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

Senta Gewalt¹, Shqipdona Lahu¹, Gijn Ndreppea¹, Costanza Pellegrini¹, Isabell Bernlochner², ³, Franz-Josef Neumann⁴, Maurizio Menichelli⁵, Tanja Morath¹, Bernhard Witzenbichler⁶, Jochen Wöhrle⁷, Katharina Hoppe¹, Gert Richardt⁸, Karl-Ludwig Laugwitz², ³, Heribert Schunkert¹, ², Adnan Kastrati¹, ², Stefanie Schüpke¹, ² and Katharina Mayer¹

¹Deutsches Herzzentrum München, Cardiology, and Technische Universität München, both in Munich, Germany
²German Center for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Germany
³Medizinische Klinik und Poliklinik Innere Medizin I (Kardiologie, Angiologie, Pneumologie), Klinikum rechts der Isar, Munich, Germany
⁴Department of Cardiology and Angiology II, University Heart Center Freiburg · Bad Krozingen, Bad Krozingen, Germany
⁵Ospedale Fabrizio Spaziani, Cardiology, Frosinone, Italy
⁶Helios Amper-Klinikum Dachau, Cardiology & Pneumology, Dachau, Germany
⁷Department of Cardiology, Medical Campus Lake Constance, Friedrichshafen, Germany
⁸Heart Center Bad Segeberg, Bad Segeberg, Germany

Aim: Sex-specific analyses of direct head-to-head comparisons between newer P2Y₁₂ 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 female¹. Women presenting with an ACS are older...
Previous studies have reported gender-specific differences in platelet biology and benefits of antiplatelet therapy, including a higher platelet reactivity, more frequent hyporesponsiveness to clopidogrel, and reduced anti-ischemic protection by aspirin 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. Exposure to ticagrelor and prasugrel (most likely related to effects of body weight and age) seems to be higher in female patients. In both pivotal randomized trials of the potent P2Y₁₂ inhibitors (prasugrel and ticagrelor), the treatment effect against clopidogrel was not modified by gender. Recent meta-analyses demonstrated a comparable or a slightly lower efficacy of newer P2Y₁₂ inhibitors in women. However, women are less likely to be treated with newer P2Y₁₂ inhibitors than men, particularly with prasugrel. The most likely reason for this undertreatment is the concern of a higher risk of bleeding in women. Furthermore, women with ACS are less likely than men to receive guideline-recommended therapies, and they are underrepresented in clinical trials of coronary artery disease 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. 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 and main results have recently been published. The trial performed a randomized head-to-head comparison of the efficacy and safety of two potent P2Y₁₂ 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. 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), 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.

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

---

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

The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial performed a randomized head-to-head comparison of the efficacy and safety of two potent P2Y₁₂ 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. 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), 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.

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) in patient groups according to sex (i.e., men versus women) was analyzed in the intention-to-treat population (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 as initially assigned, irrespective of the actual treatment received).

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
Baseline characteristics

| Characteristic                  | 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 ± 5.4         | 27.2 ± 5.0        | 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)         | 0.829   | 182 (11.9)           | 188 (12.3)          |         |
| NSTEMI–no. (%)                  | 243 (50.8)         | 229 (47.9)        | 0.681   | 687 (44.8)           | 696 (45.5)          |         |
| STEMI–no. (%)                   | 168 (35.1)         | 176 (36.8)        | 0.310   | 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              | 0.255             | 0.119   | 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 (ST<EMI, 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) | Ticagrelor (n=478) | Prasugrel (n=478) | HR [95% CI] | P value | Men (n=3,062) | 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                |             | 0.306       |         |
| Non-cardiovascular                                        |               | 3                  | 6                 |             |         | 24            | 8                 |             | 0.366       |         |
| 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                |             | 0.275       |         |
| Type 2                                                    |               | 1                  | 1                 |             |         | 3             | 2                 |             | 0.336       |         |
| Type 4a                                                   |               | 4                  | 4                 |             |         | 15            | 7                 |             | 0.475       |         |
| Type 4b                                                   |               | 3                  | 0                 |             |         | 17            | 11                |             | 0.977       |         |
| Type 5                                                    |               | 1                  | 0                 |             |         | 0             | 0                 |             | 0.916       |         |
| STEMI                                                     |               | 5                  | 2                 |             |         | 26            | 12                |             | 0.217       |         |
| 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                |             | 0.936       |         |
| Hemorrhagic                                               |               | 3                  | 1                 |             |         | 3             | 1                 |             | 0.806       |         |
| 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                |             | 0.222       |         |
| 3b                                                        |               | 14                 | 13                |             |         | 18            | 18                |             | 0.368       |         |
| 3c                                                        |               | 2                  | 1                 |             |         | 2             | 1                 |             | 0.427       |         |
| 4                                                         |               | 3                  | 0                 |             |         | 5             | 2                 |             | 0.231       |         |
| 5a                                                        |               | 0                  | 0                 |             |         | 1             | 0                 |             | 0.981       |         |
| 5b                                                        |               | 2                  | 1                 |             |         | 1             | 3                 |             | 0.691       |         |

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, P for interaction; STEMI, ST-segment elevation myocardial infarction.

*K 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
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, the subgroup with an age <75 years irrespective of weight, 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: (1) 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. Randomized clinical trials that have compared prasugrel or ticagrelor 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. 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. In the same vein, a recent meta-analysis of randomized trials of newer P2Y12 inhibitors (prasugrel, ticagrelor, or canagrelor) 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. In this meta-analysis, newer P2Y12 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, P2Y12 inhibitors increased the risk of major (non-coronary artery bypass-related) bleeding comparably in women and men. Another recent meta-analysis suggested that newer P2Y12 inhibitors might be slightly less efficacious in women than in men with ACS, although the absolute risk reduction was similar in both sexes. 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. 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.

(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. 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, clopidogrel, and prasugrel. 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. 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. 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 P2Y12 inhibitors, 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
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. 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 gender regarding the primary composite endpoint of treatment effect of ticagrelor versus prasugrel and invasive strategy, the superiority of prasugrel over

---

**References**

1)Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, D'joussé L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW, American Heart Association Council on Epidemiology and Prevention, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2020 update: A report from the American heart association. Circulation. 2020; 141: e139-e596

2)Alexander KP, Chen AY, Newby LK, Schwartz JB, Redberg RF, Hochman JS, Roe MT, Gibler WB, Ohman EM, Peterson ED, Investigators C. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes of Treatment with Anxiolytics in Patients HOSPitalized with Acute coronary syndromes) initiative. Circulation, 2006; 114: 1380-1387

3)Chandrasekhar J, Baber U, Sartori S, Faggioni M, Aquino M, Kini A, Weintraub W, Rao S, Kapadia S, Weiss S, Strauss C, Toma C, Mulestein B, DeFrancesco A, Effron M, Keller S, Baker B, Pocock S, Henry T, Mehran R. Sex-related differences in outcomes among men and women under 55 years of age with acute coronary syndrome undergoing percutaneous coronary intervention: Results from the PROMETHEUS study. Catheter Cardiovasc Interv, 2017; 89: 629-637

4)Wang TY, Angiolillo DJ, Cushman M, Sabatine MS, Bray PF, Smyth SS, Daueran HL, French PA, Becker RC. Platelet biology and response to antiplatelet therapy in women: implications for the development and use of antiplatelet pharmacotherapies for cardiovascular disease. J Am Coll Cardiol, 2012; 59: 891-900

5)Patti G, De Caterina R, Abbate R, Andreooti F, Biasucci LM, Calabro P, Cioni G, Davi G, Di Sciascio G, Golia E, Golino P, Malatesta G, Mangiacarpo F, Marcucci R, Nusca A, Parato VM, Pengo V, Prisco D, Pulcinelli F, Renda G, Ricottini E, Ruggieri B, Santilli F, Sofi F, Zimarino M, Working Group on Thrombosis of the Italian Society of C. Platelet function and long-term antiplatelet therapy in women: is there a gender-
specificity? A ‘state-of-the-art’ paper. Eur Heart J, 2014; 35: 2213-2223b
6) Price MJ, Nayak KR, Barker CM, Kandzari DE, Teirstein PS. Predictors of heightened platelet reactivity despite dual-antiplatelet therapy in patients undergoing percutaneous coronary intervention. Am J Cardiol, 2009; 103: 1339-1343
7) Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. Jama, 2006; 295: 306-313
8) Ndrepepa G, Schulz S, Neumann FJ, Byrne RA, Hoppmann P, Cassese S, Ott I, Fusaro M, Ibrahim T, Tada T, Richardt G, Laugwitz KL, Schunkert H, Kastrati A. Bleeding after percutaneous coronary intervention in women and men matched for age, body mass index, and type of antithrombotic therapy. Am Heart J, 2013; 166: 534-540
9) Teng R, Mitchell P, Butler K. Effect of age and gender on pharmacokinetics and pharmacodynamics of a single ticagrelor dose in healthy individuals. Eur J Clin Pharmacol, 2012; 68: 1175-1182
10) Riesmeyer JS, Salazar DE, Weerra kody GJ, Ni L, Wrishko RE, Ernest CS, 2nd, Luo J, Li YG, Small DS, Rohatagi S, Macias WL. Relationship between exposure to prasugrel active metabolite and clinical outcomes in the TRITON-TIMI 38 substudy. J Clin Pharmacol, 2012; 52: 789-797
11) Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Ndrepepa G, Gibson CM, Antman EM, Investigators T-T. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med, 2007; 357: 2001-2015
12) Husted S, James SK, Bach RG, Becker RC, Budaj A, Heras M, Himmelman A, Horrow J, Katus HA, Lassila R, Morais J, Nicolau JC, Steg PG, Storey RF, Wojyl dyla D, Wallentin L, group Ps. The efficacy of ticagrelor is maintained in women with acute coronary syndromes participating in the prospective, randomised, PLATel inhibition and patient Outcomes (PLATO) trial. Eur Heart J, 2014; 35: 1541-1550
13) Lau ES, Braunwald E, Murphy SA, Wiviott SD, Bonaca MP, Husted S, James SK, Wallentin L, Clemmensen P, Roe MT, Ohman EM, Harrington RA, Mega JL, Bhatt DL, Sabatine MS, O’Donoghue ML. Potent P2Y12 Inhibitors in Men Versus Women: A Collaborative Meta-Analysis of Randomized Trials. J Am Coll Cardiol, 2017; 69: 1549-1559
14) Lee KK, Welton N, Shah AS, Adamson PD, Dias S, Anand A, Newby DE, Mills NL, McAllister DA. Differences in relative and absolute effectiveness of oral P2Y12 inhibition in men and women: a meta-analysis and modelling study. Heart, 2018; 104: 657-664
15) Cirillo P, Di Serafino L, Patti G, Antonucci E, Calabro P, Gres eple P, Palareti G, Pengo V, Pignattelli P, Marcucci R. Gender-Related Differences in Antiplatelet Therapy and Impact on 1-Year Clinical Outcome in Patients Presenting With ACS: The START ANTIPLACELET Registry. Angiology, 2019; 70: 257-263
16) Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, Labresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L, Get With the Guidelines Steering C, Investigators. Sex differences in medical care and early death after acute myocardial infarction. Circulation, 2008; 118: 2803-2810
17) Kim ES, Carrigan TP, Menon V. Enrollment of women in National Heart, Lung, and Blood Institute-funded cardiovascular randomized controlled trials fails to meet current federal mandates for inclusion. J Am Coll Cardiol, 2008; 52: 672-673
18) Schupke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wohle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, Akin I, Bott-Flugel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Rollmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kfner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schuhlen H, Angiolillo DJ; Hamm CW, Haf pelmeier A, Tolg R, Trenk D, Schunkert H, Laugwitz KL, Kas trati A, Investigators 1-RT. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. N Engl J Med, 2019; 381: 1524-1534
19) Schulz S, Angiolillo DJ, Antoniucci D, Bern lochner I, Caimin J, Laubert KL, Mayer K, von Merzljak B, Morath T, Neumann FJ, Richardt G, Ulf J, Schomig G, Schuhlen H, Schunkert H, Kastrati A, Intracoronary S, Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5 Trial I. Randomized comparison of ticagrelor versus prasugrel in patients with acute coronary syndrome and planned invasive strategy–design and rationale of the iNtracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial. J Cardiovasc Transl Res, 2014; 7: 91-100
20) Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation, 2011; 123: 2736-2747
21) Verdoia M, Pergolini P, Rolla R, Nardin M, Barbieri L, Mering GO, Sopko G, Bairey Merz CN. Some thoughts on the vasculopathy of women with ischemic heart disease. J Am Coll Cardiol, 2006; 47: S30-35
22) Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med, 2005;
A Subgroup Analysis of the GLOBAL LEADERS Randomized Clinical Trial. JAMA Cardiol, 2019: 1-10

29) D’Ascenzo F, Grosso A, Abu-Assi E, Kinnaird T, Ariza-Sole A, Manzano-Fernandez S, Templin C, Velicki L, Xanthopoulou I, Cerrato E, Rognoni A, Boccuzzi G, Omede P, Montabone A, Taha S, Durante A, Gili S, Ali HH, Magnani G, Autelli M, Blanco PF, Garay A, Quadri G, Marra WG, Queija BC, Paz RC, Fernandez MC, Pousa IM, Gallo D, Morbiducci U, Dominguez-Rodriguez A, Valdes M, Cequier A, Alexopoulos D, Iniguez-Romo A, Gaita F, Raposeiras-Roubin S. Incidence and predictors of bleeding in ACS patients treated with PCI and prasugrel or ticagrelor: An analysis from the RENAMI registry. Int J Cardiol, 2018; 273: 29-33

30) Alexopoulos D, Xanthopoulou I, Storey RF, Bliden KP, Tantry US, Angiolillo DJ, Gurbel PA. Platelet reactivity during ticagrelor maintenance therapy: a patient-level data meta-analysis. Am Heart J, 2014; 168: 530-536

31) Menichelli M, Neumann FJ, Ndrepepa G, Mayer K, Währle J, Bernlochner I, Richardt G, Witzenbichler B, Sibbing D, Gewalt S, Angiolillo DJ, Lahu S, Hamm CW, Trautmann S, Trenk D, Laugwitz KL, Schunkert H, Schüppke S, Kastrati A. Age- and Weight-Adapted Dose of Prasugrel versus Standard Dose of Ticagrelor in Patients With Acute Coronary Syndromes: Results From a Randomized Trial. Ann Intern Med, 2020; 173: 436-444
### Supplementary Table 1. Angiographic Data

| Characteristic                                | Women (n=476) | Prasugrel (n=478) | P value | Men (n=1,527) | Prasugrel (n=1,523) | P value |
|-----------------------------------------------|---------------|-------------------|---------|---------------|---------------------|---------|
| Access site                                   |               |                   |         |               |                     |         |
| Femoral artery                                | 288 (60.5)    | 304 (63.6)        | 0.524   | 957 (62.7)    | 956 (62.8)          | 0.839   |
| 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                            | 288 (60.5)    | 304 (63.6)        |         | 111 (21.7)    | 110 (21.7)          |         |
| One-vessel disease                            | 172 (36.4)    | 167 (34.9)        |         | 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 (proportions; %) 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 187 men (89 in the ticagrelor group and 98 in the prasugrel group).

### Supplementary Table 2. Procedural Characteristics

| Characteristic                               | Women (n=353) | Prasugrel (n=360) | P value | Men (n=1,323) | Prasugrel (n=1,341) | P value |
|----------------------------------------------|---------------|-------------------|---------|---------------|---------------------|---------|
| Target vessel                                |               |                   |         |               |                     |         |
| Left main coronary artery                    | 8 (2.27)      | 11 (3.06)         | 0.194   | 28 (2.1)      | 27 (2.0)            | 0.918   |
| 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                                            | 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   |
| Biodegradable 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)      | 15 (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                              | P value | P value |
|----------------------------------------|------------------------------------|----------------------------------|---------|---------|
|                                        | Ticagrelor (n = 466)               | Prasugrel (n = 466)              |         |         |
| Final diagnosis – no. (%)              |                                    |                                  | 0.353   | 0.987   |
| Unstable angina                        | 50 (12.6)                          | 38 (9.64)                        |         |         |
| NSTEMI                                 | 189 (47.7)                         | 187 (47.5)                       |         |         |
| STEMI                                  | 157 (39.6)                         | 169 (42.9)                       |         |         |
| Therapy at discharge – no. (%)         |                                    |                                  |         |         |
| Aspirin                                | 423 (90.8)                         | 420 (90.1)                       | 0.824   |         |
| Ticagrelor                             | 334 (71.7)                         | 5 (1.07)                         | <0.001  | <0.001  |
| Prasugrel                              | 2 (0.43)                           | 335 (71.9)                       | <0.001  | <0.001  |
| Clopidogrel                            | 31 (6.6)                           | 31 (6.6)                         | >0.999  |         |
| Oral anticoagulant drugs               | 25 (5.4)                           | 27 (5.8)                         | 0.887   |         |
| Beta blocking agents                   | 373 (80.0)                         | 380 (81.5)                       | 0.618   |         |
| ACE inhibitor/ARB                      | 371 (79.6)                         | 389 (83.5)                       | 0.151   |         |
| Statin                                 | 407 (87.3)                         | 409 (87.8)                       | 0.921   |         |

*Shown for patients discharged alive.

---

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

| Age/Weight/Obstructive CAD | Women (n = 956) | Men (n = 3,062) | HR [95% CI] | P value |
|---------------------------|-----------------|-----------------|-------------|---------|
| ≥75 years or <60 kg       | 49/433 (11.3)   | 99/666 (14.9)   | 0.76 [0.54-1.07] | 0.119   |
| Primary endpoint          | 48/433 (11.1)   | 55/666 (8.3)    | 1.37 [0.93-2.02] | 0.108   |
| BARC type 3-5 bleeding    | 32/518 (6.2)    | 140/2,380 (5.9) | 1.05 [0.71-1.54] | 0.806   |
| <75 years and ≥60 kg      | 34/518 (6.6)    | 88/2,380 (3.7)  | 1.80 [1.21-2.68] | 0.004   |
| Primary endpoint          | 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                 | 39/608 (6.4)    | 142/2,428 (5.8) | 1.10 [0.77-1.56] | 0.611   |
| Primary endpoint          | 45/608 (7.4)    | 90/2,428 (3.7)  | 2.03 [1.42-2.90] | <0.001  |
| BARC type 3-5 bleeding    | 74/790 (9.4)    | 233/2,880 (8.1) | 1.17 [0.90-1.52] | 0.231   |
| Obstructive CAD           | 77/790 (9.7)    | 141/2,880 (4.9) | 2.06 [1.56-2.72] | <0.001  |

*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) |               | P value  | Men (n=3062) |               | P value  |
|--------------------|---------------|---------------|----------|---------------|---------------|----------|
|                    | 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 | 25/217 (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 |
| 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 |
| Obstructive coronary artery disease |               |               |          |               |               |          |
| Primary endpoint – death, myocardial infarction or stroke | 25/217 (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 |
| 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 |

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