR and lowest in those with neither HIR nor HBR (**Figs. 4A–4E**; trend $P<0.001$). There were also differences in rates of TVR (trend $P=0.008$, **Fig. 4F**) and clinically relevant bleeding (trend $P=0.04$, **Fig. 4G**).

The relative risk increase in target vessel failure for patients with ESC/EACTS–HIR features versus that in non-HIR patients was consistent in patients with HBR ($n=682$), with an HR of 1.60 (95% CI: 0.81–3.17) and in patients without HBR ($n=9,485$), with an HR of 1.45 (95% CI: 1.21–1.73; $P_{interaction}=0.443$). Patient-oriented composite outcome was significantly increased in HIR patients at HBR (15.8% in HIR vs. 11.2% in non-HIR group; adjusted HR: 1.19; 95% CI: 0.75–1.90), similar to

Table 1. Baseline and procedural characteristics according to ESC/EACTS-endorsed HIR features

Variables	Total (n = 10167)	HIR (n = 5149)	Non-HIR (n = 5018)	P value
Clinical characteristics				
Age, yrs	58.32 ± 10.25	58.86 ± 10.39	57.77 ± 10.09	< 0.001
Male	7841 (77.1)	4033 (78.4)	3808 (75.9)	0.003
Body mass index, kg/m^2	25.93 ± 3.19	26.01 ± 3.18	25.85 ± 3.19	0.013
Hypertension	6541 (64.3)	3422 (66.5)	3119 (62.2)	< 0.001
Diabetes mellitus	3042 (29.9)	2193 (42.6)	849 (16.9)	< 0.001
Chronic kidney disease	404 (4.0)	404 (7.8)	0 (0)	< 0.001
Dyslipidemia	6837 (67.2)	3536 (68.7)	3301 (65.8)	0.002
Current smoker	5814 (57.2)	2991 (58.1)	2823 (56.3)	0.062
Peripheral artery disease	267 (2.6)	147 (3.3)	120 (2.1)	< 0.001
Anemia	178 (1.8)	102 (2.0)	76 (1.5)	0.073
Prior myocardial infarction	1920 (18.9)	1659 (32.2)	261 (5.2)	< 0.001
Prior STEMI	1409 (13.9)	1409 (27.4)	0 (0)	< 0.001
Prior PCI	2421 (23.8)	1395 (27.1)	1026 (20.4)	< 0.001
Prior CABG	403 (4.0)	258 (5.0)	145 (2.9)	< 0.001
Prior stroke	1080 (10.6)	630 (12.2)	450 (9.0)	< 0.001
Prior major bleeding event	73 (0.7)	43 (0.8)	76 (1.5)	0.073
Atrial fibrillation	209 (2.1)	116 (2.3)	93 (1.9)	0.156
LVEF, %	62.84 ± 7.24	61.81 ± 7.85	63.89 ± 6.38	< 0.001
Clinical presentation				
Stable CAD	4073 (40.1)	2347 (45.6)	1726 (34.4)	< 0.001
ACS	6094 (59.9)	2802 (54.4)	3292 (65.6)	< 0.001
UA/NSTEMI	4756 (46.8)	2223 (43.2)	2533 (50.5)	< 0.001
STEMI	1338 (13.2)	579 (11.2)	759 (15.1)	< 0.001
Hemoglobin, g/dL	14.24 ± 1.53	14.25 ± 1.56	14.34 ± 1.51	0.005
Platelet count, 10^9/L	205.69 ± 55.36	203.51 ± 54.04	207.93 ± 56.60	< 0.001
White blood cell count, 10^9/L	6.74 ± 1.68	6.79 ± 1.63	6.70 ± 1.73	0.003
Creatinine clearance, ml/min	95.06 ± 18.50	93.72 ± 30.27	96.30 ± 27.66	< 0.001
PARIS thrombotic risk score	2.51 ± 1.68	2.81 ± 1.80	2.20 ± 1.49	< 0.001
PARIS bleeding risk score	3.71 ± 2.08	3.84 ± 2.17	3.58 ± 1.97	< 0.001
PRECISE-DAPT score	10.59 ± 8.49	11.22 ± 9.07	9.94 ± 7.79	< 0.001
Duration of DAPT, days	568.52 ± 208.15	577.96 ± 208.56	558.84 ± 207.31	< 0.001
Taking DAPT at 1 yr	7048 (69.3)	3667 (71.2)	3381 (67.4)	< 0.001
Taking DAPT at 2 yrs	2409 (23.7)	1298 (25.2)	1111 (22.1)	< 0.001
Oral anticoagulation therapy*	30 (0.3)	17 (0.3)	13 (0.2)	0.509
Lesion characteristics				
Number of diseased vessels	2.16 ± 0.81	2.43 ± 0.70	1.89 ± 0.81	< 0.001
Target vessel				
Left main artery	268 (2.6)	223 (4.3)	45 (0.9)	< 0.001
Left anterior descending artery	9175 (90.2)	4428 (86.0)	4747 (94.6)	< 0.001
Left circumflex artery	1808 (17.8)	1399 (27.2)	409 (8.2)	< 0.001
Right coronary artery	1875 (18.4)	1530 (29.7)	345 (6.9)	< 0.001
Bypass graft	17 (0.2)	12 (0.2)	5 (0.1)	0.100
Diffuse multivessel disease in diabetic patients	1882 (18.5)	1882 (36.6)	0 (0)	< 0.001
Bifurcation lesion	1677 (16.5)	979 (19.0)	698 (13.9)	< 0.001
Bifurcation with two stents implanted	428 (4.2)	428 (8.3)	0 (0)	< 0.001
Chronic total occlusion	836 (8.2)	836 (16.2)	0 (0)	< 0.001
In-stent restenosis lesion	447 (4.4)	266 (5.2)	181 (3.6)	< 0.001
Heavy calcified lesion	341 (3.4)	248 (4.8)	93 (1.9)	< 0.001
Thrombotic lesion	395 (3.9)	219 (4.3)	176 (3.5)	0.052
Type B2 or C lesion	7812 (76.8)	4494 (87.3)	3318 (66.1)	< 0.001

(Cont. Table 1)

Variables	Total (n = 10167)	HIR (n = 5149)	Non-HIR (n = 5018)	P value
SYNTAX score	11.70 ± 7.90	14.08 ± 8.29	9.27 ± 6.68	< 0.001
EuroSCORE	1.49 ± 1.68	1.69 ± 1.79	1.29 ± 1.54	< 0.001
Procedural characteristics				
Transradial approach	9271 (91.2)	4625 (89.8)	4646 (92.6)	< 0.001
Glycoprotein IIb/IIIa use	1649 (16.2)	988 (19.2)	661 (13.2)	< 0.001
Use of intravascular ultrasound	550 (5.4)	364 (7.1)	186 (3.7)	< 0.001
Number of lesions treated	1.42 ± 0.67	1.67 ± 0.80	1.16 ± 0.37	< 0.001
≥ 3 lesions treated	734 (7.2)	734 (14.3)	0 (0)	< 0.001
Number of stents implanted	1.92 ± 1.05	2.46 ± 1.17	1.36 ± 0.48	< 0.001
≥ 3 stents implanted	2385 (23.5)	2385 (46.3)	0 (0)	< 0.001
Total lesion length, mm	39.00 ± 27.17	52.63 ± 30.53	25.02 ± 12.36	< 0.001
Total stent length, mm	42.51 ± 26.50	56.21 ± 29.37	28.46 ± 12.14	< 0.001
Total stent length > 60 mm	2052 (20.2)	2052 (39.9)	0 (0)	< 0.001
Mean stent diameter, mm	3.01 ± 0.56	2.93 ± 0.54	3.10 ± 0.57	< 0.001
Type of DES implanted				0.963
Early-generation DES	1053 (10.4)	534 (10.4)	519 (10.3)	
New-generation DES	9114 (89.6)	4615 (89.6)	4499 (89.7)	

*Oral anticoagulation therapy means warfarin. Values are mean ± SD for continuous variables, and n (%) for categorical variables. ACS = acute coronary syndrome(s); CAD = coronary artery disease; CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; EF = ejection fraction; HIR = high ischemic risk; LV = left ventricular; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 2. Clinical outcomes according to ESC/EACTS-endorsed HIR features

			Unadjusted		MV Adjusted*	
	HIR (n = 5149)	Non-HIR (n = 5018)	HR (95% CI)	P value	HR (95% CI)	P value
Target vessel failure[a]	357 (6.9%)	219 (4.4%)	1.62 (1.37-1.91)	< 0.001	1.48 (1.25-1.74)	< 0.001
Patient-oriented composite outcome[b]	677 (13.1%)	442 (8.8%)	1.54 (1.36-1.73)	< 0.001	1.44 (1.28-1.63)	< 0.001
Target lesion failure[c]	296 (5.7%)	174 (3.5%)	1.68 (1.40-2.03)	< 0.001	1.52 (1.26-1.85)	< 0.001
All-cause death	81 (1.6%)	53 (1.1%)	1.49 (1.05-2.10)	0.025	1.37 (0.96-1.96)	0.086
Cardiac death	50 (1.0%)	22 (0.4%)	2.21 (1.34-3.65)	0.002	1.95 (1.16-3.29)	0.012
Myocardial infarction	138 (2.7%)	58 (1.2%)	2.33 (1.72-3.17)	< 0.001	2.07 (1.51-2.83)	< 0.001
Target-vessel MI	63 (1.2%)	26 (0.5%)	2.37 (1.50-3.74)	< 0.001	2.08 (1.31-3.32)	0.002
Definite/probable ST	52 (1.0%)	19 (0.4%)	2.67 (1.58-4.52)	< 0.001	2.48 (1.45-4.24)	0.001
Any revascularization	528 (10.3%)	359 (7.2%)	1.47 (1.28-1.68)	< 0.001	1.41 (1.23-1.62)	< 0.001
Target vessel revascularization	293 (5.7%)	190 (3.8%)	1.53 (1.27-1.84)	< 0.001	1.45 (1.20-1.74)	< 0.001
Target lesion revascularization	229 (4.4%)	143 (2.8%)	1.58 (1.28-1.95)	< 0.001	1.50 (1.21-1.85)	< 0.001
Stroke	101 (2.0%)	65 (1.3%)	1.51 (1.10-2.06)	< 0.001	1.44 (1.05-1.98)	0.024
Any bleeding	329 (6.4%)	367 (7.3%)	0.87 (0.75-1.01)	0.070	0.88 (0.76-1.02)	0.086
Clinically relevant bleeding[d]	130 (2.5%)	148 (2.9%)	0.85 (0.67-1.08)	0.181	0.84 (0.66-1.06)	0.143

Values are number of events (%). *Variables entered into multivariable Cox regression models were as follows: for ischemic endpoints: age, sex, body mass index, hypertension, current smoking, left ventricular ejection fraction, peripheral artery disease, prior revascularization (percutaneous coronary intervention and/or coronary artery bypass graft), acute coronary syndrome, mean stent diameter, type of DES implanted, and DAPT duration (as a time-adjusted covariate); for bleeding endpoints: age, sex, body mass index, hypertension, prior major bleeding event, anemia, oral anticoagulation use at discharge, and DAPT duration (as a time-adjusted covariate).
CI = confidence interval; HR = hazard ratio; HIR = high ischemic risk; MI = myocardial infarction; ST = stent thrombosis
[a]Target vessel failure was defined as the composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization.
[b]Patient-oriented composite outcome was defined as the composite of all-cause death, any myocardial infarction, or any revascularization.
[c]Target lesion failure was defined as the composite of cardiac death, target vessel myocardial infarction, or target lesion revascularization.
[d]Clinically relevant bleeding was defined as BARC type 2, 3, or 5 bleeding.

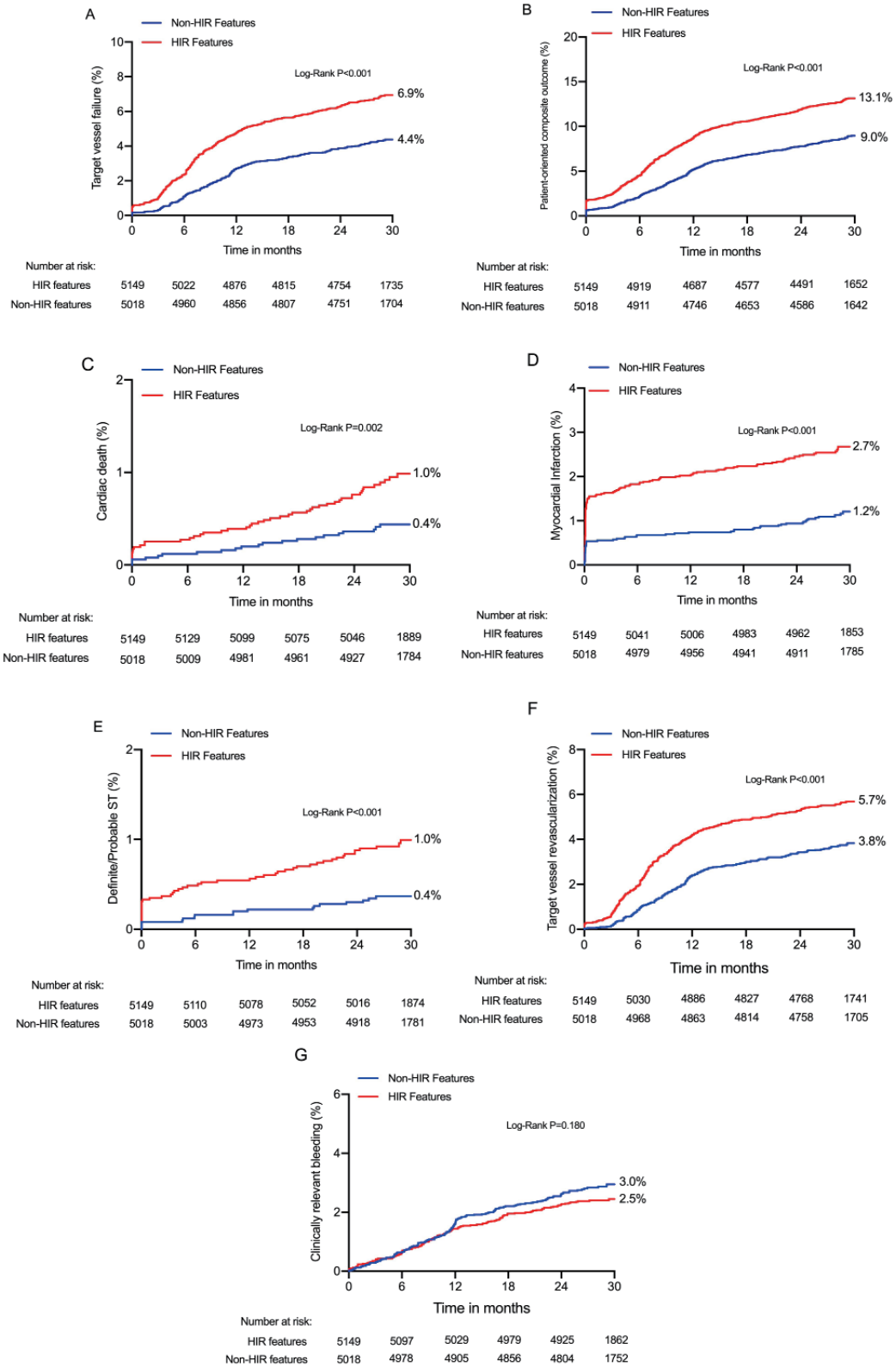

Fig. 2. Time-to-Event Curves for TVF (A), POCO (B), cardiac death (C), MI (D), definite/probable ST (E), TVR (F), and clinically relevant bleeding (G) according to ESC/EACTS-endorsed HIR features

HIR=high ischemic risk; POCO=patient-oriented composite outcome; ST=stent thrombosis; TVR=target vessel revascularization; TVF=target vessel failure

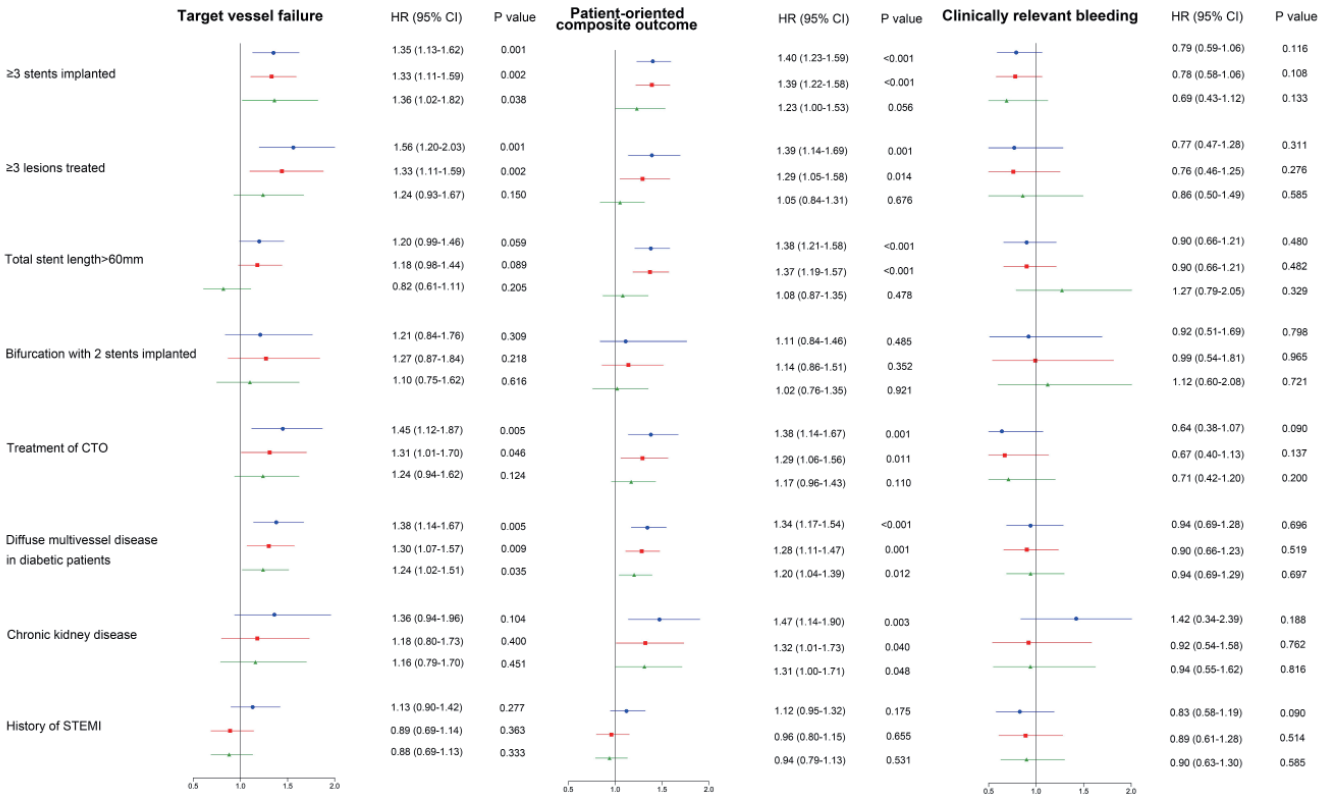

Fig. 3. Adjusted hazard ratio of each ESC/EACTS–HIR criterion for target vessel failure, patient-oriented composite outcome and clinically relevant bleeding

Blue indicates unadjusted results. Red indicates results adjusted by following variables. Green indicates results adjusted by following variables and all ESC/EACTS–HIR features. For ischemic endpoints (TVF and POCO): age, sex, body mass index, hypertension, current smoking, left ventricular ejection fraction, peripheral artery disease, prior revascularization (percutaneous coronary intervention and/or coronary artery bypass graft), acute coronary syndrome, mean stent diameter, type of DES implanted, and DAPT duration (as a time-adjusted covariate); for clinically relevant bleeding: age, sex, body mass index, hypertension, prior major bleeding event, anemia, oral anticoagulation use at discharge, and DAPT duration (as a time-adjusted covariate).
CI = confidence interval; CTO = chronic total occlusion; HR = hazard ratio; TVF = target vessel failure; POCO = patient-oriented composite outcome;

what was seen in HIR patients without HBR (12.9% vs. 8.7%; adjusted HR: 1.45; 95% CI: 1.27–1.64), $P_{interaction} = 0.948$. There was also no heterogeneity in the relative risk increase for other ischemic events in patients with ESC/EACTS–HIR features on the basis of the presence of HBR at baseline (all $P_{interaction} > 0.05$). There was no increase in the risk of clinically relevant bleeding in HIR patients compared with non-HIR patients, irrespective of the presence of HBR (adjusted HR: 0.81; 95% CI: 0.63–1.04 for patients without HBR, compared with adjusted HR: 1.11; 95% CI 0.55–2.24 for patients with HBR; $P_{interaction} = 0.517$).

Additional Analyses

Further stratification according to four bleeding risk strata from the PRECISE-DAPT score (very low risk: ≤ 10; low risk: 1–17; moderate risk: 18–24; and high-risk: ≥ 25) indicated consistent effects of ESC/EACTS–HIR features on the primary ischemic and bleeding outcomes in patients at very low, low, moderate, or high bleeding risks (for TVF, $P_{interaction} = 0.061$; for POCO, $P_{interaction} = 0.115$; and for clinically relevant bleeding, $P_{interaction} = 0.170$) **(Fig. 5)**. Use of the PARIS bleeding risk score to define HBR (score ≥ 8) yielded similar results in terms of ischemic and bleeding endpoints as the PRECISE-DAPT score ≥ 25, as presented in **Supplementary Table 5**. Likewise, outcomes were also consistent irrespective of three bleeding risk categories based on the PARIS bleeding risk score (low: 0–3, intermediate: 4–7, and high: ≥ 8 bleeding risk), with no evidence of interaction **(Supplementary Fig. 4)**. When the study population was stratified according to either ACS presentation and/or HBR (i.e.,. high-risk patient), no significant interactions were noted with respect to the primary

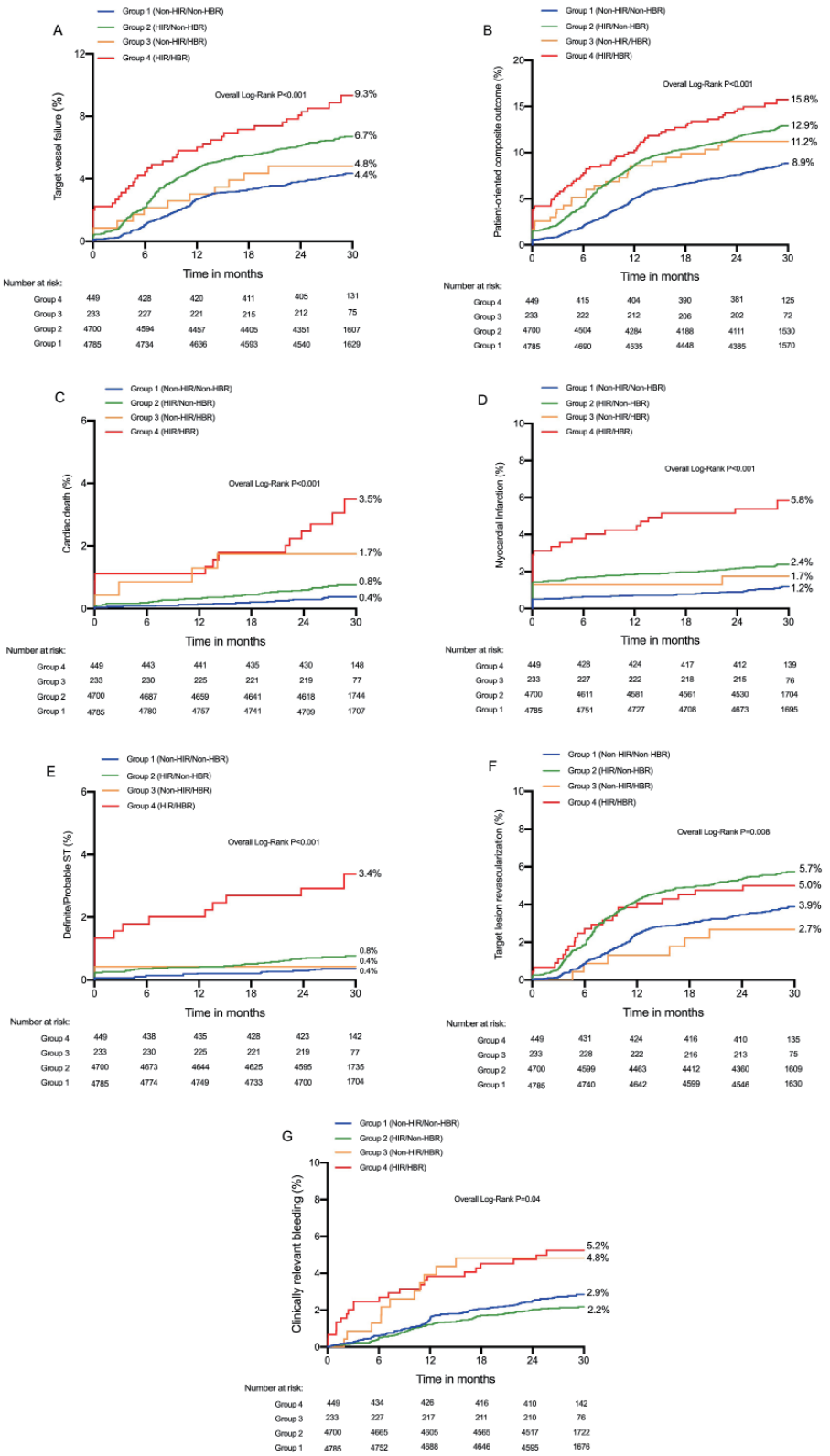

Fig. 4. Time-to-Event Curves for TVF (A), POCO (B), cardiac death (C), MI (D), definite/probable ST (E), TVR (F), and clinically relevant bleeding (G) according to ESC/EACTS-endorsed HIR features and HBR status

HIR = high ischemic risk; HBR = high bleeding risk; POCO = patient-oriented composite outcome; ST = stent thrombosis; TVR = target vessel revascularization; TVF = target vessel failure

Table 3. Adjusted HRs for adverse events associated with ESC/EACTS-endorsed HIR features stratified by HBR

	Non-HBR (PRECISE-DAPT score <25; *n* =9485)			HBR (PRECISE-DAPT score ≥ 25, *n* =682)			
	HIR (*n* =4700)	Non-HIR (*n* =4785)	Adjusted HR (95% CI)*	HIR (*n* =449)	Non-HIR (*n* =233)	Adjusted HR (95% CI)*	*P* value for interaction
Target vessel failure	316 (6.7)	208 (4.3)	1.45 (1.21-1.73)	41 (9.1)	11 (4.7)	1.60 (0.81-3.17)	0.443
Patient-oriented composite outcome	606 (12.9)	416 (8.7)	1.45 (1.27-1.64)	71 (15.8)	26 (11.2)	1.19 (0.75-1.90)	0.948
Target lesion failure	258 (5.5)	166 (3.5)	1.47 (1.20-1.79)	38 (8.5)	8 (3.4)	1.95 (0.89-4.26)	0.228
All-cause death	61 (1.3)	44 (0.9)	1.69 (1.12-2.53)	20 (4.5)	9 (3.9)	0.78 (0.33-1.85)	0.117
Cardiovascular death	35 (0.7)	18 (0.4)	2.31 (1.25-4.27)	15 (3.3)	4 (1.7)	1.23 (0.37-4.10)	0.368
Myocardial infarction	112 (2.4)	54 (1.1)	1.93 (1.38-2.68)	26 (5.8)	4 (1.7)	3.00 (1.03-8.73)	0.457
Definite/probable ST	37 (0.8)	18 (0.4)	2.03 (1.14-3.60)	15 (3.3)	1 (0.4)	6.22 (0.80-48.41)	0.293
Any revascularization	489 (10.4)	342 (7.1)	1.44 (1.25-1.65)	39 (8.7)	17 (7.3)	1.15 (0.64-2.08)	0.637
Target vessel revascularization	271 (5.8)	184 (3.8)	1.44 (1.18-1.74)	22 (4.9)	6 (2.6)	1.98 (0.78-5.00)	0.497
Target lesion revascularization	212 (4.5)	140 (2.9)	1.47 (1.18-1.82)	17 (3.8)	3 (1.3)	3.07 (0.88-10.65)	0.255
Stroke	84 (1.8)	59 (1.2)	1.45 (1.03-2.03)	17 (3.8)	6 (2.6)	1.41 (0.54-3.65)	0.973
Clinically relevant bleeding	106 (2.3)	136 (2.8)	0.81 (0.63-1.04)	24 (5.3)	12 (5.2)	1.11 (0.55-2.24)	0.517

Values are number of events (%). *Variables entered into multivariable Cox regression models were as follows: for ischemic endpoints: age, sex, body mass index, hypertension, current smoking, left ventricular ejection fraction, peripheral artery disease, prior revascularization (percutaneous coronary intervention and/or coronary artery bypass graft), acute coronary syndrome, mean stent diameter, type of DES implanted, and DAPT duration (as a time-adjusted covariate); for bleeding endpoints: age, sex, body mass index, hypertension, prior major bleeding event, anemia, oral anticoagulation use at discharge, and DAPT duration (as a time-adjusted covariate).
CI = confidence interval; HR = hazard ratio; HBR = high bleeding risk; HIR = high ischemic risk; MI = myocardial infarction; ST = stent thrombosis

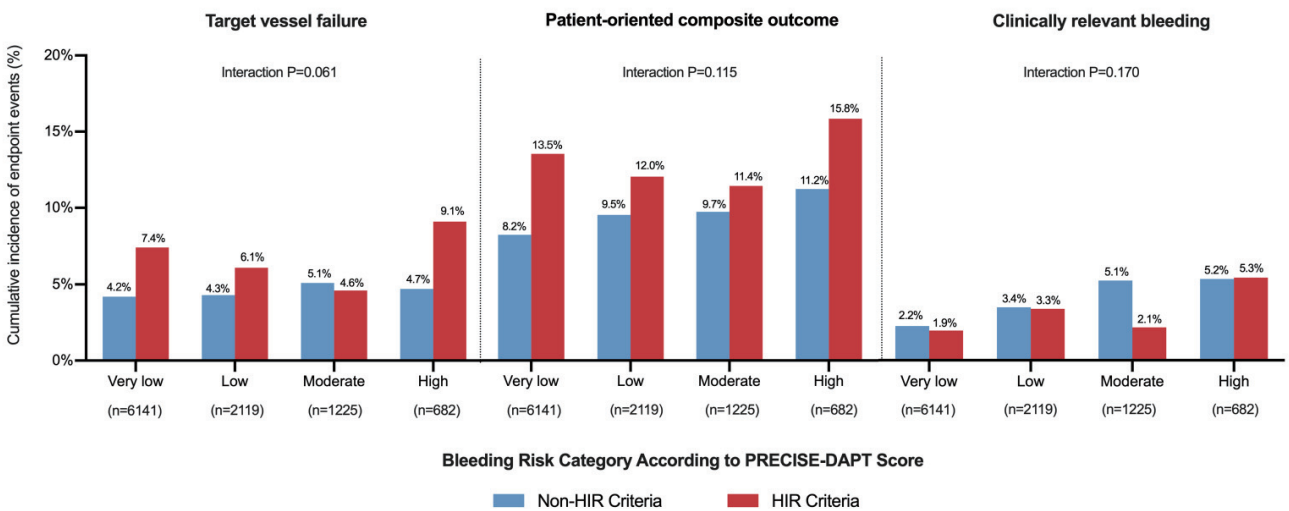

Fig. 5. Cumulative Incidence of Endpoint Events according to ESC/EACTS–HIR criteria and bleeding risk categorization

The endpoint events were stratified by ESC/EACTS-endorsed HIR criteria and four bleeding risk strata from PRECISE-DAPT score. Outcomes were analyzed comparing ESC/EACTS-endorsed HIR criteria among subgroups of patients with very low (*n*=6141), low (*n*=2119), moderate (*n*=1225), and high bleeding risk (*n*=682). Relative impact of ESC/EACTS-endorsed HIR criteria was consistent for the outcomes of TVF, POCO, and clinically relevant bleeding, independent of the bleeding risk status.
HIR = high ischemic risk; POCO = patient-oriented composite outcome; TVF = target vessel failure

ischemic and major bleeding outcome for ESC/EACTS–HIR criteria and high-risk patients **(Supplementary Table 6)**.

Discussion

The present study is the first to validate the ESC/EACTS guideline-endorsed HIR definition in a large unselected PCI cohort in an analysis involving more

than 10,000 real-world patients undergoing PCI predominantly with second-generation DES. We report the following key findings: (1) More than half of patients fulfilled at least 1 ESC/EACTS-endorsed HIR criteria, of which ≥ 3 stents implanted was the most prevalent, (2) compared with non-HIR patients, those at HIR had significantly more complex coronary artery disease and higher risk of target vessel failure and a patient-oriented composite outcome, which increased in a stepwise fashion according to the number of ESC/EACTS–HIR contributors involved; (3) ESC/EACTS-endorsed HIR features were associated with a nonsignificant increase in the rate of clinically relevant bleeding. (4) The ischemic risk was related to its individual components, and ≥ 3 stents implanted and diabetic patients with diffuse multivessel CAD were independent predictors of target vessel failure and patient-oriented composite outcome; (5) the underlying HBR status did not modify the association between the HIR features and clinical adverse events, with no evidence of statistical interaction, underscoring the importance of applying ESC/EACTS–HIR criteria judgment when tailoring the duration of DAPT.

Patients undergoing complex percutaneous coronary revascularization procedures are a sizable portion of the population, with their prevalence varying based on definitions and inclusion criteria used for patient selection[13, 14]. A targeted approach to identifying HIR patients has implications for both clinical care and evaluation of DAPT strategies for stents. In response to the lack of a widely accepted outline for computing HIR among patients undergoing PCI, the ESC/EACTS guidelines on myocardial revascularization have recently promoted more pragmatic criteria for assessment of HIR in PCI-treated patients[15]. Accordingly, our findings are important in supporting the validity of this newly introduced definition of ESC/EACTS–HIR and facilitating its future application in routine clinical practice. In our analysis, more than half of the patients (50.6%) undergoing PCI was at HIR according to the 2018 ESC/EACTS–HIR criteria, indicating that HIR patients are encountered not infrequently in our daily clinical practice. This high prevalence is comparable to that observed in the Bern PCI Registry, where 52% of patients were classified as high-risk features for stent-related ischemic events[32]. Conversely, the rates of HIR patients was low in previous randomized controlled trials (RCTs; 17.5% in the Giustino G *et al.*[7] study, 20.8% in the Costa F *et al.*[16] study, and 29.6% in the post hoc analysis of GLOBAL LEADERS trials[6]), indicating that HIR patients are more common in daily clinical practice than in the clinical trials. In the present study, the ESC/EACTS-endorsed HIR criteria successfully identified patients from an all-comer group of subjects who were at a higher risk for ischemic complications at relatively long durations of follow-up, the presence of which was strongly associated with long-term adverse device- and patient-related events. Highly significant stepwise increments in the risk of ischemic complications closely reflecting the increasing number of coexisting HIR-qualifying conditions were also seen in our study.

It is worth noting that prior data are not entirely consistent regarding the association between HIR and bleeding events[6-10, 16]. It is worth noting that we did not observe a higher risk for major bleeding in HIR patients, as reported in some prior studies[7, 8, 16], where similar rates of clinically relevant bleeding (2.5% vs. 2.9%; $P=0.181$) were observed between HIR and non-HIR patients; these findings remained consistent even after multivariable adjustment. Thus, the hazard of clinically relevant bleeding did not increase progressively with the accumulation of ESC–HIR criteria fulfilled. By contrast, Ueki *et al.*[32] found that ESC-endorsed HIR criteria incur an increased risk of BARC 3–5 bleeding (4.9% vs. 2.2%; $P<0.001$) in the Bern PCI Registry data, and there was a graded risk increase for BARC 3–5 bleeding (0: 2.2%; 1 to 2: 4.5%; and ≥ 3: 6.6%; $P<0.001$) as the number of high-risk features increased. Such discrepancies may be explained by differences in baseline demographic, clinical characteristics of patient populations, definition of HIR patients, type of $P2Y_{12}$ inhibitors, and bleeding risk.

First, the respective composition and prevalence of risk factors, at least partially, may account for the relative performance of the different HIR criteria. We notice that clinical and procedural characteristics qualifying patients as HIR significantly differ among these studies. Total stent length >60 mm (20.2%) and diffuse multivessel diabetic CAD patients (18.5%), representing the most common criterion in our study, were present in only approximately 6.5% and 2.7% of patients in the Bern PCI Registry, respectively. Of note, the higher prevalence of these two conditions might be associated with a greater relative increase in ischemic than bleeding risk in our study. By contrast, when we accepting that both CKD and anemia are well-recognized risk factors for post-discharge bleeding after PCI, then our results should be interpreted in light of the more frequency of CKD (24.7% vs. 4.0%) and anemia (11.1% vs. 1.8%) in the Bern PCI Registry compared with those in our study. Second, the 2018 ESC/EACTS-endorsed HIR criteria further included history of STEMI due to its consistent correlate of thrombotic events but not

bleeding—a parameter that might reflect more predisposition to atherothrombosis following the rupture or fissuring of an unstable atherosclerotic plaque compared with patients with stable ischemic heart disease[33, 34]. Third, it is known that compared with clopidogrel, both ticagrelor and prasugrel were associated with a significant increase in total bleeding risk. In the current findings, all patients were treated with clopidogrel as the $P2Y_{12}$ receptor antagonist, as high-potency $P2Y_{12}$ inhibitors were not widely used in China at the time of the study. Conversely, the percentages of use of potent $P2Y_{12}$ were 38.8% in the Bern PCI Registry and 76% in the GLOBAL LEADERS trial. Fourth, in this study, major bleeding events according to BARC type 2, 3, or 5 were fewer than those in previously published registry studies such as the ADAPT-DES (8.6%) and Bern PCI (5.0%) registries[10, 32], occurring in 2.7% of patients. This observation might be attributable to the high frequency of use of the transradial PCI in 91.2% of cases in our analysis, whereas femoral access was the primary vascular access site in the ADAPT-DES study (95.4%). It is clear that transradial artery access for PCI is associated with lower bleeding and vascular complications than those associated with transfemoral artery access[35]. Furthermore, part of the reason for the lack of a significant relationship between HIR features and clinically relevant bleeding is probably that most of patients were at low bleeding risk in our data set according to PRECISE-DAPT score (score≤ 17; 78.7%) and PARIS bleeding risk score (score≤ 3; 50.9%).

It would be important for physicians to better understand which individual component of ESC–HIR features allows discrimination between ischemic and bleeding events, we found that ≥ 3 stents implanted and diabetic patients with multivessel CAD were the only independent predictors for device- and patient-oriented adverse outcomes, but not bleeding, in a fully adjusted analysis of all individual features. In the report from new analysis of the PRECISE-DAPT population, independent predictors for ischemic events were CTO, at least 3 stents implanted, and >60 mm total stent length[16], whereas bifurcation with two stents implanted was the most consistently and strongly associated with increased ischemic risk in the pooled analysis of six RCTs[7]. The differential effects among studies might be mainly derived from the differences in patients' risk profiles and treatment strategies. Appropriate criteria of HIR features (i.e.,. complex PCI) as a potent risk factor for ischemic events deserve further evaluation in future study.

Patients at HBR are a challenging group with regard to selecting a stent and determining intensity and duration of DAPT management after PCI[36]. As many of risk factors for increased bleeding also pose a higher risk for thrombotic events, HBR characteristics incur not only an increased risk of bleeding but also multiple ischemic events[37]. Examination of the interplay among the HIR, HBR, and downstream adverse events has important implications for clinical practice, because selection of the most appropriate DAPT duration and intensity after PCI requires an informed understanding of both thrombotic and bleeding risks. Our study demonstrated that no significant interactions were present between ESC/EACTS–HIR criteria and HBR for any of the long-term outcomes assessed. We observed a nondifferential increase in risks for all ischemic events in HIR patients, consistently across the spectrum of bleeding risk. Notably, the observation that bleeding risk was similar for subjects who had HIR criteria and subjects who had non-HIR criteria in this study provides a valuable insight that HBR did not adversely affect the association of ESC/EACTS–HIR criteria with clinically relevant bleeding. Taken together, irrespective of HBR, rates of both patient- and device-related outcomes remain high in ESC/EACTS–HIR patients, suggesting that longer regimens of platelet inhibition might be beneficial in preventing non-DES-related ischemic complications associated with atherosclerotic disease progression outside the stented vascular segment. In recent years, several RCTs testing shorter durations of DAPT have suggested a comparable antithrombotic efficacy and a possible net benefit owing to the reduction in major bleeding in a low risk population[38, 39]. Eligibility criteria across these trials have limited the inclusion of HIR patients, so the majority of enrolled patients had low or intermediate ischemic risk. In real-world clinical practice, physicians are still reluctant to choose very short DAPT durations for HIR patients, mainly due to concerns on their higher risk for atherothrombotic ischemic events[10, 40-42]. Indeed, we observed that patients who remained on DAPT at 1 year and 2 years, as expected, were more common among patients with HIR than in the non-HIR group. In a pooled patient-level meta-analysis of six RCTs, long-term DAPT (≥ 12 months) yielded significant reductions in ischemic endpoints among complex PCI patients compared with shorter DAPT (3 or 6 months), with a magnitude that was greater for higher procedural complexity[7]. Therefore, extended-term DAPT may have a role for certain patients who are at a higher risk of recurrent cardiac ischemic events after PCI and a low risk of bleeding, as recommended by the ESC and ACC/AHA guidelines[15, 43, 44]. The values of emerging antiplatelet strategies, such as DAPT de-escalation or

short-term DAPT followed by P2Y12 inhibitor monotherapy for HIR patients in the real-world setting, require further and dedicated investigations.

Limitations

We acknowledge some limitations. First, because this study was a retrospective analysis from a large volume single center prospective PCI registry at one year; hence, the results might not apply to patients undergoing PCI in other centers and had to be considered as hypothesis-generating rather than conclusive. As with any observational study, there is the potential for confounding by unmeasured factors. Residual or unmeasured confounding variables and selection bias could not be completely controlled despite multivariable adjustment. Second, in the current study, nearly 19% of diabetic patients with multivessel CAD underwent coronary revascularization with PCI, even though both American and European guidelines stated that CABG is preferred to PCI in these patients (Class I recommendation)[15, 45]. Although the overwhelming evidence favors CABG in patients with diabetes and multivessel CAD, PCI has remained a common revascularization strategy in real-world clinical practice due to patients' preference for a less-invasive approach and improvements in PCI techniques[46-48]. In our large volume single center with heart team experience with myocardial revascularization[49, 50], patient-centric shared decision-making that balances the benefits or harms of CABG versus PCI in conjunction with the baseline risk profile (e.g., CAD complexity [SYNTAX score]) and patient preferences has been taken into account. Third, not all 10 ESC/EACTS–HIR criteria were present in our analysis; inclusion of those missed criteria would potentially lead to improved rate estimation of ischemic and bleeding events and enhanced discriminative ability. Fourth, novel high-potency antiplatelet drugs, such as prasugrel or ticagrelor, were unavailable during the Fuwai PCI Registry recruitment; as a result, our findings apply to a clopidogrel-treated PCI population. Fifth, only 6.7% and 4.6% of patients based on the PRECISE-DAPT or PARIS bleeding risk score met the threshold for HBR categorization, respectively. Due to the relatively modest sample size of HBR patients that reduces the power of statistical comparisons, significant differences in the adjusted rates of adverse events in HBR patients with HIR vs. non-HIR criteria were not observed, in contrast to those seen in the non-HBR cohort and the entire study population. However, there was no interaction between the bleeding status and the risk of clinical outcomes associated with ESC/EACTS–HIR criteria, which underlines the importance of ESC/EACTS–HIR features in determining the subsequent risk of events after PCI. Sixth, the c-statistic values indicated poor discriminative power of PRECISE-DAPT and PARIS bleeding scores in predicting clinically relevant bleeding (c-statistic=0.59 and 0.58 for PRECISE-DAPT and PARIS, respectively) in the present study. It would be preferable to use bleeding risk scores derived in the population with the same or similar ethnic and/or geographic characteristics. Thus, future studies are warranted to create a dedicated risk score specifically designed to predict bleeding events in a large Chinese observational database of patients undergoing PCI, which might improve risk assessment and support clinicians' decisions with respect to DAPT. Seventh, although current guidelines recommended triple antithrombotic therapy (oral anticoagulant, aspirin, and P2Y12 inhibitor) for patients with AF undergoing PCI during hospitalization[51], oral anticoagulant therapy was greatly underused for these patients in the present study, which was consistent with previous reports[52-54]. Part of the underlying reasons for the low use of anticoagulation therapy may be explained by: 1) concerns of bleeding complications, 2) lack of awareness of anticoagulation therapy for physicians[55], 3) limited evidence of clinical research data and consensus guidelines for management of antithrombotic therapy in AF patients undergoing PCI, and 4) unavailability of non-vitamin K antagonist oral anticoagulants during the time of enrollment in China in real-world clinical practice. Finally, given that the pattern of trade-off between ischemic events and bleeding risk can differ according to the race, the single center design of this study was based on Chinese population; therefore, caution is needed in extrapolating these results outside of China.

Conclusions

In this single center, consecutively enrolled PCI reflecting routine clinical practice, ESC/EACTS endorsed HIR criteria were present in half of the study population, the presence of which was associated with a significant increase in long-term device- and patient-oriented adverse outcomes, with no apparent increase in the risk of clinically relevant bleeding. The independent impacts of ESC/EACTS–HIR on ischemic and bleeding events are substantial and similar, irrespectively of the underlying HBR status. Finally, we demonstrate prognostic differences between individual ESC/EACTS–HIR features, with worst outcomes observed among patients with ≥ 3 stents implanted and diabetic patients with multivessel

coronary disease. The present findings provide a real-world context and support that the ESC/EACTS–HIR criteria clearly identify patients at high-risk of ischemic events and, importantly, demonstrate the importance of applying them in practice for clinical decision-making regarding optimal DAPT duration.

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Disclosures

The authors declare that they have no conflict of interest.

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Supplementary Methods

PCI Procedures

Unfractionated heparin was used for anticoagulation during the procedure to achieve an activated clotting time of 250 to 300 seconds. Treatment strategy for access site, revascularization treatment strategy, use of glycoprotein IIb/IIIa inhibitor, and use of intravascular imaging assessment were all carried out at the operators' discretion. The length and diameter of the stent were not restricted. All patients received 300 mg of aspirin orally and a 300 mg or 600 mg clopidogrel loading dose orally before PCI, unless they had previously received these antiplatelet medications. After the procedure, aspirin (100 mg orally once daily) was used indefinitely and clopidogrel (75 mg orally once daily) was maintained for at least 12 months. New $P2Y_{12}$ receptor inhibitors such as prasugrel and ticagrelor were not available during the study period in China. After the procedure, all patients were recommended to receive optimal pharmacological therapy, including statins, β-blockers, or renin-angiotensin system blockade, if indicated, following clinical guidelines[1, 2]. Patients who discontinued antiplatelet therapy as a result of clinically significant active bleeding or for other procedures were monitored carefully for cardiac events.

HIR and HBR Assessment

In the present study, patients with PARIS bleeding score ≥ 8 and 4-7 had significantly increased risk of clinically relevant bleeding (BARC 2, 3, or 5 bleeding) (PARIS bleeding score ≥ 8: HR: 2.38, 95% CI: 1.52-3.73; PARIS bleeding score 4-7: HR: 1.50, 95% CI: 1.17-1.92) compared with the reference (PARIS bleeding score: 0-3) **(Supplementary Table 1)**. The transition from a lower to a higher risk category was associated with a significant increase in clinically relevant bleeding rates (2.1% vs. 3.2% vs. 4.9%) across the bleeding risk scores **(Supplementary Table 1)**. Kaplan–Meier event curves for clinically relevant bleeding stratified by PARIS bleeding score is shown **Supplementary Fig. 1** Stratification according to the PARIS bleeding score was associated with a significant increase in terms of clinically relevant bleeding (log-rank $P<0.001$).

In our study, patients with PRECISE-DAPT score ≥ 25, 18-24, and 11-17 had significantly increased risk of clinically relevant bleeding (PRECISE-DAPT score ≥ 25: HR: 2.65, 95% CI: 1.83-3.83; PRECISE-DAPT score 18-24: HR: 1.71, 95% CI: 1.21-2.42; PRECISE-DAPT score 11-17: HR: 1.62, 95% CI: 1.21-2.17] compared with the reference (PRECISE-DAPT score ≤ 10) **(Supplementary Table 2)**. The transition from a lower to a higher risk category was associated with a significant increase in clinically relevant bleeding rates (2.1% vs. 3.4% vs. 3.5% vs. 5.3%) across the bleeding risk scores **(Supplementary Table 2)**. Then, patients were categorized into three bleeding risk strata for all scores by considering the very low (score ≤ 10) and low risk (score: 11-17) categories in PRECISE-DAPT as a unique category (i.e., low risk) [score ≤ 17]. Similarly, the predictive performances of the PRECISE-DAPT score for clinically relevant events were higher in the higher risk category (≥ 25 and 18-24) compared with the low-risk category (≤ 17) **(Supplementary Table 3)**. Kaplan–Meier event curves for clinically relevant bleeding stratified by PRECISE-DAPT score is shown **Supplementary Fig. 1**. Stratification according to the PRECISE-DAPT score was associated with a significant increase in terms of clinically relevant bleeding (log-rank $P<0.001$).

The association, discriminative capacity and calibration statistics of PRECISE-DAPT score and PARIS bleeding score for predicting clinically relevant bleeding are shown in **Supplementary Table 4**. In order to assess the risk score performance, indices of discrimination and calibration were calculated. First, discriminative power was assessed using the total risk score as a global prognostic indicator and calculating the Harrell c-statistic for censored time-to-event data with the Kaplan-Meier method. Second, calibration was evaluated with the Hosmer-Lemeshow test and with the Greenwood-Nam-D'Agostino (GND) χ^2 test approaches applied to a Cox regression model with total score as a predictor. The detailed method of Greenwood-Nam-D'Agostino goodness-of-fit tests to assess calibration has been described in previous studies[3-5].

The c-statistic values indicated modest discriminative power for PRECISE-DAPT score for predicting clinically relevant bleeding (c-statistic = 0.585, 95% CI: 0.550-0.619). The c-statistic values indicated modest discriminative power for PARIS bleeding score for predicting clinically relevant bleeding (c-statistic = 0.580, 95% CI: 0.546-0.615). The PRECISE-DAPT and PARIS bleeding scores showed good calibration for clinically relevant bleeding after PCI with drug-eluting stents implantation in our cohort **(Supplementary Fig. 2)**. The calibration of observed vs. predicted clinically relevant bleeding events was consistent for both risk scores, as assessed using the Hosmer-Lemeshow and Greenwood-Nam-D'Agostino χ^2 test ($P>0.05$).

Clinical Outcomes

The definition of bleeding event used in this

study was adapted from BARC definition[6].

• BARC type 1 bleeding was defined as bleeding that is not actionable and patient does not have unscheduled studies, hospitalization or treatment by a health care professional.

• BARC type 2 bleeding was defined as any clinically overt sign of hemorrhage that is actionable but does not meet criteria for BARC type 3, 4 or 5 bleeding but does meet at least one of the following criteria: 1) requiring medical or percutaneous intervention guided by a health care profession, includes (but are not limited to) temporary/permanent cessation of a medication, coiling, compression, local injection; 2) leading to hospitalization or an increased level of care; 3) prompting evaluation defined as an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging).

• BARC type 3a bleeding was defined as: 1) overt bleeding plus hemoglobin (Hb) drop ≥ 3 to <5g/dL (provided Hb drop is related to bleeding); 2) any transfusion with overt bleeding. BARC type 3b bleeding was defined as: 1) overt bleeding plus Hb drop ≥ 5g/dL* (Hb drop is related to bleed); 2) cardiac tamponade; 3) bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); 4) bleeding requiring intravenous vasoactive drugs. BARC type 3c bleeding was defined as: 1) intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal). subcategories: confirmed by autopsy, imaging or lumbar puncture; 2) intraocular bleed compromising vision.

• BARC type 5a bleeding was defined as probable fatal bleeding is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging. BARC type 5b bleeding was defined as definite fatal bleeding is bleeding that is directly observed (either by clinical specimen – blood, emesis, stool, etc. – or by imaging) or confirmed on autopsy.

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Supplementary Table 1. Predictive performance of PARIS bleeding score for clinically relevant bleeding

	Clinically relevant bleeding		
	(%) n/N	HR (95% CI)	*P* value
PARIS bleeding score			<0.001
Low (0-3)	2.1% (111/5178)	Reference	
Intermediate (4-7)	3.2% (144/4519)	1.50 (1.17-1.92)	
High (≥ 8)	4.9% (23/470)	2.38 (1.52-3.73)	

Clinically relevant bleeding was defined as BARC 2, 3, or 5 bleeding.

Supplementary Table 2. Predictive performance of PRECISE-DAPT score for clinically relevant bleeding

	Clinically relevant bleeding		
	(%) n/N	HR (95% CI)	*P* value
PRECISE-DAPT score			<0.001
Very low (≤ 10)	2.1% (128/6141)	Reference	
Low (11-17)	3.4% (71/2119)	1.62 (1.21-2.17)	
Moderate (18-24)	3.5% (43/1225)	1.71 (1.21-2.42)	
High (≥ 25)	5.3% (36/682)	2.65 (1.83-3.83)	

Clinically relevant bleeding was defined as BARC 2, 3, or 5 bleeding.

Supplementary Table 3. Predictive performance of PRECISE-DAPT score for clinically relevant bleeding (according three bleeding risk strata)

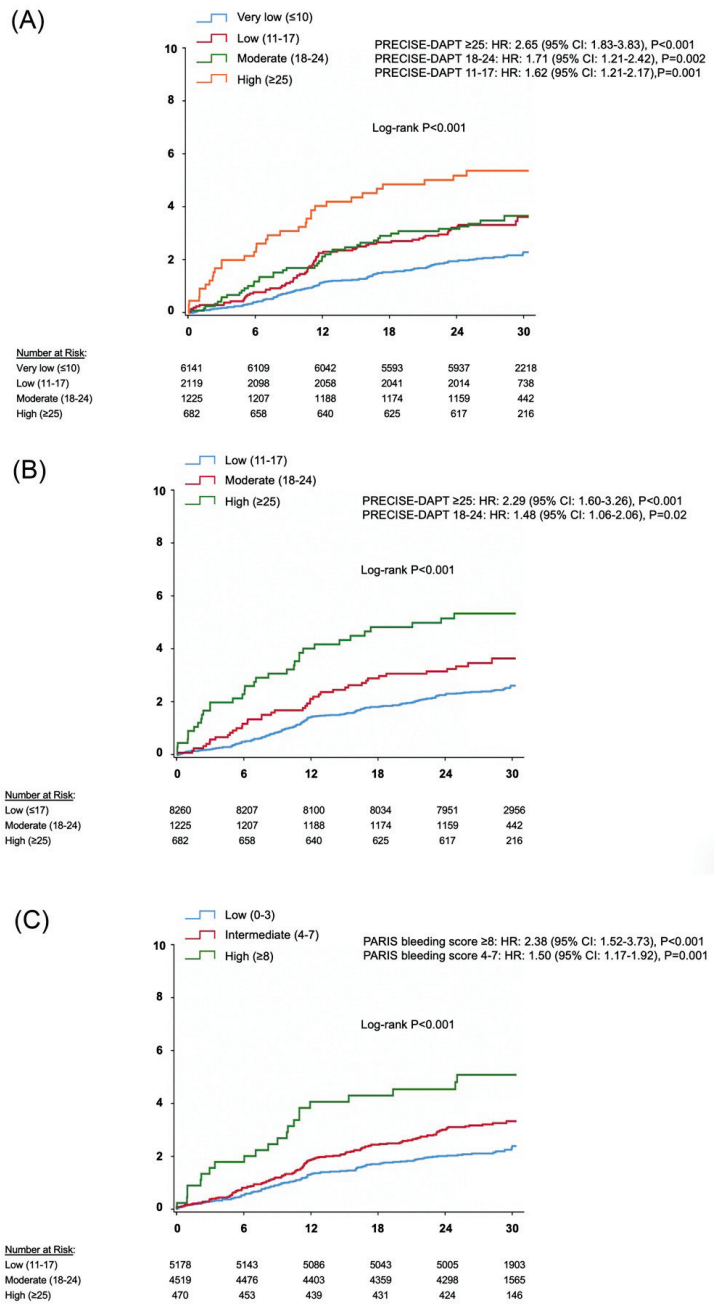
	Clinically relevant bleeding		
	(%) n/N	HR (95% CI)	*P* value
PRECISE-DAPT score			<0.001
Low (≤ 17)	2.4% (199/8260)	Reference	
Moderate (18-24)	3.5% (431225)	1.48 (1.06-2.06)	
High (≥ 25)	5.3% (36/682)	2.29 (1.60-3.26)	

Clinically relevant bleeding was defined as BARC 2, 3, or 5 bleeding.

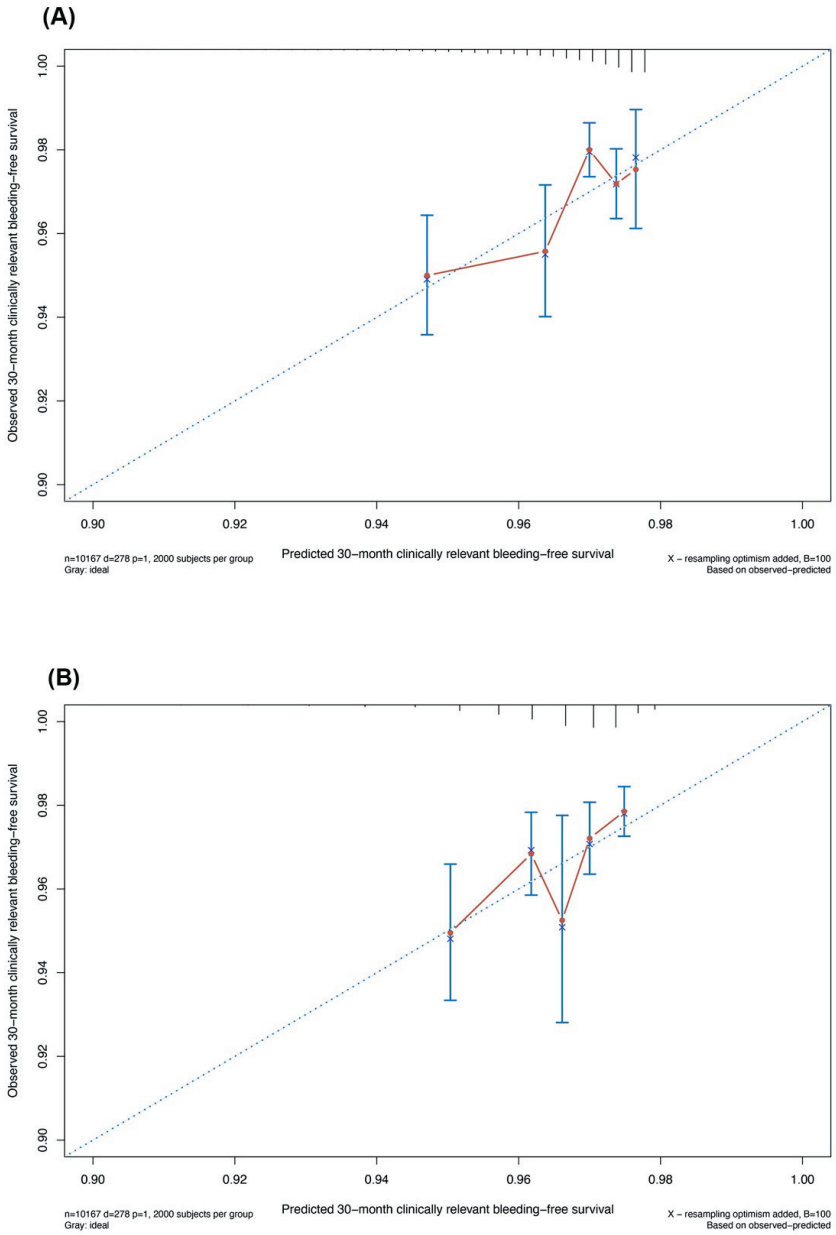
Supplementary Table 4. Association, discriminative capacity and calibration statistics of PRECISE-DAPT score and PARIS bleeding score for predicting clinically relevant bleeding at follow-up

	PRECISE-DAPT score	PARIS bleeding score
HR (95% CI)*	1.036 (1.024-1.048) *P*<0.001	1.131 (1.074-1.191) *P*<0.001
Hosmer-Lemeshow χ^2	10.84 *P*=0.211	4.45 *P*=0.487
Greenwood-Nam-D'Agostino χ^2	7.97 *P*=0.537	4.40 *P*=0.623
Harrel's C Statistic	0.585 (0.550-0.619)	0.580 (0.546-0.615)

*Using the total risk scores as a global prognostic indicator (i.e., as a continuous variable). For Greenwood-Nam-D'Agostino test, patients were categorized into deciles based on predicted probability of incident clinically relevant bleeding. Greenwood-Nam-D'Agostino test for calibration across deciles requires at least 2 events in each group; thus, deciles were collapsed as needed if <2 clinically relevant bleeding events occurred.

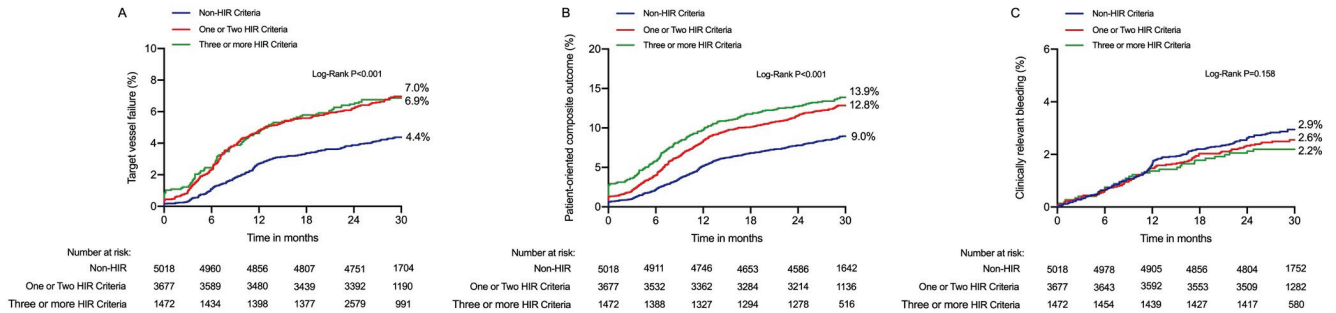


Supplementary Fig. 1. Kaplan–Meier event curves for clinically relevant bleeding stratified by (A) four PRECISE-DAPT risk strata (very low: ≤ 10, low: 11-17, moderate: 18-24, and high: ≥ 25 points), (B) three PRECISE-DAPT risk strata (low: ≤ 17, moderate: 18-24, and high: ≥ 25 points), (C) three PARIS risk strata (low: 0-3, intermediate: 4-7, and high: ≥ 8 points)



Supplementary Fig. 2. Calibration plots showing the predicted (x axis) probability vs observed (y axis) 30-month clinically relevant bleeding-free survival according to PRECISE-DAPT score (A) and PARIS bleeding score (B)

The diagonal line represents the perfect calibration (observed = calibration). Observed clinically relevant bleeding-free survival is represented with 95% confidence intervals (error bars)



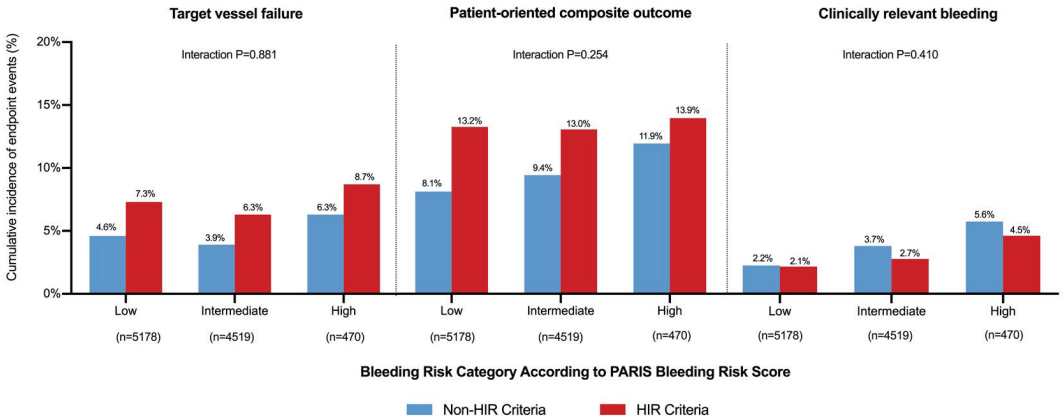
Supplementary Fig. 3. Time-to-Event Curves for TVF (A), POCO (B), and clinically relevant bleeding (C) stratified by the number of ESC/EACTS-endorsed HIR features

HIR = high ischemic risk; POCO = patient-oriented composite outcome; TVF = target vessel failure

Supplementary Table 5. Adjusted HRs for adverse events associated with ESC/EACTS-endorsed HIR features stratified by PARIS bleeding risk score (≥ 8 or < 8)

	Non-HBR (PARIS bleeding risk score < 8; *n* = 9697)			HBR (PARIS bleeding risk score ≥ 8, *n* = 470)			
	HIR (*n* = 4839)	Non-HIR (*n* = 4858)	Adjusted HR (95% CI)*	HIR (*n* = 310)	Non-HIR (*n* = 160)	Adjusted HR (95% CI)*	*P* value for interaction
Target vessel failure	330 (6.8)	209 (4.3)	1.49 (1.25-1.78)	27 (8.7)	10 (6.3)	1.15 (0.55-2.43)	0.595
Patient-oriented composite outcome	634 (13.1)	423 (8.7)	1.47 (1.30-1.67)	43 (13.9)	19 (11.9)	0.92 (0.52-1.61)	0.262
Target lesion failure	272 (5.6)	165 (3.4)	1.54 (1.26-1.87)	24 (7.7)	9 (5.6)	1.11 (0.50-2.44)	0.534
All-cause death	67 (1.4)	43 (0.9)	1.58 (1.06-2.35)	14 (4.5)	10 (6.3)	0.53 (0.21-1.36)	0.347
Cardiovascular death	40 (0.8)	16 (0.3)	2.47 (1.35-4.52)	10 (3.2)	6 (3.8)	0.58 (0.17-1.92)	0.368
Myocardial infarction	126 (2.6)	55 (1.1)	2.08 (1.51-2.88)	12 (3.9)	3 (1.9)	1.69 (0.45-6.34)	0.817
Definite/probable ST	43 (0.9)	17 (0.3)	2.52 (1.42-4.47)	9 (2.9)	2 (1.3)	2.12 (0.43-10.43)	0.802
Any revascularization	502 (10.4)	351 (7.2)	1.42 (1.23-1.63)	26 (8.4)	8 (5.0)	1.46 (0.64-3.33)	0.871
Target vessel revascularization	278 (5.7)	186 (3.8)	1.44 (1.19-1.74)	15 (4.8)	4 (2.5)	1.89 (0.60-5.97)	0.776
Target lesion revascularization	217 (4.5)	140 (2.9)	1.49 (1.20-1.85)	12 (3.9)	3 (1.9)	1.81 (0.49-6.70)	0.764
Stroke	91 (1.9)	60 (1.2)	1.50 (1.08-2.09)	10 (3.2)	5 (3.1)	0.93 (0.29-2.97)	0.485
Clinically relevant bleeding	116 (2.4)	139 (2.9)	1.03 (1.02-1.04)	14 (4.5)	9 (5.6)	1.00 (0.94-1.06)	0.869

Values are number of events (%). *Variables entered into multivariable Cox regression models were as follows: for ischemic endpoints: age, sex, body mass index, hypertension, current smoking, left ventricular ejection fraction, peripheral artery disease, prior revascularization (percutaneous coronary intervention and/or coronary artery bypass graft), acute coronary syndrome, mean stent diameter, type of DES implanted, and DAPT duration (as a time-adjusted covariate); for bleeding endpoints: age, sex, body mass index, hypertension, prior major bleeding event, anemia, oral anticoagulation use at discharge, and DAPT duration (as a time-adjusted covariate).
CI = confidence interval; HR = hazard ratio; HBR = high bleeding risk; HIR = high ischemic risk; MI = myocardial infarction; ST = stent thrombosis



Supplementary Fig. 4. Cumulative Incidence of Endpoint Events according to ESC/EACTS-HIR criteria and bleeding risk categorization

The endpoint events were stratified by ESC/EACTS-endorsed HIR criteria and three bleeding risk categories based on PARIS bleeding risk score. Outcomes were analyzed comparing ESC/EACTS-endorsed HIR criteria among subgroups of patients with low (n=5178), intermediate (n=4519), and high bleeding risk (n=470). Relative impact of ESC/EACTS-endorsed HIR criteria were consistent for the outcomes of TVF, POCO, and clinically relevant bleeding independent of the bleeding risk status.
HIR=high ischemic risk; POCO=patient-oriented composite outcome; TVF=target vessel failure

Supplementary Table 6. Adjusted HRs for adverse events associated with ESC/EACTS-endorsed HIR features stratified by high-risk patient*

	Non-high-risk patients (n=6320)			High-risk (n=3847)			
	HIR (n=2193)	Non-HIR (n=1654)	Adjusted HR (95% CI)*	HIR (n=2956)	Non-HIR (n=3364)	Adjusted HR (95% CI)*	P value for interaction
Target vessel failure	143 (6.5)	68 (4.1)	1.45 (1.08-1.95)	214 (7.2)	151 (4.5)	1.47 (1.19-1.82)	0.870
Patient-oriented composite outcome	280 (12.8)	132 (8.0)	1.57 (1.27-1.95)	397 (13.4)	310 (9.2)	1.38 (1.19-1.61)	0.443
Target lesion failure	118 (5.4)	59 (3.6)	1.38 (1.00-1.90)	178 (6.0)	115 (3.4)	1.58 (1.34-2.02)	0.437
All-cause death	29 (1.3)	8 (0.5)	2.31 (1.03-5.17)	52 (1.8)	45 (1.3)	0.93 (0.61-1.41)	0.053
Cardiovascular death	15 (0.7)	3 (0.2)	2.64 (0.74-9.44)	35 (1.2)	19 (0.6)	1.41 (0.79-2.54)	0.330
Myocardial infarction	60 (2.7)	20 (1.2)	2.19 (1.30-3.68)	78 (2.6)	38 (1.1)	2.04 (1.37-3.04)	0.786
Definite/probable ST	15 (0.7)	5 (0.3)	2.03 (0.72-5.74)	37 (1.3)	14 (0.4)	2.47 (1.31-4.64)	0.757
Any revascularization	214 (9.8)	113 (6.8)	1.39 (1.10-1.76)	314 (10.6)	246 (7.3)	1.44 (1.21-1.71)	0.713
Target vessel revascularization	122 (5.6)	62 (3.7)	1.39 (1.01-1.91)	171 (5.8)	128 (3.8)	1.47 (1.16-1.85)	0.761
Target lesion revascularization	96 (4.4)	52 (3.1)	1.32 (0.93-1.87)	133 (4.5)	91 (2.7)	1.61 (1.22-2.18)	0.347
Stroke	31 (1.4)	18 (1.1)	1.32 (0.72-2.40)	70 (2.4)	47 (1.4)	1.50 (1.02-2.19)	0.672
Clinically relevant bleeding	57 (2.6)	48 (2.9)	1.02 (0.88-1.17)	73 (2.5)	100 (3.0)	0.84 (0.73-0.97)	0.385

*High-risk patient is defined as either ACS presentation and/or HBR (PRECISE-DAPT score ≥ 25).
Values are number of events (%). *Variables entered into multivariable Cox regression models were as follows: for ischemic endpoints: age, sex, body mass index, hypertension, current smoking, left ventricular ejection fraction, peripheral artery disease, prior revascularization (percutaneous coronary intervention and/or coronary artery bypass graft), mean stent diameter, and type of DES implanted; for bleeding endpoints: age, sex, body mass index, hypertension, prior major bleeding event, anemia, oral anticoagulation use at discharge, and DAPT duration (as a time-adjusted covariate).
CI=confidence interval; HR=hazard ratio; HBR=high bleeding risk; HIR=high ischemic risk; MI=myocardial infarction; ST=stent thrombosis