Ticagrelor Monotherapy in Patients at High Bleeding Risk Undergoing Percutaneous Coronary Intervention: TWILIGHT-HBR

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ABSTRACT

Background: 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.

Methods and Results: This prespecified analysis of the TWILIGHT trial evaluated the treatment effects of ticagrelor with or without aspirin in HBR patients undergoing PCI with drug-eluting stents. Following 3 months of ticagrelor plus aspirin, event-free patients were randomized to 12-month treatment with 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 consistently in HBR (6.3% vs. 11.4%; HR 0.53, 95% CI 0.35–0.82) and non-HBR patients (3.5% vs. 5.9%; HR 0.59, 95% CI 0.46–0.77; $p_{interaction}$=0.67), but the absolute risk difference was greater in the former. A similar pattern was observed for more severe BARC 3 or 5 bleeding ($p_{interaction}$=0.15). There was no significant difference in the key secondary endpoint of death, myocardial infarction, or stroke between treatment arms, irrespective of HBR status ($p_{interaction}$=0.64).

Conclusions: Among HBR patients undergoing PCI who completed 3 months of DAPT, continuation of ticagrelor monotherapy, compared with ticagrelor plus aspirin, significantly reduced bleeding without increasing ischemic events. The absolute reduction in bleeding risk was larger in HBR than non-HBR patients, thus highlighting the benefit of appropriate bleeding-avoidance strategies in this vulnerable cohort.

Keywords: high bleeding risk; ARC-HBR; ticagrelor monotherapy; aspirin; PCI

INTRODUCTION

For over twenty years, a combination of aspirin and a $P2Y_{12}$ inhibitor has been the mainstay therapeutic 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 tradeoff between ischemic and bleeding risks. Prasugrel and ticagrelor demonstrated superior ischemic protection compared with clopidogrel among patients with acute coronary syndromes on a background aspirin therapy.[4, 5] However, such benefit was almost invariably counterbalanced by an increased bleeding risk consequent to the incremental platelet inhibition. Although formerly considered benign events, bleeding complications after PCI have shown an impact on patient prognosis similar to that of thrombotic events.[6, 7]

Contemporary advancements in device technologies and pharmacological strategies have allowed extending the indication to PCI to older and more vulnerable cohorts.[8, 9] An increasing number of patients undergoing PCI have high bleeding risk (HBR) conditions such as advanced age and anemia, 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 in patients at high risk of adverse events.[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 enrollment if they satisfied at least one clinical and one angiographic criterion associated with a high risk of ischemic or bleeding events. Clinical criteria included age ≥65 years, female sex, troponin positive acute coronary syndrome (ACS), atherosclerotic vascular disease (prior myocardial infarction, coronary revascularization or peripheral arterial 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 2 stents, obstructive left main or proximal left anterior descending lesion, and calcified target lesion requiring debulking devices. Key exclusion criteria included presentation with ST-segment elevation myocardial infarction, 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 ischemic 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 BARC type 2, 3, or 5 bleeding up to 1 year after randomization. The key secondary endpoint was the composite of all-cause death, myocardial infarction (MI), or stroke. Secondary bleeding endpoints included (BARC) type 3 or 5 bleeding, Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding, Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate or severe or bleeding, and International Society of Thrombosis or Hemostasis (ISTH) major bleeding.[15-18] Other secondary ischemic endpoints included the composite of cardiovascular death, non-fatal MI, or ischemic stroke, its individual components, and definite or probable stent thrombosis. MI was defined according to the third universal definition, and stent thrombosis were classified according to the ARC.[19, 20] 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.[14] Major criteria available for analysis were severe or end-stage chronic CKD (i.e., estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 or dialysis), hemoglobin <11 g/dL, moderate or severe thrombocytopenia (i.e., platelet count <100×10^9/L), previous major bleeding, and liver disease. Minor criteria included age ≥75 years, moderate CKD (i.e., eGFR ≥30 and <60 mL/min/1.73m^2), hemoglobin ≥11 and <13 g/dL for men and ≥11 and <12 g/dL for women, and nonsteroidal anti-inflammatory drug (NSAIDs) use.

Baseline laboratory values were obtained locally at each site and collected during the enrollment procedure. The eGFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[21] **Supplementary Table 1** summarizes the list of available major and minor criteria and their definitions compared with those provided in the original ARC-HBR document.[14] Patients without sufficient information on major or minor criteria to ascertain HBR status were excluded from the analysis.

Statistical Analyses

In the primary prespecified analysis, the treatment effects of ticagrelor monotherapy versus ticagrelor plus aspirin were evaluated according to HBR status, with formal interaction testing to assess effect modification. 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 (HR) and 95% confidence intervals (CI) were generated using Cox proportional hazards models. Absolute risk differences (ARDs) and 95% CI for ischemic and bleeding events were calculated with Kaplan-Meier estimates and Greenwood standard errors.

We performed an exploratory analysis to examine the effects of ticagrelor monotherapy according to the number of ARC-HBR criteria satisfied. An ARC-HBR score was built, assigning 0.5 point to each minor criterion and 1 point to each major criterion. Patients were then stratified into those without any criteria (0 point) or with only 1 minor criterion (0.5 point) if non-HBR, and into those with 1 major or 2 minor criteria (1 point), or with multiple ARC-HBR

criteria (≥1.5 points) if HBR. For all analyses, bleeding outcomes were assessed in the intention-to-treat cohort, while ischemic outcomes were analyzed using the per-protocol cohort. A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using Stata version 16.0 (College Station, Texas).

RESULTS

Patient Characteristics

Of the 7119 randomized patients, 587 (8.2%) were excluded due country-specific regulatory reasons and 354 (5.0%) had missing information on ARC-HBR status. Hence, the final study cohort included 6178 patients, of whom 1064 (17.2%) were HBR (**Supplementary Figure 1**). HBR patients were older, more frequently female and of nonwhite 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. Rates of presentation with non-ST-segment ACS did not differ between the two groups (62.1% vs. 63.8%; p=0.308) (**Table 1**). Among HBR patients, moderate CKD and age ≥75 years were the two most common criteria overall (55.4% and 49.4%, respectively), while hemoglobin <11 g/dL was the most common major criterion (24.2%). With respect to angiographic and procedural features, HBR patients were less likely to undergo PCI via radial access, and more often had multivessel disease, left main PCI, and calcific lesions than non-HBR patients (**Table 2**). Baseline characteristics stratified by randomized treatment arm are provided in **Supplementary Tables 2 and 3**.

At 12 months after randomization, HBR patients were less adherent to the blinded study drug (74.5% vs 83.70%, p<0.001) and ticagrelor (79.2% vs. 87.70%, p<0.001) than non-HBR

patients, while there were no significant differences between randomized treatment arms within the two groups (**Supplementary Figure 2**).

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 to 2.48; p<0.001) (**Supplementary Figure 3A**). Ticagrelor plus aspirin reduced 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 to 0.82; p=0.004) for an absolute risk difference 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 to 0.77; p<0.001) with no evidence of heterogeneity ($p_{interaction}$=0.673) (**Figure 1A, Supplementary Table 3**).

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 to 5.07; p<0.001) (**Supplementary Figure 3B**). 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 to 0.67, 0.003) and non-HBR patients (0.8% vs. 1.3%; HR 0.62, 95% CI 0.36 to 1.09, p=0.098; $p_{interaction}$=0.148), but with an ARD greater in the former group (-3.5%, 95% CI -5.6% to -1.3% vs. -0.5%, 95% CI -1.0% to 0.1%). There was no significant interaction between HBR status and treatment arm for any of the bleeding endpoints (**Figure 2**).

Ischemic 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 1.26 to 2.26; p<0.001) (**Supplementary Figure 4**). The rates of all-cause death, MI, or stroke were similar among HBR

patients randomized to ticagrelor plus placebo versus ticagrelor plus aspirin (6.5% vs. 5.6%; HR 1.16, 95% CI 0.71 to 1.90; p=0.554) for an ARD of 0.9% (95% CI -2.1% to 3.8%) (**Figure 3, Supplementary Table 4**). Furthermore, there were no significant differences between treatment arms among HBR patients with respect to the composite of cardiovascular death, MI, or ischemic stroke (5.9% vs. 5.5%), as well as for the individual rates of cardiovascular death (1.8% vs. 2.6%), MI (4.5% vs 3.6%), ischemic stroke (0.4% vs 0.2%), and definite or probable stent thrombosis (0.8% vs. 0.6%) (**Figure 4**). Similar treatment effects of ticagrelor monotherapy on 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 to 1.35, p=0.949; $p_{interaction}$=0.647) and other ischemic endpoints were observed among non-HBR patients.

Exploratory analyses

After stratification of patients by the number of ARC-HBR criteria, 3605 (58.4%) had none, 1509 (24.4%) had only 1 minor criterion, 725 (11.7%) had either 1 major or 2 minor criteria, and 339 (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 ischemic events (**Supplementary Figure 5**). The treatment effects of ticagrelor monotherapy on bleeding and ischemic endpoints were preserved across all HBR subgroups (**Supplementary Figures 6 and 7**).

DISCUSSION

The principal findings from this prespecified analysis of the TWILIGHT trial are that: 1) HBR patients experienced higher rates of both bleeding and ischemic events, with a risk proportional to the number of ARC-HBR criteria fulfilled; 2) ticagrelor monotherapy lowered the risk of clinically relevant BARC 2, 3, or 5 bleeding without increasing ischemic events, including death, MI or stroke, irrespective of HBR status; 3) the reduction in major bleeding complications associated with ticagrelor monotherapy was more pronounced in HBR versus non-HBR patients and resulted in a larger absolute risk reduction in the former group; 4) the treatment effects on ischemic 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 ischemic risk features who undergo PCI with a drug-eluting stent.

PCI indications have extended to increasingly complex patient populations over the last decade.[22] As a result, a large number of patients undergoing PCI present with clinical and comorbid conditions that increase periprocedural and long-term bleeding risk. As bleeding complications after PCI are intrinsically related to the duration and intensity of antithrombotic therapy,[23, 24] short-term and monotherapy antiplatelet regimens seem sensible among HBR patients.[25, 26] However, this attitude is hampered by the fact that, on one hand, HBR patients have been typically excluded or underrepresented in clinical research on DAPT and, on the other, they show an increased risk of ischemic events derived from more complex anatomical substrates and comorbid conditions.[10, 11] While newer stent platforms have been tested among HBR patients receiving an abbreviated DAPT regimen followed by aspirin monotherapy [27-29] 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.[30] 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 shown superior to 12-month DAPT in an all-comer population in whom 16.6% of patients were considered at HBR (as defined by a PRECISE-DAPT score ≥25).[31, 32] Conversely, ticagrelor monotherapy after 3-month DAPT, compared with ticagrelor plus aspirin, was shown to reduce bleeding without compromising antithrombotic efficacy in the TWILIGHT trial.[12] The latter specifically enrolled patients at high risk for both bleeding and ischemic events.[13] The study clinical and angiographic inclusion criteria, however, were relatively broad and only partially overlapped with current definitions of high bleeding and ischemic 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 $<100\times10^9$/L, and liver disease were also trial exclusion criteria, but some patients with these conditions were enrolled 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 to a long-term DAPT with ticagrelor could be enrolled in the trial. 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-segment ACS reserve a strategy of ticagrelor monotherapy after 3-month DAPT to low-risk patients, a recommendation justified by the lower-than-expected rates of adverse events observed in TWILIGHT at 1 year. 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 was nearly doubled in HBR vs. non-HBR patients, while BARC 3 or 5 bleeding was increased by more than 3 times. This gradient in risk was further magnified when taking into account the number of ARC-HBR criteria fulfilled. Owing to their risk profile, the relative and absolute reduction in bleeding risk realized with the experimental strategy was numerically larger in HBR than non-HBR patients. This benefit was achieved despite poorer adherence to study medications, possibly due to the higher rates of adverse events. Similar results have been reported in a subgroup analysis of the STOP DAPT-2 trial looking at the effects of 1-month DAPT followed by clopidogrel monotherapy versus 12-month DAPT among HBR patients.[33] However, the study was limited by very low bleeding rates and included only Japanese patients, known to have an ischemic-bleeding risk profile different than non-East Asian populations.[34] Following the publication of the ARC-HBR consensus, a BARC 3 o 5 bleeding rate cutoff of 4% at 1 year post-PCI has been proposed to identify actual HBR cohorts objectively.[14] Despite the initial 3-month blanking period and the randomization of event-free patients in TWILIGHT may have mitigated the 1-year event rates, 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.[35]

Avoiding a tradeoff 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, the majority of those are also at increased risk for thrombosis. This issue was markedly evident in our study where not only ischemic events, but also clinical conditions like diabetes, peripheral artery disease, and multivessel disease were more frequent among HBR patients. The lower use of an established bleeding-reduction strategy such as radial access in this group likely reflects the higher anatomical and procedural complexity. Notwithstanding, ticagrelor monotherapy, compared with ticagrelor plus aspirin, did not increase the key secondary endpoint of death, MI, or stroke, irrespective of HBR status, which may reassure on the safety of this approach among high risk cohorts.

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.[36] Nonetheless, the dichotomous nature of the ARC-HBR definition limits its ability to accurately risk stratify all the spectrum of HBR patients. It is encouraging, however, that no signals of heterogeneity in the treatment effects were seen when the ARC-HBR score was applied. Not all twenty ARC-HBR criteria were available for the analysis, and while some of those were not collected in the study case report form, others were indeed exclusion criteria (e.g., use of long-term anticoagulation). Our findings do not apply to other $P2Y_{12}$ inhibitors and to patients who do not otherwise meet the study enrollment criteria and who were not event-free and adherent to treatment at 3 months after PCI. The present study was underpowered to detect rare yet clinically relevant differences in ischemic events, and the wide confidence intervals 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 from dedicated studies using the ARC-HBR criteria.

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

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FIGURE LEGENDS

Figure 1. Rates of (a) BARC 2, 3, or 5 bleeding and (b) BARC 3 or 5 at 1 year. Kaplan-Meier curves for ticagrelor plus placebo versus ticagrelor plus aspirin in patients with and without high bleeding risk (HBR) in the intention to treat cohort. BARC: Bleeding Academic Research Consortium, HR: hazard ratio, CI: confidence interval, A: aspirin, P: placebo, T: ticagrelor.

Figure 2. Risk of bleeding events at 1 year. Forest plots showing the effect of ticagrelor plus placebo versus ticagrelor plus aspirin on the bleeding endpoints according to high bleeding risk (HBR) status. Bleeding outcomes were analyzed in the intention-to-treat cohort. HR: hazard ratio, CI: confidence interval, BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis.

Figure 3. Rates of (a) death, MI, or stroke and (b) cardiovascular death, MI, or ischemic stroke at 1 year. Kaplan-Meier curves for ticagrelor plus placebo versus ticagrelor plus aspirin in patients with and without high bleeding risk (HBR) in the per-protocol cohort. HR: hazard ratio, CI: confidence interval, A: aspirin, P: placebo, T: ticagrelor.

Figure 4. Risk of ischemic events at 1 year. Forest plots showing the effect of ticagrelor plus placebo versus ticagrelor plus aspirin on the ischemic endpoints according to high bleeding risk (HBR) status. Ischemic outcomes were analyzed in the per-protocol cohort. HR: hazard ratio, CI: confidence interval, CV: cardiovascular, MI: myocardial infarction, ST: stent thrombosis.

TABLES

Table 1. Baseline clinical characteristics.

Clinical characteristics	HBR N=1064 (17.2%)	Non-HBR N=5114 (82.8%)	p-value
Age, years	71.9±10.3	62.3±9.3	<0.001
Female sex	354 (33.3%)	1101 (21.5%)	<0.001
Nonwhite 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%)	<0.001
Anemia	708 (67.5%)	472 (9.2%)	<0.001
Current smoker	110 (10.4%)	1219 (23.8%)	<0.001
Hypercholesterolemia	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%)	<0.001
Indication for PCI			0.308
Stable CAD	403 (37.9%)	1852 (36.2%)	
ACS	661 (62.1%)	3261 (63.8%)	

Clinical characteristics	HBR N=1064 (17.2%)	Non-HBR N=5114 (82.8%)	p-value
HBR major criteria			
eGFR <30 mL/min/1.73m^2 or dialysis	73 (6.9%)	0 (0.0%)	<0.001
Hemoglobin <11 g/dL	254 (24.2%)	0 (0.0%)	<0.001
Previous major bleeding	54 (5.1%)	0 (0.0%)	<0.001
Liver disease	23 (2.2%)	0 (0.0%)	<0.001
Platelet <100×10^9/L	3 (0.3%)	0 (0.0%)	0.005
HBR minor criteria			
Age ≥75 years	526 (49.4%)	330 (6.5%)	<0.001
30≤ eGFR <60 mL/min/1.73m^2	585 (55.4%)	402 (7.9%)	<0.001
Hemoglobin (g/dL) ≥11 and <13 for men and ≥11 and <12 for women	454 (43.3%)	472 (9.2%)	<0.001
Use of NSAIDs	212 (20.3%)	305 (6.0%)	<0.001

HBR: high bleeding risk, BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACS: acute coronary syndrome, eGFR: estimated glomerular filtration rate, NSAIDS: nonsteroidal anti-inflammatory drugs.

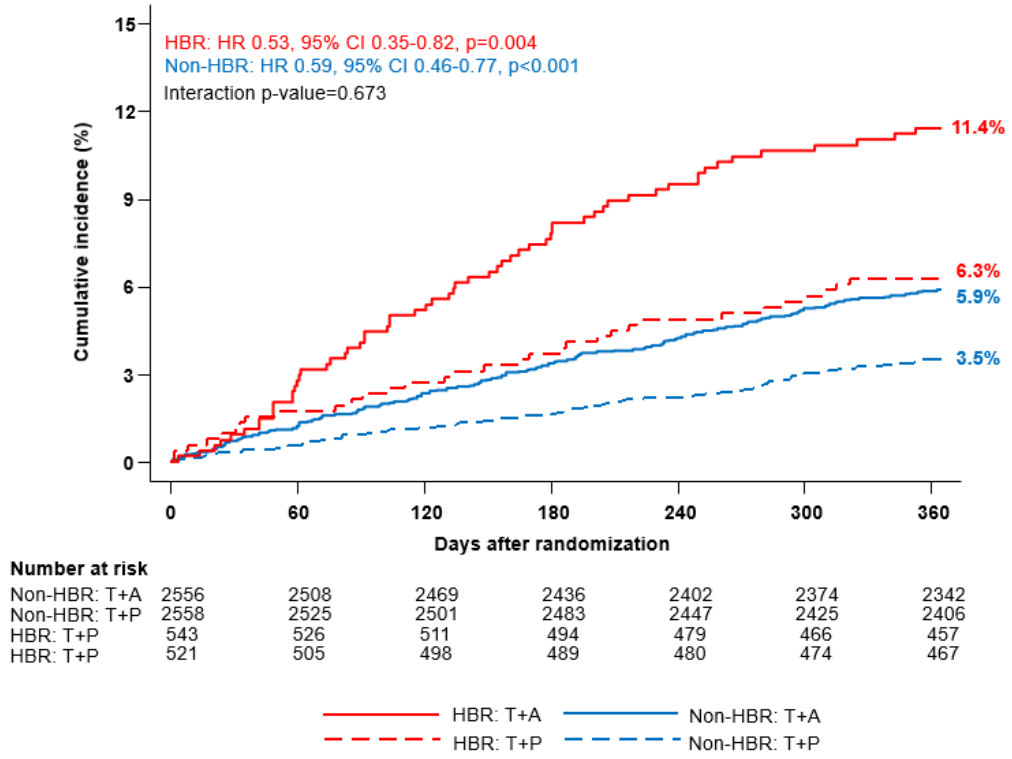
Table 2. Baseline procedural characteristics.

Procedural characteristics	**HBR N=1064 (17.2%)**	**Non-HBR N=5114 (82.8%)**	**p-value**
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
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

HBR: high bleeding risk, CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery

Figure 1. Rates of (a) BARC 2, 3, or 5 and (b) BARC 3 or 5 bleeding at 1 year.

a)



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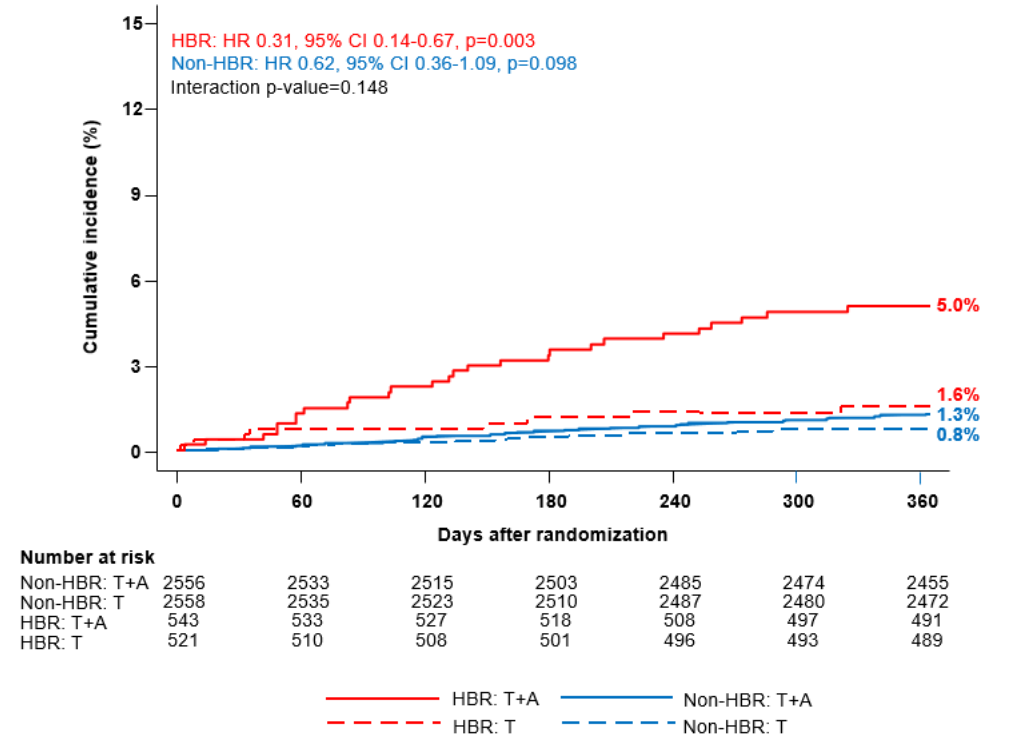


Figure 2. Risk of bleeding events at 1 year.

Bleeding events	No. of patients	Tica+Placebo no. of events (%)	Tica+Aspirin no. of events (%)	HR (95% CI)	Interaction p-value
BARC 2, 3, or 5					
Non-HBR	5114	89 (3.5%)	148 (5.9%)	0.59 (0.46 - 0.77)	0.673
HBR	1064	32 (6.3%)	61 (11.4%)	0.53 (0.35 - 0.82)	
BARC 3, or 5					
Non-HBR	5114	20 (0.8%)	32 (1.3%)	0.62 (0.36 - 1.09)	0.148
HBR	1064	8 (1.6%)	27 (5.0%)	0.31 (0.14 - 0.67)	
TIMI major					
Non-HBR	5114	13 (0.5%)	17 (0.7%)	0.76 (0.37 - 1.57)	0.080
HBR	1064	2 (0.4%)	12 (2.2%)	0.17 (0.04 - 0.78)	
GUSTO moderate or severe					
Non-HBR	5114	14 (0.6%)	17 (0.7%)	0.82 (0.41 - 1.67)	0.109
HBR	1064	8 (1.6%)	24 (4.5%)	0.35 (0.16 - 0.77)	
ISTH major					
Non-HBR	5114	22 (0.9%)	35 (1.4%)	0.63 (0.37 - 1.07)	0.203
HBR	1064	9 (1.8%)	27 (5.0%)	0.35 (0.16 - 0.73)	

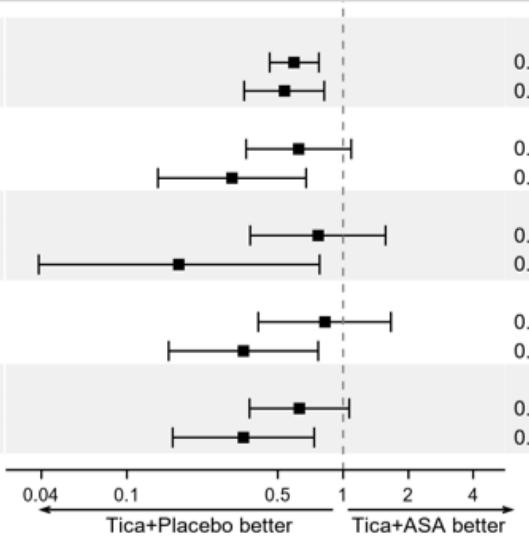
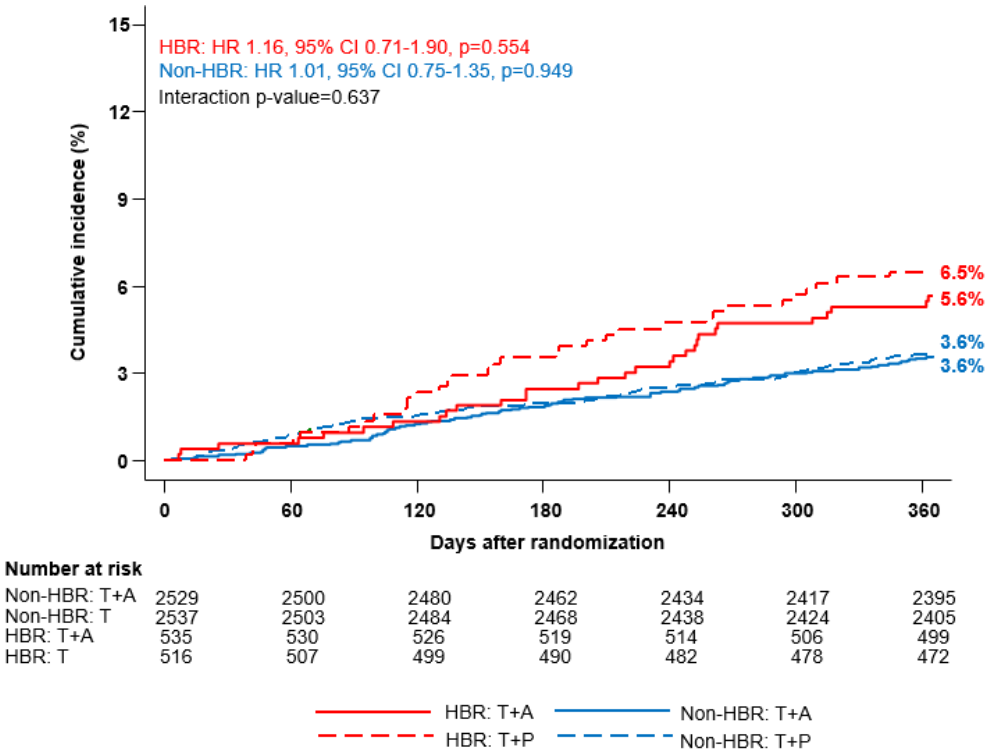


Figure 3. Rates of (a) death, MI, or stroke and (b) cardiovascular death, MI, or ischemic stroke at 1 year.

a)



b)

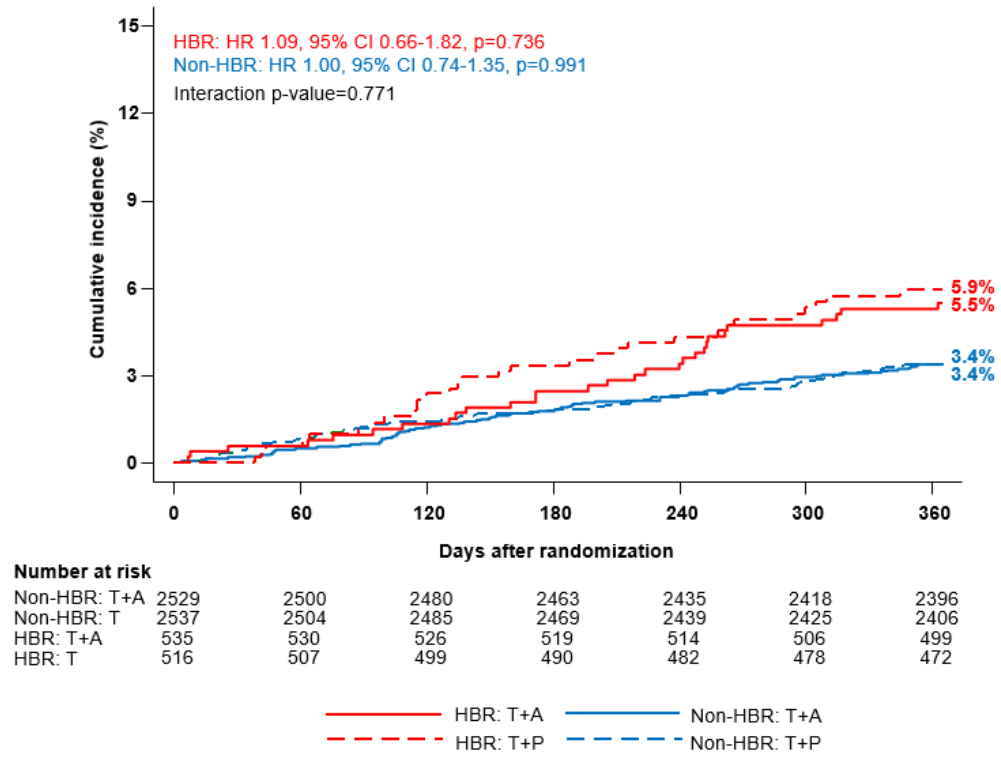
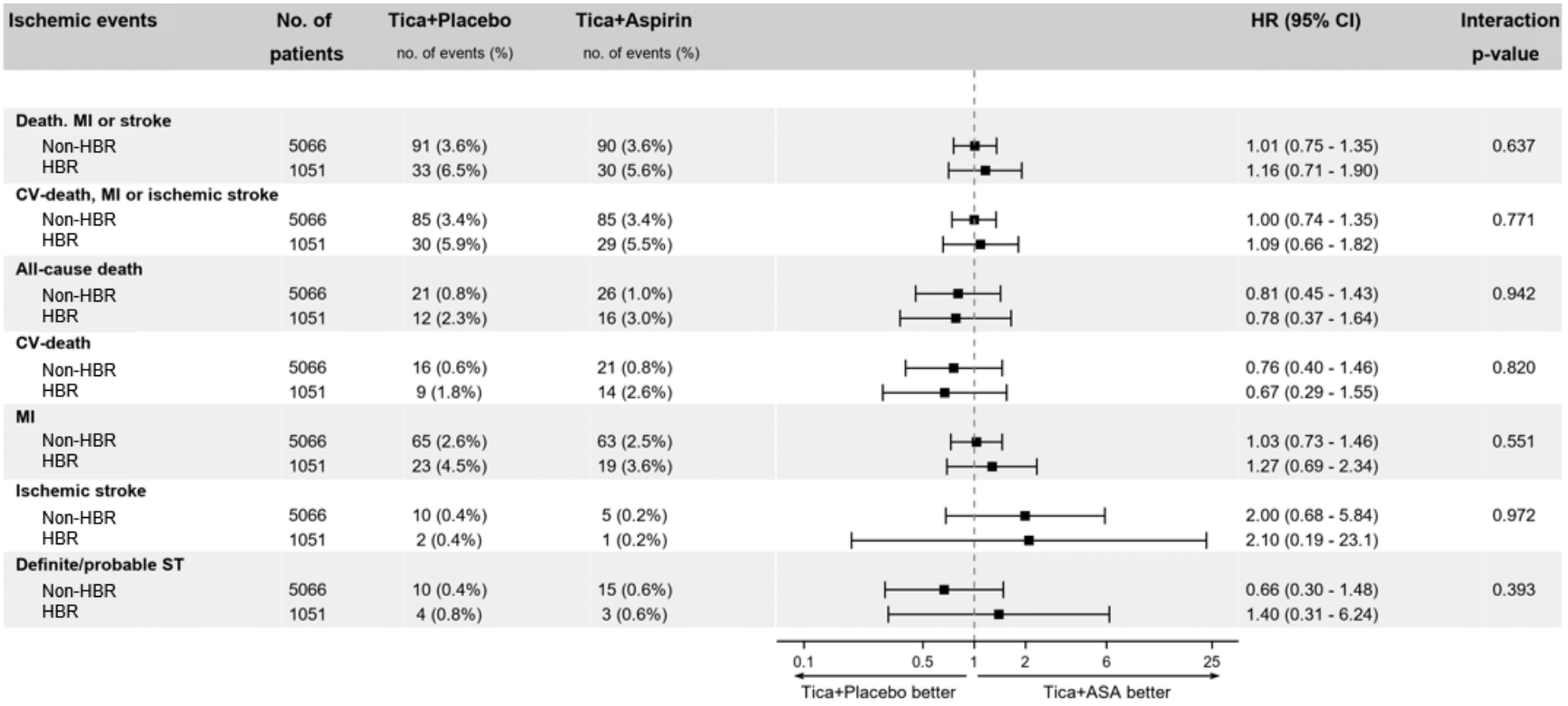


Figure 4. Risk of ischemic events at 1 year.



SUPPLEMENETARY MATERIAL

Ticagrelor Monotherapy in Patients at High Bleeding Risk Undergoing Percutaneous Coronary Intervention: TWILIGHT-HBR

Table of contents

Supplementary Table 1. Study definitions for major and minor ARC-HBR criteria compared with the original definitions from the ARC-HBR document.

ARC-HBR criteria	Study definition	ARC-HBR document definition[1]
Major criteria		
Severe/end-stage CKD	eGFR <30 mL/min	No difference
Moderate/severe anemia	Hemoglobin <11 g/dL	No difference
Thrombocytopenia	Platelet count <100x10^9/L	No difference
Liver disease	Any liver disease	Liver cirrhosis with portal hypertension
Prior major bleeding	Prior major bleeding requiring transfusion or hospitalization	Spontaneous bleeding in the past 6 months or at any time, if recurrent
	N/A	Non-deferrable major surgery on dual antiplatelet therapy
	N/A	Chronic bleeding diathesis
	N/A	Previous spontaneous ICH; traumatic ICH within the past 12 months; presence of bAVM; ischemic stroke within the past 6 months
	N/A	Recent major surgery or major trauma within 30 days before PCI
	N/A	Anticipated use of long-term oral anticoagulation
	N/A	Active malignancy within the past 12 months
Minor criteria		
Age 75+	Age ≥75 years	No difference
Moderate CKD	eGFR 30–59 mL/min	No difference
Mild anemia	Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women	No difference
Long-term use of oral NSAIDs	Long-term use of oral NSAIDs	Long-term use of oral NSAIDs or steroids
	N/A	Spontaneous bleeding within the past 12 months not meeting the major criterion
	N/A	Any ischemic stroke at any time not meeting the major criterion

ARC-HBR = Academic Research Consortium for High Bleeding Risk; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; N/A = not available; NSAIDs = nonsteroidal anti-inflammatory drugs.[1]Definitions adapted from Urban P. et al., Circulation 2019;140:240-261.

Supplementary Table 2. Baseline clinical characteristics in HBR and non-HBR patients according to treatment arm.

Clinical characteristics	HBR (N=1064)			No HBR (N=5114)		
	Tica+Placebo N=521 (49.0%)	Tica+Aspirin N=543 (51.0%)	p-value	Tica+Placebo N=2558 (50.0%)	Tica+Aspirin N=2556 (50.0%)	p-value
Age, years	71.7±10.7	72.0±10.0	0.602	62.4±9.2	62.2±9.4	0.553
Female sex	167 (32.1%)	187 (34.4%)	0.409	560 (21.9%)	541 (21.2%)	0.528
Nonwhite race	150 (28.8%)	143 (26.3%)	0.370	619 (24.2%)	593 (23.2%)	0.401
BMI, kg/m^2	28.5±5.9	28.8±6.0	0.376	29.0±5.6	28.9±5.6	0.830
Enrolling region			0.857			0.735
North America	267 (51.2%)	278 (51.2%)		1154 (45.1%)	1153 (45.1%)	
Europe	166 (31.9%)	167 (30.8%)		999 (39.1%)	1017 (39.8%)	
Asia	88 (16.9%)	98 (18.0%)		405 (15.8%)	386 (15.1%)	
Diabetes	239 (45.9%)	264 (48.6%)	0.370	900 (35.2%)	877 (34.3%)	0.512
Diabetes treated with insulin	74 (31.0%)	109 (41.3%)	0.016	214 (23.8%)	219 (25.0%)	0.558
Chronic kidney disease	304 (59.1%)	340 (62.7%)	0.232	216 (8.4%)	186 (7.3%)	0.121
Anemia	347 (67.8%)	361 (67.2%)	0.850	247 (9.7%)	225 (8.8%)	0.292
Current smoker	52 (10.0%)	58 (10.7%)	0.708	567 (22.2%)	652 (25.5%)	0.005
Hypercholesterolemia	342 (65.6%)	371 (68.3%)	0.352	1677 (65.6%)	1651 (64.6%)	0.469
Hypertension	424 (81.4%)	441 (81.2%)	0.944	1839 (71.9%)	1847 (72.3%)	0.751
Peripheral arterial disease	66 (12.7%)	66 (12.2%)	0.800	162 (6.3%)	161 (6.3%)	0.960
Previous MI	146 (28.0%)	160 (29.5%)	0.603	770 (30.1%)	760 (29.7%)	0.774
Previous PCI	232 (44.5%)	251 (46.2%)	0.579	1121 (43.8%)	1101 (43.1%)	0.589
Previous CABG	81 (15.5%)	88 (16.2%)	0.769	259 (10.1%)	241 (9.4%)	0.399
Previous major bleed	27 (5.2%)	27 (5.0%)	0.876			
Indication for PCI			0.833			0.119
Stable CAD	199 (38.2%)	204 (37.6%)		953 (37.3%)	899 (35.2%)	
ACS	322 (61.8%)	339 (62.4%)		1604 (62.7%)	1657 (64.8%)	

Clinical characteristics	HBR (N=1064)			No HBR (N=5114)		
	Tica+Placebo N=521 (49.0%)	Tica+Aspirin N=543 (51.0%)	p-value	Tica+Placebo N=2558 (50.0%)	Tica+Aspirin N=2556 (50.0%)	p-value
HBR major criteria						
eGFR <30 mL/min/1.73m^2 or dialysis	39 (7.6%)	34 (6.3%)	0.405	0 (0.0%)	0 (0.0%)	N/A
Hemoglobin < 11 g/dL	120 (23.4%)	134 (25.0%)	0.567	0 (0.0%)	0 (0.0%)	N/A
Previous major bleeding	27 (5.2%)	27 (5.0%)	0.876	0 (0.0%)	0 (0.0%)	N/A
Liver disease	15 (2.9%)	8 (1.5%)	0.115	0 (0.0%)	0 (0.0%)	N/A
Platelet <100x10^9/L	0 (0.0%)	3 (0.6%)	0.250	0 (0.0%)	0 (0.0%)	N/A
HBR minor criteria						
Age ≥75 years	265 (50.9%)	261 (48.1%)	0.362	173 (6.8%)	157 (6.1%)	0.366
30≤ eGFR <60 mL/min/1.73m^2	273 (53.1%)	312 (57.6%)	0.146	216 (8.4%)	186 (7.3%)	0.121
Hemoglobin (g/dL) ≥11 and <13 for men and ≥11 and <12 for women	227 (44.3%)	227 (42.3%)	0.500	247 (9.7%)	225 (8.8%)	0.292
Use of NSAIDs	87 (17.0%)	125 (23.4%)	0.010	151 (6.0%)	154 (6.1%)	0.885

HBR: high bleeding risk, BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACS: Acute coronary syndrome, eGFR: estimated glomerular filtration rate, N/A: not available, NSAIDs: non-steroidal anti-inflammatory drugs.

Supplementary Table 3. Baseline procedural characteristics in HBR and non-HBR patients according to treatment arm.

Procedural characteristics	HBR (N=1064)			No HBR (N=5114)		
	Tica+Placebo N=521 (49.0%)	Tica+Aspirin N=543 (51.0%)	p-value	Tica+Placebo N=2558 (50.0%)	Tica+Aspirin N=2556 (50.0%)	p-value
Radial artery access	329 (63.1%)	329 (60.6%)	0.390	1874 (73.3%)	1867 (73.0%)	0.861
Multivessel CAD	356 (68.3%)	365 (67.2%)	0.698	1603 (62.7%)	1524 (59.6%)	0.026
Target vessel						
Left Main	29 (5.6%)	38 (7.0%)	0.336	95 (3.7%)	108 (4.2%)	0.349
LAD	303 (58.2%)	288 (53.0%)	0.093	1401 (54.8%)	1446 (56.6%)	0.194
LCX	174 (33.4%)	180 (33.1%)	0.932	823 (32.2%)	818 (32.0%)	0.896
RCA	171 (32.8%)	194 (35.7%)	0.318	907 (35.5%)	885 (34.6%)	0.532
Number of vessels treated	1.3±0.5	1.3±0.5	0.749	1.3±0.5	1.3±0.5	0.349
Number of lesions treated	1.6±0.8	1.5±0.7	0.084	1.5±0.7	1.5±0.7	0.629
Lesion morphology						
Moderate/severe calcification	105 (20.2%)	116 (21.4%)	0.627	339 (13.3%)	320 (12.5%)	0.434
Bifurcation	74 (14.2%)	58 (10.7%)	0.081	296 (11.6%)	309 (12.1%)	0.567
Total occlusion	28 (5.4%)	28 (5.2%)	0.874	147 (5.7%)	139 (5.4%)	0.631
Thrombotic	44 (8.4%)	49 (9.0%)	0.738	297 (11.6%)	301 (11.8%)	0.854
Total stent length, mm	41.3±26.6	38.1±23.1	0.038	38.4±22.6	38.8±23.7	0.607
Minimum stent diameter, mm	2.8±0.5	2.8±0.5	0.950	2.8±0.5	2.9±0.5	0.573

HBR: high bleeding risk, CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, PCI: percutaneous coronary intervention

Supplementary Table 4. Absolute risk difference in bleeding events at 1 year by HBR status.

Bleeding outcomes	HBR (N=1064)				Non-HBR (N=5114)			
	Tica+ placebo (N=521)	Tica+ Aspirin (N=543)	ARD (95% CI)	p-value	Tica+ placebo (N=2558)	Tica+ Aspirin (N=2556)	ARD (95% CI)	p-value
	no. of events (%)				*no. of events (%)*			
BARC 2, 3 or 5	32 (6.3%)	61 (11.4%)	-5.1% (-8.5%, -1.7%)	0.003	89 (3.5%)	148 (5.9%)	-2.3% (-3.5%, -1.2%)	<0.001
BARC 3 or 5	8 (1.6%)	27 (5.0%)	-3.5% (-5.6%, -1.3%)	0.001	20 (0.8%)	32 (1.3%)	-0.5% (-1.0%, 0.1%)	0.093
TIMI major	2 (0.4%)	12 (2.2%)	-1.8% (-3.2%, -0.5%)	0.008	13 (0.5%)	17 (0.7%)	-0.2% (-0.6%, 0.3%)	0.458
GUSTO moderate or severe	8 (1.6%)	24 (4.5%)	-2.9% (-5.0%, -0.9%)	0.005	14 (0.6%)	17 (0.7%)	-0.1% (-0.6%, 0.3%)	0.586
ISTH major	9 (1.8%)	27 (5.0%)	-3.3% (-5.5%, -1.1%)	0.003	22 (0.9%)	35 (1.4%)	-0.5% (-1.1%, 0.1%)	0.083

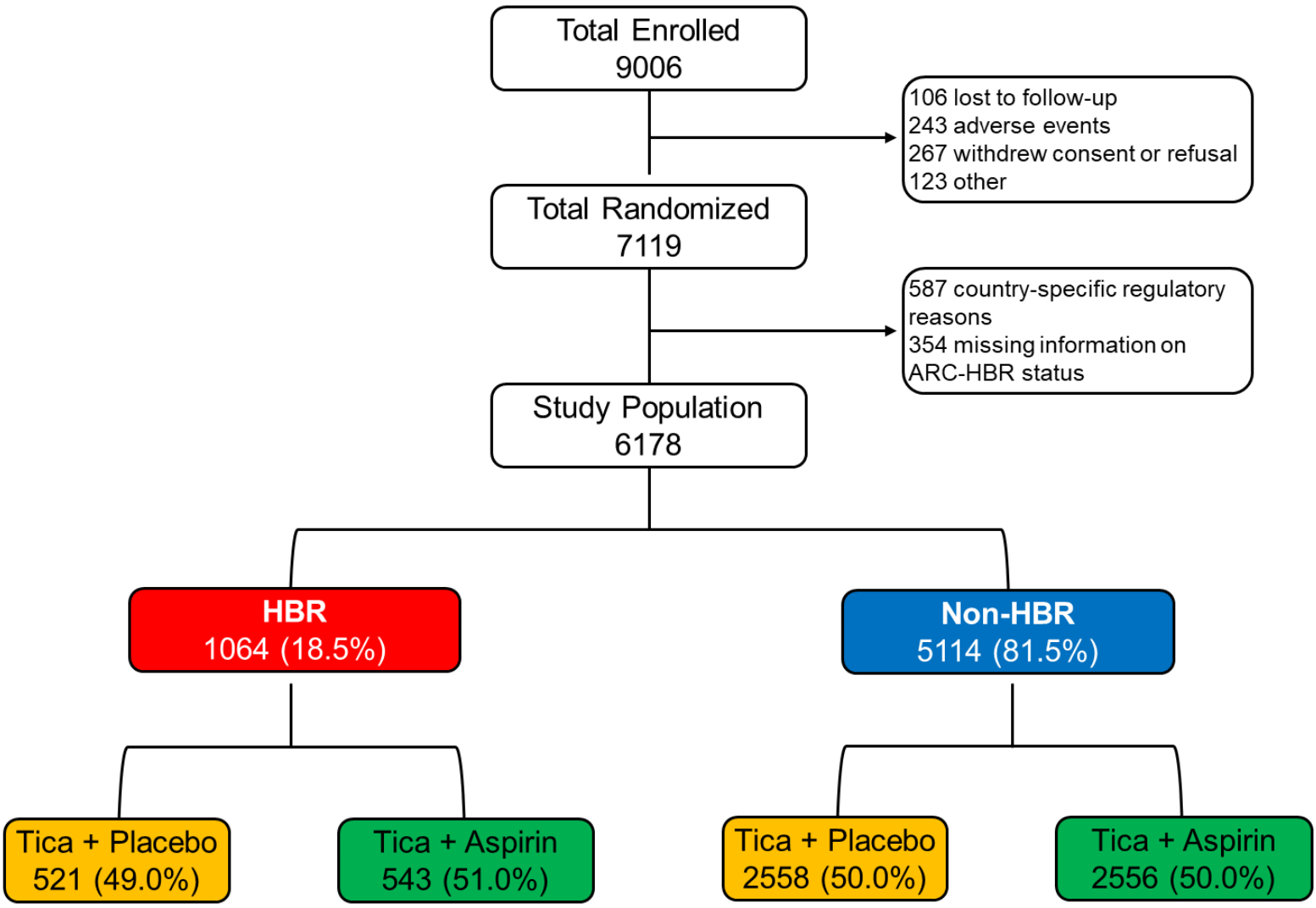
BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis.

Supplementary Table 5. Absolute risk difference in ischemic events at 1 year by HBR status.

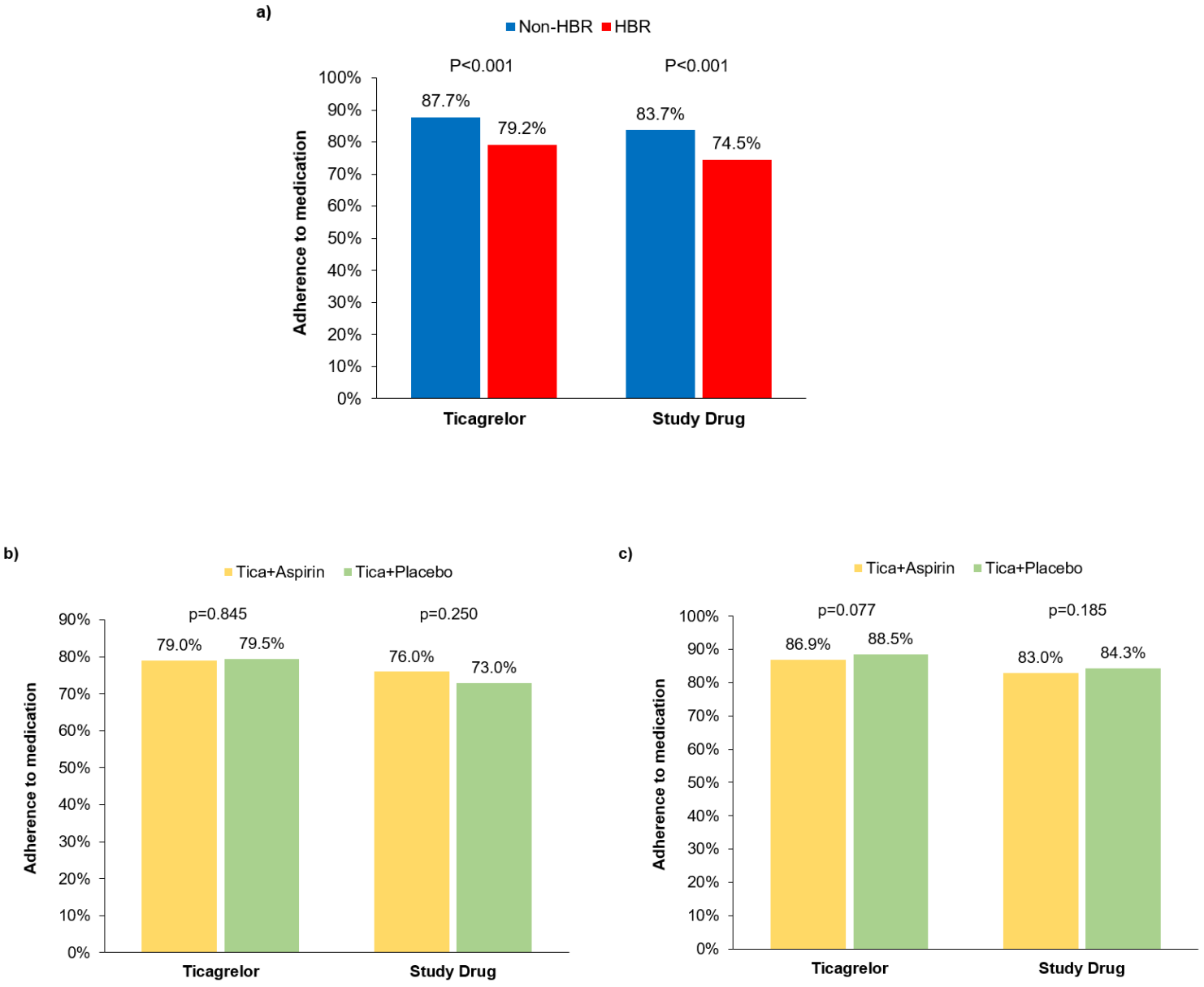
Ischemic outcomes	HBR (N=1051)				Non-HBR (N=5066)			
	Tica+ placebo (N=516)	**Tica+ Aspirin (N=535)**	**ARD (95% CI)**	**p-value**	**Tica+ placebo (N=2537)**	**Tica+ Aspirin (N=2529)**	**ARD (95% CI)**	**p-value**
	no. of events (%)				*no. of events (%)*			
Death, MI or stroke	33 (6.5%)	30 (5.6%)	0.9% (-2.1%, 3.8%)	0.566	91 (3.6%)	90 (3.6%)	0.0% (-1.0%, 1.1%)	0.965
Cardiovascular death, MI or ischemic stroke	30 (5.9%)	29 (5.5%)	0.5% (-2.4%, 3.3%)	0.749	85 (3.4%)	85 (3.4%)	-0.0% (-1.0%, 1.0%)	0.981
All-cause death	12 (2.3%)	16 (3.0%)	-0.7% (-2.6%, 1.3%)	0.505	21 (0.8%)	26 (1.0%)	-0.2% (-0.7%, 0.3%)	0.454
Cardiovascular death	9 (1.8%)	14 (2.6%)	-0.9% (-2.6%, 0.9%)	0.345	16 (0.6%)	21 (0.8%)	-0.2% (-0.7%, 0.3%)	0.402
MI	23 (4.5%)	19 (3.6%)	0.9% (-1.5%, 3.4%)	0.443	65 (2.6%)	63 (2.5%)	0.1% (-0.8%, 0.9%)	0.881
Ischemic stroke	2 (0.4%)	1 (0.2%)	0.2% (-0.5%, 0.9%)	0.541	10 (0.4%)	5 (0.2%)	0.2% (-0.1%, 0.5%)	0.197
Stent thrombosis (definite/probable)	4 (0.8%)	3 (0.6%)	0.2% (-0.8%, 1.2%)	0.666	10 (0.4%)	15 (0.6%)	-0.2% (-0.6%, 0.2%)	0.308

MI: myocardial infarction

Supplementary Figure 1. Study population.

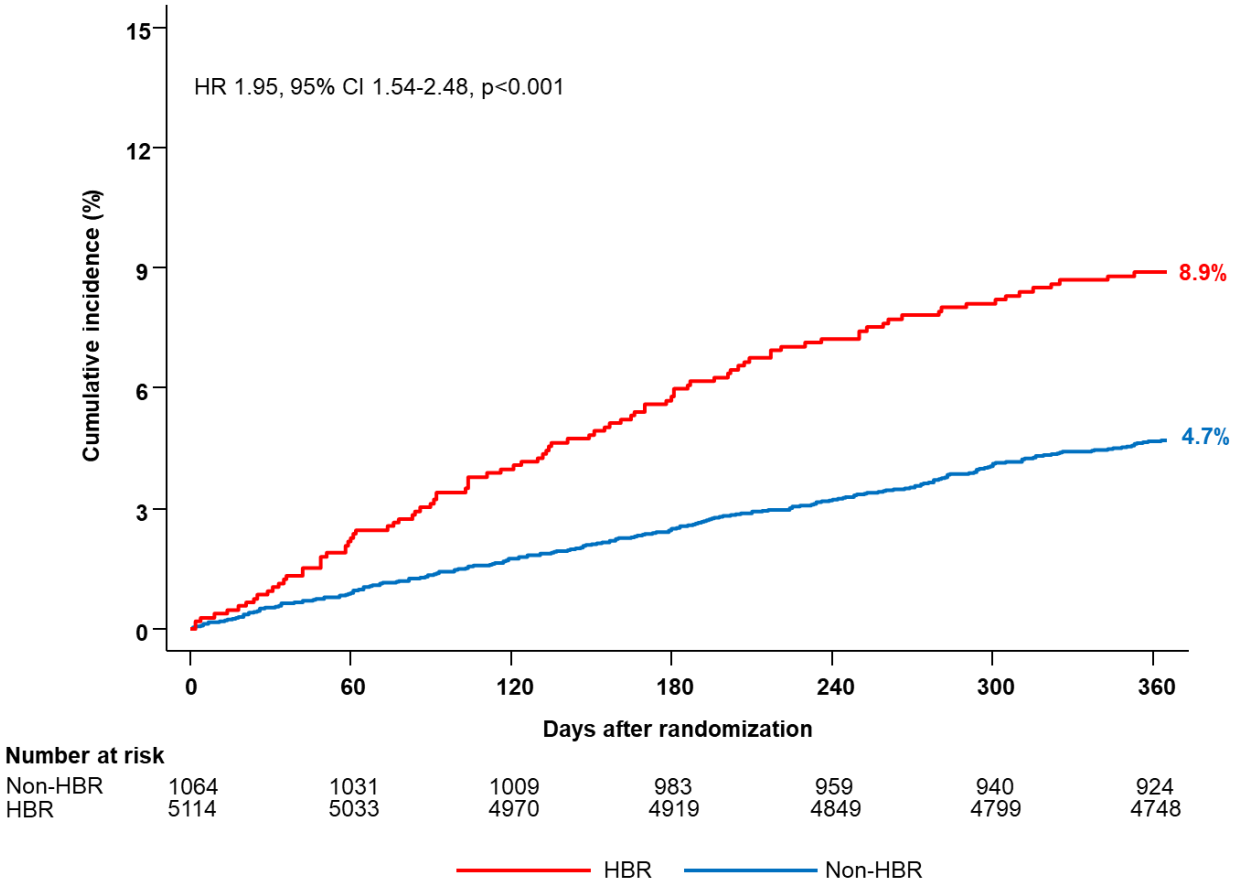


Supplementary Figure 2. Adherence rates to blinded study drug and ticagrelor at 1 year after randomization, per (a) HBR status and per treatment arm in (b) HBR and (c) non-HBR patients**.**

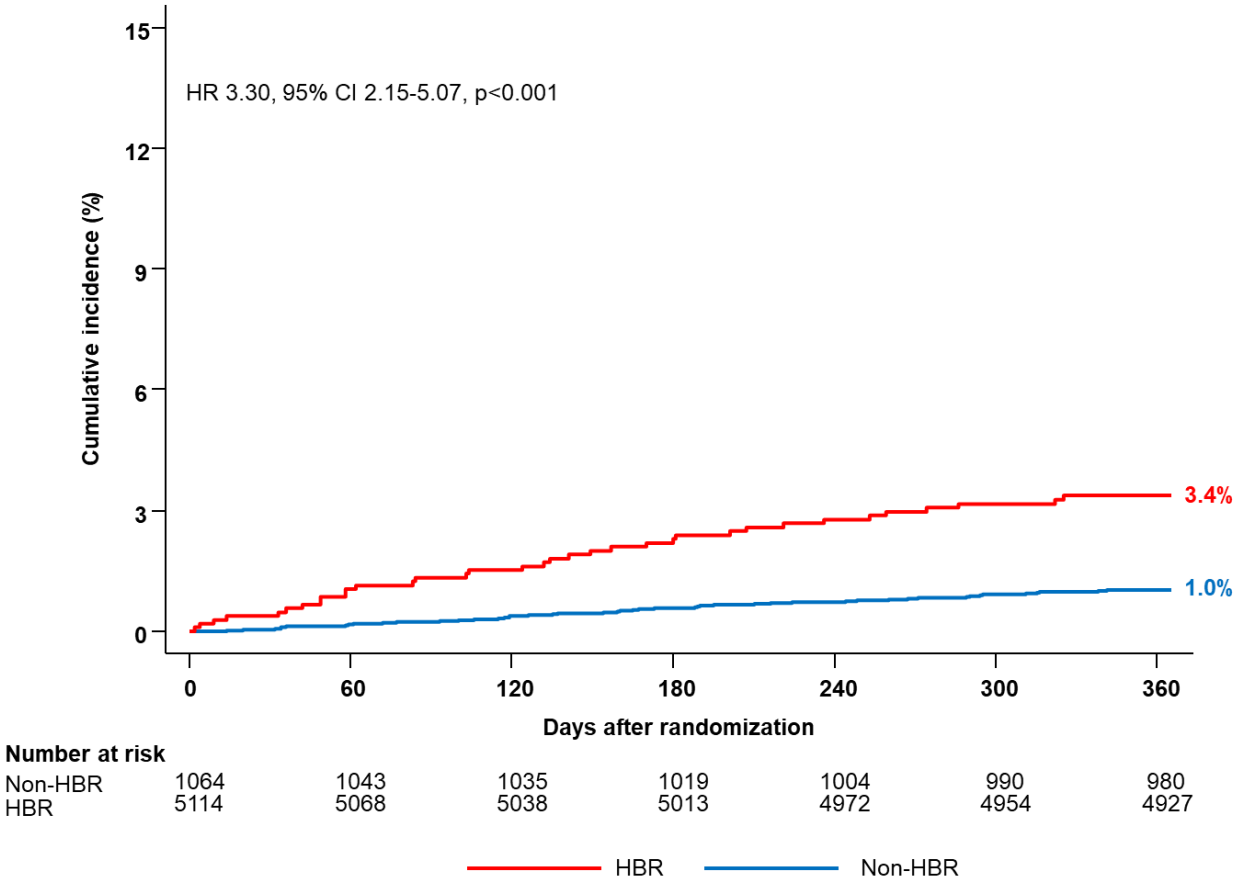


Supplementary Figure 4. Incidence of (a) BARC 2, 3, or 5 and (b) BARC 3 or 5 bleeding at 1 year by HBR status.

a) BARC 2, 3, or 5 bleeding

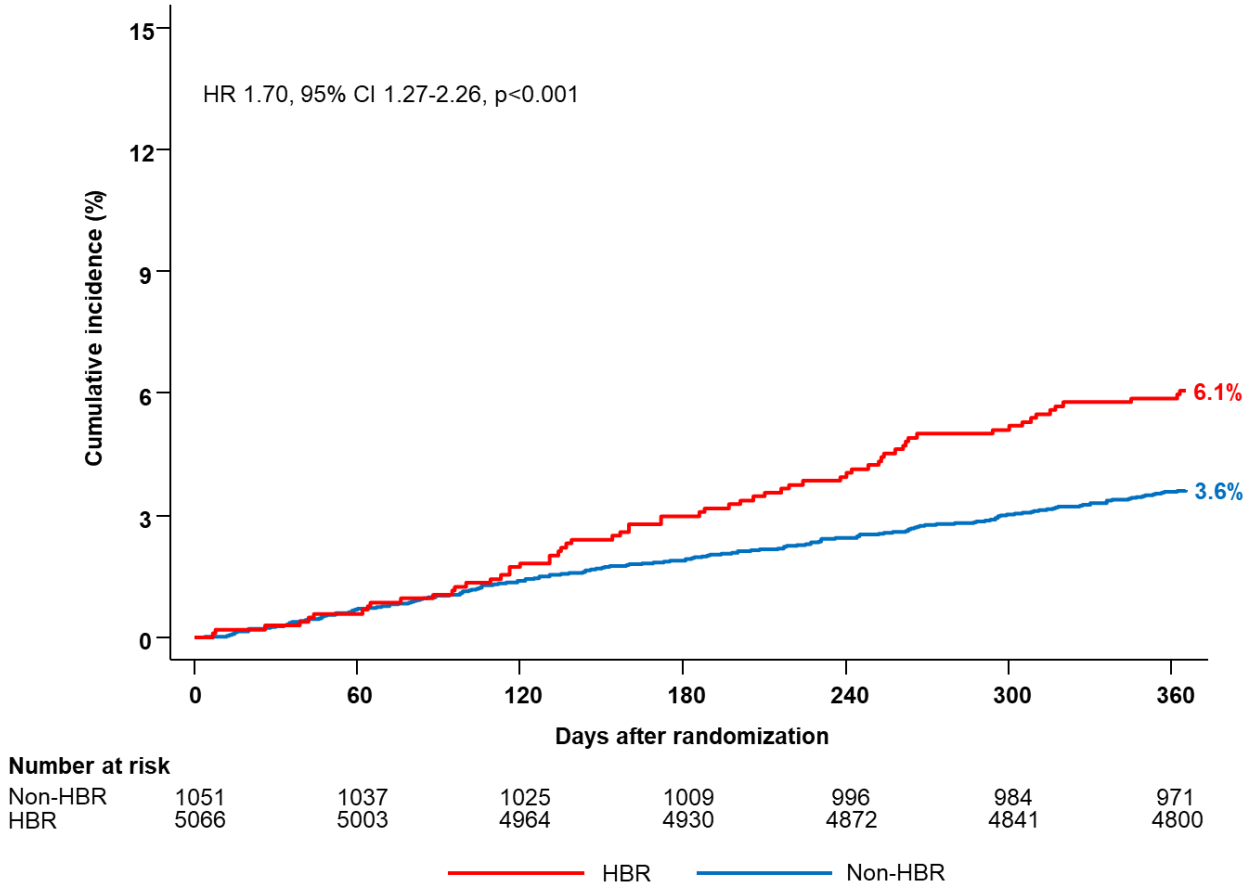


b) BARC 3 or 5 bleeding

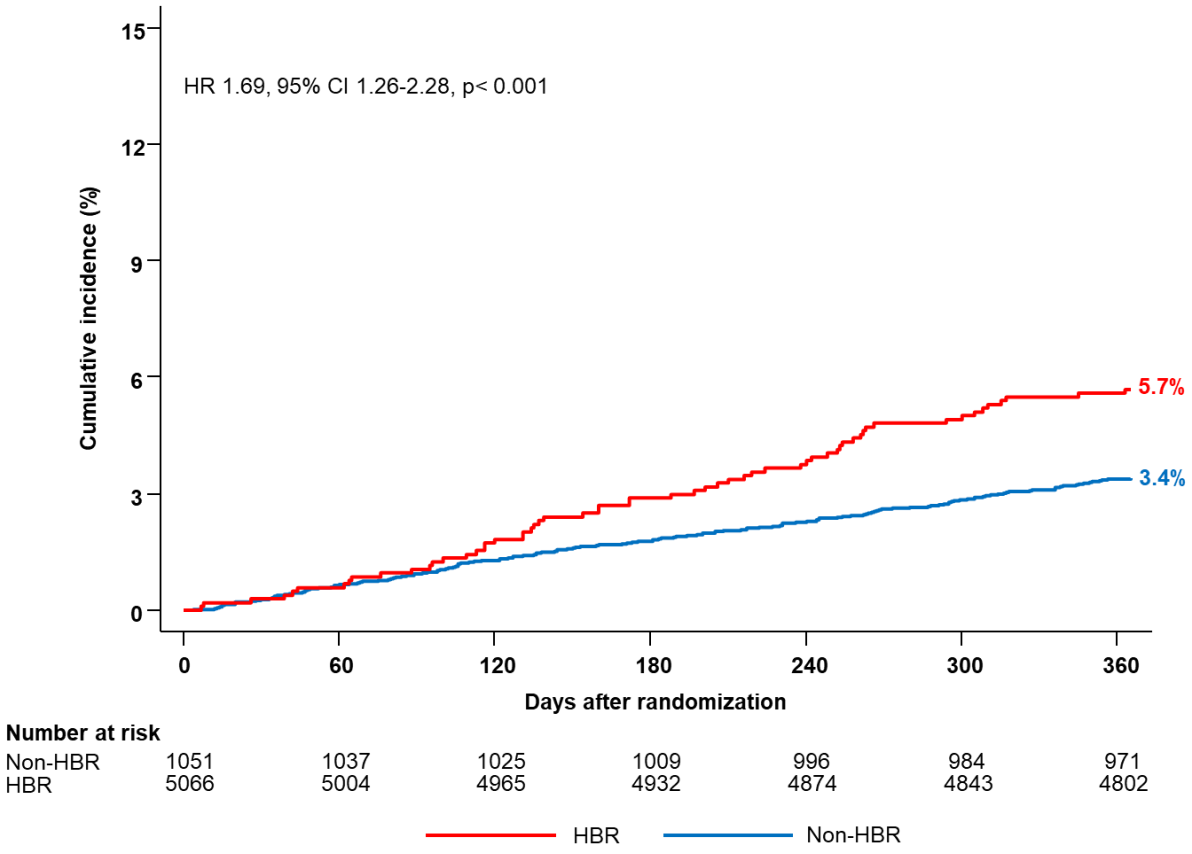


Supplementary Figure 5. Incidence of (a) death, MI, or stroke and (b) cardiovascular death, MI, or stroke at 1 year by HBR status.

a) Death, MI, or stroke

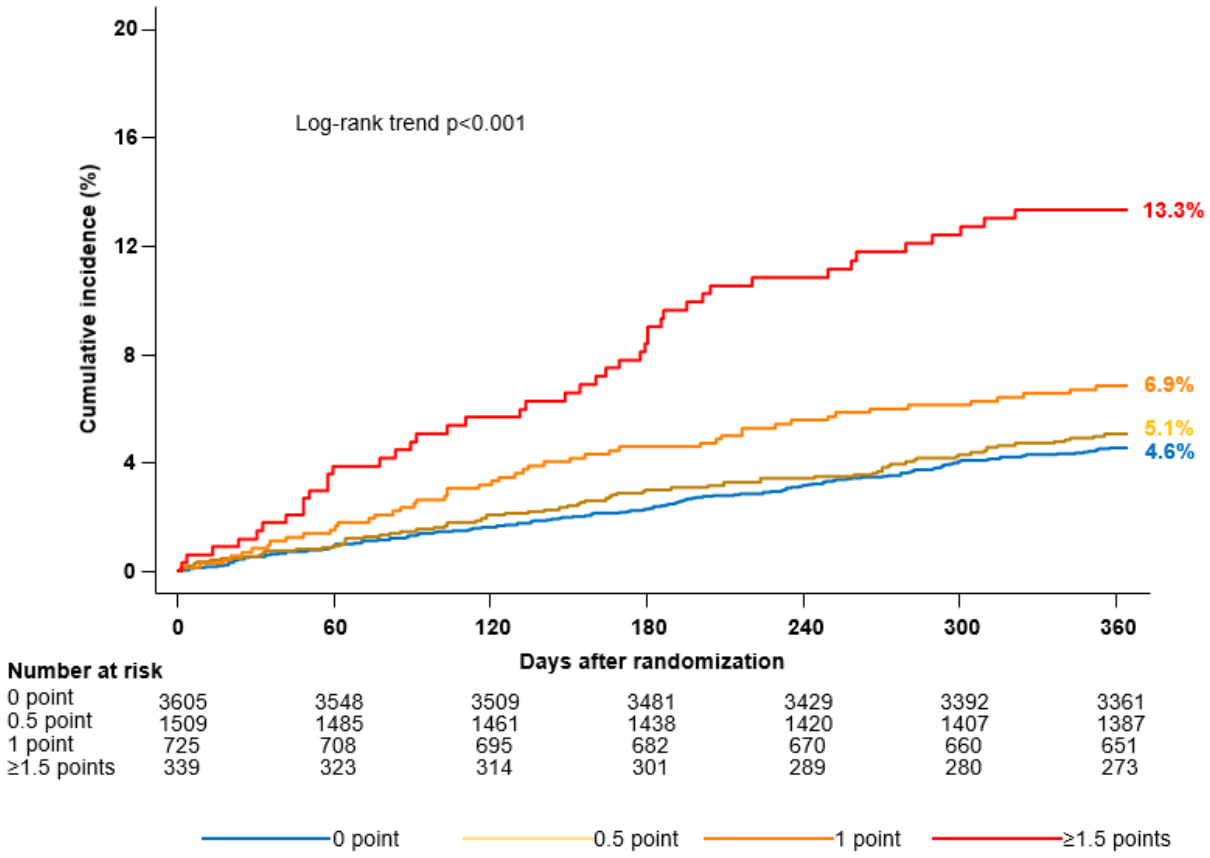


b) Cardiovascular death, MI, or stroke

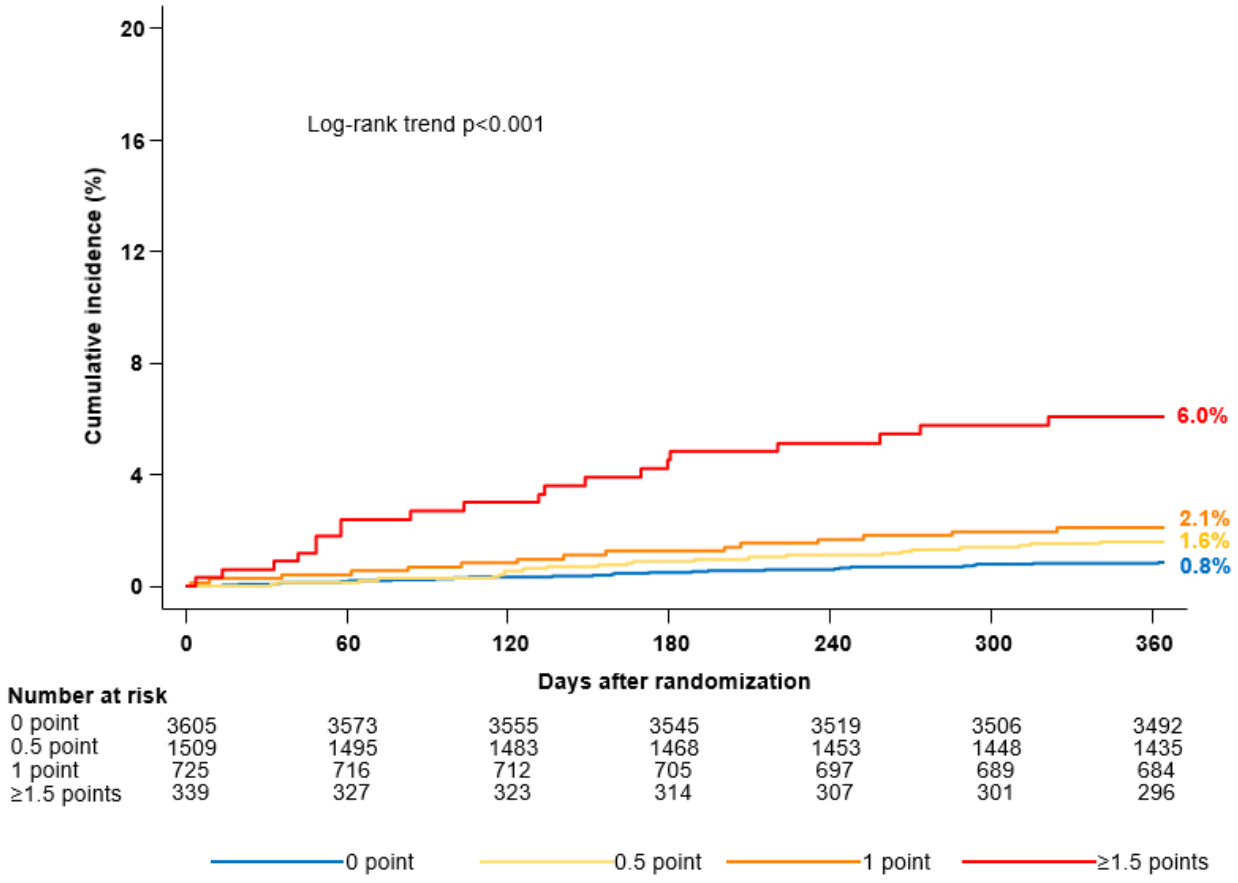


Supplementary Figure 6. Incidence of (a) BARC 2, 3, or 5 bleeding, (b) BARC 3 or 5 bleeding, (c) death, MI, or stroke and (d) cardiovascular death, MI, or stroke at 1 year by HBR score.

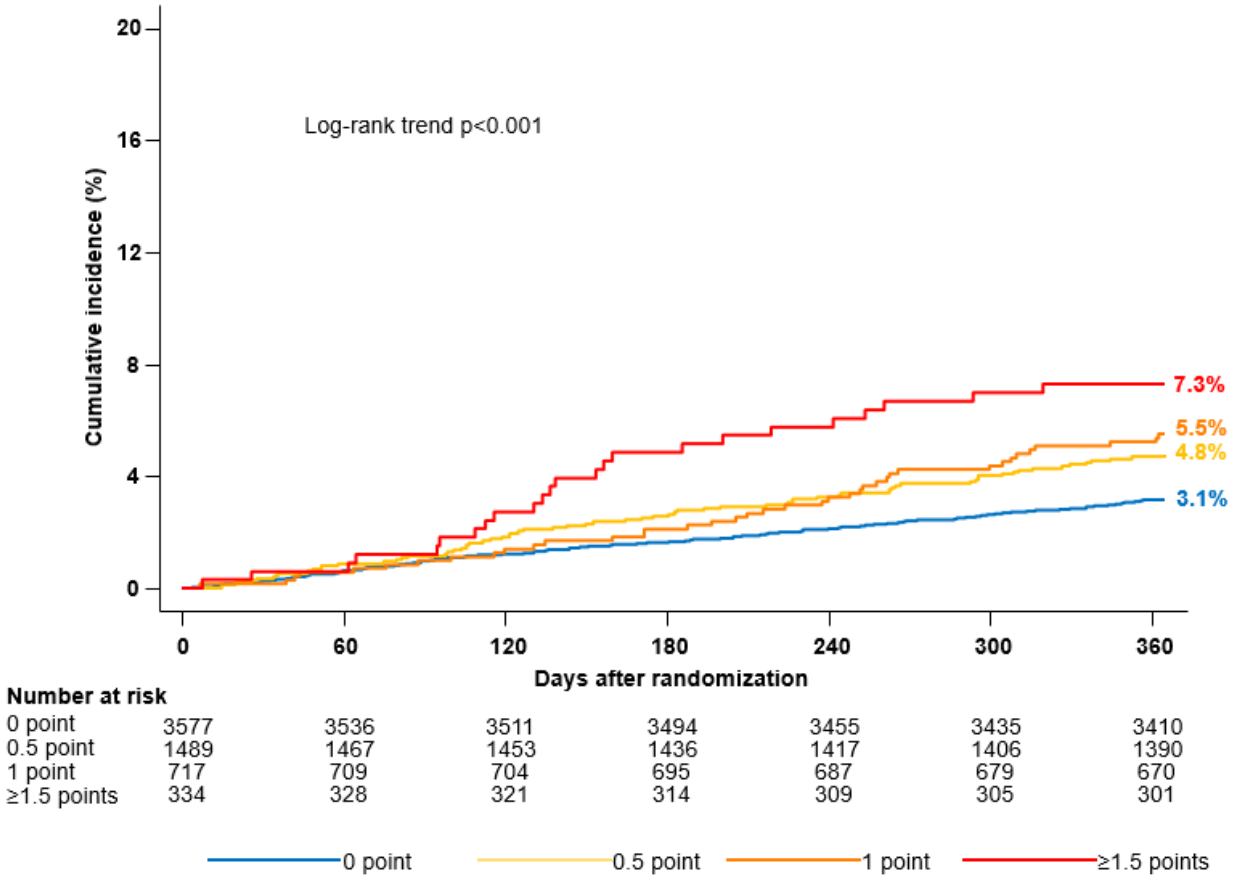
a) BARC 2, 3, or 5 bleeding



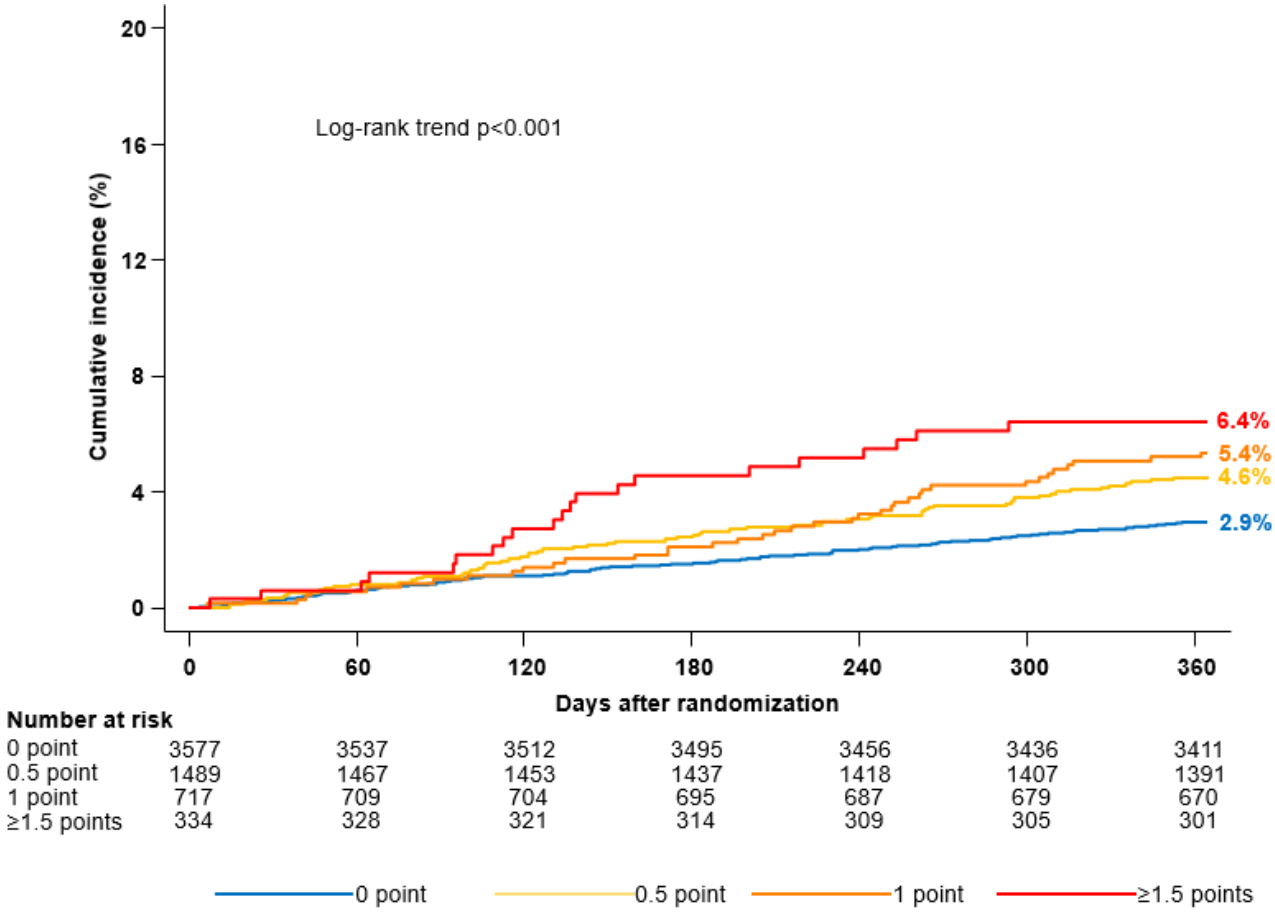
b) BARC 3 or 5 bleeding



c) Death, MI, or stroke

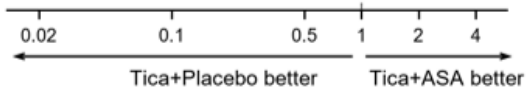


d) Cardiovascular death, MI, or stroke



Supplementary Figure 7. Risk of bleeding events at 1 year by ARC-HBR score.

Bleeding events	No. of patients	Tica+Placebo no. of events (%)	Tica+Aspirin no. of events (%)	HR (95% CI)	Interaction p-value
BARC 2, 3, or 5					
HBR: 0 point	3605	53 (3.0%)	109 (6.0%)	0.50 (0.36 - 0.69)	
HBR: 0.5 point	1509	36 (4.6%)	39 (5.5%)	0.84 (0.53 - 1.32)	0.215
HBR: 1 point	725	15 (4.2%)	34 (9.4%)	0.44 (0.24 - 0.81)	
HBR: ≥ 1.5 points	339	17 (10.9%)	27 (15.5%)	0.67 (0.37 - 1.23)	
BARC 3, or 5					
HBR: 0 point	3605	10 (0.6%)	19 (1.1%)	0.55 (0.25 - 1.17)	
HBR: 0.5 point	1509	10 (1.3%)	13 (1.8%)	0.70 (0.31 - 1.60)	0.502
HBR: 1 point	725	3 (0.8%)	12 (3.3%)	0.25 (0.07 - 0.90)	
HBR: ≥ 1.5 points	339	5 (3.2%)	15 (8.6%)	0.36 (0.13 - 0.99)	
TIMI major					
HBR: 0 point	3605	6 (0.3%)	11 (0.6%)	0.57 (0.21 - 1.53)	
HBR: 0.5 point	1509	7 (0.9%)	6 (0.8%)	1.07 (0.36 - 3.18)	0.233
HBR: 1 point	725	1 (0.3%)	6 (1.7%)	0.17 (0.02 - 1.41)	
HBR: ≥ 1.5 points	339	1 (0.6%)	6 (3.4%)	0.18 (0.02 - 1.52)	
GUSTO moderate or severe					
HBR: 0 point	3605	5 (0.3%)	11 (0.6%)	0.47 (0.16 - 1.36)	
HBR: 0.5 point	1509	9 (1.2%)	6 (0.8%)	1.37 (0.49 - 3.86)	0.210
HBR: 1 point	725	3 (0.8%)	9 (2.5%)	0.34 (0.09 - 1.25)	
HBR: ≥ 1.5 points	339	5 (3.2%)	15 (8.6%)	0.36 (0.13 - 0.99)	
ISTH major					
HBR: 0 point	3605	10 (0.6%)	21 (1.2%)	0.49 (0.23 - 1.05)	
HBR: 0.5 point	1509	12 (1.6%)	14 (2.0%)	0.78 (0.36 - 1.69)	0.529
HBR: 1 point	725	4 (1.1%)	12 (3.3%)	0.34 (0.11 - 1.05)	
HBR: ≥ 1.5 points	339	5 (3.2%)	15 (8.6%)	0.36 (0.13 - 0.99)	



Supplementary Figure 8. Risk of ischemic events at 1 year by ARC-HBR score.

Ischemic events	No. of patients	Tica+Placebo no. of events (%)	Tica+Aspirin no. of events (%)	HR (95% CI)	Interaction p-value
Death, MI or stroke					
HBR: 0 point	3577	55 (3.2%)	56 (3.1%)	1.02 (0.70 - 1.48)	
HBR: 0.5 point	1489	36 (4.7%)	34 (4.8%)	0.96 (0.60 - 1.54)	0.932
HBR: 1 point	717	20 (5.7%)	19 (5.3%)	1.09 (0.58 - 2.04)	
HBR: ≥ 1.5 points	334	13 (8.3%)	11 (6.4%)	1.30 (0.58 - 2.91)	
CV-death, MI or ischemic stroke					
HBR: 0 point	3577	51 (2.9%)	52 (2.9%)	1.02 (0.69 - 1.50)	
HBR: 0.5 point	1489	34 (4.4%)	33 (4.7%)	0.94 (0.58 - 1.52)	0.970
HBR: 1 point	717	20 (5.7%)	18 (5.0%)	1.15 (0.61 - 2.17)	
HBR: ≥ 1.5 points	334	10 (6.4%)	11 (6.4%)	1.00 (0.43 - 2.36)	
All-cause death					
HBR: 0 point	3577	11 (0.6%)	16 (0.9%)	0.71 (0.33 - 1.53)	
HBR: 0.5 point	1489	10 (1.3%)	10 (1.4%)	0.91 (0.38 - 2.19)	0.951
HBR: 1 point	717	6 (1.7%)	9 (2.5%)	0.68 (0.24 - 1.90)	
HBR: ≥ 1.5 points	334	6 (3.7%)	7 (4.0%)	0.93 (0.31 - 2.75)	
CV-death					
HBR: 0 point	3577	8 (0.5%)	11 (0.6%)	0.75 (0.30 - 1.87)	
HBR: 0.5 point	1489	8 (1.0%)	10 (1.4%)	0.73 (0.29 - 1.85)	0.910
HBR: 1 point	717	6 (1.7%)	7 (2.0%)	0.88 (0.30 - 2.61)	
HBR: ≥ 1.5 points	334	3 (1.9%)	7 (4.1%)	0.47 (0.12 - 1.82)	
MI					
HBR: 0 point	3577	42 (2.4%)	40 (2.2%)	1.09 (0.71 - 1.68)	
HBR: 0.5 point	1489	23 (3.0%)	23 (3.3%)	0.91 (0.51 - 1.62)	0.800
HBR: 1 point	717	18 (5.1%)	13 (3.6%)	1.43 (0.70 - 2.92)	
HBR: ≥ 1.5 points	334	5 (3.2%)	6 (3.5%)	0.91 (0.28 - 2.99)	
Ischemic stroke					
HBR: 0 point	3577	3 (0.2%)	3 (0.2%)	1.04 (0.21 - 5.13)	
HBR: 0.5 point	1489	7 (0.9%)	2 (0.3%)	3.20 (0.66 - 15.4)	0.797
HBR: 1 point	717	0 (0.0%)	0 (0.0%)	. (. - .)	
HBR: ≥ 1.5 points	334	2 (1.3%)	1 (0.6%)	2.20 (0.20 - 24.2)	
Definite/probable ST					
HBR: 0 point	3577	6 (0.3%)	11 (0.6%)	0.56 (0.21 - 1.52)	
HBR: 0.5 point	1489	4 (0.5%)	4 (0.6%)	0.91 (0.23 - 3.65)	0.780
HBR: 1 point	717	3 (0.9%)	2 (0.6%)	1.54 (0.26 - 9.20)	
HBR: ≥ 1.5 points	334	1 (0.7%)	1 (0.6%)	1.09 (0.07 - 17.5)