# Impact of Age on the Safety and Efficacy of Ticagrelor with or without Aspirin in High-Risk Patients undergoing Percutaneous Coronary Intervention

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## DISCLOSURES

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**ABSTRACT**

**Background:** The risk of bleeding and ischemic complications after percutaneous coronary intervention (PCI) increases with age. Discontinuation of aspirin therapy after a short course of dual antiplatelet therapy (DAPT) and maintaining $P2Y_{12}$ inhibitor monotherapy with ticagrelor has emerged as a bleeding reduction strategy. The impact of age on the safety and efficacy of this strategy is unknown.

**Methods:** In this pre-specified analysis of the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial, we evaluated the treatment effects of ticagrelor monotherapy according to age. The trial enrolled high-risk patients undergoing PCI with drug-eluting stents. Age ≥65 years was one of the clinical entry criteria. Patients also required a high-risk angiographic criterion to be enrolled. Those who were event-free after 3 months of DAPT with ticagrelor plus aspirin were randomized to ticagrelor plus placebo or ticagrelor plus aspirin for an additional 12 months. The primary endpoint was Bleeding Academic Research Consortium (BARC) type 2, 3 or 5 bleeding, while the key secondary endpoint was the composite of all-cause death, myocardial infarction, or stroke.

**Results:** A total of 3409 (52.2%) patients were ≥65 years of age. At 1 year after randomization, ticagrelor monotherapy significantly reduced BARC 2, 3, or 5 bleeding (4.6% vs. 8.2%; HR, 0.55; 95% CI, 0.42 - 0.73; p<0.001) without any tradeoff in ischemic events (4.3% vs. 4.2%; HR, 1.03; 95% CI, 0.74 - 1.44; p=0.846) as compared with ticagrelor plus aspirin among patients ≥65 years. These findings were consistent in the subgroup of patients <65 years of age with respect to the primary ($p_{interaction}$=0.895) and key secondary endpoint ($p_{interaction}$=0.711). The clinical benefit of ticagrelor monotherapy was preserved across different age categories and enhanced among

patients ≥75 years fulfilling the Academic Research Consortium for High Bleeding Risk (ARC-HBR) definition.

**Conclusions:** Among high-risk patients undergoing PCI, a strategy of ticagrelor monotherapy following 3 months of DAPT significantly reduced clinically relevant bleeding compared with ticagrelor plus aspirin without an increase in ischemic events irrespective of age.

**Key words:** age; ticagrelor monotherapy; aspirin; bleeding; thrombosis; PCI

**LIST OF ABBREVIATIONS**

ACS: Acute Coronary Syndrome

ARC: Academic Research Consortium

BARC: Bleeding Academic Research Consortium

DAPT: Dual Antiplatelet Therapy

HBR: High Bleeding Risk

GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries

ISTH: International Society on Thrombosis and Hemostasis

MI: Myocardial Infarction

PCI: Percutaneous Coronary Intervention

STEMI: ST-elevation myocardial infarction

TIMI: Thrombolysis in Myocardial Infarction

## INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the standard of care for the prevention of ischemic complications, including stent thrombosis, in patients undergoing percutaneous coronary interventions (PCI) [1, 2]. However, such ischemic benefit occurs at the expense of increased bleeding, which negatively impacts prognosis, and is enhanced with the prolongation of DAPT [1-4]. Importantly, the risk of ischemic recurrences and bleeding complications post-PCI increase with age, underscoring the need to identify antiplatelet treatment regimens that reduce bleeding without any tradeoff in antithrombotic efficacy [5, 6]. A strategy of $P2Y_{12}$ inhibitor monotherapy, after a brief period of DAPT, has recently been proposed for this purpose [7]. In particular, the Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial showed that, among high-risk PCI patients, discontinuation of aspirin after 3 months of DAPT while maintaining $P2Y_{12}$ inhibitor monotherapy with ticagrelor reduced bleeding without increasing ischemic harm [8]. The contemporary increase in life expectancy has raised interest on the safety and efficacy of antiplatelet regimens in the ever growing ageing population undergoing PCI [5, 6, 9]. Therefore, we conducted a pre-specified analysis of the TWILIGHT trial to assess the impact of age on the effects of ticagrelor monotherapy versus ticagrelor plus aspirin in high-risk patients undergoing PCI.

## METHODS

### *Trial Design and Oversight*

TWILIGHT was a randomized, placebo-controlled trial conducted at 187 sites in 11 countries. The trial rationale, design and principal results have been reported previously [10].

TWILIGHT was an investigator-initiated trials designed, coordinated, and sponsored by The Icahn School of Medicine at Mount Sinai. AstraZeneca provided an investigator-initiated grant and supplied ticagrelor for the trial but had no role in the design, collection, analysis, or interpretation of the data. The executive and steering committees were responsible for trial conduct, integrity of data analysis, and reporting of results. National regulatory agencies and institutional review boards or ethics committees of participating centers approved the trial protocol. An independent data safety monitoring board provided external oversight to ensure safety of trial participants.

***Study Population***

Patients undergoing successful PCI with at least 1 commercially available drug-eluting stent whom the treating clinician intended to discharge on ticagrelor plus aspirin were eligible to participate. Trial inclusion required the presence of at least 1 clinical and 1 angiographic feature associated with a high risk of ischemic or bleeding events [8, 10]. Age ≥65 years represented a clinical study entry criteria; other clinical criteria included female sex, troponin positive acute coronary syndrome (ACS), atherosclerotic vascular disease (prior myocardial infarction, coronary revascularization or peripheral arterial disease), diabetes mellitus requiring medication, and chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73m$^2$ or creatinine clearance <60 cc/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 lesion, and calcified target lesion requiring debulking devices. Key exclusion criteria included presentation with an ST-elevation myocardial infarction (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 (81-100 mg daily) after the index PCI. At 3 months, patients without major bleeding or ischemic events were randomized 1:1 in a double-blind fashion to aspirin or matching placebo for an additional 12 months in adjunct to open-label ticagrelor [8, 10]. Patients sustaining Bleeding Academic Research Consortium (BARC) type 3b or higher bleeds or ischemic events (stroke, myocardial infarction, or coronary revascularization) between the index PCI and 3 months were not eligible for randomization. Moreover, patients were ineligible for randomization if non-adherent to ticagrelor or aspirin. Randomization was performed using a secure web-based system; an independent statistician not involved with the trial generated the allocation sequence, which was stratified by site with randomly varying block sizes of 4, 6 or 8. Follow-up occurred 1 month after randomization via telephone and in-person at 6 and 12 months after randomization. After 12 months of protocol-mandated therapy, patients were switched to a standard-of-care antiplatelet regimen at the discretion of their treating physician followed by final telephone follow-up 3 months later.

***Outcomes***

The primary endpoint was the composite of BARC type 2, 3, or 5 bleeding up to 1 year after randomization [8, 10]. The key secondary endpoint was the composite of all-cause death, myocardial infarction (MI), or stroke [8, 10]. Secondary bleeding endpoints included BARC types 3 or 5 bleeding; Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding; Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate, severe, or life-threatening bleeding; or major bleeding as defined by the International Society of Thrombosis or Hemostasis (ISTH) [11-14]. Other secondary endpoints included cardiovascular death, non-fatal MI, ischemic stroke and definite or probable stent thrombosis. MI was defined according to the third universal

definition, and revascularization and stent thrombosis were classified according to the Academic Research Consortium [15, 16]. All clinical events were adjudicated by an independent committee, blinded to treatment assignment.

***Statistical Analyses***

For the purpose of the present analysis, the primary bleeding and secondary ischemic endpoints were evaluated according to patient age. In particular, patients ≥65 years of age, a key clinical entry criterion, were compared to those <65 years. In order to evaluate the study treatment effects across different age categories, we further stratified the overall population into 10-year intervals of age (i.e., <55, 55-64, 65-74 and ≥75 years). Moreover, in line with the consensus definitions from the Academic Research Consortium for High Bleeding Risk (ARC-HBR), exploratory analyses were performed among patients ≥75 years of age. According to the ARC-HBR, patients are considered to be at HBR if at least 1 major or 2 minor criteria are met [17]. Given that age ≥75 years is considered as a minor criterion, we evaluated treatment effects among HBR and non-HBR patients within this age category.

Clinical and procedural characteristics are summarized by randomized group using means (standard deviation) and frequencies for continuous and categorical variables, respectively. The cumulative incidence of both primary and secondary endpoints was estimated using the Kaplan-Meier method. Patients without a primary endpoint between randomization and 1 year were censored at the time of death, last known contact, or 365 days, whichever came first. Hazard ratios (HR) and 95% confidence intervals (CI) were generated using Cox proportional hazards models. Analyses of bleeding were performed using the intention-to-treat cohort, while ischemic outcomes were analyzed using the per protocol cohort [18]. Treatment effects were estimated according to patient age as defined above with formal interaction testing to assess for effect

modification. Finally, the association between age (as a continuous variable) and the 1-year rate of ischemic and bleeding events was also evaluated using a smoothing spline function. All analyses were performed using Stata version 16.0 (College Station, Texas).

## RESULTS

### *Patient Characteristics*

Among the 6532 patients randomized in the main TWILIGHT trial and available for analysis, 52.2% (n=3409) were ≥65 years of age. Of these, 50.2% were randomized to ticagrelor plus placebo and 49.8% to ticagrelor plus aspirin. Patients ≥65 years were more likely to be female, from North America and of white race than patients <65 years. They had more cardiovascular risk factors and comorbidities, but presented less often with ACS as indication for PCI (**Supplementary Table 1**). With respect to angiographic and procedural characteristics, patients ≥65 years were less likely to undergo PCI via radial access, and had more often multivessel disease and calcific lesions (**Supplementary Table 2**). **Tables 1 and 2** show the demographic, clinical and procedural characteristics, which were well balanced between treatment arms, except for a higher prevalence of multivessel disease (66.5% vs. 61.7%; p=0.004) and bifurcation lesions (13.5% vs. 11.1%; p=0.033) in the ticagrelor plus placebo group. Rates of permanent ticagrelor discontinuation at one year were similar among those ≥65 years randomized to ticagrelor plus placebo versus ticagrelor plus aspirin (16.1% vs. 16.7%; p=0.60). Analogous results for blinded study drug discontinuation were 20.2% and 20.7%; respectively (p=0.66). Among patients <65 years, permanent discontinuation rates of ticagrelor (10.3% vs. 12.3%; p=0.066) and study drug (15.1% vs. 15.7%; p=0.613) were numerically lower overall but no significantly different between randomized treatment arms.

***Bleeding events***

Bleeding events increased with age (**Figure 1A**). As shown in **Figure 2**, in the cohort of patients ≥65 years of age, the primary outcome of BARC 2, 3, or 5 bleeding occurred in 78 patients (4.6%) randomized to ticagrelor plus placebo versus 137 patients (8.2%) randomized to ticagrelor plus aspirin (HR, 0.55; 95% CI, 0.42 - 0.73; p<0.001). One-year BARC 3 or 5 bleeding rates were 1.2% and 2.3%, respectively (HR, 0.55; 95% CI 0.32 - 0.93; p=0.026). This treatment effect was consistent across different bleeding scales, including TIMI, GUSTO and ISTH (**Figure 4**). There was no significant interaction between age and treatment group with respect to the bleeding endpoints.

***Ischemic Events***

Ischemic events increased with age (**Figure 1B**). As shown in **Figure 3**, in the cohort of patients ≥65 years of age, the composite outcome of all-cause death, MI, or stroke occurred in 72 patients (4.3%) randomized to ticagrelor plus placebo versus 69 patients (4.2%) randomized to ticagrelor plus aspirin (HR, 1.03; 95% CI, 0.74 - 1.44; p=0.846). Rates of all-cause death (1.4% vs. 1.8%), MI (2.9% vs. 2.6%), ischemic stroke (0.5% vs 0.2%) and definite/probable stent thrombosis (0.2% vs. 0.4%) were similar between treatment groups (all p-values >0.1) (**Figure 5**). There was no significant interaction between age and treatment group with respect to the ischemic endpoints.

***Additional Analyses***

The subgroup analysis by 10-year age intervals showed a consistent risk reduction in BARC 2, 3, or 5 bleeding across all age categories (p interaction=0.114) with a treatment effect that appeared enhanced in patients 55-64 years and 65-74 years of age (**Supplementary Figure 1**). Similarly, there were no differences between ticagrelor monotherapy and ticagrelor plus

aspirin with respect to the key secondary endpoint of death, MI or stroke across all age strata (p interaction=0.200).

Of the 1126 patients who were ≥75 years of age, 56.5% (n=636) met the ARC definition of HBR. HBR patients ≥75 years had the highest rates of both bleeding and ischemic events at 1 year after randomization (**Supplementary Figure 2**) compared to all other age groups. The risk BARC 2, 3, or 5 bleeding associated with ticagrelor monotherapy compared with ticagrelor plus aspirin was not statistically different among patients ≥75 years with and without HBR status (p interaction=0.084). However, the magnitude of treatment effect was more pronounced in the HBR group (6.2% vs. 11.2%; HR, 0.53; 95% CI, 0.30 - 0.93; p=0.026) than in the non-HBR group (7.3% vs. 6.3%; HR, 1.15; 95% CI, 0.58 - 2.28; p=0.687) (**Supplementary Table 5**). The outcome of all-cause death, MI, or stroke was similar in patients randomized to ticagrelor plus placebo versus ticagrelor plus aspirin, regardless of the presence of HBR (**Supplementary Table 6**).

## DISCUSSION

The key findings from our pre-specified analysis evaluating the impact of age on the safety and efficacy outcomes of patients randomized in the TWILIGHT trial include: (1) the rate of adverse events increases with age, with a sharp rise after the age of 65 years for BARC 2, 3 or 5 bleeding and of 70 years for death, MI or stroke; (2) ticagrelor monotherapy, as compared with ticagrelor plus aspirin, reduced the incidence of clinically relevant BARC 2, 3, or 5 bleeding as well as major BARC 3 or 5 bleeding over one year of follow-up by almost 50% in patients ≥65 years of age; (3) among patients ≥75 years of age, the reduction in bleeding risk associated with ticagrelor monotherapy appeared to be enhanced in presence of HBR status as defined by ARC

criteria; (4) ticagrelor monotherapy was not associated with significant differences in the rate of all-cause death, MI, or stroke. Overall, these results demonstrate that the clinical benefits and safety of ticagrelor monotherapy observed in the main TWILIGHT trial cohort are preserved irrespective of age.

A number of trials have investigated the safety and efficacy of $P2Y_{12}$ inhibitor monotherapy after a minimal duration (1-3 months) of DAPT following PCI [10, 18-21]. However, TWILIGHT was the only one to be placebo-controlled and enroll patients with both clinical and angiographic features associated with an increased risk for ischemic or bleeding complications post-PCI [10]. Age ≥65 years represented a key clinical entry criterion in TWILIGHT, thereby making this important cohort of patients a large subset (52.2%; n=3409) of the trial population [8, 10]. Of note, 17.2% of the trial population (n=1126) were ≥75 years of age. Patients also required to have high-risk angiographic features to be enrolled in the study, and collectively this enabled to study a patient population enriched with ischemic and bleeding complications [8, 10]. Of the available trials assessing $P2Y_{12}$ inhibitor monotherapy, only GLOBAL LEADERS had a number of elderly patients, defined as ≥75 years of age, higher than TWILIGHT. In the pre-specified analysis of elderly patients from GLOBAL LEADERS (n=2,565), there was no differential treatment effect of ticagrelor monotherapy (after one month of DAPT) found in an all-comers population undergoing PCI with respect to the primary endpoint of all-cause mortality or new Q-wave MI and BARC 3 or 5 bleeding at 2 years [22]. These findings, however, need to be interpreted in the context of a trial that failed to meet its primary endpoint [18].

Prior studies on the potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor compared with clopidogrel in ACS patients undergoing PCI showed reduced ischemic events at the expense of increased bleeding [23]. In particular, in the TRITON-TIMI 38 (Trial to Assess Improvement in

Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction 38) trial, such excess in bleeding, including fatal bleeding, resulted in a neutral net clinical benefit in the elderly subgroup [24]. Based on these findings prasugrel is generally not recommended in patients aged ≥75 years. The increased risk for bleeding among the elderly can be attributed to increased active metabolite levels with prasugrel 10 mg suggesting the need to reduce the maintenance dose to 5 mg [25]. Although prasugrel 5 mg provides more potent platelet inhibition compared with clopidogrel among elderly patients, the differences are small and have not shown to translate into clinical benefits [26-30]. However, in the subgroup of patients aged ≥75 years from the ISAR-REACT 5 (Intracoronary Stenting and AntiThrombotic Regimen: Rapid Early Action for Coronary Treatment 5) trial, prasugrel 5 mg reduced 12-month major bleeding and had similar efficacy compared to standard dose ticagrelor [31].

There is more evidence on the safety and efficacy of ticagrelor in the elderly. In the PLATO (Platelet Inhibition and Patient Outcomes) trial, although bleeding events increased with age, they were not significantly increased in patients treated with ticagrelor versus clopidogrel across age subgroups [32, 33]. Accordingly, use of ticagrelor 90 mg bid is recommended after ACS with no specific age-related recommendations. On the contrary, in the more contemporary POPular AGE trial, clopidogrel significantly reduced net clinical outcomes due to decreased bleeding without differences in ischemic events compared with potent $P2Y_{12}$ inhibitors (mostly ticagrelor) among patients >70 years of age [34]. In the Bremen-STEMI-registry, ticagrelor was associated with decreased ischemic events and no significant increase in bleeding [35]. Differently, in the SWEDEHEART registry, ticagrelor provided similar efficacy to clopidogrel but increased bleeding and mortality [36].

It is important to note that all the above mentioned studies with the potent $P2Y_{12}$ inhibitors were conducted on a background of aspirin therapy. Aspirin is well established to be associated with bleeding complications due to its gastrointestinal side effects [37]. The physical disruption of the protective gastric phospholipid barrier induced by acetylsalicylic acid (i.e., aspirin) leads to impaired gastrointestinal protection, which enables (i.e., promoting new mucosal lesions) and propagates (i.e., worsening existing lesions) direct acid injury [37]. In the presence of impaired hemostasis such as with DAPT, the risk of bleeding complications is significantly enhanced. Moreover, the gastrointestinal toxicity induced by aspirin and the subsequent risk of bleeding can be exacerbated with increasing age [38].

Finally, it is noteworthy that a large portion of elderly patients exhibit clinical conditions, such as chronic medications and comorbidities, which further increase their bleeding risk. The results of our study showed that among patients ≥75 years of age, more than half fulfilled the ARC-HBR definition. In this subgroup, the incidence of BARC 2, 3, or 5 bleeding between 3 and 15 months post-PCI was 11.2% with ticagrelor plus aspirin compared to 6.2% with ticagrelor monotherapy. Therefore, while the benefit of ticagrelor monotherapy appeared to be consistent across all age categories, the absolute risk reduction observed among HBR patients highlight the importance of bleeding-avoidance strategies especially in old and vulnerable patients. Collectively, these observations make the elderly population ideal for considering aspirin-free approaches if alternative and effective secondary prevention antiplatelet treatment regimens are available.

The present analysis is in line with the overall findings from TWILIGHT and other trials that withdrawal of aspirin after a brief period of DAPT does not incur any increase in ischemic complications [10, 18-21]. These efficacy observations are supported by a number of in vitro and ex

vivo pharmacodynamic studies. In particular, in vitro investigations conducted in platelets from healthy volunteers treated with potent $P2Y_{12}$ inhibitors showed that aspirin provides limited additional platelet inhibition [39, 40]. Similar findings assessing thrombus formation were observed in animal studies [41]. Studies conducted in patients with CAD, including a substudy from the TWILIGHT trial, showed that while aspirin withdrawal is associated with an increase in markers sensitive to cyclooxygenase-1 blockade, this did not affect markers of $P2Y_{12}$ signaling or ex vivo platelet-dependent thrombus formation [42, 43]. It is important to note that these findings of pharmacodynamic efficacy occur in the presence of reliable and effective $P2Y_{12}$ blockade such as that achieved by ticagrelor and does not apply to clopidogrel which is characterized by less predictable and potent $P2Y_{12}$ inhibition [44]. It is furthermore important to note that elderly patients have been consistently shown to be at increased risk of having high platelet reactivity, a marker of thrombotic risk, while on treatment with clopidogrel [45]. Age-related platelet dysfunction as well as impaired drug metabolism may contribute to these findings [5, 6]. Therefore, these considerations warrants caution against a strategy of early aspirin withdrawal followed by clopidogrel monotherapy as bleeding reduction strategy in elderly patients.

***Study limitations***

Although our analysis was pre-specified, randomization was not stratified by age. Therefore, our results must be considered hypothesis-generating and warrant dedicated, prospective confirmation. Our findings may not generalize to patients treated with other oral $P2Y_{12}$ inhibitors, including prasugrel and clopidogrel. Moreover, elderly patients commonly affected by functional, social and cognitive impairment would have not been enrolled in the TWILIGHT trial and thus our findings cannot be generalized to all elderly subjects [46, 47]. The

safety and efficacy of $P2Y_{12}$ inhibitor monotherapy with STEMI was not addressed since these patients were excluded from participation in TWILIGHT. Ultimately, the power was limited to detect rare, yet clinically important differences in ischemic events, including stent thrombosis or stroke.

## CONCLUSIONS

Among high-risk patients undergoing PCI, a strategy of ticagrelor monotherapy following 3 months of DAPT significantly reduced clinically relevant bleeding compared with ticagrelor plus aspirin without an increase in ischemic events irrespective of age. These findings support such a bleeding avoidance strategy, which can be implemented without any signals for harm in elderly patients at increased risk for bleeding and ischemic complications.

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## FIGURE LEGENDS

**Figure 1. Rates of bleeding (A) and ischemic (B) events according to age.** Smoothing spline function for the rates of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding (panel A) and all-cause death, myocardial infarction, or stroke (panel B) at 1 year after randomization in the overall trial population.

**Figure 2. Rates of BARC 2, 3, or 5 bleeding at 1 year after randomization.** Kaplan–Meier estimates of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding with ticagrelor plus placebo versus ticagrelor plus aspirin in relation to age cut-off of 65 years in the intention to treat cohort. CI: confidence interval; HR: hazard ratio.

**Figure 3. Rates of death, MI, or stroke at 1 year after randomization.** Kaplan–Meier estimates of all-cause death, myocardial infarction, or stroke with ticagrelor plus placebo versus ticagrelor plus aspirin in relation to age cut-off of 65 years in the per protocol cohort. CI: confidence interval; HR: hazard ratio.

**Figure 4. Risk of bleeding events at 1 year after randomization.** Forest plots showing the effect of ticagrelor plus placebo versus ticagrelor plus aspirin on the bleeding endpoints in relation to age cut-off of 65 years. Event rates at one year were estimated using the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) with interaction p-values generated using Cox regression. BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis. *Bleeding outcomes were performed in the intention-to-treat cohort. †Interaction between randomized treatment assignment and age cut-off of 65 years.

**Figure 5. Risk of ischemic events at 1 year after randomization.** Forest plots showing the effect of ticagrelor plus placebo versus ticagrelor plus aspirin on the ischemic endpoints in relation to age cut-off of 65 years. Event rates at one year were estimated using the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) with interaction p-values generated using Cox regression. BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis. ^Ischemic outcomes were performed in the per-protocol cohort. †Interaction between randomized treatment assignment and age cut-off of 65 years.

## TABLES

### Table 1. Baseline clinical characteristics

| | Age ≥ 65 yrs (N=3409) | | | Age < 65 yrs (N=3123) | | |
|---|---|---|---|---|---|---|
| | **Tica+Placebo N=1713 (50.2%)** | **Tica+Aspirin N=1696 (49.8%)** | **p-value** | **Tica+Placebo N=1552 (49.7%)** | **Tica+Aspirin N=1571 (50.3%)** | **p-value** |
| Age, years | 72.6±5.8 | 72.7±5.7 | 0.660 | 56.1±6.4 | 56.0±6.6 | 0.842 |
| Female sex | 441 (25.7%) | 451 (26.6%) | 0.573 | 330 (21.3%) | 312 (19.9%) | 0.332 |
| Nonwhite race | 326 (19.0%) | 325 (19.2%) | 0.922 | 494 (31.8%) | 464 (29.5%) | 0.164 |
| BMI, $kg/m^2$ | 28.3±5.3 | 28.3±5.3 | 1.000 | 29.5±5.8 | 29.5±5.9 | 0.849 |
| Enrolling region | | | 0.823 | | | 0.594 |
| North America | 823 (48.0%) | 815 (48.1%) | | 661 (42.6%) | 673 (42.8%) | |
| Europe | 688 (40.2%) | 670 (39.5%) | | 563 (36.3%) | 588 (37.4%) | |
| Asia | 202 (11.8%) | 211 (12.4%) | | 328 (21.1%) | 310 (19.7%) | |
| Diabetes | 619 (36.1%) | 606 (35.7%) | 0.806 | 594 (38.3%) | 586 (37.3%) | 0.575 |
| Diabetes treated with insulin | 154 (24.9%) | 171 (28.2%) | 0.186 | 154 (25.9%) | 171 (29.2%) | 0.211 |
| Chronic kidney disease | 433 (26.4%) | 450 (27.6%) | 0.444 | 113 (7.6%) | 97 (6.4%) | 0.213 |
| Anemia | 392 (24.0%) | 396 (24.4%) | 0.808 | 216 (14.5%) | 203 (13.5%) | 0.422 |
| Current smoker | 196 (11.4%) | 216 (12.8%) | 0.244 | 460 (29.7%) | 528 (33.6%) | 0.018 |
| Hypercholesterolemia | 1197 (69.9%) | 1184 (69.8%) | 0.966 | 929 (59.9%) | 929 (59.1%) | 0.680 |
| Hypertension | 1341 (78.3%) | 1348 (79.5%) | 0.392 | 1061 (68.4%) | 1050 (66.9%) | 0.375 |
| Peripheral arterial disease | 145 (8.5%) | 145 (8.5%) | 0.929 | 93 (6.0%) | 95 (6.0%) | 0.949 |
| Previous MI | 454 (26.5%) | 450 (26.5%) | 0.984 | 518 (33.4%) | 515 (32.8%) | 0.724 |
| Previous PCI | 738 (43.1%) | 759 (44.8%) | 0.326 | 684 (44.1%) | 657 (41.8%) | 0.204 |
| Previous CABG | 244 (14.3%) | 224 (13.2%) | 0.376 | 115 (7.4%) | 120 (7.6%) | 0.809 |
| Multivessel CAD | 1139 (66.5%) | 1047 (61.7%) | 0.004 | 945 (60.9%) | 938 (59.7%) | 0.500 |
| Previous major bleed | 15 (0.9%) | 20 (1.2%) | 0.379 | 12 (0.8%) | 7 (0.4%) | 0.239 |
| Indication for PCI | | | 0.154 | | | 0.732 |
| Stable CAD | 750 (43.8%) | 702 (41.4%) | | 481 (31.0%) | 478 (30.4%) | |
| ACS | 962 (56.2%) | 994 (58.6%) | | 1071 (69.0%) | 1093 (69.6%) | |

Tica: ticagrelor, BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACS: Acute coronary syndrome

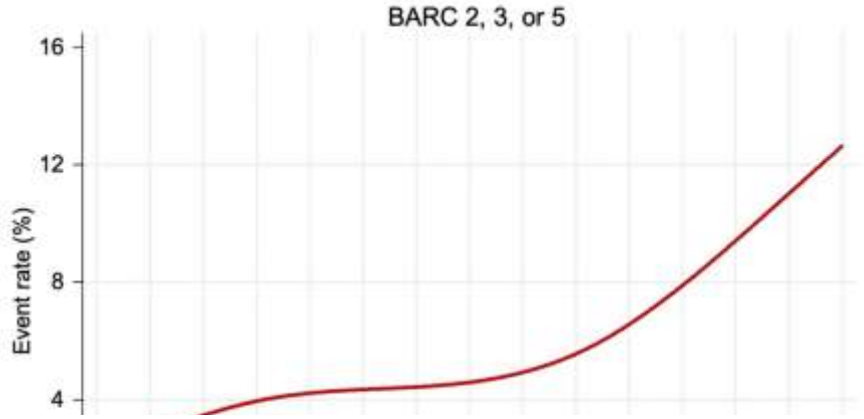
## Table 2. Baseline procedural characteristics

| | Age ≥ 65 yrs (N=3409) | | | Age < 65 yrs (N=3123) | | |
|---|---|---|---|---|---|---|
| | **Tica+Placebo N=1713 (50.2%)** | **Tica+Aspirin N=1696 (49.8%)** | **p-value** | **Tica+Placebo N=1552 (49.7%)** | **Tica+Aspirin N=1571 (50.3%)** | **p-value** |
| Radial artery access | 1178 (68.8%) | 1144 (67.5%) | 0.410 | 1145 (73.8%) | 1161 (73.9%) | 0.936 |
| Multivessel CAD | 1139 (66.5%) | 1047 (61.7%) | 0.004 | 945 (60.9%) | 938 (59.7%) | 0.500 |
| Target vessel | | | | | | |
| Left Main | 85 (5.0%) | 85 (5.0%) | 0.947 | 52 (3.4%) | 67 (4.3%) | 0.182 |
| LAD | 957 (55.9%) | 955 (56.3%) | 0.795 | 862 (55.5%) | 865 (55.1%) | 0.787 |
| LCX | 577 (33.7%) | 535 (31.5%) | 0.183 | 477 (30.7%) | 510 (32.5%) | 0.299 |
| RCA | 579 (33.8%) | 586 (34.6%) | 0.644 | 561 (36.1%) | 571 (36.3%) | 0.908 |
| Number of vessels treated | 1.3±0.5 | 1.3±0.5 | 0.611 | 1.3±0.5 | 1.3±0.5 | 0.184 |
| Number of lesions treated | 1.5±0.8 | 1.5±0.8 | 0.456 | 1.5±0.7 | 1.5±0.7 | 0.816 |
| Lesion morphology[†] | | | | | | |
| Moderate/severe calcification | 299 (17.5%) | 286 (16.9%) | 0.647 | 178 (11.5%) | 177 (11.3%) | 0.859 |
| Bifurcation | 231 (13.5%) | 188 (11.1%) | 0.033 | 171 (11.0%) | 200 (12.7%) | 0.139 |
| Total occlusion | 86 (5.0%) | 91 (5.4%) | 0.650 | 99 (6.4%) | 91 (5.8%) | 0.493 |
| Thrombotic | 152 (8.9%) | 152 (9.0%) | 0.927 | 201 (13.0%) | 219 (13.9%) | 0.418 |
| Total stent length, mm[‡] | 38.7±23.5 | 38.3±22.6 | 0.609 | 39.4±23.3 | 39.3±24.6 | 0.840 |
| Minimum stent diameter, mm | 2.8±0.5 | 2.8±0.5 | 0.374 | 2.8±0.5 | 2.9±0.5 | 0.642 |
| Complex PCI[§] | 589 (34.4%) | 571 (33.7%) | 0.659 | 441 (28.4%) | 471 (30.0%) | 0.336 |

CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery
[†]Lesion morphology assessed by operators
[‡]Stent length calculated by operators
[§]Complex PCI defined as any of the following: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, atherectomy device use, left main PCI, surgical bypass graft or chronic total occlusion as target lesions

**Figure 1. Rates of bleeding (A) and ischemic (B) events according to age**

**1A**




**1B**

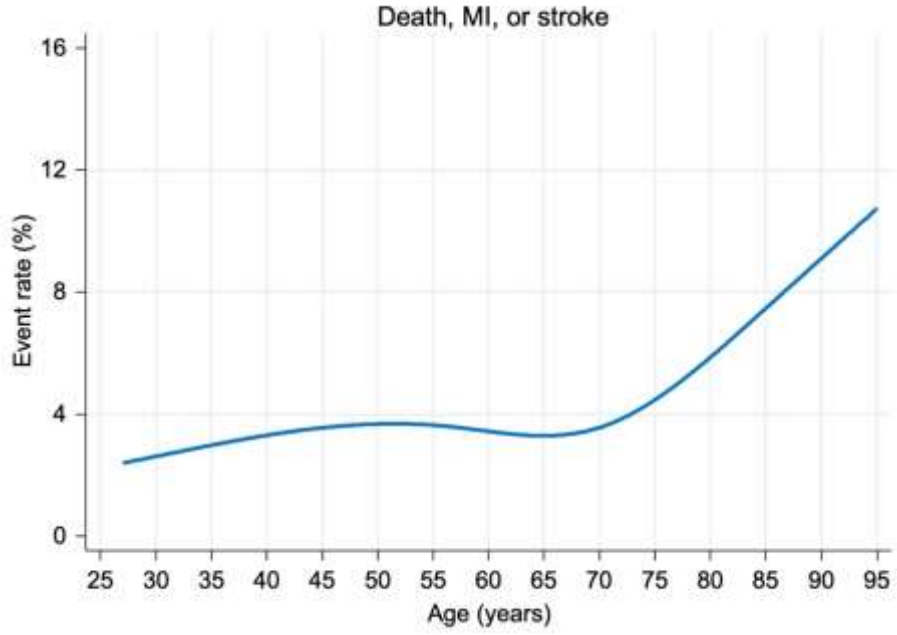


**Figure 2**

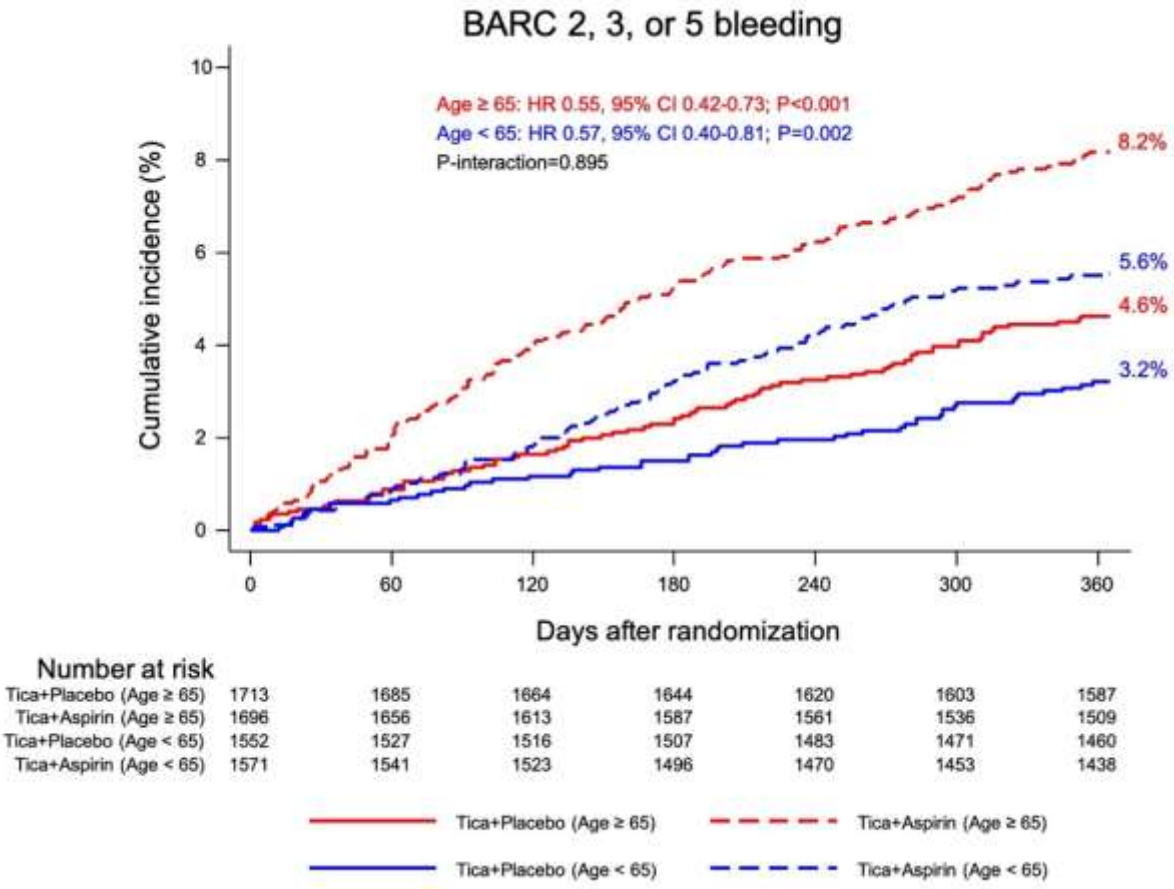

BARC 2, 3, or 5 bleeding
Age ≥ 65: HR 0.55, 95% CI 0.42-0.73; P<0.001
Age < 65: HR 0.57, 95% CI 0.40-0.81; P=0.002
P-interaction=0.895
Cumulative incidence (%)
10
8
6
4
2
0
8.2%
5.6%
4.6%
3.2%
0
60
120
180
240
300
360
Days after randomization
Number at risk
Tica+Placebo (Age ≥ 65) 1713 1685 1664 1644 1620 1603 1587
Tica+Aspirin (Age ≥ 65) 1696 1656 1613 1587 1561 1536 1509
Tica+Placebo (Age < 65) 1552 1527 1516 1507 1483 1471 1460
Tica+Aspirin (Age < 65) 1571 1541 1523 1496 1470 1453 1438
Tica+Placebo (Age ≥ 65)
Tica+Aspirin (Age ≥ 65)
Tica+Placebo (Age < 65)
Tica+Aspirin (Age < 65)

**Figure 3**

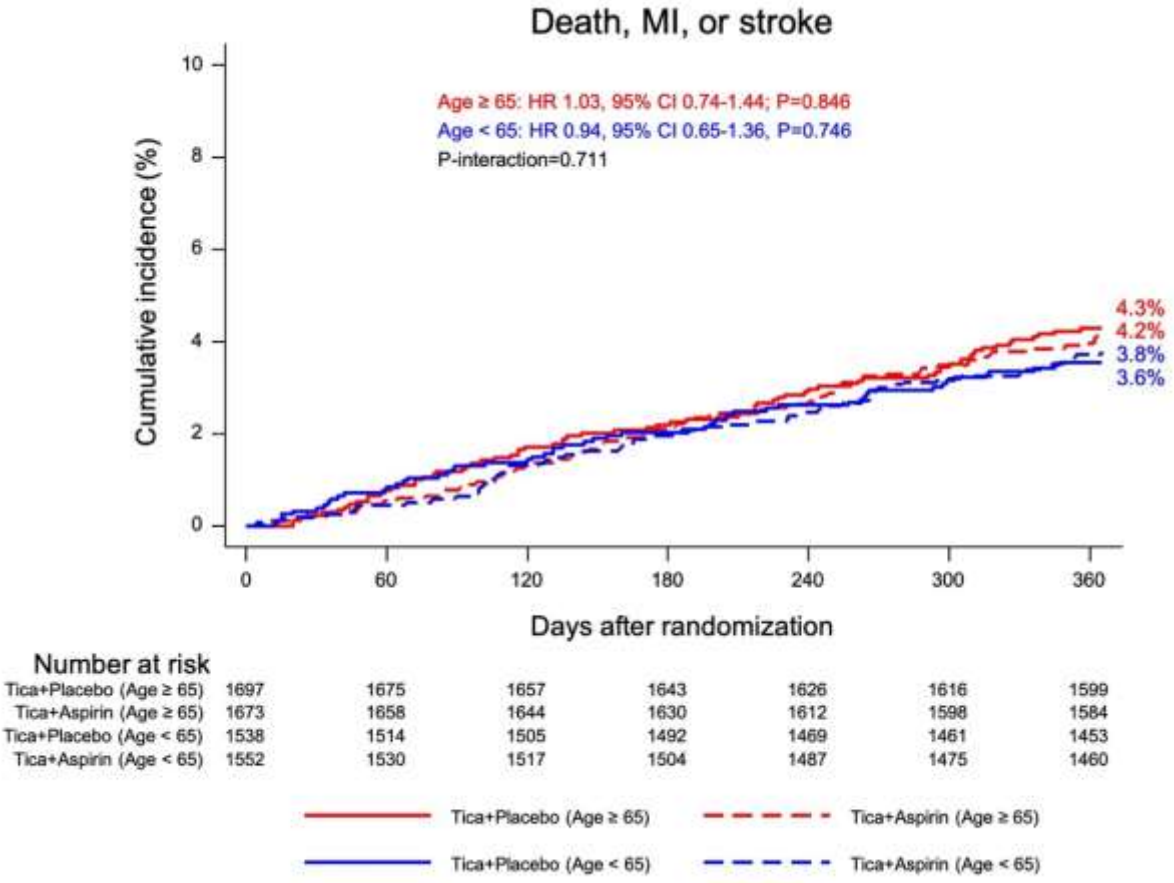
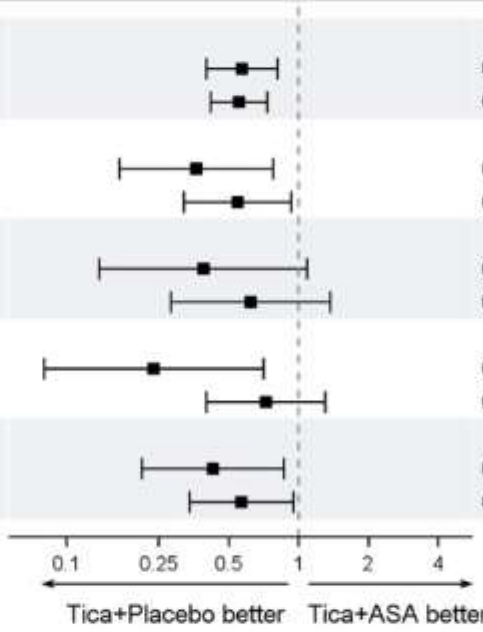

Death, MI, or stroke
Age ≥ 65: HR 1.03, 95% CI 0.74-1.44; P=0.846
Age < 65: HR 0.94, 95% CI 0.65-1.36, P=0.746
P-interaction=0.711
Cumulative incidence (%)
10
8
6
4
2
0
4.3%
4.2%
3.8%
3.6%
0
60
120
180
240
300
360
Days after randomization
Number at risk
Tica+Placebo (Age ≥ 65) 1697 1675 1657 1643 1626 1616 1599
Tica+Aspirin (Age ≥ 65) 1673 1658 1644 1630 1612 1598 1584
Tica+Placebo (Age < 65) 1538 1514 1505 1492 1469 1461 1453
Tica+Aspirin (Age < 65) 1552 1530 1517 1504 1487 1475 1460
Tica+Placebo (Age ≥ 65)
Tica+Aspirin (Age ≥ 65)
Tica+Placebo (Age < 65)
Tica+Aspirin (Age < 65)

**Figure 4**

| Bleeding events* | No. of patients | Tica+Placebo no. of patients (%) | Tica+Aspirin no. of patients (%) | HR (95% CI) | Interaction P-value** |
|---|---|---|---|---|---|
| **BARC 2, 3, or 5** | | | | | |
| < 65 yrs | 3123 | 49 (3.2%) | 86 (5.6%) | 0.57 (0.40 - 0.81) | 0.895 |
| ≥ 65 yrs | 3409 | 78 (4.6%) | 137 (8.2%) | 0.55 (0.42 - 0.73) | |
| **BARC 3, or 5** | | | | | |
| < 65 yrs | 3123 | 9 (0.6%) | 25 (1.6%) | 0.36 (0.17 - 0.78) | 0.393 |
| ≥ 65 yrs | 3409 | 21 (1.2%) | 38 (2.3%) | 0.55 (0.32 - 0.93) | |
| **TIMI major** | | | | | |
| < 65 yrs | 3123 | 5 (0.3%) | 13 (0.8%) | 0.39 (0.14 - 1.09) | 0.482 |
| ≥ 65 yrs | 3409 | 10 (0.6%) | 16 (1.0%) | 0.62 (0.28 - 1.36) | |
| **GUSTO moderate or severe** | | | | | |
| < 65 yrs | 3123 | 4 (0.3%) | 17 (1.1%) | 0.24 (0.08 - 0.71) | 0.078 |
| ≥ 65 yrs | 3409 | 19 (1.1%) | 26 (1.5%) | 0.72 (0.40 - 1.31) | |
| **ISTH major** | | | | | |
| < 65 yrs | 3123 | 11 (0.7%) | 26 (1.7%) | 0.43 (0.21 - 0.86) | 0.525 |
| ≥ 65 yrs | 3409 | 23 (1.4%) | 40 (2.4%) | 0.57 (0.34 - 0.95) | |



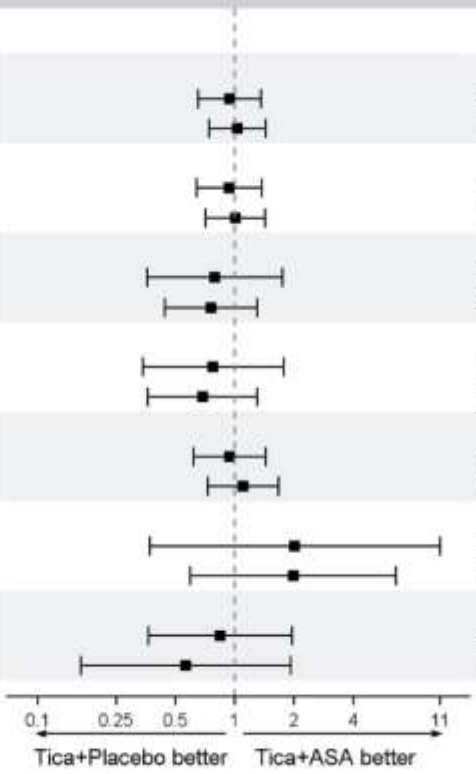

Tica: ticagrelor, CI: confidence interval, BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis

* Bleeding events were performed in intention to treatment cohort

** P value is for the interaction test between randomized treatment assignment and age above 65 versus below 65 years

**Figure 5**

| Ischemic events* | No. of patients | Tica+Placebo no. of patients (%) | Tica+Aspirin no. of patients (%) | HR (95% CI) | Interaction P-value** |
|---|---|---|---|---|---|
| **Death, MI or stroke** | | | | | |
| < 65 yrs | 3090 | 54 (3.6%) | 58 (3.8%) | 0.94 (0.65 - 1.36) | 0.711 |
| ≥ 65 yrs | 3370 | 72 (4.3%) | 69 (4.2%) | 1.03 (0.74 - 1.44) | |
| **CV-death, MI or ischemic stroke** | | | | | |
| < 65 yrs | 3090 | 52 (3.4%) | 56 (3.7%) | 0.94 (0.64 - 1.37) | 0.789 |
| ≥ 65 yrs | 3370 | 65 (3.9%) | 64 (3.9%) | 1.01 (0.71 - 1.42) | |
| **All-cause death** | | | | | |
| < 65 yrs | 3090 | 11 (0.7%) | 14 (0.9%) | 0.79 (0.36 - 1.75) | 0.923 |
| ≥ 65 yrs | 3370 | 23 (1.4%) | 30 (1.8%) | 0.76 (0.44 - 1.30) | |
| **CV-death** | | | | | |
| < 65 yrs | 3090 | 10 (0.7%) | 13 (0.8%) | 0.78 (0.34 - 1.77) | 0.819 |
| ≥ 65 yrs | 3370 | 16 (1.0%) | 23 (1.4%) | 0.69 (0.36 - 1.30) | |
| **MI** | | | | | |
| < 65 yrs | 3090 | 42 (2.8%) | 45 (2.9%) | 0.94 (0.62 - 1.43) | 0.598 |
| ≥ 65 yrs | 3370 | 48 (2.9%) | 43 (2.6%) | 1.10 (0.73 - 1.67) | |
| **Ischemic stroke** | | | | | |
| < 65 yrs | 3090 | 4 (0.3%) | 2 (0.1%) | 2.02 (0.37 - 11.0) | 0.984 |
| ≥ 65 yrs | 3370 | 8 (0.5%) | 4 (0.2%) | 1.98 (0.60 - 6.57) | |
| **Definite/probable ST** | | | | | |
| < 65 yrs | 3090 | 10 (0.7%) | 12 (0.8%) | 0.84 (0.36 - 1.95) | 0.598 |
| ≥ 65 yrs | 3370 | 4 (0.2%) | 7 (0.4%) | 0.56 (0.17 - 1.93) | |



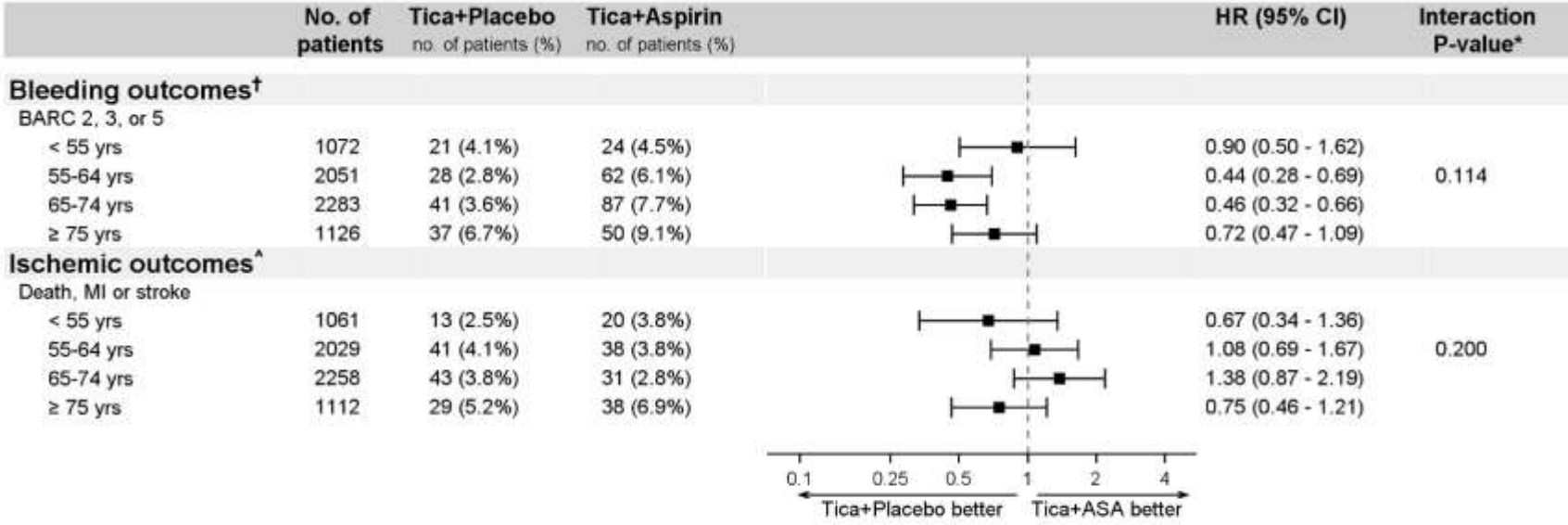

Tica: ticagrelor, CI: confidence interval, MI: myocardial infarction, CV: cardiovascular, ST: stent thrombosis
* Ischemic events were performed in per-protocol cohort
** P value is for the interaction test between randomized treatment assignment and age above 65 versus below 65 years

**SUPPLMENETARY MATERIAL**

# Impact of Age on the Safety and Efficacy of Ticagrelor with or without Aspirin in High-Risk Patients undergoing Percutaneous Coronary Intervention

**Table of contents**

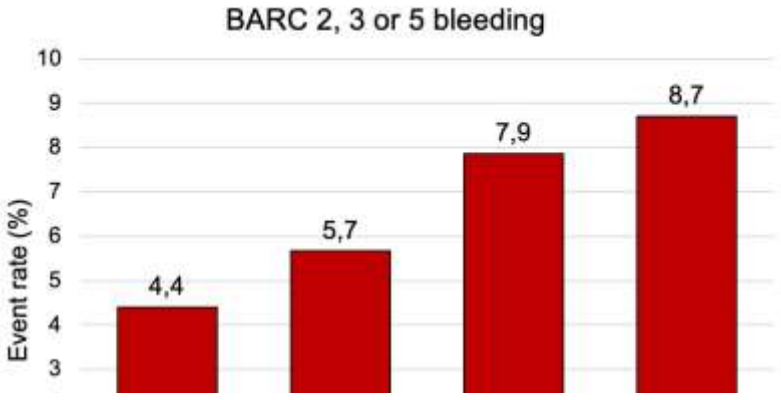
**Supplementary Figure 1. Risk of the primary and key secondary endpoints by 10-year age intervals**



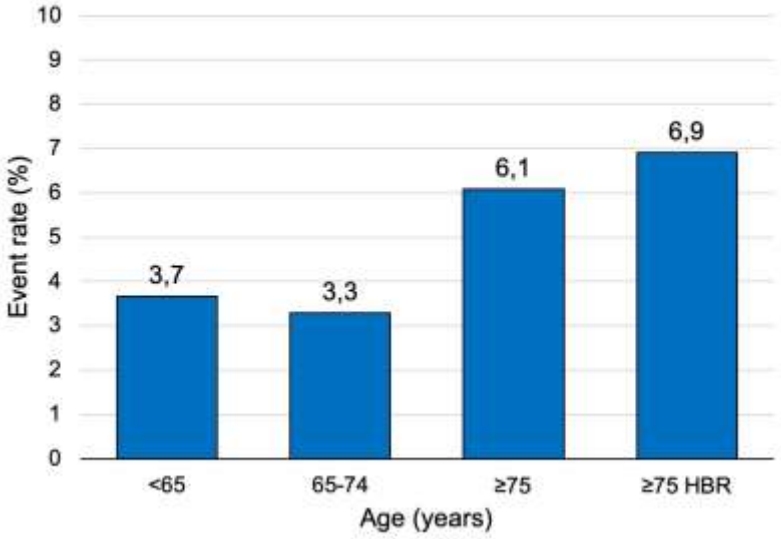

Tica: ticagrelor, CI: confidence interval, BARC: Bleeding Academic Research Consortium, MI: myocardial infarction
† Bleeding outcomes were performed in intention to treatment cohort
^ Ischemic outcomes were performed in per-protocol cohort
* P value is for the interaction test between randomized treatment assignment and age group

**Supplementary Figure 2. Rates of bleeding (A) and ischemic (B) events according to age and HBR status**

**A**




**B**



**Supplementary Table 1. Baseline clinical characteristics according to age ≥65 years**

| Clinical parameters | Overall (N=6532) | Age ≥65 yrs (N=3409) | Age <65 yrs (N=3123) | p-value |
|---|---|---|---|---|
| Age, years | 64.7±10.3 | 72.6±5.8 | 56.1±6.5 | <.001 |
| Female sex | 1534 (23.5%) | 892 (26.2%) | 642 (20.6%) | <.001 |
| Nonwhite race | 1609 (24.6%) | 651 (19.1%) | 958 (30.7%) | <.001 |
| BMI, $kg/m^2$ | 28.9±5.6 | 28.3±5.3 | 29.5±5.9 | <.001 |
| Enrolling region | | | | <.001 |
| North America | 2972 (45.5%) | 1638 (48.0%) | 1334 (42.7%) | |
| Europe | 2509 (38.4%) | 1358 (39.8%) | 1151 (36.9%) | |
| Asia | 1051 (16.1%) | 413 (12.1%) | 638 (20.4%) | |
| Diabetes | 2405 (36.8%) | 1225 (35.9%) | 1180 (37.8%) | 0.122 |
| Diabetes treated with insulin | 650 (27.0%) | 325 (26.5%) | 325 (27.5%) | 0.576 |
| Chronic kidney disease | 1093 (17.4%) | 883 (27.0%) | 210 (7.0%) | <.001 |
| Anemia | 1207 (19.3%) | 788 (24.2%) | 419 (14.0%) | <.001 |
| Current smoker | 1400 (21.4%) | 412 (12.1%) | 988 (31.6%) | <.001 |
| Hypercholesterolemia | 4239 (64.9%) | 2381 (69.8%) | 1858 (59.5%) | <.001 |
| Hypertension | 4800 (73.5%) | 2689 (78.9%) | 2111 (67.6%) | <.001 |
| Peripheral arterial disease | 478 (7.3%) | 290 (8.5%) | 188 (6.0%) | <.001 |
| Previous MI | 1937 (29.7%) | 904 (26.5%) | 1033 (33.1%) | <.001 |
| Previous PCI | 2838 (43.4%) | 1497 (43.9%) | 1341 (42.9%) | 0.428 |
| Previous CABG | 703 (10.8%) | 468 (13.7%) | 235 (7.5%) | <.001 |
| Multivessel CAD | 4069 (62.3%) | 2186 (64.1%) | 1883 (60.3%) | 0.001 |
| Previous major bleed | 54 (0.8%) | 35 (1.0%) | 19 (0.6%) | 0.062 |
| Indication for PCI | | | | <.001 |
| Stable CAD | 2411 (36.9%) | 1452 (42.6%) | 959 (30.7%) | |
| ACS | 4120 (63.1%) | 1956 (57.4%) | 2164 (69.3%) | |

BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACS: Acute coronary syndrome

**Supplementary Table 2. Baseline procedural characteristics according to age ≥65 years**

| Procedural characteristics | Overall (N=6532) | Age ≥ 65 yrs (N=3409) | Age < 65 yrs (N=3123) | p-value |
|---|---|---|---|---|
| Radial artery access | 4628 (70.9%) | 2322 (68.1%) | 2306 (73.8%) | <.001 |
| Multivessel CAD | 4069 (62.3%) | 2186 (64.1%) | 1883 (60.3%) | 0.001 |
| Target vessel | | | | |
| Left Main | 289 (4.4%) | 170 (5.0%) | 119 (3.8%) | 0.021 |
| LAD | 3639 (55.7%) | 1912 (56.1%) | 1727 (55.3%) | 0.522 |
| LCX | 2099 (32.1%) | 1112 (32.6%) | 987 (31.6%) | 0.380 |
| RCA | 2297 (35.2%) | 1165 (34.2%) | 1132 (36.2%) | 0.080 |
| Number of vessels treated | 1.3±0.5 | 1.3±0.5 | 1.3±0.5 | 0.498 |
| Number of lesions treated | 1.5±0.7 | 1.5±0.8 | 1.5±0.7 | 0.042 |
| Lesion morphology[†] | | | | |
| Moderate/severe calcification | 940 (14.4%) | 585 (17.2%) | 355 (11.4%) | <.001 |
| Bifurcation | 790 (12.1%) | 419 (12.3%) | 371 (11.9%) | 0.610 |
| Total occlusion | 367 (5.6%) | 177 (5.2%) | 190 (6.1%) | 0.118 |
| Thrombotic | 724 (11.1%) | 304 (8.9%) | 420 (13.4%) | <.001 |
| Total stent length, mm[‡] | 38.9±23.5 | 38.5±23.0 | 39.3±23.9 | 0.136 |
| Minimum stent diameter, mm | 2.8±0.5 | 2.8±0.5 | 2.9±0.5 | 0.471 |
| Complex PCI[§] | 2072 (31.7%) | 1160 (34.0%) | 912 (29.2%) | <.001 |

CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery
[†]Lesion morphology assessed by operators
[‡]Stent length calculated by operators
[§]Complex PCI defined as any of the following: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, atherectomy device use, left main PCI, surgical bypass graft or chronic total occlusion as target lesions

**Supplementary Table 3. Baseline clinical characteristics according to age ≥75 years and treatment arm**

| | Age ≥ 75 yrs (N=1126) | | | Age < 75 yrs (N=5406) | | |
|---|---|---|---|---|---|---|
| | **Tica+Placebo N=566 (50.3%)** | **Tica+Aspirin N=560 (49.7%)** | **p-value** | **Tica+Placebo N=2699 (49.9%)** | **Tica+Aspirin N=2707 (50.1%)** | **p-value** |
| Age, years | 79.5±3.8 | 79.5±3.9 | 0.823 | 61.7±8.3 | 61.6±8.5 | 0.895 |
| Female sex | 162 (28.6%) | 161 (28.8%) | 0.962 | 609 (22.6%) | 602 (22.2%) | 0.774 |
| Nonwhite race | 87 (15.4%) | 73 (13.0%) | 0.262 | 733 (27.2%) | 716 (26.4%) | 0.557 |
| BMI, $kg/m^2$ | 27.4±4.5 | 27.8±5.2 | 0.173 | 29.2±5.7 | 29.1±5.7 | 0.511 |
| Enrolling region | | | 0.485 | | | 0.969 |
| North America | 274 (48.4%) | 283 (50.5%) | | 1210 (44.8%) | 1205 (44.5%) | |
| Europe | 240 (42.4%) | 236 (42.1%) | | 1011 (37.5%) | 1022 (37.8%) | |
| Asia | 52 (9.2%) | 41 (7.3%) | | 478 (17.7%) | 480 (17.7%) | |
| Diabetes | 186 (32.9%) | 181 (32.3%) | 0.847 | 1027 (38.1%) | 1011 (37.3%) | 0.594 |
| Diabetes treated with insulin | 42 (22.6%) | 59 (32.6%) | 0.032 | 266 (25.9%) | 283 (28.0%) | 0.287 |
| Chronic kidney disease | 205 (38.1%) | 214 (39.4%) | 0.659 | 341 (13.2%) | 333 (12.8%) | 0.717 |
| Anemia | 172 (32.2%) | 159 (29.4%) | 0.326 | 436 (16.8%) | 440 (17.0%) | 0.892 |
| Current smoker | 39 (6.9%) | 48 (8.6%) | 0.287 | 617 (22.9%) | 696 (25.7%) | 0.015 |
| Hypercholesterolemia | 397 (70.1%) | 402 (71.8%) | 0.543 | 1729 (64.1%) | 1711 (63.2%) | 0.514 |
| Hypertension | 460 (81.3%) | 438 (78.2%) | 0.202 | 1942 (72.0%) | 1960 (72.4%) | 0.694 |
| Peripheral arterial disease | 65 (11.5%) | 64 (11.4%) | 0.977 | 173 (6.4%) | 176 (6.5%) | 0.891 |
| Previous MI | 134 (23.7%) | 141 (25.2%) | 0.557 | 838 (31.0%) | 824 (30.4%) | 0.628 |
| Previous PCI | 248 (43.8%) | 263 (47.0%) | 0.289 | 1174 (43.5%) | 1153 (42.6%) | 0.502 |
| Previous CABG | 92 (16.3%) | 97 (17.3%) | 0.632 | 267 (9.9%) | 247 (9.1%) | 0.334 |
| Multivessel CAD | 398 (70.3%) | 356 (63.6%) | 0.016 | 1686 (62.5%) | 1629 (60.2%) | 0.084 |
| Previous major bleed | 6 (1.1%) | 12 (2.1%) | 0.147 | 21 (0.8%) | 15 (0.6%) | 0.311 |
| Indication for PCI | | | 0.531 | | | 0.242 |
| Stable CAD | 249 (44.0%) | 236 (42.1%) | | 982 (36.4%) | 944 (34.9%) | |
| ACS | 317 (56.0%) | 324 (57.9%) | | 1716 (63.6%) | 1763 (65.1%) | |

Tica: ticagrelor, BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACS: Acute coronary syndrome

**Supplementary Table 4. Baseline procedural characteristics according to age ≥75 years and treatment arm**

| | Age ≥ 75 yrs (N=1126) | | | Age < 75 yrs (N=5406) | | |
|---|---|---|---|---|---|---|
| | **Tica+Placebo N=566 (50.3%)** | **Tica+Aspirin N=560 (49.7%)** | **p-value** | **Tica+Placebo N=2699 (49.9%)** | **Tica+Aspirin N=2707 (50.1%)** | **p-value** |
| Radial artery access | 366 (64.7%) | 352 (62.9%) | 0.528 | 1957 (72.5%) | 1953 (72.1%) | 0.766 |
| Multivessel CAD | 398 (70.3%) | 356 (63.6%) | 0.016 | 1686 (62.5%) | 1629 (60.2%) | 0.084 |
| Target vessel | | | | | | |
| Left Main | 38 (6.7%) | 39 (7.0%) | 0.868 | 99 (3.7%) | 113 (4.2%) | 0.338 |
| LAD | 329 (58.1%) | 301 (53.8%) | 0.139 | 1490 (55.2%) | 1519 (56.1%) | 0.502 |
| LCX | 195 (34.5%) | 186 (33.2%) | 0.661 | 859 (31.8%) | 859 (31.7%) | 0.941 |
| RCA | 173 (30.6%) | 194 (34.6%) | 0.144 | 967 (35.8%) | 963 (35.6%) | 0.846 |
| Number of vessels treated | 1.3±0.5 | 1.3±0.5 | 0.726 | 1.3±0.5 | 1.3±0.5 | 0.450 |
| Number of lesions treated | 1.6±0.8 | 1.5±0.7 | 0.218 | 1.5±0.7 | 1.5±0.7 | 0.884 |
| Lesion morphology[†] | | | | | | |
| Moderate/severe calcification | 125 (22.1%) | 116 (20.7%) | 0.575 | 352 (13.0%) | 347 (12.8%) | 0.807 |
| Bifurcation | 82 (14.5%) | 64 (11.4%) | 0.127 | 320 (11.9%) | 324 (12.0%) | 0.898 |
| Total occlusion | 26 (4.6%) | 26 (4.6%) | 0.969 | 159 (5.9%) | 156 (5.8%) | 0.841 |
| Thrombotic | 41 (7.2%) | 45 (8.0%) | 0.617 | 312 (11.6%) | 326 (12.0%) | 0.582 |
| Total stent length, mm[‡] | 39.6±24.6 | 37.9±21.7 | 0.208 | 38.9±23.1 | 38.9±23.9 | 0.983 |
| Minimum stent diameter, mm | 2.8±0.5 | 2.9±0.5 | 0.542 | 2.8±0.5 | 2.9±0.5 | 0.434 |
| Complex PCI[§] | 212 (37.5%) | 207 (37.0%) | 0.865 | 818 (30.3%) | 835 (30.8%) | 0.667 |

CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery
[†]Lesion morphology assessed by operators
[‡]Stent length calculated by operators
[§]Complex PCI defined as any of the following: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, atherectomy device use, left main PCI, surgical bypass graft or chronic total occlusion as target lesions

**Supplementary Table 5. Bleeding events in patients ≥75 years of age according to the presence of HBR**

| Bleeding outcomes* | HBR (N=636) | | | | Non-HBR (N=490) | | | | Interaction p-value† |
|---|---|---|---|---|---|---|---|---|---|
| | Tica+ placebo (N=318) | Tica+ Aspirin (N=318) | Hazard ratio (95% CI) | p-value | Tica+ placebo (N=248) | Tica+ Aspirin (N=242) | Hazard ratio (95% CI) | p-value | |
| | no. of patients (%) | | | | no. of patients (%) | | | | |
| BARC 2, 3 or 5 | 19 (6.2%) | 35 (11.2%) | 0.53 (0.30 - 0.93) | 0.026 | 18 (7.3%) | 15 (6.3%) | 1.15 (0.58 - 2.28) | 0.687 | 0.084 |
| BARC 3 or 5 | 8 (2.6%) | 13 (4.2%) | 0.61 (0.25 - 1.48) | 0.276 | 5 (2.0%) | 5 (2.1%) | 0.96 (0.28 - 3.30) | 0.942 | 0.565 |
| TIMI major | 3 (1.0%) | 4 (1.3%) | 0.75 (0.17 - 3.37) | 0.711 | 3 (1.2%) | 2 (0.8%) | 1.44 (0.24 - 8.60) | 0.691 | 0.585 |
| GUSTO moderate/severe | 8 (2.6%) | 11 (3.5%) | 0.72 (0.29 - 1.80) | 0.489 | 5 (2.0%) | 2 (0.8%) | 2.41 (0.47 - 12.4) | 0.293 | 0.209 |
| ISTH major | 8 (2.6%) | 14 (4.5%) | 0.57 (0.24 - 1.35) | 0.202 | 6 (2.4%) | 5 (2.1%) | 1.15 (0.35 - 3.76) | 0.821 | 0.346 |

HBR: high bleeding risk, Tica: ticagrelor, CI: confidence interval, BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis

*Bleeding outcomes were performed in the intention-to-treat cohort

†Interaction between randomized treatment assignment and whether having HBR

The percentages mentioned above represent K-M rates at 12 months after randomization

**Supplementary Table 6. Ischemic events in patients ≥75 years of age according to the presence of HBR**

| Ischemic outcomes[^] | HBR (N=630) | | | | Non-HBR (N=482) | | | | Interaction p-value[†] |
|---|---|---|---|---|---|---|---|---|---|
| | Tica+ placebo (N=315) | Tica+ Aspirin (N=315) | Hazard ratio (95% CI) | p-value | Tica+ placebo (N=245) | Tica+ Aspirin (N=237) | Hazard ratio (95% CI) | p-value | |
| | no. of patients (%) | | | | no. of patients (%) | | | | |
| Death, MI or stroke | 20 (6.5%) | 23 (7.4%) | 0.88 (0.48 - 1.60) | 0.666 | 9 (3.7%) | 15 (6.4%) | 0.57 (0.25 - 1.30) | 0.181 | 0.405 |
| Cardiovascular death, MI or ischemic stroke | 18 (5.8%) | 23 (7.4%) | 0.79 (0.43 - 1.46) | 0.451 | 9 (3.7%) | 14 (6.0%) | 0.61 (0.26 - 1.41) | 0.247 | 0.626 |
| All-cause death | 9 (2.9%) | 11 (3.5%) | 0.82 (0.34 - 1.97) | 0.656 | 0 (0.0%) | 6 (2.5%) | N/A | N/A | N/A |
| Cardiovascular death | 7 (2.3%) | 10 (3.2%) | 0.70 (0.27 - 1.85) | 0.478 | 0 (0.0%) | 5 (2.1%) | N/A | N/A | N/A |
| MI | 13 (4.2%) | 16 (5.2%) | 0.82 (0.39 - 1.70) | 0.587 | 7 (2.9%) | 8 (3.4%) | 0.83 (0.30 - 2.28) | 0.716 | 0.984 |
| Ischemic stroke | 2 (0.7%) | 1 (0.3%) | 2.03 (0.18 - 22.4) | 0.563 | 2 (0.8%) | 1 (0.4%) | 1.90 (0.17 - 21.0) | 0.599 | 0.971 |
| Stent thrombosis (definite/probable) | 3 (1.0%) | 3 (1.0%) | 1.01 (0.20 - 4.99) | 0.993 | 0 (0.0%) | 0 (0.0%) | N/A | N/A | N/A |

HBR: high bleeding risk, Tica: ticagrelor, CI: confidence interval, MI: myocardial infarction
[^]Ischemic outcomes were performed in the per-protocol cohort
[†]Interaction between randomized treatment assignment and whether having HBR
The percentages mentioned above represent K-M rates at 12 months after randomization