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Efficacy and Safety of Ticagrelor Versus Prasugrel in Women and Men with Acute Coronary Syndrome: A Pre-specified, Sex-Specific Analysis of the ISAR-REACT 5 Trial

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Aim: Sex-specific analyses of direct head-to-head comparisons between newer $P2Y_{12}$ inhibitors are limited. This study was conducted to assess the efficacy and safety of ticagrelor versus prasugrel in women and men with acute coronary syndromes (ACS) planned for an invasive strategy.

Methods: This pre-specified analysis of the ISAR-REACT 5 trial included 956 women and 3,062 men with ACS randomly assigned to either ticagrelor or prasugrel. The primary endpoint was the 12-month incidence of death, myocardial infarction, or stroke; the safety endpoint was the 12-month incidence of bleeding (type 3–5 according to the Bleeding Academic Research Consortium [BARC]).

Results: The primary endpoint occurred in 42 women (8.9%) in the ticagrelor group and 39 women (8.3%) in the prasugrel group (hazard ratio [HR] = 1.10, 95% confidence interval [CI] 0.71–1.70, $P = 0.657$) and in 142 men (9.4%) in the ticagrelor group and 98 men (6.5%) in the prasugrel group (HR = 1.47 [1.13–1.90], $P = 0.004$; P for interaction [P_{int}] = 0.275). BARC type 3–5 bleeding occurred in 36 women (9.7%) in the ticagrelor group and 34 women (9.7%) in the prasugrel group (HR = 1.04 [0.65–1.67], $P = 0.856$) and in 59 men in the ticagrelor group (4.4%) and 46 men (3.6%) in the prasugrel group (HR = 1.24 [0.85–1.83], $P = 0.266$; $P_{int} = 0.571$).

Conclusions: Although there was no significant interaction between sex and treatment effect of study drugs, the superior efficacy of prasugrel was more evident among men. No difference in bleeding between the two study groups was seen for both women and men.

(ClinicalTrials.gov, NCT01944800)

Key words: Acute coronary syndrome, Percutaneous coronary intervention, Prasugrel, Sex, Ticagrelor

Introduction

According to the American Heart Association, approximately 41% of patients discharged with the diagnosis of an acute coronary syndrome (ACS) are female[1)]. Women presenting with an ACS are older

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and have a worse cardiovascular risk profile than men, which predisposes them to both, increased thrombotic and bleeding events following an invasive therapy[2, 3].

Previous studies have reported gender-specific differences in platelet biology[4] and benefits of antiplatelet therapy[5], including a higher platelet reactivity[4], more frequent hyporesponsiveness to clopidogrel[6], and reduced anti-ischemic protection by aspirin[7] in women, which may suggest a greater benefit of more potent platelet inhibition. On the other hand, female gender is a strong and independent predictor for bleeding[8]. Exposure to ticagrelor[9] and prasugrel (most likely related to effects of body weight and age)[10] seems to be higher in female patients. In both pivotal randomized trials of the potent $P2Y_{12}$ inhibitors (prasugrel and ticagrelor), the treatment effect against clopidogrel was not modified by gender[11, 12]. Recent meta-analyses demonstrated a comparable[13] or a slightly lower[14] efficacy of newer $P2Y_{12}$ inhibitors in women. However, women are less likely to be treated with newer $P2Y_{12}$ inhibitors than men, particularly with prasugrel[15]. The most likely reason for this undertreatment is the concern of a higher risk of bleeding in women[2]. Furthermore, women with ACS are less likely than men to receive guideline-recommended therapies[16], and they are underrepresented in clinical trials of coronary artery disease[17] further accentuating uncertainty about the optimal peri-procedural and maintenance antiplatelet therapy in women presenting with an ACS.

The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial showed that prasugrel compared with ticagrelor reduces the risk for ischemic events (the composite of death, myocardial infarction, or stroke at 1 year) without increasing the risk for bleeding[18]. In this trial, a sex-based analysis of ticagrelor versus prasugrel was pre-specified. Against this background, we undertook this study to assess whether in ACS patients planned to undergo an invasive strategy the efficacy and safety of ticagrelor versus prasugrel differ according to sex.

Methods

Patient Population

This pre-specified sex-based analysis included 956 women and 3,062 men enrolled in the randomized ISAR-REACT 5 trial. The methodology[19] and main results[18] have recently been published. The trial performed a randomized head-to-head comparison of the efficacy and safety of two potent $P2Y_{12}$ inhibitors, ticagrelor and prasugrel, in patients presenting with an ACS–ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina–planned to undergo an invasive strategy. Detailed inclusion and exclusion criteria are included in the primary publication[18]. Patients were randomly assigned to receive ticagrelor (a loading dose of 180 mg as soon as possible after randomization) or prasugrel (a loading dose of 60 mg after coronary anatomy was known [i.e., no pretreatment before diagnostic coronary angiography] but before PCI [i.e., before the guidewire crossed the lesion]). In patients presenting with a STEMI, ticagrelor and prasugrel were given as soon as possible after randomization. The maintenance dose was 90 mg twice daily for ticagrelor and 10 mg once daily for prasugrel. In patients aged 75 years or older or those with a body weight of less than 60 kg, the maintenance dose of prasugrel was reduced to 5 mg daily. The recommended maintenance dose of aspirin was 75–150 mg daily. The study protocol was approved by the local ethics committee of each participating center and written informed consent was obtained from all patients.

Study Endpoints, Follow-Up, and Monitoring

The primary endpoint was a composite of all-cause death, myocardial infarction, or stroke up to 12 months after the randomization. Secondary endpoints were the incidence of bleeding defined according to criteria of the Bleeding Academic Research Consortium (BARC)[20], the individual components of the primary endpoint, and definite or probable stent thrombosis up to 12 months after randomization. Detailed endpoint definitions are reported in the primary publication[18].

Follow-up was scheduled at 1 month (±10 days), 6 months (±1 month), and 12 months (±1 month) after randomization. Information at follow-up was obtained by telephone interview, hospital or outpatient visit, or a dedicated follow-up letter. In the case of occurrence of endpoint-related adverse events, source data were solicited. All serious adverse events and all endpoint events were monitored on-site. In addition, 100% of source data were checked in at least 10% of the patients in all participating centers. All primary and secondary endpoints were adjudicated and classified based on source data by two members of the event adjudication committee who were unaware of the treatment group assignments.

Statistical Analysis

A sex-based analysis of the primary endpoint was pre-specified. Continuous data are presented as mean ± standard deviation and compared using

Student's *t*-test. Discrete variables are presented as counts and proportions (%) and compared using the chi-squared test. The cumulative incidence of the primary efficacy endpoint according to the study drug (ticagrelor or prasugrel) was computed in women and men using the Kaplan–Meier method. For all other endpoints except all-cause death, the cumulative incidence functions were computed to account for competing risk. The comparison of patients assigned to ticagrelor or prasugrel was performed using the Cox proportional hazards model after the participating center and stratification according to clinical presentation (ACS with or without ST-segment elevation) were entered into the Cox proportional hazards model as covariates along with the study treatment group. To estimate the interaction between the treatment arm and sex for the study endpoints and between the treatment arm and pre-specified subgroups in female or male populations, an interaction term was entered into the Cox proportional hazards models. Risk estimates are presented as hazard ratios [HR] with 95% confidence intervals [CI]. The efficacy endpoints were analyzed according to the intention-to-treat principle (i.e., including all patients as initially assigned, irrespective of the actual treatment received). The safety endpoint (BARC type 3 to 5 bleeding) in patient groups according to sex (i.e., men versus women) was analyzed in the intention-to-treat population (i.e., including all patients according to the randomly assigned study group, irrespective of the actual treatment received). The safety endpoint (BARC type 3 to 5 bleeding) according to study drug (ticagrelor versus prasugrel) was analyzed in a modified intention-to-treat population (i.e., including all patients with at least one application of the study drug with bleeding assessed for up to 7 days after discontinuation of the study drug). The statistical analysis was performed using the R3.6.0 Statistical Package (The R foundation for Statistical Computing, Vienna, Austria). A two-sided $P<0.05$ was considered to indicate statistical significance.

Results

This study included 956 women (23.8%) and 3,062 men (76.2%) recruited in the ISAR-REACT 5 trial. Out of 956 women, 478 were assigned to receive ticagrelor and 478 were assigned to receive prasugrel. Among the 3,062 men, 1,534 were assigned to receive ticagrelor and 1,528 were assigned to receive prasugrel. Baseline characteristics are shown in **Table 1**. In the group of women, arterial hypertension was more frequent and systolic blood pressure values were higher in patients assigned to receive ticagrelor than in patients assigned to receive prasugrel. Furthermore, the number of women diagnosed with diabetes mellitus was numerically higher in the ticagrelor arm than in the prasugrel arm. In the group of men, baseline characteristics did not significantly differ in the ticagrelor and prasugrel-assigned groups with the exception of the heart rate that was slightly (but significantly) lower in the prasugrel group.

Diagnostic coronary angiography was performed in 954 women and 3,050 men (99.8% vs. 99.6%; $P=0.403$). Main angiographic data are shown in **Supplementary Table 1**. More women than men did not have obstructive coronary artery disease (17.2% versus 5.6%, $P<0.001$). Main procedural data are shown in **Supplementary Table 2**. The number of women with complex lesions was numerically higher in the prasugrel arm; however, none of the angiographic or procedural data significantly differed according to treatment assignment in women or men.

Final diagnosis and drug therapy at discharge are shown in **Supplementary Table 3**. Data did not significantly differ according to ticagrelor or prasugrel in women or men except for the study drug *per se* and clopidogrel prescription in men (less frequent in the ticagrelor than in the prasugrel group). Compared to men, women were discharged less frequently with their respective study medication (83.7% versus 71.8%, $P<0.001$).

Clinical Outcome

One-year clinical outcome is shown in **Table 2**. Follow-up at 1 year was complete in 3,928 patients (97.8%) and incomplete in 90 patients (2.2%).

Overall, the incidence of the primary endpoint (the composite of all-cause death, myocardial infarction, or stroke at 1 year after randomization) did not significantly differ in women versus men (8.6% vs. 7.9%; hazard ratio [HR] = 1.08, 95% confidence interval [CI] 0.84 to 1.39, $P=0.561$). In the group of women, the primary endpoint (counts with Kaplan–Meier estimates in parentheses) occurred in 42 patients (8.9%) in the ticagrelor group and in 39 (8.3%) in the prasugrel group (HR = 1.10 [0.71–1.70], $P=0.657$; **Fig. 1**). There was no significant difference in the 1-year incidence of other endpoints including all-cause death, cardiovascular death, myocardial infarction, stroke, or stent thrombosis (definite or probable) among women assigned to ticagrelor or prasugrel **(Table 2)**. In the group of men, the primary endpoint occurred in 142 patients (9.4%) in the ticagrelor group and 98 (6.5%) in the prasugrel group (HR = 1.47 [1.13–1.90], $P=0.004$; **Fig. 1**). In men, prasugrel compared with ticagrelor was associated with

Table 1. Baseline characteristics

Characteristic	Women ($n=956$)			Men ($n=3,062$)		
	Ticagrelor ($n=478$)	Prasugrel ($n=478$)	*P* value	Ticagrelor ($n=1,534$)	Prasugrel ($n=1,528$)	*P* value
Age–years	69.0 ± 11.2	68.1 ± 12.2	0.269	63.1 ± 12.0	63.5 ± 11.8	0.310
Diabetes–no. (%)	121 (25.3)	97 (20.3)	0.076	342 (22.3)	332/1,527 (21.7)	0.738
Insulin-treated–no. (%)	42 (8.79)	35 (7.32)	0.476	101 (6.6)	102 (6.7)	0.977
Current smoker–no. (%)	129/474 (27.2)	134/477 (28.1)	0.818	553/1,528 (36.2)	533/1,522 (35.0)	0.524
Arterial hypertension–no. (%)	381/477 (79.9)	347 (72.6)	0.010	1,051/1,531 (68.6)	1,037/1,525 (68.0)	0.729
Hypercholesterolemia–no (%)	290/476 (60.9)	269 (56.3)	0.164	888/1,531 (58.0)	894/1,525 (58.6)	0.755
Prior myocardial infarction–no. (%)	58/477 (12.2)	52 (10.9)	0.604	253/1,533 (16.5)	268/1,527 (17.6)	0.470
Prior PCI–no. (%)	87 (18.2)	76/477 (15.9)	0.398	366 (23.9)	387/1,527 (25.3)	0.367
Prior CABG–no. (%)	16 (3.35)	22/477 (4.61)	0.404	99/1,533 (6.5)	108 (7.1)	0.548
Cardiogenic shock–no. (%)	6 (1.26)	8 (1.67)	0.788	25 (1.6)	26 (1.7)	0.989
Systolic blood pressure–mmHg	148 ± 25.1	144 ± 26.0	0.009	142 ± 24.8	143 ± 24.0	0.626
Diastolic blood pressure–mmHg	80.9 ± 14.1	80.5 ± 15.0	0.669	82.4 ± 14.7	82.2 ± 13.4	0.783
Heart rate–beats/min	78.3 ± 16.1	78.1 ± 16.8	0.869	76.6 ± 15.9	75.4 ± 15.2	0.036
Body mass index–kg/m²	27.2 ± 5.48	27.2 ± 5.09	0.911	28.0 ± 4.3	28.0 ± 4.2	0.878
Weight < 60 kg–no. (%)	85/476 (17.9)	74/473 (15.6)	0.409	23/1,527 (1.5)	20/1,515 (1.3)	0.779
Creatinine–µmol/L	77.2 ± 27.1	75.5 ± 25.2	0.310	91.0 ± 26.6	92.1 ± 30.9	0.255
Diagnosis at admission			0.651			0.786
Unstable angina–no. (%)	67 (14.0)	73 (15.3)		182 (11.9)	188 (12.3)	
NSTEMI–no. (%)	243 (50.8)	229 (47.9)		687 (44.8)	696 (45.5)	
STEMI–no. (%)	168 (35.1)	176 (36.8)		665 (43.3)	644 (42.2)	
Coronary angiography–no. (%)	476 (99.6)	478 (100)	0.499	1,527 (99.5)	1,523 (99.7)	0.778
Treatment strategy–no. (%)			0.158			0.119
PCI	353/477 (74.0)	360 (75.3)		1,323/1,531 (86.4)	1,341/1,527 (87.8)	
CABG	3/477 (0.63)	9 (1.88)		44/1,531 (2.9)	27/1,527 (1.8)	
Conservative	121/477 (25.4)	109 (22.8)		164/1,531 (10.7)	159/1,527 (10.4)	

Data are mean ± standard deviation or number of patients (%). CABG, coronary artery bypass grafting; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
Missing continuous data: Women: diastolic blood pressure: 3 patients (2 in the ticagrelor group, 1 in the prasugrel group); body mass index: 7 patients (2 in the ticagrelor group, 5 in the prasugrel group). Men: systolic blood pressure: 3 patients (1 patient in the ticagrelor group, 2 patients in the prasugrel group); diastolic blood pressure: 13 patients (5 patients in the ticagrelor group, 8 patients in the prasugrel group); heart rate: 2 patients (1 in each group); body mass index: 24 patients (10 patients in the ticagrelor group, 14 patients in the prasugrel group); creatinine: 6 patients (5 patients in the ticagrelor group, 1 patient in the prasugrel group). The remaining continuous data were complete.

numerically fewer deaths (3.2% vs. 4.4%; $P=0.080$) and significantly fewer myocardial infarctions (2.5% vs. 4.0%, $P=0.008$). Overall, there was no significant treatment arm-by-sex interaction regarding the primary endpoint (P for interaction [P_{int}] = 0.275). In addition, there was no treatment arm-by-sex interaction with respect to occurrence of death ($P_{int}=0.246$), myocardial infarction ($P_{int}=0.988$), stroke ($P_{int}=0.354$), definite stent thrombosis ($P_{int}=0.996$), or the composite endpoint of definite or probable stent thrombosis ($P_{int}=0.253$). We also assessed the incidence of the primary endpoint in patients that were discharged on study drug (1,602 patients in the ticagrelor group and 1,596 in the prasugrel group) from discharge to the time of discontinuation or the end of follow-up ("on treatment" analysis). In this subgroup, the treatment effect of ticagrelor versus prasugrel was HR 1.53, 95% CI 0.73–3.22 in women and HR 1.30, 95% CI 0.93–1.84 in men.

The analysis of the primary endpoint was performed in pre-specified subgroups of women and men according to age (≥ 75 years vs. <75 years), smoking status (active vs. not an active smoker), body weight (<60 kg vs. ≥ 60 kg), diabetes (yes vs. no), renal function (serum creatinine ≥ sex-specific median vs. < sex-specific median), cardiogenic shock (yes vs. no), clinical presentation (STEMI, NSTEMI, or unstable angina), and treatment strategy (PCI, coronary artery bypass surgery, or conservative therapy). In the group of women, there was no significant treatment arm-by-subgroup interaction

Table 2. Clinical Outcomes*

Outcome	Women (*n*=956)				Men (*n*=3,062)				P_{int}
	Ticagrelor (*n*=478)	Prasugrel (*n*=478)	HR [95% CI]	*P* value	Ticagrelor (*n*=1,534)	Prasugrel (*n*=1,528)	HR [95% CI]	*P* value	
Primary endpoint–death, myocardial infarction or stroke	42 (8.9)	39 (8.3)	1.10 [0.71-1.70]	0.657	142 (9.4)	98 (6.5)	1.47 [1.13-1.90]	0.004	0.275
Death	23 (4.9)	25 (5.3)	0.93 [0.53-1.64]	0.809	67 (4.4)	48 (3.2)	1.39 [0.96-2.02]	0.080	
Cardiovascular	20	19			43	40			
Non-cardiovascular	3	6			24	8			
Myocardial Infarction	19 (5.1)	12 (3.2)	1.62 [0.79-3.34]	0.191	77 (4.0)	48 (2.5)	1.63 [1.14-2.34]	0.008	
Type 1	10	7			42	28			
Type 2	1	1			3	2			
Type 4a	4	4			15	7			
Type 4b	3	0			17	11			
Type 5	1	0			0	0			
STEMI	5	2			26	12			
Stroke	9 (1.9)	5 (1.0)	1.76 [0.59-5.28]	0.308	13 (0.8)	14 (0.9)	0.94 [0.44-2.00]	0.877	
Ischemic	6	4			10	13			
Hemorrhagic	3	1			3	1			
Definite or probable stent thrombosis	4 (0.8)	1 (0.2)	4.27 [0.48-8.29]	0.194	22 (1.4)	19 (1.2)	1.13 [0.61-2.09]	0.692	
Definite stent thrombosis	4 (0.8)	0 (0.0)	-	-	18 (1.2)	12 (0.8)	1.46 [0.70-3.03]	0.310	
BARC type 3-5 bleeding	36/471 (9.7)	34/387 (9.7)	1.04 [0.65-1.67]	0.856	59/1,518 (4.4)	46/1,386 (3.6)	1.24 [0.85-1.83]	0.266	0.571
3a	15	19			32	22			
3b	14	13			18	18			
3c	2	1			2	1			
4	3	0			5	2			
5a	0	0			1	0			
5b	2	1			1	3			

Data are numbers of events with Kaplan-Meier estimates (%) for the primary endpoint or death or cumulative incidence (%) after accounting for competing risk for the remaining endpoints. BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; P_{int}, P for interaction; STEMI, ST-segment elevation myocardial infarction.

*Kaplan-Meier estimates or cumulative incidence of the events and risk estimates are obtained from the Cox proportional hazards model after adjustment for the participating center and stratification according to the clinical presentation (acute coronary syndrome with or without ST-segment elevation). BARC type 3 to 5 bleeding was analyzed according to the modified intention-to-treat principle.

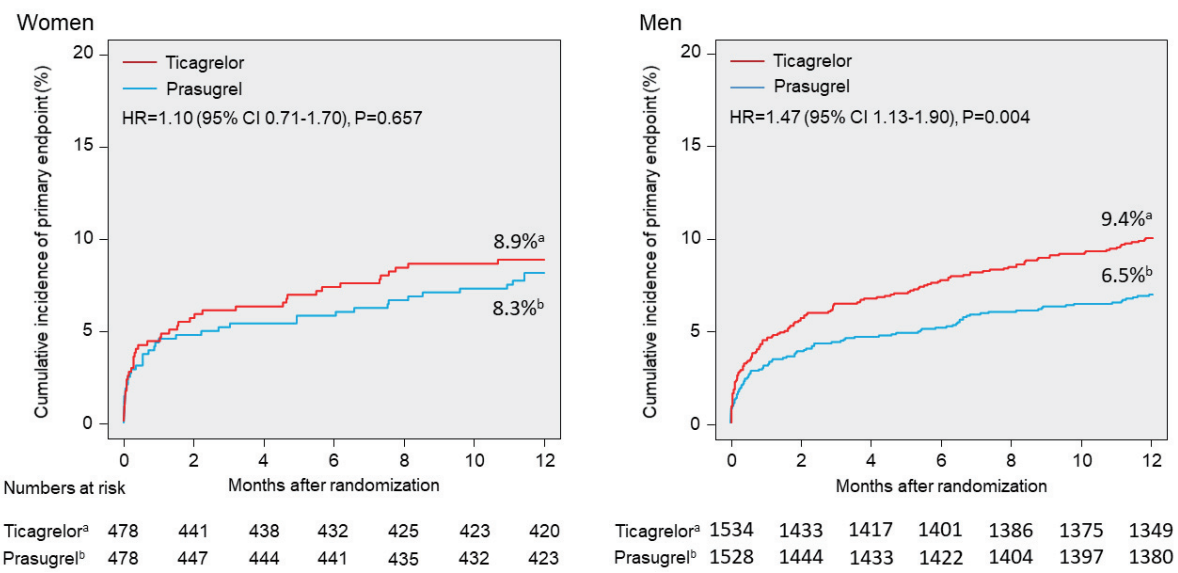

Fig. 1. Kaplan–Meier curves of 1-year incidence of the primary endpoint, a composite of death, myocardial infarction, or stroke in women and men

HR, hazard ratio; CI, confidence interval

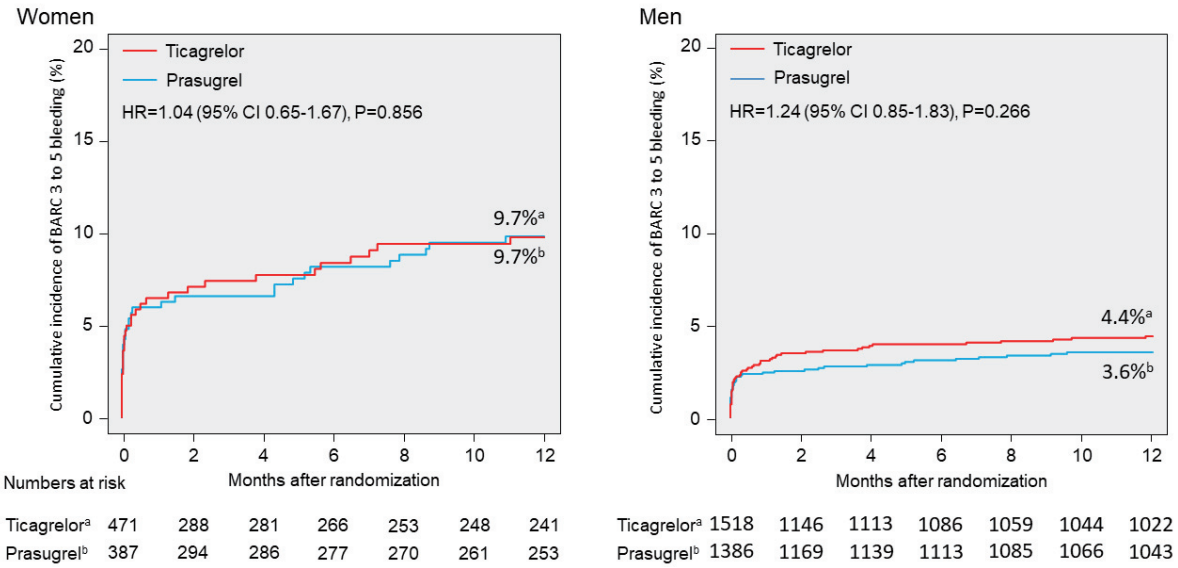

Fig. 2. Cumulative incidence of the secondary safety endpoint (1-year incidence of Bleeding Academic Research Consortium type 3 to 5 bleeding) in women and men

BARC, Bleeding Academic Research Consortium; HR, hazard ratio; CI, confidence interval

regarding the primary endpoint for any of the pre-specified subgroups **(Supplementary Fig. 1)**. In the group of men, there was a significant treatment arm-by-diabetes interaction showing better results of prasugrel than ticagrelor in men without diabetes. There was no significant treatment arm-by-subgroup interaction regarding the primary endpoint for the remaining subgroups **(Supplementary Fig. 2)**.

The 1-year incidences of bleeding events (secondary safety endpoint) are shown in **Table 2**. Overall, the incidence of BARC type 3 to 5 bleeding was significantly higher in women than in men (9.7% vs. 4.0%; HR=2.55 [1.88–3.45], $P<0.001$). In the group of women, BARC type 3 to 5 bleeding occurred in 36 patients in the ticagrelor group and 34 in the prasugrel group (1-year cumulative incidence, 9.7% vs. 9.7%, respectively; HR=1.04 [0.65–1.67], $P=0.856$). In the group of men, BARC type 3 to 5 bleeding occurred in 59 patients in the ticagrelor group and 46 in the prasugrel group (1-year cumulative incidence, 4.4% vs. 3.6%, respectively; HR=1.24 [0.85–1.83], $P=0.266$; **Fig. 2**). There was no significant treatment arm-by-sex interaction regarding the bleeding risk ($P_{int}=0.571$). The analysis of the safety endpoint in pre-specified subgroups of women and men is shown in **Supplementary Figs. 3 and 4**. There appears to be a treatment arm-by-smoking status interaction suggesting a lower risk of bleeding in smoking women assigned to ticagrelor ($P_{int}=0.041$) but not in smoking men ($P_{int}=0.681$).

The clinical outcomes were also analyzed in women versus men in the subgroups with age (≥ 75 years or <75 years) and weight (<60 kg or ≥ 60 kg) combinations and the subgroup with obstructive coronary artery disease. The results are shown in **Supplementary Table 4**. As seen, the primary endpoint did not significantly differ in women versus men in any of the subgroups. BARC type 3 to 5 bleeding was higher in women than in men in the subgroup with an age <75 years and weight ≥ 60 kg, the subgroup with an age <75 years irrespective of weight, and the subgroup with obstructive coronary artery disease. Clinical outcomes according to the study drug (ticagrelor versus prasugrel) in subgroups according to age and weight combinations and the subgroup with obstructive coronary artery disease are shown in **Supplementary Table 5**. As seen, there was no significant difference in any outcomes between ticagrelor and prasugrel in women. In the subgroups of men with an age <75 years and weight ≥ 60 kg and the subgroup with obstructive coronary artery disease, prasugrel was superior to ticagrelor in reducing the incidence of the primary endpoint. There was no significant difference in the occurrence of BARC type 3 to 5 bleeding in any subgroups in men.

Discussion

The main findings of this study are as follows: (I) In ACS patients planned for an invasive strategy, there was no significant interaction between the treatment effect of ticagrelor versus prasugrel and gender

regarding the primary composite endpoint of death, myocardial infarction, or stroke at 1 year. However, the superiority of prasugrel was more evident in men than in women. (II) Although the risk of major bleeding was higher in women than in men, it was not influenced by the type of study drug.

In the past, pharmacodynamic studies addressing sex-based differences in platelet inhibition reported conflicting results[4, 6, 21]. Randomized clinical trials that have compared prasugrel[11] or ticagrelor[12] with clopidogrel in ACS patients did not reveal a treatment assignment-by-sex interaction in terms of efficacy of either drug: The TRITON-TIMI 38 trial showed a 21% and 12% relative risk reduction for the occurrence of the primary endpoint (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) with prasugrel versus clopidogrel in men and women with ACS, respectively, albeit without a significant treatment assignment-by-sex interaction[11]. The PLATO trial did not show any sex-based difference of ticagrelor versus clopidogrel in patients with ACS in terms of the primary endpoint (cardiovascular death, myocardial infarction, or stroke), all-cause death, definite stent thrombosis, or PLATO-defined bleeding[12]. In the same vein, a recent meta-analysis of randomized trials of newer $P2Y_{12}$ inhibitors (prasugrel, ticagrelor, or cangrelor) showed no sex-related differences (or treatment assignment-by-sex interaction) regarding the occurrence of major adverse cardiovascular events (MACE) with these drugs versus clopidogrel or placebo[13]. In this meta-analysis, newer $P2Y_{12}$ inhibitors reduced the risk of major cardiovascular adverse events by 14% and stent thrombosis by 51% in women, which was comparable to the results obtained in men. Notably, $P2Y_{12}$ inhibitors increased the risk of major (non-coronary artery bypass-related) bleeding comparably in women and men[13]. Another recent meta-analysis suggested that newer $P2Y_{12}$ inhibitors might be slightly less efficacious in women than in men with ACS, although the absolute risk reduction was similar in both sexes[14]. These observations, however, should be cautiously interpreted in light of the differences across the trials and the lack of head-to-head comparisons between ticagrelor and prasugrel.

In this study, prasugrel was associated with a significant reduction of the composite endpoint of ischemic events (death, myocardial infarction, or stroke) and a significant reduction of the incidence of myocardial infarction only in men, commensurate with the results in the overall cohort of the ISAR-REACT 5 trial[18]. The following reasons may explain the finding why prasugrel did not show superiority over ticagrelor in the subgroup of women with ACS alone:

(I) The female subgroup comprises only 24% of the overall trial population. Smaller sample size inevitably results in lower precision and increase in the type II error rate. Therefore, in subgroup analyses, the group-specific p-values can be misleading particularly if the p-values for interaction are not significant[22].

(II) More female than male patients did not have significant coronary artery disease after angiography and were treated conservatively. Prior studies of ischemic heart disease have shown that microvascular dysfunction and other diagnoses are more common in women, while obstructive coronary artery disease is more common in men[23]. These differences in cardiovascular pathophysiology also impacted on the treatment strategy. The number of patients that were treated with PCI and discharged with the randomly assigned study medication was significantly lower in women than in men. The treatment effect of prasugrel was improved in women when the analysis was confined to patients that were discharged on study drug.

(III) There is some evidence to suggest that women compared to men may not achieve the same cardioprotective benefit from aspirin[24], clopidogrel[25], and prasugrel[11, 26]. In the CURE trial, addition of clopidogrel to aspirin was associated with a smaller (11% vs. 24%) reduction in the risk for MACE in women than in men with ACS, although there was no evidence of statistical heterogeneity among both genders[27]. A recent meta-analysis showed that prasugrel was beneficial in reducing MACE in men (a significant risk reduction of 16%) but not statistically significant in women (risk reduction of 6%) compared with clopidogrel, whereas ticagrelor significantly reduced the risk of MACE in both sexes[26]. Yet, the reasons for this potential sex-related difference of prasugrel (if it actually exists) remain unclear, and the results should be carefully interpreted in light of the limitations of these studies.

Congruent with recent studies of newer $P2Y_{12}$ inhibitors[28, 29], this study showed an increased risk of bleeding in women compared with men. However, there was no significant difference between ticagrelor and prasugrel in women or men and no treatment arm-by-sex interaction with respect to the risk of bleeding with these drugs in both sexes. A significant treatment arm-by-smoking status interaction showing reduced risk of bleeding with ticagrelor versus prasugrel in smoking women should be cautiously interpreted due to the possibility of being a play of chance or an effect of multiple testing, even though lower platelet reactivity in smokers compared to non-smokers under ticagrelor treatment has been

reported[30]. The use of reduced dose of prasugrel in older patients or those with low body weight–two categories of patients known to have an increased risk for bleeding–may have attenuated the increased risk of bleeding by prasugrel in this vulnerable subgroup of women and men[31]. Notably, this could have been particularly beneficial in women who are older and have more comorbidities at the time of presentation with an ACS.

This study has several limitations that should be considered. First, although the analysis according to sex was pre-specified, it carries the limitations of subgroup analyses in general. Thus, the current results ought to be considered as exploratory or hypothesis-generating. Second, randomization was not stratified according to sex and consequently hidden confounders cannot be entirely excluded. Third, although the subgroups were pre-specified, we did not adjust for multiple testing. Fourth, as emphasized above, the number of patients/events was small, particularly for women that may increase the risk of type II errors during the hypothesis testing.

In conclusion, in ACS patients planned for an invasive strategy, the superiority of prasugrel over ticagrelor was more evident in men than in women. However, there was no significant interaction between treatment effect of ticagrelor versus prasugrel and gender regarding the primary composite endpoint of death, myocardial infarction, or stroke at 1 year. No difference in bleeding between the two study groups was seen for both women and men.

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Supplementary Table 1. Angiographic Data*

Characteristic	Women			Men		
	Ticagrelor (*n* = 476)	Prasugrel (*n* = 478)	*P* value	Ticagrelor (*n* = 1,527)	Prasugrel (*n* = 1,523)	*P* value
Access site			0.524			0.839
Femoral artery	288 (60.5)	304 (63.6)		957 (62.7)	956 (62.8)	
Radial artery	183 (38.4)	171 (35.8)		565 (37.0)	560 (36.8)	
Other	5 (1.1)	3 (0.6)		5 (0.3)	7 (0.5)	
Number of diseased coronary arteries			0.904			0.746
No obstructive CAD	85 (17.9)	79 (16.5)		85 (5.6)	85 (5.5)	
One-vessel disease	147 (30.9)	147 (30.8)		454 (29.7)	435 (28.6)	
Two-vessel disease	112 (23.5)	121 (25.3)		409 (26.8)	434 (28.5)	
Three-vessel disease	132 (27.7)	131 (27.4)		579 (37.9)	569 (37.4)	
Left ventricular ejection fraction**	52.9 ± 11.4	52.7 ± 11.2	0.859	51.2 ± 11.3	51.8 ± 11.1	0.147

Data are shown as counts (proportion; %) or mean ± standard deviation. CAD, coronary artery disease.
*Angiographic data are not available for 2 women (both in the ticagrelor group) and 12 men (7 in the ticagrelor group and 5 in the prasugrel group).
**Left ventricular ejection fraction was not available in 37 women (21 in the ticagrelor group and 16 in the prasugrel group) and in 187 men (89 in the ticagrelor group and 98 in the prasugrel group).

Supplementary Table 2. Procedural Characteristics

Characteristic	Women			Men		
	Ticagrelor (*n* = 353)	Prasugrel (*n* = 360)	*P* value	Ticagrelor (*n* = 1,323)	Prasugrel (*n* = 1,341)	*P* value
Target vessel			0.194			0.918
Left main coronary artery	8 (2.27)	11 (3.06)		28 (2.1)	27 (2.0)	
LAD coronary artery	172 (48.7)	154 (42.8)		574 (43.4)	564 (42.1)	
Left circumflex coronary artery	72 (20.4)	67 (18.6)		274 (20.7)	278 (20.7)	
Right coronary artery	97 (27.5)	126 (35.0)		423 (32.0)	443 (33.0)	
Bypass graft	4 (1.13)	2 (0.56)		24 (1.8)	29 (2.2)	
Complex lesion (type B2/C)	199 (56.4)	229 (63.6)	0.058	780 (59.0)	779 (58.1)	0.679
More than 1 lesion treated	115 (32.6)	127 (35.3)	0.495	454 (34.3)	477 (35.6)	0.523
TIMI flow grade before the intervention			0.748			0.362
0	111 (31.4)	105 (29.2)		481 (36.4)	479 (35.7)	
1	26 (7.4)	34 (9.4)		101 (7.6)	121 (9.0)	
2	89 (25.2)	91 (25.3)		272 (20.6)	295 (22.0)	
3	127 (36.0)	130 (36.1)		469 (35.4)	446 (33.3)	
TIMI flow grade after the intervention			0.393			0.720
0	5 (1.4)	4 (1.1)		12 (0.9)	12 (0.9)	
1	2 (0.6)	0 (0.0)		7 (0.5)	7 (0.5)	
2	11 (3.1)	7 (1.9)		39 (3.0)	30 (2.3)	
3	335 (94.9)	349 (97.0)		1,275 (95.6)	1,292 (96.3)	
Type of intervention						
Drug-eluting stent	316 (89.5)	329 (91.4)	0.470	1,181 (89.3)	1,214 (90.5)	0.309
Bare-metal stent	0 (0.0)	1 (0.3)	>0.999	4 (0.3)	7 (0.5)	0.561
Bioresorbable vascular scaffold	19 (5.4)	22 (6.1)	0.797	80 (6.0)	74 (5.5)	0.616
Drug-eluting balloon	7 (2.0)	3 (0.8)	0.219	29 (2.2)	24 (1.8)	0.545
Plain balloon angioplasty	14 (4.0)	10 (2.8)	0.502	43 (3.3)	35 (2.6)	0.387
Maximal stent diameter (mm)	3.09 ± 0.48	3.12 ± 0.47	0.304	3.2 ± 0.5	3.2 ± 0.5	0.773
Total stented length (mm)	29.2 ± 14.7	29.6 ± 17.3	0.753	31.1 ± 16.5	30.5 ± 17.0	0.348
Successful PCI	343 (97.2)	351 (97.5)	0.965	1,297 (98.0)	1,311 (97.8)	0.723
Periprocedural antithrombotic medication						
Aspirin	312 (88.4)	318 (88.3)	>0.999	1,191 (90.5)	1,214 (90.5)	0.707
Unfractionated heparin	336 (95.2)	341 (94.7)	0.912	1,245 (94.1)	1,255 (93.6)	0.635
Low molecular weight heparin	15 (4.2)	16 (4.4)	>0.999	59 (4.5)	49 (3.7)	0.339
Bivalirudin	23 (6.5)	30 (8.3)	0.434	102 (7.7)	111 (8.3)	0.636
GPIIb/IIIa inhibitor	39 (11.0)	34 (9.4)	0.560	180 (13.6)	164 (12.2)	0.317

Data are shown as counts (proportions; %) or mean ± standard deviation.
GPIIb/IIIa, glycoprotein IIb/IIIa; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Supplementary Table 3. Diagnosis and Drug Therapy at Discharge*

Characteristic	Women			Men		
	Ticagrelor (*n*=466)	Prasugrel (*n*=466)	*P* value	Ticagrelor (*n*=1,509)	Prasugrel (*n*=1,512)	*P* value
Final diagnosis – no. (%)			0.353			0.987
Unstable angina	50 (12.6)	38 (9.64)		139 (9.7)	135 (9.5)	
NSTEMI	189 (47.7)	187 (47.5)		645 (45.0)	640 (44.1)	
STEMI	157 (39.6)	169 (42.9)		650 (45.3)	644 (45.4)	
Therapy at discharge – no. (%)						
Aspirin	423 (90.8)	420 (90.1)	0.824	1,443 (95.6)	1,458 (96.4)	0.300
Ticagrelor	334 (71.7)	5 (1.07)	<0.001	1,268 (84.0)	9 (0.6)	<0.001
Prasugrel	2 (0.43)	335 (71.9)	<0.001	19 (1.3)	1,261 (83.4)	<0.001
Clopidogrel	31 (6.6)	31 (6.6)	>0.999	59 (3.9)	86 (5.7)	0.028
Oral anticoagulant drugs	25 (5.4)	27 (5.8)	0.887	57 (3.8)	73 (4.8)	0.182
Beta blocking agents	373 (80.0)	380 (81.5)	0.618	1,268 (84.0)	1,265 (83.7)	0.823
ACE inhibitor/ARB	371 (79.6)	389 (83.5)	0.151	1,288 (85.4)	1,301 (86.0)	0.624
Statin	407 (87.3)	409 (87.8)	0.921	1,403 (93.0)	1,422 (94.0)	0.262

Data are shown as counts (proportions; %).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.
*Shown for patients discharged alive.

Supplementary Table 4. Clinical Outcomes according to Age, Weight or Obstructive Coronary Artery Disease (Women versus Men)*

	Women (*n*=956)	Men (*n*=3,062)	HR [95% CI]	*P* value
≥ 75 years or <60 kg				
Primary endpoint – death, myocardial infarction or stroke	49/433 (11.3)	99/666 (14.9)	0.76 [0.54-1.07]	0.119
BARC type 3-5 bleeding	48/433 (11.1)	55/666 (8.3)	1.37 [0.93-2.02]	0.108
<75 years and ≥ 60 kg				
Primary endpoint – death, myocardial infarction or stroke	32/518 (6.2)	140/2,380 (5.9)	1.05 [0.71-1.54]	0.806
BARC type 3-5 bleeding	34/518 (6.6)	88/2,380 (3.7)	1.80 [1.21-2.68]	0.004
≥ 75 years				
Primary endpoint – death, myocardial infarction or stroke	42/348 (12.1)	98/634 (15.5)	0.79 [0.55-1.13]	0.195
BARC type 3-5 bleeding	37/348 (10.6)	54/634 (8.5)	1.29 [0.85-1.96]	0.237
<75 years				
Primary endpoint – death, myocardial infarction or stroke	39/608 (6.4)	142/2,428 (5.8)	1.10 [0.77-1.56]	0.611
BARC type 3-5 bleeding	45/608 (7.4)	90/2,428 (3.7)	2.03 [1.42-2.90]	<0.001
Obstructive coronary artery disease				
Primary endpoint – death, myocardial infarction or stroke	74/790 (9.4)	233/2,880 (8.1)	1.17 [0.90-1.52]	0.231
BARC type 3-5 bleeding	77/790 (9.7)	141/2,880 (4.9)	2.06 [1.56-2.72]	<0.001

Data are numbers of events with Kaplan-Meier estimates (%). BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio.
*BARC type 3 to 5 bleeding was analyzed according to the intention-to-treat principle.

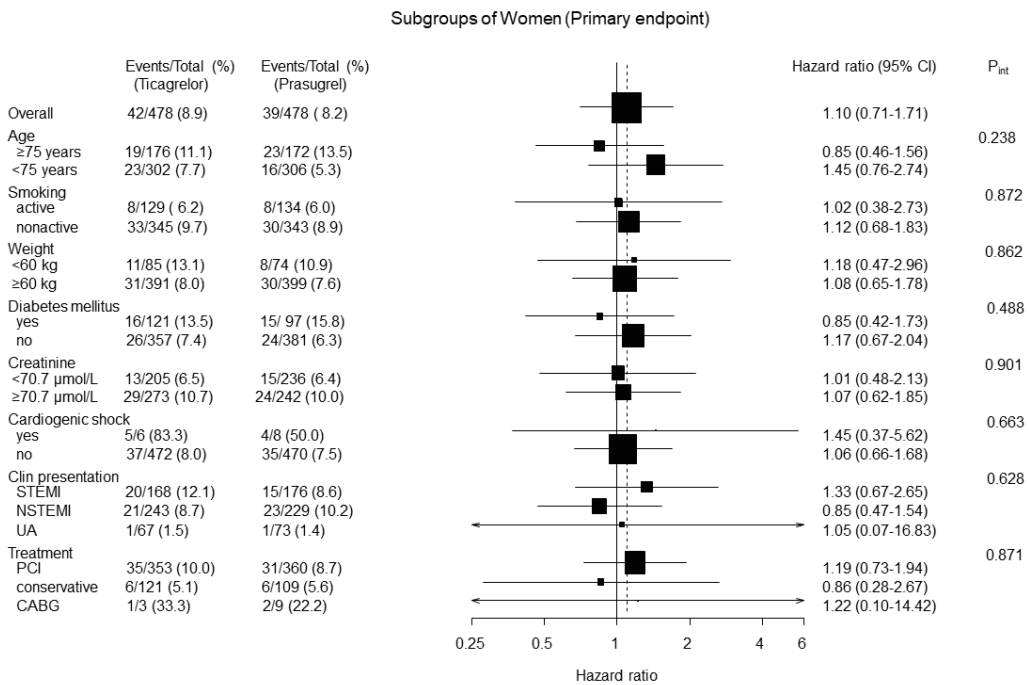
Supplementary Table 5. Clinical Outcomes according to Age, Weight or Obstructive Coronary Artery Disease (Ticagrelor versus Prasugrel)*

	Women (*n*=956)				Men (*n*=3062)			
	Ticagrelor (*n*=478)	Prasugrel (*n*=478)	HR [95% CI]	*P* value	Ticagrelor (*n*=1,534)	Prasugrel (*n*=1,528)	HR [95% CI]	*P* value
≥ 75 years or <60kg**								
Primary endpoint –death, myocardial infarction or stroke	24/222 (10.8)	25/211 (11.8)	1.00 [0.57-1.76]	0.991	56/333 (16.8)	43/333 (12.9)	1.36 [0.91-2.04]	0.132
BARC type 3-5 bleeding	22/217 (10.1)	18/170 (10.6)	1.19 [0.63-2.25]	0.601	25/331 (7.6)	16/296 (5.4)	1.77 [0.93-3.38]	0.082
<75 years and ≥ 60kg								
Primary endpoint – death, myocardial infarction or stroke	18/254 (7.1)	14/264 (5.3)	1.37 [0.67-2.78]	0.387	86/1,195 (7.2)	54/1,185 (4.6)	1.57 [1.12-2.21]	0.010
BARC type 3-5 bleeding	14/252 (5.6)	16/214 (7.5)	1.01 [0.48-2.11]	0.984	34/1,181 (2.9)	29/1,080 (2.7)	1.10 [0.67-1.80]	0.717
Obstructive coronary artery disease								
Primary endpoint – death, myocardial infarction or stroke	39/391 (10.0)	35/399 (8.8)	1.17 [0.74-1.85]	0.507	138/1,442 (9.6)	95/1,438 (6.6)	1.47 [1.13-1.91]	0.004
BARC type 3-5 bleeding	35/390 (9.0)	34/367 (9.3)	1.09 [0.68-1.76]	0.714	59/1,432 (4.1)	46/1,362 (3.4)	1.27 [0.86-1.86]	0.232

Data are numbers of events with Kaplan-Meier estimates (%). BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio.

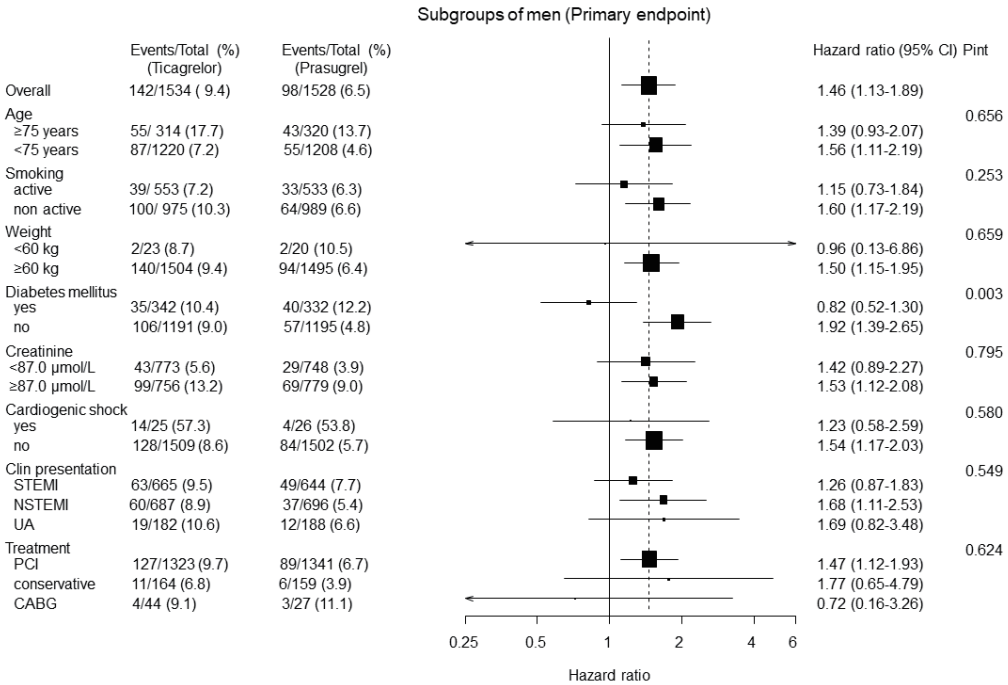
*Kaplan-Meier estimates or cumulative incidence of the events and risk estimates are obtained from the Cox proportional hazards model after adjustment for the participating center and stratification according to the clinical presentation (acute coronary syndrome with or without ST-segment elevation). BARC type 3 to 5 bleeding was analyzed according to the modified intention-to-treat principle.

**In patients with an age ≥ 75 years or a weight <60kg, a 5 mg/day maintenance dose of prasugrel was recommended.



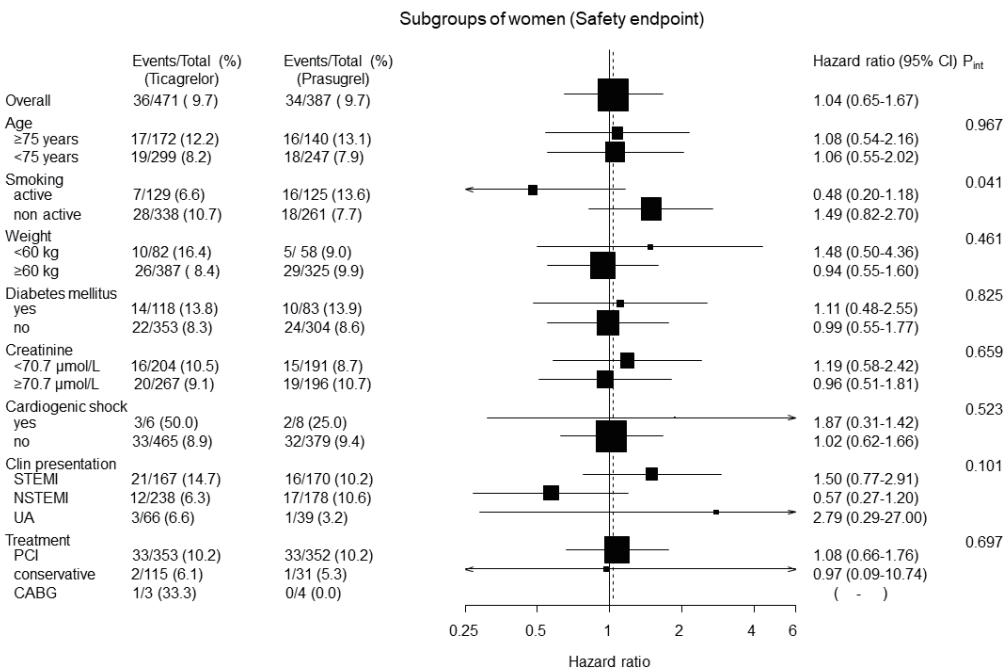
Supplementary Fig. 1. One-year incidences and hazard ratios with 95% confidence interval of the primary endpoint (death, myocardial infarction, or stroke) in subgroups of women

CABG, coronary artery bypass graft; CI, confidence interval; Clin, clinical; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina



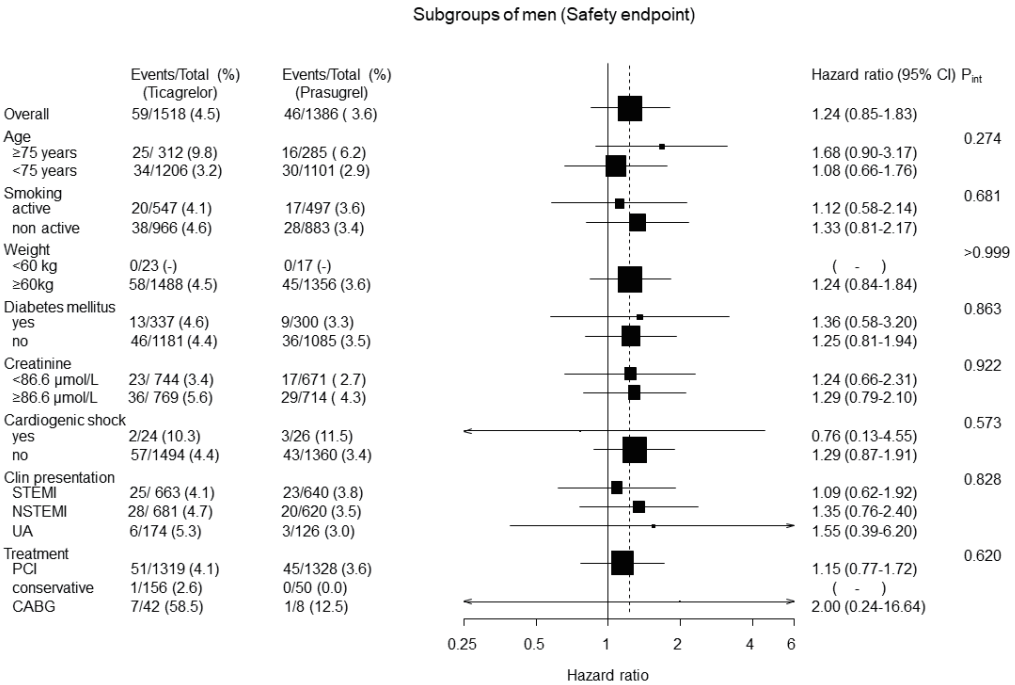
Supplementary Fig. 2. One-year incidences and hazard ratios with 95% confidence interval of the primary endpoint (death, myocardial infarction, or stroke) in subgroups of men

CABG, coronary artery bypass graft; CI, confidence interval; Clin, clinical; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina



Supplementary Fig. 3. One-year incidences and hazard ratios with 95% confidence interval of the safety endpoint (Bleeding Academic Research Consortium type 3 to 5 bleeding) in subgroups of women

CABG, coronary artery bypass graft; CI, confidence interval; Clin, clinical; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina



Supplementary Fig. 4. One-year incidences and hazard ratios with 95% confidence interval of the safety endpoint (Bleeding Academic Research Consortium type 3 to 5 bleeding) in subgroups of men

CABG, coronary artery bypass graft; CI, confidence interval; Clin, clinical; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina