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Parsimonious versus extensive bleeding score: can we simplify risk stratification after percutaneous coronary intervention and reduce bleeding events by de-escalation of the antiplatelet strategy?

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ABSTRACT

Background and aims Due to the multitude of risk factors outlined in the guidelines, personalised dual antiplatelet therapy (DAPT) guidance after percutaneous coronary intervention (PCI) is complex. A simplified method was created to facilitate the use of risk stratification. We aimed to compare the predictive and prognostic value of the 'Zuidoost Nederland Hart Registratie' (ZON-HR) classification for bleeding risk with the PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent DAPT (PRECISE-DAPT) score and to determine the effect of ticagrelor monotherapy versus DAPT in patients with or without high bleeding risk (HBR).

Methods A post hoc analysis of the GLOBAL LEADERS trial was performed to compare the predictive value of the ZON-HR classification with the PRECISE-DAPT score. Also, the outcomes stratified by either method were compared and the interaction of HBR on the treatment effect was determined.

Results The required parameters for the ZON-HR classification (3.7% HBR) and PRECISE-DAPT score (16.6% HBR) were available in 99.9% and 93% of the patients, respectively. The ZON-HR classification had a lower sensitivity (0.09 vs 0.26) and a higher specificity (0.97 vs 0.84), positive predictive value (0.13 vs 0.08) and accuracy (0.92 vs 0.82). Regression analysis showed that both methods predicted hazard for bleeding risk with HRs of 1.87 (95% CI: 1.59 to 2.18) and 2.67 (95% CI: 2.10 to 3.41) for the PRECISE-DAPT score and ZON-HR classification, respectively. The omission of aspirin reduced bleeding events only in acute coronary syndrome (ACS) patients without HBR (HR: 0.74, 95% CI: 0.61 to 0.90, p value for interaction of HBR: 0.04).

Conclusions Stratification for bleeding risk according to the ZON-HR classification was feasible in almost all patients and showed to be more conservative than the PRECISE-DAPT score with a consistent prognostic accuracy. The benefit of aspirin omission was the largest in ACS patients without HBR.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Since the introduction of dual antiplatelet therapy (DAPT), numerous studies have explored varying durations in search of an optimal balance between ischaemic and bleeding events, which resulted in multiple risk models based on patient and PCI characteristics. Due to the multitude of risk factors and risk models, personalised DAPT guidance is complex and rarely implemented in routine practice.

WHAT THIS STUDY ADDS

⇒ The simplified Zuidoost Nederland Hart Registratie (ZON-HR) classification showed a consistent accuracy compared with the acknowledged PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent DAPT score. The benefit of aspirin omission was the largest in acute coronary syndrome patients without high bleeding risk, although this finding should be interpreted with care due to the large variation in group sizes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By increasing the feasibility of bleeding risk stratification after percutaneous coronary intervention (PCI), the ZON-HR classification may augment the use of a patient-tailored antiplatelet strategy after PCI.

Trial registration number NCT01813435.

INTRODUCTION

In the prevention of thromboembolic complications after percutaneous coronary

intervention (PCI), dual antiplatelet therapy (DAPT) has for many years been the unequivocal recommendation in the guidelines.[1 2] Since the introduction of DAPT, numerous studies have explored varying durations in search of an optimal balance between ischaemic and bleeding events.[3] This ongoing pursuit has yielded multiple risk scores that estimate bleeding- and ischaemic event risks post PCI based on patient and PCI characteristics.[4–9] While these risk models have proven effective and are integrated into current guidelines, their practical application is questionable.

Due to the multitude of risk factors outlined in the guidelines, personalised DAPT guidance is complex and rarely implemented in routine practice. To facilitate the adoption and use of risk stratification among clinicians, a consortium in the South East of the Netherlands, the 'Zuidoost Nederland Hart Registratie' (ZON-HR), has developed a simplified classification which includes a limited selection of risk factors provided by previous studies.[4–7] In line with the guidelines of the European Society of Cardiology (ESC), this classification corresponds with the major Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria.[8] The selection of criteria incorporated in this classification was based on their known impact on bleeding risk (as demonstrated in the previously mentioned studies), the expected availability at the time of the procedure and excludes rare diseases. This way it can seamlessly integrate into electronic patient records for immediate stratification post PCI.

This study aimed to externally validate the ZON-HR classification for predicting high bleeding risk (HBR), focusing on patients without oral anticoagulants (OAC). As per the ARC-HBR consensus, patients on OAC are inherently considered HBR, irrespective of other risk factors.

The analysis used the GLOBAL LEADERS trial population[10] and compared the ZON-HR classification with the PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent DAPT (PRECISE-DAPT) score, endorsed by current ESC guidelines and previously validated in the GLOBAL LEADERS population.[11 12] Additionally, the study explored the impact of a de-escalation strategy by comparing P2Y12 inhibitor monotherapy after 1 month of DAPT with 12-month DAPT in patients with or without HBR, leveraging the ZON-HR classification for risk stratification.

METHODS

Study design and participants

In a post hoc analysis of the GLOBAL LEADERS trial (NCT01813435), a multicentre, open-label randomised trial comparing ticagrelor monotherapy following 1 month of DAPT with standard DAPT, we sought to examine the outcomes. The trial encompassed 15 968 patients undergoing PCI for chronic coronary syndrome (CCS) or acute coronary syndrome (ACS), with exclusion criteria applying to those on OAC. Randomisation placed patients into either the experimental group (ticagrelor monotherapy for 24 months after 1 month of ticagrelor plus aspirin) or the control group (DAPT per guidelines: clopidogrel plus aspirin for CCS and ticagrelor plus aspirin for ACS). The follow-up duration was 2 years, with the control group transitioning to aspirin monotherapy after 1 year, aligning with standard practice. Comprehensive study design, protocol, outcome details and information on data sharing are available elsewhere.[13] As this is a post hoc analysis, patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research. For this analysis, we focused on 1-year follow-up data, excluding patients with missing variables essential for the PRECISE-DAPT score or the ZON-HR classification. The Standards for Reporting of Diagnostic Accuracy Studies guidelines[14] were followed in this analysis.

Definitions

The parameters for the ZON-HR classification and PRECISE-DAPT score were derived from the patients' medical history and clinical characteristics at time of enrolment. In the ZON-HR classification, HBR is stratified according to either: a history of intracranial haemorrhage; a previous spontaneous bleeding in the past year with a Bleeding Academic Research Consortium (BARC) Score of at least 2; a haemoglobin level less than 11 g/dL at baseline or an estimated glomerular filtration rate (eGFR) below 30 mL/min at baseline. In the GLOBAL LEADERS trial,[10] previous bleeding was not restricted to bleeding events in the last 12 months before PCI, therefore we replaced this ZON-HR parameter with all prior bleeding events. Furthermore, a history of intracranial haemorrhage was an exclusion criterion for the GLOBAL LEADERS trial. Therefore, no patients met this ZON-HR criterion for HBR. The PRECISE-DAPT score was calculated for each patient based on age, creatinine clearance, haemoglobin concentration, white blood cell count and previous spontaneous bleeding.[5]

Study endpoints

We stratified the patients for HBR according to the ZON-HR classification or a PRECISE-DAPT score ≥25 and assessed the predictive performance and prognostic value of both risk stratification methods for site reported minor and major bleeding events according to the BARC classification and for major adverse cardiac and cerebral events (MACCE), consisting of site reported myocardial infarction, stroke and cardiac death at 1-year follow-up. The analyses were performed in the overall population and in subgroups for PCI indication (ACS and CCS). Furthermore, we assessed whether bleeding risk stratification according to ZON-HR is effective in patients who are randomised to P2Y12 inhibitor monotherapy after 1 month of DAPT instead of 12 months DAPT, and we determined the interaction of HBR according to ZON-HR on the treatment effect.

Statistical analysis

We summarised continuous variables as mean with SD or median with IQR. Categorical variables are summarised as counts and percentages. The predictive value of both methods are evaluated using positive predictive values (PPVs), negative predictive values (NPVs), sensitivity, specificity, accuracy and the corresponding CIs of these metrics. To make a comparison of both classification methods to the c-statistic of the continuous PRECISE-DAPT score, the sensitivity and specificity of the risk stratification according to the ZON-HR classification and according to a PRECISE-DAPT score ≥25 were depicted on the receiver operating characteristic (ROC) curve of the continuous PRECISE-DAPT score. Cohen's kappa coefficient was estimated to evaluate the level of agreement between the two methods.

Cox regression analysis was performed to estimate the HRs and 95% CIs of bleeding events and of MACCE at 1-year follow-up according to bleeding risk. The treatment effects of P2Y12 inhibitor monotherapy versus DAPT were tested for interaction between the HBR and non-HBR subgroups. All data are processed using R V.4.1.3. (R Foundation for Statistical Computing, Vienna, Austria).[15]

RESULTS

Patient population

Of the 15 968 patients included in the GLOBAL LEADERS trial, the parameters for the ZON-HR classification were available in 15 947 (99.9%) patients and the PRECISE-DAPT score could be calculated in 14 928 (93%) patients. This study included only patients with available parameters for both risk stratification methods, which was a total of 14 909 (93%). A flowchart of included patients is presented in online supplemental figure S1. Baseline differences between the included and excluded patients are presented in online supplemental table S1.

Baseline characteristics of the patient population are presented for the included population and stratified for HBR according to either PRECISE-DAPT score ≥25 or the ZON-HR classification (table 1). A total of 2467 (16.6%) patients had HBR according to a PRECISE-DAPT score ≥25 and 555 (3.7%) patients according to the ZON-HR classification, of which 485 were also deemed HBR according to a PRECISE-DAPT score ≥25. Of these 555 patients, 20.9% had an eGFR below 30 mL/min/1.73 m^2, 16.2% had a previous bleeding and 70.5% had an anaemia (7.6% of patients had two risk factors).

In addition to the differences in bleeding risk factors, table 1 shows that patients with HBR according to either classification also have more ischaemic risk factors. Allocated treatment with DAPT for 12 months or ticagrelor for 11 months after 1 month of DAPT was comparable between patients with or without HBR according to either classification.

Predictive value

Table 2 shows the PPV, NPV, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and accuracy of both risk stratifications. Although the incidence of HBR is low according to ZON-HR, these patients more often have BARC 2, 3 and 5 bleeding events (13%) compared with patients with HBR according to the PRECISE-DAPT score (8%). This results in a higher PPV, PLR, NLR and accuracy for the ZON-HR classification.

Figure 1 shows the ROC curves for the prediction of bleeding events of the continuous PRECISE-DAPT score. The sensitivity and specificity of the risk stratification according to ZON-HR and according to a PRECISE-DAPT score ≥25 are depicted on the curves. CCS and ACS subgroups are presented in online supplemental figure S2. The continuous PRECISE-DAPT score showed to have poor predictability in the GLOBAL LEADERS population with an area under the curve (AUC) of 0.60 (95% CI: 0.58 to 0.62) for BARC 2, 3 and 5 bleeding events (panel A) and an AUC of 0.65 (95% CI: 0.61 to 0.68) for BARC 3 and 5 bleedings (panel B). The sensitivity and specificity of the ZON-HR classification for predicting BARC 2, 3 or 5 bleedings lie on the ROC curve with a sensitivity of 0.09 (95% CI: 0.07 to 0.11) and specificity of 0.97 (95% CI: 0.96 to 0.97) compared with 0.26 (95% CI: 0.23 to 0.30) and 0.84 (95% CI: 0.83 to 0.85), respectively, for a PRECISE-DAPT score ≥25. Both methods showed slight better predictive performance for BARC 3 and 5 bleeding events. Cohen's kappa coefficient showed a fair level of agreement between the two methods (K=0.28).

Prognostic value for trial endpoints

Table 3 demonstrates the HRs with corresponding CIs for bleeding events and MACCE in patients with HBR versus no HBR according to the PRECISE-DAPT score and according to ZON-HR. In the overall population, patients with HBR according to either classification showed significant more BARC 2, 3 and 5 and BARC 3 and 5 bleeding events and more MACCE compared with patients without HBR. Subgroup analyses for patients with CCS and ACS showed similar results. The estimated association of the ZON-HR classification with bleeding risk was consistent for patients receiving monotherapy group with an HR of 3.47 (95% CI: 2.53 to 4.75).

The ischaemic and bleeding risks are graphically presented in the online supplemental figure S3 for CCS and ACS subgroups stratified for bleeding risk.

Treatment effect stratified by bleeding risk

The effect of P2Y12 inhibitor monotherapy after 1 month of DAPT compared with DAPT for 1 year on bleeding events stratified by bleeding risk according to ZON-HR is demonstrated separately for CCS and ACS in figure 2.

In the CCS population, clopidogrel plus aspirin was compared with ticagrelor monotherapy after 1 month of ticagrelor plus aspirin. There was no difference between treatment strategies regarding BARC 2, 3 and 5 bleedings in patients with or without HBR. However,

Table 1 Baseline characteristics stratified by HBR according to the PRECISE-DAPT Score≥25 or to the ZON-HR classification

		PRECISE-DAPT			ZON-HR		
	Total included (n=14 909)	HBR (≥25) (n=2467)	Non-HBR (<25) (n=12 442)	P value	HBR (n=555)	Non-HBR (n=14 354)	P value
Age (mean +- SD)	64.6 (10.3)	75.0 (7.9)	62.5 (9.5)	<0.001	69.5 (10.4)	64.4 (10.3)	<0.001
Female Sex	3463 (23.2%)	962 (39.0%)	2501 (20.1%)	<0.001	253 (45.6%)	3210 (22.4%)	<0.001
BMI (mean +- SD)	28.1 (4.6)	28.0 (4.5)	28.1 (4.7)	0.315	27.9 (4.8)	28.1 (4.6)	0.434
Diabetes mellitus (DM)	890 (36.1%)	2908 (23.4%)	3798 (25.5%)	<0.001	230 (41.4%)	3568 (24.9%)	<0.001
Insulin dependent DM	349 (14.1%)	791 (6.4%)	1140 (7.6%)	<0.001	110 (19.8%)	1030 (7.2%)	<0.001
Hypertension	11 057 (74.2%)	2099 (85.1%)	8958 (72.0%)	<0.001	474 (85.4%)	10 583 (73.7%)	<0.001
PVD	943 (6.3%)	254 (10.3%)	689 (5.5%)	<0.001	79 (14.2%)	864 (6.0%)	<0.001
Renal failure							
eGFR<30 mL/min/1.73 m^2	116 (0.8%)	111 (4.5%)	5 (0.0%)	<0.001	116 (20.9%)	0 (0%)	<0.001
eGFR<60 mL/min/1.73 m^2	2065 (13.9%)	1414 (57.3%)	651 (5.2%)	<0.001	281 (50.6%)	1784 (12.4%)	<0.001
Previous bleeding	90 (0.6%)	90 (3.6%)	0 (0%)	<0.001	90 (16.2%)	0 (0%)	<0.001
Anaemia (Hb<11 g/dL)	391 (2.6%)	326 (13.2%)	65 (0.5%)	<0.001	391 (70.5%)	0 (0%)	<0.001
Smoking	3915 (26.3%)	311 (12.6%)	3604 (29.0%)	<0.001	101 (18.2%)	3814 (26.6%)	<0.001
COPD	777 (5.2%)	207 (8.4%)	570 (4.6%)	<0.001	50 (9.0%)	727 (5.1%)	<0.001
Hypercholesterolaemia	10 115 (67.8%)	1697 (68.8%)	8418 (67.7%)	0.496	391 (70.5%)	9724 (67.7%)	0.376
Stroke	397 (2.7%)	117 (4.7%)	280 (2.3%)	<0.001	30 (5.4%)	367 (2.6%)	<0.001
Previous MI	3493 (23.4%)	635 (25.7%)	2858 (23.0%)	0.003	168 (30.3%)	3325 (23.2%)	<0.001
Previous PCI	4909 (32.9%)	888 (36.0%)	4021 (32.3%)	<0.001	3325 (23.2%)	4688 (32.7%)	<0.001
Previous CABG	881 (5.9%)	232 (9.4%)	649 (5.2%)	<0.001	51 (9.2%)	830 (5.8%)	0.001
Indication PCI							
CCS	7761 (52.1%)	1253 (50.8%)	6508 (52.3%)	0.175	292 (52.6%)	7469 (52.0%)	0.823
ACS	7148 (47.9%)	1214 (49.2%)	5934 (47.7%)	0.175	263 (47.4%)	6885 (48.0%)	0.823
Unstable angina	1953 (13.1%)	298 (12.1%)	1655 (13.3%)	0.107	62 (11.2%)	1891 (13.2%)	0.191
NSTEMI	3223 (21.6%)	571 (23.1%)	2652 (21.3%)	0.047	133 (24.0%)	3090 (21.5%)	0.188
STEMI	1972 (13.2%)	345 (14.0%)	1627 (13.1%)	0.237	68 (12.3%)	1904 (13.3%)	0.531
Access site							
Radial	10 914 (73.2%)	1640 (66.5%)	9274 (74.5%)	<0.001	357 (64.3%)	10 557 (73.5%)	<0.001
Femoral	3958 (26.5%)	830 (33.6%)	3128 (25.1%)	<0.001	196 (35.3%)	3762 (26.2%)	<0.001
Treatment							
DAPT	7461 (50.0%)	1227 (49.7%)	6234 (50.1%)	0.755	265 (47.7%)	7196 (50.1%)	0.290
Ticagrelor monotherapy	7448 (50.0%)	1240 (50.3%)	6208 (49.9%)	0.755	290 (52.3%)	7158 (49.9%)	0.290

Sample sizes (n), counts (%), means (±SD) or medians (25–75% IQR). eGFR was based on the Modification of Diet in Renal Disease formula.
COPD, chronic obstructive pulmonary disease
ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HBR, high bleeding risk; MI, myocardial infarction; (N)STEMI, (non) ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent DAPT; PVD, peripheral vascular disease; ZON-HR, Zuidoost Nederland Hart Registratie.

patients with HBR in the experimental group showed a numerical increase of BARC 2, 3 and 5 bleeding events compared with patients with HBR receiving standard treatment with a non-significant HR of 1.57 (95% CI: 0.80 to 3.06) (figure 2A). The cumulative incidence curve of the experimental group shows the strongest increase of bleeding events in the first month after PCI during which the patients received ticagrelor plus aspirin.

In the ACS population, ticagrelor plus aspirin was compared with ticagrelor monotherapy after 1 month of ticagrelor plus aspirin. There was a significant reduction of bleeding events in the experimental group of non-HBR patients which was not observed in patients with HBR, with a significant interaction of the bleeding risk on the treatment effect (figure 2B).

DISCUSSION

Parsimonious versus extensive score

This external validation of the PRECISE-DAPT score and the more concise ZON-HR classification for bleeding risk stratification resulted in several important and clinically

Table 2 Positive predictive values (PPVs), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) with corresponding CIs for the prediction of BARC 2, 3 and 5 bleeding events

Population	PPV (95% CI)	PLR (95% CI)	NPV (95% CI)	NLR (95% CI)	Accuracy (95% CI)
ZON-HR classification					
Total population (n=555)	0.13 (0.10 to 0.16)	2.60 (2.05 to 3.31)	0.95 (0.95 to 0.95)	0.94 (0.92 to 0.96)	0.92 (0.91 to 0.92)
CCS (n=292)	0.12 (0.09 to 0.17)	2.88 (2.07 to 4.02)	0.96 (0.95 to 0.96)	0.93 (0.90 to 0.97)	0.93 (0.92 to 0.93)
ACS (n=263)	0.13 (0.09 to 0.18)	2.37 (1.69 to 3.34)	0.94 (0.94 to 0.95)	0.95 (0.93 to 0.98)	0.91 (0.91 to 0.92)
PRECISE-DAPT score					
Total population (n=2467)	0.08 (0.07 to 0.10)	1.64 (1.45 to 1.86)	0.95 (0.95 to 0.96)	0.88 (0.84 to 0.92)	0.81 (0.80 to 0.82)
CCS (n=1253)	0.07 (0.06 to 0.09)	1.64 (1.37 to 1.97)	0.96 (0.95 to 0.96)	0.88 (0.83 to 0.94)	0.82 (0.81 to 0.82)
ACS (n=1214)	0.10 (0.08 to 0.11)	1.63 (1.39 to 1.93)	0.95 (0.94 to 0.95)	0.88 (0.83 to 0.93)	0.80 (0.79 to 0.81)

ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CCS, chronic coronary syndrome; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent dual antiplatelet therapy; ZON-HR, Zuidoost Nederland Hart Registratie.

relevant findings: In comparison to the PRECISE-DAPT score, risk stratification was more frequently possible with the ZON-HR classification. Due to the small number of commonly available risk factors, only 0.1% of the included patients in the GLOBAL LEADERS trial lacked one or more parameters required by the ZON-HR classification. This finding emphasises the main advantage of a parsimonious classification compared with a more extensive risk score. Using only variables that are commonly available periprocedural, it is more feasible for the treating physician to provide a patient-tailored antiplatelet strategy based on the bleeding risk, as is supported by the guidelines.[2] The feasibility of the currently available risk scores seems to be a pitfall as practical use is limited and the predictive capacities are poor or moderate.[11 16]

The ZON-HR classification was relatively conservative in the prediction of bleeding risk compared with the more liberal PRECISE-DAPT score, as only 3.7% of the included population had HBR according to ZON-HR compared with 16.6% according to a PRECISE-DAPT score ≥25. This conservative character of the ZON-HR classification showed several advantages and disadvantages compared with the PRECISE-DAPT score. The PPV and the specificity of the ZON-HR classification were higher, indicating that patients with low bleeding risk are less often unjustly stratified to HBR. This creates the possibility to even extend antiplatelet therapy based on thromboembolic risk in these patients, which would otherwise be advised against based on the supposed bleeding risk.

However, the ZON-HR classification may be too conservative, as the sensitivity showed to be very low indicating that a high number of patients with bleeding events were stratified to non-HBR. As the ZON-HR classification is binary, no AUC could be calculated. In order to make a comparison to the PRECISE-DAPT score, the sensitivity and specificity of both the ZON-HR classification and a PRECISE-DAPT score ≥25 were depicted on the ROC curve of the continuous PRECISE-DAPT score. The ZON-HR classification showed to lie on the ROC curve of the PRECISE-DAPT score, this suggests a comparable accuracy of the two methods in the prediction of bleeding risk. Cox regression analysis of the two methods showed that both are capable to discriminate for the risk of a bleeding as bleeding events were significantly more common in patients with HBR according to either method. This was similar for all bleedings (BARC 2, 3 and 5) and for major bleedings (BARC 3 and 5) only. The ZON-HR classification showed slightly higher HRs for bleeding events compared with the PRECISE-DAPT score. In combination with the sensitivity and specificity, this may indicate that the ZON-HR classification mainly identifies patients with a very high risk of bleeding but disregards patients with less high risk of bleeding. Although the two stratification methods partly use the same risk factors, a difference in performance can be explained by the cumulative versus separate contribution of the risk factors to the bleeding risk. According to the ZON-HR method, the separate risk factors are regarded as predictor for bleeding risk, as opposed to the cumulative contribution of the risk factors in the PRECISE-DAPT score.

Our findings are in line with a recent study that compared a simplified clinical evaluation tool in elderly patients, consisting of three major ARC-HBR criteria. Although the selection of criteria was slightly different in this study, it also proved effective in the prediction of major bleedings in elderly patients when compared with the PRECISE-DAPT score and the ARC-HBR criteria.[17] This further supports the concept of a small selection of common risk factors as a feasible tool for the prediction of bleeding risk.

Treatment effect

The cumulative event curves of treatment effect showed that P2Y12 inhibitor monotherapy only reduced bleeding events in ACS patients without HBR. This is consistent with previous findings within the GLOBAL LEADERS population.[18] Apart from clinical presentation, these results could be attributed to differences in treatment in the control group between patients with CCS and

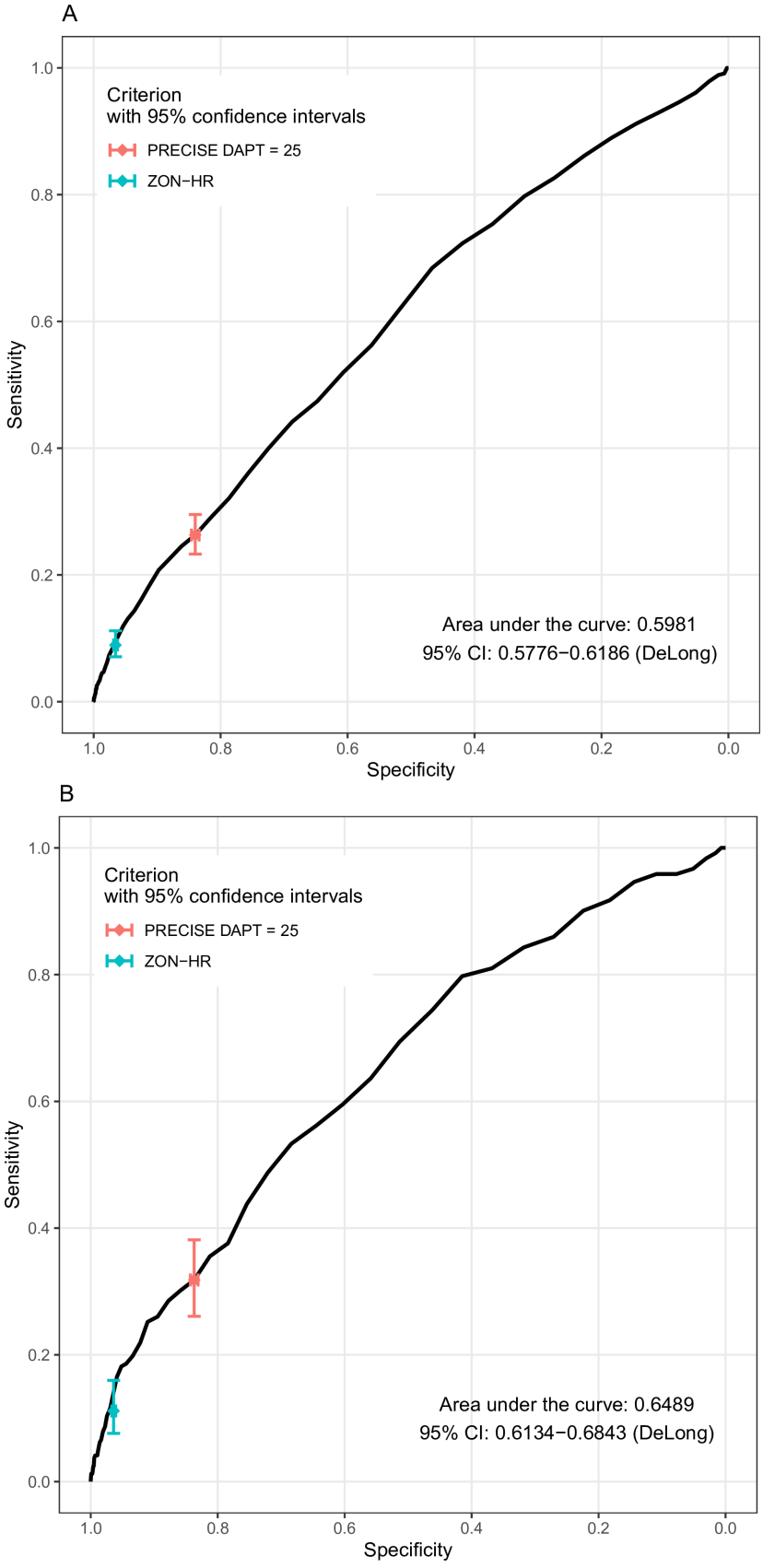

Figure 1 Receiver operating characteristics (ROC) curve of continuous PRECISE-DAPT score with the sensitivity and specificity of the PRECISE-DAPT score ≥25 and of the ZON-HR classification for BARC 2, 3 and 5 bleeding events (A) and BARC 3 and 5 bleeding events (B) depicted on the ROC curve. BARC, Bleeding Academic Research Consortium; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent dual antiplatelet therapy; ZON-HR, Zuidoost Nederland Hart Registratie.

Table 3 HRs and CIs of HBR versus non-HBR according to PRECISE-DAPT score and ZON-HR for BARC 2, 3 and 5 bleedings and BARC 3 and 5 bleedings and for MACCE

	PRECISE-DAPT			ZON-HR		
	HBR (≥25)	Non-HBR (<25)	HR (95% CI)	HBR	Non-HBR	HR (95% CI)
Overall	**N=2467**	**N=12 442**		**N=555**	**N=14 354**	
BARC 2, 3 and 5 bleedings	209 (8.47%)	586 (4.71%)	1.87 (1.59 to 2.18)	71 (12.79%)	724 (5.04%)	2.67 (2.10 to 3.41)
BARC 3 and 5 bleedings	77 (3.12%)	165 (1.33%)	2.42 (1.85 to 3.17)	27 (4.86%)	215 (1.50%)	3.38 (2.27 to 2.27)
MACCE (cardiac death, MI, stroke)	158 (6.40%)	354 (2.85%)	2.31 (1.92 to 2.79)	47 (8.47%)	465 (3.24%)	2.68 (1.99 to 3.62)
Patients with CCS	**N=1253**	**N=6508**		**N=292**	**N=7469**	
BARC 2, 3 and 5 bleedings	93 (7.42%)	268 (4.12%)	1.86 (1.47 to 2.35)	36 (12.32%)	325 (4.35%)	2.97 (2.11 to 4.19)
BARC 3 and 5 bleedings	34 (2.71%)	66 (5.27%)	2.75 (1.82 to 4.15)	13 (4.45%)	87 (1.16%)	3.97 (2.21 to 7.10)
MACCE (cardiac death, MI, stroke)	57 (4.55%)	165 (2.54%)	1.83 (1.36 to 2.48)	16 (5.48%)	206 (2.76%)	2.02 (1.22 to 3.36)
Patients with ACS	**N=1214**	**N=5934**		**N=263**	**N=6885**	
BARC 2, 3 and 5 bleedings	116 (9.56%)	318 (5.36%)	1.86 (1.50 to 2.30)	35 (13.31%)	399 (5.80%)	2.44 (1.72 to 3.44)
BARC 3 and 5 bleedings	43 (3.54%)	99 (1.67%)	2.19 (1.53 to 3.13)	14 (5.32%)	128 (1.86%)	2.99 (1.72 to 5.19)
MACCE (cardiac death, MI, stroke)	101 (8.32%)	189 (3.19%)	2.70 (2.12 to 3.43)	31 (11.79%)	259 (3.76%)	3.25 (2.24 to 4.71)

Total population and subgroups of CCS on DAPT, ACS on DAPT, CCS on monotherapy and ACS on monotherapy.
BARC, Bleeding Academic Research Consortium; CCS/ACS, chronic/acute coronary syndrome; HBR, high bleeding risk; MACCE, major adverse cardiac and cerebral events ; MI, myocardial infarction; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent dual antiplatelet therapy; ZON-HR, Zuidoost Nederland Hart Registratie.

ACS. In patients with CCS, clopidogrel plus aspirin was compared with ticagrelor monotherapy after 1 month of ticagrelor plus aspirin which may have resulted in comparable numbers of bleeding between treatment groups. Compared with clopidogrel and aspirin, CCS patients with HBR according to ZON-HR treated with ticagrelor showed a non-significant higher number of bleeding events which suggests that patients with (very) high risk of bleeding may experience more harm of ticagrelor (monotherapy) compared with clopidogrel plus aspirin. This effect was the strongest in the first days after PCI and indicates that the risk of bleeding is the highest in this period which corresponds to previous findings.[19] In patients with ACS, the control group received ticagrelor plus aspirin, which provided a fairer comparison to ticagrelor monotherapy. Our results showed that ACS patients with HBR did not benefit from ticagrelor monotherapy. In this population, the (non-significant) higher number of bleeding events in the HBR subgroup cannot be explained by antiplatelet regime as both treatment groups received ticagrelor. However, the fact that treatment with ticagrelor monotherapy did not result in a reduction of bleeding events in patients with HBR as opposed to non-HBR patients might be attributed to the potency of ticagrelor. The omission of aspirin may not be enough de-escalation in patients with HBR when co-treated with ticagrelor to prevent a bleeding event. Previous studies showed that the omission of aspirin after 1 month reduces bleeding events in patients with HBR when co-treatment (mainly) consists of clopidogrel.[20 21] A substudy of the TWILIGHT trial[22] showed similar results when comparing ticagrelor monotherapy after 3 months of DAPT to ticagrelor plus aspirin in patients with HBR. The difference in outcomes between the TWILIGHT substudy and the results found in the GLOBAL LEADERS population may be attributed to the difference in DAPT duration in the experimental groups and the differences in risk stratification, which was performed according to the ARC-HBR criteria in TWILIGHT-HBR, or by differences between inclusion and exclusion criteria. Furthermore, the relative small group size of patients with HBR may have influenced the outcomes. As our study design and outcomes are different compared with previous studies, the results regarding treatment effect should be regarded purely as hypothesis generating and require further investigation. The differences between study outcomes and the combined study effect of ticagrelor monotherapy after a short period of DAPT compared with standard DAPT in patients with or without HBR has previously been investigated and showed a comparable treatment effect.[23] The ZON-HR bleeding risk classification has been implemented within the participating centres of the ZON-HR consortium in which patients with HBR receive a shortened DAPT duration. The clinical effect of shortened DAPT in this population will be determined in future analyses.

Limitations

This external validation has several limitations. Most importantly, the inclusion and exclusion criteria of the

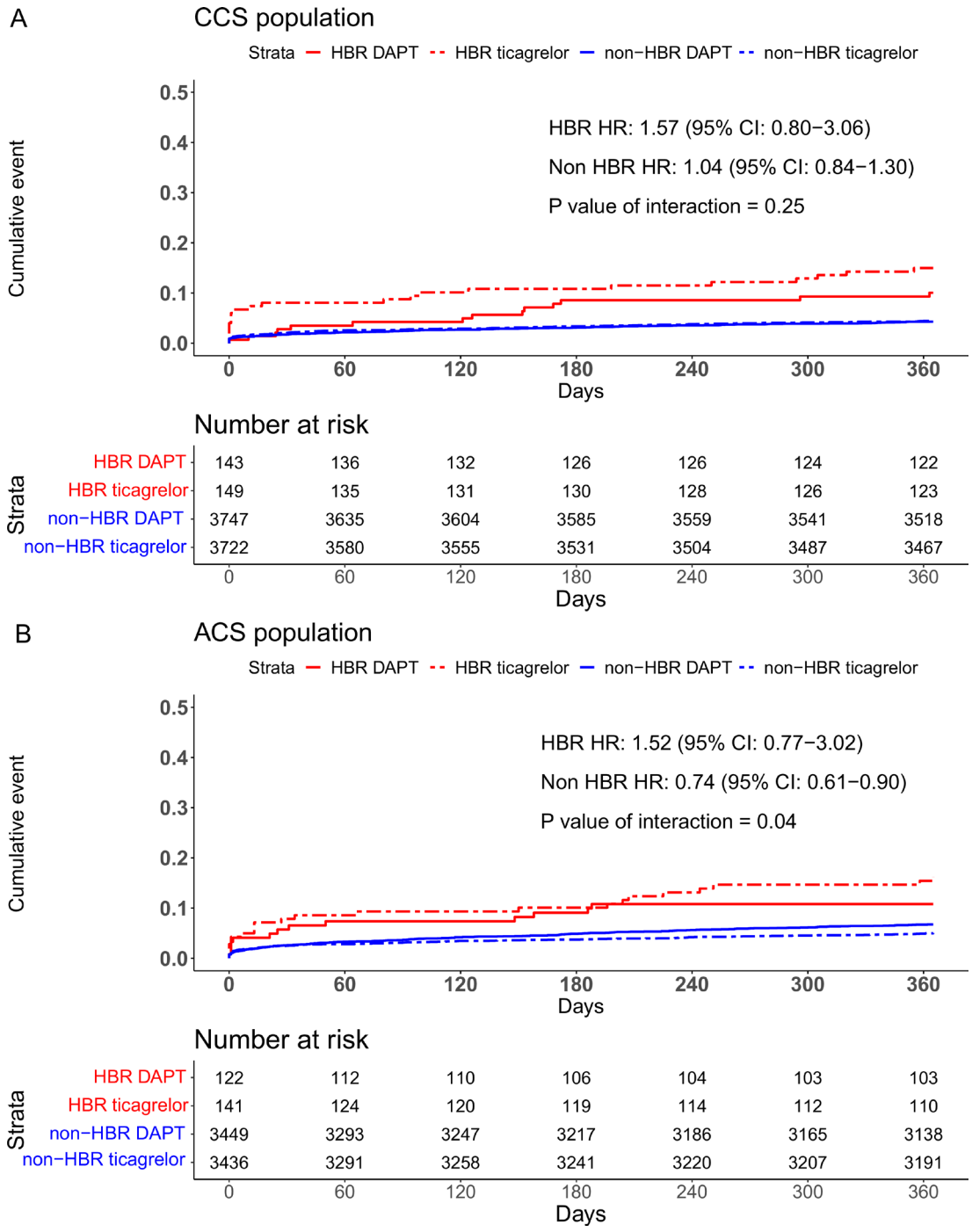

Figure 2 Treatment effect according to risk stratification in patients with CCS and ACS. ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; HBR, high bleeding risk.

GLOBAL LEADERS trial caused selection bias of the patient population. This may explain the low number of patients with HBR as the study population may have been of relatively low risk. This could also explain the relatively low c-statistic of 0.60 of the continuous PRECISE-DAPT score when compared with the derivation cohort in which the AUC showed to be 0.70 (95% CI: 0.65 to 0.74)[5] and to a previous external validation in an all-comers PCI registration showing an AUC of 0.66 (95% CI: 0.61 to 0.71).[5] Therefore, the results of our analyses cannot be directly translated to an all-comers PCI population. Also, the GLOBAL LEADERS mainly consists of a western population and included less than 1% Asian patients. East Asian patients are known to have a higher risk of bleeding events[24] and therefore may require an adjusted risk stratification such as the Japanese HBR criteria. However, it has recently been demonstrated that these criteria have a similar discriminative ability compared with the ARC-HBR criteria and the PRECISE-DAPT score in a Japanese population.[25] Furthermore, a history of intracranial haemorrhage was an exclusion criterion in the GLOBAL LEADERS trial. This is one of the four criteria of the

ZON-HR classification. As no patient fulfilled this criterion in this study, the effect of a previous intracranial haemorrhage on bleeding events could not be measured. Lastly, the analyses relating to various subgroups in the study were not part of the original study design, and it is possible that power was insufficient to detect important differences between the risk stratification methods and treatment strategies.

CONCLUSION

The ZON-HR classification demonstrated higher feasibility compared with the PRECISE-DAPT score, properly identifying bleeding risk with a selection of a limited set of commonly available ARC-HBR criteria. While conservative, it provided accuracy which was consistent with the PRECISE-DAPT Score. Notably, aspirin omission reduced bleeding events solely in ACS patients without HBR, emphasising the need for a robust de-escalation strategy in this subgroup. However, limitations in patient selection, demographic diversity and group sizes warrant caution in generalising these findings.

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