## Sex-stratified differences in early antithrombotic treatment response in patients presenting with ST-segment elevation myocardial infarction


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# Sex-stratified differences in early antithrombotic treatment response in patients presenting with ST-segment elevation myocardial infarction

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**Background** The mechanisms underlying the increased risk of bleeding that female patients with ST-segment Elevation Myocardial Infarction (STEMI) exhibit, remains unclear. The present report assessed sex-related differences in response to pre-hospital dual antiplatelet therapy (DAPT) initiation in patients with STEMI.

**Methods** The COMPARE CRUSH trial randomized patients presenting with STEMI to receive a pre-hospital loading dose of crushed or integral prasugrel tablets in the ambulance. In this substudy, we compared platelet reactivity levels and the occurrence of high platelet reactivity (HPR; defined as platelet reactivity ≥208) between sexes at 4 prespecified time points after DAPT initiation, and evaluated post-PCI bleeding between groups.

**Results** Out of 633 STEMI patients, 147 (23%) were female. Females compared with males presented with significantly higher levels of platelet reactivity and higher HPR rates at baseline (232 [IQR, 209-256] vs 195 [IQR, 171-220], $P < .01$, and 76% vs 41%, OR 4.58 [95%CI, 2.52-8.32], $P < .01$, respectively). Moreover, female sex was identified as the sole independent predictor of HPR at baseline (OR 5.67 [95%CI, 2.56-12.53], $P < .01$). Following DAPT initiation, levels of platelet reactivity and the incidence of HPR were similar between sexes. Post-PCI bleeding occurred more frequently in females compared with males (10% vs 2%, OR 6.02 [95%CI, 2.61-11.87], $P < .01$). Female sex was an independent predictor of post-PCI bleeding (OR 3.25 [95%CI, 1.09-9.72], $P = .04$).

**Conclusions** In this contemporary STEMI cohort, female STEMI patients remain at risk of bleeding complications after primary PCI. However, this is not explained by sex-specific differences in the pharmacodynamic response to pre-hospital DAPT initiation. (Am Heart J 2023;258:17–26.)

In patients presenting with ST-segment elevation myocardial infarction (STEMI), sex influences both short and long-term outcomes.[1-3] Females presenting with STEMI exhibit an increased risk of both ischemic and bleeding complications compared with males.[1,4-6] This phenomenon might be in part attributed to demographic disparities in age and prevalence of comorbidities between females and males.[2] However, even after accounting for the aforesaid differences, female sex – as a biological variable – has been proposed to act as an independent risk factor of adverse events in patients presenting with STEMI, especially for bleeding complications.[6-9] Bleeding complications after PCI have been widely associated with worse clinical outcomes and in particular with higher mortality rates. However, the exact pathophysiological mechanism underlying the discrepancy in bleeding incidence between

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female and male STEMI patients remains not fully clarified.

Potential sex-derived differences contributing to the higher incidence of bleeding in females, include anatomical features of the vascular bed, body size and fat composition, renal function, as well as aspects of platelet biology (ie, quantity and reactivity of platelets).[10,11] Discrepancies in platelet biology between females and males – including increased levels of activated platelets in females – have been previously reported in patients with stable coronary artery disease and non-ST-segment elevation myocardial infarction.[12-14] However, literature regarding sex-specific differences in response to pre-hospital antithrombotic therapy administration in patients presenting with STEMI is limited.[15]

The present prespecified substudy of the COMPARE CRUSH trial aimed to investigate sex-derived differences in the pharmacodynamics response to pre-hospital antiplatelet and anticoagulant therapy in patients presenting with STEMI planned to undergo primary percutaneous coronary intervention (PCI).

## Methods

### Study design and population

The COMPARison of pre-hospital CRUSHed vs uncrushed Prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary interventions (COMPARE CRUSH; NCT03296540) trial was a randomized, controlled, multicenter trial investigating the effect of pre-hospital crushed versus integral prasugrel loading dose (LD) tablets administration on early myocardial reperfusion in patients with STEMI planned to undergo primary PCI. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines, and all study procedures were approved by the local ethics committee. An independent data safety monitoring board was responsible for the safety and quality of the trial. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

The study design, procedures and eligibility criteria have been reported previously.[16,17] In brief, consecutive patients with suspected STEMI and symptom onset within 6 hours were screened for eligibility by the emergency medical service. Eligible patients were randomly assigned to 60 mg prasugrel LD as either crushed or integral tablets. Additionally, all study participants were treated with a standardized unisex antithrombotic treatment regimen, consisting of 500 mg aspirin and 5.000 units of unfractionated heparin, both intravenously. After this initial treatment, all study participants were transferred to the nearest interventional center to undergo emergency coronary angiography. All patients received a second perprocedural bolus of unfractionated heparin, dosed at the operator's discretion. Emergency coronary angiography and optional primary PCI were performed in accordance with international guidelines.

The primary end points of the COMPARE CRUSH trial were thrombolysis in myocardial infarction (TIMI) 3 flow in the infarct-related artery at initial angiography, and complete (≥70%) ST-segment resolution (STR) on the ECG one hour post-PCI. Pre-hospital crushed compared with integral prasugrel LD administration did not result in improved early myocardial reperfusion in STEMI patients undergoing primary PCI. This effect of crushed versus integral prasugrel was consistent across females and males.[17]

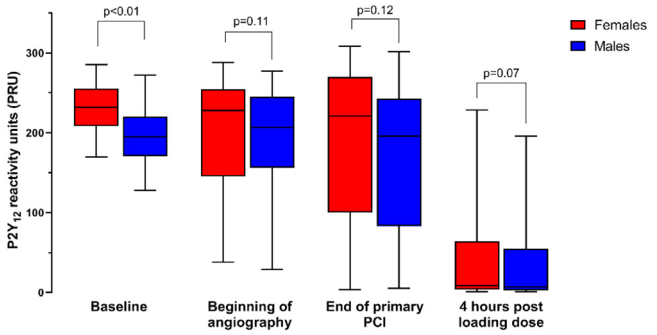
For the present sex-stratified substudy, we included all COMPARE CRUSH patients with a final diagnosis of STEMI ($n = 633$). Additional exclusion criteria were the use of clopidogrel and/or oral anticoagulation therapy at time of randomization ($n = 19$), and 2 or more missing or excluded pharmacodynamic measurements at any time point, including non-usable measurements due to glycoprotein inhibitor bailout during PCI, and non-usable blood samples due to suspected hemolysis or violation of the analysis time window ($n = 173$).

### Pharmacodynamic assessments

The COMPARE CRUSH trial included serial prespecified platelet reacitivity measurements for a prespecified pharmacodynamic substudy, and study procedures regaring the pharmacodynamic analysis have been previously described.[16,18] In brief, peripheral blood samples were collected at 4 time points throughout the study: at baseline before antithrombotic therapy initiation, at initial angiography, at the end of primary PCI, and 4 hours after study treatment initiation. The baseline PD measurement was included in the trial design to assist interpretation of platelet reactivity data after prasugrel administration. During blood sampling a dummy container was drawn prior to the formal blood sample. The first sample was drawn from a Venflon, the second and third samples from the arterial sheath, and the last sample was drawn either from the Venflon or by a new venous puncture. After sample collection, all samples were gently blended to prevent cloth formation, after which they were gently transported to the laboratory for analysis. The first 3 samples were analyzed at once in a consecutive order directly after primary PCI. Platelet reactivity was analyzed using the VerifyNow system (Werfen/Accriva, Barcelona, Spain), and was expressed in P2Y12 reactivity units (PRU). All blood samples were analyzed within fifteen minutes to 4 hours after sample collection.

Pre-PCI activated clotting time (ACT) measurements (Hemochron; Werfen, Barcelona, Spain) were performed prior to a second perprocedural dose of unfractionated heparin, and at the end of primary PCI before sheath removal. Glycoprotein IIb/IIIa inihibitor use was limited to perprocedural bailout only. A deferred consent pro-

**Figure 1**




Pharmacodynamic response to pre-hospital DAPT initiation in female versus male STEMI patients. The whiskers represent a 95% confidence interval.

cedure was used to obtain informed consent within 4 hours after randomization. All patients received standardized post-PCI medical care in accordance with national and international guidelines.

### Study outcomes

Our primary objective was to evaluate sex-related differences in pharmacodynamic response to DAPT therapy in the ambulance. Therefore we assessed platelet reactivity and the occurrence of high platelet reactivity (HPR), defined as PRU ≥208, at 4 prespecified time points in the first hours after prasugrel LD administration.[18,19] Secondary objectives included the pharmacodynamic response of pre-hospital and in-hospital unfractionated heparin administration using pre-PCI and post-PCI ACT measurements. ACT levels exceeding 300 seconds were considered substantially prolonged.

Clinical outcomes were assessed at 48 hours and at 30 days (for descriptive purposes only). Bleeding was classified according to the Bleeding Academic Research Criteria (BARC) and the TIMI bleeding definitions.[20,21] Major adverse cardiac and cerebral events (MACCE) was defined as the composite of death, myocardial infarction, urgent revascularization, stent thrombosis or stroke. All clinical events were adjudicated by a blinded, independent event committee.

### Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics (version 25.0.0.2) software for Windows. We compared platelet reactivity and ACT measurements between sexes using the Mann-Whitney *U* test. HPR rates were compared between groups using Pearson's chi-square test. Univariate and multivariable logistic regression were used to identify predictors of HPR at baseline. Differences in clinical outcomes were assessed using logistic regression and reported as odds ratios (OR) with 95% confidence intervals (CI). Bleeding outcomes were assessed using univariate logistic regression and multivariable logistic regression with adjustment for baseline discrepancies between females and males. For all statistical analyses, a two-sided *P*-value of <.05 was considered statistically significant.

## Results

### Patient population

The COMPARE CRUSH trial enrolled 633 STEMI patients between November 2017 and March 2020. Of these 633 patients, 147 (23%) were female. Baseline and procedural characteristics are shown in Table I. Female STEMI patients were older and weighed less compared with male STEMI patients (66 ± 12 vs 61 ± 12 years, *P* < .01, and 74 [IQR, 63-84] kg vs 85 [IQR, 76-95] kg, *P* < .01, respectively). Hypertension was more common in females than in males (49% vs 35%, *P* < .01). In contrast, smoking was less common in females compared with males (39% vs 45%, *P* == .24). The time intervals between onset of symptoms and start of primary PCI were similar between sexes (52 [IQR, 113-239] min vs 147 [IQR, 107-223] min, *P* == .26).

The radial artery was the predominant arterial access site in the COMPARE CRUSH trial (97% in total). However, femoral access was numerically more frequently used in females than in males (5% vs 2%, *P* == .09). At initial angiography, females significantly more often had TIMI 3 flow in the IRA pre-PCI compared with males (39.1% vs 29.6%, OR 1.53 [95%CI, 1.03-2.28], *P* == .04). In female STEMI patients, emergency coronary angiography was less often followed by primary PCI than in male STEMI patients (93% vs 98%, *P* == .01). Reasons for not performing primary PCI were myocardial infarction with non-obstructive coronary arteries (2.7% vs 0.6%, *P* == .05), aborted STEMI (2.0% vs 0.4%, *P* == .09), spontaneous coronary artery dissection (0.7% vs 0%,

**Table I.** Baseline patient and procedural characteristics

| | Females $N = 147$ | Males $N = 486$ | *P*-value |
|---|---|---|---|
| Patient characteristics | | | |
| Age - y | 66 ± 12 | 61 ± 12 | <.01 |
| Caucasian - no. (%) | 136/146 (93.2) | 441/481 (91.7) | .57 |
| Weight - kg | 74 [63-84] / 110 | 85 [76-95] / 346 | <.01 |
| BMI - kg/m$^2$ | 27 [24-30] / 101 | 27 [25-30] / 318 | .37 |
| Cardiovascular risk factors - no. (%) | | | |
| Hypertension | 71/146 (48.6) | 166/481 (34.5) | <.01 |
| Diabetes mellitus | 26/144 (18.1) | 68/478 (14.2) | .26 |
| Dyslipidemia | 36/139 (25.9) | 116/454 (25.6) | .93 |
| Smoking | 56/142 (39.4) | 211/468 (45.1) | .24 |
| Family history of CVD | 54/142 (38.0) | 188/468 (40.2) | .77 |
| Medical history - no. (%) | | | |
| MI | 10/147 (6.8) | 47/486 (9.7) | .28 |
| CABG | 2/147 (1.4) | 9/486 (1.9) | .69 |
| Presentation | | | |
| Time onset symptoms to FMC - min | 65 [33-139] | 56 [29-127] | .29 |
| Time FMC to Tx - min | 25 [18-30] | 20 [15-28] | <.01 |
| KILLIP Class > I - no. (%) | 3/146 (2.1) | 20/481 (4.2) | .24 |
| Procedural details | | | |
| Time Tx to sheath in - min | 43 [33-51] / 136 | 45 [36-57] / 472 | .05 |
| Femoral access - no. (%) | 7/136 (5.1) | 11/472 (2.3) | .09 |
| TIMI 3 flow in the IRA pre-PCI - no. (%) | 54 (39.1) | 134 (29.6) | .04 |
| Culprit vessel - no. (%) | | | |
| LAD | 48/146 (32.9) | 213/481 (44.3) | .02 |
| RCA | 79/146 (54.1) | 176/481 (36.6) | <.01 |
| Cx | 13/146 (8.9) | 80/481 (16.6) | .02 |
| Multivessel disease - no. (%) | 59/147 (40.1) | 199/486 (40.9) | .86 |
| Primary PCI - no. (%) | 137/147 (93.2) | 476/486 (97.9) | .01 |
| Thrombectomy | 21/137 (15.3) | 102/474 (21.5) | .11 |
| Predilatation | 75/137 (54.7) | 291/474 (61.4) | .16 |
| DES | 130/137 (94.9) | 457/474 (96.4) | .49 |
| Postdilatation | 74/137 (54.0) | 271/474 (57.2) | .51 |
| Time sheath in to sheath out - min | 32 [24-47] | 36 [26-50] | .06 |
| Total ischemic time - min | 152 [113-239] | 147 [107-223] | .26 |
| Medication administration | | | |
| Analgesics (ambulance) - no. (%) | 23/111 (20.7) | 87/380 (22.9) | .63 |
| Crushed prasugrel LD - no. (%) | 76/147 (51.7) | 257/486 (52.8) | .80 |
| Glycoprotein bailout - no. (%) | 8/136 (5.9) | 45/472 (9.5) | .19 |
| UFH dose - IU*10$^3$ | | | |
| In ambulance | 5 [5-5] | 5 [5-5] | .07 |
| In catheterization laboratory | 7.5 [5-7.5] | 7.5 [7.5-7.5] | <.01 |

BMI, body mass index; CABG, coronary artery bypass graft; CVD, cardiovascular diseases; Cx, circumflex; DES, drug eluting stent; FMC, first medical contact; IRA, infarct-related artery; IU – international units; LAD, left anterior descending; LD, loading dose; MI, myocardial infarction; PCI, percutaneous coronary intervention; pPCI, primary percutaneous coronary intervention; RCA, right coronary artery; Tx, study treatment; TIMI, thrombolysis in myocardial infarction.

$P == .23$), or surgical revascularization with emergency coronary artery bypass grafting surgery instead of primary PCI (1.4% vs 1.0%, $P == .66$).

## Platelet reactivity and ACT

Pharmacodynamic and ACT assessments are summarized in Table II. At baseline before antithrombotic therapy initiation, females had higher levels of platelet reactivity than males (232 [IQR, 209-256] PRU vs 195 [IQR, 171-220] PRU, $P < .01$, Figure 1). Accordingly, the proportion of female STEMI patients exhibiting HPR at baseline was higher than in males (76% vs 41%, OR 4.58 [95%CI, 2.52-8.32], $P < .01$, Figure 2). Moreover, multivariable analysis identified female sex as the sole independent predictor of HPR at baseline (OR 5.67 [95%CI, 2.56-12.53], $P < .01$, Table III).

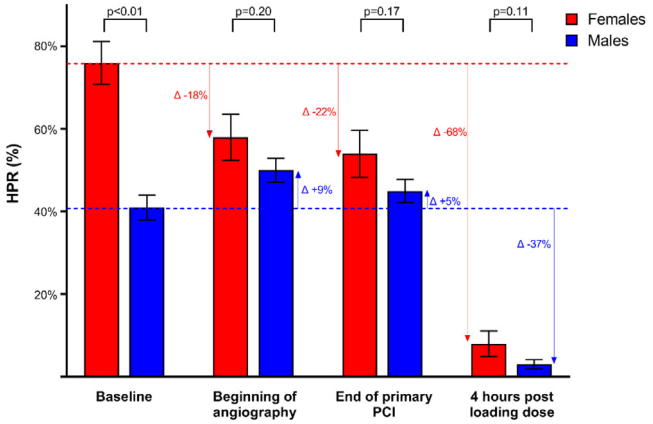
After antithrombotic therapy initiation, platelet reactivity levels at initial angiography, at the end of primary PCI and 4 hours after therapy initiation no longer differed significantly between females and males (228 [IQR, 146-255] PRU vs 207 [IQR, 156-245] PRU, $P == .11$; 221 [IQR, 100-270] PRU vs 196 [IQR, 83-243] PRU, $P == .12$; and 9 [IQR, 4-64] PRU vs 7 [IQR, 3-56] PRU, $P == .07$, respectively). In line, HPR rates at initial angiography, at the end of primary PCI and 4 hours after therapy initiation were comparable between sexes (58% vs 59%,

**Table II.** Sex-specific pharmacodynamic response to pre-hospital DAPT therapy

| Variable | Females | Males | Odds ratio (95%CI) | *P*-value |
|---|---|---|---|---|
| Baseline | | | | |
| PR - PRU | 232 [209-256] / 70 | 195 [171-220] / 269 | - | <.01 |
| HPR - no. (%) | 53 (75.7) / 70 | 109 (40.5) / 269 | 4.58 [2.52-8.32] | <.01 |
| At beginning of angiography | | | | |
| PR - PRU | 228 [146-255] / 78 | 207 [156-245] / 307 | - | .11 |
| HPR - no. (%) | 45/78 (57.7) / 78 | 152/307 (49.5) / 307 | 1.39 [0.84-2.30] | .20 |
| At the end of PCI | | | | |
| PR - PRU | 221 [100-270] / 78 | 196 [83-243] / 315 | - | .12 |
| HPR - no. (%) | 42/78 (53.8) / 78 | 142/315 (45.1) / 315 | 1.42 [0.86-2.34] | .17 |
| 4 hours post-LD | | | | |
| PR - PRU | 9 [4-64] / 77 | 7 [3-56] / 260 | - | .07 |
| HPR - no. (%) | 6 (7.8) / 77 | 9 (3.5) / 260 | 2.36 [0.81-6.84] | .11 |

High platelet reactivity was defined as PRU ≥208.
ACT, activated clotting time; CI, confidence interval; HPR – high platelet reactivity; LD, loading dose; PCI, primary percutaneous coronary intervention; PR, platelet reactivity; PRU, $P2Y_{12}$ reactivity unit.

**Figure 2**




Incidence of high platelet reactivity (defined as platelet reactivity ≥208 PRU) in response to pre-hospital DAPT initiation in female versus male STEMI patients. The error bars represent standard errors. HPR, high platelet reactivity; PCI, percutaneous coronary intervention.

OR 1.39, [95%CI, 0.84-2.30], $P$ == .20; 54% vs 45%, OR 1.42, [95%CI, 0.86-2.34], $P$ == .17; and 8% vs 4%; HPR, OR 2.36, [95%CI, 0.81-6.84], $P$ == .11, respectively). An additional sensitivity analysis, in which we excluded patients with missing baseline measurements, showed similar results between sexes (*Supplemental Table S1*).

All patients received a standardized unisex bolus of 5,000 units of unfractionated heparin in the ambulance. As a result, female STEMI patients were treated with a significantly higher heparin per kilogram ratio compared with males (68 ± 13 IU/kg vs 59 ± 9 IU/kg, $P$ < .01). In line, median ACT at the beginning of coronary angiography was significantly higher in females compared with males (161 [IQR, 140-198] sec vs 147 [IQR, 127-169] second, $P$ < .01, Table IV). The proportion of patients with ACT exceeding 300 sec was similar between groups (8% vs 5%, OR 1.52 [95%CI, 0.71-3.28], $P$ == .28). In line with the pre-hospital heparin dose, the second dose of heparin/kg at start of angiography was significantly higher in females tan in males (98 ± 27 IU/kg vs 87 ± 21 IU/kg, $P$ < .01). ACT measurements at the end of primary PCI remained significantly more prolonged in female STEMI patients (225 [IQR, 213-301] second vs 219 [IQR, 184-250] second, $P$ < .01), and ACT levels exceeding 300 sec occurred in 25.4% of the female STEMI patients vs 11.7% of the male STEMI patients (OR 2.58 [95%CI, 1.54-4.35], $P$ < .01).

**Table III.** Univariate and multivariable predictors of high platelet reactivity at baseline

| Variable | Univariate analysis Odds ratio (95% CI) | *P*-value | Multivariable analysis Odds ratio (95% CI) | *P*-value |
|---|---|---|---|---|
| Age* | 1.09 [0.92-1.30] | .31 | 0.98 [0.96-1.01] | .16 |
| Non-Caucasian ethnicity | 1.30 [0.62-2.73] | .49 | - | - |
| Female sex | 4.64 [2.53-8.52] | <.01 | 5.67 [2.56-12.53] | <.01 |
| Weight* | 0.84 [0.71-0.99] | .03 | 0.96 [0.89-1.03] | .25 |
| BMI | 0.97 [0.91-1.03] | .26 | - | - |
| Hypertension | 1.14 [0.74-1.76] | .56 | - | - |
| Diabetes mellitus | 0.79 [0.44-1.40] | .41 | - | - |
| Dyslipidemia | 1.05 [0.63-1.75] | .85 | - | - |
| Smoking | 0.87 [0.56-1.34] | .52 | 0.63 [0.34-1.18] | .15 |
| Family history of CVD | 0.99 [0.64-1.53] | .97 | - | - |
| Previous MI | 0.91 [0.42-1.96] | .80 | - | - |
| Time between onset and FMC* | 1.00 [0.98-1.01] | .66 | - | - |
| Time between FMC and Tx* | 1.06 [0.87-1.28] | .59 | - | - |
| KILIP score >1 | 0.79 [0.27-2.33] | .67 | - | - |
| LAD culprit | 0.76 [0.50-1.17] | .22 | - | - |
| RCA culprit | 1.12 [0.73-1.72] | .60 | - | - |
| Cx culprit | 1.17 [0.64-2.16] | .61 | - | - |
| Multivessel disease | 0.76 [0.50-1.16] | .20 | - | - |
| Beta blocker use | 1.54 [0.80-2.99] | .20 | - | - |
| ACE-I use | 1.06 [0.49-2.30] | .88 | - | - |
| ARB use | 0.92 [0.44-1.95] | .83 | - | - |
| Statins use | 0.96 [0.54-1.70] | .88 | - | - |
| CCB use | 0.92 [0.440-1.95] | .83 | - | - |

*Per 10 units increase.Univariate and multivariable predictor analyses were performed in the PD study cohort ($n = 441$).

**Table IV.** Sex-specific pharmacodynamic response to pre-hospital and in hospital UFH

| | Females | Males | OR | *P*-value |
|---|---|---|---|---|
| At beginning of angiography | | | | |
| ACT - sec | 161 [140-198] / 126 | 147 [127-169] / 448 | - | <.01 |
| ACT > 300 sec - no. (%) | 10 (7.9) / 126 | 24 (5.4) / 448 | 1.52 [0.71-3.28] | .28 |
| At the end of PCI | | | | |
| ACT - sec | 225 [213-301] / 114 | 219 [184-250] / 403 | - | <.01 |
| ACT > 300 sec - no. (%) | 29 (25.4) / 114 | 47 (11.7) / 493 | 2.58 [1.54-4.35] | <.01 |

ACT, activated clotting time; OR, odds ratio; PCI, percutaneous coronary intervention

### Clinical outcomes

Unadjusted and adjusted bleeding at 48 hours was significantly more common in females than in males (*Supplemental Table S2 and S3*). Bleeding of any type were reported in 15 females and 9 males (10.1% vs 1.9%, unadjusted OR 6.02 [95%CI, 2.58-14.07], $P < .01$; adjusted OR 3.25 [95%CI, 1.09-9.72], $P == .04$). This higher incidence was mainly driven by an increased incidence of BARC type I and II bleedings in the female group. The majority of all bleedings that occurred within 48 hours were directly access site related (females; 93% vs 67%, $P == .09$) and involved mostly the radial access site (88% of the total bleeds). There were 3 femoral related bleedings, which all occurred in females.

At 30 days, the incidence of MACCE was similar between groups (5.6% vs 4.6%, OR 1.22 [95%CI, 0.53-2.81], $P == .64$). Moreover, occurrence of the individual end points death, myocardial infarction, acute stent thrombosis, stroke or urgent revascularization rates were comparable between females and males.

## Discussion

Our key findings can be summarized as follows. First, we found that female STEMI patients exhibit higher platelet reactivity levels at presentation baseline compared with males. Moreover, female sex was identified as the sole independent predictor for HPR at baseline. Second, we found no sex-specific differences in the pharmacodynamic response to pre-hospital DAPT initiation in our cohort. Lastly, in this contemporary cohort female sex was independently associated with an increased risk of post-PCI bleeding.

The present substudy is – to the best of our knowledge – the largest pharmacodynamic substudy assessing sex-related differences in early response to $P2Y_{12}$ inhibitors in STEMI patients. We observed higher platelet

reactivity levels and a higher prevalence of HPR at baseline in female STEMI patients, with female sex identified as a strong independent predictor for baseline HPR. Increased HPR rates in females have been previously described in both stable and STEMI patients undergoing PCI.[15,22,23] In general, females tend to have higher platelet counts and a higher platelet aggregability than males.[24] Furthermore, estrogen modulates platelet function through estrogen specific membrane receptors towards a pro-aggregation state.[25] However, irrespective of the underlying biological phenomenon, the clinical impact of our findings remains unclear. Since the absolute levels of platelet reactivity between sexes did no longer differ after initiation of antiplatelet therapy, it is hence not considered to influence the observed increase in early bleeding events in females.

Evidence regarding sex-derived differences in early pharmacodynamics response to antithrombotic therapy in STEMI patients is scarce, especially when administered in a pre-hospital setting. Our results showed that the early pharmacodynamic response to prasugrel was similar between females and males, both pre and post-PCI. These findings were in line with the recently published sub analysis of the randomized ON-TIME 3 trial, reporting a similar sex-specific pharmacodynamic response measured directly post-PCI to pre-hospital administered crushed ticagrelor in 195 STEMI patients.[26] Moreover, similar results were seen in a subanalysis of the APACHE trial, which reviewed sex-differences in platelet reactivity in 125 patients with acute coronary syndrome (out of which approximately 60% with STEMI), treated with triple antiplatelet therapy.[27] Notably, the course of HPR throughout the first 4 hours did differ between sexes in our study. In male patients we noticed an initial increase in HPR at the beginning of primary PCI, whereas in females there was a consistent downward trend in HPR over time. This might be attributable to sex-derived differences in pharmacokinetics, as discussed by Tavenier et al.[26]

International guidelines recommend an initial unfractionated heparin bolus of 70 to 100 IU/kilogram in STEMI treatment.[3,27] In addition, for patients who have received unfractionated heparin treatment before entering the hospital, a second bolus is recommended to be administered directly before PCI, aimed to target ACT levels of 250 to 300s (Hemotec) or 300 to 350s (Hemachron).[27] In the Netherlands, the national STEMI protocol includes pre-hospital unfractionated heparin treatment initiation at first medical contact with the emergency medical service, consisting of a standardized bolus of 5,000 IU. After transfer to the catheterization laboratory, all patients received an additional bolus of unfractionated heparin, dosed at the operators discretion. In the present cohort we observed that female STEMI patients received significantly higher doses of pre-hospital and in-hospital heparin/kilogram compared with male STEMI patients. Since females had a lower body weight than males, this unisex unfractionated heparin dosing strategy resulted in a significantly higher total heparin/kilogram ratio in females compared with males. Accordingly, female STEMI patients had higher ACT levels pre and post-PCI, and more often exhibited ACT levels exceeding 300 sec post-PCI. Importantly, the excess use of parenteral therapies in females has been previously associated with an increase in bleeding.[28,29] Whereas we found no sex-specific differences regarding the pharmacodynamic response to pre-hospital DAPT initiation, this observed difference in heparin/kilogram dose administration might have contributed to the increased post-PCI bleeding rate in females. Future studies in contemporary STEMI cohorts are needed to investigate whether previous recommendations regarding heparin dosing and target ACTs are still valid, or whether lower dosing of anticoagulation therapy using lower target ACTs in the pre and in-hospital setting has the potential to decrease bleeding events without increasing ischemic risk, especially in female patients.

In the present analysis, we found a six-fold higher risk of bleeding of any type within the first 48 hours in females compared with males. Notably, a substantial part of these early bleedings were BARC type I and II classified bleedings. Abundant evidence demonstrates that bleeding events in patients presenting with acute coronary syndromes and those undergoing PCI have worse clinical outcomes than those patients who do not bleed.[1,6,30] Importantly, also milder degree of bleeds such as BARC type II have been associated with worse with long-term adverse outcomes and mortality.[31,32]

In our cohort, bleedings in the first 48 hours after PCI were predominantly access site related (80%), despite the fact that over 95% of patients were treated by a radial access route. The use of the femoral artery access site for PCI is well known for its association with an increase in early bleeding.[33] Furthermore, femoral compared to radial access use during primary PCI has been associated with an increased risk of 30-day mortality.[34] Whereas in our cohort the overall use of a femoral access was very low (3%), the femoral access site was used more frequently in females than in males. This is most likely explained by differences in anatomy with smaller radial diameter in female patients and increased occurrence of arterial spasm. However, excluding all femoral access cases in a sensitivity analysis (data not shown), did not seem to influence the significant increase in bleeding risk in females. In line, dedicated studies examining femoral versus radial access site for PCI did not show any significant interaction with sex regarding bleeding complications based on femoral access site.[35,36]

While age and presence of comorbidities have been linked to increase of bleeding and mortality in females, the available literature shows conflicting results regarding the role of female sex as an independent predictor

for bleeding. In line with the present substudy, 2 large registries investigating predictors of short-term bleeding in patients with ACS undergoing PCI indicated that female sex independently predicted perprocedural and in-hospital bleeding.[6,7] However, the sex-specific analysis of the ATLANTIC trial could not identify female sex as an independent predictor for early bleeding.[2] Accordingly, the authors of the academic research consortium high bleeding risk (ARC-HBR) consensus document refrained from identifying gender as a criterion for increased bleeding risk in their most recent publication.[37]

## Limitations

Our results should be reviewed in the light of several limitations. First, the results of the present post-hoc analysis have to be interpreted as hypothesis generating only. Importantly, this substudy was not powered to assess clinical end points. Second, female STEMI patients were underrepresented in the current analysis, comprising only 23% of the total cohort. However, the presentation of females included in this study is comparable to other randomized trials with STEMI patients. Third, the present analysis was not powered to detect differences in or assess predictors of clinical outcomes. Moreover, this analysis was not primarily powered to assess differences in platelet reactivity status between females and males. Fourth, platelet reactivity measurements were missing or not usable in approximately 30% of all patients, due to analysis time frame violation, suspected hemolysis and the use of glycoprotein IIb/IIIa inhibitor bailout. However, missing measurements were distributed even between sexes. Moreover, despite these missing measurements the present substudy remains – to the best of our knowledge – one of the largest pharmacodynamic trials in STEMI patients to date.

## Conclusion

In the contemporary era of STEMI management, females presenting with STEMI remain more prone for post-PCI bleeding complications after primary PCI compared with males. Importantly, this increased risk of bleeding is not explained by a sex-specific difference in pharmacodynamic response to pre-hospital DAPT initiation. However, abundant unfractionated heparin administration in females might represent as a potential risk factor for post-PCI bleeding, and warrants further investigation. These data add to the further understanding of the influence of sex on risk of complications in STEMI patients undergoing primary PCI.

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## Supplementary materials

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