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Women with STEMI, a high risk group for short-term mortality. Insights from the ATLANTIC study

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Manuscripts

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3 **Women with STEMI, a high risk group for short-term mortality. Insights**
4 **from the ATLANTIC study.**
5

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31 **ticagrelor**
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Abstract

Objectives

To evaluate gender differences in outcomes in STEMI patients treated with PPCI

Settings

A pre-specified gender analysis of the multicenter, randomised, double-blind ATLANTIC trial

Participants

Between September 2011 and October 2013, 1862 patients with STEMI and symptom duration less than 6 hours were included

Interventions

Patients were assigned to pre-hospital versus in-hospital administration of 180mg ticagrelor.

Outcomes

The main objective was to study the association between gender and primary and secondary outcomes of the main study with a focus on the clinical efficacy and safety outcomes.

Primary: The proportion of patients who did not have $\geq 70\%$ resolution of ST segment elevation and did not meet the criteria for TIMI flow 3 at initial angiography.

Secondary: the composite of death, MI, stent thrombosis, stroke, or urgent revascularisation and major or minor bleeding at 30 days.

Results

Women were older, had higher TIMI risk score, longer pre-hospital delays and better TIMI flow in the infarct related. Women had a 3-fold higher risk for all-cause mortality compared to men (5.7% vs 1.9%, HR 3.13, 95% CI 1.78 – 5.51). However, after adjustment for baseline characteristics, the difference was lesser and no longer significant (HR 1.98, 95% CI 0.97 – 4.04). Female gender was not an independent predictor of risk for bleeding after multivariable adjustments (PLATO major HR 1.52, 95% CI 0.76-3.03, TIMI major HR 1.41, 95% CI 0.52-3.88, BARC type 3-5 HR 1.52, 95% CI 0.74-3.09). There was no interaction between gender and efficacy or safety of randomised treatment.

Conclusion

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3 In STEMI patients treated with current PCI-techniques and modern antiplatelet therapy,
4 gender differences in short term mortality and inhospital bleeds could mainly be explained by
5 older age and clustering of comorbidities in women. Pre-hospital administration of ticagrelor
6 had a similar efficacy and safety profile in men and women with STEMI.
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12 **CLINICAL TRIAL REGISTRATION:** clinicaltrials.gov identifier: NCT01347580.
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15 **Strengths and limitations**

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17 Patients were treated according to the current guidelines of STEMI, current PCI techniques
18 and modern antiplatelet therapy including ticagrelor in addition to aspirin as soon as possible
19 after the first medical contact.
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24 The large imbalance in the proportion of men and women included in the ATLANTIC trial,
25 caused a reduced power for detecting significant differences in outcomes between the
26 genders.
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Introduction

Recent studies have provided evidence of gender differences in the pathophysiology and the clinical expression of atherosclerosis.(1) Several registries in patients with ST-segment elevation myocardial infarction (STEMI) have consistently shown a considerably higher risk of adverse outcomes in women compared to men. Nevertheless, there are conflicting results regarding whether gender is an independent contributor to this observation or the higher risk in women depends on differences in baseline characteristics and comorbidities between genders.(2-8) Although registries of STEMI patients usually include large, unselected populations, they share some inherent limitations. Their results are certainly influenced by differences between genders in the use of timely reperfusion therapy and evidence based drug therapies as well as undetected confounding factors.(9) Therefore, reports of gender-based analyses of randomised controlled trials are of crucial importance in an effort to minimise inequality in the management and evaluate gender as a potential independent risk factor for adverse outcome. Only a few randomised trials of STEMI patients treated with primary PCI (PPCI) have reported results in the context of gender.(10, 11) New treatments (e.g. ticagrelor or prasugrel), special efforts to reduce bleeding (i.e. increased use of radial arterial access, provisional rather than routine use of glycoprotein (GP) IIb/IIIa inhibitor), shorter delay times to reperfusion and a growing awareness regarding gender differences in the management and importance of adherences to evidence based treatment could contribute to improved ischemic and bleeding outcomes in female STEMI patients.

In the ATLANTIC trial, prehospital administration of ticagrelor appeared to be safe but did not significantly improve outcome compared to in hospital administration in patients with STEMI, treated with PPCI according to the current modern standards.(12)

We present a pre-specified gender analysis of the ATLANTIC trial, with the aim of studying the association between gender and outcome.

Methods

The ATLANTIC study was an international, randomised, double-blind, placebo-controlled study with 30 days follow-up. The design of the study, inclusion and exclusion criteria, outcome definitions and principal results have previously been described.(12, 13) Briefly, 1862 patients presenting with STEMI, less than 6 hours after symptom onset, were included and randomised to pre-hospital (in the ambulance) versus in-hospital (in the catheterisation laboratory) treatment with a loading dose of ticagrelor (180mg) in addition to aspirin and

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3 standard clinical care. All patients were to subsequently receive ticagrelor 90 mg twice daily
4 for 30 days, after which it was recommended that ticagrelor should be continued for up to 12
5 months. Pre-hospital administration of a GP IIb/IIIa inhibitor was left to the physician's
6 discretion. Peri-procedural use of parenteral anticoagulants was also left to the physician's
7 discretion, according to the local practice.
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11 The proportion of patients who did not have $\geq 70\%$ resolution of ST segment elevation before
12 PCI and / or did not meet the criteria for TIMI flow 3 in the infarct related artery (IRA) at
13 initial angiography was the primary outcome of the ATLANTIC trial. Secondary outcomes
14 (clinical efficacy outcomes) included the composite of death, MI, stent thrombosis, stroke, or
15 urgent revascularisation at 30 days and definite stent thrombosis at 30 days. Safety outcomes
16 included major and minor bleeding over the 30-day treatment period. Bleeding risk was
17 evaluated using the TIMI (The Thrombolysis In Myocardial Infarction), BARC (Bleeding
18 Academic Research Consortium) and PLATO (Study of Platelet Inhibition and Patient
19 Outcomes) bleeding definitions.(13)
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23 The main objective of our analysis was to study the association between gender and primary
24 and secondary outcomes of the main study with a special focus on the clinical efficacy and
25 safety outcomes. The interaction of gender subgroups with randomised treatment effects was
26 also investigated.
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30 The trial design and protocol were approved by the national regulatory authorities in all the
31 participating countries and by the local ethics committee or institutional review board at each
32 participating site. All patients provided written informed consent.
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35 36 37 38 39 40 41 42 43 **Statistical analysis**

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45 Continuous variables are presented by their mean and standard deviation (SD) or median and
46 25th -75th percentiles as appropriate. Categorical variables are presented as counts and
47 percentages. Baseline and peri-procedural characteristics were compared according to gender
48 by chi-square tests for categorical variables and Student's t-test or Mann Whitney U test for
49 continuous variables, depending on if the variable of interest was normally distributed or not.
50 A p-value < 0.05 is considered to indicate statistical significance.
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54 The incidence of events over time by gender is presented by Kaplan-Meier curves.
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3 In order to study the association between gender and the clinical efficacy and safety
4 outcomes, independent of randomised treatment as well as the possible interactions between
5 gender and randomised treatment with respect to the outcomes, hazard ratios [HR] with 95%
6 confidence intervals [CI] were derived from Cox proportional-hazards models. In the
7 unadjusted (crude) model, gender was the only explanatory variable whereas in the adjusted
8 multivariable model, gender was forcibly included and the other variables were chosen by
9 using a forward stepwise selection algorithm with a significant cut-off level of 0.05 for
10 inclusion. Adjustment variables included age, weight, prior MI, prior PCI, history of diabetes,
11 hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to
12 pre-PCI electrocardiogram [ECG], admission Killip class (as a dichotomous variable 1 / >1),
13 baseline hemoglobin, estimated glomerular filtration rate (eGFR) according to the MDRD
14 formula, use of GP IIIb/IIa inhibitor and location of MI. To evaluate the importance of early
15 mortality, a landmark analysis of the clinical efficacy outcomes was also performed from 48
16 hours after randomisation (arbitrarily defined) to the end of the study. In order to explore the
17 importance of bleeding on the clinical efficacy outcomes, a separate analysis was also
18 performed by censoring the patients who reported a PLATO major bleeding at the time of the
19 onset of a bleeding event.

20
21 A comparable statistical process was used to compare gender differences in the effect of
22 randomised treatment by constructing logistic regression models. Odds ratios [OR] with 95%
23 CI are presented. The above process for Cox regression and logistic regression was also used
24 to explore the interaction effect of gender and treatment.

25
26 For most of the variables included in the multivariable models, only few patients had missing
27 data (<10 patients). However, 7% of patients had missing values for creatinine, 5% for
28 hemoglobin and 4% for Killip class. The number of patients with complete data for
29 multivariable Cox proportional-hazard models of the primary outcome was 1613 (88%). To
30 investigate the influence of missing values, multivariable analysis was performed before and
31 after simple missing values imputation as well as with only gender and age as explanatory
32 variables (because these variables had no missing values).

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34 All the analyses were performed using SAS[®] version 9.3.

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Baseline and peri-procedural characteristics stratified by gender

Demographic and clinical characteristics

The study population consisted of 369 (20 %) women. They were older (mean age 69 vs. 59 years, $p<0.01$), had lower body mass index (BMI), higher TIMI risk score, more often had a history of hypertension, chronic obstructive pulmonary disease (COPD) and stroke. Men had more frequent prior PCI. No difference was observed between genders with respect to acute heart failure (Killip class > 1) and only a minority of patients presented with cardiogenic shock (**Table 1**).

Time delays

Women had significantly longer delay times, both from symptom onset to prehospital ECG (median 88 vs 70 minutes, $p<0.01$) and from pre-PCI to post-PCI angiography (median 36 vs 32 minutes, $p=0.03$).

Procedural characteristics, angiographic findings, and medication during the index event

Coronary angiography was more often performed by femoral access in women (39.7% vs 30.4%, $p<0.01$). The genders did not differ according to IRA, with the left anterior descending artery involved in 38% of women and 39% of men. PPCI, with or without stent, was performed significantly more often in men (88.5% vs 83.7%, $p<0.01$) whereas the use of drug eluting stents (DES) was similar. Thromboaspiration, GP IIb/IIIa inhibitors and intravenous anticoagulants were used less often in women. (**Table 1**)

Table 1. Baseline, clinical and periprocedural characteristics according to gender.

Characteristics	Women (n=369)	Men (n=1493)	P- value
Age, years; mean (SD)	69 (13.0)	59 (11)	<0.01
Age ≥ 75 years	153 (41.5)	151 (10.1)	<0.01
BMI, kg/m^2 ; median (IQR)	25.6 (22.5-29.1)	26.5 (24.3-29.4)	<0.01
Prior history			
Diabetes mellitus	48 (13.0)	205 (13.7)	0.72
Hypertension	190 (51.5)	605 (40.5)	<0.01
Dyslipidemia	117 (31.7)	536 (35.9)	0.13
Angina	36 (9.8)	157 (10.5)	0.67

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3	Prior myocardial infarction	24 (6.5)	135 (9.0)	0.67
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5	Prior PCI	16 (4.3)	124 (8.3)	<0.01
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7	Prior CABG	1 (0.3)	11 (0.7)	0.32
8				
9	Prior non-haemorrhagic stroke	8 (2.2)	10 (0.7)	<0.01
10				
11	Chronic obstructive pulmonary disease	22 (6.0)	54 (3.6)	0.04
12				
13	Gastrointestinal bleeding	1 (0.3)	16 (1.1)	0.15
14				
15	Chronic renal disease	7 (1.9)	27 (1.8)	0.91
16	Index event information			
17	First medical contact in ambulance	280 (75.9)	1132 (75.8)	0.24
18				
19	Minutes from symptom onset to pre-hospital ECG, median (IQR)	88 (49-169)	70 (41-129)	<0.01
20				
21	Minutes from prehospital ECG to PCI, median (IQR)	83 (68-101)	80 (66-96)	0.03
22				
23	Minutes from pre-PCI angiography to post-PCI angiography, median (IQR)	36 (24-52)	32 (23-45)	0.03
24				
25	Received first loading dose	369 (100)	1488 (99.7)	0.27
26				
27	Risk level at admission			
28	Killip class			
29				
30	I	332 (90.0)	1349 (90.4)	0.82
31	IV	2 (0.5)	3 (0.2)	
32				
33	TIMI risk score			
34	0-2	119 (32.2)	1006 (67.4)	<0.01
35	3-6	231 (62.6)	471 (31.5)	
36	>6	19 (5.1)	16 (1.1)	
37				
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39	Culprit vessel			
40	Left main artery	4 (1.1)	18 (1.2)	0.63
41				
42	Left anterior descending artery	141 (38.8)	571 (39.0)	
43				
44	Right coronary artery	150 (41.3)	590 (40.3)	
45				
46	Left circumflex	39 (10.7)	196 (13.4)	
47	No culprit vessel identified	28 (7.7)	85 (5.8)	
48				
49	Normal coronary angiography	27 (7.4)	76 (5.2)	0.1
50	Procedures for index event			
51	Femoral access	144 (39.7)	445 (30.4)	<0.01
52				
53	Thromboaspiration	160 (43.4)	781 (52.3)	<0.01
54				
55	PCI	309 (83.7)	1321 (88.5)	0.01
56	With any stent	288 (78.0)	1248 (83.6)	0.01
57	With DES	185 (50.1)	761 (51.0)	0.77
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Coronary artery bypass grafting	4 (1.1)	21 (1.4)	0.63
No revascularisation	56 (15.2)	151 (10.1)	<0.01
Any glycoprotein IIb/IIIa inhibitor use	115 (31.2)	598 (40.1)	<0.01
Glycoprotein IIb/IIIa inhibitor use before angiography	14 (3.8)	116 (7.8)	<0.01
Intravenous anticoagulant prior to pre-PCI angiography	231 (62.6)	1027 (68.8)	0.02
Intravenous anticoagulant during hospitalisation †	310 (84.0)	1332 (89.2)	<0.01
Heparin only	135 (36.6)	584 (39.1)	0.02
Bivalirudin only	29 (7.9)	65 (4.4)	0.02

Variables presented as numbers (percentages) unless otherwise indicated.

BMI, body mass index; CABG, coronary artery bypass grafting; DES, drug-eluting stent; IQR, interquartile range (25th–75th percentile); PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, Thrombolysis In Myocardial Infarction.

† Includes all IV medications given on the date of the qualifying ECG and /or index PCI

Association between gender and outcomes independent of randomised treatment

Female gender was associated with significantly higher risk for the composite outcome of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis compared to male gender (6.8% vs 3.9%, crude HR 1.79, 95% CI 1.12 – 2.86) (**Figure 1**). This difference was mainly driven by a 3-fold higher risk for all-cause mortality in women compared to men (5.7% vs 1.9%, HR 3.13, 95% CI 1.78 – 5.51). However, in the multivariable model, the gender effect was lower and not significantly associated with the composite primary outcome (HR 1.34, 95% CI 0.77 – 2.32) or with all-cause mortality (HR 1.98, 95% CI 0.97 – 4.04) (**Figure 2 and table 2**). The age-adjusted model showed age to be the most important predictor of mortality (age-adjusted all-cause mortality, women vs men HR 1.53, 95% CI 0.82 – 2.84). Landmark analysis for events occurring within 48 hours, and between 48 hours and 30 days showed that 38% of the women and 36% of the men who did not survive the first month died within 48 hours. Comparison after excluding patients from further analysis at the time point of a PLATO major bleeding event still revealed a statistically significant association between women and all-cause mortality (4.3% vs 1.4%. HR 3.20, 95% CI 1.67 – 6.13). However, as for the whole population, this difference was no longer significant in the multivariable model (HR 1.89, 95% CI 0.81-4.44).

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3 Female gender was associated with lower risk for TIMI flow < 3 in the IRA at initial
4 angiography (OR 0.64, 95% CI 0.46-0.91). The risk of incomplete ST-segment elevation
5 resolution (<70%) before PCI did not differ significantly between the genders (adjusted OR
6 1.15, 95% CI 0.75-1.76). The risk of abnormal TIMI flow in the IRA and incomplete ST
7 segment elevation resolution after PCI was similar in both genders (**Figure 3**).

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11 Women had significantly higher risk for major bleeding complications compared to men,
12 irrespective of the bleeding definition used (30-day PLATO major bleeding 4.6% vs 2.2%,
13 HR 2.15, 95% CI 1.18 – 3.85, TIMI major bleeding at 30 days 2.7% vs 0.9%, HR 2.95, 95%
14 CI 1.31 – 6.65, BARC type 3-5 bleeding 4.3% vs 2.1%, HR 2.15, 95% CI 1.18 – 3.93)
15 (**Figure 4**). However, after adjustment for baseline and clinical characteristics, female gender
16 was no longer an independent predictor of risk for bleeding at 30 days. (**Table 2 and figure**
17 **2**)

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20 To assess whether missing values may have influenced our results, multivariable analyses for
21 the primary, secondary and safety outcomes were performed adjusting for age and gender as
22 the only explanatory variables; these models provided similar results (data not shown).
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26 Furthermore, multivariable analyses for the primary and secondary outcomes were performed
27 before and after simple missing value imputation and showed similar results (data not
28 shown).
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54 **Table 2** Association between gender and clinical outcomes independent of randomised treatment
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Outcomes	Female (n=369)	Male (n=1489)	Crude hazard ratio (95%CI) (n included=1858)	Adjusted hazard ratio (95%CI)* (n included=1613)	P-value *
	Patients with endpoint, n (%)	Patients with endpoint, n (%)			
Mortality and cardiovascular outcomes					
Composite of death/MI/stroke/urgent revascularisation/definite acute stent thrombosis	25 (6.8)	58 (3.9)	1.79 (1.12-2.86)	1.34 (0.77-2.32)	0.30
Composite of death/MI/urgent revascularisation	23 (6.2)	50 (3.4)	1.91 (1.17-3.13)	1.32 (0.74-2.36)	0.35
All-cause mortality	21 (5.7)	28 (1.9)	3.13 (1.78-5.51)	1.98 (0.97-4.04)	0.06
Myocardial infarction	3 (0.8)	14 (0.9)	0.90 (0.26-3.13)	0.82 (0.23-2.85)	0.75
Stroke	3 (0.8)	3 (0.2)	4.18 (0.84-20.70)	4.14 (0.84-20.53)	0.08
Urgent revascularisation	2 (0.5)	11 (0.7)	0.75 (0.17-3.38)	0.69 (0.15-3.11)	0.63
Definite acute stent thrombosis	3 (0.8)	10 (0.7)	1.23 (0.34-4.49)	1.29 (0.35-4.76)	0.70
Acute stent thrombosis (definite or probable)	11 (3.0)	30 (2.0)	1.53 (0.77-3.05)	0.88 (0.39-1.98)	0.76
Safety outcomes					
PLATO major bleeding **	17 (4.6)	33 (2.2)	2.15 (1.20-3.85)	1.52 (0.76-3.03)	0.24
TIMI major bleeding **	10 (2.7)	14 (0.9)	2.95 (1.31-6.65)	1.41 (0.52-3.88)	0.50
TIMI major or minor bleeding**	18 (4.9)	54 (3.6)	1.38 (0.81-2.35)	1.0 (0.54-1.86)	0.99

BARC type 3-5 (major) bleeding**	16 (4.3)	31 (2.1)	2.15 (1.18-3.93)	1.52 (0.74-3.09)	0.25
BARC type 2-5 (major or minor) bleeding**	20 (5.4)	56 (3.8)	1.48 (0.89-2.47)	1.09 (0.60-1.97)	0.78

*Hazard ratio (for female versus male) and p-value calculated from logistic regression model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

**Non-CABG related bleeding occurring up to the date of the last study visit (to the maximum of 32 days) are included in the table

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; PLATO, Study of Platelet Inhibition and Patient Outcomes; TIMI, Thrombolysis in Myocardial Infarction

Association between gender and efficacy and safety of randomised treatment

Pre-hospital administration of ticagrelor compared to in-hospital administration resulted in a non-significant difference in the primary, secondary and safety outcomes. No significant interactions between randomised treatment and gender in terms of these outcomes were found in the unadjusted or adjusted model (test for interaction in the multivariable models; $p=0.86$ for the primary outcome, $p=0.93$ for all-cause mortality, $p=0.19$ for absence of TIMI flow grade 3 in the IRA at initial angiography, $p=0.71$ for absence of $\geq 70\%$ resolution of pre-PCI ST segment elevation, and $p=0.28$ for TIMI major bleeding at 30 days). (Supplementary tables 1, 2 and 3).

Discussion

In the present analysis, unadjusted data showed a significantly higher risk of the composite outcome of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis in women, mainly driven by a three times higher risk for short-term mortality. After multivariable adjustment female gender was not an independent predictor of worse outcome.

Undoubtedly, older age and clustering of comorbidities in women could explain a large part of the observed difference in short term clinical outcomes in our study. However, the adjusted risk for death, while not statistically significant, was still considerably higher in women, generating the hypothesis that gender could be an independent predictor of early mortality if the population of the study was larger. Any possible contribution of gender, as independent risk factor, on adverse outcome may depend on the population studied. The age gap between genders in our population was substantially higher compared to previous studies, with a mean age difference of 10 years.^(11, 16) In spite of appropriate statistical methods that were used for adjustment, adjustment for such age-difference is awkward. Additionally, the age difference may indicate a selection bias. As identification and randomisation took place in the ambulance, young women with suspected STEMI were possibly not included in the study as alternative reasons for ST-segment elevation on prehospital ECG may have been considered more plausible in this group. These factors may explain the observed trend toward increased adjusted risk for early mortality in women.

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3 A plethora of observational studies in STEMI cohorts and a meta-analysis have shown a
4 higher risk of early mortality in women.(6, 7, 14, 15) Significant differences in the rate of
5 reperfusion therapy between genders and hidden confounders such as frailty in elderly
6 women with STEMI may partially explain their results. In accordance with our results,
7 previous gender analyses of RCTs have shown that the impact of gender on mortality could
8 mainly be explained by differences in age and comorbidities between genders.(10, 11, 16-18)
9 In the CADILLAC study,(10) women had a 4-fold higher unadjusted risk for 30 days
10 mortality but after adjustment no significant difference remained. In STEMI treated with
11 thrombolysis Motovska et al showed that gender was not an independent predictor of
12 outcome,(11) The recent PLATO trial showed concurred results but NSTEMI and STEMI
13 patients were pooled in the gender analysis, despite the fact that the relationship between
14 gender and outcome depends on the type of ACS.(19) Most of these studies do not reflect
15 current treatment of STEMI patients. Despite evolving PCI techniques and novel
16 pharmacological treatment, women still have worse short term outcome and special effort,
17 with respect to their advanced age and comorbidities, to improve their outcomes are
18 warranted.
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30 Some well-known gender disparities in the concomitant management of STEMI patients
31 remained unchanged. Women were less likely to be treated with GP IIb/IIIa inhibitors and
32 thrombo-aspiration during PPCI despite lack of gender difference in protection from major
33 adverse outcomes by GP IIb/IIIa inhibitors (20) and benefit of thrombo-aspiration at the time
34 when the study was conducted.(21) Similar findings have been provided by large
35 registries.(7, 8) Some of these lower rates of utilization may be “appropriate” given the
36 higher TIMI 3 flow rates in the IRA pre-PPCI and lower rates of PPCI in women vs. men.
37 Furthermore, physician’s concern for higher risk of bleeding in older women with STEMI
38 have certainly contributed to the lower use of GP IIb/IIIa inhibitors in women.
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46 Although the impact of early reperfusion on mortality in STEMI patients is now
47 unquestionable,(22) patients’ delay from symptom onset to prehospital ECG was not an
48 independent predictor of mortality in our study, in agreement with results from previous
49 gender analyses.(23, 24) A plausible explanation is an association between age and delay,
50 and thus adjustment for age minimizes the relative impact of delay. Furthermore, in PPCI,
51 female gender has been associated with similar or even smaller infarct size than that in male
52 gender, due to longer prehospital delays, indicating that other factors than larger infarct size
53 secondary to longer prehospital delay mainly contribute to the observed higher unadjusted
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3 short term mortality.(23) The proportion of 30 day mortality that occurred within 48 hours of
4 admission was similar in women and men (38% vs 36% respectively) contrasting previous
5 data where gender differences in early mortality were accounted for by excess very early
6 (within 24-48 hours) deaths in women with STEMI.(7, 25) Cardiogenic shock and
7 hemodynamic instability were key exclusion criteria in the ATLANTIC trial which may have
8 influenced these results. Cardiogenic shock has been shown to be more common in women
9 and female gender has been highly associated with mortality in shock patients.(26)

10
11 In the present study, women had a 2-3 times higher unadjusted risk for non-CABG related
12 bleedings, depending on the definition used. After adjustment for baseline characteristics, no
13 significant difference remained. Female gender has previously been associated with higher
14 risk for bleeding complications in patients with ACS.(27-30) Known predictors of bleedings
15 like advanced age, diabetes, hypertension, renal insufficiency and anemia, are usually more
16 often encountered in women with STEMI.(31) Additionally, smaller body and vessel size,
17 higher use of femoral access and overdosing of antithrombotic medication in women may
18 explain the higher observed risk for bleeding. Procedural-related improvement such as
19 increased use of radial access or smaller femoral sheaths and careful dose adjustment of
20 antithrombotic medication, have resulted in a significant decline in the risk of
21 bleeding/vascular complication during cardiovascular interventions the last years and have
22 probably contributed to our results. (32)

23
24 The negative impact of bleedings on prognosis in patients with STEMI is well established.
25 (31) Our data showed that even after excluding patients from further analysis at the time of a
26 PLATO major bleeding, the unadjusted HR for early mortality in women vs men remained
27 unchanged, implying that reducing the rate of major bleeding in women may improve their
28 prognosis but is not the main reason for the observed difference between genders in the early
29 mortality.

30
31 In terms of ST-segment elevation resolution and TIMI flow 3 rates before and after PCI, no
32 significant difference between genders was observed apart from a lower risk of abnormal
33 coronary flow in IRA at initial angiography in women. The higher rate of TIMI flow 3 at
34 initial angiography may be explained by the higher rate of normal coronary arteries as well as
35 the less obstructive coronary artery disease in women with STEMI, which is in concordance
36 with previous data.(24)

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3 The analysis of the effect of gender on outcomes dependent on the randomised treatment
4 showed no statistically significant interactions. Pre-hospital administration of ticagrelor did
5 not improve pre- or post-PCI coronary reperfusion as assessed by TIMI flow in IRA and
6 resolution of ST elevation pre-PCI. Clinical efficacy outcomes were not significantly
7 improved either. However, prehospital administration of ticagrelor was safe in both genders
8 with similar rate of major and minor bleedings.
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13 14 15 **Strengths and limitations**

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17 The present study has some important limitations. The ATLANTIC trial was not stratified by
18 gender. The large imbalance in the proportion of men and women included, commonly
19 encountered in a STEMI population, caused a reduced power for detecting significant
20 differences in outcomes between the genders or to definitely exclude an interaction between
21 gender and the randomised treatment.
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26 The most important strength of our analysis is that patients were treated according to the
27 current guidelines of STEMI, with PPCI as the reperfusion strategy of choice, administration
28 of the modern ADP receptor-blocker ticagrelor in addition to aspirin as soon as possible after
29 the first medical contact, high use of radial access during catheterisation and adjuvant
30 pharmacologic treatment during PPCI with UFH or bivalirudin. (33) Therefore our study
31 provides important information about differences and similarities between genders in STEMI
32 patients treated with current PCI techniques and pharmacologic treatment.
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39 40 **Conclusion**

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42 In patients with STEMI, treated with PPCI women have significantly higher mortality and
43 bleeding complications. However, after adjustment for baseline characteristics, the observed
44 gender differences were attenuated and no longer statistically significant, indicating that at
45 least part of the observed difference is explained by older age and clustering of comorbidities
46 in women. Regardless, female gender identifies a group of patients with high risk of early
47 mortality in whom prompt efforts to improve outcome are warranted. Prehospital
48 administration of ticagrelor had a similar efficacy and safety profile in men and women with
49 STEMI.
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Author's contribution

E. Swahn is responsible for the conception and design of the gender substudy of the ATLANTIC trial.

D. Venetsanos is responsible for analyses and interpretation of the data and drafted the manuscript.

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3 S. Sederholm Lawesson, J. Alfredsson, M. Janzon, A.Cequier, M. Chettibi, S.G. Goodman, A.W. van't
4 Hof and G. Montalescot have critically revised the manuscript and added important intellectual
5 content.
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7 All authors have participated in the work and have read and approved the manuscript.
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For peer review only

References

1. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *Journal of the American College of Cardiology*. 2006 Feb 7;47(3 Suppl):S21-9. PubMed PMID: 16458167.
2. Mehta RH, Stebbins AS, Lopes RD, Califf RM, Pieper KS, Armstrong PW, et al. Comparison of incidence of bleeding and mortality of men versus women with ST-elevation myocardial infarction treated with fibrinolysis. *The American journal of cardiology*. 2012 Feb 1;109(3):320-6. PubMed PMID: 22078221.
3. Kyto V, Sipila J, Rautava P. Gender and in-hospital mortality of ST-segment elevation myocardial infarction (from a multihospital nationwide registry study of 31,689 patients). *The American journal of cardiology*. 2015 Feb 1;115(3):303-6. PubMed PMID: 25488357.
4. Jakobsen L, Niemann T, Thorsgaard N, Nielsen TT, Thuesen L, Lassen JF, et al. Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2012 Dec 20;8(8):904-11. PubMed PMID: 23253544.
5. Kang SH, Suh JW, Yoon CH, Cho MC, Kim YJ, Chae SC, et al. Sex differences in management and mortality of patients with ST-elevation myocardial infarction (from the Korean Acute Myocardial Infarction National Registry). *The American journal of cardiology*. 2012 Mar 15;109(6):787-93. PubMed PMID: 22196789.
6. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. A gender perspective on short- and long term mortality in ST-elevation myocardial infarction--a report from the SWEDEHEART register. *International journal of cardiology*. 2013 Sep 30;168(2):1041-7. PubMed PMID: 23168004.
7. de Boer SP, Roos-Hesselink JW, van Leeuwen MA, Lenzen MJ, van Geuns RJ, Regar E, et al. Excess mortality in women compared to men after PCI in STEMI: an analysis of 11,931 patients during 2000-2009. *International journal of cardiology*. 2014 Sep 20;176(2):456-63. PubMed PMID: 25127966.
8. Leurent G, Garlantezec R, Auffret V, Hacot JP, Coudert I, Filippi E, et al. Gender differences in presentation, management and inhospital outcome in patients with ST-segment elevation myocardial infarction: data from 5000 patients included in the ORBI prospective French regional registry. *Archives of cardiovascular diseases*. 2014 May;107(5):291-8. PubMed PMID: 24910083.
9. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. Time trends in STEMI--improved treatment and outcome but still a gender gap: a prospective observational cohort study from the SWEDEHEART register. *BMJ open*. 2012;2(2):e000726. PubMed PMID: 22457480. Pubmed Central PMCID: 3323814.
10. Lansky AJ, Pietras C, Costa RA, Tsuchiya Y, Brodie BR, Cox DA, et al. Gender differences in outcomes after primary angioplasty versus primary stenting with and without abciximab for acute myocardial infarction: results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation*. 2005 Apr 5;111(13):1611-8. PubMed PMID: 15811868.
11. Motovska Z, Widimsky P, Aschermann M, Investigators PSG. The impact of gender on outcomes of patients with ST elevation myocardial infarction transported for percutaneous coronary intervention: analysis of the PRAGUE-1 and 2 studies. *Heart*. 2008 Mar;94(3):e5. PubMed PMID: 17693459.
12. Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *The New England journal of medicine*. 2014 Sep 11;371(11):1016-27. PubMed PMID: 25175921.

13. Montalescot G, Lassen JF, Hamm CW, Lapostolle F, Silvain J, ten Berg JM, et al. Ambulance or in-catheterization laboratory administration of ticagrelor for primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: rationale and design of the randomized, double-blind Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) study. *American heart journal*. 2013 Apr;165(4):515-22. PubMed PMID: 23537967.
14. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. *JAMA internal medicine*. 2014 Nov;174(11):1822-30. PubMed PMID: 25265319.
15. Benamer H, Tafflet M, Bataille S, Escolano S, Livarek B, Fourchard V, et al. Female gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI: insights from the greater Paris area PCI Registry. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2011 Apr;6(9):1073-9. PubMed PMID: 21518679.
16. Wijnbergen I, Tijssen J, van 't Veer M, Michels R, Pijls NH. Gender differences in long-term outcome after primary percutaneous intervention for ST-segment elevation myocardial infarction. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2013 Sep 1;82(3):379-84. PubMed PMID: 23553888.
17. Husted S, James SK, Bach RG, Becker RC, Budaj A, Heras M, et al. The efficacy of ticagrelor is maintained in women with acute coronary syndromes participating in the prospective, randomized, PLATElet inhibition and patient Outcomes (PLATO) trial. *European heart journal*. 2014 Jun 14;35(23):1541-50. PubMed PMID: 24682844. Pubmed Central PMCID: 4057642.
18. De Luca G, Gibson CM, Gyongyosi M, Zeymer U, Dudek D, Arntz HR, et al. Gender-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty and glycoprotein IIb/IIIa inhibitors: insights from the EGYPT cooperation. *Journal of thrombosis and thrombolysis*. 2010 Oct;30(3):342-6. PubMed PMID: 20213259.
19. Champney KP, Frederick PD, Bueno H, Parashar S, Foody J, Merz CN, et al. The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction. *Heart*. 2009 Jun;95(11):895-9. PubMed PMID: 19147625. Pubmed Central PMCID: 3065924.
20. Cho L, Topol EJ, Balog C, Foody JM, Booth JE, Cabot C, et al. Clinical benefit of glycoprotein IIb/IIIa blockade with Abciximab is independent of gender: pooled analysis from EPIC, EPILOG and EPISTENT trials. *Evaluation of 7E3 for the Prevention of Ischemic Complications. Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stent*. *Journal of the American College of Cardiology*. 2000 Aug;36(2):381-6. PubMed PMID: 10933346.
21. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet*. 2008 Jun 7;371(9628):1915-20. PubMed PMID: 18539223.
22. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation*. 2004 Mar 16;109(10):1223-5. PubMed PMID: 15007008.
23. Sadowski M, Gasior M, Gierlotka M, Janion M, Polonski L. Gender-related differences in mortality after ST-segment elevation myocardial infarction: a large multicentre national registry. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2011 Apr;6(9):1068-72. PubMed PMID: 21518678.
24. Otten AM, Maas AH, Ottervanger JP, Kloosterman A, van 't Hof AW, Dambrink JH, et al. Is the difference in outcome between men and women treated by primary percutaneous coronary intervention age dependent? Gender difference in STEMI stratified on age. *European heart*

1
2
3 journal Acute cardiovascular care. 2013 Dec;2(4):334-41. PubMed PMID: 24338292. Pubmed Central
4 PMCID: 3821825.

5 25. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, et al. Sex
6 differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008 Dec
7 16;118(25):2803-10. PubMed PMID: 19064680.

8 26. Suessenbacher A, Doerler J, Alber H, Aichinger J, Altenberger J, Benzer W, et al.
9 Gender-related outcome following percutaneous coronary intervention for ST-elevation myocardial
10 infarction: data from the Austrian acute PCI registry. *EuroIntervention : journal of EuroPCR in*
11 *collaboration with the Working Group on Interventional Cardiology of the European Society of*
12 *Cardiology*. 2008 Aug;4(2):271-6. PubMed PMID: 19110794.

13 27. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, et al. Bleeding in acute
14 coronary syndromes and percutaneous coronary interventions: position paper by the Working
15 Group on Thrombosis of the European Society of Cardiology. *European heart journal*. 2011
16 Aug;32(15):1854-64. PubMed PMID: 21715717.

17 28. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to
18 predict bleeding in patients with acute coronary syndromes. *Journal of the American College of*
19 *Cardiology*. 2010 Jun 8;55(23):2556-66. PubMed PMID: 20513595.

20 29. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, et al. Bleeding
21 complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet
22 inhibition and patient Outcomes (PLATO) trial. *European heart journal*. 2011 Dec;32(23):2933-44.
23 PubMed PMID: 22090660.

24 30. Mathews R, Peterson ED, Chen AY, Wang TY, Chin CT, Fonarow GC, et al. In-hospital
25 major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and
26 validation of a model from the ACTION Registry(R)-GWTG. *The American journal of cardiology*. 2011
27 Apr 15;107(8):1136-43. PubMed PMID: 21324428.

28 31. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, et al. Impact of
29 major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary
30 syndromes: an analysis from the ACUITY Trial. *Journal of the American College of Cardiology*. 2007
31 Mar 27;49(12):1362-8. PubMed PMID: 17394970.

32 32. Ahmed B, Piper WD, Malenka D, VerLee P, Robb J, Ryan T, et al. Significantly improved
33 vascular complications among women undergoing percutaneous coronary intervention: a report
34 from the Northern New England Percutaneous Coronary Intervention Registry. *Circulation*
35 *Cardiovascular interventions*. 2009 Oct;2(5):423-9. PubMed PMID: 20031752.

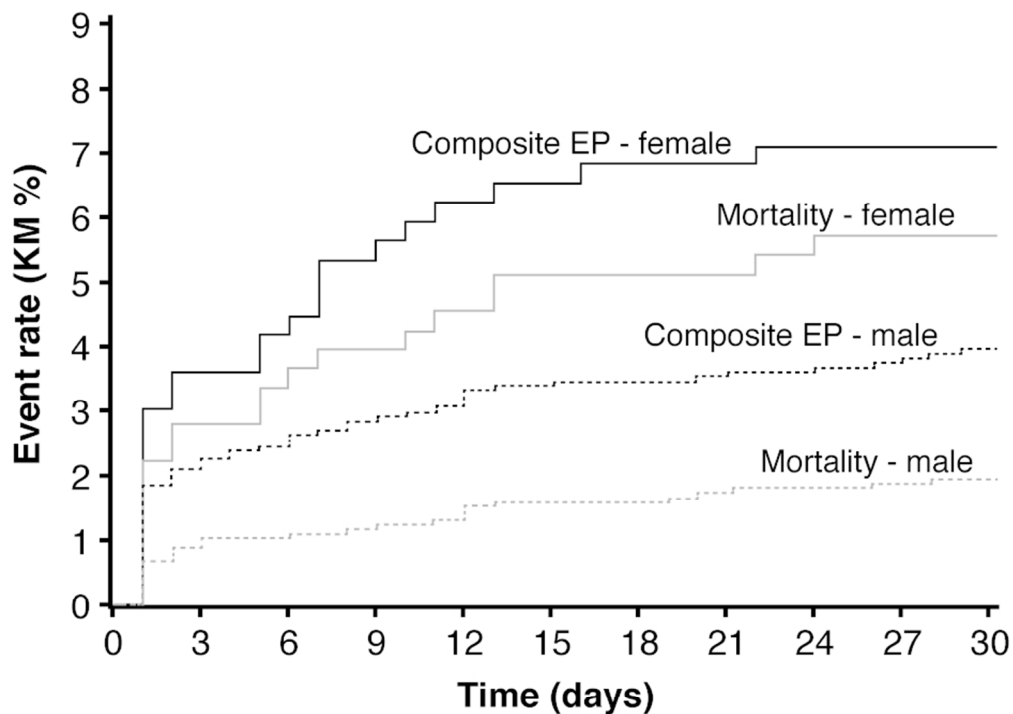
36 33. Wessler JD, Stant J, Duru S, Rabbani L, Kirtane AJ. Updates to the ACCF/AHA and ESC
37 STEMI and NSTEMI guidelines: putting guidelines into clinical practice. *The American journal of*
38 *cardiology*. 2015 Mar 14;115(5 Suppl):23A-8A. PubMed PMID: 25728971.

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Composite endpoint	All-cause mortality
Female 25/369 (6.8%)	Female 21/369 (5.7%)
Male 58/1489 (3.9%)	Male 28/1489 (1.9%)

Figure 1. Cumulative Kaplan-Meier estimates of the incidence of the composite endpoint of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis and all-cause mortality at 30 days by gender.

79x70mm (300 x 300 DPI)

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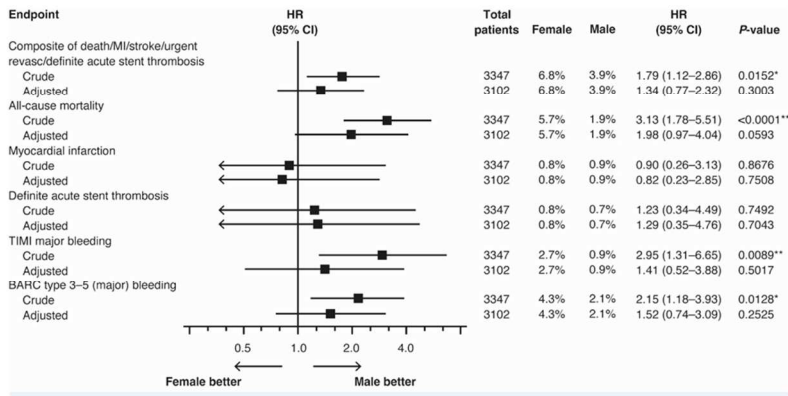


Figure 2. Association between gender and clinical outcomes independent of randomised treatment.

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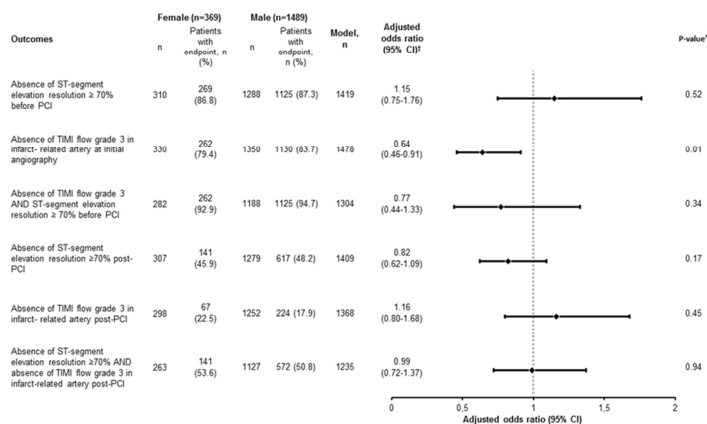
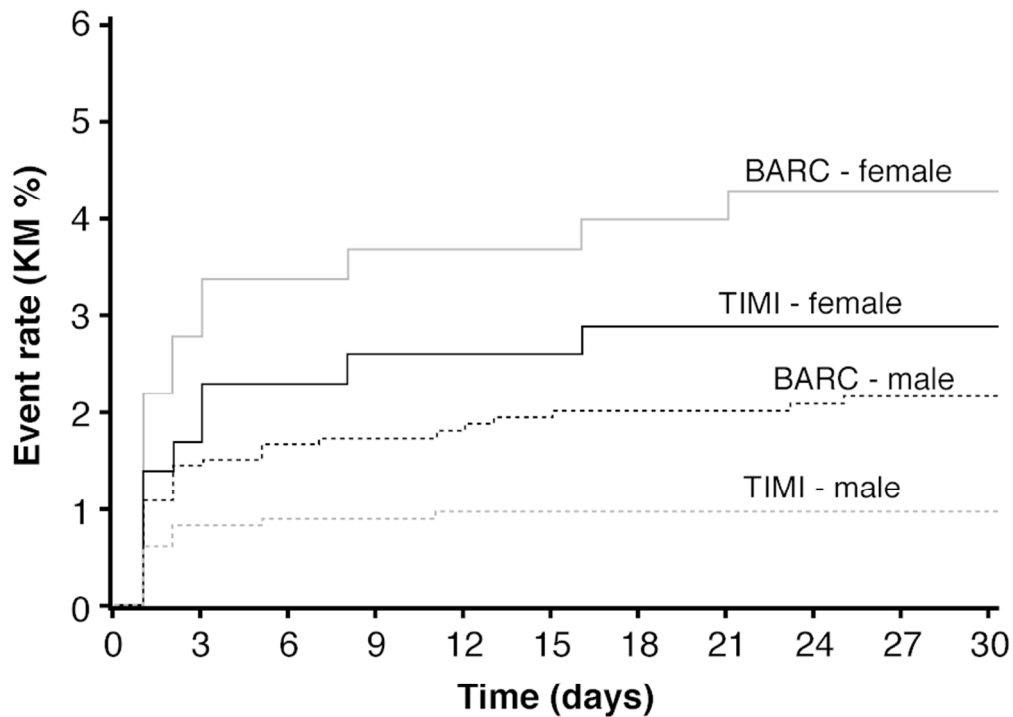


Figure 3. †Odds ratio (for female versus male) and p-value calculated from logistic regression model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-haemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline haemoglobin, estimated glomerular filtration rate, glycoprotein Iib/IIIa inhibitor use during index procedure, location of myocardial infarction

338x190mm (96 x 96 DPI)

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TIMI major bleed	BARC type 3–5 bleed
Female 10/369 (2.7%)	Female 16/369 (4.3%)
Male 14/1489 (0.9%)	Male 31/1489 (2.1%)

Figure 4. Cumulative Kaplan-Meier estimates of the incidence of the TIMI major bleeding and BARC type 3-5 bleeding at 30 days by gender.

79x69mm (300 x 300 DPI)

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Supplementary table 1 Association between gender and efficacy of randomised treatment – clinical outcomes

Outcomes	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model, n	Adjusted hazard ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
Composite of Death/MI/Stroke/Urgent Revasc/Definite Acute Stent Thrombosis	Female	173	13 (7.5)	196	12 (6.1)	1613	0.98 (0.42-2.27)	0.87
	Male	733	28 (3.8)	756	30 (4.0)		0.90 (0.51-1.59)	
Composite of Death/MI/Urgent Revasc	Female	173	13 (7.5)	196	10 (5.1)	1613	1.32 (0.55-3.20)	0.55
	Male	733	26 (3.5)	756	24 (3.2)		0.95 (0.52-1.76)	
All-cause mortality	Female	173	13 (7.5)	196	8 (4.1)	1613	1.59 (0.61-4.12)	0.93
	Male	733	17 (2.3)	756	11 (1.5)		1.50 (0.60-3.74)	
Myocardial infarction	Female	173	1 (0.6)	196	2 (1.0)	1613	0.44 (0.04-4.95)	0.72
	Male	733	6 (0.8)	756	8 (1.1)		0.72 (0.25-2.09)	
Stroke	Female	173	1 (0.6)	196	2 (1.0)	1613	0.54 (0.05-5.90)	0.99
	Male	733	3 (0.4)	756	0 (0.0)		Nt estimated	
Urgent revascularization	Female	173	1 (0.6)	196	1 (0.5)	1613	0.86 (0.05-14.07)	0.76
	Male	733	4 (0.5)	756	7 (0.9)		0.54 (0.15-1.87)	
Definite Acute Stent Thrombosis	Female	173	1 (0.6)	196	2 (1.0)	1613	0.37 (0.03-4.27)	0.49
	Male	733	1 (0.1)	756	9 (1.2)		0.12 (0.01-1.02)	
Acute Stent Thrombosis (definite or probable)	Female	173	7 (4.0)	196	4 (2.0)	1613	1.31 (0.37-4.69)	0.52
	Male	733	14 (1.9)	756	16 (2.1)		0.80 (0.35-1.80)	

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≠ Adjusted hazard (for female versus male) and p-values for interaction was calculated from Cox proportional hazard model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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Supplementary table 2 Association between gender and efficacy of randomised treatment – primary and secondary outcomes

Outcomes	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model N ≠	Adjusted odds ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
Absence of ST segment elevation resolution ≥ 70% pre-PCI	Female	142	122 (85.9)	168	147 (87.5)	1419	0.75 (0.37-1.53)	0.71
	Male	632	550 (87.0)	656	575 (87.7)		0.85 (0.59-1.23)	
Absence of TIMI flow grade 3 in infarct related artery at initial angiography	Female	155	127 (81.9)	175	135 (77.1)	1478	1.36 (0.76-2.41)	0.19
	Male	669	554 (82.8)	681	576 (84.6)		0.88 (0.64-1.20)	
Absence of ST segment resolution ≥ 70% AND absence of TIMI flow grade 3 in infarct related artery pre-PCI	Female	129	120 (93.0)	153	142 (92.8)	1304	1.07 (0.41-2.81)	0.84
	Male	590	557 (94.4)	598	568 (95.0)		0.96 (0.57-1.62)	
Absence of ST-segment resolution ≥70% after PCI	Female	144	61 (42.4)	163	80 (49.1)	1409	0.76 (0.47-1.25)	0.51
	Male	629	291 (46.3)	650	326 (50.2)		0.92 (0.72-1.17)	
Absence of TIMI flow grade 3 in infarct related artery after PCI	Female	144	30 (20.8)	154	37 (24.0)	1368	0.93 (0.51-1.71)	0.98
	Male	621	107 (17.2)	631	117 (18.5)		0.92 (0.68-1.26)	
Absence of ST segment resolution ≥70% AND absence of TIMI flow grade 3 in infarct related artery after PCI	Female	125	60 (48.0)	138	81 (58.7)	1235	0.64 (0.38-1.10)	0.13
	Male	562	282 (50.2)	565	290 (51.3)		1.01 (0.78-1.32)	

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3 ≠ Adjusted odds ratio (for female versus male) and p-values for interaction was calculated from
4 logistic regression model including gender, age, weight, prior myocardial infarction, prior
5 percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke,
6 gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class,
7 baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during
8 index procedure, location of myocardial infarction
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Supplementary table 3 Association between gender and safety of randomised treatment (safety outcomes)

End point	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model N ≠	Adjusted hazard ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
PLATO major bleeding	Female	173	6 (3.5)	196	11 (5.6)	1613	0.61 (0.21-1.83)	0.23
	Male	733	19 (2.6)	756	14 (1.9)		1.39 (0.66-2.93)	
PLATO major and minor bleeding	Female	173	7 (4.0)	196	13 (6.6)	1613	0.59 (0.22-1.61)	0.19
	Male	733	33 (4.5)	756	26 (3.4)		1.27 (0.73-2.21)	
TIMI major bleeding	Female	173	3 (1.7)	196	7 (3.6)	1613	0.60 (0.14-2.54)	0.28
	Male	733	9 (1.2)	756	5 (0.7)		1.62 (0.53-4.98)	
TIMI major and minor bleeding	Female	173	6 (3.5)	196	12 (6.1)	1613	0.55 (0.19-1.60)	0.24
	Male	733	29 (4.0)	756	25 (3.3)		1.14 (0.64-2.03)	
BARC type 3-5 (major) bleeding	Female	173	6 (3.5)	196	10 (5.1)	1613	0.69 (0.23-2.11)	0.26
	Male	733	18 (2.5)	756	13 (1.7)		1.51 (0.70-3.26)	
BARC type 2-5 (major and minor) bleeding	Female	173	7 (4.0)	196	13 (6.6)	1613	0.59 (0.22-1.60)	0.21
	Male	733	31 (4.2)	756	25 (3.3)		1.23 (0.70-2.17)	

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3 #Adjusted hazard (for female versus male) and p-values for interaction was calculated from Cox
4 proportional hazard model including gender, age, weight, prior myocardial infarction, prior
5 percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke,
6 gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class,
7 baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during
8 index procedure, location of myocardial infarction
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5, 6
		(b) Describe any methods used to examine subgroups and interactions	5, 6
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	4 NA (SEE PAGE 4)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7, 8, 9 6 NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 10, 11, 12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9, 10, 11, 12 yes
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	13, 14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13, 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association between gender and short term outcome in STEMI patients planned for primary PCI and novel antiplatelet therapy.

A pre-specified gender analysis of the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial – a multicenter, randomised, placebo-controlled study.

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Association between gender and short term outcome in STEMI patients planned for primary PCI and novel antiplatelet therapy.

A pre-specified gender analysis of the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial – a multicenter, randomised, placebo-controlled study.

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Keywords: myocardial infarction, STEMI, gender, primary PCI, ATLANTIC, ticagrelor

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Abstract

Objectives

To evaluate gender differences in outcomes in STEMI patients treated with PPCI

Settings

A pre-specified gender analysis of the multicenter, randomised, double-blind ATLANTIC trial

Participants

Between September 2011 and October 2013, 1862 patients with STEMI and symptom duration less than 6 hours were included

Interventions

Patients were assigned to pre-hospital versus in-hospital administration of 180 mg ticagrelor.

Outcomes

The main objective was to study the association between gender and primary and secondary outcomes of the main study with a focus on the clinical efficacy and safety outcomes.

Primary: The proportion of patients who did not have $\geq 70\%$ resolution of ST segment elevation and did not meet the criteria for TIMI flow 3 at initial angiography.

Secondary: the composite of death, MI, stent thrombosis, stroke, or urgent revascularisation and major or minor bleeding at 30 days.

Results

Women were older, had higher TIMI risk score, longer pre-hospital delays and better TIMI flow in the infarct related artery. Women had a 3-fold higher risk for all-cause mortality compared to men (5.7% vs 1.9%, HR 3.13, 95% CI 1.78 – 5.51). However, after adjustment for baseline characteristics, the difference was lesser and no longer significant (HR 1.98, 95% CI 0.97 – 4.04). Female gender was not an independent predictor of risk for bleeding after multivariable adjustments (PLATO major HR 1.52, 95% CI 0.76-3.03, TIMI major HR 1.41, 95% CI 0.52-3.88, BARC type 3-5 HR 1.52, 95% CI 0.74-3.09). There was no interaction between gender and efficacy or safety of randomised treatment.

Conclusion

In STEMI patients treated with current PCI-techniques and modern antiplatelet therapy, gender differences in short term mortality and in hospital bleeds could mainly be explained by older age and clustering of comorbidities in women. Pre-hospital administration of ticagrelor had a similar efficacy and safety profile in men and women with STEMI.

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3 **CLINICAL TRIAL REGISTRATION:** clinicaltrials.gov identifier: NCT01347580.
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6 **Strengths and limitations**

- 7 • This is a pre-specified analysis of a randomised control trial
- 8 • All patients were planned for primary PCI
- 9 • Current PCI techniques and novel antiplatelet therapy were used
- 10 • Appropriate statistical methods were used to adjust for baseline differences between
- 11 genders
- 12 • The large imbalance in the proportion of men and women included caused a reduced
- 13 study power for definitely excluding significant differences in outcomes
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24 **Introduction**

25 Recent studies have provided evidence of gender differences in the pathophysiology and the
26 clinical expression of atherosclerosis.(1) Several registries in patients with ST-segment
27 elevation myocardial infarction (STEMI) have consistently shown a considerably higher risk
28 of adverse outcomes in women compared to men. Nevertheless, there are conflicting results
29 regarding whether gender is an independent contributor to this observation or the higher risk
30 in women depends on differences in baseline characteristics and comorbidities between
31 genders.(2-8) Although registries of STEMI patients usually include large, unselected
32 populations, they share some inherent limitations. Their results are certainly influenced by
33 differences between genders in the use of timely reperfusion therapy and evidence based drug
34 therapies as well as undetected confounding factors.(9, 10) Therefore, reports of gender-
35 based analyses of randomised controlled trials are of crucial importance in an effort to
36 minimise inequality in the management and evaluate gender as a potential independent risk
37 factor for adverse outcome. Only a few randomised trials of STEMI patients treated with
38 primary PCI (PPCI) have reported results in the context of gender.(11, 12) New treatments
39 (e.g. ticagrelor or prasugrel), special efforts to reduce bleeding (i.e. increased use of radial
40 arterial access, provisional rather than routine use of glycoprotein (GP) IIb/IIIa inhibitor),
41 shorter delay times to reperfusion and a growing awareness regarding gender differences in
42 the management and importance of adherences to evidence based treatment could contribute
43 to improved ischemic and bleeding outcomes in female STEMI patients.
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3 In the ATLANTIC trial, prehospital administration of ticagrelor appeared to be safe but did
4 not significantly improve outcome compared to in hospital administration in patients with
5 STEMI, treated with PPCI according to the current modern standards.(13)
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8 We present a pre-specified gender analysis of the ATLANTIC trial, with the aim of studying
9 the association between gender and outcome.
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11 12 13 **Methods**

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15 The ATLANTIC study was an international, randomised, double-blind, placebo-controlled
16 study with 30 days follow-up. The design of the study, inclusion and exclusion criteria,
17 outcome definitions and principal results has previously been described.(13, 14) Briefly, 1862
18 patients presenting with STEMI, less than 6 hours after symptom onset, were included and
19 randomised to pre-hospital (in the ambulance) versus in-hospital (in the catheterisation
20 laboratory) treatment with a loading dose of ticagrelor (180mg) in addition to aspirin and
21 standard clinical care. All patients were to subsequently receive ticagrelor 90 mg twice daily
22 for 30 days, after which it was recommended that ticagrelor should be continued for up to 12
23 months. Pre-hospital administration of a GP IIb/IIIa inhibitor was left to the physician's
24 discretion. Peri-procedural use of parenteral anticoagulants was also left to the physician's
25 discretion, according to the local practice.
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34 The proportion of patients who did not have $\geq 70\%$ resolution of ST segment elevation before
35 PCI and / or did not meet the criteria for TIMI flow 3 in the infarct related artery (IRA) at
36 initial angiography was the primary outcome of the ATLANTIC trial. Secondary outcomes
37 (clinical efficacy outcomes) included the composite of death, MI, stent thrombosis, stroke, or
38 urgent revascularisation at 30 days and definite stent thrombosis at 30 days. Safety outcomes
39 included major and minor bleeding over the 30-day treatment period. Bleeding risk was
40 evaluated using the TIMI (The Thrombolysis In Myocardial Infarction), BARC (Bleeding
41 Academic Research Consortium) and PLATO (Study of Platelet Inhibition and Patient
42 Outcomes) bleeding definitions.(14)
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49 The main objective of our analysis was to study the association between gender and primary
50 and secondary outcomes of the main study with a special focus on the clinical efficacy and
51 safety outcomes. The interaction of gender subgroups with randomised treatment effects was
52 also investigated.
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3 The trial design and protocol were approved by the national regulatory authorities in all the
4 participating countries and by the local ethics committee or institutional review board at each
5 participating site. All patients provided written informed consent.
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10 11 **Statistical analysis**

12 Continuous variables are presented by their mean and standard deviation (SD) or median and
13 25th -75th percentiles as appropriate. Categorical variables are presented as counts and
14 percentages. Baseline and peri-procedural characteristics were compared according to gender
15 by chi-square tests for categorical variables and Student's t-test or Mann Whitney U test for
16 continuous variables, depending on if the variable of interest was normally distributed or not.
17 A p-value <0.05 is considered to indicate statistical significance.
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20 The incidence of events over time by gender is presented by Kaplan-Meier curves.
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22 In order to study the association between gender and the clinical efficacy and safety
23 outcomes, independent of randomised treatment as well as the possible interactions between
24 gender and randomised treatment with respect to the outcomes, hazard ratios [HR] with 95%
25 confidence intervals [CI] were derived from Cox proportional-hazards models. In the
26 unadjusted (crude) model, gender was the only explanatory variable whereas in the adjusted
27 multivariable model, gender was forcibly included and the other variables were chosen by
28 using a forward stepwise selection algorithm with a significant cut-off level of 0.05 for
29 inclusion. Adjustment variables included age, weight, prior MI, prior PCI, history of diabetes,
30 hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to
31 pre-PCI electrocardiogram [ECG], admission Killip class (as a dichotomous variable 1 / >1),
32 baseline hemoglobin, estimated glomerular filtration rate (eGFR) according to the MDRD
33 formula, use of GP IIIb/IIa inhibitor and location of MI. To evaluate the importance of early
34 mortality, a landmark analysis of the clinical efficacy outcomes was also performed from 48
35 hours after randomisation (arbitrarily defined) to the end of the study. In order to explore the
36 importance of bleeding on the clinical efficacy outcomes, a separate analysis was also
37 performed by censoring the patients who reported a PLATO major bleeding at the time of the
38 onset of a bleeding event.
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53 A comparable statistical process was used to compare gender differences in the effect of
54 randomised treatment by constructing logistic regression models. Odds ratios [OR] with 95%
55 CI are presented. The above process for Cox regression and logistic regression was also used
56 to explore the interaction effect of gender and treatment.
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3 For most of the variables included in the multivariable models, only few patients had missing
4 data (<10 patients). However, 7% of patients had missing values for creatinine, 5% for
5 hemoglobin and 4% for Killip class. The number of patients with complete data for
6 multivariable Cox proportional-hazard models of the primary outcome was 1613 (88%). To
7 investigate the influence of missing values, multivariable analysis was performed before and
8 after simple missing values imputation as well as with only gender and age as explanatory
9 variables (because these variables had no missing values).
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15 All the analyses were performed using SAS[®] version 9.3.
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18 19 Results

20 21 Baseline and peri-procedural characteristics stratified by gender

22 23 *Demographic and clinical characteristics*

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25 The study population consisted of 369 (20 %) women. They were older (mean age 69 vs. 59
26 years, $p<0.01$), had lower body mass index (BMI), higher TIMI risk score, more often had a
27 history of hypertension, chronic obstructive pulmonary disease (COPD) and stroke. Men had
28 more frequent prior PCI. No difference was observed between genders with respect to acute
29 heart failure (Killip class > 1) and only a minority of patients presented with cardiogenic
30 shock (**Table 1**).
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35 36 *Time delays*

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38 Women had significantly longer delay times, both from symptom onset to prehospital ECG
39 (median 88 vs 70 minutes, $p<0.01$) and from pre-PCI to post-PCI angiography (median 36 vs
40 32 minutes, $p=0.03$).
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44 45 *Procedural characteristics, angiographic findings, and medication during the index event*

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47 Coronary angiography was more often performed by femoral access in women (39.7% vs
48 30.4%, $p<0.01$). The genders did not differ according to IRA, with the left anterior
49 descending artery involved in 38% of women and 39% of men. PPCI, with or without stent,
50 was performed significantly more often in men (88.5% vs 83.7%, $p<0.01$) whereas the use of
51 drug eluting stents (DES) was similar. Thromboaspiration, GP IIb/IIIa inhibitors and
52 intravenous anticoagulants were used less often in women. (**Table 1**)
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Table 1. Baseline, clinical and peri-procedural characteristics according to gender.

Characteristics	Women (n=369)	Men (n=1493)	P- value
Age, years; mean (SD)	69 (13.0)	59 (11)	<0.01
Age ≥75 years	153 (41.5)	151 (10.1)	<0.01
BMI, kg/m ² ; median (IQR)	25.6 (22.5-29.1)	26.5 (24.3-29.4)	<0.01
Prior history			
Diabetes mellitus	48 (13.0)	205 (13.7)	0.72
Hypertension	190 (51.5)	605 (40.5)	<0.01
Dyslipidemia	117 (31.7)	536 (35.9)	0.13
Angina	36 (9.8)	157 (10.5)	0.67
Prior myocardial infarction	24 (6.5)	135 (9.0)	0.67
Prior PCI	16 (4.3)	124 (8.3)	<0.01
Prior CABG	1 (0.3)	11 (0.7)	0.32
Prior non-haemorrhagic stroke	8 (2.2)	10 (0.7)	<0.01
Chronic obstructive pulmonary disease	22 (6.0)	54 (3.6)	0.04
Gastrointestinal bleeding	1 (0.3)	16 (1.1)	0.15
Chronic renal disease	7 (1.9)	27 (1.8)	0.91
Index event information			
First medical contact in ambulance	280 (75.9)	1132 (75.8)	0.24
Minutes from symptom onset to pre-hospital ECG, median (IQR)	88 (49-169)	70 (41-129)	<0.01
Minutes from prehospital ECG to PCI, median (IQR)	83 (68-101)	80 (66-96)	0.03
Minutes from pre-PCI angiography to post-PCI angiography, median (IQR)	36 (24-52)	32 (23-45)	0.03
Received first loading dose	369 (100)	1488 (99.7)	0.27
Risk level at admission			
Killip class			
I	332 (90.0)	1349 (90.4)	0.82
IV	2 (0.5)	3 (0.2)	
TIMI risk score			
0-2	119 (32.2)	1006 (67.4)	<0.01
3-6	231 (62.6)	471 (31.5)	
>6	19 (5.1)	16 (1.1)	
Culprit vessel			
Left main artery	4 (1.1)	18 (1.2)	0.63

Left anterior descending artery	141 (38.8)	571 (39.0)	
Right coronary artery	150 (41.3)	590 (40.3)	
Left circumflex	39 (10.7)	196 (13.4)	
No culprit vessel identified	28 (7.7)	85 (5.8)	
Normal coronary angiography	27 (7.4)	76 (5.2)	0.1
Procedures for index event			
Femoral access	144 (39.7)	445 (30.4)	<0.01
Thromboaspiration	160 (43.4)	781 (52.3)	<0.01
PCI	309 (83.7)	1321 (88.5)	0.01
With any stent	288 (78.0)	1248 (83.6)	0.01
With DES	185 (50.1)	761 (51.0)	0.77
Coronary artery bypass grafting	4 (1.1)	21 (1.4)	0.63
No revascularisation	56 (15.2)	151 (10.1)	<0.01
Any glycoprotein IIb/IIIa inhibitor use	115 (31.2)	598 (40.1)	<0.01
Glycoprotein IIb/IIIa inhibitor use before angiography	14 (3.8)	116 (7.8)	<0.01
Intravenous anticoagulant prior to pre-PCI angiography	231 (62.6)	1027 (68.8)	0.02
Intravenous anticoagulant during hospitalisation †	310 (84.0)	1332 (89.2)	<0.01
Heparin only	135 (36.6)	584 (39.1)	0.02
Bivalirudin only	29 (7.9)	65 (4.4)	0.02

Variables presented as numbers (percentages) unless otherwise indicated.

BMI, body mass index; CABG, coronary artery bypass grafting; DES, drug-eluting stent; IQR, interquartile range (25th–75th percentile); PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, Thrombolysis In Myocardial Infarction.

† Includes all IV medications given on the date of the qualifying ECG and /or index PCI

Association between gender and outcomes independent of randomised treatment

Female gender was associated with significantly higher risk for the composite outcome of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis compared to male gender (6.8% vs 3.9%, crude HR 1.79, 95% CI 1.12 – 2.86) (**Figure 1**). This difference was mainly driven by a 3-fold higher risk for all-cause mortality in women compared to men (5.7% vs 1.9%, HR 3.13, 95% CI 1.78 – 5.51). However, in the multivariable model, the gender effect was lower and not significantly associated with the composite primary outcome

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3 (HR 1.34, 95% CI 0.77 – 2.32) or with all-cause mortality (HR 1.98, 95% CI 0.97 – 4.04)
4 (**Figure 2 and table 2**). The age-adjusted model showed age to be the most important
5 predictor of mortality (age-adjusted all-cause mortality, women vs men HR 1.53, 95% CI
6 0.82 – 2.84). Landmark analysis for events occurring within 48 hours, and between 48 hours
7 and 30 days showed that 38% of the women and 36% of the men who did not survive the first
8 month died within 48 hours. Comparison after excluding patients from further analysis at the
9 time point of a PLATO major bleeding event still revealed a statistically significant
10 association between women and all-cause mortality (4.3% vs 1.4%. HR 3.20, 95% CI 1.67 –
11 6.13). However, as for the whole population, this difference was no longer significant in the
12 multivariable model (HR 1.89, 95% CI 0.81-4.44).

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Female gender was associated with lower risk for TIMI flow < 3 in the IRA at initial
angiography (OR 0.64, 95% CI 0.46-0.91). The risk of incomplete ST-segment elevation
resolution (<70%) before PCI did not differ significantly between the genders (adjusted OR
1.15, 95% CI 0.75-1.76). The risk of abnormal TIMI flow in the IRA and incomplete ST
segment elevation resolution after PCI was similar in both genders (**Figure 3**).

Women had significantly higher risk for major bleeding complications compared to men,
irrespective of the bleeding definition used (30-day PLATO major bleeding 4.6% vs 2.2%,
HR 2.15, 95% CI 1.18 – 3.85, TIMI major bleeding at 30 days 2.7% vs 0.9%, HR 2.95, 95%
CI 1.31 – 6.65, BARC type 3-5 bleeding 4.3% vs 2.1%, HR 2.15, 95% CI 1.18 – 3.93)
(**Figure 4**). However, after adjustment for baseline and clinical characteristics, female gender
was no longer an independent predictor of risk for bleeding at 30 days. (**Table 2 and figure
2**)

To assess whether missing values may have influenced our results, multivariable analyses for
the primary, secondary and safety outcomes were performed adjusting for age and gender as
the only explanatory variables; these models provided similar results (data not shown).

Furthermore, multivariable analyses for the primary and secondary outcomes were performed
before and after simple missing value imputation and showed similar results (data not
shown).

Table 2 Association between gender and clinical outcomes independent of randomised treatment

Outcomes	Female (n=369)	Male (n=1489)	Crude hazard ratio (95%CI) (n included=1858)	Adjusted hazard ratio (95%CI)* (n included=1613)	P-value *
	Patients with endpoint, n (%)	Patients with endpoint, n (%)			
Mortality and cardiovascular outcomes					
Composite of death/MI/stroke/urgent revascularisation/definite acute stent thrombosis	25 (6.8)	58 (3.9)	1.79 (1.12-2.86)	1.34 (0.77-2.32)	0.30
Composite of death/MI/urgent revascularisation	23 (6.2)	50 (3.4)	1.91 (1.17-3.13)	1.32 (0.74-2.36)	0.35
All-cause mortality	21 (5.7)	28 (1.9)	3.13 (1.78-5.51)	1.98 (0.97-4.04)	0.06
Myocardial infarction	3 (0.8)	14 (0.9)	0.90 (0.26-3.13)	0.82 (0.23-2.85)	0.75
Stroke	3 (0.8)	3 (0.2)	4.18 (0.84-20.70)	4.14 (0.84-20.53)	0.08
Urgent revascularisation	2 (0.5)	11 (0.7)	0.75 (0.17-3.38)	0.69 (0.15-3.11)	0.63
Definite acute stent thrombosis	3 (0.8)	10 (0.7)	1.23 (0.34-4.49)	1.29 (0.35-4.76)	0.70
Acute stent thrombosis (definite or probable)	11 (3.0)	30 (2.0)	1.53 (0.77-3.05)	0.88 (0.39-1.98)	0.76
Safety outcomes					
PLATO major bleeding **	17 (4.6)	33 (2.2)	2.15 (1.20-3.85)	1.52 (0.76-3.03)	0.24
TIMI major bleeding **	10 (2.7)	14 (0.9)	2.95 (1.31-6.65)	1.41 (0.52-3.88)	0.50
TIMI major or minor bleeding**	18 (4.9)	54 (3.6)	1.38 (0.81-2.35)	1.0 (0.54-1.86)	0.99

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BARC type 3-5 (major) bleeding**	16 (4.3)	31 (2.1)	2.15 (1.18-3.93)	1.52 (0.74-3.09)	0.25
BARC type 2-5 (major or minor) bleeding**	20 (5.4)	56 (3.8)	1.48 (0.89-2.47)	1.09 (0.60-1.97)	0.78

*Hazard ratio (for female versus male) and p-value calculated from logistic regression model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

**Non-CABG related bleeding occurring up to the date of the last study visit (to the maximum of 32 days) are included in the table

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; PLATO, Study of Platelet Inhibition and Patient Outcomes; TIMI, Thrombolysis in Myocardial Infarction

Association between gender and efficacy and safety of randomised treatment

Pre-hospital administration of ticagrelor compared to in-hospital administration resulted in a non-significant difference in the primary, secondary and safety outcomes. No significant interactions between randomised treatment and gender in terms of these outcomes were found in the unadjusted or adjusted model (test for interaction in the multivariable models; $p=0.86$ for the primary outcome, $p=0.93$ for all-cause mortality, $p=0.19$ for absence of TIMI flow grade 3 in the IRA at initial angiography, $p=0.71$ for absence of $\geq 70\%$ resolution of pre-PCI ST segment elevation, and $p=0.28$ for TIMI major bleeding at 30 days). (Supplementary tables 1, 2 and 3).

Discussion

In the present analysis, unadjusted data showed a significantly higher risk of the composite outcome of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis in women, mainly driven by a three times higher risk for short-term mortality. After multivariable adjustment female gender was not an independent predictor of worse outcome.

Undoubtedly, older age and clustering of comorbidities in women could explain a large part of the observed difference in short term clinical outcomes in our study. However, the adjusted risk for death, while not statistically significant, was still considerably higher in women, generating the hypothesis that gender could be an independent predictor of early mortality if the population of the study was larger. Any possible contribution of gender, as independent risk factor, on adverse outcome may depend on the population studied. The age gap between genders in our population was substantially higher compared to previous studies, with a mean age difference of 10 years.(12, 15) In spite of appropriate statistical methods that were used for adjustment, adjustment for such age-difference is awkward. Additionally, the age difference may indicate a selection bias. As identification and randomisation took place in the ambulance, young women with suspected STEMI were possibly not included in the study as alternative reasons for ST-segment elevation on prehospital ECG may have been considered more plausible in this group. These factors may explain the observed trend toward increased adjusted risk for early mortality in women.

A plethora of observational studies in STEMI cohorts and a meta-analysis have shown a higher risk of early mortality in women.(6, 7, 16, 17) Significant differences in the rate of

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3 reperfusion therapy between genders and hidden confounders such as frailty in elderly
4 women with STEMI may partially explain their results. In accordance with our results,
5 previous gender analyses of RCTs have shown that the impact of gender on mortality could
6 mainly be explained by differences in age and comorbidities between genders.(11, 12, 15, 18,
7 19) In the CADILLAC study,(11) women had a 4-fold higher unadjusted risk for 30 days
8 mortality but after adjustment no significant difference remained. In STEMI treated with
9 thrombolysis Motovska et al showed that gender was not an independent predictor of
10 outcome,(12) The recent PLATO trial showed concurred results but NSTEMI and STEMI
11 patients were pooled in the gender analysis, despite the fact that the relationship between
12 gender and outcome depends on the type of ACS.(20) Most of these studies do not reflect
13 current treatment of STEMI patients. Despite evolving PCI techniques and novel
14 pharmacological treatment, women still have worse short term outcome and special effort,
15 with respect to their advanced age and comorbidities, to improve their outcomes are
16 warranted.
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27 Some well-known gender disparities in the concomitant management of STEMI patients
28 remained unchanged. Women were less likely to be treated with GP IIb/IIIa inhibitors and
29 thrombo-aspiration during PPCI despite lack of gender difference in protection from major
30 adverse outcomes by GP IIb/IIIa inhibitors (21) and benefit of thrombo-aspiration at the time
31 when the study was conducted.(22) Similar findings have been provided by large
32 registries.(7, 8) Some of these lower rates of utilization may be “appropriate” given the
33 higher TIMI 3 flow rates in the IRA pre-PPCI and lower rates of PPCI in women vs. men.
34 Furthermore, physician’s concern for higher risk of bleeding in older women with STEMI has
35 certainly contributed to the lower use of GP IIb/IIIa inhibitors in women.
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42 Although the impact of early reperfusion on mortality in STEMI patients is now
43 unquestionable,(23) patients’ delay from symptom onset to prehospital ECG was not an
44 independent predictor of mortality in our study, in agreement with results from previous
45 gender analyses.(24, 25) A plausible explanation is an association between age and delay,
46 and thus adjustment for age minimizes the relative impact of delay. Furthermore, in PPCI,
47 female gender has been associated with similar or even smaller infarct size than that in male
48 gender, due to longer prehospital delays, indicating that other factors than larger infarct size
49 secondary to longer prehospital delay mainly contribute to the observed higher unadjusted
50 short term mortality.(24) The proportion of 30 day mortality that occurred within 48 hours of
51 admission was similar in women and men (38% vs 36% respectively) contrasting previous
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3 data where gender differences in early mortality were accounted for by excess very early
4 (within 24-48 hours) deaths in women with STEMI.(7, 26) Cardiogenic shock and
5 hemodynamic instability were key exclusion criteria in the ATLANTIC trial which may have
6 influenced these results. Cardiogenic shock has been shown to be more common in women
7 and female gender has been highly associated with mortality in shock patients.(27)

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11 In the present study, women had a 2-3 times higher unadjusted risk for non-CABG related
12 bleedings, depending on the definition used. After adjustment for baseline characteristics, no
13 significant difference remained. Female gender has previously been associated with higher
14 risk for bleeding complications in patients with ACS.(28-31) Known predictors of bleedings
15 like advanced age, diabetes, hypertension, renal insufficiency and anemia, are usually more
16 often encountered in women with STEMI.(32) Additionally, smaller body and vessel size,
17 higher use of femoral access and overdosing of antithrombotic medication in women may
18 explain the higher observed risk for bleeding. Procedural-related improvement such as
19 increased use of radial access or smaller femoral sheaths and careful dose adjustment of
20 antithrombotic medication, have resulted in a significant decline in the risk of
21 bleeding/vascular complication during cardiovascular interventions the last years and have
22 probably contributed to our results. (33)

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33 The negative impact of bleedings on prognosis in patients with STEMI is well established.
34 (32) Our data showed that even after excluding patients from further analysis at the time of a
35 PLATO major bleeding, the unadjusted HR for early mortality in women vs men remained
36 unchanged, implying that reducing the rate of major bleeding in women may improve their
37 prognosis but is not the main reason for the observed difference between genders in the early
38 mortality.

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52 In terms of ST-segment elevation resolution and TIMI flow 3 rates before and after PCI, no
53 significant difference between genders was observed apart from a lower risk of abnormal
54 coronary flow in IRA at initial angiography in women. The higher rate of TIMI flow 3 at
55 initial angiography may be explained by the higher rate of normal coronary arteries as well as
56 the less obstructive coronary artery disease in women with STEMI, which is in concordance
57 with previous data.(25)

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3 resolution of ST elevation pre-PCI. Clinical efficacy outcomes were not significantly
4 improved either. However, prehospital administration of ticagrelor was safe in both genders
5 with similar rate of major and minor bleedings.
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10 **Strengths and limitations**

11 The present study has some important limitations. The ATLANTIC trial was not stratified by
12 gender. The large imbalance in the proportion of men and women included, commonly
13 encountered in a STEMI population, caused a reduced power for detecting significant
14 differences in outcomes between the genders or to definitely exclude an interaction between
15 gender and the randomised treatment. As this is a gender analysis performed on data from a
16 randomised trial the generalisability to a “real-life” situation of STEMI-patients is limited.
17 The current study was planned as a pre-specified gender analysis in the randomised,
18 controlled ATLANTIC trial. The most important strength of our analysis is that patients were
19 treated according to the current guidelines of STEMI, with PPCI as the reperfusion strategy
20 of choice, administration of the modern ADP receptor-blocker ticagrelor in addition to aspirin
21 as soon as possible after the first medical contact, high use of radial access during
22 catheterisation and adjuvant pharmacologic treatment during PPCI with UFH or bivalirudin.
23 (34) Therefore our study provides important information about differences and similarities
24 between genders in STEMI patients treated with current PCI techniques and pharmacologic
25 treatment.
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39 **Conclusion**

40 In patients with STEMI, treated with PPCI women have significantly higher mortality and
41 bleeding complications. However, after adjustment for baseline characteristics, the observed
42 gender differences were attenuated and no longer statistically significant, indicating that at
43 least part of the observed difference is explained by older age and clustering of comorbidities
44 in women. Regardless, female gender identifies a group of patients with high risk of early
45 mortality in whom prompt efforts to improve outcome are warranted. Prehospital
46 administration of ticagrelor had a similar efficacy and safety profile in men and women with
47 STEMI.
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D.V. reports that he has no relationships relevant to the contents of this paper to disclose.

S.S.L. reports that she has no relationships relevant to the contents of this paper to disclose.

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E. Swahn reports receiving lecture fees from AstraZeneca.

Author's contribution

E. Swahn is responsible for the conception and design of the gender substudy of the ATLANTIC trial. D. Venetsanos is responsible for analyses and interpretation of the data and drafted the manuscript. S. Sederholm Lawesson, J. Alfredsson, M. Janzon, A.Cequier, M. Chettibi, S.G. Goodman, A.W. van't Hof and G. Montalescot have critically revised the manuscript and added important intellectual content.

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All authors have participated in the work and have read and approved the manuscript.

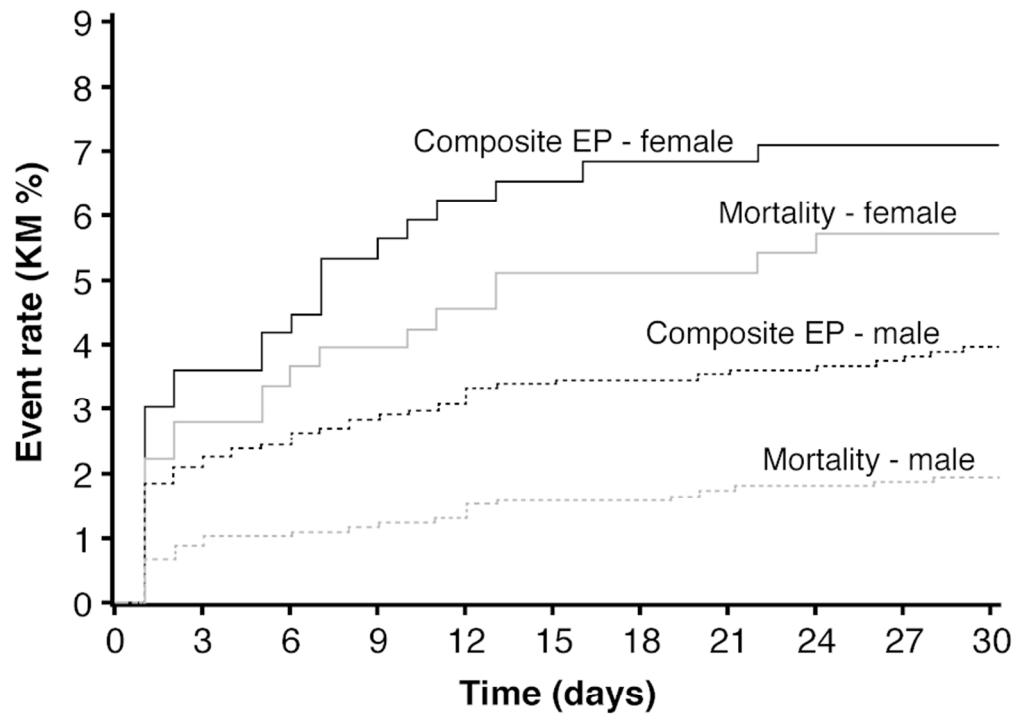
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References

1. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *Journal of the American College of Cardiology*. 2006;47(3 Suppl):S21-9.
2. Mehta RH, Stebbins AS, Lopes RD, Califf RM, Pieper KS, Armstrong PW, et al. Comparison of incidence of bleeding and mortality of men versus women with ST-elevation myocardial infarction treated with fibrinolysis. *The American journal of cardiology*. 2012;109(3):320-6.
3. Kyto V, Sipila J, Rautava P. Gender and in-hospital mortality of ST-segment elevation myocardial infarction (from a multihospital nationwide registry study of 31,689 patients). *The American journal of cardiology*. 2015;115(3):303-6.
4. Jakobsen L, Niemann T, Thorsgaard N, Nielsen TT, Thuesen L, Lassen JF, et al. Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2012;8(8):904-11.
5. Kang SH, Suh JW, Yoon CH, Cho MC, Kim YJ, Chae SC, et al. Sex differences in management and mortality of patients with ST-elevation myocardial infarction (from the Korean Acute Myocardial Infarction National Registry). *The American journal of cardiology*. 2012;109(6):787-93.
6. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. A gender perspective on short- and long term mortality in ST-elevation myocardial infarction--a report from the SWEDEHEART register. *International journal of cardiology*. 2013;168(2):1041-7.
7. de Boer SP, Roos-Hesselink JW, van Leeuwen MA, Lenzen MJ, van Geuns RJ, Regar E, et al. Excess mortality in women compared to men after PCI in STEMI: an analysis of 11,931 patients during 2000-2009. *International journal of cardiology*. 2014;176(2):456-63.
8. Leurent G, Garlantezec R, Auffret V, Hacot JP, Coudert I, Filippi E, et al. Gender differences in presentation, management and inhospital outcome in patients with ST-segment elevation myocardial infarction: data from 5000 patients included in the ORBI prospective French regional registry. *Archives of cardiovascular diseases*. 2014;107(5):291-8.
9. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. Time trends in STEMI--improved treatment and outcome but still a gender gap: a prospective observational cohort study from the SWEDEHEART register. *BMJ open*. 2012;2(2):e000726.
10. Pilgrim T, Heg D, Tal K, Erne P, Radovanovic D, Windecker S, et al. Age- and Gender-related Disparities in Primary Percutaneous Coronary Interventions for Acute ST-segment elevation Myocardial Infarction. *PloS one*. 2015;10(9):e0137047.
11. Lansky AJ, Pietras C, Costa RA, Tsuchiya Y, Brodie BR, Cox DA, et al. Gender differences in outcomes after primary angioplasty versus primary stenting with and without abciximab for acute myocardial infarction: results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation*. 2005;111(13):1611-8.
12. Motovska Z, Widimsky P, Aschermann M, Investigators PSG. The impact of gender on outcomes of patients with ST elevation myocardial infarction transported for percutaneous coronary intervention: analysis of the PRAGUE-1 and 2 studies. *Heart*. 2008;94(3):e5.
13. Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *The New England journal of medicine*. 2014;371(11):1016-27.
14. Montalescot G, Lassen JF, Hamm CW, Lapostolle F, Silvain J, ten Berg JM, et al. Ambulance or in-catheterization laboratory administration of ticagrelor for primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: rationale and design of the randomized, double-blind Administration of Ticagrelor in the cath Lab or in the Ambulance for New

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3 ST elevation myocardial infarction to open the Coronary artery (ATLANTIC) study. *American heart*
4 *journal*. 2013;165(4):515-22.
- 5 15. Wijnbergen I, Tijssen J, van 't Veer M, Michels R, Pijls NH. Gender differences in long-
6 term outcome after primary percutaneous intervention for ST-segment elevation myocardial
7 infarction. *Catheterization and cardiovascular interventions : official journal of the Society for*
8 *Cardiac Angiography & Interventions*. 2013;82(3):379-84.
- 9 16. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-
10 term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by
11 primary percutaneous intervention: a meta-analysis. *JAMA internal medicine*. 2014;174(11):1822-30.
- 12 17. Benamer H, Tafflet M, Bataille S, Escolano S, Livarek B, Fourchard V, et al. Female
13 gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI:
14 insights from the greater Paris area PCI Registry. *EuroIntervention : journal of EuroPCR in*
15 *collaboration with the Working Group on Interventional Cardiology of the European Society of*
16 *Cardiology*. 2011;6(9):1073-9.
- 17 18. Husted S, James SK, Bach RG, Becker RC, Budaj A, Heras M, et al. The efficacy of
18 ticagrelor is maintained in women with acute coronary syndromes participating in the prospective,
19 randomized, PLATelet inhibition and patient Outcomes (PLATO) trial. *European heart journal*.
20 2014;35(23):1541-50.
- 21 19. De Luca G, Gibson CM, Gyongyosi M, Zeymer U, Dudek D, Arntz HR, et al. Gender-
22 related differences in outcome after ST-segment elevation myocardial infarction treated by primary
23 angioplasty and glycoprotein IIb/IIIa inhibitors: insights from the EGYPT cooperation. *Journal of*
24 *thrombosis and thrombolysis*. 2010;30(3):342-6.
- 25 20. Champney KP, Frederick PD, Bueno H, Parashar S, Foody J, Merz CN, et al. The joint
26 contribution of sex, age and type of myocardial infarction on hospital mortality following acute
27 myocardial infarction. *Heart*. 2009;95(11):895-9.
- 28 21. Cho L, Topol EJ, Balog C, Foody JM, Booth JE, Cabot C, et al. Clinical benefit of
29 glycoprotein IIb/IIIa blockade with Abciximab is independent of gender: pooled analysis from EPIC,
30 EPILOG and EPISTENT trials. *Evaluation of 7E3 for the Prevention of Ischemic Complications.*
31 *Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with*
32 *Abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stent.* *Journal of the*
33 *American College of Cardiology*. 2000;36(2):381-6.
- 34 22. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, et al.
35 Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous
36 coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study.
37 *Lancet*. 2008;371(9628):1915-20.
- 38 23. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and
39 mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts.
40 *Circulation*. 2004;109(10):1223-5.
- 41 24. Sadowski M, Gasior M, Gierlotka M, Janion M, Polonski L. Gender-related differences
42 in mortality after ST-segment elevation myocardial infarction: a large multicentre national registry.
43 *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional*
44 *Cardiology of the European Society of Cardiology*. 2011;6(9):1068-72.
- 45 25. Otten AM, Maas AH, Ottervanger JP, Kloosterman A, van 't Hof AW, Dambrink JH, et
46 al. Is the difference in outcome between men and women treated by primary percutaneous
47 coronary intervention age dependent? Gender difference in STEMI stratified on age. *European heart*
48 *journal Acute cardiovascular care*. 2013;2(4):334-41.
- 49 26. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Marea AO, et al. Sex
50 differences in medical care and early death after acute myocardial infarction. *Circulation*.
51 2008;118(25):2803-10.
- 52 27. Suessenbacher A, Doerler J, Alber H, Aichinger J, Altenberger J, Benzer W, et al.
53 Gender-related outcome following percutaneous coronary intervention for ST-elevation myocardial
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3 infarction: data from the Austrian acute PCI registry. *EuroIntervention* : journal of EuroPCR in
4 collaboration with the Working Group on Interventional Cardiology of the European Society of
5 Cardiology. 2008;4(2):271-6.
- 6 28. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, et al. Bleeding in acute
7 coronary syndromes and percutaneous coronary interventions: position paper by the Working
8 Group on Thrombosis of the European Society of Cardiology. *European heart journal*.
9 2011;32(15):1854-64.
- 10 29. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to
11 predict bleeding in patients with acute coronary syndromes. *Journal of the American College of*
12 *Cardiology*. 2010;55(23):2556-66.
- 13 30. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, et al. Bleeding
14 complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATElet
15 inhibition and patient Outcomes (PLATO) trial. *European heart journal*. 2011;32(23):2933-44.
- 16 31. Mathews R, Peterson ED, Chen AY, Wang TY, Chin CT, Fonarow GC, et al. In-hospital
17 major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and
18 validation of a model from the ACTION Registry(R)-GWTG. *The American journal of cardiology*.
19 2011;107(8):1136-43.
- 20 32. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, et al. Impact of
21 major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary
22 syndromes: an analysis from the ACUITY Trial. *Journal of the American College of Cardiology*.
23 2007;49(12):1362-8.
- 24 33. Ahmed B, Piper WD, Malenka D, VerLee P, Robb J, Ryan T, et al. Significantly improved
25 vascular complications among women undergoing percutaneous coronary intervention: a report
26 from the Northern New England Percutaneous Coronary Intervention Registry. *Circulation*
27 *Cardiovascular interventions*. 2009;2(5):423-9.
- 28 34. Wessler JD, Stant J, Duru S, Rabbani L, Kirtane AJ. Updates to the ACCF/AHA and ESC
29 STEMI and NSTEMI guidelines: putting guidelines into clinical practice. *The American journal of*
30 *cardiology*. 2015;115(5 Suppl):23A-8A.
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**Composite endpoint**

Female 25/369 (6.8%)

Male 58/1489 (3.9%)

All-cause mortality

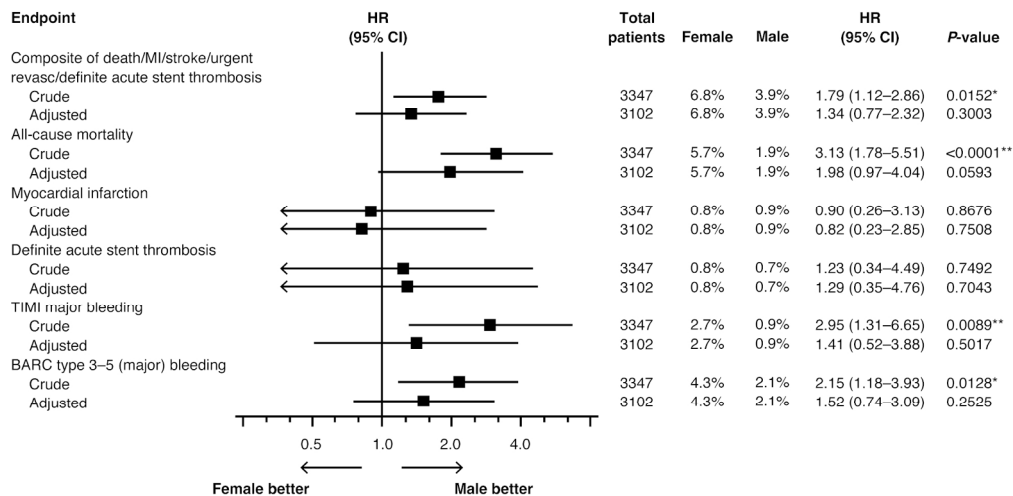
Female 21/369 (5.7%)

Male 28/1489 (1.9%)

Figure 1. Cumulative Kaplan-Meier estimates of the incidence of the composite endpoint of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis and all-cause mortality at 30 days by gender.

79x70mm (300 x 300 DPI)

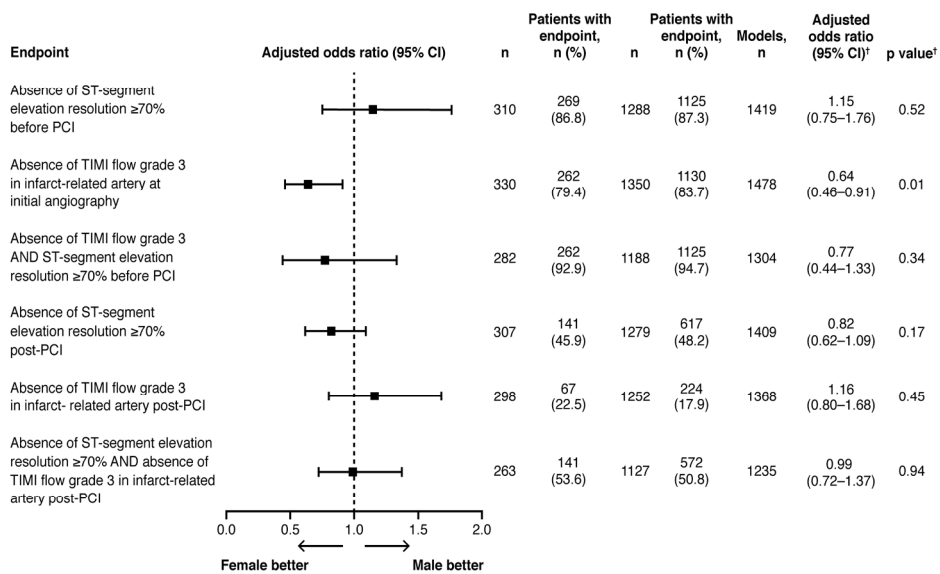
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Association between gender and clinical efficacy and safety outcomes independent of randomised treatment.

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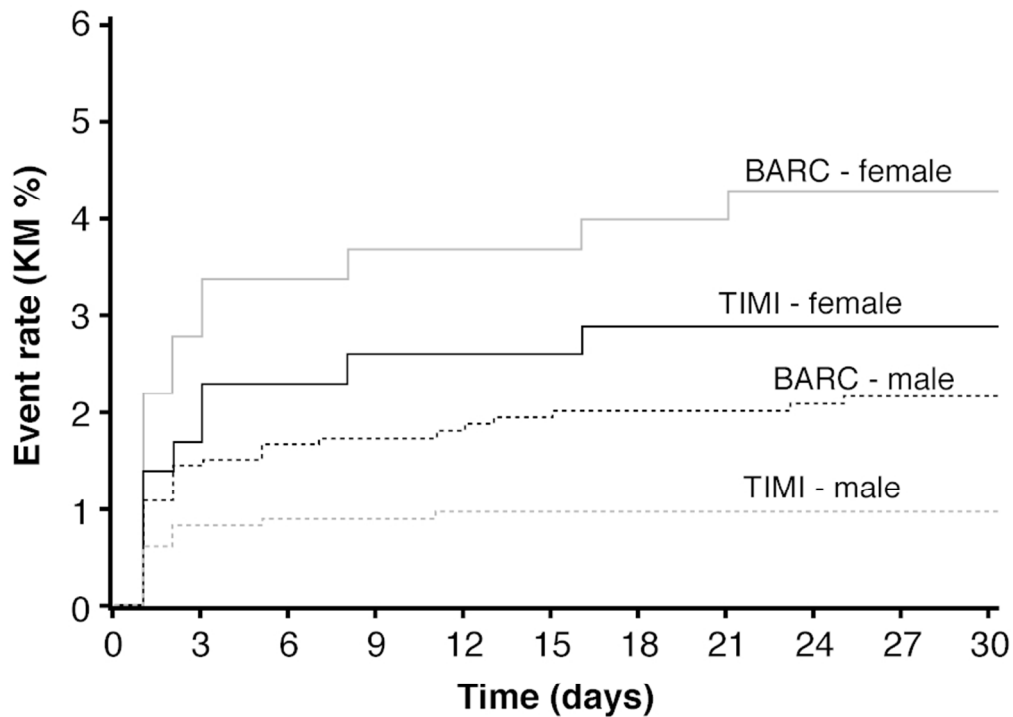
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Association between gender and primary and secondary outcomes, independent of randomised treatment.

228x140mm (300 x 300 DPI)

Review only



TIMI major bleed	BARC type 3–5 bleed
Female 10/369 (2.7%)	Female 16/369 (4.3%)
Male 14/1489 (0.9%)	Male 31/1489 (2.1%)

Figure 4. Cumulative Kaplan-Meier estimates of the incidence of the TIMI major bleeding and BARC type 3-5 bleeding at 30 days by gender.

79x69mm (300 x 300 DPI)

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Supplementary table 1 Association between gender and efficacy of randomised treatment – clinical outcomes

Outcomes	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model , n	Adjusted hazard ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
Composite of Death/MI/Stroke/Urgent Revasc/Definite Acute Stent Thrombosis	Female	173	13 (7.5)	196	12 (6.1)	1613	0.98 (0.42-2.27)	0.87
	Male	733	28 (3.8)	756	30 (4.0)		0.90 (0.51-1.59)	
Composite of Death/MI/Urgent Revasc	Female	173	13 (7.5)	196	10 (5.1)	1613	1.32 (0.55-3.20)	0.55
	Male	733	26 (3.5)	756	24 (3.2)		0.95 (0.52-1.76)	
All-cause mortality	Female	173	13 (7.5)	196	8 (4.1)	1613	1.59 (0.61-4.12)	0.93
	Male	733	17 (2.3)	756	11 (1.5)		1.50 (0.60-3.74)	
Myocardial infarction	Female	173	1 (0.6)	196	2 (1.0)	1613	0.44 (0.04-4.95)	0.72
	Male	733	6 (0.8)	756	8 (1.1)		0.72 (0.25-2.09)	
Stroke	Female	173	1 (0.6)	196	2 (1.0)	1613	0.54 (0.05-5.90)	0.99
	Male	733	3 (0.4)	756	0 (0.0)		Nt estimated	
Urgent revascularization	Female	173	1 (0.6)	196	1 (0.5)	1613	0.86 (0.05-14.07)	0.76
	Male	733	4 (0.5)	756	7 (0.9)		0.54 (0.15-1.87)	
Definite Acute Stent Thrombosis	Female	173	1 (0.6)	196	2 (1.0)	1613	0.37 (0.03-4.27)	0.49
	Male	733	1 (0.1)	756	9 (1.2)		0.12 (0.01-1.02)	
Acute Stent Thrombosis (definite or probable)	Female	173	7 (4.0)	196	4 (2.0)	1613	1.31 (0.37-4.69)	0.52
	Male	733	14 (1.9)	756	16 (2.1)		0.80 (0.35-1.80)	

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≠ Adjusted hazard (for female versus male) and p-values for interaction was calculated from Cox proportional hazard model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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Supplementary table 2 Association between gender and efficacy of randomised treatment – primary and secondary outcomes

Outcomes	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model N ≠	Adjusted odds ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
Absence of ST segment elevation resolution ≥ 70% pre-PCI	Female	142	122 (85.9)	168	147 (87.5)	1419	0.75 (0.37-1.53)	0.71
	Male	632	550 (87.0)	656	575 (87.7)		0.85 (0.59-1.23)	
Absence of TIMI flow grade 3 in infarct related artery at initial angiography	Female	155	127 (81.9)	175	135 (77.1)	1478	1.36 (0.76-2.41)	0.19
	Male	669	554 (82.8)	681	576 (84.6)		0.88 (0.64-1.20)	
Absence of ST segment resolution ≥ 70% AND absence of TIMI flow grade 3 in infarct related artery pre-PCI	Female	129	120 (93.0)	153	142 (92.8)	1304	1.07 (0.41-2.81)	0.84
	Male	590	557 (94.4)	598	568 (95.0)		0.96 (0.57-1.62)	
Absence of ST-segment resolution ≥70% after PCI	Female	144	61 (42.4)	163	80 (49.1)	1409	0.76 (0.47-1.25)	0.51
	Male	629	291 (46.3)	650	326 (50.2)		0.92 (0.72-1.17)	
Absence of TIMI flow grade 3 in infarct related artery after PCI	Female	144	30 (20.8)	154	37 (24.0)	1368	0.93 (0.51-1.71)	0.98
	Male	621	107 (17.2)	631	117 (18.5)		0.92 (0.68-1.26)	
Absence of ST segment resolution ≥70% AND absence of TIMI flow grade 3 in infarct related artery after PCI	Female	125	60 (48.0)	138	81 (58.7)	1235	0.64 (0.38-1.10)	0.13
	Male	562	282 (50.2)	565	290 (51.3)		1.01 (0.78-1.32)	

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≠ Adjusted odds ratio (for female versus male) and p-values for interaction was calculated from logistic regression model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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Supplementary table 3 Association between gender and safety of randomised treatment (safety outcomes)

End point	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model N ≠	Adjusted hazard ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
PLATO major bleeding	Female	173	6 (3.5)	196	11 (5.6)	1613	0.61 (0.21-1.83)	0.23
	Male	733	19 (2.6)	756	14 (1.9)		1.39 (0.66-2.93)	
PLATO major and minor bleeding	Female	173	7 (4.0)	196	13 (6.6)	1613	0.59 (0.22-1.61)	0.19
	Male	733	33 (4.5)	756	26 (3.4)		1.27 (0.73-2.21)	
TIMI major bleeding	Female	173	3 (1.7)	196	7 (3.6)	1613	0.60 (0.14-2.54)	0.28
	Male	733	9 (1.2)	756	5 (0.7)		1.62 (0.53-4.98)	
TIMI major and minor bleeding	Female	173	6 (3.5)	196	12 (6.1)	1613	0.55 (0.19-1.60)	0.24
	Male	733	29 (4.0)	756	25 (3.3)		1.14 (0.64-2.03)	
BARC type 3-5 (major) bleeding	Female	173	6 (3.5)	196	10 (5.1)	1613	0.69 (0.23-2.11)	0.26
	Male	733	18 (2.5)	756	13 (1.7)		1.51 (0.70-3.26)	
BARC type 2-5 (major and minor) bleeding	Female	173	7 (4.0)	196	13 (6.6)	1613	0.59 (0.22-1.60)	0.21
	Male	733	31 (4.2)	756	25 (3.3)		1.23 (0.70-2.17)	

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≠Adjusted hazard (for female versus male) and p-values for interaction was calculated from Cox proportional hazard model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5, 6
		(b) Describe any methods used to examine subgroups and interactions	5, 6
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	4 NA (SEE PAGE 4)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7, 8, 9 6 NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 10, 11, 12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9, 10, 11, 12 yes
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	13, 14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13, 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between gender and short term outcome in STEMI patients planned for primary PCI and novel antiplatelet therapy.

A pre-specified gender analysis of the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial – a multicenter, randomised, placebo-controlled study.

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A pre-specified gender analysis of the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial – a multicenter, randomised, placebo-controlled study.

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Keywords: myocardial infarction, STEMI, gender, primary PCI, ATLANTIC, ticagrelor

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Abstract

Objectives

To evaluate gender differences in outcomes in STEMI patients planned for PPCI

Settings

A pre-specified gender analysis of the multicenter, randomised, double-blind ATLANTIC trial

Participants

Between September 2011 and October 2013, 1862 patients with STEMI and symptom duration less than 6 hours were included

Interventions

Patients were assigned to pre-hospital versus in-hospital administration of 180mg ticagrelor.

Outcomes

The main objective was to study the association between gender and primary and secondary outcomes of the main study with a focus on the clinical efficacy and safety outcomes.

Primary: The proportion of patients who did not have $\geq 70\%$ resolution of ST segment elevation and did not meet the criteria for TIMI flow 3 at initial angiography. Secondary: the composite of death, MI, stent thrombosis, stroke, or urgent revascularisation and major or minor bleeding at 30 days.

Results

Women were older, had higher TIMI risk score, longer pre-hospital delays and better TIMI flow in the infarct related artery. Women had a 3-fold higher risk for all-cause mortality compared to men (5.7% vs 1.9%, HR 3.13, 95% CI 1.78 – 5.51). After adjustment, the difference was attenuated but remained statistically significant (HR 2.08, 95% CI 1.03 – 4.20). The incidence of major bleeding events was 2 to 3-fold higher in women compared to men. In the multivariable model, female gender was not an independent predictor of bleeding (PLATO major HR 1.45, 95% CI 0.73-2.86, TIMI major HR 1.28, 95% CI 0.47-3.48, BARC type 3-5 HR 1.45, 95% CI 0.72-2.91). There was no interaction between gender and efficacy or safety of randomised treatment.

Conclusion

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3 In STEMI patients planned for PPCI-techniques and treated with modern antiplatelet therapy,
4 female gender was an independent predictor of short term mortality. In contrast, the higher
5 incidence of bleeding complications in women could mainly be explained by older age and
6 clustering of comorbidities..
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13 **CLINICAL TRIAL REGISTRATION:** clinicaltrials.gov identifier: NCT01347580.
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15 16 17 **Strengths and limitations** 18

- 19 • This is a prespecified analysis of a randomised control trial
- 20 • All patients were planned for primary PCI
- 21 • Current PCI techniques and novel antiplatelet therapy were used
- 22 • Appropriate statistical methods used to adjust for baseline differences between
23 genders
- 24 • The large imbalance in the proportion of men and women included caused a reduced
25 study power for definitely excluding significant differences in outcomes
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53 **Introduction** 54

55 Recent studies have provided evidence of gender differences in the pathophysiology and the
56 clinical expression of atherosclerosis.(1) Several registries in patients with ST-segment
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3 elevation myocardial infarction (STEMI) have consistently shown a considerably higher risk
4 of adverse outcomes in women compared to men. Nevertheless, there are conflicting results
5 regarding whether gender is an independent contributor to this observation or the higher risk
6 in women depends on differences in baseline characteristics and comorbidities between
7 genders.(2-8) Although registries of STEMI patients usually include large, unselected
8 populations, they share some inherent limitations. Their results are certainly influenced by
9 differences between genders in the use of timely reperfusion therapy and evidence based drug
10 therapies as well as undetected confounding factors.(9, 10) Therefore, reports of gender-
11 based analyses of randomised controlled trials are of crucial importance in an effort to
12 minimise inequality in the management and evaluate gender as a potential independent risk
13 factor for adverse outcome. Only a few randomised trials of STEMI patients treated with
14 primary PCI (PPCI) have reported results in the context of gender.(11, 12) New treatments
15 (e.g. ticagrelor or prasugrel), special efforts to reduce bleeding (i.e. increased use of radial
16 arterial access, provisional rather than routine use of glycoprotein (GP) IIb/IIIa inhibitor),
17 shorter delay times to reperfusion and a growing awareness regarding gender differences in
18 the management and importance of adherences to evidence based treatment could contribute
19 to improved ischemic and bleeding outcomes in female STEMI patients.

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21 In the ATLANTIC trial, prehospital administration of ticagrelor appeared to be safe but did
22 not significantly improve outcome compared to in hospital administration in patients with
23 STEMI, treated with PPCI according to the current modern standards.(13)

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25 We present a pre-specified gender analysis of the ATLANTIC trial, with the aim of studying
26 the association between gender and outcome.
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31 32 33 34 35 36 37 38 39 40 41 42 **Methods**

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44 The ATLANTIC study was an international, randomised, double-blind, placebo-controlled
45 study with 30 days follow-up. The design of the study, inclusion and exclusion criteria,
46 outcome definitions and principal results have previously been described.(13, 14) Briefly,
47 1862 patients presenting with STEMI, less than 6 hours after symptom onset, were included
48 and randomised to pre-hospital (in the ambulance) versus in-hospital (in the catheterisation
49 laboratory) treatment with a loading dose of ticagrelor (180mg) in addition to aspirin and
50 standard clinical care. All patients were to subsequently receive ticagrelor 90 mg twice daily
51 for 30 days, after which it was recommended that ticagrelor should be continued for up to 12
52 months. Pre-hospital administration of a GP IIb/IIIa inhibitor was left to the physician's
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3 discretion. Peri-procedural use of parenteral anticoagulants was also left to the physician's
4 discretion, according to the local practice.
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7 The proportion of patients who did not have $\geq 70\%$ resolution of ST segment elevation before
8 PCI and / or did not meet the criteria for TIMI flow 3 in the infarct related artery (IRA) at
9 initial angiography was the primary outcome of the ATLANTIC trial. Secondary outcomes
10 (clinical efficacy outcomes) included the composite of death, MI, stent thrombosis, stroke, or
11 urgent revascularisation at 30 days and definite stent thrombosis at 30 days. Safety outcomes
12 included major and minor bleeding over the 30-day treatment period. Bleeding risk was
13 evaluated using the TIMI (The Thrombolysis In Myocardial Infarction), BARC (Bleeding
14 Academic Research Consortium) and PLATO (Study of Platelet Inhibition and Patient
15 Outcomes) bleeding definitions.(14)
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22 The main objective of our analysis was to study the association between gender and primary
23 and secondary outcomes of the main study with a special focus on the clinical efficacy and
24 safety outcomes. The interaction of gender subgroups with randomised treatment effects was
25 also investigated.
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29 The trial design and protocol were approved by the national regulatory authorities in all the
30 participating countries and by the local ethics committee or institutional review board at each
31 participating site. All patients provided written informed consent.
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38 **Statistical analysis**

39 Continuous variables are presented by their mean and standard deviation (SD) or median and
40 25th -75th percentiles as appropriate. Categorical variables are presented as counts and
41 percentages. Baseline and peri-procedural characteristics were compared according to gender
42 by chi-square tests for categorical variables and Student's t-test or Mann Whitney U test for
43 continuous variables, depending on if the variable of interest was normally distributed or not.
44 A p-value < 0.05 is considered to indicate statistical significance.
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49 The incidence of events over time by gender is presented by Kaplan-Meier curves.
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51 In order to study the association between gender and the clinical efficacy and safety
52 outcomes, independent of randomised treatment as well as the possible interactions between
53 gender and randomised treatment with respect to the outcomes, hazard ratios [HR] with 95%
54 confidence intervals [CI] were derived from Cox proportional-hazards models. In the
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3 unadjusted (crude) model, gender was the only explanatory variable whereas in the adjusted
4 multivariable model, gender was forcibly included and the other variables were chosen by
5 using a forward stepwise selection algorithm with a significant cut-off level of 0.05 for
6 inclusion. Adjustment variables included age, weight, prior MI, prior PCI, history of diabetes,
7 hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to
8 pre-PCI electrocardiogram [ECG], admission Killip class (as a dichotomous variable 1 / >1),
9 baseline hemoglobin, estimated glomerular filtration rate (eGFR) according to the MDRD
10 formula, access site, use of GP IIIb/IIa inhibitor, bivalirudin and UFH, location of MI and
11 revascularisation. To evaluate the importance of early mortality, a landmark analysis of the
12 clinical efficacy outcomes was also performed from 48 hours after randomisation (arbitrarily
13 defined) to the end of the study. In order to explore the importance of bleeding on the clinical
14 efficacy outcomes, a separate analysis was also performed by censoring the patients who
15 reported a PLATO major bleeding at the time of the onset of a bleeding event.

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25 A comparable statistical process was used to compare gender differences in the effect of
26 randomised treatment by constructing logistic regression models. Odds ratios [OR] with 95%
27 CI are presented. The above process for Cox regression and logistic regression was also used
28 to explore the interaction effect of gender and treatment.

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32 For most of the variables included in the multivariable models, only few patients had missing
33 data (<10 patients). However, 7% of patients had missing values for creatinine, 5% for
34 hemoglobin and 4% for Killip class. The number of patients with complete data for
35 multivariable Cox proportional-hazard models of the primary outcome was 1613 (88%).

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39 All the analyses were performed using SAS[®] version 9.3.
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46 Results

47 Baseline and peri-procedural characteristics stratified by gender

48 *Demographic and clinical characteristics*

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53 The study population consisted of 369 (20 %) women. They were older (mean age 69 vs. 59
54 years, $p < 0.01$), had lower body mass index (BMI), higher TIMI risk score, more often had a
55 history of hypertension, chronic obstructive pulmonary disease (COPD) and stroke. Men had
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3 more frequent prior PCI. No difference was observed between genders with respect to acute
4 heart failure (Killip class > 1) and only a minority of patients presented with cardiogenic
5 shock (**Table 1**).

8 9 *Time delays*

10 Women had significantly longer delay times, both from symptom onset to prehospital ECG
11 (median 88 vs 70 minutes, $p<0.01$) and from pre-PCI to post-PCI angiography (median 36 vs
12 32 minutes, $p=0.03$).

13 14 15 16 17 *Procedural characteristics, angiographic findings, and medication during the index event*

18 Coronary angiography was more often performed by femoral access in women (39.7% vs
19 30.4%, $p<0.01$). The genders did not differ according to IRA, with the left anterior
20 descending artery involved in 38% of women and 39% of men. PPCI, with or without stent,
21 was performed significantly more often in men (88.5% vs 83.7%, $p<0.01$) whereas the use of
22 drug eluting stents (DES) was similar. Thromboaspiration, GP IIb/IIIa inhibitors and
23 intravenous anticoagulants were used less often in women. (**Table 1**)

24 25 26 27 28 29 30 **Association between gender and outcomes independent of randomised treatment**

31 Female gender was associated with significantly higher risk for the composite outcome of
32 death, MI, stroke, urgent revascularisation or definite acute stent thrombosis compared to
33 male gender (6.8% vs 3.9%, crude HR 1.79, 95% CI 1.12 – 2.86) (**Figure 1**). This difference
34 was mainly driven by a 3-fold higher risk for all-cause mortality in women compared to men
35 (5.7% vs 1.9%, HR 3.13, 95% CI 1.78 – 5.51). Although the difference was attenuated in the
36 multivariable model, gender was still associated with all-cause mortality at 30 days (HR 2.08,
37 95% CI 1.03 – 4.20) (**Figure 2 and table 2**). Landmark analysis for events occurring within
38 48 hours, and between 48 hours and 30 days showed that 38% of the women and 36% of the
39 men who did not survive the first month died within 48 hours. Comparison after excluding
40 patients from further analysis at the time point of a PLATO major bleeding event still
41 revealed a statistically significant association between women and all-cause mortality (4.3%
42 vs 1.4%. HR 3.20, 95% CI 1.67 – 6.13). Similar result was obtained after adjustment but the
43 difference between genders did not reach statistical significance (HR 2.15, 95% CI 0.93-
44 5.00).

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56 Female gender was associated with lower risk for TIMI flow < 3 in the IRA at initial
57 angiography (adjusted OR 0.67, 95% CI 0.47-0.96). The risk of incomplete ST-segment
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3 elevation resolution (<70%) before PCI did not differ significantly between the genders
4 (adjusted OR 1.11, 95% CI 0.73-1.71). The risk of abnormal TIMI flow in the IRA and
5 incomplete ST segment elevation resolution after PCI was similar in both genders (**Figure 3**).

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8 Women had significantly higher risk for major bleeding complications compared to men,
9 irrespective of the bleeding definition used (30-day PLATO major bleeding 4.6% vs 2.2%,
10 HR 2.15, 95% CI 1.18 – 3.85, TIMI major bleeding at 30 days 2.7% vs 0.9%, HR 2.95, 95%
11 CI 1.31 – 6.65, BARC type 3-5 bleeding 4.3% vs 2.1%, HR 2.15, 95% CI 1.18 – 3.93)
12 (**Figure 4**). However, after adjustment for baseline and clinical characteristics, female gender
13 was no longer an independent predictor of risk for bleeding at 30 days. (**Table 2 and figure**
14 **2**)

20 **Association between gender and efficacy and safety of randomised treatment**

21 Pre-hospital administration of ticagrelor compared to in-hospital administration resulted in a
22 non- significant difference in the primary, secondary and safety outcomes. No significant
23 interactions between randomised treatment and gender in terms of these outcomes were found
24 in the unadjusted or adjusted model (test for interaction in the multivariable models; p=0.94
25 for all-cause mortality, p=0.55 for absence of TIMI flow grade 3 in the IRA at initial
26 angiography, p=0.71 for absence of $\geq 70\%$ resolution of pre-PCI ST segment elevation, and
27 p=0.31 for TIMI major bleeding at 30 days). (**Supplementary tables 1, 2 and 3**).

38 **Discussion**

39 In the present analysis, unadjusted data showed a significantly higher risk of short term
40 mortality and bleeding complications in women. After multivariable adjustment female
41 gender remained an independent predictor of mortality whereas advanced age and
42 comorbidities could mainly explain the higher incidence of bleeding complications in
43 women.

44 Undoubtedly, older age and clustering of comorbidities in women could explain a large part
45 of the observed difference in short term clinical outcomes in our study. However, the adjusted
46 risk for death was still significantly higher in women. The contribution of gender, as
47 independent risk factor, on adverse outcome may depend on the population studied. The age
48 gap between genders in our population was substantially higher compared to previous
49 studies, with a mean age difference of 10 years.(12, 15) In spite of appropriate statistical

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3 methods that were used for adjustment, adjustment for such age-difference is awkward.
4 Additionally, the age difference may indicate a selection bias. As identification and
5 randomisation took place in the ambulance, young women with suspected STEMI were
6 possibly not included in the study as alternative reasons for ST-segment elevation on
7 prehospital ECG may have been considered more plausible in this group. Furthermore, a
8 trend toward increased mortality with prehospital ticagrelor was observed in the ATLANTIC
9 trial that was mainly attributed to a plausible imbalance between the two groups in terms of
10 the severity of the presenting event. Given the low rate of all-cause mortality, unobserved
11 confounders in elderly women with STEMI may have significantly contributed to our results
12 and the findings of the main study. These factors may have a significant impact on the
13 remaining higher adjusted risk for short-term mortality in women.
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22 Previous observational studies in STEMI cohorts, without focus on PPCI treated patients
23 have shown a higher risk for early mortality in women.(6, 16, 17) Significant differences in
24 the rate of reperfusion therapy between genders and hidden confounders such as frailty in
25 elderly women with STEMI may have influenced their results. Recent observational studies
26 including patients treated with PPCI(4, 18, 19) and pre-specified gender analysis of RCTs(11,
27 12, 15, 20, 21) have shown that the impact of gender on mortality could mainly be explained
28 by differences in age and comorbidities between genders.. On the contrary, an observational
29 study and a meta-analysis have reported higher multivariable adjusted risk of early mortality
30 in women with STEMI treated with PPCI.(22, 23) Differences in the population studied and
31 in the covariates included in the multivariable analysis between studies may explain the
32 conflicting results. Previous studies have clearly demonstrated the importance of body
33 surface area and the eGFR on prognosis.(24, 25) In a meta-analysis, Berger et al showed that
34 female gender was an independent predictor of early mortality in STEMI patients. However,
35 30-day mortality was not statistically significant different between genders after additional
36 adjustment for angiographic disease severity.(26)
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47 In the present study, women had a 2-3 times higher unadjusted risk for non-CABG related
48 bleedings, depending on the definition used. After adjustment for baseline characteristics, no
49 significant difference remained. Female gender has previously been associated with higher
50 risk for bleeding complications in patients with ACS.(27-30) Known predictors of bleedings
51 like advanced age, diabetes, hypertension, renal insufficiency and anemia, are usually more
52 often encountered in women with STEMI.(31) Additionally, smaller body and vessel size,
53 higher use of femoral access and overdosing of antithrombotic medication in women may
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3 explain the higher observed risk for bleeding. Procedural-related improvement such as
4 increased use of radial access or smaller femoral sheaths and careful dose adjustment of
5 antithrombotic medication, have resulted in a significant decline in the risk of
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7 bleeding/vascular complication during cardiovascular interventions the last years and have
8 probably contributed to our results.(32) The negative impact of bleedings on prognosis in
9 patients with STEMI is well established. (31) Our data showed that even after excluding
10 patients from further analysis at the time of a PLATO major bleeding, the HR for early
11 mortality in women vs men remained unchanged, implying that reducing the rate of major
12 bleeding in women may improve their prognosis but is not the main reason for the observed
13 difference between genders in the early mortality.
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23 Some well-known gender disparities in the concomitant management of STEMI patients
24 remained unchanged. Women were less likely to be treated with GP IIb/IIIa inhibitors and
25 thrombo-aspiration during PPCI despite lack of gender difference in protection from major
26 adverse outcomes by GP IIb/IIIa inhibitors (33) and benefit of thrombo-aspiration at the time
27 when the study was conducted.(34) Similar findings have been provided by large
28 registries.(7, 8) Some of these lower rates of utilization may be “appropriate” given the
29 higher TIMI 3 flow rates in the IRA pre-PPCI and lower rates of PPCI in women vs. men.
30 Furthermore, physician’s concern for higher risk of bleeding in older women with STEMI
31 have certainly contributed to the lower use of GP IIb/IIIa inhibitors in women.
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38 Although the impact of early reperfusion on mortality in STEMI patients is now
39 unquestionable,(35) patients’ delay from symptom onset to prehospital ECG was not an
40 independent predictor of mortality in our study, in agreement with results from previous
41 gender analyses.(36, 37) A plausible explanation is an association between age and delay,
42 and thus adjustment for age minimizes the relative impact of delay. Furthermore, in PPCI,
43 female gender has been associated with similar or even smaller infarct size than that in male
44 gender, due to longer prehospital delays, indicating that other factors than larger infarct size
45 secondary to longer prehospital delay mainly contribute to the observed higher unadjusted
46 short term mortality.(36) The proportion of 30 day mortality that occurred within 48 hours of
47 admission was similar in women and men (38% vs 36% respectively) contrasting previous
48 data where gender differences in early mortality were accounted for by excess very early
49 (within 24-48 hours) deaths in women with STEMI.(7, 17) Cardiogenic shock and
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3 hemodynamic instability were key exclusion criteria in the ATLANTIC trial which may have
4 influenced these results. Cardiogenic shock has been shown to be more common in women
5 and female gender has been highly associated with mortality in shock patients.(19)
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9 In terms of ST-segment elevation resolution and TIMI flow 3 rates before and after PCI, no
10 significant difference between genders was observed apart from a lower risk of abnormal
11 coronary flow in IRA at initial angiography in women. The higher rate of TIMI flow 3 at
12 initial angiography may be explained by the higher rate of normal coronary arteries as well as
13 the less obstructive coronary artery disease in women with STEMI, which is in concordance
14 with previous data.(37)
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19 The analysis of the effect of gender on outcomes dependent on the randomised treatment
20 showed no statistically significant interactions. Pre-hospital administration of ticagrelor did
21 not improve pre- or post-PCI coronary reperfusion as assessed by TIMI flow in IRA and
22 resolution of ST elevation pre-PCI. Clinical efficacy outcomes were not significantly
23 improved either. However, prehospital administration of ticagrelor was safe in both genders
24 with similar rate of major and minor bleedings.
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30 31 **Strengths and limitations** 32

33 The present study has some important limitations. The ATLANTIC trial was not stratified by
34 gender. The large imbalance in the proportion of men and women included, commonly
35 encountered in a STEMI population, caused a reduced power for detecting or definitely
36 excluding significant differences in some outcomes between the genders or to definitely
37 exclude an interaction between gender and the randomised treatment.
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42 The current study was planned as a pre-specified gender analysis in the randomised,
43 controlled ATLANTIC trial. The most important strength of our analysis is that patients were
44 treated according to the current guidelines of STEMI, with PPCI as the reperfusion strategy
45 of choice, administration of the modern ADP receptor-blocker ticagrelor in addition to aspirin
46 as soon as possible after the first medical contact, high use of radial access during
47 catheterisation and adjuvant pharmacologic treatment during PPCI with UFH or bivalirudin.
48 (38) Therefore our study provides important information about differences and similarities
49 between genders in STEMI patients treated with current PCI techniques and pharmacologic
50 treatment.
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Conclusion

In patients with STEMI, planned for PPCI and treated with modern antiplatelet therapy, female gender identifies a group of patients with high risk of early mortality in whom prompt efforts to improve outcome are warranted. Female gender was not an independent predictor of bleeding but advanced age and clustering of comorbidities in women could mainly explain their higher unadjusted risk for bleeding events compared to men. Prehospital administration of ticagrelor had a similar efficacy and safety profile in men and women with STEMI.

For peer review only

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Data sharing statement

Original data are available on request. Please contact the corresponding author for further information.

Interest statement

D.V. reports that he has no relationships relevant to the contents of this paper to disclose.

S.S.L. reports that she has no relationships relevant to the contents of this paper to disclose.

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M.J. reports receiving lecture fees from AstraZeneca and Sanofi.

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M.C. reports that he has no relationships relevant to the contents of this paper to disclose.

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Author's contribution

E. Swahn is responsible for the conception and design of the gender substudy of the ATLANTIC trial. D. Venetsanos is responsible for analyses and interpretation of the data and drafted the manuscript. S. Sederholm Lawesson, J. Alfredsson, M. Janzon, A. Cequier, M. Chettibi, S.G. Goodman, A.W. van't Hof and G. Montalescot have critically revised the manuscript and added important intellectual content.

All authors have participated in the work and have read and approved the manuscript.

For peer review only

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References

1. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *Journal of the American College of Cardiology*. 2006 Feb 7;47(3 Suppl):S21-9. PubMed PMID: 16458167.
2. Mehta RH, Stebbins AS, Lopes RD, Califf RM, Pieper KS, Armstrong PW, et al. Comparison of incidence of bleeding and mortality of men versus women with ST-elevation myocardial infarction treated with fibrinolysis. *The American journal of cardiology*. 2012 Feb 1;109(3):320-6. PubMed PMID: 22078221.
3. Kyto V, Sipila J, Rautava P. Gender and in-hospital mortality of ST-segment elevation myocardial infarction (from a multihospital nationwide registry study of 31,689 patients). *The American journal of cardiology*. 2015 Feb 1;115(3):303-6. PubMed PMID: 25488357.
4. Jakobsen L, Niemann T, Thorsgaard N, Nielsen TT, Thuesen L, Lassen JF, et al. Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2012 Dec 20;8(8):904-11. PubMed PMID: 23253544.
5. Kang SH, Suh JW, Yoon CH, Cho MC, Kim YJ, Chae SC, et al. Sex differences in management and mortality of patients with ST-elevation myocardial infarction (from the Korean Acute Myocardial Infarction National Registry). *The American journal of cardiology*. 2012 Mar 15;109(6):787-93. PubMed PMID: 22196789.
6. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. A gender perspective on short- and long term mortality in ST-elevation myocardial infarction--a report from the SWEDEHEART register. *International journal of cardiology*. 2013 Sep 30;168(2):1041-7. PubMed PMID: 23168004.
7. de Boer SP, Roos-Hesselink JW, van Leeuwen MA, Lenzen MJ, van Geuns RJ, Regar E, et al. Excess mortality in women compared to men after PCI in STEMI: an analysis of 11,931 patients during 2000-2009. *International journal of cardiology*. 2014 Sep 20;176(2):456-63. PubMed PMID: 25127966.
8. Leurent G, Garlantezec R, Auffret V, Hacot JP, Coudert I, Filippi E, et al. Gender differences in presentation, management and inhospital outcome in patients with ST-segment elevation myocardial infarction: data from 5000 patients included in the ORBI prospective French regional registry. *Archives of cardiovascular diseases*. 2014 May;107(5):291-8. PubMed PMID: 24910083.
9. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. Time trends in STEMI--improved treatment and outcome but still a gender gap: a prospective observational cohort study from the SWEDEHEART register. *BMJ open*. 2012;2(2):e000726. PubMed PMID: 22457480. Pubmed Central PMCID: 3323814.
10. Pilgrim T, Heg D, Tal K, Erne P, Radovanovic D, Windecker S, et al. Age- and Gender-related Disparities in Primary Percutaneous Coronary Interventions for Acute ST-segment elevation Myocardial Infarction. *PloS one*. 2015;10(9):e0137047. PubMed PMID: 26352574. Pubmed Central PMCID: 4564139.
11. Lansky AJ, Pietras C, Costa RA, Tsuchiya Y, Brodie BR, Cox DA, et al. Gender differences in outcomes after primary angioplasty versus primary stenting with and without abciximab for acute myocardial infarction: results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation*. 2005 Apr 5;111(13):1611-8. PubMed PMID: 15811868.
12. Motovska Z, Widimsky P, Aschermann M, Investigators PSG. The impact of gender on outcomes of patients with ST elevation myocardial infarction transported for percutaneous coronary intervention: analysis of the PRAGUE-1 and 2 studies. *Heart*. 2008 Mar;94(3):e5. PubMed PMID: 17693459.

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2
3 13. Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *The New England journal of medicine*. 2014 Sep 11;371(11):1016-27. PubMed PMID: 25175921.
- 4
5
6 14. Montalescot G, Lassen JF, Hamm CW, Lapostolle F, Silvain J, ten Berg JM, et al. Ambulance or in-catheterization laboratory administration of ticagrelor for primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: rationale and design of the randomized, double-blind Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) study. *American heart journal*. 2013 Apr;165(4):515-22. PubMed PMID: 23537967.
- 7
8
9
10
11
12 15. Wijnbergen I, Tijssen J, van 't Veer M, Michels R, Pijls NH. Gender differences in long-term outcome after primary percutaneous intervention for ST-segment elevation myocardial infarction. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2013 Sep 1;82(3):379-84. PubMed PMID: 23553888.
- 13
14
15
16 16. Champney KP, Frederick PD, Bueno H, Parashar S, Foody J, Merz CN, et al. The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction. *Heart*. 2009 Jun;95(11):895-9. PubMed PMID: 19147625. Pubmed Central PMCID: 3065924.
- 17
18
19
20
21 17. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Marea AO, et al. Sex differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008 Dec 16;118(25):2803-10. PubMed PMID: 19064680.
- 22
23
24
25 18. Jackson EA, Moscucci M, Smith DE, Share D, Dixon S, Greenbaum A, et al. The association of sex with outcomes among patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction in the contemporary era: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). *American heart journal*. 2011 Jan;161(1):106-12 e1. PubMed PMID: 21167341.
- 26
27
28
29
30 19. Suessenbacher A, Doerler J, Alber H, Aichinger J, Altenberger J, Benzer W, et al. Gender-related outcome following percutaneous coronary intervention for ST-elevation myocardial infarction: data from the Austrian acute PCI registry. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2008 Aug;4(2):271-6. PubMed PMID: 19110794.
- 31
32
33
34
35 20. Husted S, James SK, Bach RG, Becker RC, Budaj A, Heras M, et al. The efficacy of ticagrelor is maintained in women with acute coronary syndromes participating in the prospective, randomized, PLATElet inhibition and patient Outcomes (PLATO) trial. *European heart journal*. 2014 Jun 14;35(23):1541-50. PubMed PMID: 24682844. Pubmed Central PMCID: 4057642.
- 36
37
38
39
40 21. De Luca G, Gibson CM, Gyongyosi M, Zeymer U, Dudek D, Arntz HR, et al. Gender-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty and glycoprotein IIb/IIIa inhibitors: insights from the EGYPT cooperation. *Journal of thrombosis and thrombolysis*. 2010 Oct;30(3):342-6. PubMed PMID: 20213259.
- 41
42
43
44
45 22. Benamer H, Tafflet M, Bataille S, Escolano S, Livarek B, Fourchard V, et al. Female gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI: insights from the greater Paris area PCI Registry. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2011 Apr;6(9):1073-9. PubMed PMID: 21518679.
- 46
47
48
49
50 23. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. *JAMA internal medicine*. 2014 Nov;174(11):1822-30. PubMed PMID: 25265319.
- 51
52
53
54 24. Peterson ED, Lansky AJ, Kramer J, Anstrom K, Lanzilotta MJ, National Cardiovascular Network Clinical I. Effect of gender on the outcomes of contemporary percutaneous coronary intervention. *The American journal of cardiology*. 2001 Aug 15;88(4):359-64. PubMed PMID: 11545754.
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2
3 25. Sederholm Lawesson S, Todt T, Alfredsson J, Janzon M, Stenstrand U, Swahn E.
4 Gender difference in prevalence and prognostic impact of renal insufficiency in patients with ST-
5 elevation myocardial infarction treated with primary percutaneous coronary intervention. *Heart*.
6 2011 Feb;97(4):308-14. PubMed PMID: 21212134.
- 7 26. Berger JS, Elliott L, Gallup D, Roe M, Granger CB, Armstrong PW, et al. Sex differences
8 in mortality following acute coronary syndromes. *JAMA : the journal of the American Medical*
9 *Association*. 2009 Aug 26;302(8):874-82. PubMed PMID: 19706861. Pubmed Central PMCID:
10 2778841.
- 11 27. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, et al. Bleeding in acute
12 coronary syndromes and percutaneous coronary interventions: position paper by the Working
13 Group on Thrombosis of the European Society of Cardiology. *European heart journal*. 2011
14 Aug;32(15):1854-64. PubMed PMID: 21715717.
- 15 28. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to
16 predict bleeding in patients with acute coronary syndromes. *Journal of the American College of*
17 *Cardiology*. 2010 Jun 8;55(23):2556-66. PubMed PMID: 20513595.
- 18 29. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, et al. Bleeding
19 complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATElet
20 inhibition and patient Outcomes (PLATO) trial. *European heart journal*. 2011 Dec;32(23):2933-44.
21 PubMed PMID: 22090660.
- 22 30. Mathews R, Peterson ED, Chen AY, Wang TY, Chin CT, Fonarow GC, et al. In-hospital
23 major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and
24 validation of a model from the ACTION Registry(R)-GWTG. *The American journal of cardiology*. 2011
25 Apr 15;107(8):1136-43. PubMed PMID: 21324428.
- 26 31. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, et al. Impact of
27 major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary
28 syndromes: an analysis from the ACUITY Trial. *Journal of the American College of Cardiology*. 2007
29 Mar 27;49(12):1362-8. PubMed PMID: 17394970.
- 30 32. Ahmed B, Piper WD, Malenka D, VerLee P, Robb J, Ryan T, et al. Significantly improved
31 vascular complications among women undergoing percutaneous coronary intervention: a report
32 from the Northern New England Percutaneous Coronary Intervention Registry. *Circulation*
33 *Cardiovascular interventions*. 2009 Oct;2(5):423-9. PubMed PMID: 20031752.
- 34 33. Cho L, Topol EJ, Balog C, Foody JM, Booth JE, Cabot C, et al. Clinical benefit of
35 glycoprotein IIb/IIIa blockade with Abciximab is independent of gender: pooled analysis from EPIC,
36 EPILOG and EPISTENT trials. Evaluation of 7E3 for the Prevention of Ischemic Complications.
37 Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with
38 Abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stent. *Journal of the*
39 *American College of Cardiology*. 2000 Aug;36(2):381-6. PubMed PMID: 10933346.
- 40 34. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, et al.
41 Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous
42 coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study.
43 *Lancet*. 2008 Jun 7;371(9628):1915-20. PubMed PMID: 18539223.
- 44 35. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and
45 mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts.
46 *Circulation*. 2004 Mar 16;109(10):1223-5. PubMed PMID: 15007008.
- 47 36. Sadowski M, Gasior M, Gierlotka M, Janion M, Polonski L. Gender-related differences
48 in mortality after ST-segment elevation myocardial infarction: a large multicentre national registry.
49 *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional*
50 *Cardiology of the European Society of Cardiology*. 2011 Apr;6(9):1068-72. PubMed PMID: 21518678.
- 51 37. Otten AM, Maas AH, Ottervanger JP, Kloosterman A, van 't Hof AW, Dambrink JH, et
52 al. Is the difference in outcome between men and women treated by primary percutaneous
53 coronary intervention age dependent? Gender difference in STEMI stratified on age. *European heart*
54 *journal*. 2011 Jun 16;32(12):1403-10. PubMed PMID: 21644444.
- 55
56
57
58
59
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2
3 journal Acute cardiovascular care. 2013 Dec;2(4):334-41. PubMed PMID: 24338292. Pubmed Central
4 PMCID: 3821825.

5 38. Wessler JD, Stant J, Duru S, Rabbani L, Kirtane AJ. Updates to the ACCF/AHA and ESC
6 STEMI and NSTEMI guidelines: putting guidelines into clinical practice. The American journal of
7 cardiology. 2015 Mar 14;115(5 Suppl):23A-8A. PubMed PMID: 25728971.
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11 **Figure legends**

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14 Figure 1. Cumulative Kaplan-Meier estimates of the incidence of the composite endpoint of
15 death, MI, stroke, urgent revascularisation or definite acute stent thrombosis and all-cause
16 mortality at 30 days by gender.

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18 Figure 2. Association between gender and clinical efficacy and safety outcomes independent of
19 randomised treatment.

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21 Figure 3. Association between gender and primary and secondary outcomes, independent of
22 randomised treatment.

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24 Figure 4. Cumulative Kaplan-Meier estimates of the incidence of the TIMI major bleeding and
25 BARC type 3-5 bleeding at 30 days by gender.
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Table 1. Baseline, clinical and periprocedural characteristics according to gender.

Characteristics	Women (n=369)	Men (n=1493)	P- value
Age, years; mean (SD)	69 (13.0)	59 (11)	<0.01
Age ≥75 years	153 (41.5)	151 (10.1)	<0.01
BMI, kg/m ² ; median (IQR)	25.6 (22.5-29.1)	26.5 (24.3-29.4)	<0.01
Prior history			
Diabetes mellitus	48 (13.0)	205 (13.7)	0.72
Hypertension	190 (51.5)	605 (40.5)	<0.01
Dyslipidemia	117 (31.7)	536 (35.9)	0.13
Angina	36 (9.8)	157 (10.5)	0.67
Prior myocardial infarction	24 (6.5)	135 (9.0)	0.67
Prior PCI	16 (4.3)	124 (8.3)	<0.01
Prior CABG	1 (0.3)	11 (0.7)	0.32
Prior non-haemorrhagic stroke	8 (2.2)	10 (0.7)	<0.01
Chronic obstructive pulmonary disease	22 (6.0)	54 (3.6)	0.04
Gastrointestinal bleeding	1 (0.3)	16 (1.1)	0.15
Chronic renal disease	7 (1.9)	27 (1.8)	0.91
Index event information			
First medical contact in ambulance	280 (75.9)	1132 (75.8)	0.24
Minutes from symptom onset to pre-hospital ECG, median (IQR)	88 (49-169)	70 (41-129)	<0.01
Minutes from prehospital ECG to PCI, median (IQR)	83 (68-101)	80 (66-96)	0.03
Minutes from pre-PCI angiography to post-PCI angiography, median (IQR)	36 (24-52)	32 (23-45)	0.03
Received first loading dose	369 (100)	1488 (99.7)	0.27
Risk level at admission			
Killip class			
I	332 (90.0)	1349 (90.4)	0.82
IV	2 (0.5)	3 (0.2)	
TIMI risk score			
0-2	119 (32.2)	1006 (67.4)	0.01
3-6	231 (62.6)	471 (31.5)	
>6	19 (5.1)	16 (1.1)	
Culprit vessel			
Left main artery	4 (1.1)	18 (1.2)	0.63

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Left anterior descending artery	141 (38.8)	571 (39.0)	
Right coronary artery	150 (41.3)	590 (40.3)	
Left circumflex	39 (10.7)	196 (13.4)	
No culprit vessel identified	28 (7.7)	85 (5.8)	
Normal coronary angiography	27 (7.4)	76 (5.2)	0.1
Procedures for index event			
Femoral access	144 (39.7)	445 (30.4)	<0.01
Thromboaspiration	160 (43.4)	781 (52.3)	<0.01
PCI	309 (83.7)	1321 (88.5)	0.01
With any stent	288 (78.0)	1248 (83.6)	0.01
With DES	185 (50.1)	761 (51.0)	0.77
Coronary artery bypass grafting	4 (1.1)	21 (1.4)	0.63
No revascularisation	56 (15.2)	151 (10.1)	<0.01
Any glycoprotein IIb/IIIa inhibitor use	115 (31.2)	598 (40.1)	<0.01
Glycoprotein IIb/IIIa inhibitor use before angiography	14 (3.8)	116 (7.8)	<0.01
Intravenous anticoagulant prior to pre-PCI angiography	231 (62.6)	1027 (68.8)	0.02
Intravenous anticoagulant during hospitalisation †	310 (84.0)	1332 (89.2)	<0.01
Heparin only	135 (36.6)	584 (39.1)	0.02
Bivalirudin only	29 (7.9)	65 (4.4)	0.02

Variables presented as numbers (percentages) unless otherwise indicated.

BMI, body mass index; CABG, coronary artery bypass grafting; DES, drug-eluting stent; IQR, interquartile range (25th–75th percentile); PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, Thrombolysis In Myocardial Infarction.

† Includes all IV medications given on the date of the qualifying ECG and /or index PCI

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Table 2 Association between gender and clinical outcomes independent of randomised treatment

Outcomes	Female (n=369)	Male (n=1489)	Crude hazard ratio (95%CI) (n included=1858)	Adjusted hazard ratio (95%CI)* (n included=1613)	P-value *
	Patients with endpoint, n (%)	Patients with endpoint, n (%)			
Mortality and cardiovascular outcomes					
Composite of death/MI/stroke/urgent revascularisation/definite acute stent thrombosis	25 (6.8)	58 (3.9)	1.79 (1.12-2.86)	1.32 (0.77-2.27)	0.32
Composite of death/MI/urgent revascularisation	23 (6.2)	50 (3.4)	1.91 (1.17-3.13)	1.33 (0.75-2.36)	0.32
All-cause mortality	21 (5.7)	28 (1.9)	3.13 (1.78-5.51)	2.08 (1.03-4.20)	0.04
Myocardial infarction	3 (0.8)	14 (0.9)	0.90 (0.26-3.13)	0.82 (0.23-2.85)	0.76
Stroke	3 (0.8)	3 (0.2)	4.18 (0.84-20.70)	4.14 (0.84-20.51)	0.08
Urgent revascularisation	2 (0.5)	11 (0.7)	0.75 (0.17-3.38)	0.69 (0.15-3.11)	0.63
Definite acute stent thrombosis	3 (0.8)	10 (0.7)	1.23 (0.34-4.49)	1.29 (0.35-4.76)	0.70
Acute stent thrombosis (definite or probable)	11 (3.0)	30 (2.0)	1.53 (0.77-3.05)	0.88 (0.39-1.98)	0.76
Safety outcomes					
PLATO major bleeding **	17 (4.6)	33 (2.2)	2.15 (1.20-3.85)	1.45 (0.73-2.86)	0.29
TIMI major bleeding **	10 (2.7)	14 (0.9)	2.95 (1.31-6.65)	1.28 (0.47-3.48)	0.63

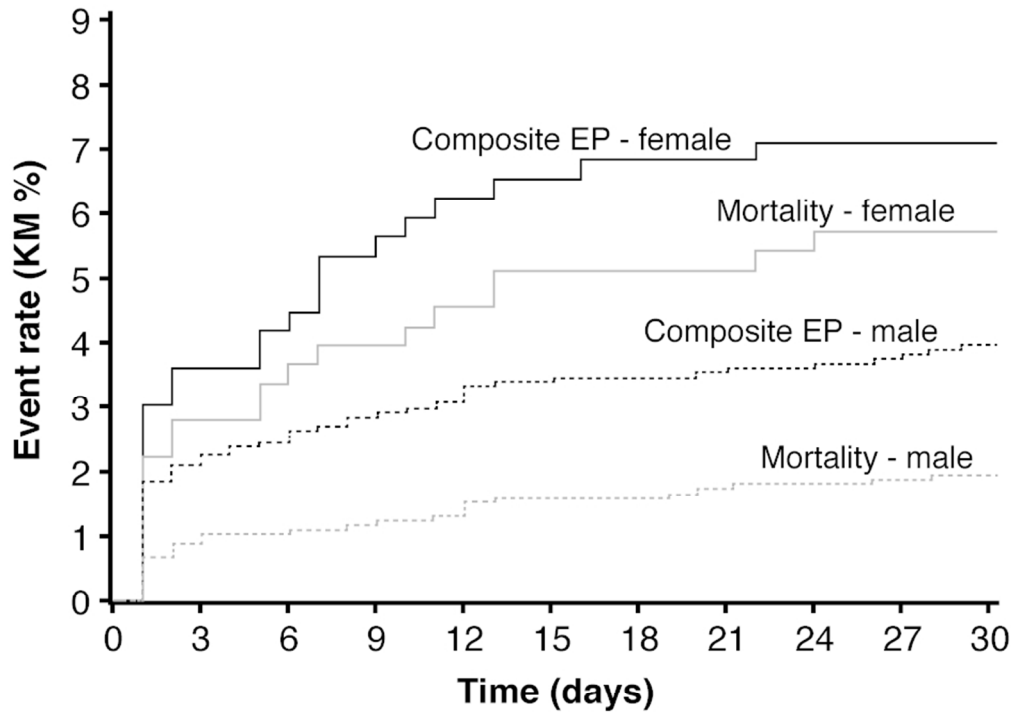
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TIMI major or minor bleeding**	18 (4.9)	54 (3.6)	1.38 (0.81-2.35)	0.94 (0.51-1.74)	0.85
BARC type 3-5 (major) bleeding**	16 (4.3)	31 (2.1)	2.15 (1.18-3.93)	1.45 (0.72-2.91)	0.30
BARC type 2-5 (major or minor) bleeding**	20 (5.4)	56 (3.8)	1.48 (0.89-2.47)	1.03 (0.57-1.84)	0.93

*Hazard ratio (for female versus male) and p-value calculated from logistic regression model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, access site, glycoprotein IIb/IIIa inhibitor, bivalirudin or unfractionated heparin use during index procedure, revascularization and location of myocardial infarction

**Non-CABG related bleeding occurring up to the date of the last study visit (to the maximum of 32 days) are included in the table

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; PLATO, Study of Platelet Inhibition and Patient Outcomes; TIMI, Thrombolysis in Myocardial Infarction



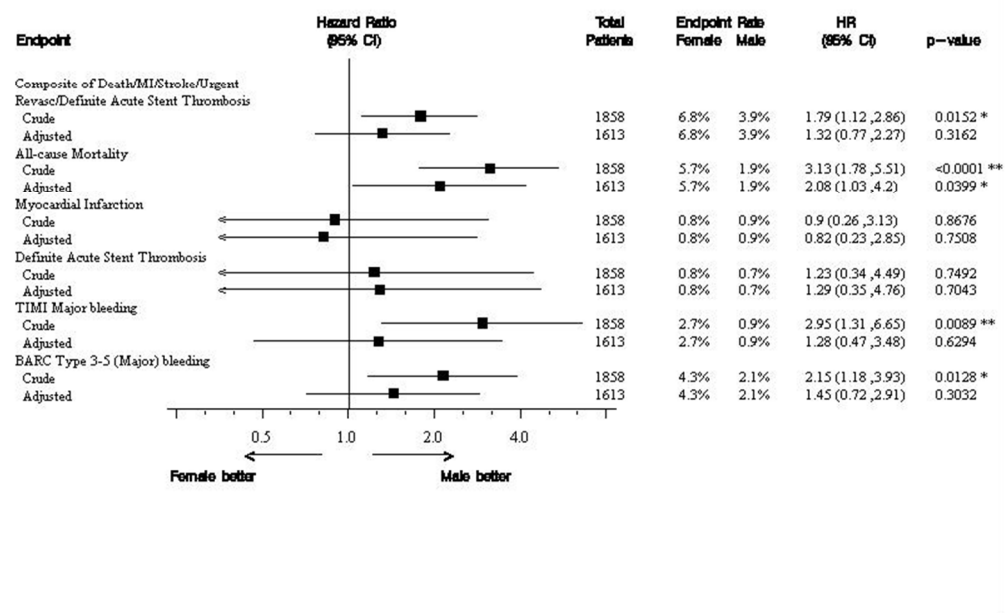
Composite endpoint	All-cause mortality
Female 25/369 (6.8%)	Female 21/369 (5.7%)
Male 58/1489 (3.9%)	Male 28/1489 (1.9%)

Caption : Figure 1. Cumulative Kaplan-Meier estimates of the incidence of the composite endpoint of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis and all-cause mortality at 30 days by gender.

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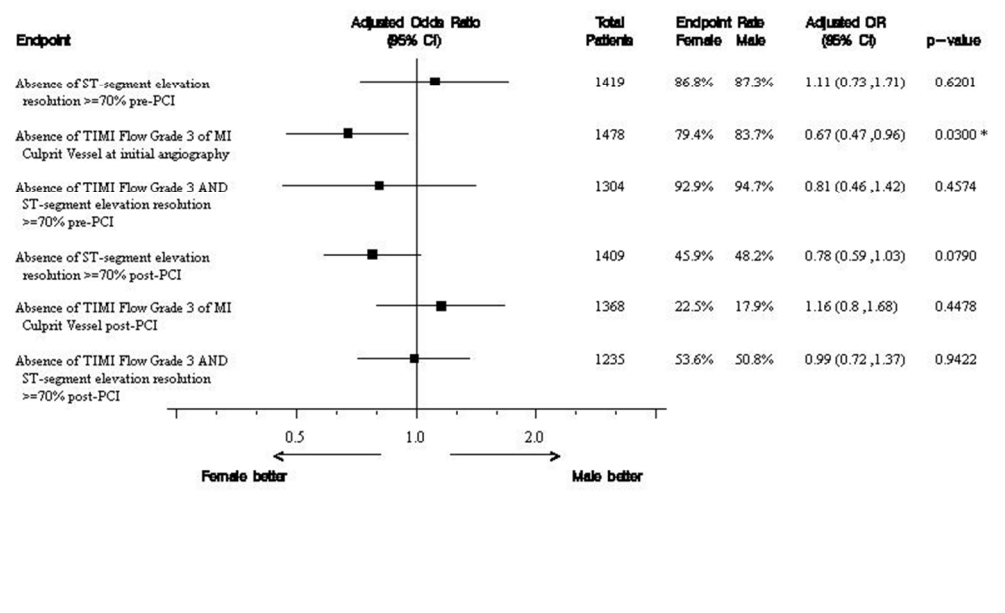
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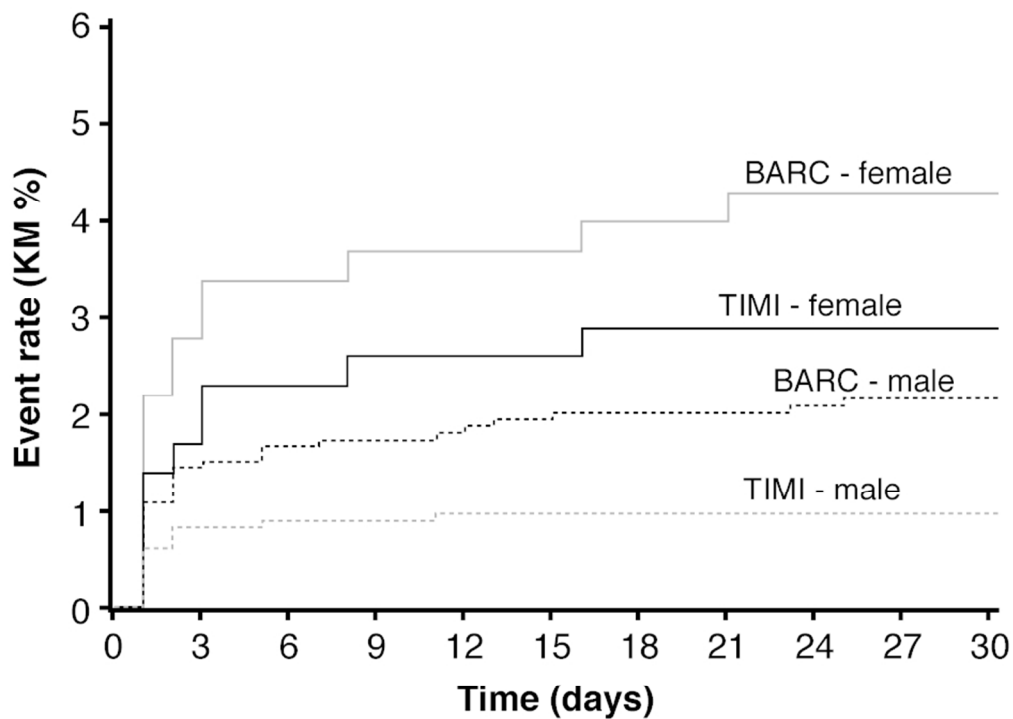
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TIMI major bleed	BARC type 3–5 bleed
Female 10/369 (2.7%)	Female 16/369 (4.3%)
Male 14/1489 (0.9%)	Male 31/1489 (2.1%)

Caption : Figure 4. Cumulative Kaplan-Meier estimates of the incidence of the TIMI major bleeding and BARC type 3-5 bleeding at 30 days by gender.

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Supplementary table 1 Association between gender and efficacy of randomised treatment – clinical outcomes

Outcomes	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model , n	Adjusted hazard ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
Composite of Death/MI/Stroke/Urgent Revasc/Definite Acute Stent Thrombosis	Female	173	13 (7.5)	196	12 (6.1)	1613	0.98 (0.42-2.27)	0.87
	Male	733	28 (3.8)	756	30 (4.0)		0.90 (0.51-1.59)	
Composite of Death/MI/Urgent Revasc	Female	173	13 (7.5)	196	10 (5.1)	1613	1.32 (0.55-3.20)	0.55
	Male	733	26 (3.5)	756	24 (3.2)		0.95 (0.52-1.76)	
All-cause mortality	Female	173	13 (7.5)	196	8 (4.1)	1613	1.59 (0.61-4.12)	0.93
	Male	733	17 (2.3)	756	11 (1.5)		1.50 (0.60-3.74)	
Myocardial infarction	Female	173	1 (0.6)	196	2 (1.0)	1613	0.44 (0.04-4.95)	0.72
	Male	733	6 (0.8)	756	8 (1.1)		0.72 (0.25-2.09)	
Stroke	Female	173	1 (0.6)	196	2 (1.0)	1613	0.54 (0.05-5.90)	0.99
	Male	733	3 (0.4)	756	0 (0.0)		Nt estimated	
Urgent revascularization	Female	173	1 (0.6)	196	1 (0.5)	1613	0.86 (0.05-14.07)	0.76
	Male	733	4 (0.5)	756	7 (0.9)		0.54 (0.15-1.87)	
Definite Acute Stent Thrombosis	Female	173	1 (0.6)	196	2 (1.0)	1613	0.37 (0.03-4.27)	0.49
	Male	733	1 (0.1)	756	9 (1.2)		0.12 (0.01-1.02)	
Acute Stent Thrombosis (definite or probable)	Female	173	7 (4.0)	196	4 (2.0)	1613	1.31 (0.37-4.69)	0.52
	Male	733	14 (1.9)	756	16 (2.1)		0.80 (0.35-1.80)	

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≠ Adjusted hazard (for female versus male) and p-values for interaction was calculated from Cox proportional hazard model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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Supplementary table 2 Association between gender and efficacy of randomised treatment – primary and secondary outcomes

Outcomes	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model N ≠	Adjusted odds ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
Absence of ST segment elevation resolution ≥ 70% pre-PCI	Female	142	122 (85.9)	168	147 (87.5)	1419	0.75 (0.37-1.53)	0.71
	Male	632	550 (87.0)	656	575 (87.7)		0.85 (0.59-1.23)	
Absence of TIMI flow grade 3 in infarct related artery at initial angiography	Female	155	127 (81.9)	175	135 (77.1)	1478	1.36 (0.76-2.41)	0.19
	Male	669	554 (82.8)	681	576 (84.6)		0.88 (0.64-1.20)	
Absence of ST segment resolution ≥ 70% AND absence of TIMI flow grade 3 in infarct related artery pre-PCI	Female	129	120 (93.0)	153	142 (92.8)	1304	1.07 (0.41-2.81)	0.84
	Male	590	557 (94.4)	598	568 (95.0)		0.96 (0.57-1.62)	
Absence of ST-segment resolution ≥70% after PCI	Female	144	61 (42.4)	163	80 (49.1)	1409	0.76 (0.47-1.25)	0.51
	Male	629	291 (46.3)	650	326 (50.2)		0.92 (0.72-1.17)	
Absence of TIMI flow grade 3 in infarct related artery after PCI	Female	144	30 (20.8)	154	37 (24.0)	1368	0.93 (0.51-1.71)	0.98
	Male	621	107 (17.2)	631	117 (18.5)		0.92 (0.68-1.26)	
Absence of ST segment resolution ≥70% AND absence of TIMI flow grade 3 in infarct related artery after PCI	Female	125	60 (48.0)	138	81 (58.7)	1235	0.64 (0.38-1.10)	0.13
	Male	562	282 (50.2)	565	290 (51.3)		1.01 (0.78-1.32)	

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≠ Adjusted odds ratio (for female versus male) and p-values for interaction was calculated from logistic regression model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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Supplementary table 3 Association between gender and safety of randomised treatment (safety outcomes)

End point	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model N ≠	Adjusted hazard ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
PLATO major bleeding	Female	173	6 (3.5)	196	11 (5.6)	1613	0.61 (0.21-1.83)	0.23
	Male	733	19 (2.6)	756	14 (1.9)		1.39 (0.66-2.93)	
PLATO major and minr bleeding	Female	173	7 (4.0)	196	13 (6.6)	1613	0.59 (0.22-1.61)	0.19
	Male	733	33 (4.5)	756	26 (3.4)		1.27 (0.73-2.21)	
TIMI major bleeding	Female	173	3 (1.7)	196	7 (3.6)	1613	0.60 (0.14-2.54)	0.28
	Male	733	9 (1.2)	756	5 (0.7)		1.62 (0.53-4.98)	
TIMI major and minr bleeding	Female	173	6 (3.5)	196	12 (6.1)	1613	0.55 (0.19-1.60)	0.24
	Male	733	29 (4.0)	756	25 (3.3)		1.14 (0.64-2.03)	
BARC type 3-5 (major) bleeding	Female	173	6 (3.5)	196	10 (5.1)	1613	0.69 (0.23-2.11)	0.26
	Male	733	18 (2.5)	756	13 (1.7)		1.51 (0.70-3.26)	
BARC type 2-5 (major and minr) bleeding	Female	173	7 (4.0)	196	13 (6.6)	1613	0.59 (0.22-1.60)	0.21
	Male	733	31 (4.2)	756	25 (3.3)		1.23 (0.70-2.17)	

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≠Adjusted hazard (for female versus male) and p-values for interaction was calculated from Cox proportional hazard model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5, 6
		(b) Describe any methods used to examine subgroups and interactions	5, 6
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	6
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	4 NA (SEE PAGE 4)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7, 8, 9 6 NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 10, 11, 12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9, 10, 11, 12 yes
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	13, 14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13, 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association between gender and short term outcome in ST elevation myocardial infarction patients participating in the international, prospective, randomised Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) trial: a prespecified analysis

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Manuscripts

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5 **Association between gender and short term outcome in ST elevation**
6 **myocardial infarction patients participating in the international, prospective,**
7 **randomised Administration of Ticagrelor in the cath Lab or in the Ambulance**
8 **for New ST elevation myocardial Infarction to open the Coronary artery**
9 **(ATLANTIC) trial: a prespecified analysis**
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44 **ticagrelor**
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Abstract

Objectives

To evaluate gender differences in outcomes in STEMI patients planned for PPCI

Settings

A pre-specified gender analysis of the multicenter, randomised, double-blind ATLANTIC trial

Participants

Between September 2011 and October 2013, 1862 patients with STEMI and symptom duration less than 6 hours were included

Interventions

Patients were assigned to pre-hospital versus in-hospital administration of 180mg ticagrelor.

Outcomes

The main objective was to study the association between gender and primary and secondary outcomes of the main study with a focus on the clinical efficacy and safety outcomes.

Primary: The proportion of patients who did not have $\geq 70\%$ resolution of ST segment elevation and did not meet the criteria for TIMI flow 3 at initial angiography. Secondary: the composite of death, MI, stent thrombosis, stroke, or urgent revascularisation and major or minor bleeding at 30 days.

Results

Women were older, had higher TIMI risk score, longer pre-hospital delays and better TIMI flow in the infarct related artery. Women had a 3-fold higher risk for all-cause mortality compared to men (5.7% vs 1.9%, HR 3.13, 95% CI 1.78 – 5.51). After adjustment, the difference was attenuated but remained statistically significant (HR 2.08, 95% CI 1.03 – 4.20). The incidence of major bleeding events was 2 to 3-fold higher in women compared to men. In the multivariable model, female gender was not an independent predictor of bleeding (PLATO major HR 1.45, 95% CI 0.73-2.86, TIMI major HR 1.28, 95% CI 0.47-3.48, BARC type 3-5 HR 1.45, 95% CI 0.72-2.91). There was no interaction between gender and efficacy or safety of randomised treatment.

Conclusion

In STEMI patients planned for PPCI-techniques and treated with modern antiplatelet therapy, female gender was an independent predictor of short term mortality. In contrast, the higher

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3 incidence of bleeding complications in women could mainly be explained by older age and
4 clustering of comorbidities.
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10 **CLINICAL TRIAL REGISTRATION:** clinicaltrials.gov identifier: NCT01347580.
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12 13 14 **Strengths and limitations**

- 15 • All patients were planned for primary PCI
- 16 • Current PCI techniques and novel antiplatelet therapy were used
- 17 • Appropriate statistical methods used to adjust for baseline differences between
- 18 genders
- 19 • Our analysis, though prespecified, is applicable to the population studied
- 20 • The large imbalance in the proportion of men and women included caused a reduced
- 21 study power for definitely excluding significant differences in outcomes
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Introduction

Recent studies have provided evidence of gender differences in the pathophysiology and the clinical expression of atherosclerosis.(1) Several registries in patients with ST-segment elevation myocardial infarction (STEMI) have consistently shown a considerably higher risk of adverse outcomes in women compared to men. Nevertheless, there are conflicting results regarding whether gender is an independent contributor to this observation or the higher risk in women depends on differences in baseline characteristics and comorbidities between genders.(2-8) Although registries of STEMI patients usually include large, unselected populations, they share some inherent limitations. Their results are certainly influenced by differences between genders in the use of timely reperfusion therapy and evidence based drug therapies as well as undetected confounding factors.(9, 10) Therefore, reports of gender-based analyses of randomised controlled trials are of crucial importance in an effort to minimise inequality in the management and evaluate gender as a potential independent risk factor for adverse outcome. Only a few randomised trials of STEMI patients treated with primary PCI (PPCI) have reported results in the context of gender.(11, 12) New treatments (e.g. ticagrelor or prasugrel), special efforts to reduce bleeding (i.e. increased use of radial arterial access, provisional rather than routine use of glycoprotein (GP) IIb/IIIa inhibitor), shorter delay times to reperfusion and a growing awareness regarding gender differences in the management and importance of adherences to evidence based treatment could contribute to improved ischemic and bleeding outcomes in female STEMI patients.

In the ATLANTIC trial, prehospital administration of ticagrelor appeared to be safe but did not significantly improve outcome compared to in hospital administration in patients with STEMI, treated with PPCI according to the current modern standards.(13)

We present a pre-specified gender analysis of the ATLANTIC trial, with the aim of studying the association between gender and outcome.

Methods

The ATLANTIC study was an international, randomised, double-blind, placebo-controlled study with 30 days follow-up. The design of the study, inclusion and exclusion criteria, outcome definitions and principal results have previously been described.(13, 14) Briefly, 1862 patients presenting with STEMI, less than 6 hours after symptom onset, were included and randomised to pre-hospital (in the ambulance) versus in-hospital (in the catheterisation laboratory) treatment with a loading dose of ticagrelor (180mg) in addition to aspirin and

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3 standard clinical care. All patients were to subsequently receive ticagrelor 90 mg twice daily
4 for 30 days, after which it was recommended that ticagrelor should be continued for up to 12
5 months. Pre-hospital administration of a GP IIb/IIIa inhibitor was left to the physician's
6 discretion. Peri-procedural use of parenteral anticoagulants was also left to the physician's
7 discretion, according to the local practice.
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11 The proportion of patients who did not have $\geq 70\%$ resolution of ST segment elevation before
12 PCI and / or did not meet the criteria for TIMI flow 3 in the infarct related artery (IRA) at
13 initial angiography was the primary outcome of the ATLANTIC trial. Secondary outcomes
14 (clinical efficacy outcomes) included the composite of death, MI, stent thrombosis, stroke, or
15 urgent revascularisation at 30 days and definite stent thrombosis at 30 days. Safety outcomes
16 included major and minor bleeding over the 30-day treatment period. Bleeding risk was
17 evaluated using the TIMI (The Thrombolysis In Myocardial Infarction), BARC (Bleeding
18 Academic Research Consortium) and PLATO (Study of Platelet Inhibition and Patient
19 Outcomes) bleeding definitions.(14)
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23 The main objective of our analysis was to study the association between gender and primary
24 and secondary outcomes of the main study with a special focus on the clinical efficacy and
25 safety outcomes. The interaction of gender subgroups with randomised treatment effects was
26 also investigated.
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30 The trial design and protocol were approved by the national regulatory authorities in all the
31 participating countries and by the local ethics committee or institutional review board at each
32 participating site. All patients provided written informed consent.
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35 36 37 38 39 40 41 42 43 **Statistical analysis**

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45 Continuous variables are presented by their mean and standard deviation (SD) or median and
46 25th -75th percentiles as appropriate. Categorical variables are presented as counts and
47 percentages. Baseline and peri-procedural characteristics were compared according to gender
48 by chi-square tests for categorical variables and Student's t-test or Mann Whitney U test for
49 continuous variables, depending on if the variable of interest was normally distributed or not.
50 A p-value < 0.05 is considered to indicate statistical significance.
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54 The incidence of events over time by gender is presented by Kaplan-Meier curves.
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3 In order to study the association between gender and the clinical efficacy and safety
4 outcomes, independent of randomised treatment as well as the possible interactions between
5 gender and randomised treatment with respect to the outcomes, hazard ratios [HR] with 95%
6 confidence intervals [CI] were derived from Cox proportional-hazards models. In the
7 unadjusted (crude) model, gender was the only explanatory variable whereas in the adjusted
8 multivariable model, gender was forcibly included and the other variables were chosen by
9 using a forward stepwise selection algorithm with a significant cut-off level of 0.05 for
10 inclusion. Selection of covariates included in the multivariable analysis was based on
11 previous studies (3, 4, 6, 15) and clinical experience. Univariate analysis was not performed.
12 However, this is a common practice in observational studies and we included 18 covariates in
13 our multivariable analysis that, we believe, incorporated all possible predictors of adverse
14 outcomes in a STEMI population.

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16 Adjustment variables included age, weight, prior MI, prior PCI, history of diabetes,
17 hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to
18 pre-PCI electrocardiogram [ECG], admission Killip class (as a dichotomous variable 1 / >1),
19 baseline hemoglobin, estimated glomerular filtration rate (eGFR) according to the MDRD
20 formula, access site, use of GP IIb/IIIa inhibitor, bivalirudin and UFH, location of MI and
21 revascularisation. To evaluate the importance of early mortality, a landmark analysis of the
22 clinical efficacy outcomes was also performed from 48 hours after randomisation (arbitrarily
23 defined) to the end of the study. In order to explore the importance of bleeding on the clinical
24 efficacy outcomes, a separate analysis was also performed by censoring the patients who
25 reported a PLATO major bleeding at the time of the onset of a bleeding event.

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27 A comparable statistical process was used to compare gender differences in the effect of
28 randomised treatment by constructing logistic regression models. Odds ratios [OR] with 95%
29 CI are presented. The above process for Cox regression and logistic regression was also used
30 to explore the interaction effect of gender and treatment.

31
32 For most of the variables included in the multivariable models, only few patients had missing
33 data (<10 patients). However, 7% of patients had missing values for creatinine, 5% for
34 hemoglobin and 4% for Killip class. The number of patients with complete data for
35 multivariable Cox proportional-hazard models of the primary outcome was 1613 (88%).

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Results

Baseline and peri-procedural characteristics stratified by gender

Demographic and clinical characteristics

The study population consisted of 369 (20 %) women. They were older (mean age 69 vs. 59 years, $p<0.01$), had lower body mass index (BMI), higher TIMI risk score, more often had a history of hypertension, chronic obstructive pulmonary disease (COPD) and stroke. Men had more frequent prior PCI. No difference was observed between genders with respect to acute heart failure (Killip class > 1) and only a minority of patients presented with cardiogenic shock (**Table 1**).

Time delays

Women had significantly longer delay times, both from symptom onset to prehospital ECG (median 88 vs 70 minutes, $p<0.01$) and from pre-PCI to post-PCI angiography (median 36 vs 32 minutes, $p=0.03$).

Procedural characteristics, angiographic findings, and medication during the index event

Coronary angiography was more often performed by femoral access in women (39.7% vs 30.4%, $p<0.01$). The genders did not differ according to IRA, with the left anterior descending artery involved in 38% of women and 39% of men. PPCI, with or without stent, was performed significantly more often in men (88.5% vs 83.7%, $p<0.01$) whereas the use of drug eluting stents (DES) was similar. Thromboaspiration, GP IIb/IIIa inhibitors and intravenous anticoagulants were used less often in women. (**Table 1**)

Association between gender and outcomes independent of randomised treatment

Female gender was associated with significantly higher risk for the composite outcome of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis compared to male gender (6.8% vs 3.9%, crude HR 1.79, 95% CI 1.12 – 2.86) (**Figure 1**). This difference was mainly driven by a 3-fold higher risk for all-cause mortality in women compared to men (5.7% vs 1.9%, HR 3.13, 95% CI 1.78 – 5.51). Although the difference was attenuated in the multivariable model, gender was still associated with all-cause mortality at 30 days (HR 2.08, 95% CI 1.03 – 4.20) (**Figure 2 and table 2**). Landmark analysis for events occurring within

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3 48 hours, and between 48 hours and 30 days showed that 38% of the women and 36% of the
4 men who did not survive the first month died within 48 hours. Comparison after excluding
5 patients from further analysis at the time point of a PLATO major bleeding event still
6 revealed a statistically significant association between women and all-cause mortality (4.3%
7 vs 1.4%. HR 3.20, 95% CI 1.67 – 6.13). Similar result was obtained after adjustment but the
8 difference between genders did not reach statistical significance (HR 2.15, 95% CI 0.93-
9 5.00).

10
11 Female gender was associated with lower risk for TIMI flow < 3 in the IRA at initial
12 angiography (adjusted OR 0.67, 95% CI 0.47-0.96). The risk of incomplete ST-segment
13 elevation resolution (<70%) before PCI did not differ significantly between the genders
14 (adjusted OR 1.11, 95% CI 0.73-1.71). The risk of abnormal TIMI flow in the IRA and
15 incomplete ST segment elevation resolution after PCI was similar in both genders (**Figure 3**).

16
17 Women had significantly higher risk for major bleeding complications compared to men,
18 irrespective of the bleeding definition used (30-day PLATO major bleeding 4.6% vs 2.2%,
19 HR 2.15, 95% CI 1.18 – 3.85, TIMI major bleeding at 30 days 2.7% vs 0.9%, HR 2.95, 95%
20 CI 1.31 – 6.65, BARC type 3-5 bleeding 4.3% vs 2.1%, HR 2.15, 95% CI 1.18 – 3.93)
21 (**Figure 4**). However, after adjustment for baseline and clinical characteristics, female gender
22 was no longer an independent predictor of risk for bleeding at 30 days. (**Table 2 and figure**
23 **2**)

24 25 26 27 28 29 30 31 32 33 34 35 36 37 **Association between gender and efficacy and safety of randomised treatment**

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39 Pre-hospital administration of ticagrelor compared to in-hospital administration resulted in a
40 non-significant difference in the primary, secondary and safety outcomes. No significant
41 interactions between randomised treatment and gender in terms of these outcomes were found
42 in the unadjusted or adjusted model (test for interaction in the multivariable models; p=0.94
43 for all-cause mortality, p=0.55 for absence of TIMI flow grade 3 in the IRA at initial
44 angiography, p=0.71 for absence of $\geq 70\%$ resolution of pre-PCI ST segment elevation, and
45 p=0.31 for TIMI major bleeding at 30 days). (**Supplementary tables 1, 2 and 3**).

51 52 53 54 **Discussion**

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56 In the present analysis, unadjusted data showed a significantly higher risk of short term
57 mortality and bleeding complications in women. After multivariable adjustment female
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3 gender remained an independent predictor of mortality whereas advanced age and
4 comorbidities could mainly explain the higher incidence of bleeding complications in
5 women.
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9 Undoubtedly, older age and clustering of comorbidities in women could explain a large part
10 of the observed difference in short term clinical outcomes in our study. However, the adjusted
11 risk for death was still significantly higher in women. The contribution of gender, as
12 independent risk factor, on adverse outcome may depend on the population studied. The age
13 gap between genders in our population was substantially higher compared to previous
14 studies, with a mean age difference of 10 years.(12, 16) In spite of appropriate statistical
15 methods that were used for adjustment, adjustment for such age-difference is awkward.
16
17 Additionally, the age difference may indicate a selection bias. As identification and
18 randomisation took place in the ambulance, young women with suspected STEMI were
19 possibly not included in the study as alternative reasons for ST-segment elevation on
20 prehospital ECG may have been considered more plausible in this group. Furthermore, a
21 trend toward increased mortality with prehospital ticagrelor was observed in the ATLANTIC
22 trial that was mainly attributed to a plausible imbalance between the two groups in terms of
23 the severity of the presenting event. Given the low rate of all-cause mortality, unobserved
24 confounders in elderly women with STEMI may have significantly contributed to our results
25 and the findings of the main study. These factors may have a significant impact on the
26 remaining higher adjusted risk for short-term mortality in women.
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30 Previous observational studies in STEMI cohorts, without focus on PPCI treated patients
31 have shown a higher risk for early mortality in women.(6, 17, 18) Significant differences in
32 the rate of reperfusion therapy between genders and hidden confounders such as frailty in
33 elderly women with STEMI may have influenced their results. Recent observational studies
34 including patients treated with PPCI(4, 19, 20) and pre-specified gender analysis of RCTs(11,
35 12, 16, 21, 22) have shown that the impact of gender on mortality could mainly be explained
36 by differences in age and comorbidities between genders.. On the contrary, an observational
37 study and a meta-analysis have reported higher multivariable adjusted risk of early mortality
38 in women with STEMI treated with PPCI.(23, 24) Differences in the population studied and
39 in the covariates included in the multivariable analysis between studies may explain the
40 conflicting results. Previous studies have clearly demonstrated the importance of body
41 surface area and the eGFR on prognosis.(25, 26) In a meta-analysis, Berger et al showed that
42 female gender was an independent predictor of early mortality in STEMI patients. However,
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3 30-day mortality was not statistically significant different between genders after additional
4 adjustment for angiographic disease severity.(27)
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7 In the present study, women had a 2-3 times higher unadjusted risk for non-CABG related
8 bleedings, depending on the definition used. After adjustment for baseline characteristics, no
9 significant difference remained. Female gender has previously been associated with higher
10 risk for bleeding complications in patients with ACS.(28-31) Known predictors of bleedings
11 like advanced age, diabetes, hypertension, renal insufficiency and anemia, are usually more
12 often encountered in women with STEMI.(15) Additionally, smaller body and vessel size,
13 higher use of femoral access and overdosing of antithrombotic medication in women may
14 explain the higher observed risk for bleeding. Procedural-related improvement such as
15 increased use of radial access or smaller femoral sheaths and careful dose adjustment of
16 antithrombotic medication, have resulted in a significant decline in the risk of
17 bleeding/vascular complication during cardiovascular interventions the last years and have
18 probably contributed to our results.(32) The negative impact of bleedings on prognosis in
19 patients with STEMI is well established. (15) Our data showed that even after excluding
20 patients from further analysis at the time of a PLATO major bleeding, the HR for early
21 mortality in women vs men remained unchanged, implying that reducing the rate of major
22 bleeding in women may improve their prognosis but is not the main reason for the observed
23 difference between genders in the early mortality.
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38 Some well-known gender disparities in the concomitant management of STEMI patients
39 remained unchanged. Women were less likely to be treated with GP IIb/IIIa inhibitors and
40 thrombo-aspiration during PPCI despite lack of gender difference in protection from major
41 adverse outcomes by GP IIb/IIIa inhibitors (33) and benefit of thrombo-aspiration at the time
42 when the study was conducted.(34) Similar findings have been provided by large
43 registries.(7, 8) Some of these lower rates of utilization may be “appropriate” given the
44 higher TIMI 3 flow rates in the IRA pre-PPCI and lower rates of PPCI in women vs. men.
45 Furthermore, physician’s concern for higher risk of bleeding in older women with STEMI
46 have certainly contributed to the lower use of GP IIb/IIIa inhibitors in women.
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53 Although the impact of early reperfusion on mortality in STEMI patients is now
54 unquestionable,(35) patients’ delay from symptom onset to prehospital ECG was not an
55 independent predictor of mortality in our study, in agreement with results from previous
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3 gender analyses.(36, 37) A plausible explanation is an association between age and delay,
4 and thus adjustment for age minimizes the relative impact of delay. Furthermore, in PPCI,
5 female gender has been associated with similar or even smaller infarct size than that in male
6 gender, due to longer prehospital delays, indicating that other factors than larger infarct size
7 secondary to longer prehospital delay mainly contribute to the observed higher unadjusted
8 short term mortality.(36) The proportion of 30 day mortality that occurred within 48 hours of
9 admission was similar in women and men (38% vs 36% respectively) contrasting previous
10 data where gender differences in early mortality were accounted for by excess very early
11 (within 24-48 hours) deaths in women with STEMI.(7, 18) Cardiogenic shock and
12 hemodynamic instability were key exclusion criteria in the ATLANTIC trial which may have
13 influenced these results. Cardiogenic shock has been shown to be more common in women
14 and female gender has been highly associated with mortality in shock patients.(20)

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24 In terms of ST-segment elevation resolution and TIMI flow 3 rates before and after PCI, no
25 significant difference between genders was observed apart from a lower risk of abnormal
26 coronary flow in IRA at initial angiography in women. The higher rate of TIMI flow 3 at
27 initial angiography may be explained by the higher rate of normal coronary arteries as well as
28 the less obstructive coronary artery disease in women with STEMI, which is in concordance
29 with previous data.(37)

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34 The analysis of the effect of gender on outcomes dependent on the randomised treatment
35 showed no statistically significant interactions. Pre-hospital administration of ticagrelor did
36 not improve pre- or post-PCI coronary reperfusion as assessed by TIMI flow in IRA and
37 resolution of ST elevation pre-PCI. Clinical efficacy outcomes were not significantly
38 improved either. However, prehospital administration of ticagrelor was safe in both genders
39 with similar rate of major and minor bleedings.

40 41 42 43 44 45 46 **Strengths and limitations**

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48 The present study has some important limitations. Our results are applicable to the
49 populations studied, STEMI patients pretreated with ticagrelor and planned for primary PCI.
50 The ATLANTIC study population is from a randomized controlled trial, with inclusion and
51 exclusion criteria contributing to differences relative to populations treated in routine clinical
52 practice, and thereby limiting generalisability. However, the proportion of elderly patients
53 (>75 years) was higher than in the PLATO trial, especially for women, and

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3 underrepresentation of women in clinical trials is a well recognised problem. Moreover, the
4 study was conducted at several centers and countries increasing external validity. Taken
5 together our results should be applied to a real-world STEMI population with caution.
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7 Additionally, the ATLANTIC trial was not stratified by gender. The large imbalance in the
8 proportion of men and women included, commonly encountered in a STEMI population,
9 caused a reduced power for detecting or definitely excluding significant differences in some
10 outcomes between the genders or to definitely exclude an interaction between gender and the
11 randomised treatment.
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17 The most important strength of our analysis is that patients were treated according to the
18 current guidelines of STEMI, with PPCI as the reperfusion strategy of choice, administration
19 of the modern ADP receptor-blocker ticagrelor in addition to aspirin as soon as possible after
20 the first medical contact, high use of radial access during catheterisation and adjuvant
21 pharmacologic treatment during PPCI with UFH or bivalirudin. (38) Therefore our study
22 provides important information about differences and similarities between genders in STEMI
23 patients treated with current PCI techniques and pharmacologic treatment.
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30 Conclusion

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32 In patients with STEMI, planned for PPCI and treated with modern antiplatelet therapy,
33 female gender identifies a group of patients with high risk of early mortality in whom prompt
34 efforts to improve outcome are warranted. Female gender was not an independent predictor
35 of bleeding but advanced age and clustering of comorbidities in women could mainly explain
36 their higher unadjusted risk for bleeding events compared to men. Prehospital administration
37 of ticagrelor had a similar efficacy and safety profile in men and women with STEMI.
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Data sharing statement

Original data are available on request. Please contact the corresponding author for further information.

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Author's contribution

E. Swahn is responsible for the conception and design of the gender substudy of the ATLANTIC trial. D. Venetsanos is responsible for analyses and interpretation of the data and drafted the manuscript. S. Sederholm Lawesson, J. Alfredsson, M. Janzon, A. Cequier, M. Chettibi, S.G. Goodman, A.W. van't Hof and G. Montalescot have critically revised the manuscript and added important intellectual content.

All authors have participated in the work and have read and approved the manuscript.

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References

1. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *Journal of the American College of Cardiology*. 2006 Feb 7;47(3 Suppl):S21-9. PubMed PMID: 16458167.
2. Mehta RH, Stebbins AS, Lopes RD, Califf RM, Pieper KS, Armstrong PW, et al. Comparison of incidence of bleeding and mortality of men versus women with ST-elevation myocardial infarction treated with fibrinolysis. *The American journal of cardiology*. 2012 Feb 1;109(3):320-6. PubMed PMID: 22078221.
3. Kyto V, Sipila J, Rautava P. Gender and in-hospital mortality of ST-segment elevation myocardial infarction (from a multihospital nationwide registry study of 31,689 patients). *The American journal of cardiology*. 2015 Feb 1;115(3):303-6. PubMed PMID: 25488357.
4. Jakobsen L, Niemann T, Thorsgaard N, Nielsen TT, Thuesen L, Lassen JF, et al. Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2012 Dec 20;8(8):904-11. PubMed PMID: 23253544.
5. Kang SH, Suh JW, Yoon CH, Cho MC, Kim YJ, Chae SC, et al. Sex differences in management and mortality of patients with ST-elevation myocardial infarction (from the Korean Acute Myocardial Infarction National Registry). *The American journal of cardiology*. 2012 Mar 15;109(6):787-93. PubMed PMID: 22196789.
6. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. A gender perspective on short- and long term mortality in ST-elevation myocardial infarction--a report from the SWEDHEART register. *International journal of cardiology*. 2013 Sep 30;168(2):1041-7. PubMed PMID: 23168004.
7. de Boer SP, Roos-Hesselink JW, van Leeuwen MA, Lenzen MJ, van Geuns RJ, Regar E, et al. Excess mortality in women compared to men after PCI in STEMI: an analysis of 11,931 patients during 2000-2009. *International journal of cardiology*. 2014 Sep 20;176(2):456-63. PubMed PMID: 25127966.
8. Leurent G, Garlantezec R, Auffret V, Hacot JP, Coudert I, Filippi E, et al. Gender differences in presentation, management and inhospital outcome in patients with ST-segment elevation myocardial infarction: data from 5000 patients included in the ORBI prospective French regional registry. *Archives of cardiovascular diseases*. 2014 May;107(5):291-8. PubMed PMID: 24910083.

- 1
2
3 9. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. Time trends in STEMI--improved
4 treatment and outcome but still a gender gap: a prospective observational cohort study from the
5 SWEDHEART register. *BMJ open*. 2012;2(2):e000726. PubMed PMID: 22457480. Pubmed Central
6 PMCID: 3323814.
7
8
9
10 10. Pilgrim T, Heg D, Tal K, Erne P, Radovanovic D, Windecker S, et al. Age- and Gender-
11 related Disparities in Primary Percutaneous Coronary Interventions for Acute ST-segment
12 elevation Myocardial Infarction. *PloS one*. 2015;10(9):e0137047. PubMed PMID: 26352574.
13 Pubmed Central PMCID: 4564139.
14
15 11. Lansky AJ, Pietras C, Costa RA, Tsuchiya Y, Brodie BR, Cox DA, et al. Gender
16 differences in outcomes after primary angioplasty versus primary stenting with and without
17 abciximab for acute myocardial infarction: results of the Controlled Abciximab and Device
18 Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation*. 2005 Apr
19 5;111(13):1611-8. PubMed PMID: 15811868.
20
21
22 12. Motovska Z, Widimsky P, Aschermann M, Investigators PSG. The impact of gender
23 on outcomes of patients with ST elevation myocardial infarction transported for percutaneous
24 coronary intervention: analysis of the PRAGUE-1 and 2 studies. *Heart*. 2008 Mar;94(3):e5. PubMed
25 PMID: 17693459.
26
27
28 13. Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, et al.
29 Prehospital ticagrelor in ST-segment elevation myocardial infarction. *The New England journal of*
30 *medicine*. 2014 Sep 11;371(11):1016-27. PubMed PMID: 25175921.
31
32
33 14. Montalescot G, Lassen JF, Hamm CW, Lapostolle F, Silvain J, ten Berg JM, et al.
34 Ambulance or in-catheterization laboratory administration of ticagrelor for primary percutaneous
35 coronary intervention for ST-segment elevation myocardial infarction: rationale and design of the
36 randomized, double-blind Administration of Ticagrelor in the cath Lab or in the Ambulance for
37 New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) study. *American*
38 *heart journal*. 2013 Apr;165(4):515-22. PubMed PMID: 23537967.
39
40
41 15. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, et al. Impact of
42 major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary
43 syndromes: an analysis from the ACUITY Trial. *Journal of the American College of Cardiology*. 2007
44 Mar 27;49(12):1362-8. PubMed PMID: 17394970.
45
46
47 16. Wijnbergen I, Tijssen J, van 't Veer M, Michels R, Pijls NH. Gender differences in
48 long-term outcome after primary percutaneous intervention for ST-segment elevation myocardial
49 infarction. *Catheterization and cardiovascular interventions : official journal of the Society for*
50 *Cardiac Angiography & Interventions*. 2013 Sep 1;82(3):379-84. PubMed PMID: 23553888.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 17. Champney KP, Frederick PD, Bueno H, Parashar S, Foody J, Merz CN, et al. The joint
4 contribution of sex, age and type of myocardial infarction on hospital mortality following acute
5 myocardial infarction. *Heart*. 2009 Jun;95(11):895-9. PubMed PMID: 19147625. Pubmed Central
6 PMCID: 3065924.
7
8
9 18. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Marea AO, et al. Sex
10 differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008 Dec
11 16;118(25):2803-10. PubMed PMID: 19064680.
12
13
14 19. Jackson EA, Moscucci M, Smith DE, Share D, Dixon S, Greenbaum A, et al. The
15 association of sex with outcomes among patients undergoing primary percutaneous coronary
16 intervention for ST elevation myocardial infarction in the contemporary era: Insights from the Blue
17 Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). *American heart journal*. 2011
18 Jan;161(1):106-12 e1. PubMed PMID: 21167341.
19
20
21
22 20. Suessenbacher A, Doerler J, Alber H, Aichinger J, Altenberger J, Benzer W, et al.
23 Gender-related outcome following percutaneous coronary intervention for ST-elevation
24 myocardial infarction: data from the Austrian acute PCI registry. *EuroIntervention : journal of
25 EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European
26 Society of Cardiology*. 2008 Aug;4(2):271-6. PubMed PMID: 19110794.
27
28
29 21. Husted S, James SK, Bach RG, Becker RC, Budaj A, Heras M, et al. The efficacy of
30 ticagrelor is maintained in women with acute coronary syndromes participating in the prospective,
31 randomized, PLATelet inhibition and patient Outcomes (PLATO) trial. *European heart journal*. 2014
32 Jun 14;35(23):1541-50. PubMed PMID: 24682844. Pubmed Central PMCID: 4057642.
33
34
35 22. De Luca G, Gibson CM, Gyongyosi M, Zeymer U, Dudek D, Arntz HR, et al. Gender-
36 related differences in outcome after ST-segment elevation myocardial infarction treated by
37 primary angioplasty and glycoprotein IIb-IIIa inhibitors: insights from the EGYPT cooperation.
38 *Journal of thrombosis and thrombolysis*. 2010 Oct;30(3):342-6. PubMed PMID: 20213259.
39
40
41 23. Benamer H, Tafflet M, Bataille S, Escolano S, Livarek B, Fourchard V, et al. Female
42 gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI:
43 insights from the greater Paris area PCI Registry. *EuroIntervention : journal of EuroPCR in
44 collaboration with the Working Group on Interventional Cardiology of the European Society of
45 Cardiology*. 2011 Apr;6(9):1073-9. PubMed PMID: 21518679.
46
47
48 24. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-
49 term all-cause mortality among patients with ST-segment elevation myocardial infarction treated
50 by primary percutaneous intervention: a meta-analysis. *JAMA internal medicine*. 2014
51 Nov;174(11):1822-30. PubMed PMID: 25265319.
52
53
54
55
56
57
58
59
60

1
2
3 25. Peterson ED, Lansky AJ, Kramer J, Anstrom K, Lanzilotta MJ, National Cardiovascular
4 Network Clinical I. Effect of gender on the outcomes of contemporary percutaneous coronary
5 intervention. *The American journal of cardiology*. 2001 Aug 15;88(4):359-64. PubMed PMID:
6 11545754.

7
8
9 26. Sederholm Lawesson S, Todt T, Alfredsson J, Janzon M, Stenestrand U, Swahn E.
10 Gender difference in prevalence and prognostic impact of renal insufficiency in patients with ST-
11 elevation myocardial infarction treated with primary percutaneous coronary intervention. *Heart*.
12 2011 Feb;97(4):308-14. PubMed PMID: 21212134.

13
14
15 27. Berger JS, Elliott L, Gallup D, Roe M, Granger CB, Armstrong PW, et al. Sex
16 differences in mortality following acute coronary syndromes. *JAMA : the journal of the American*
17 *Medical Association*. 2009 Aug 26;302(8):874-82. PubMed PMID: 19706861. Pubmed Central
18 PMCID: 2778841.

19
20
21 28. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, et al. Bleeding in acute
22 coronary syndromes and percutaneous coronary interventions: position paper by the Working
23 Group on Thrombosis of the European Society of Cardiology. *European heart journal*. 2011
24 Aug;32(15):1854-64. PubMed PMID: 21715717.

25
26
27 29. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score
28 to predict bleeding in patients with acute coronary syndromes. *Journal of the American College of*
29 *Cardiology*. 2010 Jun 8;55(23):2556-66. PubMed PMID: 20513595.

30
31
32 30. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, et al. Bleeding
33 complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATElet
34 inhibition and patient Outcomes (PLATO) trial. *European heart journal*. 2011 Dec;32(23):2933-44.
35 PubMed PMID: 22090660.

36
37
38 31. Mathews R, Peterson ED, Chen AY, Wang TY, Chin CT, Fonarow GC, et al. In-hospital
39 major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation
40 and validation of a model from the ACTION Registry(R)-GWTG. *The American journal of cardiology*.
41 2011 Apr 15;107(8):1136-43. PubMed PMID: 21324428.

42
43
44 32. Ahmed B, Piper WD, Malenka D, VerLee P, Robb J, Ryan T, et al. Significantly
45 improved vascular complications among women undergoing percutaneous coronary intervention:
46 a report from the Northern New England Percutaneous Coronary Intervention Registry. *Circulation*
47 *Cardiovascular interventions*. 2009 Oct;2(5):423-9. PubMed PMID: 20031752.

48
49
50 33. Cho L, Topol EJ, Balog C, Foody JM, Booth JE, Cabot C, et al. Clinical benefit of
51 glycoprotein IIb/IIIa blockade with Abciximab is independent of gender: pooled analysis from EPIC,
52 EPILOG and EPISTENT trials. Evaluation of 7E3 for the Prevention of Ischemic Complications.
53 Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome
54 with Abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stent. *Journal of*
55 *the American College of Cardiology*. 2000 Aug;36(2):381-6. PubMed PMID: 10933346.

- 1
2
3 34. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet*. 2008 Jun 7;371(9628):1915-20. PubMed PMID: 18539223.
- 4
5
6
7
8
9 35. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation*. 2004 Mar 16;109(10):1223-5. PubMed PMID: 15007008.
- 10
11
12
13
14 36. Sadowski M, Gasior M, Gierlotka M, Janion M, Polonski L. Gender-related differences in mortality after ST-segment elevation myocardial infarction: a large multicentre national registry. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2011 Apr;6(9):1068-72. PubMed PMID: 21518678.
- 15
16
17
18
19
20
21
22 37. Otten AM, Maas AH, Ottervanger JP, Kloosterman A, van 't Hof AW, Dambrink JH, et al. Is the difference in outcome between men and women treated by primary percutaneous coronary intervention age dependent? Gender difference in STEMI stratified on age. *European heart journal Acute cardiovascular care*. 2013 Dec;2(4):334-41. PubMed PMID: 24338292. Pubmed Central PMCID: 3821825.
- 23
24
25
26
27
28
29 38. Wessler JD, Stant J, Duru S, Rabbani L, Kirtane AJ. Updates to the ACCF/AHA and ESC STEMI and NSTEMI guidelines: putting guidelines into clinical practice. *The American journal of cardiology*. 2015 Mar 14;115(5 Suppl):23A-8A. PubMed PMID: 25728971.
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Figure legends

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39 Figure 1. Cumulative Kaplan-Meier estimates of the incidence of the composite endpoint of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis and all-cause mortality at 30 days by gender.

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43 Figure 2. Association between gender and clinical efficacy and safety outcomes independent of randomised treatment.

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46 Figure 3. Association between gender and primary and secondary outcomes, independent of randomised treatment.

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49 Figure 4. Cumulative Kaplan-Meier estimates of the incidence of the TIMI major bleeding and BARC type 3-5 bleeding at 30 days by gender.

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Table 1. Baseline, clinical and periprocedural characteristics according to gender.

Characteristics	Women (n=369)	Men (n=1493)	P- value
Age, years; mean (SD)	69 (13.0)	59 (11)	<0.01
Age ≥75 years	153 (41.5)	151 (10.1)	<0.01
BMI, kg/m ² ; median (IQR)	25.6 (22.5-29.1)	26.5 (24.3-29.4)	<0.01
Prior history			
Diabetes mellitus	48 (13.0)	205 (13.7)	0.72
Hypertension	190 (51.5)	605 (40.5)	<0.01
Dyslipidemia	117 (31.7)	536 (35.9)	0.13
Angina	36 (9.8)	157 (10.5)	0.67
Prior myocardial infarction	24 (6.5)	135 (9.0)	0.67
Prior PCI	16 (4.3)	124 (8.3)	<0.01
Prior CABG	1 (0.3)	11 (0.7)	0.32
Prior non-haemorrhagic stroke	8 (2.2)	10 (0.7)	<0.01
Chronic obstructive pulmonary disease	22 (6.0)	54 (3.6)	0.04
Gastrointestinal bleeding	1 (0.3)	16 (1.1)	0.15
Chronic renal disease	7 (1.9)	27 (1.8)	0.91
Index event information			
First medical contact in ambulance	280 (75.9)	1132 (75.8)	0.24
Minutes from symptom onset to pre-hospital ECG, median (IQR)	88 (49-169)	70 (41-129)	<0.01
Minutes from prehospital ECG to PCI, median (IQR)	83 (68-101)	80 (66-96)	0.03
Minutes from pre-PCI angiography to post-PCI angiography, median (IQR)	36 (24-52)	32 (23-45)	0.03
Received first loading dose	369 (100)	1488 (99.7)	0.27
Risk level at admission			
Killip class			
I	332 (90.0)	1349 (90.4)	0.82
IV	2 (0.5)	3 (0.2)	
TIMI risk score			
0-2	119 (32.2)	1006 (67.4)	0.01
3-6	231 (62.6)	471 (31.5)	
>6	19 (5.1)	16 (1.1)	
Culprit vessel			
Left main artery	4 (1.1)	18 (1.2)	0.63

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3	Left anterior descending artery	141 (38.8)	571 (39.0)	
4	Right coronary artery	150 (41.3)	590 (40.3)	
5	Left circumflex	39 (10.7)	196 (13.4)	
6	No culprit vessel identified	28 (7.7)	85 (5.8)	
7	Normal coronary angiography	27 (7.4)	76 (5.2)	0.1
8	Procedures for index event			
9	Femoral access	144 (39.7)	445 (30.4)	<0.01
10	Thromboaspiration	160 (43.4)	781 (52.3)	<0.01
11	PCI	309 (83.7)	1321 (88.5)	0.01
12	With any stent	288 (78.0)	1248 (83.6)	0.01
13	With DES	185 (50.1)	761 (51.0)	0.77
14	Coronary artery bypass grafting	4 (1.1)	21 (1.4)	0.63
15	No revascularisation	56 (15.2)	151 (10.1)	<0.01
16	Any glycoprotein IIb/IIIa inhibitor use	115 (31.2)	598 (40.1)	<0.01
17	Glycoprotein IIb/IIIa inhibitor use before angiography	14 (3.8)	116 (7.8)	<0.01
18	Intravenous anticoagulant prior to pre-PCI angiography	231 (62.6)	1027 (68.8)	0.02
19	Intravenous anticoagulant during hospitalisation †	310 (84.0)	1332 (89.2)	<0.01
20	Heparin only	135 (36.6)	584 (39.1)	0.02
21	Bivalirudin only	29 (7.9)	65 (4.4)	0.02

Variables presented as numbers (percentages) unless otherwise indicated.

BMI, body mass index; CABG, coronary artery bypass grafting; DES, drug-eluting stent; IQR, interquartile range (25th–75th percentile); PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, Thrombolysis In Myocardial Infarction.

† Includes all IV medications given on the date of the qualifying ECG and /or index PCI

Table 2 Association between gender and clinical outcomes independent of randomised treatment

Outcomes	Female (n=369)	Male (n=1489)	Crude hazard ratio (95%CI) (n included=1858)	Adjusted hazard ratio (95%CI)* (n included=1613)	P-value *
	Patients with endpoint, n (%)	Patients with endpoint, n (%)			
Mortality and cardiovascular outcomes					
Composite of death/MI/stroke/urgent revascularisation/definite acute stent thrombosis	25 (6.8)	58 (3.9)	1.79 (1.12-2.86)	1.32 (0.77-2.27)	0.32
Composite of death/MI/urgent revascularisation	23 (6.2)	50 (3.4)	1.91 (1.17-3.13)	1.33 (0.75-2.36)	0.32
All-cause mortality	21 (5.7)	28 (1.9)	3.13 (1.78-5.51)	2.08 (1.03-4.20)	0.04
Myocardial infarction	3 (0.8)	14 (0.9)	0.90 (0.26-3.13)	0.82 (0.23-2.85)	0.76
Stroke	3 (0.8)	3 (0.2)	4.18 (0.84-20.70)	4.14 (0.84-20.51)	0.08
Urgent revascularisation	2 (0.5)	11 (0.7)	0.75 (0.17-3.38)	0.69 (0.15-3.11)	0.63
Definite acute stent thrombosis	3 (0.8)	10 (0.7)	1.23 (0.34-4.49)	1.29 (0.35-4.76)	0.70
Acute stent thrombosis (definite or probable)	11 (3.0)	30 (2.0)	1.53 (0.77-3.05)	0.88 (0.39-1.98)	0.76
Safety outcomes					
PLATO major bleeding **	17 (4.6)	33 (2.2)	2.15 (1.20-3.85)	1.45 (0.73-2.86)	0.29
TIMI major bleeding **	10 (2.7)	14 (0.9)	2.95 (1.31-6.65)	1.28 (0.47-3.48)	0.63

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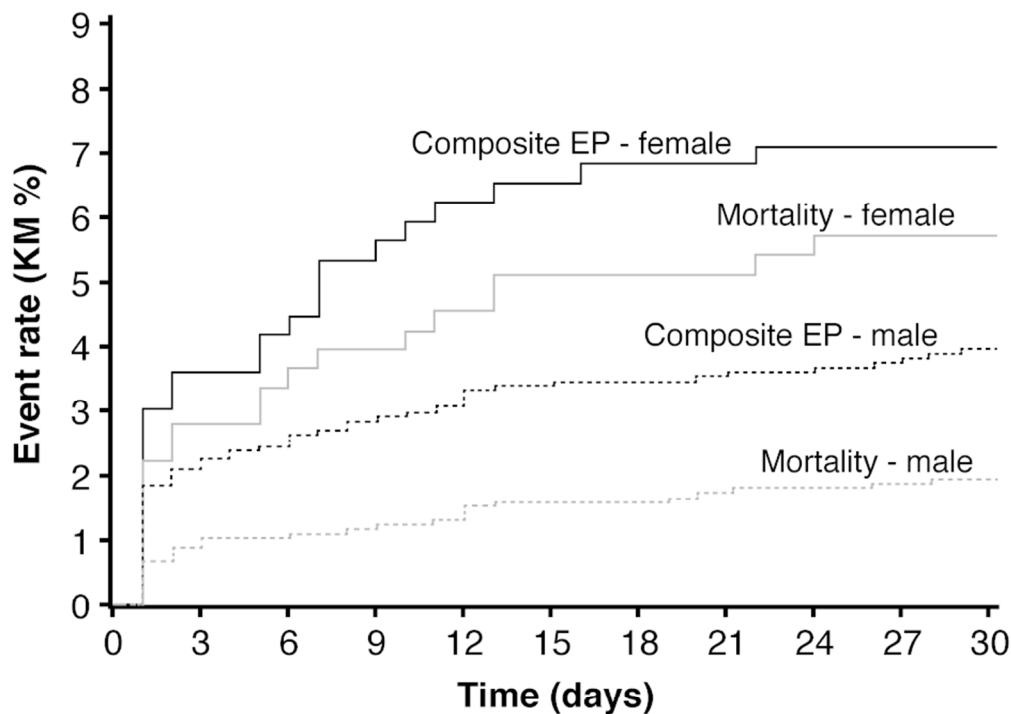
TIMI major or minor bleeding**	18 (4.9)	54 (3.6)	1.38 (0.81-2.35)	0.94 (0.51-1.74)	0.85
BARC type 3-5 (major) bleeding**	16 (4.3)	31 (2.1)	2.15 (1.18-3.93)	1.45 (0.72-2.91)	0.30
BARC type 2-5 (major or minor) bleeding**	20 (5.4)	56 (3.8)	1.48 (0.89-2.47)	1.03 (0.57-1.84)	0.93

*Hazard ratio (for female versus male) and p-value calculated from logistic regression model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, access site, glycoprotein IIb/IIIa inhibitor, bivalirudin or unfractionated heparin use during index procedure, revascularization and location of myocardial infarction

**Non-CABG related bleeding occurring up to the date of the last study visit (to the maximum of 32 days) are included in the table

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; PLATO, Study of Platelet Inhibition and Patient Outcomes; TIMI, Thrombolysis in Myocardial Infarction

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Composite endpoint	All-cause mortality
Female 25/369 (6.8%)	Female 21/369 (5.7%)
Male 58/1489 (3.9%)	Male 28/1489 (1.9%)

Caption : Figure 1. Cumulative Kaplan-Meier estimates of the incidence of the composite endpoint of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis and all-cause mortality at 30 days by gender.

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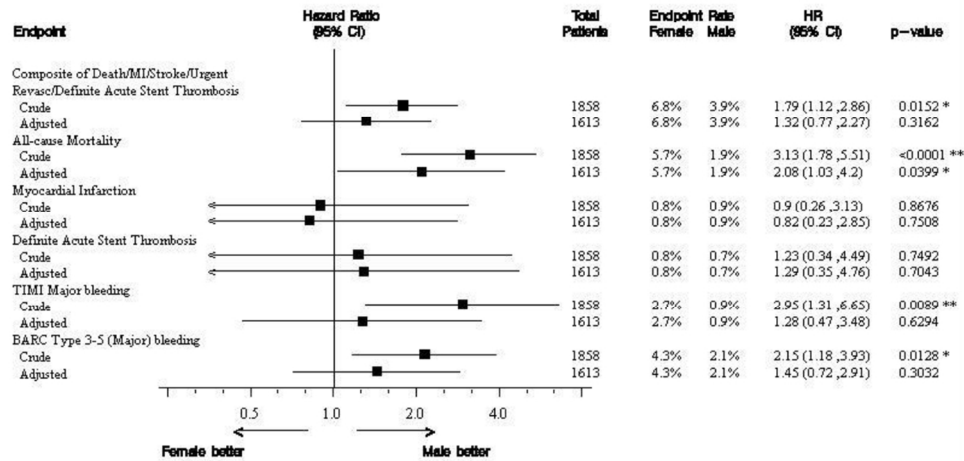


Figure 2. Association between gender and clinical efficacy and safety outcomes independent of randomised treatment.

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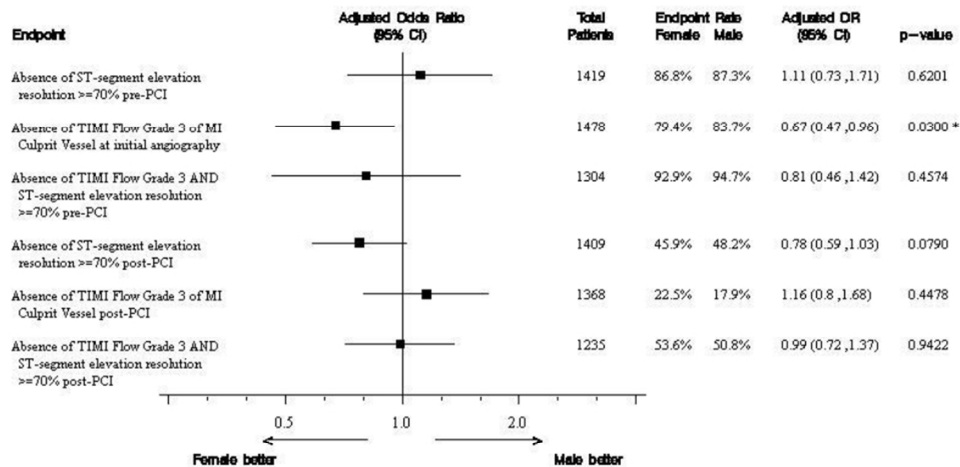
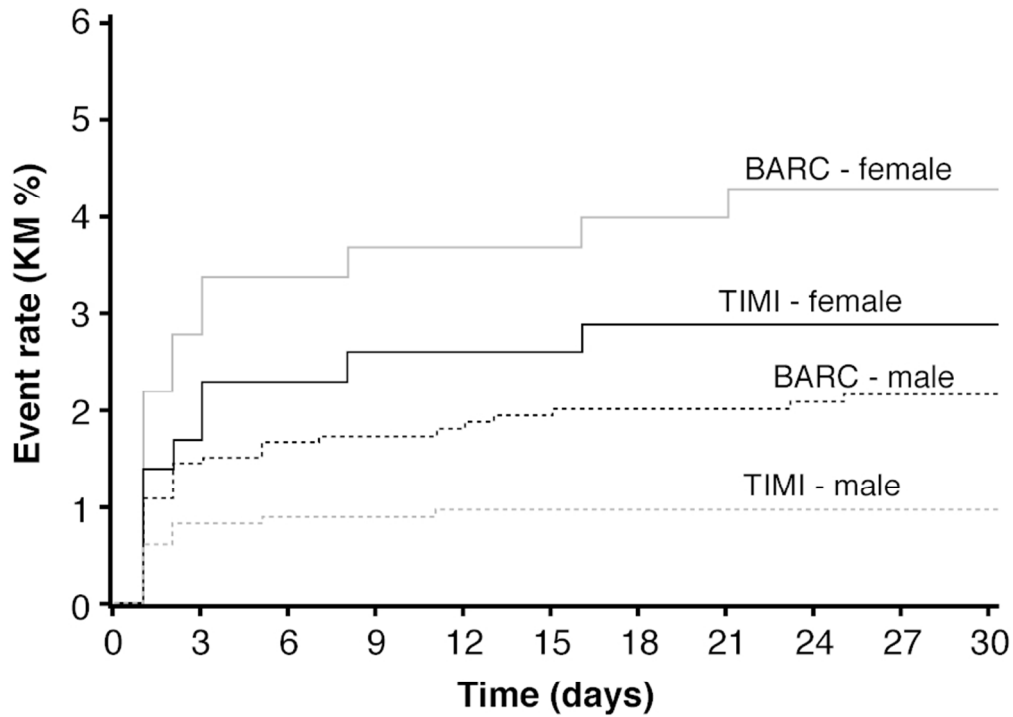


Figure 3. Association between gender and primary and secondary outcomes, independent of randomised treatment.

84x53mm (300 x 300 DPI)

view only



TIMI major bleed	BARC type 3–5 bleed
Female 10/369 (2.7%)	Female 16/369 (4.3%)
Male 14/1489 (0.9%)	Male 31/1489 (2.1%)

Caption : Figure 4. Cumulative Kaplan-Meier estimates of the incidence of the TIMI major bleeding and BARC type 3-5 bleeding at 30 days by gender.

79x69mm (300 x 300 DPI)

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Supplementary table 1 Association between gender and efficacy of randomised treatment – clinical outcomes

Outcomes	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model, n	Adjusted hazard ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
Composite of Death/MI/Stroke/Urgent Revasc/Definite Acute Stent Thrombosis	Female	173	13 (7.5)	196	12 (6.1)	1613	0.98 (0.42-2.27)	0.87
	Male	733	28 (3.8)	756	30 (4.0)		0.90 (0.51-1.59)	
Composite of Death/MI/Urgent Revasc	Female	173	13 (7.5)	196	10 (5.1)	1613	1.32 (0.55-3.20)	0.55
	Male	733	26 (3.5)	756	24 (3.2)		0.95 (0.52-1.76)	
All-cause mortality	Female	173	13 (7.5)	196	8 (4.1)	1613	1.59 (0.61-4.12)	0.93
	Male	733	17 (2.3)	756	11 (1.5)		1.50 (0.60-3.74)	
Myocardial infarction	Female	173	1 (0.6)	196	2 (1.0)	1613	0.44 (0.04-4.95)	0.72
	Male	733	6 (0.8)	756	8 (1.1)		0.72 (0.25-2.09)	
Stroke	Female	173	1 (0.6)	196	2 (1.0)	1613	0.54 (0.05-5.90)	0.99
	Male	733	3 (0.4)	756	0 (0.0)		Nt estimated	
Urgent revascularization	Female	173	1 (0.6)	196	1 (0.5)	1613	0.86 (0.05-14.07)	0.76
	Male	733	4 (0.5)	756	7 (0.9)		0.54 (0.15-1.87)	
Definite Acute Stent Thrombosis	Female	173	1 (0.6)	196	2 (1.0)	1613	0.37 (0.03-4.27)	0.49
	Male	733	1 (0.1)	756	9 (1.2)		0.12 (0.01-1.02)	
Acute Stent Thrombosis (definite or probable)	Female	173	7 (4.0)	196	4 (2.0)	1613	1.31 (0.37-4.69)	0.52
	Male	733	14 (1.9)	756	16 (2.1)		0.80 (0.35-1.80)	

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≠ Adjusted hazard (for female versus male) and p-values for interaction was calculated from Cox proportional hazard model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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Supplementary table 2 Association between gender and efficacy of randomised treatment – primary and secondary outcomes

Outcomes	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model N ≠	Adjusted odds ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
Absence of ST segment elevation resolution ≥ 70% pre-PCI	Female	142	122 (85.9)	168	147 (87.5)	1419	0.75 (0.37-1.53)	0.71
	Male	632	550 (87.0)	656	575 (87.7)		0.85 (0.59-1.23)	
Absence of TIMI flow grade 3 in infarct related artery at initial angiography	Female	155	127 (81.9)	175	135 (77.1)	1478	1.36 (0.76-2.41)	0.19
	Male	669	554 (82.8)	681	576 (84.6)		0.88 (0.64-1.20)	
Absence of ST segment resolution ≥ 70% AND absence of TIMI flow grade 3 in infarct related artery pre-PCI	Female	129	120 (93.0)	153	142 (92.8)	1304	1.07 (0.41-2.81)	0.84
	Male	590	557 (94.4)	598	568 (95.0)		0.96 (0.57-1.62)	
Absence of ST-segment resolution ≥70% after PCI	Female	144	61 (42.4)	163	80 (49.1)	1409	0.76 (0.47-1.25)	0.51
	Male	629	291 (46.3)	650	326 (50.2)		0.92 (0.72-1.17)	
Absence of TIMI flow grade 3 in infarct related artery after PCI	Female	144	30 (20.8)	154	37 (24.0)	1368	0.93 (0.51-1.71)	0.98
	Male	621	107 (17.2)	631	117 (18.5)		0.92 (0.68-1.26)	
Absence of ST segment resolution ≥70% AND absence of TIMI flow grade 3 in infarct related artery after PCI	Female	125	60 (48.0)	138	81 (58.7)	1235	0.64 (0.38-1.10)	0.13
	Male	562	282 (50.2)	565	290 (51.3)		1.01 (0.78-1.32)	

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≠ Adjusted odds ratio (for female versus male) and p-values for interaction was calculated from logistic regression model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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Supplementary table 3 Association between gender and safety of randomised treatment (safety outcomes)

End point	Gender	Pre-hospital ticagrelor (n=906)		In-hospital ticagrelor (n=952)		Model N ≠	Adjusted hazard ratio ≠ (95% CI)	P-value (interaction) ≠
		N	Patients with endpoint, n (%)	N	Patients with endpoint, n (%)			
PLATO major bleeding	Female	173	6 (3.5)	196	11 (5.6)	1613	0.61 (0.21-1.83)	0.23
	Male	733	19 (2.6)	756	14 (1.9)		1.39 (0.66-2.93)	
PLATO major and minor bleeding	Female	173	7 (4.0)	196	13 (6.6)	1613	0.59 (0.22-1.61)	0.19
	Male	733	33 (4.5)	756	26 (3.4)		1.27 (0.73-2.21)	
TIMI major bleeding	Female	173	3 (1.7)	196	7 (3.6)	1613	0.60 (0.14-2.54)	0.28
	Male	733	9 (1.2)	756	5 (0.7)		1.62 (0.53-4.98)	
TIMI major and minor bleeding	Female	173	6 (3.5)	196	12 (6.1)	1613	0.55 (0.19-1.60)	0.24
	Male	733	29 (4.0)	756	25 (3.3)		1.14 (0.64-2.03)	
BARC type 3-5 (major) bleeding	Female	173	6 (3.5)	196	10 (5.1)	1613	0.69 (0.23-2.11)	0.26
	Male	733	18 (2.5)	756	13 (1.7)		1.51 (0.70-3.26)	
BARC type 2-5 (major and minor) bleeding	Female	173	7 (4.0)	196	13 (6.6)	1613	0.59 (0.22-1.60)	0.21
	Male	733	31 (4.2)	756	25 (3.3)		1.23 (0.70-2.17)	

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≠Adjusted hazard (for female versus male) and p-values for interaction was calculated from Cox proportional hazard model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-hospital ECG, admission Killip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5, 6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5, 6
		(b) Describe any methods used to examine subgroups and interactions	5, 6
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, 8,
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	7,8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, 8
		(b) Report category boundaries when continuous variables were categorized	yes
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N7A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7, 8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8, 9, 10, 11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	3, 11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.