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ORIGINAL ARTICLE
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PRECISE-DAPT score for bleeding risk prediction in patients on dual or single antiplatelet regimens: insights from the GLOBAL LEADERS and GLASSY

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Aims The five-item PRECISE-DAPT, integrating age, haemoglobin, white-blood-cell count, creatinine clearance, and prior bleeding, predicts bleeding risk in patients on dual antiplatelet therapy (DAPT) after stent implantation. We sought to assess whether the bleeding risk prediction offered by the PRECISE-DAPT remains valid among patients receiving ticagrelor monotherapy from 1 month onwards after coronary stenting instead of standard DAPT and having or not having centrally adjudicated bleeding endpoints.

Methods and results The PRECISE-DAPT was calculated in 14 928 and 7134 patients from GLOBAL LEADERS and GLASSY trials, respectively. The ability of the score to predict Bleeding Academic Research Consortium 3 or 5 bleeding was assessed and compared among patients on ticagrelor monotherapy (experimental strategy) or standard DAPT (reference strategy) from 1 month after drug-eluting stent implantation. Bleeding endpoints were investigator-reported or centrally adjudicated in GLOBAL LEADERS and GLASSY, respectively. At 2 years, the *c*-indexes for

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the score among patients treated with the experimental or reference strategy were 0.67 [95% confidence interval (CI): 0.63–0.71] vs. 0.63 (95% CI: 0.59–0.67) in GLOBAL LEADERS ($P = 0.27$), and 0.67 (95% CI: 0.61–0.73) vs. 0.66 (95% CI: 0.61–0.72) in GLASSY ($P = 0.88$). Decision curve analysis showed net benefit using the PRECISE-DAPT to guide bleeding risk assessment under both treatment strategies. Results were consistent between investigator-reported and adjudicated endpoints and using the simplified four-item PRECISE-DAPT.

Conclusion The PRECISE-DAPT offers a prediction model that proved similarly effective to predict clinically relevant bleeding among patients on ticagrelor monotherapy from 1 month after coronary stenting compared with standard DAPT and appears to be unaffected by the presence or absence of adjudicated bleeding endpoints.

Keywords Dual antiplatelet therapy • Ticagrelor • Aspirin • Bleeding • Percutaneous coronary intervention

Introduction

Dual antiplatelet therapy (DAPT) reduces the risk of stent-related and spontaneous ischaemic events in patients undergoing percutaneous coronary intervention (PCI).[1–4] This benefit comes with an increased risk of bleeding, which can offset the ischaemic benefit and adversely impact prognosis.[3,4] Therefore, the assessment of bleeding risk after PCI is crucial to guide clinicians' decisions with respect to antiplatelet therapies.[1,5] The PRECISE-DAPT is a five-item score that has been developed to predict bleeding risk during DAPT[6] and was endorsed by a Class IIB recommendation to identify high bleeding risk patients (i.e. score ≥25), in whom the benefits of shorter DAPT (i.e. 3–6 months) can outweigh the risks of extended treatment duration.[1,7] Since its generation, the performance of the score has been tested in contemporary PCI cohorts treated with standard DAPT consisting of aspirin plus a P2Y12 inhibitor (i.e. 6–12 months) followed by aspirin monotherapy.[8–10] Recently, several trials have challenged current DAPT paradigm and provided evidence that early discontinuation of aspirin followed by the continuation of potent P2Y12 inhibitors is able to reduce overall bleeding risks without an apparent trade-off in efficacy.[11–14] Whether PRECISE-DAPT score retains consistent bleeding risk prediction capability in patients receiving potent P2Y12 inhibitor monotherapy is unclear. Moreover, no study so far has assessed whether the PRECISE-DAPT performance might be affected by the presence or absence of centrally adjudicated bleeding endpoints, which carries relevant implications for practice.

The GLOBAL LEADERS trial[11] and its Adjudication Sub-Study (GLASSY)[15] randomized patients to receive 1-month DAPT followed by 23-month ticagrelor monotherapy or 12-month DAPT followed by aspirin alone after new-generation drug-eluting stenting.

We sought to assess the performance of PRECISE-DAPT score to predict bleeding risk in patients receiving either ticagrelor 90 mg twice daily monotherapy from 1 month after PCI or standard DAPT in the setting of GLOBAL LEADERS, based on investigator-reported endpoints, and GLASSY, based on centrally adjudicated endpoints.

Methods

Study design and participants

GLOBAL LEADERS (NCT01813435) is a multicenter randomized trial investigating two antiplatelet strategies in all-comer patients receiving drug-eluting stent for acute coronary syndromes (ACS) or stable coronary artery disease (CAD).[11] After coronary angiography, 15 991 patients were randomized (1:1) using a web-based-system stratified by centre and clinical presentation. The experimental strategy consisted of 1-month DAPT (aspirin 75–100 mg plus ticagrelor 90 mg b.i.d.) followed by 23-month ticagrelor 90 mg b.i.d. monotherapy. The reference strategy consisted of standard 12-month DAPT (aspirin 75–100 mg plus clopidogrel 75 mg if stable CAD or ticagrelor 90 mg b.i.d. if ACS) followed by aspirin alone for 12 months.

GLASSY (NCT03231059) is a sub-study of the GLOBAL LEADERS including adjudicated events from all 7585 patients enrolled at the 20 highest recruiting sites, whereby investigator-reported events and triggered potential unreported events were centrally adjudicated by an independent Clinical Events Committee (CEC) blinded to treatment groups.[15]

All participants provided written informed consent. The protocols were approved by ethic committees of participating institutions.

PRECISE-DAPT score calculation

The PRECISE-DAPT is a five-item bleeding risk score, which has been generated for the prediction of thrombosis in myocardial infarction (TIMI) out-of-hospital bleeding in patients on DAPT using age, creatinine clearance, white-blood-cell count, haemoglobin, and history of bleeding at baseline.[6] The PRECISE-DAPT has the potential to inform clinicians' decision with respect to the optimal DAPT duration post PCI, selecting high bleeding risk patients (score ≥25) for a shorter treatment (i.e. 3–6 months) and non-high-risk patients for prolonged treatment (i.e. ≥12 months). A simplified four-item version of the score, lacking white-blood-cells count, has also been developed and validated.[16] In the present analysis, PRECISE-DAPT was calculated and assigned to each participant as in the development cohort. The simplified four-item version of the score was also computed.[6] All data for score calculations were prospectively collected.

Study endpoints

The primary endpoint was bleeding type 3 or 5 defined according to the Bleeding Academic Research Consortium (BARC) scale,[17] which was investigator-reported in GLOBAL LEADERS and CEC-adjudicated in GLASSY. The primary endpoint was analysed in the overall populations and separately in the experimental and control groups, and across 2 years or with landmark at 1 year.

Statistical analysis

The PRECISE-DAPT score was calculated using data collected at index PCI. Patients were stratified into four groups according to study treatment and PRECISE-DAPT (≥25 vs. <25). Continuous variables are expressed as mean (standard deviation) or median (interquartile range),

and categorical variables as numbers and percentages. Differences were calculated using *t*-test and Wilcoxon test for continuous data and χ^2 or Fisher's tests for categorical data. Kaplan–Meier method was used to estimate cumulative event rates and log-rank test to examine differences across score strata. The association between the primary endpoint and risk categories was calculated as hazard ratios (HR), considering very-low risk patients as reference. Discrimination was assessed using Harrell's *c*-statistic, and compared through treatment strategies using a nonparametric test. Calibration was assessed by Grønnesby–Borgan χ^2 test and plotted as observed vs. predicted outcomes using Arjas plots. Continuous relation between the risk (as HR) and incidence of BARC 3 or 5 bleeding at follow-up and PRECISE-DAPT was assessed using restricted cubic splines. Net clinical benefit was determined by means of decision curve analyses.[18] All analyses were performed at 2 years and with landmark at 1 year. A two-sided $P < 0.05$ was considered statistically significant. Analyses were performed using STATA 16.1 (Stata Corp., College Station, TX, USA).

Results

Study patients

Of the 15 991 and 7585 patients enrolled in GLOBAL LEADERS and GLASSY, the PRECISE-DAPT was available in 14 928 (93.3%) and 7134 (94.0%), respectively. The mean score was 16.5 ± 8.8 in the parental trial and 16.5 ± 8.7 in the adjudication sub-study, while the median score was 15.0 (interquartile range: 10.0–21.0) in both studies (*Tables 1* and *2*). A total of 2483 (16.6%) patients in GLOBAL LEADERS and 1180 (16.5%) in GLASSY had a PRECISE-DAPT score ≥25. Score distribution was similar in the experimental and control groups (*Figure 1*).

In both studies, baseline characteristics were well balanced between the experimental and control group within PRECISE-DAPT strata (*Tables 1* and *2* and Supplementary material online). Patients with high vs. non-high PRECISE-DAPT differed for the 5 score covariates and were more frequently female, had lower body-mass index and higher rates of cardiovascular risk factors, prior myocardial infarction, coronary revascularization, and stroke; they also received less frequent radial access, single lesion intervention, or direct stenting.

Bleeding risk stratification by PRECISE-DAPT score

The risk of bleeding as estimated by Kaplan–Meier event curves differed significantly according to PRECISE-DAPT score with similar stratification effect for the experimental and reference strategy (*Figure 2*). At 2 years, GLOBAL LEADERS patients with

Table 1 Baseline characteristics of the GLOBAL LEADERS population stratified by PRECISE-DAPT

	PRECISE-DAPT ≥25			PRECISE-DAPT <25			
	Experimental group (*n* = 1248)	Control group (*n* = 1235)	*P*-value	Experimental group (*n* = 6210)	Control group (*n* = 6235)	*P*-Value	*P*-value ≥25 vs. <25
Age (years)	74.9 ± 8.0	75.0 ± 7.9	0.58	62.5 ± 9.5	62.5 ± 9.5	0.93	<0.001
Females	499 (40.0%)	470 (38.1%)	0.34	1261 (20.3%)	1241 (19.9%)	0.57	<0.001
Body mass index (kg/m^2)	28.0 ± 4.5	27.9 ± 4.7	0.59	28.2 ± 4.6	28.3 ± 4.6	0.69	0.001
Diabetes mellitus	465 (37.3%)	432 (35.0%)	0.22	1463 (23.6%)	1446 (23.2%)	0.62	<0.001
Insulin-dependent diabetes mellitus	174 (14.0%)	176 (14.3%)	0.86	389 (6.3%)	402 (6.5%)	0.68	<0.001
Hypertension	1092 (87.6%)	1019 (82.7%)	0.001	4475 (72.3%)	4486 (72.2%)	0.87	<0.001
Hypercholesterolaemia	847 (70.3%)	854 (70.8%)	0.82	4167 (69.5%)	4253 (70.5%)	0.23	0.55
Current smoker	160 (12.8%)	154 (12.5%)	0.80	1776 (28.6%)	1830 (29.4%)	0.36	<0.001
Previous myocardial infarction	309 (24.8%)	332 (27.0%)	0.23	1408 (22.7%)	1450 (23.3%)	0.45	0.002
Previous PCI	433 (34.8%)	461 (37.4%)	0.18	2013 (32.4%)	2008 (32.2%)	0.81	<0.001
Previous coronary artery by-pass graft	107 (8.6%)	127 (10.3%)	0.15	307 (4.9%)	342 (5.5%)	0.18	<0.001
Previous stroke	57 (4.6%)	60 (4.9%)	0.77	142 (2.3%)	138 (2.2%)	0.80	<0.001
Peripheral vascular disease	125 (10.1%)	130 (10.6%)	0.74	324 (5.3%)	365 (5.9%)	0.12	<0.001
Previous major bleeding	43 (3.5%)	47 (3.8%)	0.66	0 (0.0%)	0 (0.0%)	—	<0.001
Impaired renal function	721 (57.8%)	694 (56.2%)	0.44	329 (5.3%)	322 (5.2%)	0.74	<0.001
Chronic obstructive pulmonary disease	104 (8.4%)	103 (8.4%)	1.00	278 (4.5%)	293 (4.7%)	0.54	<0.001
Clinical presentation							
Stable coronary artery disease	619 (49.6%)	637 (51.6%)	0.33	3255 (52.4%)	3255 (52.2%)	0.81	0.11
Acute coronary syndrome	629 (50.4%)	598 (48.4%)	0.33	2955 (47.6%)	2980 (47.8%)	0.81	0.11
Unstable angina	161 (12.9%)	148 (12.0%)	0.50	813 (13.1%)	842 (13.5%)	0.50	0.25
Non-STEMI	272 (21.8%)	301 (24.4%)	0.12	1329 (21.4%)	1323 (21.2%)	0.81	0.05
STEMI	196 (15.7%)	149 (12.1%)	0.009	813 (13.1%)	815 (13.1%)	0.97	0.28
PRECISE-DAPT							
Mean score	31.4 ± 6.6	31.0 ± 6.3	0.11	13.6 ± 5.8	13.6 ± 5.8	0.96	
Median score	29.0 (27.0–34.0)	29.0 (27.0–33.0)	0.28	14.0 (9.0–18.0)	14.0 (9.0–18.0)	0.95	

Sample sizes (*n*), counts (%), means (±standard deviations), or medians (25–75% interquartile range).
PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Table 2 Baseline characteristics of the GLASSY population stratified by PRECISE-DAPT

	PRECISE-DAPT score ≥25			PRECISE-DAPT score <25			
	Experimental group (*n* = 607)	Control group (*n* = 573)	*P*-Value	Experimental group (*n* = 2956)	Control group (*n* = 2998)	*P*-Value	*P*-Value ≥25 vs. <25
Age (years)	75.5 ± 7.7	75.9 ± 7.6	0.48	62.8 ± 9.4	62.7 ± 9.5	0.62	<0.001
Females	256 (42.2%)	225 (39.3%)	0.31	606 (20.5%)	603 (20.1%)	0.72	<0.001
Body mass index (kg/m^2)	27.8 ± 4.3	27.5 ± 4.4	0.32	28.0 ± 4.6	28.0 ± 4.5	0.75	0.02
Diabetes mellitus	213 (35.1%)	195 (34.0%)	0.71	656 (22.2%)	663 (22.1%)	0.95	<0.001
Insulin-dependent diabetes mellitus	80 (13.2%)	75 (13.1%)	1.00	166 (5.6%)	175 (5.8%)	0.73	<0.001
Hypertension	525 (86.5%)	473 (82.5%)	0.06	2117 (71.6%)	2146 (71.6%)	1.00	<0.001
Hypercholesterolaemia	397 (65.4%)	379 (66.1%)	0.89	1897 (64.2%)	2002 (66.8%)	0.02	0.72
Current smoker	96 (15.8%)	83 (14.5%)	0.57	932 (31.5%)	962 (32.1%)	0.65	<0.001
Previous myocardial infarction	149 (24.5%)	165 (28.8%)	0.09	666 (22.5%)	683 (22.8%)	0.85	0.004
Previous PCI	204 (33.6%)	234 (40.8%)	0.01	950 (32.1%)	984 (32.8%)	0.58	0.002
Previous coronary artery by-pass graft	39 (6.4%)	55 (9.6%)	0.05	154 (5.2%)	170 (5.7%)	0.45	0.001
Previous stroke	33 (5.4%)	25 (4.4%)	0.42	62 (2.1%)	66 (2.2%)	0.79	<0.001
Peripheral vascular disease	79 (13.0%)	74 (12.9%)	1.00	165 (5.6%)	207 (6.9%)	0.03	<0.001
Previous major bleeding	25 (4.1%)	18 (3.1%)	0.43	0 (0.0%)	0 (0.0%)	–	<0.001
Impaired renal function	349 (57.5%)	315 (55.0%)	0.41	142 (4.8%)	152 (5.1%)	0.67	<0.001
Chronic obstructive pulmonary disease	53 (8.7%)	56 (9.8%)	0.61	136 (4.6%)	139 (4.6%)	0.95	<0.001
Clinical presentation							
Stable coronary artery disease	260 (42.8%)	268 (46.8%)	0.17	1449 (49.0%)	1488 (49.6%)	0.64	0.004
Acute coronary syndrome	347 (57.2%)	305 (53.2%)	0.17	1507 (51.0%)	1510 (50.4%)	0.64	0.004
Unstable angina	83 (13.7%)	67 (11.7%)	0.33	392 (13.3%)	418 (13.9%)	0.45	0.42
Non-STEMI	138 (22.7%)	148 (25.8%)	0.22	588 (19.9%)	559 (18.6%)	0.22	<0.001
STEMI	126 (20.8%)	90 (15.7%)	0.02	527 (17.8%)	533 (17.8%)	0.97	0.67
PRECISE-DAPT							
Mean score	31.3 ± 6.7	30.6 ± 5.9	0.68	13.6 ± 5.7	13.6 ± 5.8	0.65	
Median score	29.0 (26.0–34.0)	29.0 (26.0–33.0)	0.27	14.0 (9.0–18.0)	14.0 (9.0–18.0)	0.69	

Sample sizes (*n*), counts (%), means (±standard deviations), or medians (25–75% interquartile range).
PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

PRECISE-DAPT ≥25 had significantly increased risk of BARC 3 or 5 bleeding in both the experimental group [HR: 4.37; 95% confidence interval (CI): 2.64–7.23; $P < 0.001$] and control group (HR: 3.81; 95% CI: 2.30–6.30; $P < 0.001$) compared with the reference (score ≤10). In GLASSY, patients with high PRECISE-DAPT showed an HR of 4.71 in the experimental group (95% CI: 2.44–9.07; $P < 0.001$) and of 3.39 in the control group (95% CI: 1.78–6.57; $P < 0.001$). Results were consistent in the overall study populations (Supplementary material online, *Figure S1*).

The PRECISE-DAPT showed a continuous association with the risk (in terms of HR) as well as the incidence of BARC 3 or 5 bleeding at 1 and 2 years, which was consistent between the experimental and control groups (*Figure 3* and Supplementary material online, *Figures S2 and S3*).

PRECISE-DAPT performance for bleeding prediction

PRECISE-DAPT was effective to predict BARC 3 or 5 bleeding in patients receiving either the experimental or reference strategy (*Tables* 3 and 4 and Supplementary material online, *Figures S4 and S5*).

In GLOBAL LEADERS, the score showed moderate discrimination with *c*-index of 0.67 (95% CI: 0.63–0.71) in the experimental group vs. 0.63 (95% CI: 0.59–0.67) in the control group at 2 years ($P = 0.27$). In GLASSY, the *c*-index was 0.67 (95% CI: 0.61–0.73) in the experimental group and 0.66 (95% CI: 0.61–0.72) in the control group ($P = 0.88$). The score was moderately calibrated in both treatment strategies, although the predicted and observed probability approximated more closely in GLOBAL LEADERS than GLASSY.

Results were consistent at landmark analysis. In GLOBAL LEADERS, *c*-index estimates during the first and second year of follow-up were 0.68 and 0.64 in the experimental group, and 0.62 and 0.66 in the control group, respectively. Similarly, in GLASSY, *c*-index values before and after the 1-year landmark were 0.69 and 0.61 in the experimental arm, and 0.64 and 0.75 in the control arm (*Tables 3* and 4 and Supplementary material online, *Figure S5*).

Discriminative ability of the four-item PRECISE-DAPT was similar to the score including white-blood-cell count and consistent with respect to randomized treatment strategies, although this score iteration appeared less well calibrated (*Tables 3* and 4 and Supplementary material online, *Figure S6*).

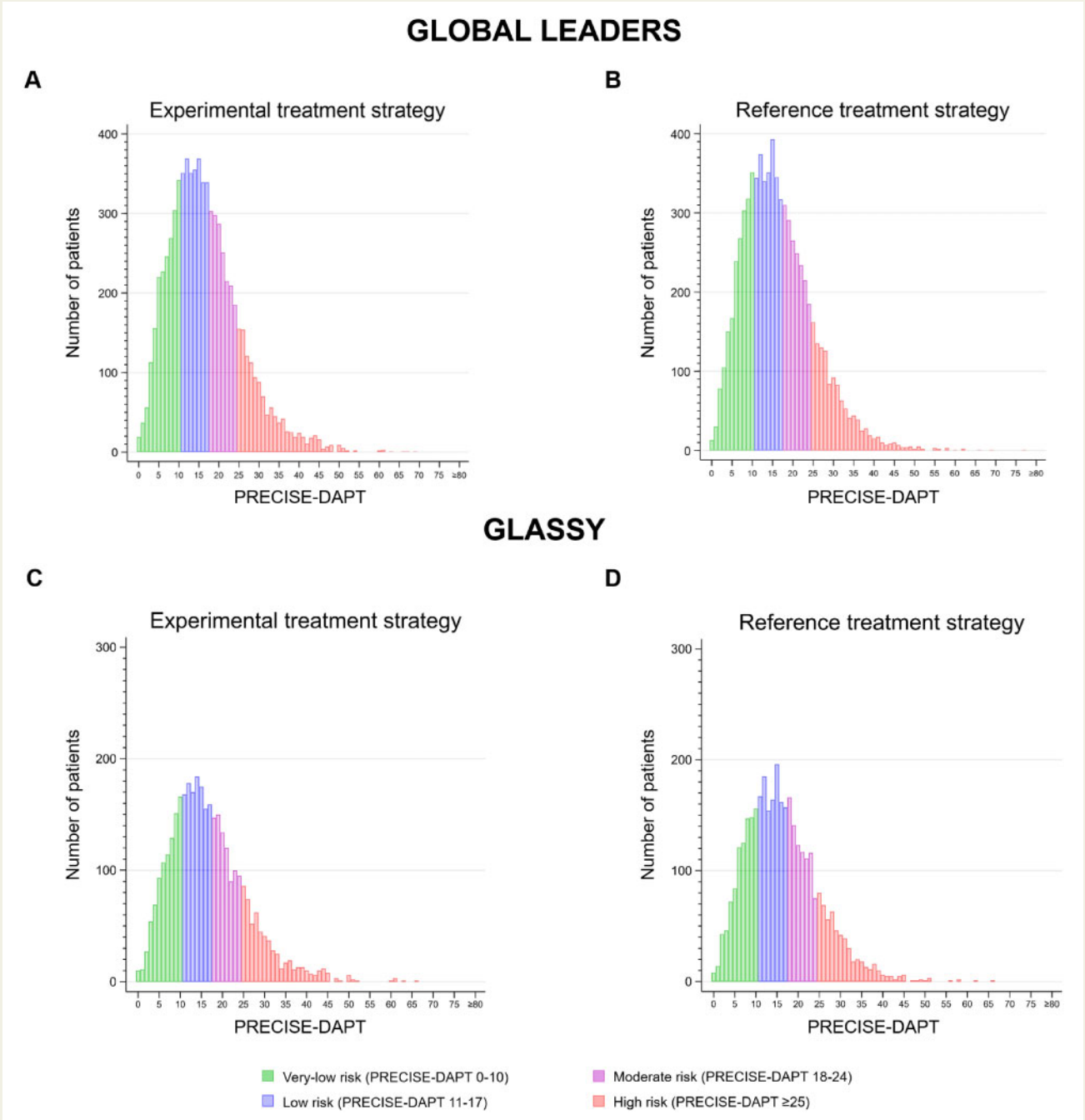

Figure 1 PRECISE-DAPT score distribution in GLOBAL LEADERS and GLASSY according to the treatment strategy. Experimental and control groups in GLOBAL LEADERS (*A* and *B*) and GLASSY (*C* and *D*).

Net clinical benefit

Figure 4 compares the decision curves to classify individuals using PRECISE-DAPT and its four-item version assuming that all patients will bleed (i.e., all are at high risk of bleeding) or that no patient will bleed (i.e., all are at low risk of bleeding). For BARC 3 or 5 bleeding, decision curves showed that both scores were superior to the scenario of 'not using scores' for risk thresholds from 1% to 8% in all study groups (*Figure 2* and Supplementary material online, *Figure S4*). For instance, in the experimental group of GLOBAL LEADERS, applying a risk threshold of 3% for BARC 3 or 5 events, the use of PRECISE-DAPT would result in a net benefit gain of +0.27% (+0.32% for the four-item score) and of +1.12% (1.17% for the four-item score) compared with the scenario of 'assuming all as high-risk' (Supplementary material online, *Table S3*). In other words, the net benefit of using the PRECISE-DAPT score leads to 37.3 (39 for the four-item score) and 9 (10.6 for the four-item score) more

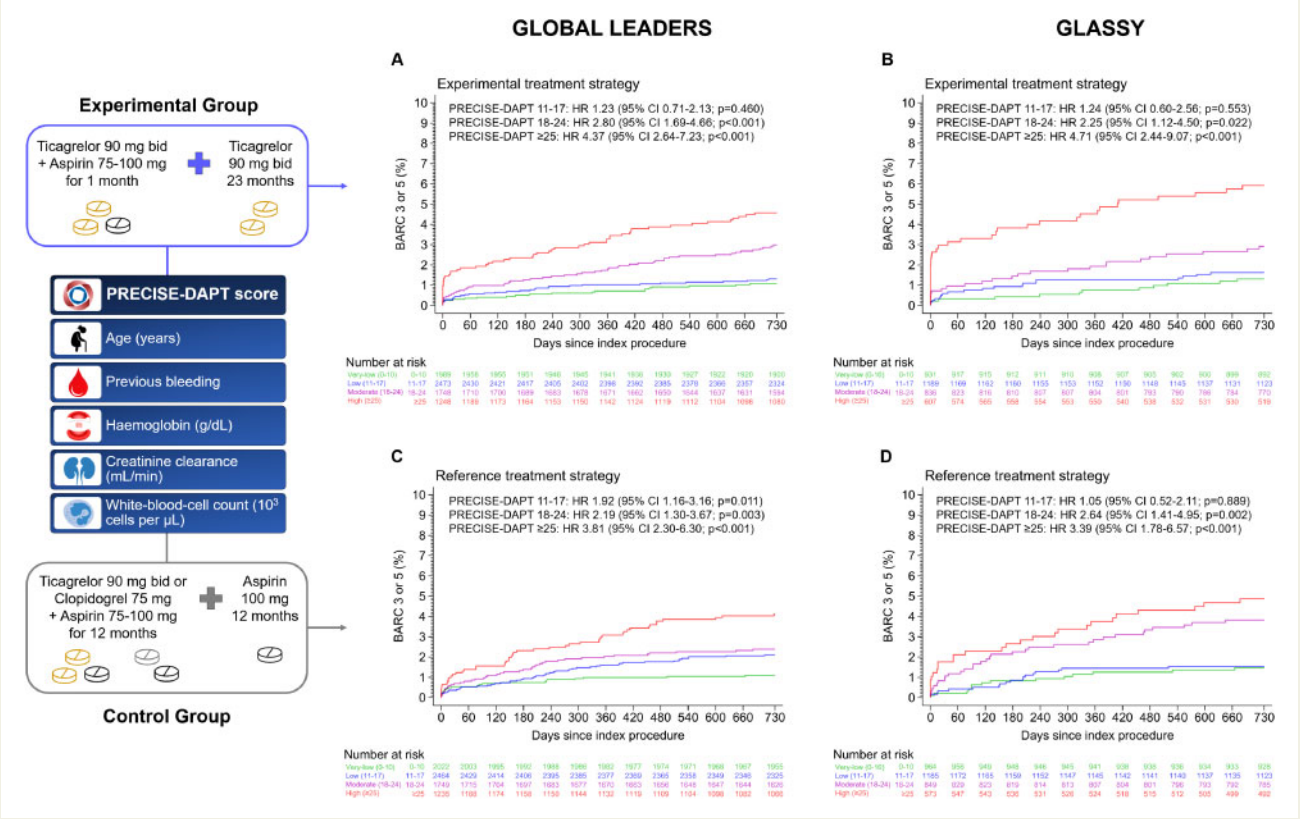

Figure 2 BARC 3 or 5 bleeding at 2 years in GLOBAL LEADERS and GLASSY stratified by PRECISE-DAPT score. Kaplan–Meier event curves for BARC 3 or 5 bleeding at 2 years. Experimental and control groups in GLOBAL LEADERS (*A* and *C*) and GLASSY (*B* and *D*). BARC, Bleeding Academic Research Consortium Criteria; HR, hazard ratio.

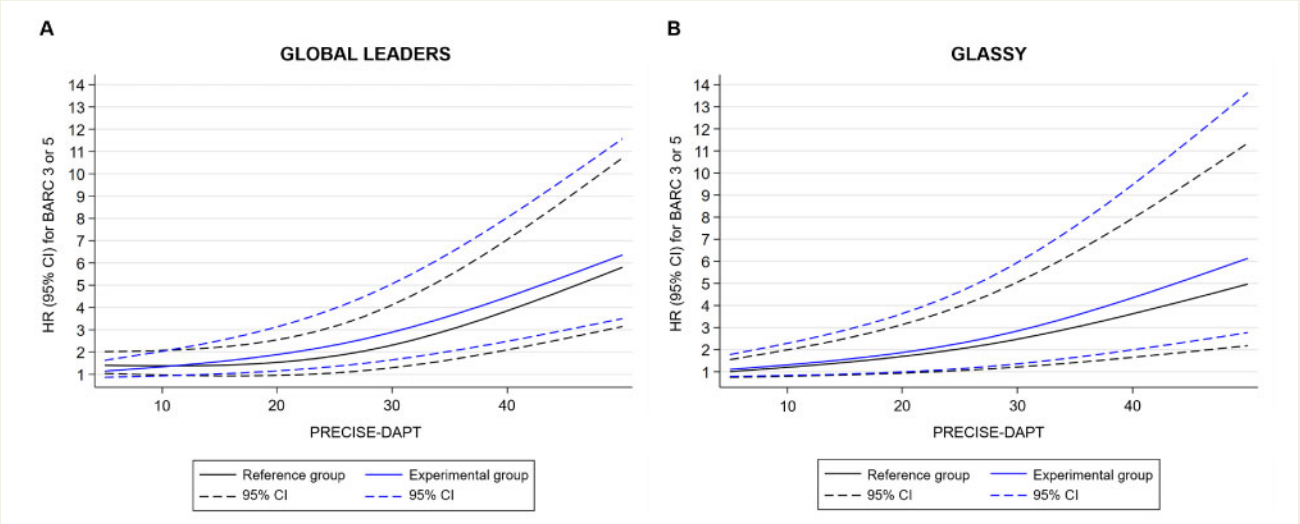

Figure 3 Spline functions of BARC 3 or 5 bleeding risk at 2 years according to PRECISE-DAPT. Experimental and control groups in GLOBAL LEADERS (*A*) and GLASSY (*B*). BARC, Bleeding Academic Research Consortium Criteria; CI, confidence interval; HR, hazard ratio.

Table 3 Harrell's c-indexes and goodness-of-fit for BARC 3 or 5 bleeding in GLOBAL LEADERS

	Overall				Experimental group				Control group				
	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	P-Value c-Index Experimental vs. control
At 1 year													
PRECISE-DAPT	244/14 928	0.65 (0.61–0.68)	2.3	0.79	113/7458	0.68 (0.63–0.73)	1.5	0.91	131/7470	0.62 (0.58–0.67)	2.6	0.75	0.27
Four-item PRECISE-DAPT		0.63 (0.60–0.67)	10.2	0.07		0.68 (0.62–0.73)	9.8	0.08		0.60 (0.55–0.65)	5.2	0.39	0.14
At 2 years													
PRECISE-DAPT	322/14 928	0.65 (0.62–0.68)	2.7	0.75	159/7458	0.67 (0.63–0.71)	2.3	0.81	163/7470	0.63 (0.59–0.67)	2.8	0.73	0.27
Four-item PRECISE-DAPT		0.65 (0.61–0.67)	7.8	0.16		0.68 (0.64–0.72)	11	0.05		0.61 (0.57–0.65)	5.2	0.39	0.14
Landmark 1–2 years													
PRECISE-DAPT	78/14 302	0.65 (0.59–0.71)	1.2	0.94	46/7145	0.64 (0.56–0.72)	2.5	0.77	32/7157	0.66 (0.57–0.76)	2.6	0.75	0.83
Four-item PRECISE-DAPT		0.67 (0.62–0.73)	4.5	0.48		0.69 (0.61–0.76)	3.2	0.67		0.66 (0.57–0.75)	13.6	0.01	0.74

BARC, Bleeding Academic Research Consortium; CI, confidence interval.

Table 4 Harrell's c-indexes and goodness-of-fit for BARC 3 or 5 bleeding in GLASSY

	Overall				Experimental group				Control group				
	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	P-Value c-Index Experimental vs. control
At 1 year													
PRECISE-DAPT	140/7134	0.66 (0.62–0.71)	4.3	0.51	66/3563	0.69 (0.62–0.75)	5.1	0.40	74/3571	0.64 (0.58–0.71)	6.5	0.26	0.50
Four-item PRECISE-DAPT		0.66 (0.61–0.70)	6.6	0.25		0.70 (0.63–0.76)	5.1	0.40		0.63 (0.57–0.69)	4.7	0.45	0.30
At 2 years													
PRECISE-DAPT	181/7134	0.67 (0.63–0.71)	4.5	0.48	90/3563	0.67 (0.61–0.73)	5.9	0.31	91/3571	0.66 (0.61–0.72)	7.3	0.19	0.88
Four-item PRECISE-DAPT		0.67 (0.63–0.71)	9.5	0.09		0.69 (0.63–0.74)	7.4	0.19		0.65 (0.60–0.71)	5.6	0.34	0.51
Landmark 1–2 years													
PRECISE-DAPT	41/6827	0.67 (0.58–0.76)	5.6	0.34	24/3412	0.61 (0.49–0.73)	3.2	0.66	17/3415	0.75 (0.64–0.87)	2.9	0.71	0.42
Four-item PRECISE-DAPT		0.70 (0.62–0.78)	7.3	0.19		0.66 (0.55–0.77)	5.3	0.37		0.74 (0.62–0.86)	9.3	0.09	0.30

BARC, Bleeding Academic Research Consortium; CI, confidence interval.

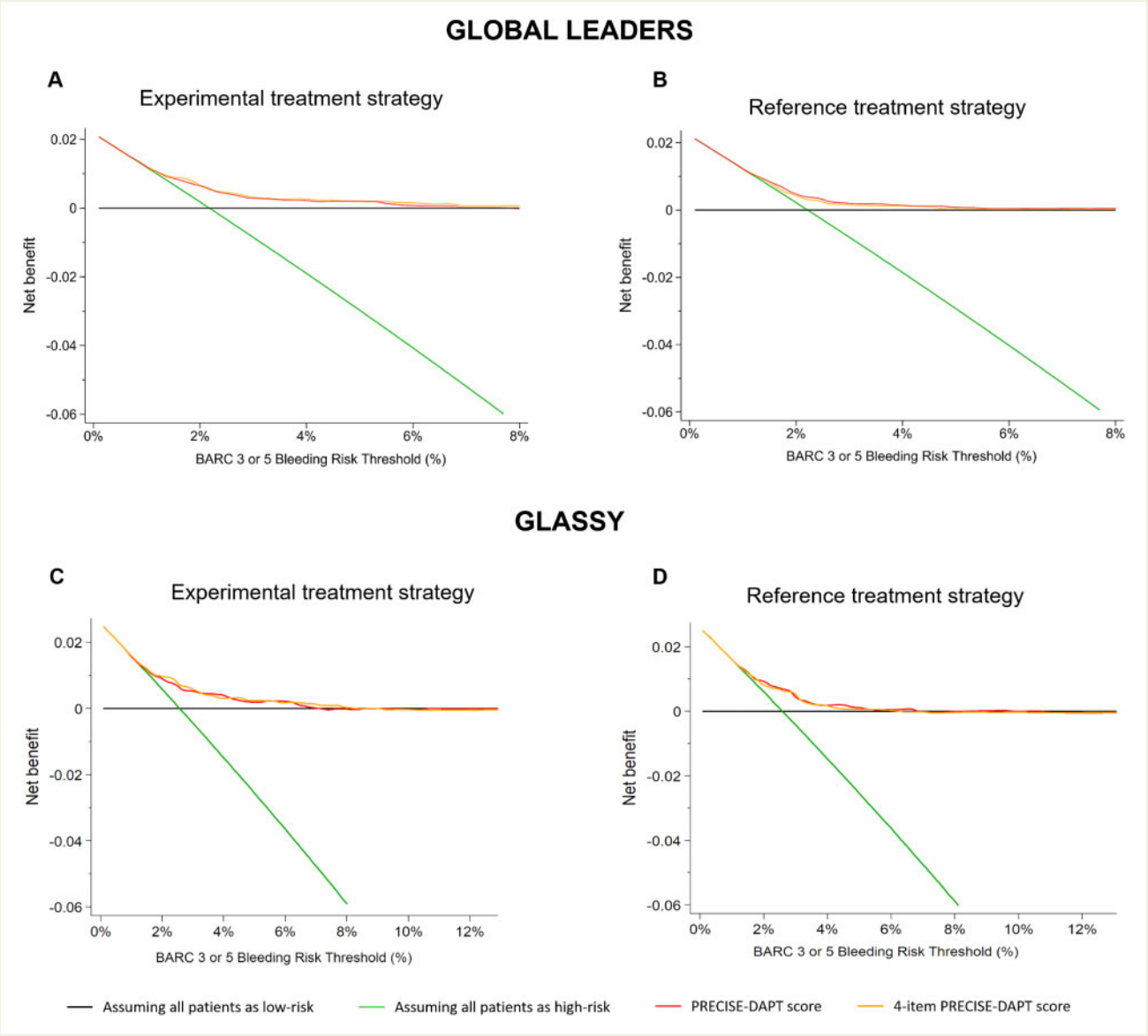

Figure 4 Decision curves showing net benefit of using the PRECISE-DAPT or the four-item PRECISE-DAPT for predicting BARC 3 or 5 bleeding at 2 years. Experimental and control groups in GLOBAL LEADERS (*A* and *B*) and GLASSY (*C* and *D*). Black horizontal line: treat all assuming at low risk of bleeding. Green line: treat all assuming at high-risk of bleeding. Red curve: PRECISE-DAPT. Yellow curve: four-item PRECISE-DAPT. Decision curves are drawn by plotting net benefit (*y*-axis) at different risk thresholds (*x*-axis) to visually estimate and compare the benefit offered by different strategies. BARC, Bleeding Academic Research Consortium Criteria.

true-positive cases per 100 patients without additional false-positives (i.e., 'net' true-positives) compared with 'assuming all as high-risk' and 'assuming all as low-risk', respectively. Additional case examples are reported in Supplementary material online, *Tables S4–S6*.

Discussion

In the current analysis, which included >14 000 participants of the GLOBAL LEADERS trial and its GLASSY sub-study, we evaluated the performance of PRECISE-DAPT score in patients having or not adjudicated bleeding endpoints and treated with ticagrelor plus aspirin for 1 month followed by 23-month ticagrelor monotherapy or standard 12-month DAPT followed by aspirin monotherapy after PCI. The main findings are the following:

- The PRECISE-DAPT score was able to stratify bleeding risk to a similar extent in patients with or without DAPT, consisting of a 12 month combination of aspirin and ticagrelor or aspirin and clopidogrel followed by 12-month aspirin monotherapy or 23-month ticagrelor monotherapy from 1 month after coronary stenting.
- The score provided modest but consistent discrimination and good calibration for the prediction of BARC-defined bleeding in both study arms, with a net benefit compared with the scenario of not using risk scores.

- The score performance remained consistent for bleeding prediction within the first year, where mainly ticagrelor monotherapy was compared with a DAPT regimen, as well as during the second year, where ticagrelor monotherapy was compared with aspirin monotherapy.
- The score performance remained comparable when investigator-reported bleeding, within GLOBAL LEADERS, or centrally adjudicated bleeding endpoints, within GLASSY, were separately appraised.
- The four-item PRECISE-DAPT score appeared very similar to the five-item iteration, offering a credible option for bleeding risk assessment if white-blood-cell count is not available.

Current guidelines recommend with a class IIB—pending prospective validation—the use of bleeding prediction models to individualize DAPT duration in patients undergoing PCI.[1,6] The PRECISE-DAPT score was developed in a large PCI-treated population receiving standard antiplatelet treatment, typically consisting of DAPT for 6–12 months followed by aspirin alone after P2Y12 inhibitors discontinuation.[3,6] Multiple studies have assessed the score performance showing a consistent ability to predict bleeding among patients receiving standard DAPT.[8–10]

Yet, recent studies have challenged current DAPT paradigm by investigating the potential of early aspirin discontinuation after PCI. The GLOBAL LEADERS[11] and its Adjudication Sub-study GLASSY[15] pioneered this approach and provided reassuring data on the safety and efficacy of ticagrelor monotherapy, but failed to show its superiority over standard DAPT. In the STOPDAPT-2[12] and SMART-CHOICE,[13] P2Y12 monotherapy—principally clopidogrel—after 1 or 3 months of DAPT was associated with a lower incidence of bleeding than 12-month DAPT, without an apparent difference in ischaemic endpoints. The TWILIGHT[14] and TICO[19] trials provided additional support by demonstrating lower bleeding risks with ticagrelor monotherapy (after 3-month DAPT) over conventional treatment while preserving ischaemic efficacy.

Whether the PRECISE-DAPT score retains its potential to reasonably forecast bleeding in patients undergoing treatment with a single antiplatelet agent, including a potent P2Y12 inhibitor or aspirin, remains unclear. In addition, PRECISE-DAPT was generated and externally validated in the context of centrally adjudicated bleeding endpoints, and it remained unclear if its performance might be affected by investigator-reported endpoints.

We showed that PRECISE-DAPT, as well as its four-item simplified version, retains a similar capacity to stratify bleeding risk in PCI patients on ticagrelor monotherapy after 1-month DAPT as among those on standard DAPT. Regardless of the assigned treatment, the higher the score, the higher the risk of clinically relevant bleeding, which increased by a factor of more than two in patients with 18–24 points and more than four-fold in those with ≥25 points. In GLASSY, a PRECISE-DAPT score of 25 conferred a 1-year risk of adjudicated BARC 3 or 5 bleeding that ∼4% at the upper limit of the 95% CI—a threshold that has been recently proposed to select high bleeding risk patients by the Academic Research Consortium for High Bleeding Risk.[5] The lower rate of BARC 3 or 5 events in GLOBAL LEADERS compared with GLASSY might be explained by the under-reporting of clinical events due to the use of investigator-reported vs. centrally adjudicated endpoints, respectively. In addition, the use of PRECISE-DAPT was consistently better than 'not using risk scores' at decision curve analysis, irrespective of the implemented antiplatelet treatment. Indeed, under both treatment strategies, we observed a net benefit in terms of fewer false-positive cases across a wide range of bleeding risk thresholds, in the absence of any potential drawbacks. Of note, despite the pragmatic study design, the proportion of patients with score ≥25 in GLOBAL LEADERS and GLASSY was ∼16% and relatively low compared with previous studies.[6,9]

During ticagrelor monotherapy, similarly to standard DAPT, PRECISE-DAPT was reasonably accurate to distinguish patients who would have bled from those who would have not (discrimination) and predicted the level of risk subsequently observed in reality (calibration). We noticed a slightly better score calibration in the parental trial, while the *c*-index estimates were slightly higher but less precise (in terms of 95% CI) in GLASSY. The evaluation of scores performance requires appropriate sample size of preferably ≥100 events, whereas a lower number of events can negatively affect calibration and (to a lesser extent) *c*-index estimates.[20] GLASSY included about half of patients and events included in the parent trial, and this may reasonably account for the less precise calibration and *c*-index estimates observed in this cohort, with a less apparent effect on the latter.

No other risk score has been so far tested for bleeding risk prediction with ticagrelor monotherapy. Several risk scores have been designed to predict in-hospital or 30-day bleeding (i.e., CRUSADE, ACUITY). At variance from these models, PRECISE-DAPT predicts long-term bleeding risk and therefore appears more suited for patients on ticagrelor monotherapy after a short course of DAPT. The comparative performance of PRECISE-DAPT vs. other bleeding risk scores remains unclear.

We also observed that score performance remained consistent among patients receiving aspirin monotherapy (i.e., reference group during the second year). Though interesting, these data should be interpreted cautiously considering the low number of events in this Subgroup.

Applying the score to GLOBAL LEADERS and GLASSY gave us the opportunity to test the score in the context of investigator-reported or adjudicated bleeding events. Our data showed the ability of PRECISE-DAPT to offer consistent bleeding prediction inside and outside the context of CEC-adjudication, which carries relevant implications for practice.

In the present analysis, PRECISE-DAPT performance was reasonable in both GLOBAL LEADERS and GLASSY (*c*-index of 0.65 and 0.67, respectively), but somewhat lower than that reported in the derivation and PLATO cohorts (*c*-index of 0.73 and 0.70, respectively).[6] The relative performance of the score in different studies can be explained, at least in part, by differences in bleeding definitions and patients' characteristics. At variance with our analysis, which included all post-PCI bleeding graded by BARC scale, the score has been developed to predict out-of-hospital bleeding according to TIMI scale.[6] Noteworthy, when the score had been tested in its derivation cohort to predict all post-PCI bleeding (rather than out-of-hospital events), its discriminative ability for TIMI major or minor occurrences was slightly lower (*c*-index of 0.68) and closer to our estimates. Moreover, when BARC 3 or 5 bleeding has been used as endpoint, the score has shown a *c*-index of 0.69 and 0.65 for post-PCI and

post-discharge bleeding, respectively, in contemporary PCI registries,[6,10] in line with our findings. A recent study of 904 PCI patients showed a c-index of 0.81 for BARC ≥3a.[8] However, the retrospective design, small sample size, the exclusive inclusion of Asian patients, and much higher than expected BARC ≥3a bleeding (17% at 1 year) potentially limit data generalizability.[8] Higher score performance for predicting BARC 3 or 5 bleeding (c-index of 0.73) has also been reported in 1926 ACS patients.[9] Yet, differences in bleeding characterization (out-of-hospital events assessed through medical records), population's characteristics, and study design can possibly account for these discrepancies [9].

Our study has several limitations. First, this analysis was prespecified, yet the results should be considered hypothesis-generating. Second, the PRECISE-DAPT was not available in ∼6% of patients that were excluded. Third, differences in bleeding definition used as compared with the derivation cohort may have affected the score performance. Finally, ∼20% of GLOBAL LEADERS and GLASSY patients were non-adherent to study treatment. Prior on- vs. off-treatment analyses suggested higher score performance for the former compared with the latter.

Conclusions

The PRECISE-DAPT consistently predicts bleeding risk in patients on ticagrelor monotherapy after 1-month DAPT or on aspirin monotherapy after 12-month DAPT when compared with patients on standard DAPT after drug-eluting stent implantation. Our analysis also suggests that the score performance is unaffected by the presence or absence of adjudicated bleeding endpoints, which carries relevant implications for practice.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F-J, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–260.
2. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
3. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting. *Circulation* 2012;**125**:2015–2026.
4. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand S-LT, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Lee P, Ver Rinaldi MJ, Massaro JM. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;**371**:2155–2166.
5. Ueki Y, Bär S, Losdat S, Otsuka T, Zanchin C, Zanchin T, Gragnano F, Gargiulo G, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Heg D, Valgimigli M, Windecker S, Räber L. Validation of bleeding risk criteria (ARC-HBR) in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores. *Eurointervention* 2020;**16**:371–379.
6. Costa F, Klaveren D, van James S, Heg D, Räber L, Feres F, Pilgrim T, Hong M-KK, Kim H-SS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet

therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;**389**:1025–1034.
7. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
8. Choi SY, Kim MH, Cho Y-R, Sung Park J, Min Lee K, Park T-H, Yun S-C. Performance of PRECISE-DAPT score for predicting bleeding complication during dual antiplatelet therapy. *Circ Cardiovasc Interv* 2018;**11**:e006837.
9. Abu-Assi E, Raposeiras-Roubin S, Cobas-Paz R, Caneiro-Queija B, Martínez-Reglero C, Rodríguez-Rodríguez JM, Baz A, Íñiguez-Romo A. Assessing the performance of the PRECISE-DAPT and PARIS risk scores for predicting one-year out-of-hospital bleeding in acute coronary syndrome patients. *Eurointervention* 2018;**13**:1914–1922.
10. Bianco M, D'ascenzo F, Raposeiras Roubin S, Kinnaird T, Peyracchia M, Ariza-Solé A, Cerrato E, Manzano-Fernández S, Gravinese C, Templin C, Destefanis P, Velicki L, Luciano A, Xanthopoulou I, Rinaldi M, Rognoni A, Varbella F, Boccuzzi G, Omedè P, Montabone A, Bernardi A, Taha S, Rossini R, Durante A, Gili S, Magnani G, Autelli M, Grosso A, Blanco PF, Giustetto C, Garay A, Quadri G, Queija BC, Srdanovic I, Paz RC, Fernández MC, Pousa IM, Gallo D, Morbiducci U, Dominguez-Rodriguez A, Lopez-Cuenca Á, Cequier A, Alexopoulos D, Iñiguez-Romo A, Pozzi R, Assi EA, Valgimigli M. Comparative external validation of the PRECISE-DAPT and PARIS risk scores in 4424 acute coronary syndrome patients treated with prasugrel or ticagrelor. *Int J Cardiol* 2020;**301**:200–206.
11. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Möllmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S; GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018;**392**:940–949.
12. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, Hata Y, Yagi M, Suematsu N, Yokomatsu T, Takamisawa I, Doi M, Noda T, Okayama H, Seino Y, Tada T, Sakamoto H, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Hanaoka KI, Morino Y, Kozuma K, Kadota K, Furukawa Y, Nakagawa Y, Kimura T.; for the STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI. *JAMA* 2019;**321**:2414.
13. Hahn J-Y, Song Y, Bin Oh J-H, Chun WJ, Park YH, Jang WJ, Im E-S, Jeong J-O, Cho BR, Oh SK, Yun KH, Cho D-K, Lee J-Y, Koh Y-Y, Bae J-W, Choi JW, Lee WS, Yoon HJ, Lee SU, Cho JH, Choi WG, Rha S-W, Lee JM, Park TK, Yang JH, Choi J-H, Choi S-H, Lee SH, Gwon H-C; for the SMART-CHOICE Investigators. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention. *Jama* 2019;**321**:2428.
14. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, Džavík V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta SR, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han Y-L, Pocock S, Gibson CM. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med* 2019;**381**:2032–2042.
15. Franzone A, McFadden E, Leonardi S, Piccolo R, Vranckx P, Serruys PW, Benit E, Liebetrau C, Janssens L, Ferrario M, Zurakowski A, Diletti R, Dominici M, Huber K, Slagboom T, Buszman P, Bolognese L, Tumscitz C, Bryniarski K, Aminian A, Vrolix M, Petrov I, Garg S, Naber C, Prokopczuk J, Hamm C, Steg PG, Heg D, Jüni P, Windecker S, Valgimigli M. Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. *J Am Coll Cardiol* 2019;**74**:2223–2234.
16. Costa F, van Klaveren D, Colombo A, Feres F, Räber L, Pilgrim T, Hong M-K, Kim HS, Windecker S, Steyerberg EW, Valgimigli M. A 4-item PRECISE-DAPT score for dual antiplatelet therapy duration decision-making. *Am Heart J* 2020;**223**:44–47.
17. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials. *Circulation* 2011;**123**:2736–2747.
18. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Mak* 2006;**26**:565–574.
19. Jang Y. Ticagrelor with or without aspirin in acute coronary syndrome after PCI (TICO). *American College of Cardiology Annual Scientific Session*, 2020.
20. Collins GS, Ogundimu EO, Altman DG. size considerations for the external validation of a multivariable prognostic model: a resampling study. *Stat Med* 2016;**35**:214–226.