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FASTTRACK CLINICAL RESEARCH
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Ticagrelor monotherapy in patients at high bleeding risk undergoing percutaneous coronary intervention: TWILIGHT-HBR

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Aims Patients at high bleeding risk (HBR) represent a prevalent subgroup among those undergoing percutaneous coronary intervention (PCI). Early aspirin discontinuation after a short course of dual antiplatelet therapy (DAPT) has emerged as a bleeding avoidance strategy. The aim of this study was to assess the effects of ticagrelor monotherapy after 3-month DAPT in a contemporary HBR population.

Methods and results This prespecified analysis of the TWILIGHT trial evaluated the treatment effects of early aspirin withdrawal followed by ticagrelor monotherapy in HBR patients undergoing PCI with drug-eluting stents. After 3 months of ticagrelor plus aspirin, event-free patients were randomized to 12 months of aspirin or placebo in addition to ticagrelor. A total of 1064 (17.2%) met the Academic Research Consortium definition for HBR. Ticagrelor monotherapy reduced the incidence of the primary endpoint of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding compared with ticagrelor plus aspirin in HBR (6.3% vs. 11.4%; hazard ratio (HR) 0.53, 95% confidence interval (CI) 0.35–0.82) and non-HBR patients (3.5% vs. 5.9%; HR 0.59, 95% CI 0.46–0.77) with similar relative ($P_{interaction} = 0.67$) but a trend towards greater absolute risk reduction in the former [-5.1% vs. -2.3%; difference in absolute risk differences (ARDs) -2.8%, 95% CI -6.4% to 0.8%, $P = 0.130$]. A similar pattern was observed for more severe BARC 3 or 5 bleeding with a larger absolute risk reduction in HBR patients (-3.5% vs. -0.5%; difference in

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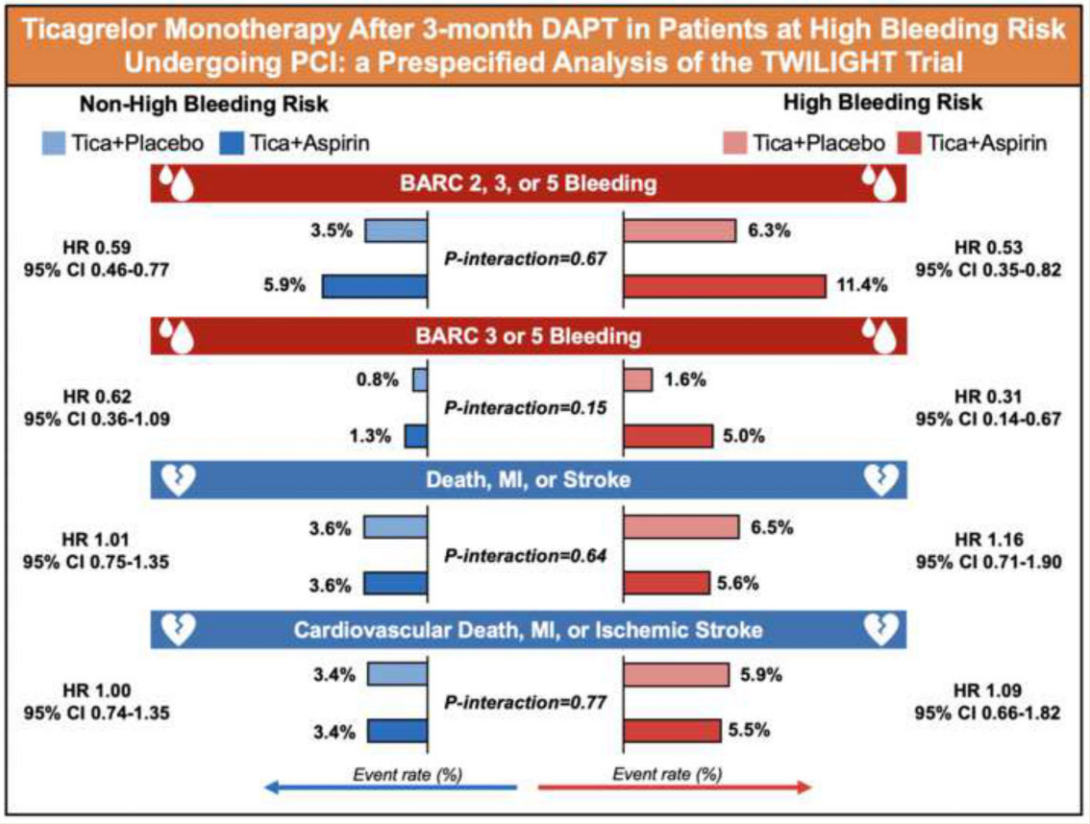
ARDs -3.0%, 95% CI -5.2% to -0.8%, $P = 0.008$). There was no significant difference in the key secondary endpoint of death, myocardial infarction, or stroke between treatment arms, irrespective of HBR status.

Conclusions Among HBR patients undergoing PCI who completed 3-month DAPT without experiencing major adverse events, aspirin discontinuation followed by ticagrelor monotherapy significantly reduced bleeding without increasing ischaemic events, compared with ticagrelor plus aspirin. The absolute risk reduction in major bleeding was larger in HBR than non-HBR patients.

Graphical Abstract



Effects of ticagrelor plus placebo vs. ticagrelor plus aspirin on bleeding and ischaemic events among high bleeding risk and non-high bleeding risk patients who tolerated 3 months of dual antiplatelet therapy after percutaneous coronary intervention with a drug-eluting stent. BARC, Bleeding Academic Research Consortium; CI, confidence interval; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; tica, ticagrelor.

Keywords High bleeding risk • ARC-HBR • Ticagrelor monotherapy • Aspirin • PCI

Introduction

For over 20 years, a combination of aspirin and a $P2Y_{12}$ inhibitor has been the mainstay antithrombotic strategy in patients undergoing percutaneous coronary intervention (PCI).[1] This drug combination, referred to as dual antiplatelet therapy (DAPT), has been proven superior to aspirin alone in preventing cardiovascular events after stent implantation, although at the expense of increased bleeding.[2,3] The introduction of potent $P2Y_{12}$ inhibitors further compounded the trade-off between ischaemic and bleeding risks. Prasugrel and ticagrelor demonstrated superior ischaemic protection compared with clopidogrel among patients with an acute coronary syndromes (ACS) on background aspirin therapy.[4,5] However, this benefit was counterbalanced by an increased bleeding risk consequent to the incremental platelet inhibition. Although once considered benign events, in recent years, bleeding complications after PCI have been associated with a similar adverse prognosis as thrombotic events.[6,7]

Contemporary advances in device technologies and pharmacological strategies have allowed extending PCI to older and more vulnerable cohorts.[8,9] As such, an increasing number of patients undergoing PCI have high bleeding risk (HBR) conditions, which make a standard DAPT regimen clinically undesirable.[10,11] The TWILIGHT trial recently demonstrated that ticagrelor monotherapy after a short course of DAPT is an effective and safe bleeding avoidance strategy among high-risk patients undergoing PCI.[12] The trial enrolled patients at high risk for both bleeding and thrombosis according to a broad range of clinical and angiographic criteria.[13] To investigate the treatment effects of ticagrelor monotherapy compared with ticagrelor plus aspirin in a contemporary HBR population, we conducted a prespecified analysis of the TWILIGHT trial using the Academic Research Consortium (ARC) criteria for HBR.[14]

Methods

Trial design and population

TWILIGHT was a randomized, placebo-controlled trial conducted at 187 sites in 11 countries. The trial rationale, design, and principal results have been reported previously.[12,13] TWILIGHT was designed, coordinated, and sponsored by The Icahn School of Medicine at Mount Sinai. AstraZeneca provided an investigator-initiated grant and supplied ticagrelor for the trial but had no role in the design, collection, analysis, or interpretation of the data. National regulatory agencies and institutional review boards or ethics committees of participating sites approved the trial protocol.

Patients undergoing successful PCI with a drug-eluting stent were eligible for study enrolment if they satisfied at least one clinical and one angiographic criterion associated with a high risk of ischaemic or bleeding events. Clinical criteria included age ≥65 years, female sex, troponin positive ACS, atherosclerotic vascular disease [prior myocardial infarction (MI), coronary revascularization or peripheral artery disease], diabetes mellitus requiring medication, and chronic kidney disease (CKD). Angiographic criteria included multivessel coronary artery disease, total stent length >30 mm, thrombotic target lesion, bifurcation lesion requiring two stents, obstructive left main or proximal left anterior descending lesion, and calcified target lesion requiring debulking devices. Key exclusion criteria included presentation with ST-elevation MI, cardiogenic shock, prior stroke, or need for oral anticoagulation.

All enrolled patients received open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81–100 mg daily) after the index PCI. At 3 months, patients who had been adherent to treatment and without major bleeding or ischaemic events were randomized 1:1 in a double-blind fashion to aspirin or matching placebo for an additional 12 months in addition to open-label ticagrelor. Follow-up occurred 1 month after randomization via telephone and in-person at 6 and 12 months after randomization.[13]

Endpoints

The primary endpoint was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding up to 1 year after randomization. The key secondary endpoint was the composite of all-cause death, MI, or stroke. Moreover, we considered BARC 3 or 5 bleeding and the composite of cardiovascular death, MI, or ischaemic stroke, as outcomes of interest for this analysis in line with the recommendations of the ARC on HBR trial design principles.[15] Other secondary bleeding endpoints included Thrombolysis in Myocardial Infarction (TIMI) major bleeding, Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate or severe or bleeding, and International Society on Thrombosis and Haemostasis (ISTH) major bleeding.[16–19] Other secondary ischaemic endpoints included all-cause death, cardiovascular death, non-fatal MI, ischaemic stroke, and definite or probable stent thrombosis. MI was defined according to the third universal definition, and stent thrombosis was classified according to the ARC.[20,21] All clinical events were adjudicated by an independent committee, blinded to treatment assignment.

High bleeding risk assessment

Patients were considered as HBR if they fulfilled at least one major or two minor criteria as defined by the ARC-HBR consensus statement.[14] Major criteria available for analysis were severe or end-stage CKD [i.e. estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or dialysis], haemoglobin <11 g/dL, moderate or severe thrombocytopenia (i.e. platelet count $<100 \times 10^9$/L), previous major bleeding, and liver disease. Minor criteria included age ≥75 years, moderate CKD (i.e. eGFR ≥30 and <60 mL/min/1.73 m^2), haemoglobin ≥11 and <13 g/dL for men and ≥11 and <12 g/dL for women, and non-steroidal anti-inflammatory drug use. Baseline laboratory values were obtained locally at each site during the enrolment procedure. The eGFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[22] Supplementary material online, *Table S1* summarizes the list of available major and minor criteria and their definitions compared with those provided in the original ARC-HBR document.[14] Patients with missing data on at least one major or two minor criteria were excluded from the analysis, unless they had other fulfilled criteria that identified them as HBR.

Statistical analyses

In the primary prespecified analysis, the treatment effects of ticagrelor monotherapy vs. ticagrelor plus aspirin were evaluated according to HBR status.[12] Clinical and procedural features are summarized by the presence or absence of HBR and randomized group using means (standard deviation) for continuous variables and frequencies for categorical variables. The cumulative incidence of primary and secondary endpoints was estimated using the Kaplan–Meier method. Patients without a primary endpoint between randomization and 1 year were censored at the time of death, last known contact, or 365 days, whichever came first. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated using Cox proportional hazards models, with formal interaction testing to assess effect modification. Absolute risk differences (ARDs) and 95% CIs for ischaemic and bleeding events were calculated with Kaplan–Meier estimates and Greenwood standard errors. Interaction *P*-values on the absolute scale were calculated with the *Z*-test to assess whether the differences in ARDs between HBR and non-HBR patients were significantly different than zero.

In addition, we performed an exploratory analysis to examine the effects of ticagrelor monotherapy according to the number of ARC-HBR criteria satisfied. Given that HBR was defined by the presence of (at least) one major or two minor criteria, an ARC-HBR score was computed by taking into account the relative weight of each major and minor HBR criterion (i.e. 0.5 point assigned to each minor criterion and 1 point assigned to each major criterion).[23] Patients were then stratified into four groups: (i) those without any criteria (0 point), (ii) with only one minor criterion (0.5 point), (iii) with one major or two minor criteria (1 point), and (iv) with multiple ARC-HBR criteria (≥1.5 points).[23] For all analyses, bleeding outcomes were assessed in the intention-to-treat cohort, while ischaemic outcomes were analysed using the per-protocol cohort. A sensitivity analysis of bleeding outcomes was performed in the per-protocol cohort. A two-sided *P*-value of <0.05 was considered statistically significant. All

Table 1 Baseline characteristics

	HBR (*n* = 1064, 17.2%)	Non-HBR (*n* = 5114, 82.8%)	*P*-value
Clinical characteristics			
Age (years)	71.9 ± 10.3	62.3 ± 9.3	
Female sex	354 (33.3%)	1101 (21.5%)	<0.001
Non-white race	293 (27.5%)	1212 (23.7%)	0.008
BMI (kg/m^2)	28.6 ± 6.0	28.9 ± 5.6	0.103
Enrolling region			<0.001
North America	545 (51.2%)	2307 (45.1%)	
Europe	333 (31.3%)	2016 (39.4%)	
Asia	186 (17.5%)	791 (15.5%)	
Diabetes	503 (47.3%)	1777 (34.7%)	<0.001
Diabetes treated with insulin	183 (36.4%)	433 (24.4%)	<0.001
Chronic kidney disease	644 (61.0%)	402 (7.9%)	
Anaemia	708 (67.5%)	472 (9.2%)	
Current smoker	110 (10.4%)	1219 (23.8%)	<0.001
Hypercholesterolaemia	713 (67.0%)	3328 (65.1%)	0.227
Hypertension	865 (81.3%)	3686 (72.1%)	<0.001
Peripheral arterial disease	132 (12.4%)	323 (6.3%)	<0.001
Previous MI	306 (28.8%)	1530 (29.9%)	0.452
Previous PCI	483 (45.4%)	2222 (43.4%)	0.245
Previous CABG	169 (15.9%)	500 (9.8%)	<0.001
Previous major bleed	54 (5.1%)	0 (0.0%)	
Indication for PCI			0.308
Stable CAD	403 (37.9%)	1852 (36.2%)	
ACS	661 (62.1%)	3261 (63.8%)	
ARC-HBR criteria			
Major criteria			
eGFR <30 mL/min/1.73 m^2 or dialysis	73 (6.9%)	0 (0.0%)	
Haemoglobin <11 g/dL	254 (24.2%)	0 (0.0%)	
Previous major bleeding	54 (5.1%)	0 (0.0%)	
Liver disease	23 (2.2%)	0 (0.0%)	
Platelet <100 × 10^9/L	3 (0.3%)	0 (0.0%)	
Minor criteria			
Age ≥75 years	526 (49.4%)	330 (6.5%)	
30≤ eGFR <60 mL/min/1.73 m^2	585 (55.4%)	402 (7.9%)	
Haemoglobin (g/dL) ≥11 and <13 for men and ≥11 and <12 for women	454 (43.3%)	472 (9.2%)	
Use of NSAIDs	212 (20.3%)	305 (6.0%)	
Procedural characteristics			
Radial artery access	658 (61.8%)	3741 (73.2%)	<0.001
Multivessel CAD	721 (67.8%)	3127 (61.1%)	<0.001
Target vessel			
Left main	67 (6.3%)	203 (4.0%)	<0.001
LAD	591 (55.5%)	2847 (55.7%)	0.940
LCX	354 (33.3%)	1641 (32.1%)	0.453
RCA	365 (34.3%)	1792 (35.0%)	0.647
Number of vessels treated	1.3 ± 0.5	1.3 ± 0.5	0.126
Number of lesions treated	1.5 ± 0.8	1.5 ± 0.7	0.157
Lesion morphology			
Moderate/severe calcification	221 (20.8%)	659 (12.9%)	<0.001
Bifurcation	132 (12.4%)	605 (11.8%)	0.598
Total occlusion	56 (5.3%)	286 (5.6%)	0.669
Thrombotic	93 (8.7%)	598 (11.7%)	0.005

Continued

Table 1 *Continued*

	HBR (*n* = 1064, 17.2%)	Non-HBR (*n* = 5114, 82.8%)	*P*-value
Total stent length (mm)	39.6 ± 24.9	38.6 ± 23.1	0.204
Minimum stent diameter (mm)	2.8 ± 0.5	2.8 ± 0.5	0.220

ACS, acute coronary syndrome; ARC, Academic Research Consortium; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; LAD, left anterior descending artery; LCX, left circumflex artery; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; RCA, right coronary artery.

analyses were performed using Stata version 16.0 (Stata Corp., College Station, TX, USA).

Results

Patient characteristics

A total of 9006 patients undergoing PCI were enrolled in the trial. Of the 7119 patients randomized at 3 months post-PCI, 941 were excluded for country-specific regulatory reasons ($n = 587$) or for missing information on major or minor criteria required to ascertain ARC-HBR status ($n = 354$). Hence, the final study cohort included 6178 patients, of whom 1064 (17.2%) were HBR (Supplementary material online, *Figure S1*). Details regarding the reasons for enrolled patients not undergoing randomization according to HBR status are provided in Supplementary material online, *Table S2*. HBR patients were older, more frequently female and of non-white race compared with non-HBR patients. They had more cardiovascular risk factors and comorbidities, including hypertension, diabetes, and peripheral artery disease, and were less frequently active smokers. Among HBR patients, moderate CKD and age ≥75 years were the two most common minor criteria (55.4% and 49.4%, respectively), while haemoglobin <11 g/dL was the most common major criterion (24.2%). With respect to angiographic and procedural features, HBR patients were less likely to have undergone PCI via radial access, and more often had multivessel disease, left main PCI, and calcific lesions than non-HBR patients (*Table 1*). Baseline characteristics stratified by randomized treatment arm are provided in Supplementary material online, *Tables S3 and S4*.

At 12 months after randomization, HBR patients were less adherent to the blinded study drug (74.5% vs. 83.7%, $P < 0.001$) and ticagrelor (79.2% vs. 87.7%, $P < 0.001$) than non-HBR patients, while there were no significant differences between randomized treatment arms within the two groups (Supplementary material online, *Figure S2*). Reasons for non-adherence to study drug and ticagrelor are listed in Supplementary material online, *Tables S5 and S6*, respectively.

Bleeding events

The primary endpoint of BARC 2, 3, or 5 bleeding occurred in 93 patients (8.9%) in the HBR group and in 237 patients (4.7%) in the non-HBR group (HR 1.95, 95% CI 1.54–2.48; $P < 0.001$) (Supplementary material online, *Figure S3A*). There was a significant reduction in the incidence of BARC 2, 3, or 5 bleeding in HBR patients randomized to ticagrelor plus placebo compared with those randomized to ticagrelor plus aspirin (6.3% vs. 11.4%; HR 0.53, 95% CI 0.35–0.82; $P = 0.004$) for an ARD of -5.1% (95% CI -8.5% to -1.7%). Treatment effects on BARC 2, 3, or 5 bleeding were consistent among non-HBR patients (3.5% vs. 5.9%; ARD -2.3%, 95% CI -3.5% to -1.2%; HR 0.59, 95% CI 0.46–0.77; $P < 0.001$) with no evidence of heterogeneity ($P_{interaction} = 0.673$; difference in ARDs -2.8%, 95% CI -6.4% to 0.8%; $P = 0.130$) (*Figure 1A* and Supplementary material online, *Table S7*).

The incidence of BARC 3 or 5 bleeding was significantly higher in HBR than non-HBR patients (3.4% vs. 1.0%; HR 3.30, 95% CI 2.15–5.07; $P < 0.001$) (Supplementary material online, *Figure S3B*). Ticagrelor plus placebo resulted in lower rates of BARC 3 or 5 bleeding in both HBR (1.6% vs. 5.0%; HR 0.31, 95% CI 0.14–0.67, 0.003) and non-HBR patients (0.8% vs. 1.3%; HR 0.62, 95% CI 0.36–1.09, $P = 0.098$; $P_{interaction} = 0.148$) (*Figure 1B*), but with an ARD significantly larger in the former group (-3.5%, 95% CI -5.6% to -1.3% vs. -0.5%, 95% CI -1.0% to 0.1%; difference in ARDs -3.0%, 95% CI -5.2% to -0.8%; $P = 0.008$). A similar pattern was observed for other major bleeding endpoints according to the TIMI, GUSTO and ISTH scale (*Figure 2* and Supplementary material online, *Table S7*). The sensitivity analysis of bleeding outcomes in the per-protocol cohort was consistent with the results of the intention-to-treat cohort (Supplementary material online, *Table S8*).

Ischaemic events

A total of 66 (6.1%) key secondary endpoint events occurred in HBR patients as compared with 181 (3.6%) in those without HBR (HR 1.70, 95% CI 1.27–2.26; $P < 0.001$) (Supplementary material online, *Figure S4*). Rates of all-cause death, MI, or stroke were not significantly different between HBR patients randomized to ticagrelor plus placebo vs. ticagrelor plus aspirin (6.5% vs. 5.6%; HR 1.16, 95% CI 0.71–1.90; $P = 0.554$) for an ARD of 0.9% (95% CI -2.1% to 3.8%) (*Figure 3A*). Furthermore, there were no significant differences between treatment arms among HBR patients with respect to the composite of cardiovascular death, MI, or ischaemic stroke (5.9% vs. 5.5%) (*Figure 3B*), as well as for the individual rates of cardiovascular death (1.8% vs. 2.6%), MI (4.5% vs. 3.6%), ischaemic stroke (0.4% vs. 0.2%), and definite or probable stent thrombosis (0.8% vs. 0.6%). Results were consistent among non-HBR patients for the key secondary endpoint (3.6% vs. 3.6%; ARD -0.0%, 95% CI -1.0% to 1.1%; HR 1.01, 95% CI 0.75–1.35, $P = 0.949$; $P_{interaction} = 0.637$) and other ischaemic endpoints (*Figure 4* and Supplementary material online, *Table S9*).

Exploratory analyses

After stratification of patients by the number of ARC-HBR criteria, 3605 (58.4%) had none, 1509 (24.4%) had only one minor criterion, 725 (11.7%) had either one major or two minor criteria, and 339

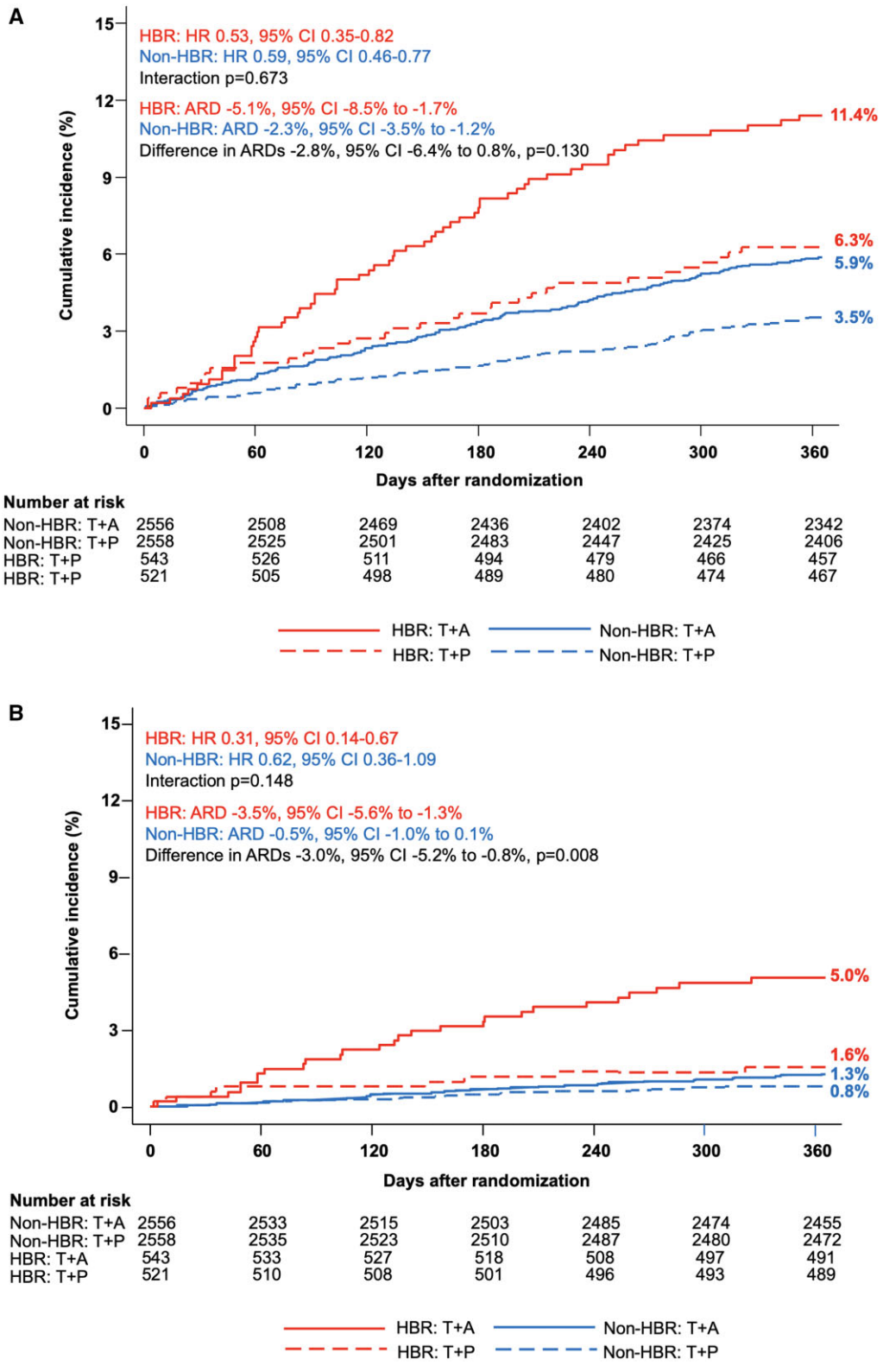


Figure 1 Rates of (*A*) Bleeding Academic Research Consortium 2, 3, or 5 bleeding and (*B*) Bleeding Academic Research Consortium 3 or 5 at 1 year. Kaplan–Meier curves for ticagrelor plus placebo vs. ticagrelor plus aspirin in patients with and without high bleeding risk in the intention-to-treat cohort. A, aspirin; ARD, absolute risk difference; CI, confidence interval; HBR, high bleeding risk; HR, hazard ratio; P, placebo; T, ticagrelor.

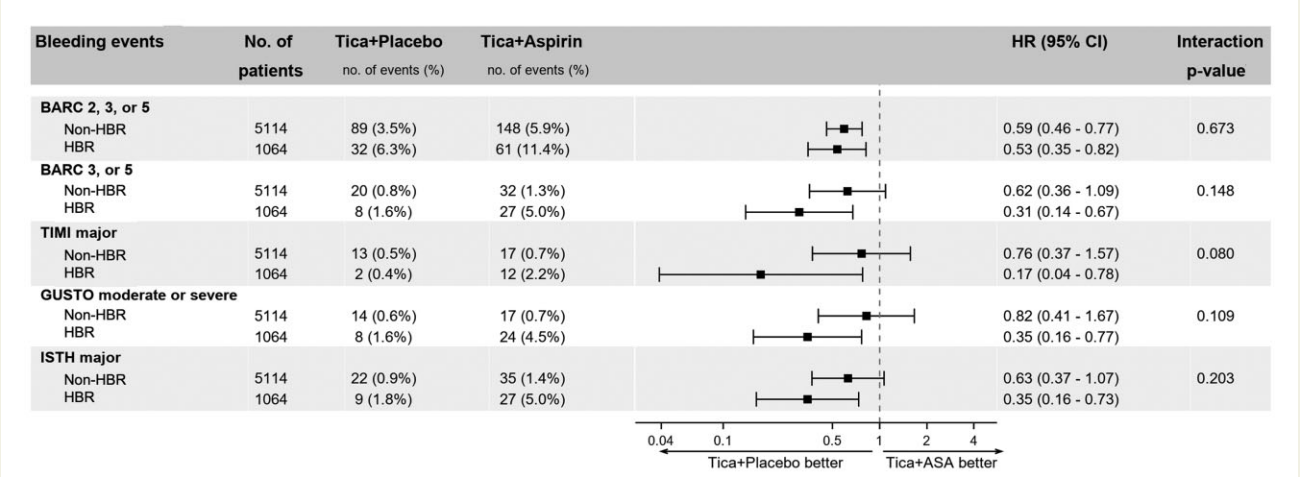


Figure 2 Risk of bleeding events at 1 year. Forest plot showing the effect of ticagrelor plus placebo vs. ticagrelor plus aspirin on the bleeding endpoints according to high bleeding risk status. Bleeding outcomes were analysed in the intention-to-treat cohort. BARC, Bleeding Academic Research Consortium; CI, confidence interval; GUSTO, Global Use of Strategies to Open Occluded Arteries; HBR, high bleeding risk; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis in Myocardial Infarction.

(5.5%) had more. There was a progressive increase in the risk of BARC 2, 3, or 5 as a function of the number of ARC-HBR criteria satisfied, with the 1-year event rate increasing from 4.6% to 5.1%, 6.9%, and 13.3% across the four groups. Similarly, the rate of BARC 3 or 5 bleeding increased from 0.8% to 1.6%, 2.1%, and 6.0%. A comparable pattern was observed for ischaemic events (Supplementary material online, *Figure S5*). The relative treatment effects of ticagrelor monotherapy on bleeding and ischaemic endpoints were consistent across all HBR subgroups (Supplementary material online, *Figures S6 and S7*).

Discussion

The principal findings from this prespecified analysis of the TWILIGHT trial are that: (i) HBR patients experienced higher rates of not only bleeding but also ischaemic events than non-HBR patients, with a risk proportional to the number of fulfilled ARC-HBR criteria; (ii) ticagrelor monotherapy lowered the risk of clinically relevant BARC 2, 3, or 5 bleeding without increasing ischaemic events, including death, MI or stroke, irrespective of HBR status; (iii) the absolute reduction in major bleeding complications associated with ticagrelor monotherapy was more pronounced in HBR than non-HBR patients; (iv) the treatment effects on ischaemic and bleeding events were consistent across different ARC-HBR risk categories. Altogether, these findings highlight the role of 3-month DAPT followed by ticagrelor monotherapy as a safe and effective bleeding avoidance strategy among HBR patients enriched with high ischaemic risk features who undergo PCI with a drug-eluting stent (*Graphical abstract*).

Percutaneous coronary intervention indications have extended to increasingly complex patient populations over the last decade.[24] As a result, a large number of patients undergoing PCI present with clinical and comorbid conditions that increase the risk of both periprocedural and late bleeding. As bleeding complications after PCI are intrinsically related to the duration and intensity of antithrombotic therapy,[25,26] short-term and single-drug antiplatelet regimens seem sensible among HBR patients.[27,28] However, use of these strategies is not straightforward because HBR patients have generally been excluded or underrepresented in clinical research on DAPT and they often are at increased risk of ischaemic events as well.[10,11] While newer stent platforms have been tested among HBR patients receiving an abbreviated DAPT regimen followed by aspirin monotherapy,[29–31] most of these studies did not provide comparative data on the benefits and risks associated with different DAPT durations and, therefore, the optimal approach to HBR patients remains largely unknown.

Recently, a strategy of early aspirin discontinuation followed by $P2Y_{12}$ inhibitor monotherapy has been suggested as an alternative to standard DAPT.[32] The first large randomized study to test this novel paradigm in antiplatelet therapy was GLOBAL LEADERS. In this trial, 23-month ticagrelor monotherapy after 1-month DAPT was not superior to 12-month DAPT in an all-comers population in whom 16.6% of patients were considered at HBR (as defined by a PRECISE-DAPT score ≥25).[33,34] Conversely, in the TWILIGHT trial, which preferentially enrolled patients at high risk for both bleeding and ischaemic events, ticagrelor monotherapy after 3-month DAPT, compared with ticagrelor plus aspirin, was shown to reduce bleeding without compromising antithrombotic efficacy.[12,13] The study clinical and angiographic inclusion criteria, however, were relatively broad and only partially overlapped with current definitions of high bleeding and ischaemic risk. Patients with an indication for chronic oral anticoagulation, which is generally the most prevalent inclusion criterion in HBR trials, prior stroke, planned surgery within 90 days, or other disorders at extreme risk for major bleeding were excluded. Dialysis, platelet count $<100 \times 10^9$/L, and liver disease were also trial exclusion criteria, but some patients with these conditions were enrolled

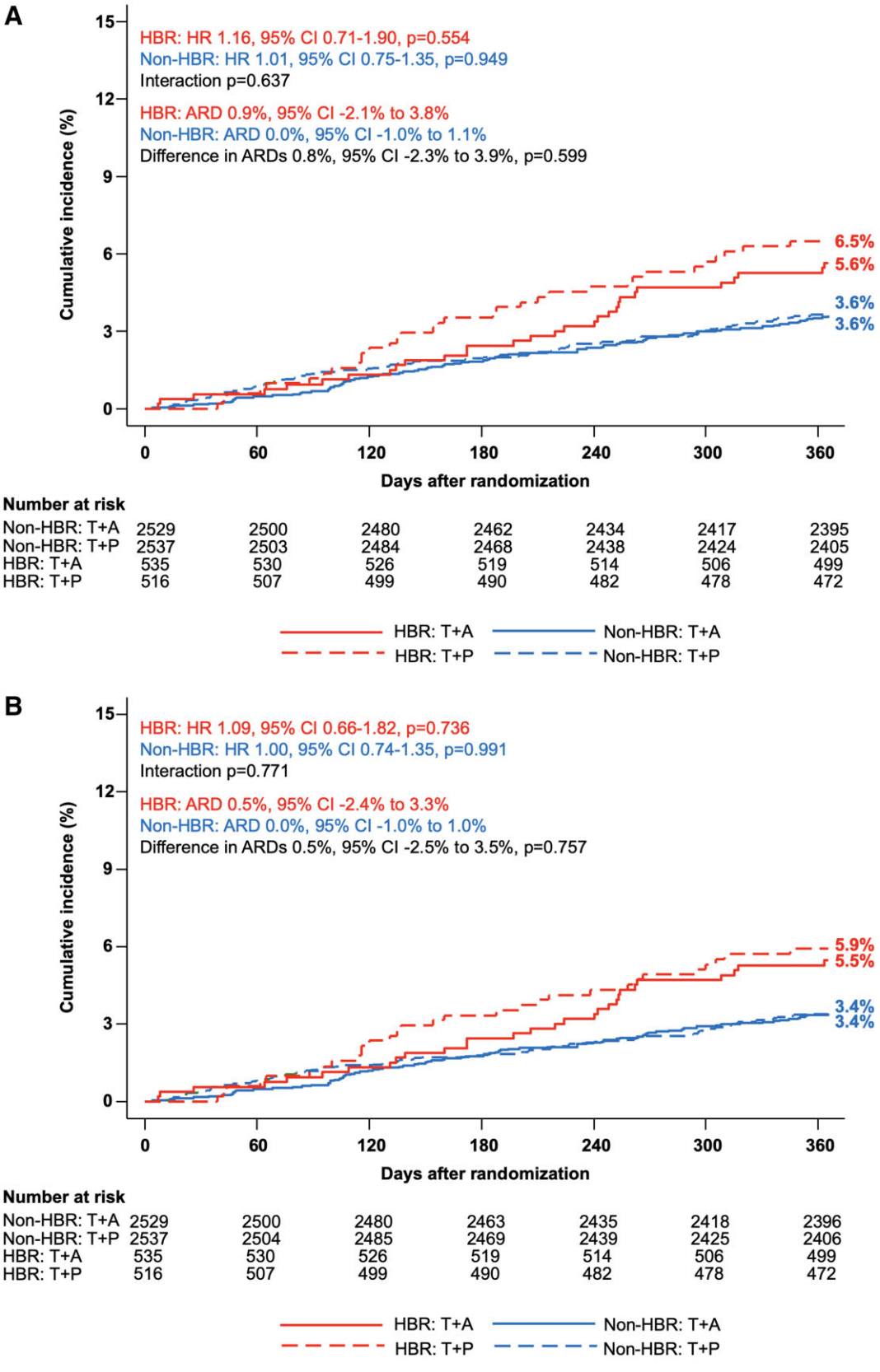


Figure 3 Rates of (*A*) death, myocardial infarction, or stroke and (*B*) cardiovascular death, myocardial infarction, or ischaemic stroke at 1 year. Kaplan–Meier curves for ticagrelor plus placebo vs. ticagrelor plus aspirin in patients with and without high bleeding risk in the per-protocol cohort. A, aspirin; ARD, absolute risk difference; CI, confidence interval; HBR, high bleeding risk; HR, hazard ratio; P, placebo; T, ticagrelor.

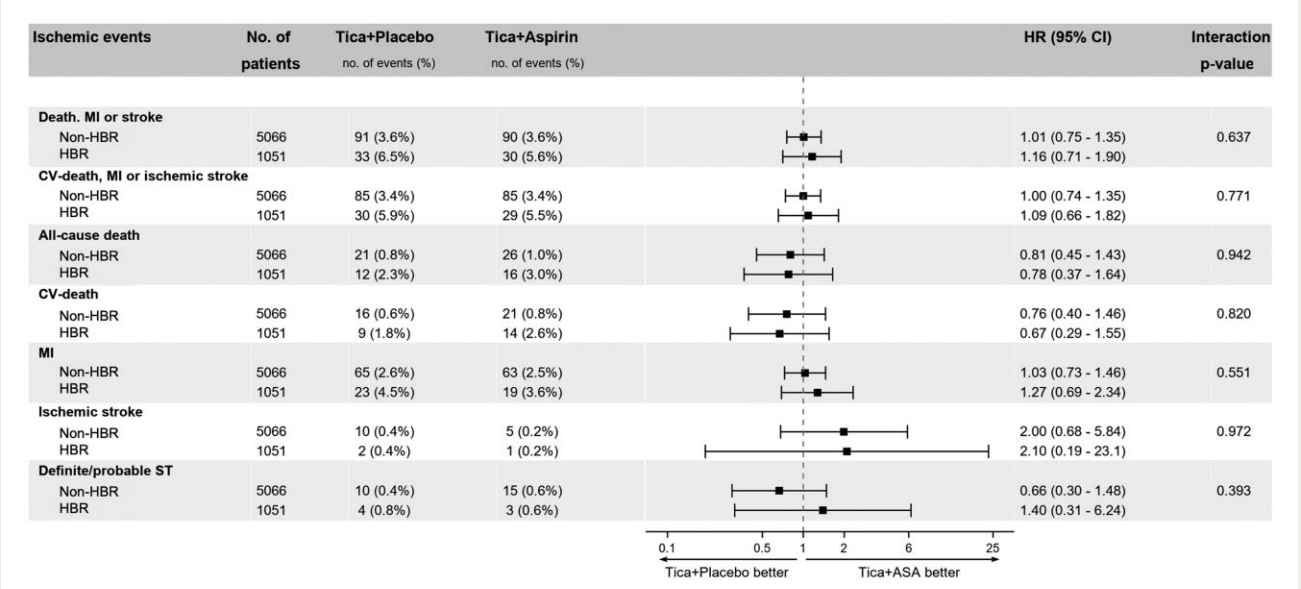


Figure 4 Risk of ischaemic events at 1 year. Forest plot showing the effect of ticagrelor plus placebo vs. ticagrelor plus aspirin on the ischaemic endpoints according to high bleeding risk status. Ischaemic outcomes were analysed in the per-protocol cohort. CI, confidence interval, CV, cardiovascular, HBR, high bleeding risk; HR, hazard ratio, MI, myocardial infarction, ST, stent thrombosis.

and thus were considered for the analysis. While the proportion of ARC-defined HBR patients in the present study (17.2%) was lower than what was reported in previous all-comer registries, it must be noted that only patients deemed eligible for long-term DAPT with ticagrelor could be enrolled in the trial. A large number of TWILIGHT patients were indeed at high ischaemic risk with two-thirds undergoing PCI for non-ST-elevation ACS, one-third having a complex PCI procedure and 37% being diabetic.[35–37] In this context, ticagrelor monotherapy after 3-month DAPT represents an important bleeding avoidance strategy among HBR patients with concomitantly elevated ischaemic risk whom the treating physician intend to discharge on a potent $P2Y_{12}$ inhibitor. Furthermore, the distribution of major and minor criteria, except for those excluded, was comparable with that of previous ARC-HBR validation studies, thereby supporting the external validity of our findings.[10,11]

Current European guidelines on non-ST-elevation ACS reserve a strategy of ticagrelor monotherapy after 3-month DAPT for low-risk patients, a recommendation justified by the lower than expected rates of adverse events observed in TWILIGHT at 1 year.[38] Against this background, our results suggest that the treatment effects of ticagrelor monotherapy reported in the main trial are preserved in higher risk cohorts who meet the ARC-HBR definition. Of note, the incidence of the primary BARC 2, 3, or 5 bleeding endpoint was nearly doubled in HBR vs. non-HBR patients, while BARC 3 or 5 bleeding was increased by more than three times. This gradient in risk was even greater when considering the number of ARC-HBR criteria fulfilled. Owing to their risk profile, the absolute reduction in bleeding risk realized with the experimental strategy was significantly larger in HBR than non-HBR patients. This benefit was achieved despite poorer adherence to study medications, partly due to the higher event rates. Similar results have been reported in a subgroup analysis of the STOPDAPT-2 trial looking at the effects of 1-month DAPT followed by clopidogrel monotherapy vs. 12-month DAPT among HBR patients.[39] However, that study was limited by very low bleeding rates and included only Japanese patients—a group known to have an ischaemic-bleeding risk profile different than non-East Asian populations.[40]

Following the publication of the ARC-HBR consensus, a BARC 3 or 5 bleeding rate cut-off of 4% at 1 year post-PCI has been proposed to identify actual HBR cohorts objectively.[14] In TWILIGHT, the initial 3-month blanking period and the exclusion of patients ineligible to 12-month DAPT with ticagrelor (such as those on chronic oral anticoagulant therapy) may have led to a BARC 3 or 5 bleeding rate slightly below this threshold. Nonetheless, ticagrelor monotherapy reduced the incidence of BARC 3 or 5 bleeding in HBR patients from 5.0% to 1.6%. Importantly, the bleeding-related benefit of early aspirin discontinuation seem to extend beyond the first year post-PCI, as suggested by a recent head-to-head comparison between clopidogrel and aspirin monotherapy for secondary cardiovascular prevention.[41]

Avoiding a trade-off in antithrombotic efficacy is the most challenging aspect of any bleeding reduction strategy involving short DAPT. Although shortened exposure to DAPT may be particularly beneficial in HBR patients, many such patients are also at increased risk for thrombosis.[42] In fact, in TWILIGHT, ischaemic event rates were ~70% higher in presence of HBR—reflecting the fact that clinical conditions such as diabetes, peripheral artery disease, and multivessel disease were more common among these patients. Notwithstanding this correlation, ticagrelor monotherapy, compared with ticagrelor plus aspirin, did not increase the key secondary endpoint of death, MI, or stroke, in either HBR or non-HBR patients. The net treatment effects of ticagrelor monotherapy are consistent with pharmacodynamic observations of a marginal antiplatelet effect of aspirin when

added to potent $P2Y_{12}$ inhibitors,[43,44] although data specific to HBR cohorts are lacking. Last, risk prediction models, such as the ARC-HBR trade-off model, may help clinicians in tailoring antithrombotic therapies based on the estimated ischaemic and bleeding risk of each individual.[42] Future studies should evaluate the utility of these new risk assessment tools in personalized medicine to improve outcomes of HBR patients.

Despite being a prespecified analysis from a large randomized, placebo-controlled clinical trial, our study has important limitations inherent to all subgroup analyses. HBR status was determined according to the ARC-HBR definition, which has been validated previously.[23] Nonetheless, the dichotomous nature of the ARC-HBR definition limits its ability to accurately risk stratify across the spectrum of HBR patients. It is encouraging, however, that no signals of heterogeneity in the relative treatment effects were seen when the ARC-HBR score was applied. Not all ARC-HBR criteria were available for the analysis, and while some of those were not collected in the study case report form, others were actually exclusion criteria for the trial. Our findings do not apply to other $P2Y_{12}$ inhibitors and to patients who do not otherwise meet the study enrolment criteria and who were not event-free and adherent to treatment at 3 months after PCI. The present study was underpowered to detect clinically relevant differences in ischaemic events, and the wide CIs do not rule out a potential for harm of the experimental strategy among HBR patients. Hence, our findings must be seen as hypothesis-generating and warrant prospective confirmation in dedicated studies using the ARC-HBR criteria.

In conclusion, among selected HBR patients who tolerated 3 months of DAPT with ticagrelor after PCI with a drug-eluting stent, withdrawing aspirin and continuing ticagrelor monotherapy significantly decreased clinically relevant as well as major bleeding events without compromising ischaemic protection, as compared with ticagrelor plus aspirin. As a bleeding avoidance strategy, ticagrelor monotherapy was associated with a larger absolute reduction in major bleeding events among HBR vs. non-HBR patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

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

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