Sex differences among high-risk patients receiving ticagrelor with or without aspirin after percutaneous coronary intervention: Results from the TWILIGHT Study

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Key Points

Question: Do treatment effects of early aspirin withdrawal with continuation of ticagrelor after percutaneous coronary intervention (PCI) in patients at high risk for bleeding or ischemic events vary by sex?

Findings: In TWILIGHT, women, compared with men, experienced higher risk for bleeding complications but similar risk for ischemic events. In this high-risk PCI population, the benefits of early aspirin withdrawal with continuation of ticagrelor were generally comparable in women and men.

Meaning: These findings have important implications for antiplatelet regimens after PCI and should motivate dedicated studies to further explore the benefits of this approach in women.

Abstract

Importance: Shortened dual antiplatelet therapy (DAPT) followed by monotherapy with a potent $P2Y_{12}$ inhibitor reduces bleeding without increasing ischemic events after percutaneous coronary intervention (PCI).

Objective: Explore sex differences and evaluate the association of sex with outcomes among patients treated with ticagrelor monotherapy vs. ticagrelor plus aspirin.

Design: Pre-specified secondary analysis of TWILIGHT, an investigator-initiated randomized, placebo-controlled trial.

Setting: 187 sites across 11 countries.

Participants: Patients after successful PCI with drug-eluting stent and planned for discharge on ticagrelor plus aspirin. Additionally, ≥1 clinical and ≥1 angiographic feature for high risk of ischemic or bleeding events.

Interventions: At 3 months post-PCI patients adherent to ticagrelor and aspirin without major adverse event were randomized to either aspirin or placebo for an additional 12 months along with ticagrelor.

Main Outcomes and Measures: Primary endpoint was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 at 12 months after randomization. Primary ischemic endpoint was a composite of death, myocardial infarction, or stroke.

Results: Of 9006 enrolled patients, 7119 underwent randomization (23.9% women). Women were older than men with higher prevalence of insulin-dependent diabetes, chronic kidney disease, anemia, and hypertension but lower rates of smoking and known coronary artery disease. Women more often underwent PCI for an acute coronary syndrome indication and had less multivessel disease.

The primary bleeding endpoint occurred more often in women than men. Multivariate adjustment attenuated the increased bleeding risk associated with female sex. Ischemic events were similar in women and men.

Ticagrelor plus placebo vs. ticagrelor plus aspirin was associated with lower risk of BARC type 2, 3, or 5 bleeding in women (5.0% vs. 8.6%; hazard ration [HR] 0.57, 95% confidence interval [CI] 0.39-0.83) and men (3.7% vs. 6.6%; HR 0.55, 95% CI 0.43-0.70; p_{int}=0.888). Ischemic endpoints were similar between treatment groups in both sexes.

Conclusions and Relevance: Women, compared with men, experienced higher risk for bleeding but similar risk for ischemic events. Adjustment for baseline risk attenuated the increased bleeding risk associated with female sex. In this high-risk PCI population, the benefits of early aspirin withdrawal with continuation of ticagrelor were generally comparable in women and men.

Introduction

Prolonged dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor and aspirin has been proven to decrease the risk of ischemic events after percutaneous coronary intervention (PCI) but is also associated with an increase in bleeding.[1] Recently, the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) study has shown that monotherapy with a potent $P2Y_{12}$ inhibitor following a short period of DAPT compared with continued DAPT leads to reduced bleeding without an increase in ischemic events among patients at high risk for bleeding or ischemic events after PCI.[2] Whether these effects vary in relation to sex remains unknown. This distinction is clinically relevant as women, compared with men, are characterized by an increased risk for bleeding after PCI. While these associations may reflect differences in baseline risk factors (i.e. older age, renal impairment) that are more common in women, other reports suggest an independent biological effect of female sex on hemorrhagic risk. Accordingly, we performed a pre-specified secondary analysis to explore sex differences in the TWILIGHT population and to evaluate the association of sex with outcomes among patients treated with ticagrelor monotherapy vs. ticagrelor plus aspirin.

Methods

Study design and oversight

TWILIGHT was a randomized, placebo-controlled trial that was conducted in 187 sites across 11 countries. The trial rationale, design, and main findings have been reported previously.[2,3] The Icahn School of Medicine at Mount Sinai designed and sponsored the trial supported by an investigator-initiated grant from AstraZeneca. AstraZeneca provided financial support and supplied ticagrelor for the trial but had no role in the design, collection, analysis, or interpretation of the data. National regulatory agencies and institutional review boards or ethics committees of participating centers approved the trial

protocol. An independent Data Safety Monitoring Board provided external oversight to ensure safety of all trial participants. All patients provided written, informed consent prior to participation.

Study population

To be eligible for enrollment, a patient had to have undergone successful PCI with at least one locally approved drug-eluting stent (DES) with a plan for discharge on ticagrelor plus aspirin. In addition, at least one clinical and one angiographic feature for high risk of ischemic or bleeding events were required. The clinical features for high risk included age ≥65 years, female sex, troponin-positive acute coronary syndrome (ACS), established vascular disease, diabetes mellitus treated with medications, and chronic kidney dysfunction (CKD; defined as an estimated glomerular filtration rate <60 ml/min/1.73m2 or creatinine clearance <60 ml/min). The angiographic features for high risk included multivessel coronary artery disease (CAD), total stent length >30 mm, and treatment of a thrombotic target lesion, a bifurcation lesion treated requiring two stents, an obstructive left main or proximal left anterior descending coronary artery (LAD) lesion, or treatment of a calcified target lesion with atherectomy. Key exclusion criteria included presentation with ST-segment elevation myocardial infarction, cardiogenic shock, ongoing long-term treatment with oral anticoagulants, or contraindication to aspirin or ticagrelor.

Study regimen

After the index PCI, all patients received open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81 to 100 mg daily). At three months after hospital discharge, patients who had been adherent to treatment and had not experienced a major bleeding event (Bleeding Academic Research Consortium [BARC] type 3b or higher) or an ischemic event (stroke, myocardial infarction [MI], or coronary revascularization) were eligible to be randomized to either aspirin or matching placebo for an additional 12 months along with continuation of open-label ticagrelor. Follow-up was performed by

telephone at one month after randomization 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 a final telephone follow-up three months later.

Outcomes

The primary endpoint was the first occurrence of BARC type 2, 3, or 5 bleeding between randomization and 12 months after randomization. The primary ischemic endpoint was a composite of death from any cause, nonfatal MI, or nonfatal stroke. Secondary bleeding endpoints included BARC type 3 or 5 bleeding;[4] Thrombolysis in Myocardial Infarction (TIMI) major bleeding;[5] Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) moderate, severe, or life-threatening bleeding;[6] or major bleeding as defined by the International Society of Thrombosis or Haemostasis (ISTH).[7] Other ischemic endpoints included cardiovascular death, MI, ischemic stroke, and definite or probable stent thrombosis. Myocardial infarction was defined according to the third universal definition,[8] and revascularization and stent thrombosis were classified according to the Academic Research Consortium.[9] All clinical events were adjudicated by an independent external committee, the members of whom were unaware of the treatment group assignments.

Statistical analysis

Baseline clinical and procedural characteristics were summarized by sex, and by randomized treatment assignment stratified by sex using means (standard deviation) and frequencies for continuous and categorical variables, respectively. The cumulative incidences of the primary and secondary endpoints were estimated by the Kaplan-Meier method. Patients without a primary endpoint between randomization and one 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 with Cox proportional-hazards models. Associations between sex and bleeding and ischemic outcomes were examined using Cox regression. Treatment effects of ticagrelor monotherapy vs. ticagrelor plus aspirin were evaluated by sex, and formal interaction testing using Cox regression was performed to assess for effect modification. Bleeding and ischemic endpoints were analyzed in the intention-to-treat (N=7119) and per-protocol populations (N=7039), respectively. Patients who underwent randomization and did not fulfill enrollment criteria were not eligible for randomization, or never received protocol-mandated therapy were excluded from the per-protocol analysis (N=80). A p-value <0.05 indicates statistical significance. All analyses were performed using Stata version 16.0 (College Station, Texas).

Results

Baseline clinical and procedural characteristics

A total of 9006 patients were enrolled, of whom 7119 underwent randomization. Of the randomized patients, 23.9% (n=1698) were women.

Baseline clinical and procedural characteristics are reported in Table 1. Compared with men, women were older (65.5±9.6 years vs. 63.4±10.3 years; p<0.001) and more likely non-white with a higher prevalence of insulin-dependent diabetes, CKD, anemia, and hypertension. Conversely, women were less likely to be current smokers and to have a history of MI, PCI or coronary artery bypass grafting. Women were more likely to have undergone PCI for an ACS indication (68.4% vs. 63.7%; p<0.001).

Compared with men, women had less multivessel CAD (55.4% vs. 65.0%; p<0.001). There were no significant differences with regard to lesion morphology between the sexes. However, mean total stent length and mean minimum stent diameter were lower in women.

Baseline clinical and procedural characteristics according to randomized treatment assignment stratified by sex are reported in Supplementary Tables 1 and 2.

Outcomes by sex

The incidences of bleeding endpoints at one year are reported in Figure 1. The primary endpoint of BARC 2, 3 or 5 bleeding occurred more often in women compared with men (6.8% versus 5.2%; HR 1.32, 95% CI 1.06-1.64; p=0.013). Similarly, women experienced higher rates of BARC 3 or 5 bleeding (2.0% versus 1.3%; HR 1.57 95% CI 1.04-2.37; p=0.030). While TIMI major bleeding was similar between the sexes, the incidences of GUSTO moderate or severe bleeding and ISTH major bleeding were numerically higher in women than men; however, these differences reached only borderline statistical significance. Following multivariate adjustment, the association between female sex and bleeding risk was attenuated.

The incidences of ischemic endpoints at one year are reported in Figure 2. No significant differences between women and men were found in the incidences of the composite of death, MI or stroke; the composite of cardiovascular death, MI or ischemic stroke; and the individual endpoints of all-cause death; cardiovascular death; MI; ischemic stroke; and definite or probable stent thrombosis. After multivariable adjustment results were largely unchanged.

Outcomes according to treatment strategy by sex

Bleeding and ischemic outcomes, according to treatment strategy, are shown in Table 2. Ticagrelor plus placebo vs. ticagrelor plus aspirin was associated with lower risk of BARC type 2, 3, or 5 bleeding in women (5.0% vs. 8.6%; HR 0.57, 95% CI 0.39-0.83; p=0.004) and men (3.7% vs. 6.6%; HR 0.55, 95% CI 0.43-0.70; p<0.001) without significant interaction between randomized treatment and sex (p_{int}=0.888) (Figure 3A). The reductions in TIMI major bleeding were not statistically significant in either of the sexes. Although the reductions in BARC 3 or 5 bleeding; GUSTO moderate or severe bleeding; and

ISTH major bleeding were statistically significant in men but not in women, the analyses did not show significant interactions between randomized treatment and sex for these endpoints.

The incidences of the composite of death, MI or stroke were similar in the group randomized to ticagrelor plus placebo and the group randomized to ticagrelor plus aspirin in both woman (3.5% vs. 3.5%; HR 0.99, 95% CI 0.59-1.66; p=0.981) and men (4.0% vs. 4.1%; HR 0.98, 95% CI 0.75-1.29; p=0.906) with no significant interaction between randomized treatment and sex (p_{int}=0.974) (Figure 3B). Similar results were found for the other ischemic endpoints except for all-cause death that was similar in both treatment groups in men (1.2% vs. 1.2%; HR 0.94, 95% CI 0.57-1.53; p=0.800) but lower in women treated with ticagrelor plus placebo vs. ticagrelor plus aspirin (0.4% vs. 1.4%; HR 0.25, 95% CI 0.07-0.88; p=0.031) with borderline significant interaction between randomized treatment and sex (p_{int}=0.054).

Discussion

In the TWILIGHT trial, women were older and displayed a higher prevalence of baseline risk factors for bleeding and ischemic events as compared with men. While women experienced higher risk for most bleeding endpoints, ischemic risk was similar between sexes. After adjustment for baseline characteristics incremental bleeding risk associated with female sex was attenuated. Withdrawing aspirin while continuing ticagrelor after three months of DAPT in patients at high risk for bleeding or ischemic events after PCI with DES implantation was associated with a reduction in bleeding and preserved ischemic benefits in women and men. Borderline significant interaction between randomized treatment and sex was observed due to significant reduction of mortality associated with ticagrelor monotherapy vs. ticagrelor plus aspirin among women but not men.

Increased bleeding risk in women compared with men after PCI and/or ACS has been documented by numerous studies. In some of these studies, the increased risk of bleeding was mostly attributed to factors such as women's older age, higher rate of CKD and lower BMI. For example, an

analysis from the PROMETHEUS study including clopidogrel and prasugrel treated patients following ACS-PCI found an increased risk of bleeding in women that was attenuated after adjustment for differences in baseline risk (HR 1.31; 95% CI 0.85-2.04 at one year). These results are in keeping with the current analysis, in which the increased bleeding risk in women was attenuated after adjustment for age, CKD, anemia and other differences in baseline risk between the sexes. However, there was only modest risk attenuation for BARC type 3 or 5 bleeding with a decrease of the HR from 1.57 to 1.49, suggesting additional unknown and/or unmeasured factors that contribute to women's increased bleeding risk. Indeed, in many studies the risk of bleeding after PCI and/or ACS remained significantly greater in women than men after multivariate adjustment.[10-12] Of note, in these trials clopidogrel and to a lesser extent prasugrel were the predominant $P2Y_{12}$ inhibitors. In contrast, LEADERS FREE is one of the few studies that have not found sex-related differences in long-term bleeding after PCI between the sexes with similar risk of BARC types 3 to 5 bleedings in women and men.[13] The LEADERS FREE trial enrolled only patients at high risk for bleeding, and differences in measured but also unmeasured confounders for bleeding risk between women and men may have been less prominent in this study population compared to others.[13] In addition, DAPT duration was reduced to one month after PCI in LEADERS FREE.

To reduce the risk of bleeding after PCI, several studies have been performed to investigate the efficacy and safety of shortening of DAPT by early aspirin withdrawal.[14-17] SMART-CHOICE[15] and TICO[16] reported decreased bleeding and similar ischemic risk with $P2Y_{12}$ monotherapy after three months of DAPT vs. 12 months of DAPT with no interaction between treatment strategy and sex. Both study populations were of modest size, which prohibits definite conclusions, especially in subgroup-analyses. In GLOBAL LEADERS, 23 months of ticagrelor monotherapy after one month of DAPT vs. 12 months of DAPT followed by 12 months of aspirin was associated with a lower risk of bleeding in men (HR 0.72; 95% CI 0.53-0.98) but not in women (HR 1.23; 95% CI 0.80-1.89; p_{int}=0.045) at one year, while at two

years, there was no difference in the efficacy and safety of the two antiplatelet strategies between the sexes.[18] Authors noted that these results were driven by an increased risk of bleeding with ticagrelor monotherapy compared with standard DAPT (clopidogrel plus aspirin) in female patients with stable CAD, and suggested that potent $P2Y_{12}$ inhibitors should be used with caution in women who present with stable CAD. The use of clopidogrel in patients with stable CAD in the comparator arm in this study is only one of the differences between GLOBAL LEADERS and TWILIGHT that may have contributed to the contradictory results. Other differences pertain to the trial design (open-label vs. double-blind), the study population (all comers vs. high-risk patients), modes of bleeding ascertainment (site-reported vs. adjudicated), and protocol adherence.[2] The results from TWILIGHT suggest substantial bleeding reduction and preserved ischemic benefit with a strategy of early aspirin withdrawal in both women and men. The pharmacodynamic effects of this strategy were investigated in the TWILIGHT platelet substudy, which showed that markers sensitive to cyclo-oxygenase-1 blockade, including platelet reactivity in response to arachidonic acid and collagen stimuli were higher in the absence of aspirin, however, the antithrombotic potency of ticagrelor monotherapy was similar to that of ticagrelor plus aspirin with respect to ex vivo blood thrombogenicity.[19] Although a sensitivity analysis to control for sex was performed and showed similar results, further investigations are needed to investigate sex-specific aspects of blood thrombogenicity and platelet reactivity associated with shortening of DAPT by early aspirin withdrawal.

Of note, in TWILIGHT all-cause death was similar in both treatment groups in men but lower in women treated with ticagrelor plus placebo vs. ticagrelor plus aspirin with borderline significant interaction between randomized treatment and sex. Although this mortality benefit associated with ticagrelor monotherapy vs. ticagrelor plus aspirin in women compared with men cannot be considered definite, it may deserve some consideration. Other than by play of chance, it may be explained by a potentially greater mortality benefit associated with bleeding reduction in women vs. men. Although the

association of post-PCI bleeding with mortality is well documented,[20-22] data on the impact of sex on this association is limited and conflicting. While a post-hoc analysis from the PARIS registry did not find any sex-related differences in the mortality risk associated with actionable bleeding after PCI,[23] at least one analysis from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium registry suggested that women had greater bleeding-associated in-hospital mortality compared with men.[24] Conversely, an analysis from the SWEDEHART registry in patients hospitalized with MI found increased one-year mortality associated with in-hospital bleeding in men vs. women.[25] Similar results come from the EARLY-ACS trial, in which the risk of 30-day mortality associated with bleeding was higher in men than women.[26] Of note, in the latter study, 15% of women (compared to 6% of men) had normal coronary arteries, and authors hypothesized that women were, therefore, at lower risk for ischemic events due to DAPT cessation after bleeding, which is thought to be a major cause of bleeding-associated mortality. Other reasons to explain the higher mortality associated with bleeding in men vs. women included the higher rate of access site-related bleeding in women which may be easier to identify and treat compared with higher rates of non-access site-related bleeding in men that are more likely to be fatal.[27,28] However, these factors do not play a role in our analysis since all patients had substantial CAD and randomization took place three months after the initial PCI and potential access site-related bleedings. Further research is needed to investigate sex-specific aspects in bleeding-associated mortality risk. Nevertheless, similar relative risk reduction for bleeding coupled with a higher rate of bleeding in women compared with men implies a larger absolute risk reduction in women. This finding is reinforced by the suggestion of a potential late mortality benefit in women. Taken together, the results of this analysis suggest that strong consideration should be given to early withdrawal of aspirin in women after PCI, especially if they are being treated with ticagrelor-based DAPT.

Limitations

Although this subgroup analysis was pre-specified, our findings should be considered hypothesis-generating only and require confirmation in future studies. Randomization was not stratified by sex, and we did not account for multiplicity, thereby increasing the chance for a type 1 error. The female subgroup was modest in size, and there were some imbalances in patient characteristics by treatment assignment, which may have confounded the results. Neither of the sex-specific subgroups was individually powered to draw definite conclusions on the effect of ticagrelor monotherapy vs. ticagrelor plus aspirin on the bleeding and ischemic endpoints. Furthermore, our findings are not generalizable but specific to a PCI population at high risk for bleeding or ischemic events according to the inclusion and exclusion criteria of the trial. Finally, our analyses considered only patients who tolerated an initial three months of DAPT with ticagrelor plus aspirin without any major adverse events.

Conclusion

Women, compared with men, experienced higher risk for bleeding complications but similar risk for ischemic events after PCI. Adjustment for differences in baseline risk attenuated the increased bleeding risk associated with female sex. In this high-risk PCI population, the benefits of early aspirin withdrawal with continuation of ticagrelor were generally comparable in women and men. These findings have important implications for antiplatelet regimens after PCI and should motivate dedicated studies to further explore the benefits of this approach in women.

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Conflict of interest

Dr. Baber reports speaker honoraria from AstraZeneca and Boston Scientific. **Dr. Cohen** reports receiving grant support, paid to his institution, and consulting fees from AstraZeneca, Medtronic, and Abbott Vascular, and grant support, paid to his institution, from Boston Scientific. **Dr. Sharma** has received from Abbott Vascular, Boston Scientific, and Cardiovascular Systems, Inc. **Dr. Angiolillo** has received payment as an individual for: reports receiving payments as an individual for: a) Consulting fee or honorarium from Abbott, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company; b) Participation in review activities from CeloNova and St. Jude Medical. Institutional payments for grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions and the Scott R. MacKenzie Foundation. **Dr. Collier** has served on Data Monitoring Committees sponsored by AstraZeneca, Boston Scientific, Daiichi-Sankyo, Devax, Infraredx, Medtronic, Pfizer, and Zoll. **Dr. Dangas** reports receiving consulting fees and advisory board fees from AstraZeneca, consulting fees from Biosensors, and previously holding stock in Medtronic. **Dr. Escaned** reports receiving consulting fees and lecture fees from Abbott, Philips, Boston Scientific, and Medtronic, and lecture fees from Abiomed, Terumo, and Biosensors. **Dr. Krucoff** reports consulting fees or honoraria and research grants from Abbott Vascular, Biosensors, Boston Scientific, Celonova, Medtronic, OrbusNeich. **Dr. Kunadian** has received personal fees/honoraria from Bayer, Astra Zeneca, Abbott, Amgen, Daichii Sankyo. **Dr. Mehta** reports receiving grant support from and serving on an executive committee and as site investigator for AstraZeneca. **Dr. Moliterno** reports grants from AstraZeneca, during the conduct of the study. **Dr. Ohman** has received consulting fees from 3D Communications, ACI Clinical, Biotie, Cara Therapeutics, Cardinal Health, Faculty Connection, Imbria, Impulse Medical, Janssen Pharmaceuticals, Medscape, Milestone Pharmaceuticals, and XyloCor, grant support and consulting fees from Abiomed, and grant support from Chiesi and Portola. **Dr. Gibson** reports receiving grant support and consulting fees from Angel Medical, Bayer, CSL Behring, Janssen Pharmaceuticals, Johnson & Johnson, and Portola Pharmaceuticals, 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 Corporation, Boston Scientific, Impact Bio, MedImmume, Medtelligence, MicroPort, PERT Consortium, and GE Healthcare, holding equity in nference, serving as chief executive officer of Baim Institute, and receiving grant support, paid to Baim Institute, from Bristol-Myers Squibb; Dr. Huber reports receiving lecture fees from AstraZeneca and Bayer. **Dr. Pocock** has received has received research grants and consultancy honoraria from AstraZeneca. **Dr. Huber** has received lecture fees from AstraZeneca and Bayer. Dr. Mehran reports grants from Abbott Laboratories, AstraZeneca, Bayer, Beth Israel Deaconess, Bristol Myers Squibb, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, OrbusNeich; personal fees

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Table 1. Baseline clinical and procedural characteristics

Parameters	Women N=1698 (23.9%)	Men N=5421 (76.1%)	p-value
Age, years	65.5±9.6	63.4±10.3	<.001
Nonwhite race	572 (33.7%)	1624 (30.0%)	0.004
BMI, kg/m^2	28.8±6.4	28.5±5.3	0.116
Enrolling region			0.003
North America	725 (42.7%)	2247 (41.4%)	
Europe	545 (32.1%)	1964 (36.2%)	
Asia	428 (25.2%)	1210 (22.3%)	
Diabetes	618 (36.4%)	2002 (36.9%)	0.690
Diabetes treated with insulin	207 (33.5%)	502 (25.1%)	<.001
Chronic kidney disease	347 (21.2%)	764 (14.7%)	<.001
Anemia	379 (23.2%)	950 (18.3%)	<.001
Current smoker	288 (17.0%)	1260 (23.3%)	<.001
Hypercholesterolemia	1000 (58.9%)	3303 (60.9%)	0.134
Hypertension	1299 (76.5%)	3855 (71.1%)	<.001
Peripheral arterial disease	112 (6.6%)	377 (7.0%)	0.610
Previous MI	355 (20.9%)	1685 (31.1%)	<.001
Previous PCI	552 (32.5%)	2446 (45.1%)	<.001
Previous CABG	108 (6.4%)	602 (11.1%)	<.001
Previous major bleed	19 (1.1%)	44 (0.8%)	0.238
Indication for PCI			<.001
Stable CAD	537 (31.6%)	1966 (36.3%)	

Parameters	Women N=1698 (23.9%)	Men N=5421 (76.1%)	p-value
ACS	1160 (68.4%)	3454 (63.7%)	
Radial artery access	1196 (70.4%)	3990 (73.6%)	0.010
Multivessel CAD	941 (55.4%)	3525 (65.0%)	<.001
Target vessel			
Left Main	75 (4.4%)	278 (5.1%)	0.239
LAD	1031 (60.7%)	2972 (54.8%)	<.001
LCX	445 (26.2%)	1852 (34.2%)	<.001
RCA	593 (34.9%)	1907 (35.2%)	0.848
Number of vessels treated	1.3±0.5	1.3±0.5	0.044
Number of lesions treated	1.5±0.7	1.5±0.8	<.001
Lesion morphology†			
Moderate/severe calcification	250 (14.7%)	737 (13.6%)	0.241
Bifurcation	200 (11.8%)	666 (12.3%)	0.577
Total occlusion	92 (5.4%)	354 (6.5%)	0.099
Thrombotic	178 (10.5%)	571 (10.5%)	0.953
Total stent length, mm‡	37.6±22.1	40.6±24.9	<.001
Minimum stent diameter, mm	2.8±0.5	2.9±0.5	<.001

ACS: Acute coronary syndrome, BMI: body mass index, CABG: coronary artery bypass grafting, CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, MI: myocardial infarction, PCI: percutaneous coronary intervention, RCA: right coronary artery

†Lesion morphology assessed by operators

‡Stent length calculated by operators

Table 2. Outcomes according to randomized treatment assignment by sex

Bleeding outcomes*	Women (N=1698)				Men (N=5421)				Interaction p-value†
	Tica+ placebo (N= 846)	Tica+ Aspirin (N= 852)	Hazard ratio (95% CI)	p-value	Tica+ placebo (N=2709)	Tica+ Aspirin (N=2712)	Hazard ratio (95% CI)	p-value	
BARC 2, 3 or 5	42 (5.0%)	72 (8.6%)	0.57 (0.39 - 0.83)	0.004	99 (3.7%)	178 (6.6%)	0.55 (0.43 - 0.70)	<.001	0.888
BARC 3 or 5	14 (1.7%)	20 (2.4%)	0.70 (0.35 - 1.38)	0.297	20 (0.8%)	49 (1.8%)	0.41 (0.24 - 0.69)	<.001	0.227
TIMI major	3 (0.4%)	10 (1.2%)	0.30 (0.08 - 1.09)	0.067	14 (0.5%)	24 (0.9%)	0.59 (0.30 - 1.13)	0.112	0.361
GUSTO moderate or severe	9 (1.1%)	16 (1.9%)	0.56 (0.25 - 1.27)	0.165	17 (0.6%)	33 (1.2%)	0.52 (0.29 - 0.93)	0.027	0.877

Bleeding outcomes*	Women (N=1698)				Men (N=5421)				Interaction p-value†
	Tica+ placebo (N= 846)	Tica+ Aspirin (N= 852)	Hazard ratio (95% CI)	p-value	Tica+ placebo (N=2709)	Tica+ Aspirin (N=2712)	Hazard ratio (95% CI)	p-value	
ISTH major	15 (1.8%)	20 (2.4%)	0.75 (0.38 - 1.46)	0.389	24 (0.9%)	52 (1.9%)	0.46 (0.28 - 0.75)	0.002	0.258
Ischemic outcomes^	**Women (N=1676)**				**Men (N=5363)**				
	Tica+ placebo (N= 840)	Tica+ Aspirin (N= 836)	Hazard ratio (95% CI)	p-value	Tica+ placebo (N=2684)	Tica+ Aspirin (N=2679)	Hazard ratio (95% CI)	p-value	Interaction p-value†
Death, MI or stroke	29 (3.5%)	29 (3.5%)	0.99 (0.59 - 1.66)	0.981	106 (4.0%)	108 (4.1%)	0.98 (0.75 - 1.29)	0.906	0.974
Cardiovascular death, MI or ischemic stroke	27 (3.2%)	27 (3.3%)	0.99 (0.58 - 1.69)	0.979	99 (3.7%)	103 (3.9%)	0.96 (0.73 - 1.27)	0.793	0.924
All-cause death	3 (0.4%)	12 (1.4%)	0.25 (0.07 - 0.88)	0.031	31 (1.2%)	33 (1.2%)	0.94 (0.57 - 1.53)	0.800	0.054
Cardiovascular death	2 (0.2%)	9 (1.1%)	0.22 (0.05 - 1.01)	0.052	24 (0.9%)	28 (1.1%)	0.86 (0.50 - 1.48)	0.587	0.100
MI	21 (2.5%)	20 (2.4%)	1.04 (0.56 - 1.92)	0.901	74 (2.8%)	75 (2.8%)	0.99 (0.72 - 1.36)	0.945	0.888
Ischemic stroke	5 (0.6%)	2 (0.2%)	2.49 (0.48 - 12.8)	0.275	11 (0.4%)	6 (0.2%)	1.84 (0.68 - 4.97)	0.230	0.761
Stent thrombosis (definite/probable)	2 (0.2%)	4 (0.5%)	0.49 (0.09 - 2.69)	0.414	12 (0.5%)	15 (0.6%)	0.80 (0.38 - 1.71)	0.569	0.607

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; MI: myocardial infarction

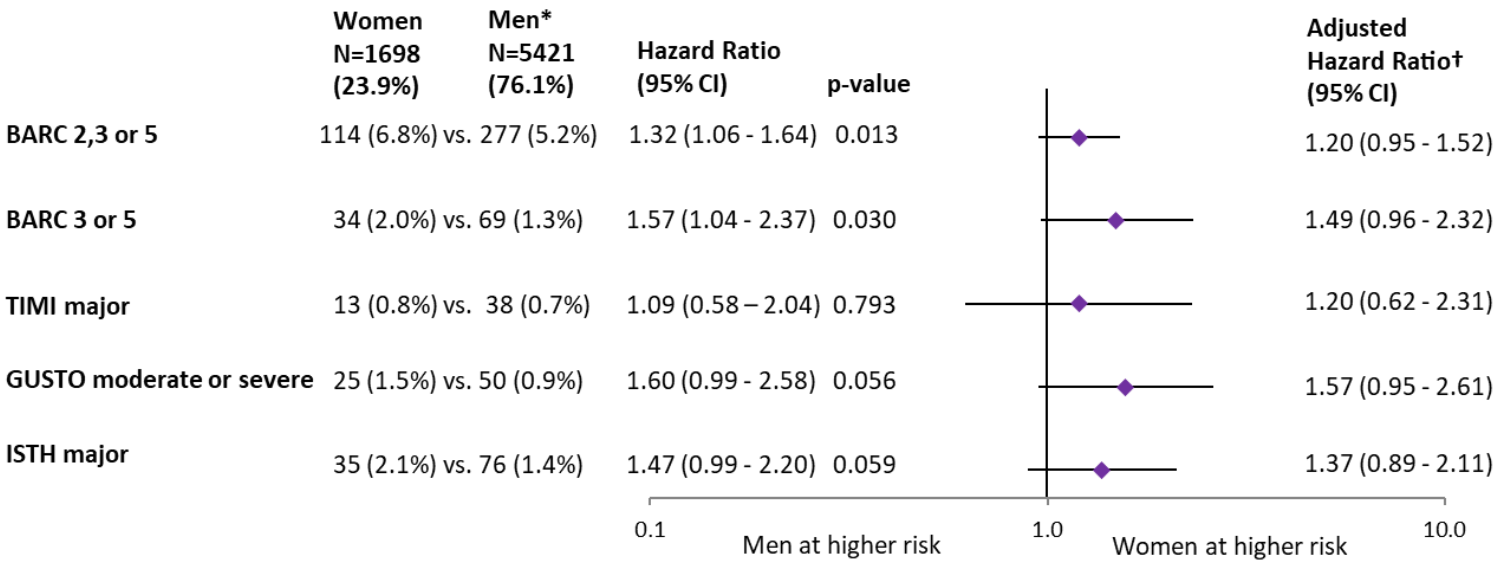
*Bleeding outcomes were performed in the intention-to-treat cohort

^Ischemic outcomes were performed in the per-protocol cohort

†Interaction test between randomized treatment assignment and sex

The percentages mentioned above represent Kaplan-Meier rates at 12 months after randomization.

Figure 1. Bleeding events^ by sex at 12 months after randomization



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

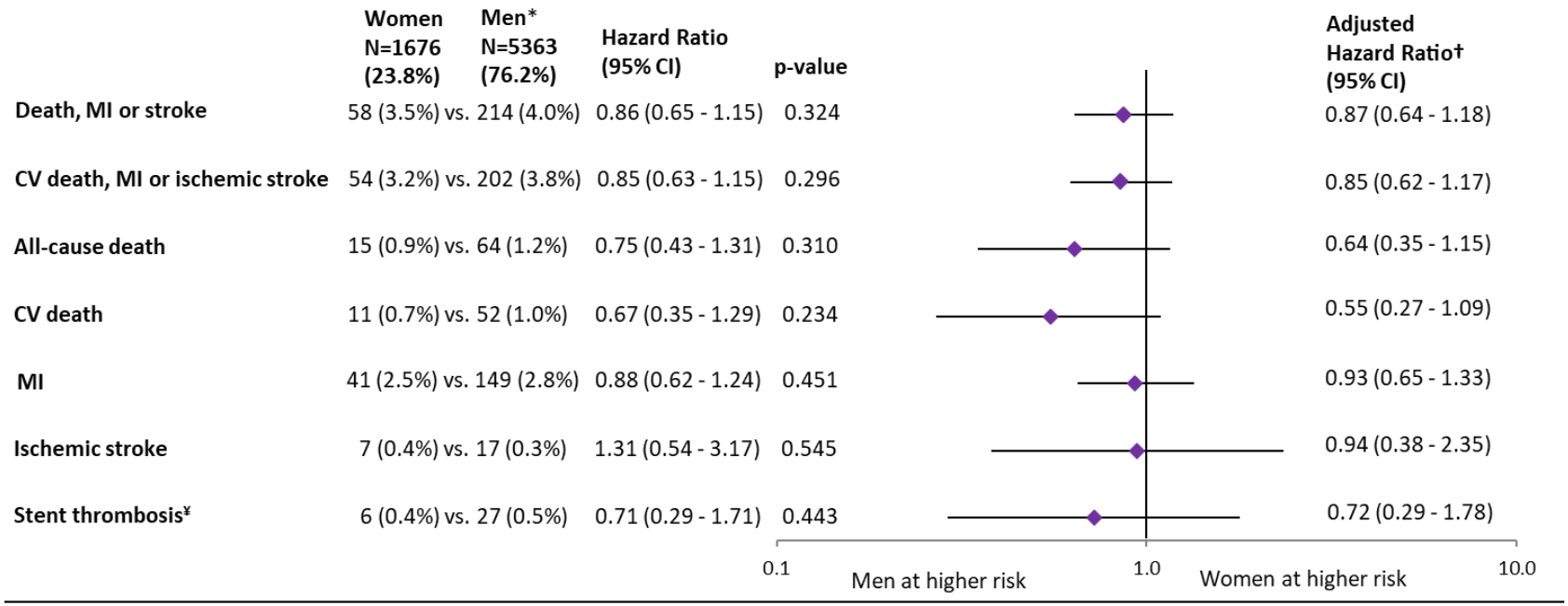
^Bleeding outcomes were performed in the intention-to-treat cohort

*reference

†Model adjusted for age (years), non-white race, region of enrollment, insulin-treated diabetes, chronic kidney disease, anemia, current smoker, hypertension, previous MI, previous coronary revascularization (previous PCI or previous CABG), multi-vessel CAD, indication for PCI, radial artery access, whether LAD is treated, whether LCX is treated, number of lesions treated, and minimum stent diameter (mm).

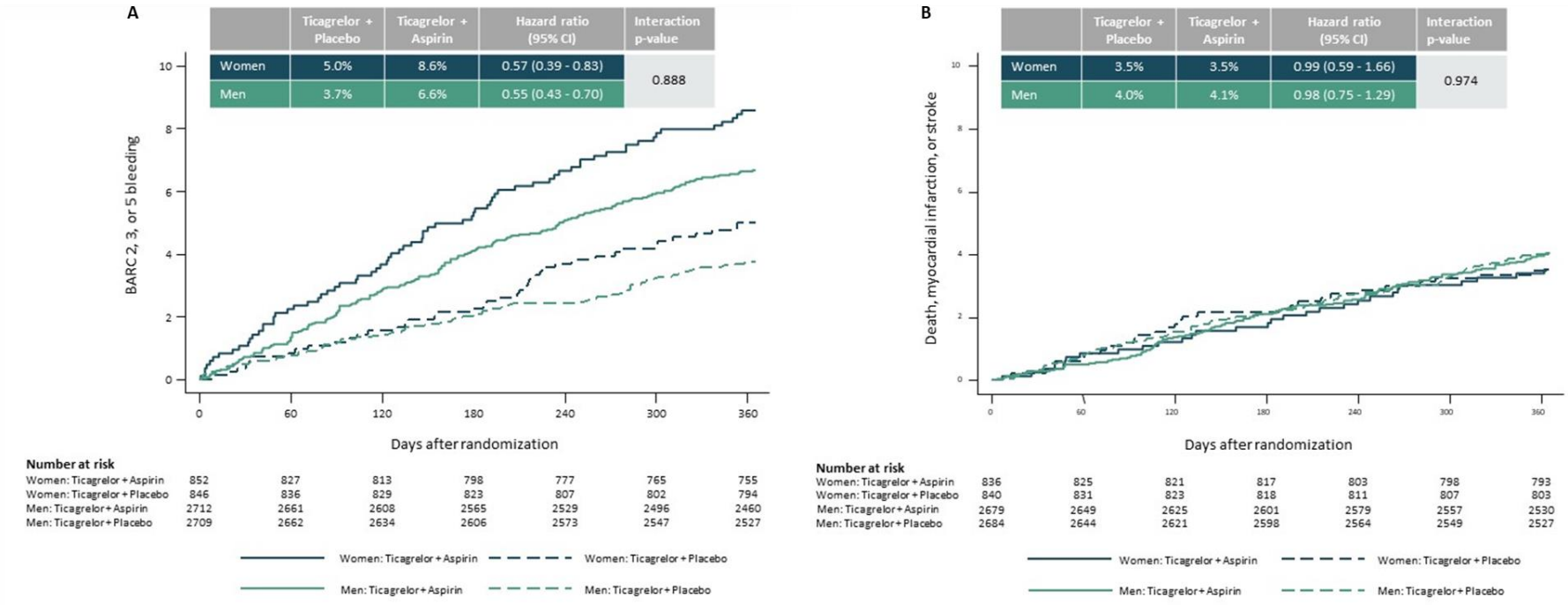
The percentages mentioned above represent Kaplan-Meier rates at 12 months after randomization.

Figure 2. Ischemic events^ by sex at 12 months after randomization



CI: confidence interval, CV: cardiovascular, MI: myocardial infarction
^Ischemic outcomes were performed in the per-protocol cohort
¥definite or probable
*reference
†Model adjusted for age (years), non-white race, region of enrollment, insulin-treated diabetes, chronic kidney disease, anemia, current smoker, hypertension, previous MI, previous coronary revascularization (previous PCI or previous CABG), multi-vessel CAD, indication for PCI, radial artery access, whether LAD is treated, whether LCX is treated, number of lesions treated, and minimum stent diameter (mm).
The percentages mentioned above represent Kaplan-Meier rates at 12 months after randomization.

Figure 3. Outcomes according to randomized treatment assignment by sex at 12 months



CI: confidence interval, BARC: Bleeding Academic Research Consortium

Kaplan-Meier estimates and hazard ratios for BARC 2, 3, or 5 bleeding (intention-to-treat cohort; A) and for death, myocardial infarction, or stroke (per-protocol cohort; B) at 12 months after randomization comparing ticagrelor plus placebo vs. ticagrelor plus aspirin in women and men.

Clinical Parameters	Women (N=1698)			Men (N=5421)		
	Tica+placebo N= 846 (49.8%)	Tica+Aspirin N= 852 (50.2%)	p-value	Tica+placebo N=2709 (50.0%)	Tica+Aspirin N=2712 (50.0%)	p-value
Age, years	65.4±9.6	65.7±9.5	0.606	63.4±10.2	63.3±10.4	0.608
Nonwhite race	289 (34.2%)	283 (33.2%)	0.680	821 (30.3%)	803 (29.6%)	0.575
BMI, kg/m^2	28.8±6.4	28.8±6.4	0.927	28.5±5.2	28.5±5.3	0.823
Enrolling region			0.075			0.435
North America	339 (40.1%)	386 (45.3%)		1145 (42.3%)	1102 (40.6%)	
Europe	289 (34.2%)	256 (30.0%)		962 (35.5%)	1002 (36.9%)	
Asia	218 (25.8%)	210 (24.6%)		602 (22.2%)	608 (22.4%)	
Diabetes	308 (36.4%)	310 (36.4%)	0.993	1011 (37.3%)	991 (36.5%)	0.552
Diabetes treated with insulin	83 (26.9%)	124 (40.0%)	<.001	252 (24.9%)	250 (25.2%)	0.876
Chronic kidney disease	154 (18.9%)	193 (23.5%)	0.021	400 (15.4%)	364 (14.0%)	0.141
Anemia	190 (23.5%)	189 (22.9%)	0.793	485 (18.7%)	465 (17.9%)	0.461
Current smoker	136 (16.1%)	152 (17.9%)	0.322	590 (21.8%)	670 (24.7%)	0.011
Hypercholesterolemia	477 (56.4%)	523 (61.4%)	0.036	1680 (62.0%)	1623 (59.8%)	0.102
Hypertension	641 (75.8%)	658 (77.2%)	0.478	1939 (71.6%)	1916 (70.7%)	0.464
Peripheral arterial disease	50 (5.9%)	62 (7.3%)	0.257	195 (7.2%)	182 (6.7%)	0.481
Previous MI	181 (21.4%)	174 (20.4%)	0.622	839 (31.0%)	846 (31.2%)	0.859
Previous PCI	258 (30.5%)	294 (34.5%)	0.078	1244 (45.9%)	1202 (44.3%)	0.237
Previous CABG	53 (6.3%)	55 (6.5%)	0.877	309 (11.4%)	293 (10.8%)	0.480

Clinical Parameters	Women (N=1698)			Men (N=5421)		
	Tica+placebo N= 846 (49.8%)	**Tica+Aspirin N= 852 (50.2%)**	**p-value**	**Tica+placebo N=2709 (50.0%)**	**Tica+Aspirin N=2712 (50.0%)**	**p-value**
Previous major bleed	8 (0.9%)	11 (1.3%)	0.499	23 (0.8%)	21 (0.8%)	0.759
Indication for PCI			0.858			0.064
Stable CAD	266 (31.4%)	271 (31.8%)		1015 (37.5%)	951 (35.1%)	
ACS	580 (68.6%)	580 (68.2%)		1693 (62.5%)	1761 (64.9%)	

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

Procedural characteristics	Women (N=1698)			Men (N=5421)		
	Tica+placebo N= 846 (49.8%)	Tica+Aspirin N= 852 (50.2%)	p-value	Tica+placebo N=2709 (50.0%)	Tica+Aspirin N=2712 (50.0%)	p-value
Radial artery access	618 (73.0%)	578 (67.8%)	0.019	1982 (73.2%)	2008 (74.0%)	0.463
Multivessel CAD	458 (54.1%)	483 (56.7%)	0.290	1814 (67.0%)	1711 (63.1%)	0.003
Target vessel						
Left Main	35 (4.1%)	40 (4.7%)	0.576	131 (4.8%)	147 (5.4%)	0.329
LAD	514 (60.8%)	517 (60.7%)	0.975	1479 (54.6%)	1493 (55.1%)	0.736
LCX	204 (24.1%)	241 (28.3%)	0.051	947 (35.0%)	905 (33.4%)	0.218
RCA	294 (34.8%)	299 (35.1%)	0.882	949 (35.0%)	958 (35.3%)	0.821
Number of vessels treated	1.2±0.5	1.3±0.5	0.046	1.3±0.5	1.3±0.5	0.900
Number of lesions treated	1.4±0.7	1.5±0.7	0.069	1.6±0.8	1.5±0.8	0.181
Lesion morphology[†]						
Moderate/severe calcification	139 (16.4%)	111 (13.0%)	0.048	359 (13.3%)	378 (13.9%)	0.461
Bifurcation	105 (12.4%)	95 (11.2%)	0.420	329 (12.1%)	337 (12.4%)	0.752
Total occlusion	42 (5.0%)	50 (5.9%)	0.411	180 (6.6%)	174 (6.4%)	0.733
Thrombotic	97 (11.5%)	81 (9.5%)	0.188	272 (10.0%)	299 (11.0%)	0.238
Total stent length, mm[‡]	38.1±22.1	37.1±22.0	0.388	40.7±24.8	40.4±24.9	0.652
Minimum stent diameter, mm	2.8±0.5	2.8±0.5	0.794	2.9±0.5	2.9±0.5	0.213

CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, Tica: ticagrelor

[†]Lesion morphology assessed by operators

[‡]Stent length calculated by operators