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Bleeding and Ischemic Risks of Ticagrelor Monotherapy after Coronary Interventions

Short Title: Ticagrelor Monotherapy after PCI

Authors: Guiomar Mendieta MD, PhD, MSc[1*], Shamir Mehta, MD, MSc[2*], Usman Baber, MD, MS[3], Dominick J. Angiolillo MD, PhD[4], Carlo Briguori, MD, PhD[5], David Cohen, MD, MSc[6,7], Timothy Collier, MSc[8], George Dangas, MD, PhD[9], Dariusz Dudek, MD, PhD[10], Javier Escaned, MD, PhD[11], Robert Gil, MD, PhD[10], Birgit Vogel, MD[9], Davide Cao, MD[9], Alessandro Spirito MD[9], Kurt Huber, MD[12], Adnan Kastrati, MD[13], Upendra Kaul, MD[14], Ran Kornowski, MD[15], Mitchell W. Krucoff, MD[16], Vijay Kunadian, MBBS, MD[17], David J. Moliterno, MD[18], E. Magnus Ohman, MD[19], Gennaro Sardella, MD[20], Samantha Sartori, PhD[9], Samin Sharma, MD[9], Richard Shlofmitz, MD[21], Phillipe Gabriel Steg, MD[22], Han Ya-Ling, MD, PhD[23], Stuart Pocock, PhD[8], C. Michael Gibson, MD, MS[24] and Roxana Mehran, MD[9]

Affiliations:

1. Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain
2. Department of Cardiology, Hamilton Health Sciences, Hamilton, ON L8N 3Z5, Canada
3. Cardiovascular Disease Section, Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
4. Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL 32218, USA
5. Mediterranea Cardiocentro, Naples, Italy

6. St. Francis Hospital, Roslyn NY
7. Cardiovascular Research Foundation, New York, NY, USA
8. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom
9. The Zena and Michael A. Weiner Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA
10. State Medical Isntitute of the Ministry of the Interior and Administration
11. Hospital Clínico San Carlos IDISCC, Complutense University of Madrid, Madrid, Spain
12. 3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminen Hospital, and Sigmund Freud University, Medical Faculty, Vienna, Austria
13. Deutsches Herzzentrum München, Technische Universität München, Munich, and DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany
14. Batra Hospital and Medical Research Center, New Delhi, India
15. Cardiology Department, Rabin Medical Center, Petach Tikva, Israel
16. Duke University Medical Center-Duke Clinical Research Institute, Durham, NC, USA
17. Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University and Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom
18. Division of Cardiovascular Medicine, University of Kentucky, Lexington, KY, USA
19. Duke University Medical Center-Duke Clinical Research Institute, Durham, NC, USA
20. Department of Cardiology, Policlinico Umberto I University, 00161 Roma, Italy
21. Department of Cardiology, St. Francis Hospital, Roslyn, 100 Port Washington Blvd, Roslyn, NY 11576, USA

22. Université Paris Cité, AP-HP, Hôpital Bichat, 46 Rue Henri Huchard, 75018 Paris, France
23. Department of Cardiology, General Hospital of Shenyang Military Region, Shenyang, Liaoning, China
24. Department of Cardiology, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA

* Guiomar Mendieta and Shamir Mehta contributed equally to this manuscript.

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Corresponding Author:

Roxana Mehran, MD

Mount Sinai Hospital

One Gustave L. Levy Place, Box 1030

New York, New York 10029

Tel: 212-659-9649; Fax: 212-241-0273

E-mail: roxana.mehran@mountsinai.org

ABSTRACT

Background: In TWILIGHT, among high-risk patients undergoing percutaneous coronary intervention (PCI), ticagrelor monotherapy versus continuation of dual antiplatelet therapy (DAPT) with aspirin and ticagrelor after completing a 3-month course of DAPT was associated with reduced bleeding, without an increase in ischemic events.

Objectives: To study the clinical benefit of ticagrelor monotherapy versus DAPT by simultaneously modeling its associated potential bleeding benefits and ischemic harms on an individual patient basis.

Methods: Multivariable Cox regression models for a) Bleeding Academic Research Consortium 2, 3 or 5 (BARC-2/3/5); and b) cardiovascular death, nonfatal MI and nonfatal ischemic stroke (MACCE) were developed using stepwise forward variable selection. The coefficients in the BARC-2/3/5 and MACCE models were used to calculate bleeding and ischemic risk scores, respectively, for each patient (excluding the coefficient for randomized treatment).

Results: In the total study population (N=7,119), BARC-2/3/5 occurred in 391 (5.5%) patients and MACCE occurred in 258 (3.6%). There was a consistent reduction in bleeding events associated with ticagrelor monotherapy compared with DAPT across both bleeding and ischemic risk strata (interaction p=0.54 and 0.11, respectively). Importantly, this benefit associated with ticagrelor monotherapy was not offset by an increase in MACCE at any level of bleeding or ischemic risk.

Conclusion: Three months after PCI, discontinuing aspirin and maintaining ticagrelor monotherapy reduces bleeding in both higher- and lower-bleeding-risk patients compared to continued DAPT. This benefit does not appear to be offset by greater ischemic risk.

CONDENSED ABSTRACT

In TWILIGHT, among high-risk patients undergoing percutaneous coronary intervention, ticagrelor monotherapy versus continuation of dual antiplatelet therapy (DAPT) with aspirin and ticagrelor after completing a 3-month course of DAPT was associated with reduced bleeding without an increase in ischemic events. Herein, we studied the clinical benefit of ticagrelor monotherapy versus DAPT by simultaneously modeling its associated potential bleeding benefits and ischemic harms on an individual patient basis. Ticagrelor monotherapy reduces bleeding in both higher- and lower-bleeding-risk patients compared to continued DAPT without an increase in ischemic events regardless of patients' bleeding or ischemic risk.

KEY WORDS

Monotherapy, Dual Antiplatelet Therapy, Aspirin, Ticagrelor.

ABBREVIATIONS

ASA = Aspirin

BARC-2/3/5 = Bleeding Academic Research Consortium 2, 3 or 5

DAPT = Dual antiplatelet therapy

DES = Drug-eluting stents

MACCE = Cardiovascular death, nonfatal MI and nonfatal ischemic stroke

MI = Myocardial infarction

PCI = Percutaneous coronary intervention

RS = Risk score

P2Y12i = $P2Y_{12}$ inhibitor

INTRODUCTION

Dual antiplatelet therapy (DAPT) is the cornerstone of post-percutaneous coronary intervention (PCI) therapy because it reduces the risk of stent thrombosis and myocardial infarction (MI)[1]. However, the benefits of DAPT in the prevention of thrombotic events after stent implantation[2] occur at the cost of increased bleeding[3,4], particularly with the use of potent $P2Y_{12}$ inhibitors (P2Y12i) such as prasugrel and ticagrelor[5-7]. Importantly, the effects on patient prognosis associated with bleeding complications are comparable to that of ischemic events[8,9].

Several bleeding reduction strategies have been investigated in randomized controlled trials (RCTs): reducing the intensity of DAPT by de-escalation or shortening its duration by either dropping aspirin (ASA) or the P2Y12i after a short period of DAPT (1 to 3 months)[10]. In this context, and given that DAPT duration trials have consistently supported the safety (i.e., the protection against ischemic events) of shortened DAPT if new generation drug-eluting stents (DES) are used, an ASA-free strategy consisting of the early discontinuation of ASA followed by P2Y12i monotherapy has been proposed[11]. The TWILIGHT study tested this novel alternative to standard 12-month DAPT, demonstrating that ticagrelor monotherapy after a 3-month course of DAPT post-PCI is an effective and safe bleeding-avoidance strategy in high-risk PCI patients treated with current-generation DES[12].

Despite these results, clinical judgment of an individual PCI patient's baseline risk remains complex, and risk score (RS) models simultaneously predicting both 1-year bleeding and ischemic risks in patients following an ASA-free strategy with ticagrelor after a 3-month course of DAPT post-PCI are currently lacking. Using data from the TWILIGHT trial, we developed two multivariable prediction models integrating several baseline, readily available patient and index procedure-related risk factors for a) Bleeding Academic Research Consortium 2, 3 or 5 bleeding (BARC-2/3/5); and b) major adverse cardiac and

cerebrovascular events (MACCE) including cardiovascular (CV) death, nonfatal MI or nonfatal ischemic stroke. The identification of the factors most strongly associated with bleeding and ischemic risk may help assess the clinical benefit of ticagrelor monotherapy *versus* DAPT on an individual patient basis.

METHODS

Trial design and oversight

The study design, rationale and main results of the TWILIGHT trial have been previously published[12,13]. The trial was sponsored by the Icahn School of Medicine at Mount Sinai. Ticagrelor was supplied by AstraZeneca, who provided an investigator-initiated grant but did not participate in the design, collection, analysis, or interpretation of the data. The Executive and Steering Committees were responsible for trial conduct, preserving the integrity of the data and its analysis, and reporting results. The trial protocol was approved by the National Regulatory Agencies and Institutional Review Boards or Ethics Committees of all participating sites. An independent Data Monitoring Committee oversaw the safety of trial participants. All participants provided informed consent prior to enrolment. This study complied with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement[14].

Study population

Patients undergoing successful DES implantation were eligible for study enrolment if they met at least one clinical and one angiographic criterion associated with a high-risk PCI profile[13]. Key exclusion criteria were ST-elevation myocardial infarction, salvage PCI, need for oral anticoagulation (OAC) and planned coronary revascularization.

Study regimen

From July 2015 to December 2017, 9,006 patients enrolled in the trial, receiving a 3-month course of open-label ticagrelor (90 mg twice daily) and enteric-coated ASA (81-100

mg daily) (i.e., DAPT) after index PCI. At 3 months post-PCI, only those patients with adequate compliance to treatment and no adverse events (whether bleeding or ischemic in nature) were then randomized in a 1:1 double-blind fashion to ASA or matching placebo in addition to open-label ticagrelor for 12 months (N=7,119).

Study endpoints and predictor definitions

The trial's primary endpoint was time to first occurrence of the composite of BARC-2/3/5 bleeding during 12 months follow-up after randomization[15]. The key secondary ischemic endpoint was a composite of death from any cause, myocardial infarction (MI), or stroke. Another secondary ischemic endpoint was the composite of MACCE, which included CV death, nonfatal MI or nonfatal ischemic stroke.

Liver disease was defined as cirrhosis, bilirubin above twice normal values, or liver enzymes above three times normal values prior to index PCI. PCI complexity criteria was met by index procedures which included three or more of the following: treatment of 3 vessels, three or more lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, use of any atherectomy device, left main as target vessel, surgical bypass graft or chronic total occlusion as target lesions[16].

Statistical methods

Multivariable Cox proportional hazard (PH) models were used to investigate the relationship between patient and index procedure-related variables at baseline to outcome incidence for (i) the primary outcome of BARC-2/3/5 and (ii) the secondary composite of MACCE.

Firstly, on the basis of subject matter knowledge, a pre-selection of baseline candidate predictor variables was conducted for each outcome (26 for BARC-2/3/5 and 25 for MACCE). Associations between each of the outcomes and the pre-selected candidate predictors were investigated using univariable Cox PH regression. A threshold $p \leq 0.2$ was

used to consider variables for inclusion in the final model. However, if prior scientific evidence for an association between a predictor and the outcome was strong, the predictor was considered for inclusion regardless of the univariable p-value. Since missing data was minimal (maximum missing for any variable was 4.1%), the imputation of the missing values using single imputation methods was performed. In brief, missing observations for continuous predictors were imputed with the predicted value obtained from a linear regression model adjusted for covariates associated with the predictor on the basis of scientific knowledge, and categorical predictors were imputed with the most frequently observed value for the variable. Secondly, multivariable model building was conducted using a forward stepwise variable selection approach with $p<0.05$ required for inclusion in the BARC-2/3/5 and MACCE risk models. Thirdly, patients were categorized into roughly equal-sized thirds of increasing risk for each outcome based on the distributions of the bleeding and ischemic RSs calculated from the multivariable models (excluding the coefficient for randomized treatment). Model discrimination (using Harrell's c-statistic) and calibration (by plotting the observed versus predicted 1-year risk by thirds of the RS) were evaluated for both outcomes.

The number of events and estimated Kaplan-Meier (KM) percentages within each risk category and by treatment group were calculated to evaluate the effect of randomized treatment by risk groups. Relative and absolute risk differences at 1 year between the two treatment arms in patients within each risk category were calculated. Treatment by risk group interactions across bleeding and ischemic risk strata were evaluated.

Interaction tests on the absolute scale were used to examine whether the association between the incidence of BARC-2/3/5 and bleeding risk category varied across ischemic risk groups and, conversely, whether the association between the incidence of MACCE and ischemic risk category varied across bleeding risk groups.

Cox PH regression models were used to study the impact of nonfatal bleeding (BARC types 2 and 3) and nonfatal ischemic (MI and ischemic stroke) events on all-cause mortality. These were fitted as time-updated covariates with all-cause death as the outcome variable.

The PARIS and PRECISE-DAPT RSs were calculated for each patient following the original definitions used in their respective development cohorts[17,18], and their discrimination of bleeding (PARIS and PRECISE-DAPT) and ischemic (PARIS) risks was assessed using Harrell's c-statistic (results addressed in discussion section and presented in Supplementary Table 5).

Analyses were performed using STATA, version 17.0 (StataCorp LLC). All p-values were from 2-sided tests, and results were deemed statistically significant if $p<0.05$.

RESULTS

During a 12 months follow-up after randomization, BARC-2/3/5 occurred in 391 (5.5%) patients and the secondary ischemic endpoint of MACCE occurred in 258 (3.6%) patients of the intention-to-treat population (N=7,119)[19].

Development of models for bleeding and ischemic risk

The candidate predictor variables (17 for the BARC-2/3/5 bleeding prediction model and 16 for the MACCE prediction model) taken forward for consideration in the multivariable risk prediction models for BARC-2/3/5 and MACCE, respectively, are listed in Supplementary Table 1.

The multivariable prediction model for BARC-2/3/5 bleeding included baseline hemoglobin levels, absence of proton-pump inhibitor (PPI) treatment, increasing age, liver disease, and active smoking (in decreasing order of strength of association). Randomized treatment persisted as highly predictive of bleeding after adjustment for the 5 baseline predictors (Table 1). The prediction model for MACCE included performance of the index PCI for a troponin-positive acute coronary syndrome (ACS), prior coronary artery bypass

graft (CABG) surgery, diabetes mellitus, prior PCI, peripheral artery disease (PAD), active smoking, increasing age, a history of congestive heart failure (CHF), prior MI, complex PCI and baseline eGFR <60 mL/min/1.73m² (in decreasing order of strength of association).

Baseline characteristics for all variables selected are shown in Table 2. Patients had a mean age of 64 years and approximately a quarter were active smokers. Almost half of the trial population had undergone a prior PCI, 37% were diabetic and 29% had experienced a prior MI. Importantly, 50% had a baseline hemoglobin level above 14 g/dL and 4% below 11 g/dL.

Performance of bleeding and ischemic risk models

Figure 1 shows the distribution of bleeding (panel A) and ischemic (panel B) RSs (from low to high) for individual patients calculated using the coefficients in the BARC-2/3/5 and the MACCE models, respectively. From the two overall RSs, patients were categorized into a) thirds of bleeding risk (as per the BARC-2/3/5 risk prediction model); and b) thirds of ischemic risk (as per the MACCE risk prediction model). In each third, containing about 2,300 patients, there was good agreement between the observed and predicted patient risks, both expressed as the KM percentage having an event (BARC-2/3/5 for the bleeding risk model and MACCE for the ischemic risk model) at 1 year, suggesting good model calibration (see Figure 2). Comparing the top and bottom thirds of risk, the observed event rates were 7.8% versus 3.7% for BARC-2/3/5 (Figure 2, Panel A) and 6.8% versus 1.2% for MACCE (Figure 2, Panel B).

The predictive model for bleeding events showed only modest discrimination: c=0.64, [95% confidence interval (95%CI) 0.62-0.68]. It mainly discriminated between the top-third of risk versus the two lower-thirds (see Figure 3, Panel A) with around a 2-fold increase in risk. The predictive model for ischemic events discriminated better: c=0.71, (95%CI 0.68-0.77). While it did show some separation between the bottom and middle thirds of risk (see

Figure 3, panel B), the real "take-off" in risk was observed in the top-third. Panel A in the Central Illustration, where the lower-thirds of risk have been condensed into one lower risk category, shows an almost doubling in the risk of a BARC-2/3/5 bleeding between the lower versus the top-third risk categories (from 4.3% to 7.9%) over 1 year [hazard ratio (HR) 1.86, 95%CI 1.53-2.27; p<0.001], whereas for the risk of a MACCE it more than triples from 2.1% to 6.9% over 1 year (HR 3.42, 95%CI 2.66-4.40; p<0.0001) (see Central Illustration, Panel B). Hence, our main analyses concentrated on the top-third *versus* the two lower-thirds for a) bleeding risk and then b) ischemic risk.

Assessment of the effect of ASA by bleeding and ischemic risk patient categories

The relative effect of DAPT *versus* ticagrelor monotherapy on BARC-2/3/5 bleeding was similar for lower and top bleeding risk patients: risk ratio (RR) 1.85, 95%CI 1.40–2.46 and RR 1.61, 95%CI 1.21–2.14, respectively (interaction p=0.54) (see Figure 4 and Supplementary Table 2). The same was true for lower and higher ischemic risk patients: RR 2.01, 95%CI 1.55–2.60 and RR 1.43, 95%CI 1.04–1.96, respectively (interaction p=0.11). A similar pattern was seen for absolute risk differences, though we note a numerically higher excess risk of bleeds on DAPT in patients at higher bleeding risk. In addition, the incidence of BARC-2/3/5 across bleeding risk strata was not influenced by ischemic risk (interaction p=0.24) (see Supplementary Table 3). Importantly, there was no evidence of an effect of DAPT *versus* ticagrelor monotherapy on the risk of ischemic events, irrespective of individual patient bleeding or ischemic risk (interaction p=0.42 and p=0.47, respectively). Furthermore, the incidence of ischemic events across different ischemic risk strata was not modified by bleeding risk (interaction p=0.14) (see Supplementary Table 4).

Impact of nonfatal bleeding and ischemic events on all-cause mortality

All-cause death occurred in 82 (1.2%) of 7,119 patients during the 1-year follow-up since randomization. Table 3 shows the number of deaths occurring after specific nonfatal

bleeding and ischemic events. Amongst the nonfatal outcomes, MIs were the greatest contributors to subsequent mortality risk: mortality incidence was 10.9% after MIs, 8.3% after ischemic strokes, 4.9% after BARC-3, and 2.1% after BARC-2. In addition, BARC-2 or BARC-3 bleeding was associated with a higher risk of all-cause death during follow-up after the bleeding event [HR 2.71, 95% CI 1.09–6.75; p=0.06 for BARC-2, and HR 6.08, 95% CI 2.21–16.70; p=0.006 for BARC-3]. However, the risk of death was much higher if the nonfatal event was ischemic in nature (HR 19.93, 95% CI 11.54–34.42; p<0.001 for MIs, and HR 6.47, 95% CI 0.95–49.54; p=0.14 for ischemic strokes).

DISCUSSION

In this study, we have developed two separate prognostic models for the outcomes of BARC-2/3/5 and MACCE at 1 year after 3 months of ticagrelor-based DAPT post-PCI. The novel findings from this analysis of the TWILIGHT trial suggest the benefit of preventing bleeding by discontinuing ASA after 3 months of DAPT post-PCI for both higher and lower bleeding-risk patients. There is a consistent reduction in bleeding events in ticagrelor monotherapy compared with DAPT across both bleeding and ischemic risk strata (interaction p=0.54 and 0.11, respectively). Importantly, this benefit associated with ticagrelor monotherapy does not appear to be offset by an increase in MACCE at any level of bleeding or ischemic risk (see Central illustration, Panel C). Our work is the first to provide an individualized patient-risk assessment to evaluate the efficacy and safety of ticagrelor monotherapy by simultaneously modeling its associated potential bleeding benefits and ischemic harms.

Bleeding risk prediction

The MACCE prediction model showed reasonably good discrimination of ischemic risk (c-statistic 0.71, 95%CI 0.68-0.77), but the BARC-2/3/5 model's accuracy was only moderate (c-statistic 0.64, 95%CI 0.62-0.68). Indeed, prior bleeding RSs have repeatedly

shown poorer discrimination compared to ischemic RSs, with c-statistics between 0.64 to 0.73 in their respective development cohorts[19,20]. An explanation may be that high bleeding risk factors (e.g., thrombocytopenia, coagulation disorders, etc.) are less frequent amongst PCI patients, or are not well captured (e.g., frailty, social deprivation), or are not recorded at all in the derivation datasets (e.g., malignancy, nutritional status). In addition, currently available bleeding RSs are quite heterogeneous as per the bleeding definitions used and the patient populations included, ranging from only ACS patients (BleeMacs)[21] to both stable and unstable patient populations (PARIS score and PRECISE-DAPT)[17,18] and only stable, event-free patients at 1-year follow-up (DAPT score)[22]. More notably, they all have focused on long *versus* short DAPT post-PCI duration schemes and have included bleeding events taking place starting from within the first 30 days of the index PCI, except for the DAPT score, which predicted major bleeding between 12 and 30 months after PCI. Also, prior RSs developed using RCT data have all examined treatment strategies involving the withdrawal of P2Y12i, whereas, in this analysis, we have modeled bleeding and ischemic risk on the basis of the discontinuation of ASA after 3 months of standard DAPT post-PCI. Finally, both bleeding and thrombotic risk have only been evaluated in the DAPT and the PARIS scores, and the ARC-HBR Trade-off Model[23].

While most of the factors associated with an increased risk of BARC-2/3/5 we have identified are common to prior bleeding risk models (i.e., older age, lower hemoglobin levels, and active smoking), our score incorporates no PPI treatment at discharge from index PCI (absent in all prior RSs), and liver disease, which was also found to be a predictor of BARC types 3 and 5 in the most recent ARC-HBR trade-off model. Of note, both women and chronic kidney disease (CKD) patients have an increased risk of bleeding after PCI, and yet these were not included in our bleeding risk model. This is because the higher bleeding risk amongst women and CKD patients is accounted for by other factors in the bleeding RS which

are also associated with female sex and CKD (mainly older age and lower hemoglobin levels). Nonetheless, this result is consistent with prior TWILIGHT subgroup analyses showing the effect of randomized treatment on bleeding was uniform irrespective of sex or renal dysfunction[24,25]. Perhaps the identification of no PPI treatment at discharge from index PCI as a factor associated to increased risk for BARC-2/3/5 bleeding is a direct reflection of ASA's gastrointestinal (GI) toxicity: the absence of gut protection was the second strongest predictor of the model precisely because those patients on ASA had the highest bleeding event rates. Through our bleeding RS, concentrating on an ASA-free strategy rather than the duration of DAPT, we have identified an important and easily applicable bleeding-avoidance patient optimization strategy: ensuring PPI treatment is on board at discharge from the index PCI.

Ischemic risk prediction

There was also considerable overlap between our MACCE risk model predictors and those found in prior, post-PCI ischemic risk models. Active smoking, diabetes mellitus, troponin-positive ACS and prior revascularizations (PCI and CABG) were also found to be predictive of ischemia in the PARIS score and the ARC-HBR Trade-off Model. Except for age, hypertension and stent type and diameter, the DAPT score included the same ischemic risk predictors found in our MACCE model.

Effect of ticagrelor monotherapy across different levels of patient bleeding and ischemic risk

We have studied the spectrum of risk for bleeding and ischemic events. As per BARC-2/3/5 bleeding, the absolute benefit of ticagrelor monotherapy past the first 3 months of standard post-PCI DAPT appears somewhat greater in top bleeding risk patients compared to lower risk. Together with the findings of TWILIGHT's complex procedure and diabetes subgroup analyses[26,27], which showed that treatment effect was uniform in high ischemic risk

patients and in line with previously published data[28], our results regarding potential ischemic harm from ticagrelor monotherapy are consistent with there being no difference across ischemic risk strata. Hence, our findings are reassuring in that no signals suggest that a lack of ASA is harmful in patients at a higher risk for MACCE after 3 months of DAPT post-PCI (see Central Illustration).

Further, the association between the risk of a BARC-2/3/5 event and individual patient bleeding risk category, regardless of treatment effect, was not influenced by the patient's individual ischemic risk level: the incidence of a bleeding event was predominantly dependent on the patient's individual bleeding risk. These results are consistent with prior published data indicating that bleeding risk is to be considered over ischemic risk when tailoring DAPT intensity by shortening its duration[29]. Therefore, our findings show there is benefit in preventing a bleeding event by discontinuing ASA after 3-months of DAPT post-PCI for both top and lower bleeding risk patients, and this benefit does not appear to be offset by greater individual patient ischemic harm, irrespective of bleeding and/or ischemic risk category.

Contribution of nonfatal bleeding and ischemic events to subsequent all-cause mortality

Bleeding after PCI is a prognostic marker of adverse events[8], including ischemic outcomes, but ischemic risk is more important with regard to mortality, as shown by our results. Although both nonfatal bleeding and ischemic events were associated with a greater risk of all-cause death, this risk was much greater if the nonfatal event was ischemic in nature. Interpretation of the latter should additionally consider that event rates were quite low in TWILIGHT, partly due to trial design, as patients experiencing major bleeding and/or ischemic events during the 3 months after index PCI were excluded from randomization. Our findings suggest that continuing ASA beyond the first 3 months of post-PCI DAPT does not provide better protection from ischemia, but rather incurs greater risk of bleeding

complications, further reinforcing the safety of ticagrelor monotherapy as per all-cause mortality.

Evaluation of other risk scores

Existing RSs showed poorer discrimination of bleeding (PARIS and PRECISE-DAPT) and ischemic risk (PARIS) in the TWILIGHT population compared to our bleeding and ischemic RSs (data presented in Supplementary Table 5). Because the DAPT score was designed to predict net adverse clinical events and RS points were not facilitated for the models separately (i.e., for bleeding risk prediction alone and ischemic risk prediction alone)[22], we could not apply the bleeding and ischemic RSs to our population. We were also unable to test the BLEEMACS[21] and ARC-HBR models[23] because we were missing some of the variables (e.g., malignancy, COPD).

Study limitations

First, the trial's 3-month enrollment period and the randomization of only event-free patients into the study may have precluded the inclusion of patients with high bleeding risk factors (such as *prior major bleeding* or *NSAID use*) with a potentially important prognostic impact, thereby mitigating the generalisability of the RSs. However, these models were developed from a large trial database with rigorous event adjudication on the basis of well-established and standardized bleeding and ischemic definitions and included baseline, readily available patient and index procedure-related risk factors, most of which had already been identified in previously published bleeding and ischemic risk models. Second, the trial's inclusion criteria only partially covered current bleeding risk definitions; in fact, only 17.2% of the TWILIGHT cohort satisfied ARC-HBR criteria[30]. Because patients randomized into the study had to complete a 12-month course of ticagrelor monotherapy, from an ethical standpoint, exclusion criteria posing a maximal risk for bleeding (and thus strongly predictive of bleeding) such as chronic OAC or prior stroke, were inevitable and have been largely

missed. However, our bleeding risk model is novel in specifically predicting the 1-year risk of BARC-2/3/5 bleeding in high-risk PCI patients after 3 months of standard DAPT post-PCI. Third, baseline laboratory parameters were assessed at index PCI (not at randomization), and information on post-randomization changes to medication, such as PPI treatment, was not assessed. Importantly, our study's main objective was to develop multivariable prediction models for bleeding and ischemia as a means to provide a further, in-depth understanding of both outcomes on an individual patient basis rather than for usage as a clinical decision-making tool. However, it should be noted that the applicability of our findings is restricted to patients meeting TWILIGHT's enrolment criteria, who are adherent to treatment and event-free after 3 months of ticagrelor-based DAPT. Nonetheless, and because limited generalisability tends to be the main flaw of prognostic models derived from clinical databases, we encourage further validation of our prediction models in other high-risk PCI populations.

CONCLUSION

Three months after PCI, prognostic models can readily determine who is at higher bleeding risk and/or higher ischemic risk. After a 3-month course of DAPT with aspirin and ticagrelor post-PCI, discontinuing aspirin reduces bleeding in both higher- and lower-bleeding-risk patients compared to continued DAPT. This benefit does not appear to be offset by greater ischemic risk.

CLINICAL PERSPECTIVES

Competency in Patient Care and Procedural Skills: Ticagrelor monotherapy (without aspirin) beginning 3 months after PCI is associated with less bleeding than dual antiplatelet

therapy (DAPT) without an increase in major adverse cardiovascular events across the spectra of bleeding and ischemic risk.

Translational Outlook: Further research is needed to determine optimum antithrombotic strategies beyond the first year after PCI.

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Figure 1.

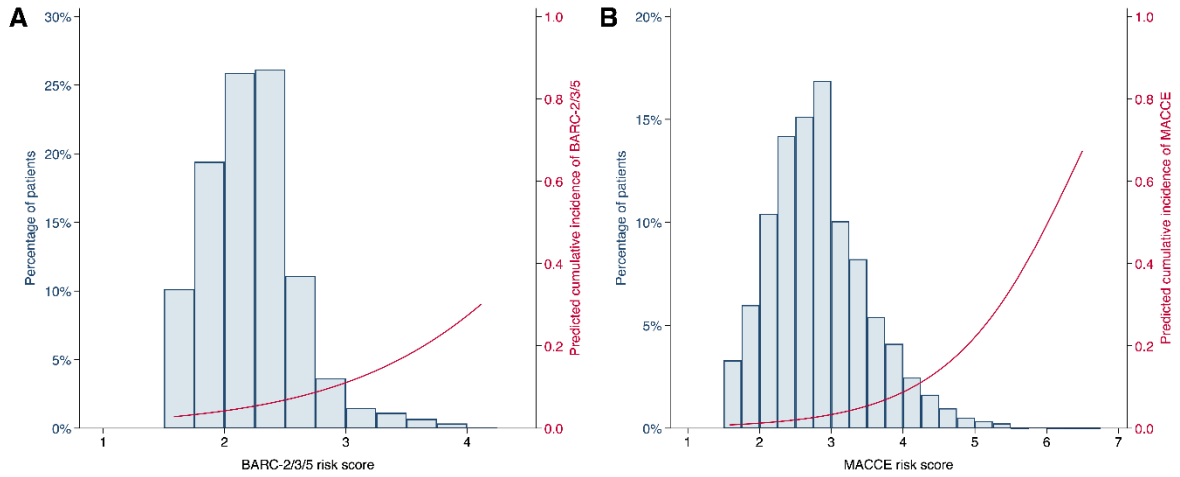
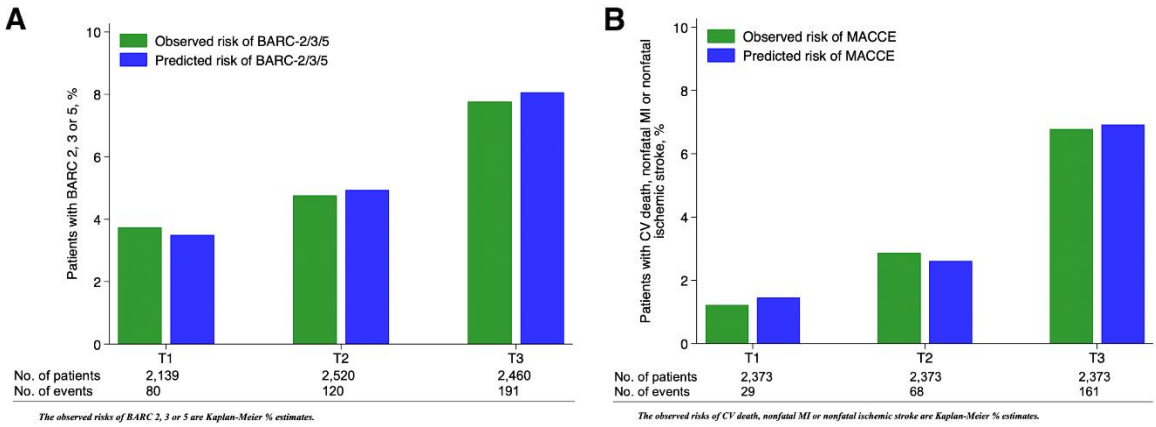


Figure 1

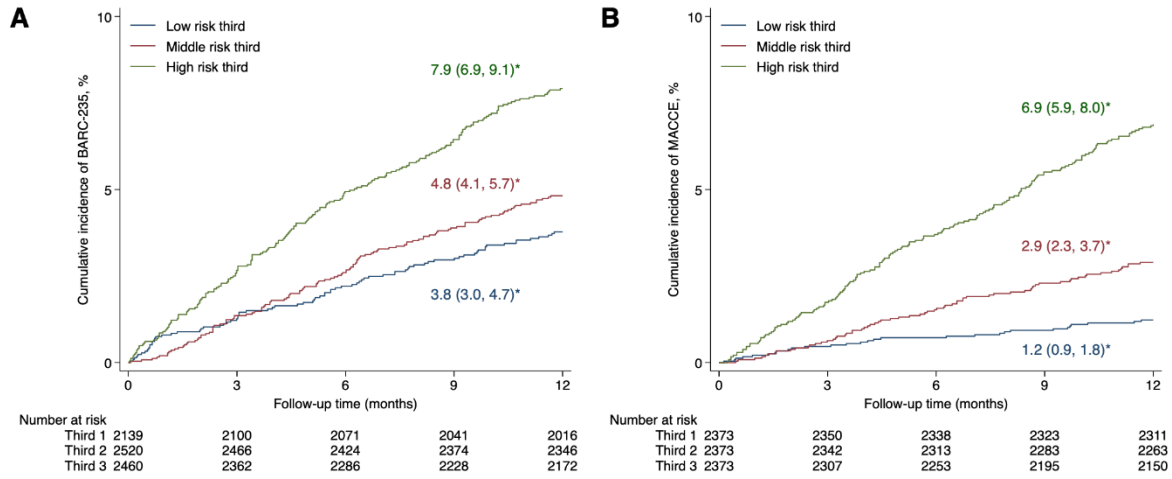
BARC-2/3/5 and MACCE risk scores. Panel A: Distribution of BARC-2/3/5 risk score for 7,119 patients and model-based relation between risk score and probability of BARC-2/3/5 at 1 year. (The predicted risk of a BARC-2/3/5 at 1 year was calculated as $R_{1yr} = 1 - S_{01yr}^{\{exp(XB)\}}$ where S_{01yr} is the estimated baseline survival at 1-year obtained from the Cox model and XB is the risk score.). **Panel B:** Distribution of MACCE risk score for 7,119 patients and model-based relation between risk score and probability of MACCE including CV death, nonfatal MI or nonfatal ischemic stroke at 1 year. (The predicted risk of a MACCE at 1 year was calculated as $R_{1yr} = 1 - S_{01yr}^{\{exp(XB)\}Ticagrelor\ monotherapy\ reduces\ l}$ where S_{01yr} is the estimated baseline survival at 1-year obtained from the Cox model and XB is the risk score.).

Figure 2.



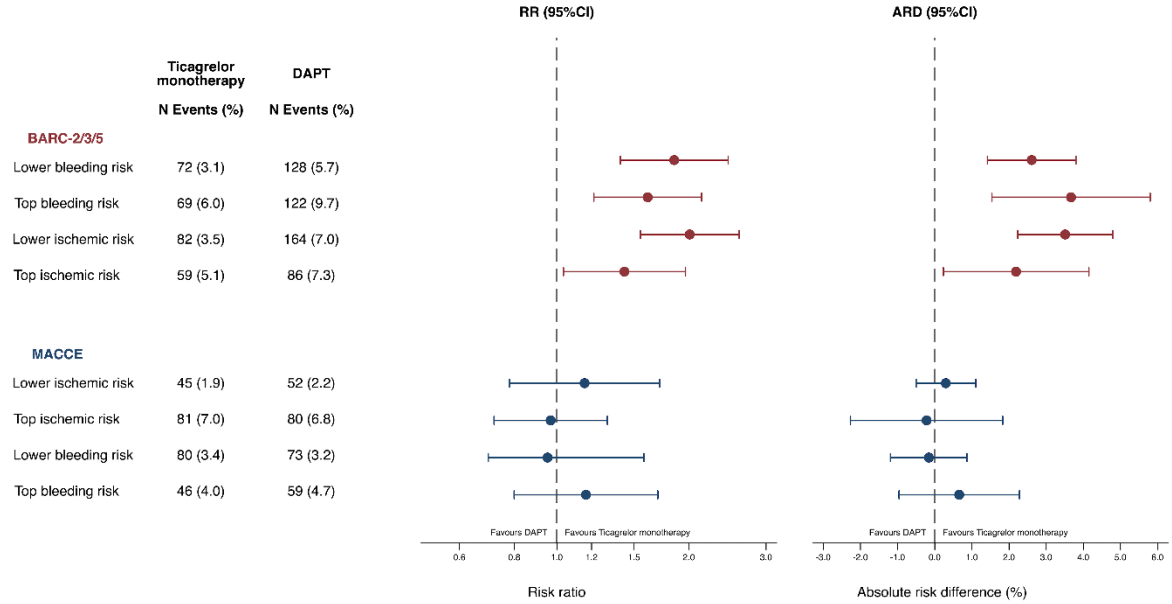
Model calibration plots. Panel A: BARC-2/3/5 risk score: plot of observed *versus* predicted risk of BARC 2, 3 or 5. **Panel B:** MACCE risk score: plot of observed *versus* predicted risk of ischemic events. BARC-2/3/5, Bleeding Academic Research Consortium 2, 3, or 5; CV, cardiovascular; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; No., number.

Figure 3.



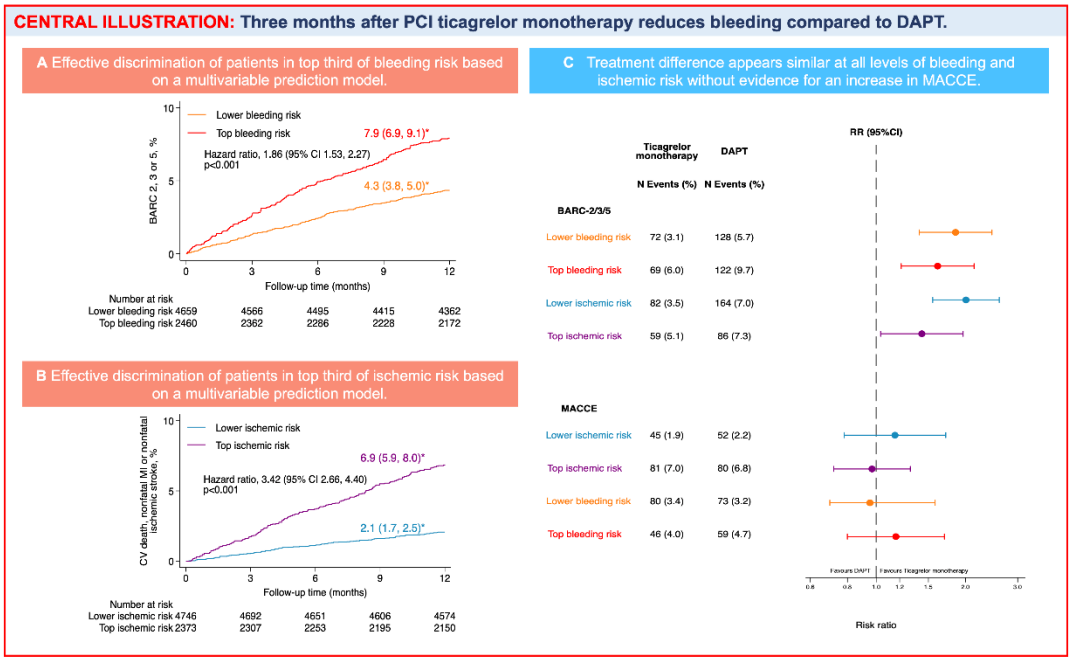
Cumulative incidence of bleeding and ischemic events by thirds of the bleeding and ischemic risk scores. Panel A: Cumulative incidence of BARC 2, 3 or 5 by thirds of the BARC-2/3/5 risk score. **Panel B:** Cumulative incidence of ischemic events by thirds of the MACCE risk score. Bleeding Academic Research Consortium 2, 3, or 5; MACCE, major adverse cardiac and cerebrovascular events. *Kaplan-Meier % estimates.

Figure 4.



Randomized treatment effect on outocmes by risk category. BARC-2/3/5, Bleeding Academic Research Consortium 2, 3, or 5; CI, confidence interval; DAPT, dual-antiplatelet therapy; MACCE, major adverse cardiac and cerebrovascular events; N, number.

Central Illustration.



Three months after PCI ticagrelor monotherapy reduces bleeding compared to DAPT. Multivariable predictive models can identify patients at higher bleeding risk (Panel A) and patients at high risk of MACCE (Panel B). The benefit of ticagrelor monotherapy is consistent across different levels of risk (Panel C). *Kaplan-Meier % estimates. BARC-2/3/5, Bleeding Academic Research Consortium 2, 3, or 5; CI, confidence interval; CV, cardiovascular; DAPT, dual-antiplatelet therapy; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; N, number.

TABLES

Table 1. Multivariable predictors of BARC-2/3/5 and MACCE at 1 year (N=7,119)				
Multivariable predictors of BARC-2, -3 or -5 bleeding (BARC-2/3/5) at 1 year				
Predictor	**HR (95% CI)**	**χ2 statistic**	**Coefficient (SE)[a]**	**p-value[b]**
Haemoglobin (g/dL)				<0.001
<11	3.40 (2.37, 4.86)	36.2	1.22 (0.18)	
11-13.9	1.31 (1.05, 1.62)		0.27 (0.11)	
≥14	1.00 (reference)		0.00 (reference)	
No PPI treatment at discharge	1.55 (1.27, 1.90)	18.5	0.44 (0.10)	<0.001
Age (per 10 years)[c]	1.30 (1.13, 1.50)	13.1	0.26 (0.07)	0.0003
Liver disease[d]	4.56 (1.88, 11.05)	7.3	1.52 (0.45)	0.007
Active smoking	1.32 (1.04, 1.69)	4.8	0.28 (0.12)	0.03
ASA+Ticagrelor[e]	1.79 (1.45, 2.20)	31.6	0.58 (0.11)	<0.001
Multivariable predictors of CV death, MI and ischemic stroke (MACCE) at 1 year				
Predictor	**HR (95% CI)**	**χ2 statistic**	**Coefficient (SE)[a]**	**p-value[b]**
Troponin positive ACS	2.13 (1.64, 2.79)	29.0	0.76 (0.14)	<0.001
Prior CABG	2.09 (1.54, 2.83)	20.0	0.73 (0.16)	<0.001
Diabetes	1.67 (1.30, 2.15)	15.7	0.51 (0.13)	0.0001
Prior PCI	1.73 (1.30, 2.30)	14.2	0.55 (0.15)	0.0002
PAD	1.90 (1.35, 2.68)	11.9	0.64 (0.18)	0.0006
Active smoking	1.57 (1.17, 2.10)	8.6	0.45 (0.15)	0.003
Age (per 10 years)[c]	1.30 (1.09, 1.56)	8.1	0.26 (0.09)	0.005
CHF	1.77 (1.22, 2.58)	8.0	0.57 (0.19)	0.005
Prior MI	1.46 (1.10, 1.93)	7.0	0.38 (0.14)	0.008
PCI complexity criteria[f]				0.01
0-2	1.00 (reference)	6.4	0.00 (reference)	
≥3	1.95 (1.22, 3.11)		0.67 (0.24)	
eGFR <60 mL/min/1.73m^2 [g]	1.42 (1.05, 1.93)	5.0	0.35 (0.15)	0.03
ASA+Ticagrelor[e]	1.02 (0.80, 1.31)	0.0	0.02 (0.12)	0.85

[a] Coefficient (SE) is the log-hazard ratio and its standard error.
[b] P-value from a likelihood-ratio test.
[c] Truncated below the age of 60.
[d] Defined as cirrhosis, bilirubin >2x normal, or liver enzymes >3x normal prior to PCI.
[e] Compared to Ticagrelor+Placebo.
[f] Defined as fulfilling 0-2 or ≥3 of the following criteria: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, use of any atherectomy device, left main as target vessel, surgical bypass graft or chronic total occlusion as target lesions.
[g] Calculated using CKD-EPI equation.
ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton-pump inhibitor.
Harrell's C 0.64 (95%CI 0.62-0.68) for the bleeding risk model.

Harrell's C 0.71 (95%CI 0.68-0.77) for the ischemic risk model.

Table 2. Overall baseline predictors by occurrence of BARC-2/3/5 and occurrence of MACCE over 1 year's follow-up						
			BARC-2/3/5		**MACCE[a]**	
Predictors		**Total (N=7,119)**	**Yes (N=391)**	**No (N=6,728)**	**Yes (N=258)**	**No (N=6,861)**
Randomized treatment	Ticagrelor+Placebo	3555 (50)	141 (36)	3414 (51)	126 (49)	3429 (50)
	Ticagrelor+ASA	3564 (50)	250 (64)	3314 (49)	132 (51)	3432 (50)
Demographics						
Age, years	Mean±SD	63.9±10.2	65.4±11.0	63.8±10.1	65.7±11.1	63.8±10.1
Lifestyle						
Active smoking		1548 (22)	92 (24)	1456 (22)	70 (27)	1478 (22)
	Missing	4 (0.1)	1 (0.3)	3 (0.0)	0 (0.0)	4 (0.1)
Medical history						
Diabetes		2620 (37)	144 (37)	2476 (37)	129 (50)	2491 (36)
eGFR <60, mL/min/1.73m² [b]		1111 (16)	74 (20)	1037 (15)	70 (27)	1041 (15)
	Missing	284 (4)	15 (4)	269 (4)	8 (3)	276 (4)
Liver disease [c]		27 (0.4)	5 (1)	22 (0.3)	1 (0.4)	26 (0.4)
PAD		489 (7)	32 (8)	457 (7)	44 (17)	445 (6)
CHF		366 (5)	30 (8)	336 (5)	35 (14)	331 (5)
Prior MI		2040 (29)	108 (28)	1932 (29)	113 (44)	1927 (28)
Prior PCI		2998 (42)	161 (41)	2837 (42)	152 (59)	2846 (41)
Prior CABG		710 (10)	50 (13)	660 (10)	60 (23)	650 (9)
	Missing	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)
Biochemistry						
Troponin positive ACS		2053 (29)	109 (28)	1944 (29)	95 (37)	1958 (29)
Haemoglobin, g/dL	<11	271 (4)	39 (10)	232 (4)	14 (5)	257 (4)
	11-13.9	3034 (43)	183 (47)	2851 (42)	115 (45)	2919 (43)
	≥14	3523 (50)	154 (39)	3369 (50)	121 (47)	3402 (50)
	Missing	291 (4.1)	15 (3.8)	276 (4.1)	8 (3.1)	283 (4.1)
Co-medications at discharge						
Proton-pump inhibitors		3601 (51)	164 (42)	3437 (51)	151 (59)	3450 (50)
Procedural						

PCI complexity items[d]	0-2	6811 (96)	371 (95)	6440 (96)	239 (93)	6572 (96)
	≥3	308 (4)	20 (5)	288 (4)	19 (7)	289 (4)

Numbers are counts (%) unless stated otherwise. Missing observations have been specified where appropriate.

[a] Including CV death, nonfatal MI or nonfatal ischaemic stroke.

[b] Calculated using CKD-EPI equation.

[c] Defined as cirrhosis, bilirubin >2x normal, or liver enzymes >3x normal prior to PCI.

[d] Defined as fulfilling 0-2 or ≥3 of the following criteria: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, use of any atherectomy device, left main as target vessel, surgical bypass graft or chronic total occlusion as target lesions.

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; BARC-2/3/5, Bleeding Academic Research Consortium 2, 3, or 5; CABG, coronary artery bypass graft; CHF, congestive heart failure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PAD, peripheral artery disease; and PCI, percutaneous coronary intervention.

Table 3. All-cause mortality after nonfatal events				
Type of event	**Total N**	**N of deaths (%)**	**HR (95%CI)**	**p-value[a]**
BARC-2[b]	293	6 (2.1)	2.71 (1.09, 6.75)	0.06
BARC-3[c]	103	5 (4.9)	6.08 (2.21, 16.70)	0.006
MI	192	21 (10.9)	19.93 (11.54, 34.42)	<0.001
Ischemic stroke	24	2 (8.3)	6.47 (0.95, 49.54)	0.14
None of the above	6,542	54 (0.8)	1.00 (reference)	-

[a] P-value from a likelihood-ratio test.

[b] Defined as any clinically overt sign of haemorrhage that is actionable but does not meet criteria for type 3, 4 or 5. Must meet at least 1 of following criteria: a) requires intervention; b) leads to hospitalization; and c) prompts evaluation.

[c] Defined as clinical, laboratory, and/or imaging evidence of bleeding, with healthcare provider responses.

- **BARC type 3a: any transfusion with overt bleeding, overt bleeding + haemoglobin drop ≥3 to <5 g/dL.**
- **BARC type 3b: overt bleeding + haemoglobin drop >5 g/dL, cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid), bleeding requiring intravenous vasoactive drugs.**
- **BARC type 3c: intracranial haemorrhage, subcategories confirmed by autopsy, imaging or lumbar puncture, intraocular bleed compromising vision.**

BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; and MI, myocardial infarction.

SUPPLEMENTARY MATERIAL

Bleeding and Ischemic Risks of Ticagrelor Monotherapy after Coronary Interventions

Short Title: Ticagrelor Monotherapy after PCI

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SUPPLEMENTARY TABLES

Supplementary Table 1. Candidate predictor variables considered for inclusion in the BARC-2/3/5 and MACCE risk prediction models

BARC-2/3/5		MACCE	
Randomized treatment	Prior CABG	Age	Prior MI
Age	Haemoglobin	Active smoking	Prior PCI
Sex	eGFR <60[c]	CAD family history	Prior CABG
Weight <65 kg	PPI treatment at discharge	Multivessel CAD	Troponin positive ACS
Active smoking	Statin treatment at discharge	Hypertension	eGFR <60[c]
CAD family history	Platelet count <150	Dyslipidaemia	PCI complexity items[d]
Hypertension	PCI complexity items[d]	Diabetes	
Liver disease[a]		PAD	
Congestive heart failure		Congestive heart failure	
Prior major bleeding[b]		TIA	

[a] Defined as cirrhosis, bilirubin >2x normal, or liver enzymes >3x normal prior to PCI.
[b] Requiring transfusion or hospitalisation.
[c] Calculated using CKD-EPI equation.
[d] Defined as fulfilling 0-2 or ≥3 of the following criteria: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, use of any atherectomy device, left main as target vessel, surgical bypass graft or chronic total occlusion as target lesions.
ACS, acute coronary syndrome; BARC-2/3/5, Bleeding Academic Research Consortium 2, 3, or 5; CABG, coronary artery bypass graft; CAD, coronary artery disease; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and TIA, transient ischaemic attack.

Supplementary Table 2. Randomized treatment effect by patient risk categories for bleeding and ischemic outcomes

Bleeding event rates by treatment group in the top third of risk *versus* the 2 lower thirds of the BARC-2/3/5 and MACCE risk scores for BARC 2, 3 or 5 at 1 year

Risk categories	Treatment arm[a]	Total (N=7,119)	Events, n (KM %)	RR (95% CI)[b]	ARD (95% CI)[b]
Lower thirds of BARC-2/3/5 risk	Placebo	2,379	72 (3.1)	1.85 (1.40, 2.46)	2.61% (1.42, 3.80)
	ASA	2,280	128 (5.7)		
Top third of BARC-2/3/5 risk	Placebo	1,176	69 (6.0)	1.61 (1.21, 2.14)	3.67% (1.54, 5.80)
	ASA	1,284	122 (9.7)		
Lower thirds of MACCE risk	Placebo	2,377	82 (3.5)	2.01 (1.55, 2.60)	3.51% (2.23, 4.79)
	ASA	2,369	164 (7.0)		
Top third of MACCE risk	Placebo	1,178	59 (5.1)	1.43 (1.04, 1.96)	2.19% (0.23, 4.15)
	ASA	1,195	86 (7.3)		

Ischemic event rates by treatment group in the top third of risk *versus* the 2 lower thirds of the MACCE and BARC-2/3/5 risk scores for CV death, nonfatal MI or nonfatal ischemic stroke at 1 year

Risk categories	Treatment arm[a]	Total (N=7,119)	Events, n (KM %)	RR (95% CI)[b]	ARD (95% CI)[b]
Lower thirds of MACCE risk	Placebo	2,377	45 (1.9)	1.16 (0.78, 1.72)	0.30% (-0.50, 1.10)
	ASA	2,369	52 (2.2)		
Top third of MACCE risk	Placebo	1,178	81 (7.0)	0.97 (0.72, 1.30)	-0.22% (-2.27, 1.83)
	ASA	1,195	80 (6.8)		
Lower thirds of BARC-2/3/5 risk	Placebo	2,379	80 (3.4)	0.95 (0.70, 1.58)	-0.16% (-1.19, 0.87)
	ASA	2,280	73 (3.2)		
Top third of BARC-2/3/5 risk	Placebo	1,176	46 (4.0)	1.17 (0.80, 1.70)	0.66% (-0.96, 2.28)
	ASA	1,284	59 (4.7)		

[a] Administered on top of ticagrelor.

[b] ASA+ticagrelor *versus* placebo+ticagrelor.

ARD, absolute risk difference; ASA, acetylsalicylic acid; BARC-2/3/5, Bleeding Academic Research Consortium 2, 3, or 5; CI, confidence interval; KM, Kaplan-Meier; MACCE, major adverse cardiac and cerebrovascular events; RR, risk ratio.

Supplementary Table 3. BARC-2/3/5 and MACCE risk scores and KM estimate of BARC-2/3/5 at 1 year (95%CI)			
	MACCE		
BARC-2/3/5	**Lower thirds**	**Top third**	**Total**
Lower thirds	3,361 146 4.4 (3.7, 5.1)	1,298 54 4.2 (3.3, 5.5)	4,659 200 4.3 (3.8, 5.0)
Top third	1,385 100 7.3 (6.1, 8.8)	1,075 91 8.7 (7.1, 10.6)	2,460 191 7.9 (6.9, 9.1)
Total	4,746 245 5.2 (4.6, 5.9)	2,373 146 6.3 (5.3, 7.4)	7,119 391 5.6 (5.1, 6.1)

Numbers within each combination of risk correspond to numbers of patients, numbers of events, and KM % estimate of BARC-2/3/5 at 1 year (95%CI), respectively.

BARC-2/3/5, Bleeding Academic Research Consortium 2, 3, or 5; CI, confidence interval; KM, Kaplan-Meier; MACCE, major adverse cardiac and cerebrovascular events.

Supplementary Table 4. BARC-2/3/5 and MACCE and KM estimate of MACCE at 1 year (95%CI)			
	MACCE		
BARC-2/3/5	**Lower thirds**	**Top third**	**Total**
Lower thirds	3,354 60 1.8 (1.4, 2.3)	1,305 93 7.3 (6.0, 8.8)	4,659 153 3.3 (2.8, 3.9)
Top third	1,392 37 2.7 (2.0, 3.7)	1,068 68 6.5 (5.1, 8.1)	2,460 105 4.3 (3.6, 5.2)
Total	4,746 97 2.1 (1.7, 2.5)	2,373 161 6.9 (5.9, 8.0)	7,119 258 3.7 (3.3, 4.1)

Numbers within each combination of risk correspond to numbers of patients, numbers of events, and KM % estimate of MACCE at 1 year (95%CI), respectively.

BARC-2/3/5, Bleeding Academic Research Consortium 2, 3, or 5; CI, confidence interval; CV, cardiovascular; KM, Kaplan-Meier; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

Supplementary Table 5. Evaluation of other risk scores				
Risk score (year of publication)	**Bleeding risk model**		**Ischemic risk model**	
	Predictors	**C-statistic (95% CI)**	**Predictors**	**C-statistic (95% CI)**
PARIS (2016)	Age, BMI, OAC [a], anaemia, active smoking, renal dysfunction.	0.54 (*0.53-0.61)*	ACS, prior revascularization, diabetes mellitus, renal dysfunction and active smoking.	0.65 (*0.53-0.69)*
PRECISE-DAPT (2017) [b]	Age, haemoglobin, WBCc, Crcl and prior bleeding.	0.5*5* (0.5*4*-0.*72*)	NA	NA
TWILIGHT	Haemoglobin levels, PPI treatment, age, liver disease, active smoking.	0.64 (*0.62-0.68*)	Troponin positive ACS, prior CABG, diabetes, prior PCI, PAD, active smoking, age, CHF, prior MI, PCI complexity [c], eGFR <60mL/min/1.73m^2.	0.71 (0.68-0.*77*)

[a] OAC was a TWILIGHT trial exclusion criterion.

[b] Only predicted bleeding risk.

[c] Defined as fulfilling 0-2 or ≥3 of the following criteria: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, use of any atherectomy device, left main as target vessel, surgical bypass graft or chronic total occlusion as target lesions.

ACS, acute coronary syndrome; BMI, body-mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; Crcl, creatinine clearance; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NA, not applicable; OAC, oral anti-coagulation; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton-pump inhibitor; WBCc, white-blood-cell count.