Ticagrelor With or Without Aspirin in High-Risk Patients With Anemia Undergoing Percutaneous Coronary Intervention: a subgroup analysis of the TWILIGHT trial

Alessandro Spirito*, MD[a], Adnan Kastrati*, MD[b], Davide Cao, MD[a,c], Usman Baber, MD, MS[d], Samantha Sartori, PHD[a], Dominick J. Angiolillo, MD, PHD[e], Carlo Briguori, MD, PhD[f], David J. Cohen, MD, MSc [g,h], George Dangas, MD[a], Dariusz Dudek, MD, PHD[i], Javier Escaned, MD, PHD[j], C. Michael Gibson, MD, MSc[k], Zhongjie Zhang, MPH[a], Kurt Huber, MD[l], Upendra Kaul, MD[m], Ran Kornowski, MD[n], Vijay Kunadian, MBBS, MD[o], Ya-Ling Han, MD, PhD[p], Shamir R. Mehta, MD [q], Gennaro Sardella, MD[r], Samin Sharma, MD[a], Richard A. Shlofmitz, MD[s], Birgit Vogel, MD[a], Timothy Collier, MSC[t], Stuart Pocock, PhD[t], Roxana Mehran, MD[a]

*These authors contributed equally to this work.

[a] The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[b] Deutsches Herzzentrum München, Munich, Germany
[c] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele-Milan, Italy
[d] Department of Cardiology, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
[e] Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida, USA;
[f] Mediterranea Cardiocentro, Naples, Italy
[g] Cardiovascular Research Foundation, New York, New York, USA
[h] St. Francis Hospital, Roslyn, Roslyn, New York, USA
[i] Jagiellonian University Medical College, Krakow, Poland
[j] Hospital Clínico San Carlos IDISCC, Complutense University of Madrid, Madrid, Spain
[k] Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
[l] Third Department Medicine, Cardiology and Intensive Care Medicine, Wilhelminen Hospital, and Sigmund Freud University, Medical Faculty, Vienna, Austria
[m] Batra Hospital and Medical Research Centre, New Delhi, India
[n] Rabin Medical Center, Petach Tikva, Israel
[o] 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
[p] Shenyang North Hospital, Shenyang, China.
[q] Hamilton Health Sciences, Hamilton, Ontario, Canada
[r] Policlinico Umberto I University, Rome, Italy
[s] St. Francis Hospital, Roslyn, Roslyn, New York, USA
[t] Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom

Brief title: Ticagrelor monotherapy after PCI in patients with anemia

Word count (introduction to conclusion, including references, tables and figure legends): 4,986

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

© The Author(s) 2023. Published by Oxford University Press on behalf of the European Society of Cardiology. All rights reserved.
For permissions, please e-mail: journals.permissions@oup.com

Corresponding author:
Roxana Mehran, MD
Professor of Medicine
Icahn School of Medicine at Mount Sinai
1 Gustav L. Levy Place, Box 1030,
New York, NY 10029
roxana.mehran@mountsinai.org

Abstract

Aim: The aim of this study was to assess the effect of ticagrelor monotherapy among high-risk patients with anemia undergoing percutaneous coronary intervention (PCI).

Methods and Results: In the TWILIGHT trial (Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention), after 3 months of ticagrelor plus aspirin, high-risk patients were maintained on ticagrelor and randomized to aspirin or placebo for 1 year. Anemia was defined as hemoglobin <13 g/dL for men and <12 g/dL for women. The primary endpoint was Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding. The key secondary endpoint was a composite of all-cause death, myocardial infarction, or stroke.

Out of 6,828 patients, 1,329 (19.5%) had anemia and were more likely to have comorbidities, multivessel disease, and to experience bleeding or ischemic complications than non-anemic patients. Among anemic patients, BARC 2, 3, or 5 bleeding occurred less frequently with ticagrelor monotherapy than with ticagrelor plus aspirin (6.4% vs. 10.7%; HR 0.60; 95% CI 0.41 to 0.88; p= 0.009); the rate of the key secondary endpoint was similar in the two arms (5.2% vs. 4.8%; HR 1.07; 95% CI 0.66 to 1.74; p= 0.779). These effects were consistent in patients without anemia (interaction p-value 0.671 and 0.835, respectively).

Conclusions: In high-risk patients undergoing PCI, ticagrelor monotherapy after 3 months of ticagrelor-based DAPT was associated with a reduced risk of clinically relevant bleeding without any increase in ischemic events irrespective of anemia status. (TWILIGHT: NCT02270242)

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

Key words: anemia; bleeding; percutaneous coronary intervention; ticagrelor monotherapy; outcomes

ABBREVIATIONS AND ACRONYMS

ACS: Acute coronary syndrome

ARC: Academic Research Consortium

BARC: Bleeding Academic Research Consortium

CKD: Chronic Kidney Disease

DAPT: Dual Antiplatelet Therapy

GUSTO: Global Use of Strategies to Open Occluded Arteries

Hb: Hemoglobin

HBR: High Bleeding Risk

ISTH: International Society on Thrombosis and Haemostasis

MI: Myocardial Infarction

PCI: Percutaneous Coronary Intervention

TIMI: Thrombolysis In Myocardial Infarction

TWILIGHT: Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

Introduction

Dual antiplatelet therapy (DAPT), which refers to the combination of aspirin and a P2Y12 inhibitor, is the standard of care for the prevention of ischemic events in patients undergoing percutaneous coronary intervention (PCI) [1,2]. However, this benefit occurs at the expense of higher rate of bleeding complications, which gradually increases with prolonged or more potent DAPT [3,4]. Given the enhanced morbidity and mortality associated with bleeding events, novel antiplatelet treatment regimens have been examined to reduce the risk of bleeding while maintaining protection from ischemic events after PCI [5]. Among those, a short period of DAPT followed by P2Y12 inhibitor monotherapy has emerged as a promising bleeding reduction strategy in several studies [6-8]. The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial showed that among high-risk patients undergoing PCI, after 3 months of DAPT, P2Y12 inhibitor monotherapy with ticagrelor reduced bleeding without increasing ischemic harm compared with a standard ticagrelor-based DAPT [9].

Anemia is a common condition in patients undergoing PCI, with prevalence >30% in all-comer cohorts [10]. Anemia is a marker of frailty and comorbidity and has been associated with increased mortality, bleeding, and ischemic complications after PCI [11,12]. Several bleeding scores and the criteria proposed by the Academic Research Consortium (ARC) to identify patients at high bleeding risk (HBR) include anemia [13-15]. Several studies have confirmed that shorter DAPT regimens after PCI are effective in reducing bleeding risk without increasing ischemic events in HBR patients [7,8,16,17]. However, specific evidence for patients with anemia is lacking.

Accordingly, we aimed to assess the effect of ticagrelor monotherapy versus ticagrelor plus aspirin among patients with anemia included in the TWILIGHT trial.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

METHODS

TWILIGHT (NCT02270242) was a randomized, placebo-controlled trial conducted at 187 sites in 11 countries. The rationale, design, and principal results of the trial have been reported previously [18]. TWILIGHT was an investigator-initiated trial designed, coordinated, and sponsored by the Icahn School of Medicine at Mount Sinai. Astra Zeneca 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. The executive and steering committees were responsible for trial conduct, integrity of data analysis, and reporting of results. The trial protocol was approved by National regulatory agencies and Institutional Review Boards or ethics committees of participating centers. The safety of trial participants was ensured by an external and independent data and safety monitoring board.

Study population

Patients were eligible to participate if they underwent a successful PCI with at least 1 commercially available drug-eluting stent and were prescribed at discharge a regimen of ticagrelor plus aspirin by the treating clinician. The presence of at least 1 clinical and 1 angiographic feature associated with a high risk for ischemic or bleeding events was required for trial inclusion [9,18]. Clinical criteria were: age ≥65 years, female sex, troponin-positive acute coronary syndrome (ACS), atherosclerotic vascular disease (prior myocardial infarction [MI], coronary revascularization, or peripheral arterial disease), diabetes mellitus requiring medication, and chronic kidney disease (CKD) (estimated glomerular filtration rate <60 ml/min/1.73 m2 or creatinine clearance <60 ml/min). 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 coronary artery lesion, and calcified

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

target lesion requiring debulking devices. Key exclusion criteria included presentation with an ST-segment elevation MI (STEMI), cardiogenic shock, prior stroke, need for oral anticoagulation, or contraindication to aspirin or ticagrelor.

All enrolled patients received open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81 to 100 mg/day) after index PCI. At 3 months, patients were randomized 1:1 in a double-blind fashion to aspirin or matching placebo for 12 months in addition to open-label ticagrelor [9,18]. Patients who were non adherent to ticagrelor or aspirin or who experienced Bleeding Academic Research Consortium (BARC) type 3b or higher bleeding events or ischemic events (stroke, MI, or coronary revascularization) between the index PCI and 3 months were not eligible for randomization. (**Figure 1**). Follow-up occurred 1 month after randomization via telephone and in person at 6 and 12 months after randomization. At the end of protocol-mandated therapy, patients were switched to a standard-of-care antiplatelet regimen at the discretion of their treating physicians, followed by final telephone follow-up 3 months later.

Clinical endpoints

The primary endpoint was the composite of BARC type 2, 3, or 5 bleeding through 1 year after randomization [9,18]. The key secondary endpoint was the composite of all-cause death, MI, or stroke. Other secondary bleeding endpoints included BARC type 3 or 5 bleeding; TIMI (Thrombolysis In Myocardial Infarction) major or minor bleeding; GUSTO (Global Use of Strategies to Open Occluded Arteries) moderate, severe, or life-threatening bleeding; and major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) [9,18].

Additional secondary endpoints were cardiovascular death, nonfatal MI, ischemic stroke, and definite or probable stent thrombosis. MI was defined according to the third universal

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

definition, and stent thrombosis was classified according to the ARC definition [9,18]. All clinical events were adjudicated by an independent committee, blinded to treatment assignment.

Statistical analysis

In this post-hoc analysis, patients were stratified in two groups according to the presence or absence of anemia at time of index PCI, defined as hemoglobin (Hb) <13 g/dL for men and <12g/dL for women. For additional analyses, anemia was further classified into mild (Hb between 11–12.9 g/dL for men and between 11–11.9 g/dL for women) and moderate-severe (Hb<11 g/dL for both sexes). These definitions were in line with those proposed by the ARC-HBR consensus [15]. Patients with any Hb value were included, only subjects with missing Hb values were excluded.

Clinical and procedural characteristics were summarized by anemia status and randomized group as mean and standard deviation for continuous variables and frequencies and percentages for categorical variables. The cumulative incidence of both primary and secondary endpoints was estimated using the Kaplan-Meier method. Patients without primary endpoints between randomization and 1 year were censored at the time of death, last known contact, or 365 days, whichever came first. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using unadjusted Cox proportional hazards models.

Analyses for the bleeding outcomes were performed in the intention-to-treat cohort, ischemic outcomes in the per protocol cohort (i.e., randomized participants who completed all study-related contacts without any major protocol deviations) [9,18]. Treatment effects were estimated according to anemia status with formal interaction testing to assess for effect modification. Finally, the association between Hb (as a continuous variable) and the rates of the primary and key secondary endpoint was also evaluated fitting a smoothing spline curve with 4

ORIGINAL UNEDITED MA

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

knots placed at equally spaced percentiles across the range of Hb. All analyses were performed using Stata version 16.0 (StataCorp, College Station, Texas).

RESULTS

Population characteristics

Among 6,828 patients randomized in the TWILIGHT trial with available Hb values at baseline, 1,329 (19.5%) had anemia (**Figure 1**). Of these, 50.8% were randomized to ticagrelor plus placebo and 49.2% to ticagrelor plus aspirin. Among non-randomized patients, not included in this analysis, frequency of anemia was slightly higher (24.9%).

Compared to patients without anemia, anemic patients were on average older, more likely to be women, from North America or Asia, of non-white race, and to have comorbidities, such as diabetes, hypertension, prior coronary artery bypass graft surgery, peripheral artery disease, CKD and a history of major bleeding (**Supplemental Table 1**). Mean Hb was 11.6±1.1 g/dL in anemic patients and 14.5±1.2 g/dL in non-anemic patients and was similar in the two randomized arms (**Table 1**). Among patients with anemia, femoral artery access, multivessel coronary artery disease and calcific lesions were more common (**Supplemental Table 2**).

Within patients with or without anemia, demographic, clinical, and procedural characteristics were well balanced between treatment arms, except for the rates of current smoking and total stent length, which were higher in the ticagrelor plus placebo than in the ticagrelor plus aspirin arm (**Table 1** and **Supplemental Table 3**).

At 1 year after randomization, patients with anemia were more likely to have permanently discontinued ticagrelor (17.1% vs 12.4%, p <0.001) or the study drug (21.9% vs 16.3%, p <0.001) than patients without anemia.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

Bleeding events

Bleeding events rates were inversely associated with hemoglobin values (**Figure 2A**). Patients with anemia compared to those without anemia had a significantly higher rates of BARC 2, 3 or 5 (8.3% vs 4.9%) and BARC 3 or 5 bleeding (3.1% vs 1.1%) (**Supplementary Table 4**).

Among patients with anemia, the primary outcome of BARC type 2, 3, or 5 bleeding occurred in 42 patients (6.4%) randomized to ticagrelor plus placebo and 67 patients (10.4%) randomized to ticagrelor plus aspirin (HR: 0.60; 95% CI: 0.41 to 0.88; p = 0.009) (**Figure 3A**). In anemic patients, rates of BARC type 3 or 5 bleeding were 1.7% in the ticagrelor plus placebo group and 4.5% in the ticagrelor plus aspirin group, (HR: 0.37; 95% CI 0.18 to 0.73; p = 0.005) (**Figure 4**). This treatment effect was consistent across different bleeding scales, including TIMI, GUSTO, and ISTH (**Table 2**).

There was no significant interaction between anemia status and treatment group with respect to any of the bleeding endpoints.

Ischemic events

The key secondary endpoint of all-cause death, MI or stroke increased with decreasing values of Hb (**Figure 2B**) and was significantly higher in patients with anemia than without anemia (5.0% vs 3.7%); this difference was driven by an excess of all-cause death in anemic patients (**Supplementary Table 4**). Among patients with anemia, all-cause death, MI, or stroke occurred in 34 patients (5.2%) randomized to ticagrelor plus placebo versus 31 patients (4.8%) randomized to ticagrelor plus aspirin (HR: 1.07; 95% CI: 0.66 to 1.74; p = 0.779) (**Figure 3B**).

Rates of all-cause death (1.5% vs. 2.2%), MI (3.5% vs. 3.5%), ischemic stroke (0.5% vs. 0.3%), and definite or probable stent thrombosis (0.5% vs. 0.8%) were similar between treatment

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

groups (p > 0.20 for all) (**Figure 4**). There was no significant interaction between anemia status and treatment group with respect to the ischemic endpoints.

Outcomes by anemia severity

The risk of clinically relevant or major bleeding increased progressively in patients with mild (6.7%) and moderate-severe anemia (14.7%), as compared to non-anemic patients (4.9%). Moreover, moderate-severe anemia was associated with significantly higher risk of all-cause death and MI as compared to no anemia (5.7% vs 3.7%) (**Supplementary Table 5**).

The reduction in BARC type 2, 3, or 5 bleeding associated with ticagrelor monotherapy was consistent across levels of anemia severity (p interaction = 0.769) (**Figure 5**). In contrast to the findings for our primary endpoint, the extent of relative risk reduction in major bleeding tended to be larger in patients with moderate-severe anemia than patients with no anemia irrespective of the bleeding scale applied (**Figure 5 and Supplementary Table 6**). There were no differences between the two treatment arms with respect to the key secondary endpoint of death, MI, or stroke between the three groups (p interaction = 0.962) (**Figure 5** and **Supplementary Table 6**).

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

DISCUSSION

In this post-hoc analysis of the TWILIGHT trial, we assessed the effect on clinical outcomes of ticagrelor with or without aspirin after 3 months of ticagrelor-based DAPT in 1,329 patients with anemia undergoing PCI. The key findings from our analysis can be summarized as follows:

1) patients with anemia were older, had more comorbidities, were more likely to have multivessel disease, and experienced higher rates of bleeding complications and - to a lesser extent - of death, MI or stroke than patients without anemia
2) in anemic patients, ticagrelor monotherapy reduced the 1-year risk of clinically relevant BARC 2, 3, or 5 bleeding by 40%, of BARC 3 or 5 bleeding by 63% and was not associated with an increased risk of all-cause death, MI, or stroke as compared to ticagrelor plus aspirin
3) the treatment effects of ticagrelor monotherapy with respect to ischemic and bleeding outcomes were consistent irrespective of the presence of anemia or its severity; the benefit on major bleeding reduction tended to belarger in patients with moderate-severe anemia

In real world PCI cohorts, anemia can be found in more than 30% of patients and is also one of the most frequently fulfilled ARC-HBR criteria among HBR patients [10,11,19]. Anemic patients are more likely to discontinue antiplatelet therapy than non-anemic patients [20] and to receive suboptimal therapy for secondary prevention after PCI, including antiplatelet therapy [21,22]. Several studies confirmed that in HBR patients shorter DAPT regimens after PCI are effective in reducing bleeding risk without ischemic harm. However, analyses focusing on patients with anemia are limited.

In this study, anemia, which was defined based on the ARC-HBR definition as Hb <13 g/dL in men and <12g/dL in women, was found in 19.5% of included patients. The lower

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

frequency of anemia compared to all-comer observational studies is probably due to the exclusion from the trial of patients on dialysis, with cardiogenic shock, STEMI or liver cirrhosis, that frequently present with low Hb values, and to the selection of event-free patients for randomization. Indeed, the prevalence of anemia was slightly higher (24.9%) among non-randomized subjects. In agreement with the overall findings from TWILIGHT, we found that the withdrawal of aspirin after a brief period of DAPT significantly reduced bleeding and did not incur any increase in ischemic complications irrespective of anemia status. Interestingly, the reduction of major bleeding associated with aspirin withdrawal seemed to be amplified in patients with anemia irrespective of the bleeding scale used (BARC, TIMI, GUSTO or ISTH), especially in patients with moderate or severe anemia.

A number of trials have investigated the safety and efficacy of P2Y12 inhibitor monotherapy after a minimal duration (1 to 3 months) of DAPT following PCI [6-8]. However, TWILIGHT was the only trial to be placebo controlled and to enroll patients with both clinical and angiographic features associated with increased risk for ischemic or bleeding complications post-PCI. In some of the above-mentioned trials, the effect of P2Y12 inhibitor monotherapy was assessed in HBR patients, whereas analyses focused on anemic patients are lacking. The benefit of ticagrelor monotherapy in reducing bleeding complications in patients with anemia (40% for BARC 2, 3 or 5 and 63% for BARC 3 or 5) was similar to that observed in the HBR cohort of the TWILIGHT trial (47% for BARC 2, 3 or 5 and 69% for BARC 3 or 5) [17].

In keeping with previous studies, our study confirms that anemic patients have a high burden of comorbidities, an increased risk of bleeding events and — to a lesser extent— a higher risk of ischemic complications after PCI [11,12,20,21,23]. The increased rate of complications in anemic patients undergoing PCI has been attributed to their old age and the associated comorbidities [21,24,25] but also to direct pathophysiologic changes due to anemia. Indeed, anemia

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

leads to impaired oxygen delivery to the myocardium and induces myocardial cell ischemia [26]; it also increases myocardial oxygen demand through increments in heart rate, cardiac index, and stroke volume [27]. In addition, patients with anemia have high platelet reactivity on clopidogrel [28,29], probably related to the inflammatory status generated by the same chronic diseases that promote anemia.

Several interventions were tested to improve outcomes of anemic patients undergoing PCI. Routine blood transfusion or erythropoietin administration have been shown to be harmful in the context of PCI [30,31]. Blood transfusion remains an effective measure in presence of low hemoglobin values (≤8 g/dL) and symptoms [32]. Other bleeding avoidance strategies, such as use of transradial access and use of bivalirudin or enoxaparin rather than unfractionated heparin in ACS might reduce the risk of bleeding, even though dedicated studies in patients with anemia are lacking [5].

Our analysis demonstrated that aspirin withdrawal after a short period of ticagrelor-based DAPT represents an effective intervention to prevent bleeding events in patients with anemia.

Limitations

These results should be interpreted in light of several limitations. First, this analysis was not prespecified; therefore, the findings should be considered exploratory. Additional caution is needed in interpreting the results in the context of an underpowered subgroup analysis. In particular patients with moderate-severe anemia represented a small proportion of the study population. Moreover, the diagnosis of anemia was based on the Hb levels at time of index PCI, which reflects solely the status of the patients before PCI. The cause of anemia and additional data such as mean corpuscular volume, mean corpuscular Hb, and iron studies were not available. In this study, since pharmacodynamics or platelet function data were not collected, mechanistic

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

insights on the interaction between antiplatelet agents and platelet function in anemic patients could not be provided and should be explored in dedicated studies. Our findings may not generalize to patients treated with other oral P2Y12 inhibitors, particularly clopidogrel or to patients presenting with STEMI, who were excluded from participation in TWILIGHT. Finally, limitations of the main trial also apply to the current analysis, including the lack of power to detect differences in the risk of important yet rare clinical events (e.g., stent thrombosis and stroke) and applicability of the findings restricted to patients who were able to adhere to 3 months of DAPT without experiencing any major bleeding or ischemic event.

CONCLUSIONS

Among high-risk patients undergoing PCI, ticagrelor monotherapy following 3 months of DAPT significantly reduced clinically relevant bleeding compared with ticagrelor plus aspirin without evident ischemic harm, irrespective of the presence of baseline anemia. The reduction in major bleeding tended to be greater in patients with moderate-severe anemia. These findings support that ticagrelor monotherapy can be implemented without any signals for harm in patients with anemia and concomitant increased risk for ischemic complications.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

Funding

The TWILIGHT trial was an investigator-initiated trial designed, coordinated, and sponsored by the Icahn School of Medicine at Mount Sinai. Astra Zeneca 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.

Dr Spirito received a research grant from the Swiss National Science Foundation (SNSF).
Dr. Mehran reports institutional research payments from Abbott, Abiomed, Alleviant Medical, Amgen, AM-Pharma, Arena, AstraZeneca, Atricure, Bayer, Biosensors, Biotronik, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CeloNova, Chiesi, Concept Medical, CSL Behring, Cytosorbents, Daiichi Sankyo, Element Science, Faraday, Humacyte, Idorsia Pharmaceuticals, Janssen, Medtronic, Novartis, OrbusNeich, PhaseBio, Philips, Pi-Cardia, PLx Pharma, RenalPro, RM Global, Shockwave, Vivasure, Zoll; personal fees from Cine-Med Research, Novartis, WebMD; Equity <1% in Applied Therapeutics, Elixir Medical, Stel, ControlRad (spouse); Scientific Advisory Board for AMA, ACC (BOT Member), SCAI (Women in Innovations Committee Member), JAMA Associate Editor; Faculty CRF (no fee). Dr. Kastrati is an inventor in a patent application related to drug-eluting stent technology; he also serves in the Data and Safety Monitoring Board of the TARGET IV trial sponsored by the Cardiovascular Research Foundation in New York, USA.
Dr. Angiolillo declares that he has received consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx Pharma, Pfizer, and Sanofi; D.J.A. also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, and the Scott R. MacKenzie Foundation.
Dr Baber has received honoraria from AstraZeneca and Boston Scientific.
Dr Cohen has received grant support, paid to his institution, and consulting fees from AstraZeneca, Medtronic, and Abbott Vascular; and has received grant support, paid to his institution, from Boston Scientific
Dr Dangas has received consulting fees and advisory board fees from AstraZeneca; has received consulting fees from Biosensors; and previously held stock in Medtronic
Dr Escaned has received consulting and lecture fees from Abbott, Philips, Boston Scientific, and Medtronic; and has received lecture fees from Abiomed, Terumo, and Biosensors.
Dr. Gibson has received grant support and consulting fees from Angel Medical, Bayer, CSL Behring, Janssen Pharmaceuticals, Johnson & Johnson, and Portola Pharmaceuticals; has received consulting fees from The Medicines Company, Eli Lilly, Gilead Sciences, Novo Nordisk, WebMD, UpToDate Cardiovascular Medicine, Amarin Pharma, Amgen, Boehringer Ingelheim, Chiesi, Merck, PharmaMar, Sanofi, Somahlution, Verreseon, Boston Scientific, Impact Bio, MedImmume, Medtelligence, MicroPort, the PERT Consortium, and GE Healthcare; holds equity in Inference; serves as chief executive officer of the Baim Institute; and has received grant support, paid to the Baim Institute, from Bristol Myers Squibb and Astra Zeneca.
Dr Huber has received lecture fees from AstraZeneca and Bayer.
Dr Mehta has received grant support from and has served on an executive committee and as site investigator for AstraZeneca.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

Acknowledgments

We thank all patients who participated in the TWILIGHT trial.

Data availability

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

References

1. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM*, et al.* 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e4-e17. doi: 10.1161/CIR.0000000000001039
2. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A*, et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)*. Eur Heart J* 2018;**39**:213-260. doi: 10.1093/eurheartj/ehx419
3. Genereux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ*, et al.* Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2015;**66**:1036-1045. doi: 10.1016/j.jacc.2015.06.1323
4. Mehran R, Pocock S, Nikolsky E, Dangas GD, Clayton T, Claessen BE*, et al.* Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. *JACC Cardiovasc Interv* 2011;**4**:654-664. doi: 10.1016/j.jcin.2011.02.011
5. Capodanno D, Bhatt DL, Gibson CM, James S, Kimura T, Mehran R*, et al.* Bleeding avoidance strategies in percutaneous coronary intervention. *Nat Rev Cardiol* 2022;**19**:117-132. doi: 10.1038/s41569-021-00598-1
6. Capodanno D, Baber U, Bhatt DL, Collet JP, Dangas G, Franchi F*, et al.* P2Y12 inhibitor monotherapy in patients undergoing percutaneous coronary intervention. *Nat Rev Cardiol* 2022;**19**:829-844. doi: 10.1038/s41569-022-00725-6
7. Valgimigli M, Frigoli E, Heg D, Tijssen J, Juni P, Vranckx P*, et al.* Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. *N Engl J Med* 2021;**385**:1643-1655. doi: 10.1056/NEJMoa2108749
8. Valgimigli M, Gragnano F, Branca M, Franzone A, Baber U, Jang Y*, et al.* P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *BMJ* 2021;**373**:n1332. doi: 10.1136/bmj.n1332
9. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C*, et al.* Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med* 2019;**381**:2032-2042. doi: 10.1056/NEJMoa1908419

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

10. Corpataux N, Spirito A, Gragnano F, Vaisnora L, Galea R, Svab S*, et al.* Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. *Eur Heart J* 2020;**41**:3743-3749. doi: 10.1093/eurheartj/ehaa671
11. Kwok CS, Tiong D, Pradhan A, Andreou AY, Nolan J, Bertrand OF*, et al.* Meta-Analysis of the Prognostic Impact of Anemia in Patients Undergoing Percutaneous Coronary Intervention. *Am J Cardiol* 2016;**118**:610-620. doi: 10.1016/j.amjcard.2016.05.059
12. Wester A, Attar R, Mohammad MA, Andell P, Hofmann R, Jensen J*, et al.* Impact of Baseline Anemia in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: A Prespecified Analysis From the VALIDATE-SWEDEHEART Trial. *J Am Heart Assoc* 2019;**8**:e012741. doi: 10.1161/JAHA.119.012741
13. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S*, et al.* Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. *J Am Coll Cardiol* 2016;**67**:2224-2234. doi: 10.1016/j.jacc.2016.02.064
14. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F*, et al.* Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;**389**:1025-1034. doi: 10.1016/S0140-6736(17)30397-5
15. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D*, et al.* Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. *Circulation* 2019;**140**:240-261. doi: 10.1161/CIRCULATIONAHA.119.040167
16. Costa F, Van Klaveren D, Feres F, James S, Raber L, Pilgrim T*, et al.* Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. *J Am Coll Cardiol* 2019;**73**:741-754. doi: 10.1016/j.jacc.2018.11.048
17. Escaned J, Cao D, Baber U, Nicolas J, Sartori S, Zhang Z*, et al.* Ticagrelor monotherapy in patients at high bleeding risk undergoing percutaneous coronary intervention: TWILIGHT-HBR. *Eur Heart J* 2021;**42**:4624-4634. doi: 10.1093/eurheartj/ehab702
18. Baber U, Dangas G, Cohen DJ, Gibson CM, Mehta SR, Angiolillo DJ*, et al.* Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: Rationale and design of the TWILIGHT study. *Am Heart J* 2016;**182**:125-134. doi: 10.1016/j.ahj.2016.09.006
19. Cao D, Mehran R, Dangas G, Baber U, Sartori S, Chandiramani R*, et al.* Validation of the Academic Research Consortium High Bleeding Risk Definition in Contemporary PCI Patients. *J Am Coll Cardiol* 2020;**75**:2711-2722. doi: 10.1016/j.jacc.2020.03.070
20. Faggioni M, Baber U, Sartori S, Chandrasekhar J, Cohen DJ, Henry TD*, et al.* Influence of Baseline Anemia on Dual Antiplatelet Therapy Cessation and Risk of Adverse Events After Percutaneous Coronary Intervention. *Circ Cardiovasc Interv* 2019;**12**:e007133. doi: 10.1161/CIRCINTERVENTIONS.118.007133
21. Mamas MA, Kwok CS, Kontopantelis E, Fryer AA, Buchan I, Bachmann MO*, et al.* Relationship Between Anemia and Mortality Outcomes in a National Acute Coronary Syndrome Cohort: Insights From the UK Myocardial Ischemia National Audit Project Registry. *J Am Heart Assoc* 2016;**5**. doi: 10.1161/JAHA.116.003348
22. Stucchi M, Cantoni S, Piccinelli E, Savonitto S, Morici N. Anemia and acute coronary syndrome: current perspectives. *Vasc Health Risk Manag* 2018;**14**:109-118. doi: 10.2147/VHRM.S140951
23. Pilgrim T, Vetterli F, Kalesan B, Stefanini GG, Raber L, Stortecky S*, et al.* The impact of anemia on long-term clinical outcome in patients undergoing revascularization with the unrestricted use of drug-eluting stents. *Circ Cardiovasc Interv* 2012;**5**:202-210. doi: 10.1161/CIRCINTERVENTIONS.111.965749
24. Farhan S, Baber U, Mehran R. Anemia and Acute Coronary Syndrome: Time for Intervention Studies. *J Am Heart Assoc* 2016;**5**. doi: 10.1161/JAHA.116.004908
25. Lanser L, Fuchs D, Scharnagl H, Grammer T, Kleber ME, Marz W*, et al.* Anemia of Chronic Disease in Patients With Cardiovascular Disease. *Front Cardiovasc Med* 2021;**8**:666638. doi: 10.3389/fcvm.2021.666638

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

26. Levy PS, Quigley RL, Gould SA. Acute dilutional anemia and critical left anterior descending coronary artery stenosis impairs end organ oxygen delivery. *J Trauma* 1996;**41**:416-423. doi: 10.1097/00005373-199609000-00006
27. Duke M, Abelmann WH. The hemodynamic response to chronic anemia. *Circulation* 1969;**39**:503-515. doi: 10.1161/01.cir.39.4.503
28. Wadowski PP, Kopp CW, Koppensteiner R, Lang IM, Pultar J, Lee S*, et al.* Decreased platelet inhibition by P2Y12 receptor blockers in anaemia. *Eur J Clin Invest* 2018;**48**. doi: 10.1111/eci.12861
29. Giustino G, Kirtane AJ, Baber U, Genereux P, Witzenbichler B, Neumann FJ*, et al.* Impact of Anemia on Platelet Reactivity and Ischemic and Bleeding Risk: From the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents Study. *Am J Cardiol* 2016;**117**:1877-1883. doi: 10.1016/j.amjcard.2016.03.034
30. Najjar SS, Rao SV, Melloni C, Raman SV, Povsic TJ, Melton L*, et al.* Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction: REVEAL: a randomized controlled trial. *JAMA* 2011;**305**:1863-1872. doi: 10.1001/jama.2011.592
31. Kwok CS, Sherwood MW, Watson SM, Nasir SB, Sperrin M, Nolan J*, et al.* Blood transfusion after percutaneous coronary intervention and risk of subsequent adverse outcomes: a systematic review and meta-analysis. *JACC Cardiovasc Interv* 2015;**8**:436-446. doi: 10.1016/j.jcin.2014.09.026
32. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, Lemesle G, Cachanado M, Durand-Zaleski I*, et al.* Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia: The REALITY Randomized Clinical Trial. *JAMA* 2021;**325**:552-560. doi: 10.1001/jama.2021.0135

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

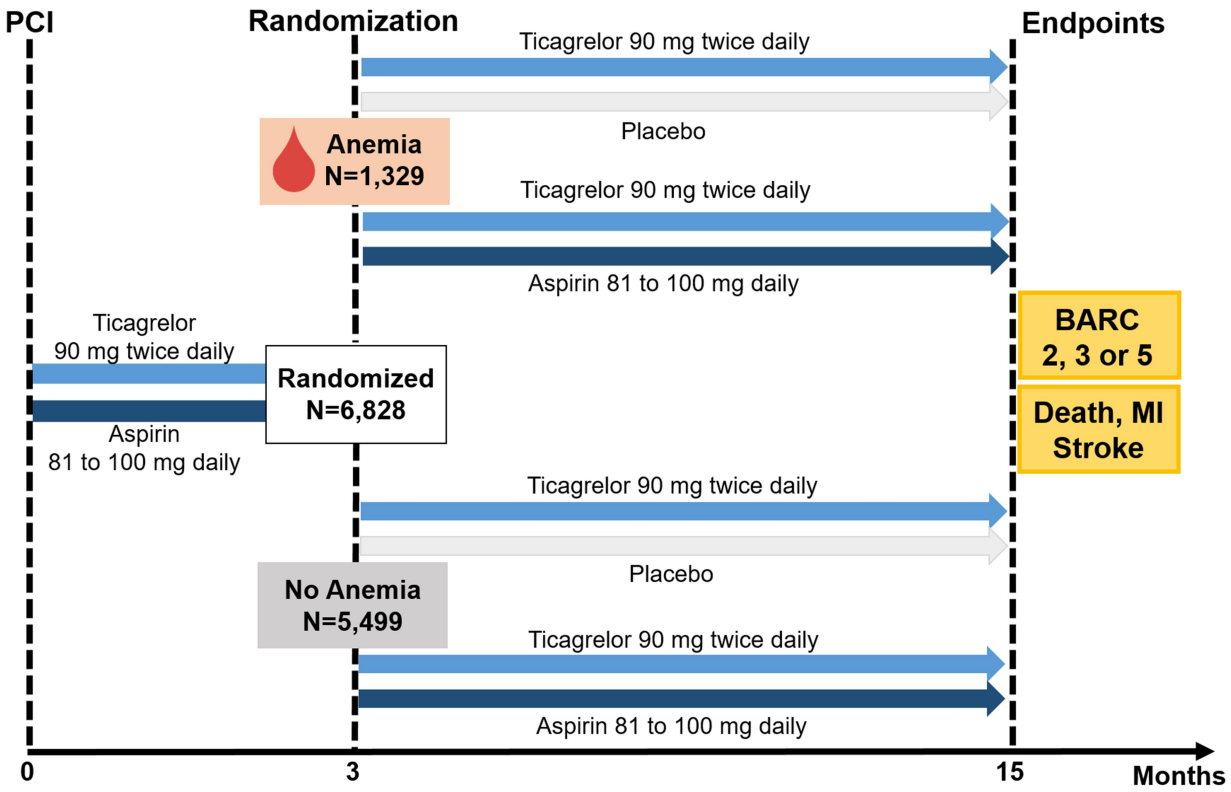

Figure 1. Study design. The TWILIGHT trial enrolled patients undergoing PCI and at high risk of ischemic or bleeding complications, After 3-month of ticagrelor-based DAPT patients free from ischemic or bleeding events and adherent to DAPT were randomized to aspirin or matching placebo for 12 months in addition to open-label ticagrelor. Outcomes were assessed at 12 months after randomization.

BARC= Bleeding Academic Research Consortium, MI= myocardial infarction

ORIGINAL UNEDITED MS

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

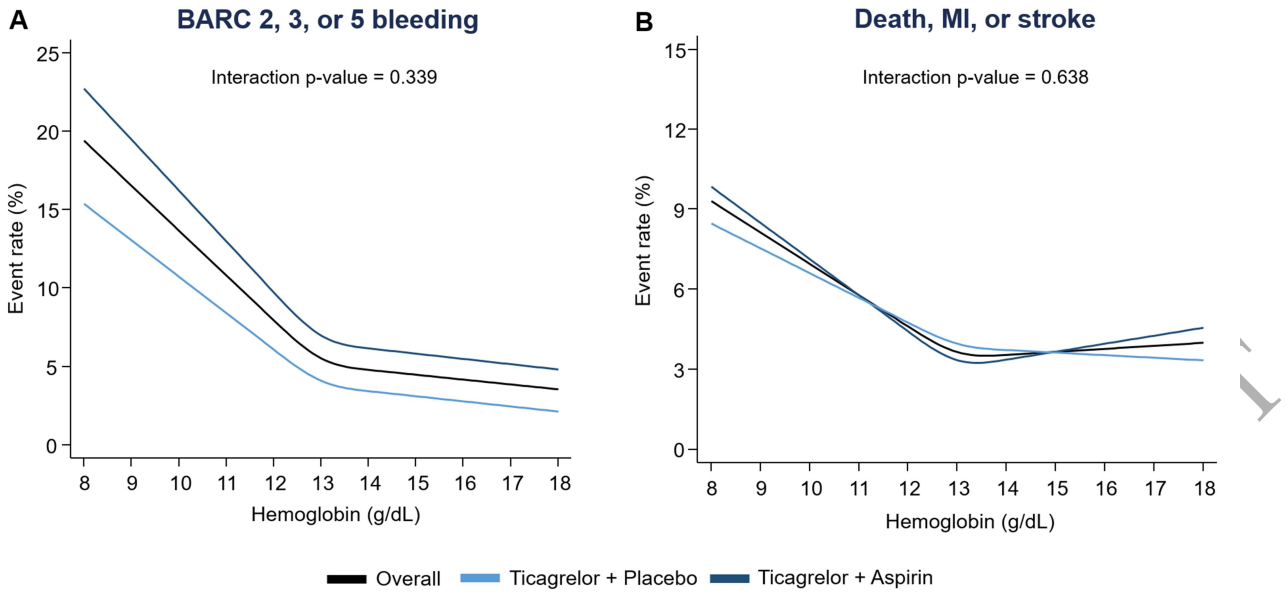

Figure 2. One-year rates of bleeding (A) and ischemic (B) events according to baseline hemoglobin values. A smoothing spline curve was used to plot the rates of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding (A) and all-cause death, myocardial infarction (MI), or stroke (B) at 1 year after randomization. The lines indicate Kaplan-Meier estimated event rates in the overall population (black), in the ticagrelor plus placebo (light blue) and ticagrelor plus aspirin arm (dark blue). The mean hemoglobin value was 13.9±1.6 g/dL in the overall population.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

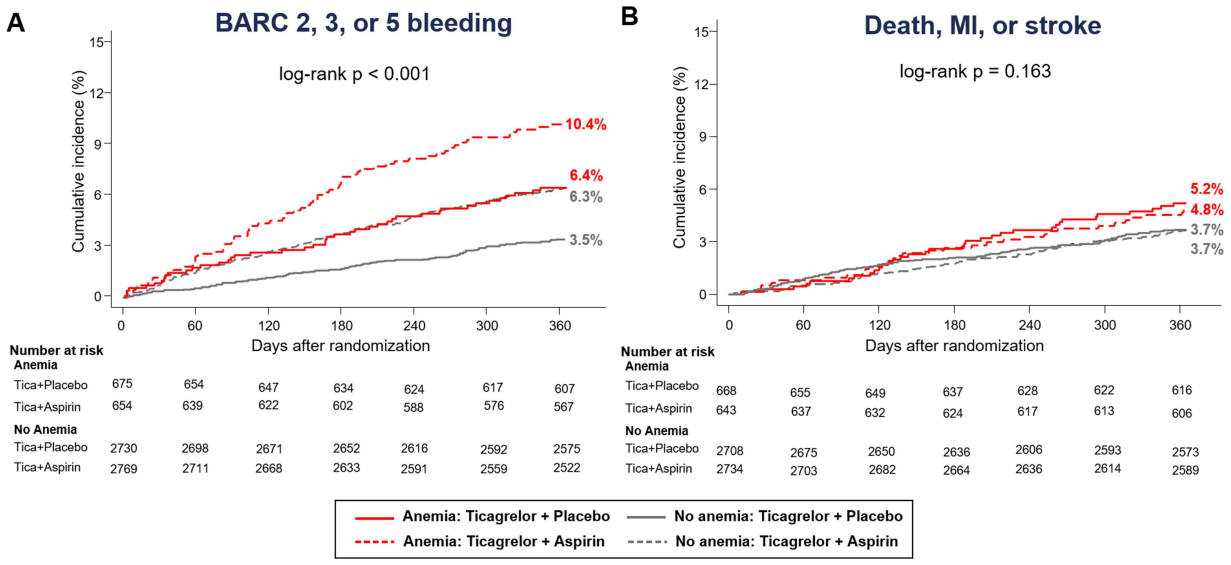

Figure 3. Kaplan-Meier curves for BARC 2, 3 or 5 bleeding (A) and death, MI or stroke (B) in patients with or without anemia stratified by randomized treatment.

BARC= Bleeding Academic Research Consortium, MI= myocardial infarction

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

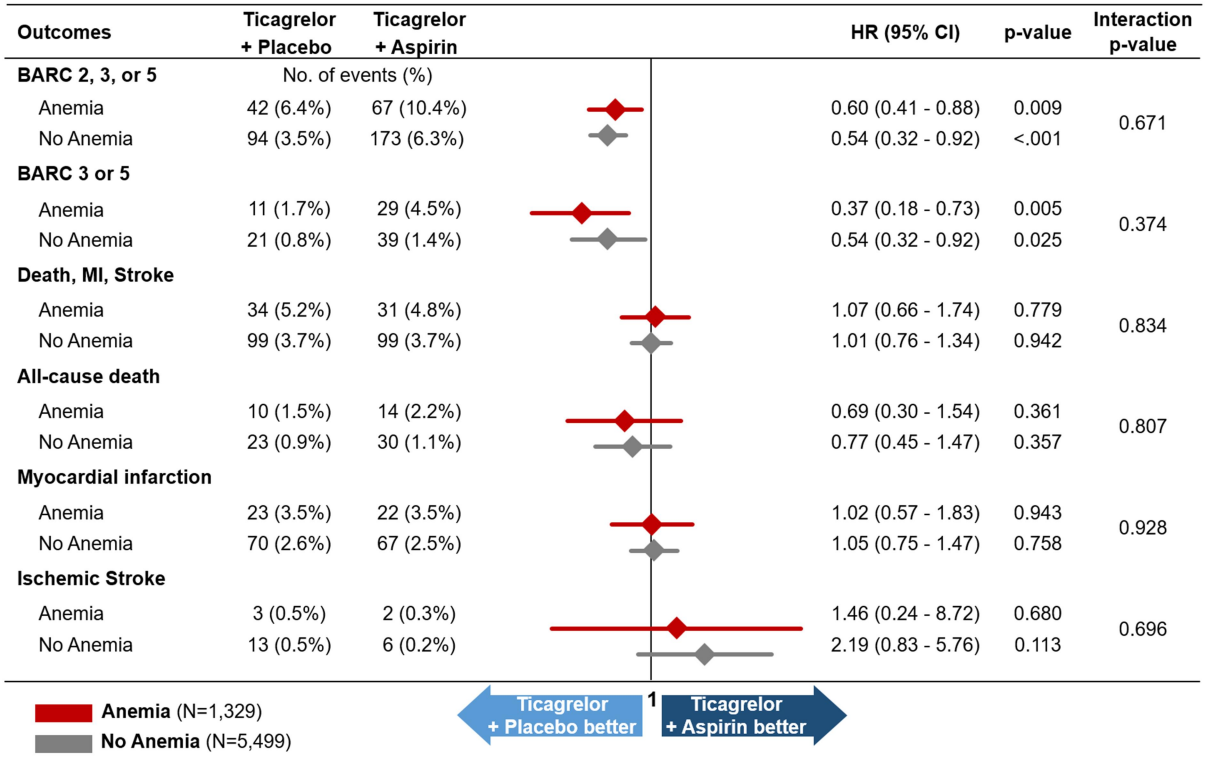

Figure 4. Effect of randomized treatment on events at 1 year after randomization in patients with or without anemia.

BARC= Bleeding Academic Research Consortium, MI= myocardial infarction

ORIGINAL UNEDITED MA

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

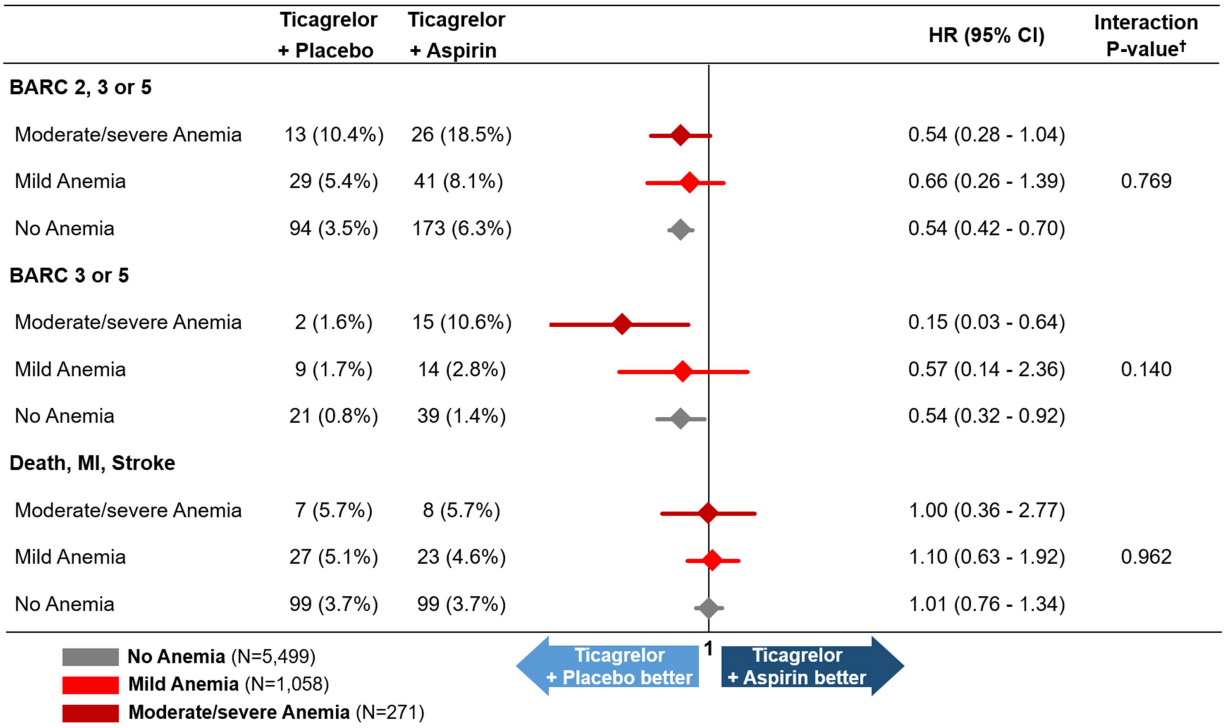

Figure 5. Effect of randomized treatment on events at 1 year after randomization according to degree of anemia severity. Mild anemia was defined as hemoglobin between 11–12.9 g/dL for men and between 11–11.9 g/dL for women; moderate-severe as hemoglobin <11 g/dL in both sexes.

BARC= Bleeding Academic Research Consortium, MI= myocardial infarction

ORIGINAL UNEDITED MA

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023

Table 1. Baseline clinical characteristics.

	Anemia (N=1,329)			No anemia (N=5,499)		
	Tica+Placebo N=675	**Tica+Aspirin N=654**	**p-value**	**Tica+Placebo N=2,730**	**Tica+Aspirin N=2,769**	**p-value**
Age, years	66.8±10.7	67.1±9.9	0.630	63.1±9.8	63.1±10.1	0.883
Female sex	190 (28.1%)	189 (28.9%)	0.762	620 (22.7%)	636 (23.0%)	0.820
Nonwhite race	317 (47.0%)	284 (43.4%)	0.195	750 (27.5%)	757 (27.3%)	0.911
BMI, kg/m^2	28.2±6.2	27.9±5.6	0.450	28.7±5.4	28.7±5.6	0.806
Enrolling region			0.943			0.946
North America	296 (43.9%)	288 (44.0%)		1147 (42.0%)	1169 (42.2%)	
Europe	162 (24.0%)	152 (23.2%)		1016 (37.2%)	1035 (37.4%)	
Asia	217 (32.1%)	214 (32.7%)		567 (20.8%)	565 (20.4%)	
Diabetes	323 (47.9%)	322 (49.2%)	0.614	941 (34.5%)	938 (33.9%)	0.642
Diabetes treated with insulin	91 (28.2%)	112 (34.8%)	0.071	228 (24.2%)	249 (26.5%)	0.249
Chronic kidney disease	193 (29.0%)	205 (31.6%)	0.303	355 (13.1%)	347 (12.6%)	0.613
Current smoker	77 (11.4%)	95 (14.5%)	0.088	620 (22.7%)	699 (25.3%)	0.028
Hypercholesterolemia	384 (56.9%)	375 (57.3%)	0.868	1690 (61.9%)	1700 (61.4%)	0.697
Hypertension	511 (75.7%)	501 (76.6%)	0.700	1960 (71.8%)	1979 (71.5%)	0.806
Peripheral arterial disease	58 (8.6%)	62 (9.5%)	0.572	179 (6.6%)	174 (6.3%)	0.680
Previous MI	201 (29.8%)	198 (30.3%)	0.843	773 (28.3%)	778 (28.1%)	0.857
Previous PCI	293 (43.4%)	295 (45.1%)	0.533	1157 (42.4%)	1148 (41.5%)	0.488
Previous CABG	74 (11.0%)	81 (12.4%)	0.419	274 (10.0%)	256 (9.2%)	0.318
Previous major bleed	9 (1.3%)	12 (1.8%)	0.464	20 (0.7%)	20 (0.7%)	0.964
Hemoglobin (g/dL)	11.7±1.0	11.6±1.2	0.185	14.5±1.2	14.5±1.2	0.808
Indication for PCI			0.259			0.246
Stable CAD	240 (35.6%)	213 (32.6%)		975 (35.7%)	948 (34.2%)	
ACS	435 (64.4%)	440 (67.4%)		1754 (64.3%)	1821 (65.8%)	

Anemia was defined as baseline hemoglobin <13 g/dL for men and <12g/dL for women.
ACS: acute coronary syndrome, BMI: body mass index, CABG: coronary artery bypass graft, CAD: coronary artery disease artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, Tica: ticagrelor.

ORIGIN

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvad006/6989842 by London School of Hygiene & Tropical Medicine user on 20 January 2023