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

In STEMI patients treated with current PCI-techniques and modern antiplatelet therapy, gender differences in short term mortality and inhospital 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.

CLINICAL TRIAL REGISTRATION: clinicaltrials.gov identifier: NCT01347580.

Strengths and limitations

Patients were treated according to the current guidelines of STEMI, current PCI techniques and modern antiplatelet therapy including ticagrelor in addition to aspirin as soon as possible after the first medical contact.

The large imbalance in the proportion of men and women included in the ATLANTIC trial, caused a reduced power for detecting significant differences in outcomes between the genders.

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

standard clinical care. All patients were to subsequently receive ticagrelor 90 mg twice daily for 30 days, after which it was recommended that ticagrelor should be continued for up to 12 months. Pre-hospital administration of a GP IIb/IIIa inhibitor was left to the physician's discretion. Peri-procedural use of parenteral anticoagulants was also left to the physician's discretion, according to the local practice.

The proportion of patients who did not have ≥70% resolution of ST segment elevation before PCI and / or did not meet the criteria for TIMI flow 3 in the infarct related artery (IRA) at initial angiography was the primary outcome of the ATLANTIC trial. Secondary outcomes (clinical efficacy outcomes) included the composite of death, MI, stent thrombosis, stroke, or urgent revascularisation at 30 days and definite stent thrombosis at 30 days. Safety outcomes included major and minor bleeding over the 30-day treatment period. Bleeding risk was evaluated using the TIMI (The Thrombolysis In Myocardial Infarction), BARC (Bleeding Academic Research Consortium) and PLATO (Study of Platelet Inhibition and Patient Outcomes) bleeding definitions.(13)

The main objective of our analysis was to study the association between gender and primary and secondary outcomes of the main study with a special focus on the clinical efficacy and safety outcomes. The interaction of gender subgroups with randomised treatment effects was also investigated.

The trial design and protocol were approved by the national regulatory authorities in all the participating countries and by the local ethics committee or institutional review board at each participating site. All patients provided written informed consent.

Statistical analysis

Continuous variables are presented by their mean and standard deviation (SD) or median and 25th -75th percentiles as appropriate. Categorical variables are presented as counts and percentages. Baseline and peri-procedural characteristics were compared according to gender by chi-square tests for categorical variables and Student`s t-test or Mann Whitney U test for continuous variables, depending on if the variable of interest was normally distributed or not. A p-value <0.05 is considered to indicate statistical significance.

The incidence of events over time by gender is presented by Kaplan-Meier curves.

In order to study the association between gender and the clinical efficacy and safety outcomes, independent of randomised treatment as well as the possible interactions between gender and randomised treatment with respect to the outcomes, hazard ratios [HR] with 95% confidence intervals [CI] were derived from Cox proportional-hazards models. In the unadjusted (crude) model, gender was the only explanatory variable whereas in the adjusted multivariable model, gender was forcibly included and the other variables were chosen by using a forward stepwise selection algorithm with a significant cut-off level of 0.05 for inclusion. Adjustment variables included age, weight, prior MI, prior PCI, history of diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-PCI electrocardiogram [ECG], admission Killip class (as a dichotomous variable 1 / >1), baseline hemoglobin, estimated glomerular filtration rate (eGFR) according to the MDRD formula, use of GP IIIb/IIa inhibitor and location of MI. To evaluate the importance of early mortality, a landmark analysis of the clinical efficacy outcomes was also performed from 48 hours after randomisation (arbitrarily defined) to the end of the study. In order to explore the importance of bleeding on the clinical efficacy outcomes, a separate analysis was also performed by censoring the patients who reported a PLATO major bleeding at the time of the onset of a bleeding event.

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

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

All the analyses were performed using SAS® version 9.3.

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**)

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
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 (25^{th}–75^{th} 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).

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)	Adjusted hazard ratio (95%CI)*	P-value *
	Patients with endpoint, n (%)	Patients with endpoint, n (%)	(n included=1858)	(n included=1613)	
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 ≥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.

A plethora of observational studies in STEMI cohorts and a meta-analysis have shown a higher risk of early mortality in women.(6, 7, 14, 15) Significant differences in the rate of reperfusion therapy between genders and hidden confounders such as frailty in elderly women with STEMI may partially explain their results. In accordance with our results, previous gender analyses of RCTs have shown that the impact of gender on mortality could mainly be explained by differences in age and comorbidities between genders.(10, 11, 16-18) In the CADILLAC study,(10) women had a 4-fold higher unadjusted risk for 30 days mortality but after adjustment no significant difference remained. In STEMI treated with thrombolysis Motovska et al showed that gender was not an independent predictor of outcome,(11) The recent PLATO trial showed concurred results but NSTEMI and STEMI patients were pooled in the gender analysis, despite the fact that the relationship between gender and outcome depends on the type of ACS.(19) Most of these studies do not reflect current treatment of STEMI patients. Despite evolving PCI techniques and novel pharmacological treatment, women still have worse short term outcome and special effort, with respect to their advanced age and comorbidities, to improve their outcomes are warranted.

Some well-known gender disparities in the concomitant management of STEMI patients remained unchanged. Women were less likely to be treated with GP IIb/IIIa inhibitors and thrombo-aspiration during PPCI despite lack of gender difference in protection from major adverse outcomes by GP IIb/IIIa inhibitors (20) and benefit of thrombo-aspiration at the time when the study was conducted.(21) Similar findings have been provided by large registries.(7, 8) Some of these lower rates of utilization may be “appropriate” given the higher TIMI 3 flow rates in the IRA pre-PPCI and lower rates of PPCI in women vs. men. Furthermore, physician’s concern for higher risk of bleeding in older women with STEMI have certainly contributed to the lower use of GP IIb/IIIa inhibitors in women.

Although the impact of early reperfusion on mortality in STEMI patients is now unquestionable,(22) patients’ delay from symptom onset to prehospital ECG was not an independent predictor of mortality in our study, in agreement with results from previous gender analyses.(23, 24) A plausible explanation is an assosiation between age and delay, and thus adjustment for age minimizes the relative impact of delay. Furthermore, in PPCI, female gender has been associated with similar or even smaller infarct size than that in male gender, due to longer prehospital delays, indicating that other factors than larger infarct size secondary to longer prehospital delay mainly contribute to the observed higher unadjusted

short term mortality.(23) The proportion of 30 day mortality that occurred within 48 hours of admission was similar in women and men (38% vs 36% respectively) contrasting previous data where gender differences in early mortality were accounted for by excess very early (within 24-48 hours) deaths in women with STEMI.(7, 25) Cardiogenic shock and hemodynamic instability were key exclusion criteria in the ATLANTIC trial which may have influenced these results. Cardiogenic shock has been shown to be more common in women and female gender has been highly associated with mortality in shock patients.(26)

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

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

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

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

Strengths and limitations

The present study has some important limitations. The ATLANTIC trial was not stratified by gender. The large imbalance in the proportion of men and women included, commonly encountered in a STEMI population, caused a reduced power for detecting significant differences in outcomes between the genders or to definitely exclude an interaction between gender and the randomised treatment.

The most important strength of our analysis is that patients were treated according to the current guidelines of STEMI, with PPCI as the reperfusion strategy of choice, administration of the modern ADP receptor-blocker ticagrelor in addition to aspirin as soon as possible after the first medical contact, high use of radial access during catheterisation and adjuvant pharmacologic treatment during PPCI with UFH or bivalirudin. (33) Therefore our study provides important information about differences and similarities between genders in STEMI patients treated with current PCI techniques and pharmacologic treatment.

Conclusion

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

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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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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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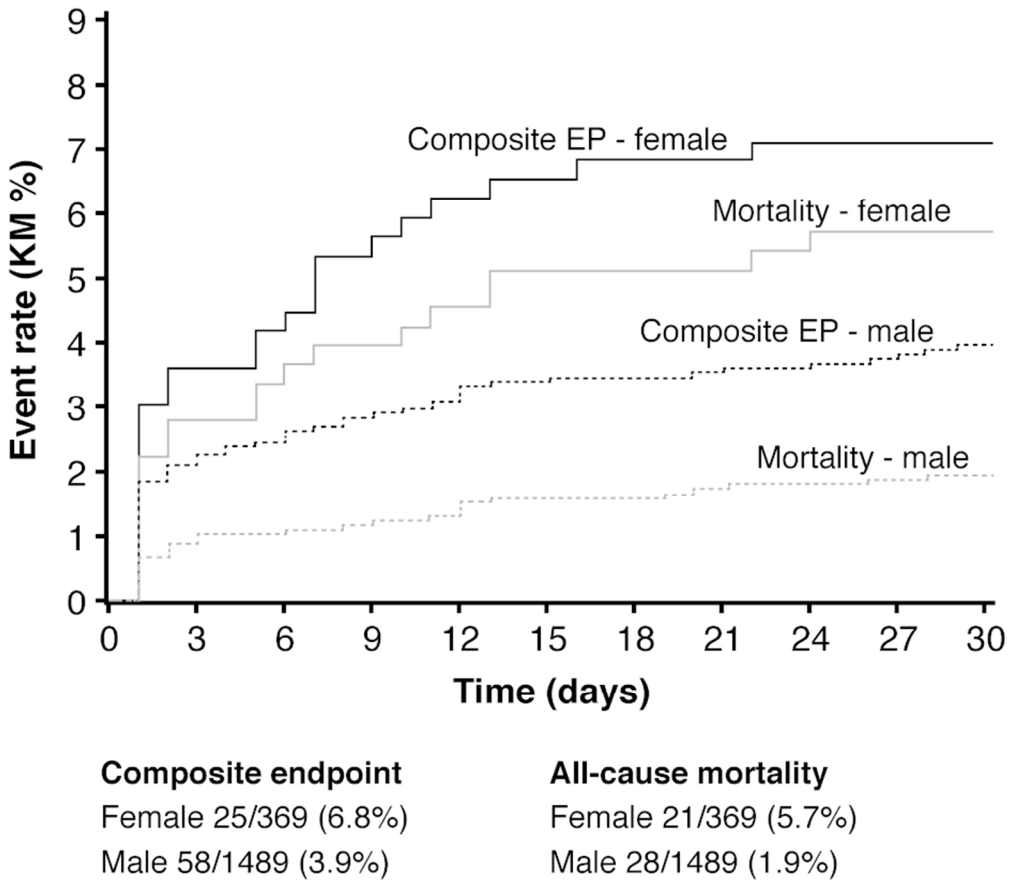

Figure 1. Cumulative Kaplan-Meier estimates of the incidence of the composite endpoint of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis and all-cause mortality at 30 days by gender.

79x70mm (300 x 300 DPI)

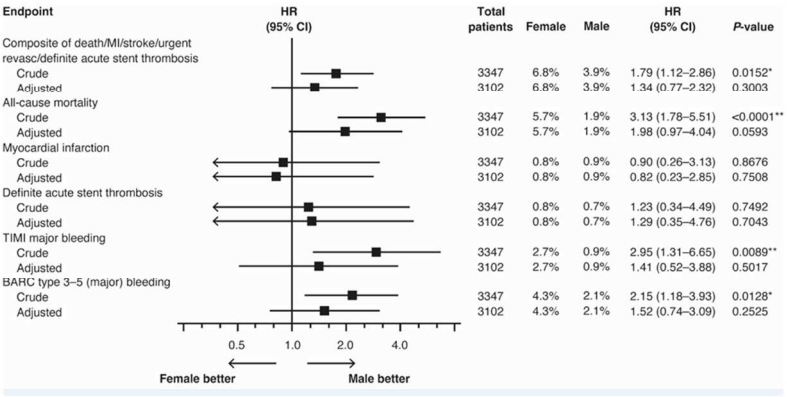

Figure 2. Association between gender and clinical outcomes independent of randomised treatment.

338x190mm (96 x 96 DPI)

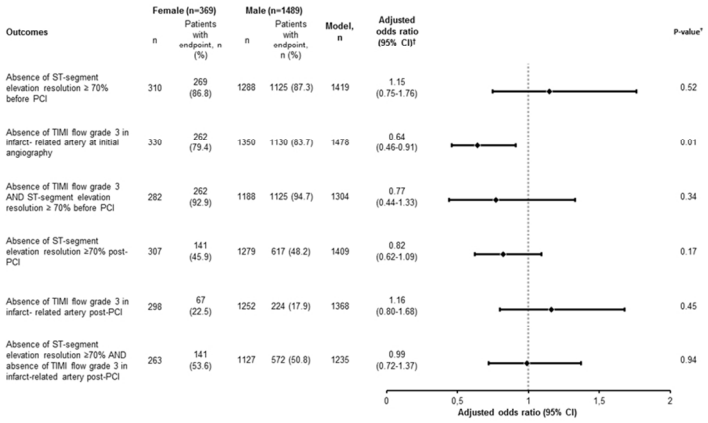

Figure 3. †Odds ratio (for female versus male) and p-value calculated from logistic regression model including gender, age, weight, prior myocardial infarction, prior percutaneous coronary intervention, diabetes, hypertension, non-haemorrhagic stroke, gastrointestinal bleeding, time from symptom onset 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)

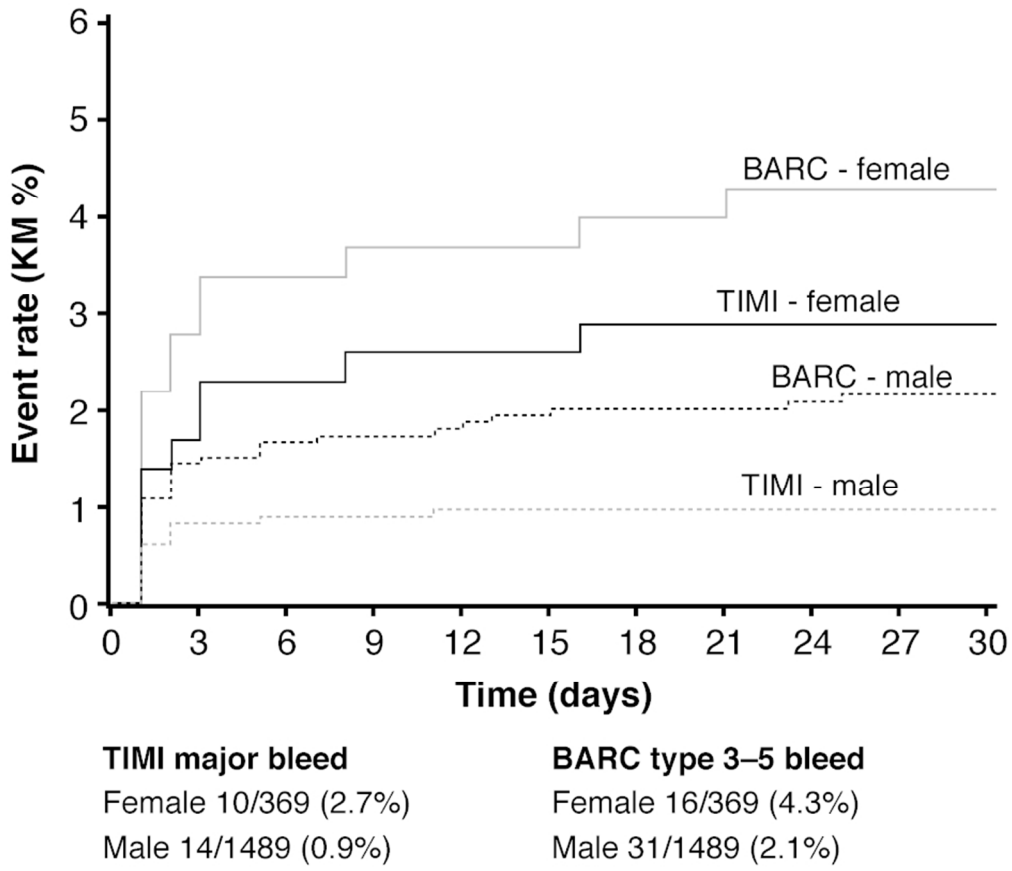

Figure 4. Cumulative Kaplan-Meier estimates of the incidence of the TIMI major bleeding and BARC type 3-5 bleeding at 30 days by gender.

79x69mm (300 x 300 DPI)

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)**	

≠ 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

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 endpoin, 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)**	

≠≠ 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

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)**	

≠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

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	4
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	NA (SEE PAGE 4)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, 8, 9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	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	9, 10, 11, 12
		(*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	
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 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 ≥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.

CLINICAL TRIAL REGISTRATION: clinicaltrials.gov identifier: NCT01347580.

Strengths and limitations

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

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 has 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 standard clinical care. All patients were to subsequently receive ticagrelor 90 mg twice daily for 30 days, after which it was recommended that ticagrelor should be continued for up to 12 months. Pre-hospital administration of a GP IIb/IIIa inhibitor was left to the physician's discretion. Peri-procedural use of parenteral anticoagulants was also left to the physician's discretion, according to the local practice.

The proportion of patients who did not have ≥70% resolution of ST segment elevation before PCI and / or did not meet the criteria for TIMI flow 3 in the infarct related artery (IRA) at initial angiography was the primary outcome of the ATLANTIC trial. Secondary outcomes (clinical efficacy outcomes) included the composite of death, MI, stent thrombosis, stroke, or urgent revascularisation at 30 days and definite stent thrombosis at 30 days. Safety outcomes included major and minor bleeding over the 30-day treatment period. Bleeding risk was evaluated using the TIMI (The Thrombolysis In Myocardial Infarction), BARC (Bleeding Academic Research Consortium) and PLATO (Study of Platelet Inhibition and Patient Outcomes) bleeding definitions.(14)

The main objective of our analysis was to study the association between gender and primary and secondary outcomes of the main study with a special focus on the clinical efficacy and safety outcomes. The interaction of gender subgroups with randomised treatment effects was also investigated.

The trial design and protocol were approved by the national regulatory authorities in all the participating countries and by the local ethics committee or institutional review board at each participating site. All patients provided written informed consent.

Statistical analysis

Continuous variables are presented by their mean and standard deviation (SD) or median and 25th -75th percentiles as appropriate. Categorical variables are presented as counts and percentages. Baseline and peri-procedural characteristics were compared according to gender by chi-square tests for categorical variables and Student`s t-test or Mann Whitney U test for continuous variables, depending on if the variable of interest was normally distributed or not. A p-value <0.05 is considered to indicate statistical significance.

The incidence of events over time by gender is presented by Kaplan-Meier curves.

In order to study the association between gender and the clinical efficacy and safety outcomes, independent of randomised treatment as well as the possible interactions between gender and randomised treatment with respect to the outcomes, hazard ratios [HR] with 95% confidence intervals [CI] were derived from Cox proportional-hazards models. In the unadjusted (crude) model, gender was the only explanatory variable whereas in the adjusted multivariable model, gender was forcibly included and the other variables were chosen by using a forward stepwise selection algorithm with a significant cut-off level of 0.05 for inclusion. Adjustment variables included age, weight, prior MI, prior PCI, history of diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-PCI electrocardiogram [ECG], admission Killip class (as a dichotomous variable 1 / >1), baseline hemoglobin, estimated glomerular filtration rate (eGFR) according to the MDRD formula, use of GP IIIb/IIa inhibitor and location of MI. To evaluate the importance of early mortality, a landmark analysis of the clinical efficacy outcomes was also performed from 48 hours after randomisation (arbitrarily defined) to the end of the study. In order to explore the importance of bleeding on the clinical efficacy outcomes, a separate analysis was also performed by censoring the patients who reported a PLATO major bleeding at the time of the onset of a bleeding event.

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

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

All the analyses were performed using SAS® version 9.3.

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**)

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 (25^{th}–75^{th} 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).

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

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 ≥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

reperfusion therapy between genders and hidden confounders such as frailty in elderly women with STEMI may partially explain their results. In accordance with our results, previous gender analyses of RCTs have shown that the impact of gender on mortality could mainly be explained by differences in age and comorbidities between genders.(11, 12, 15, 18, 19) In the CADILLAC study,(11) women had a 4-fold higher unadjusted risk for 30 days mortality but after adjustment no significant difference remained. In STEMI treated with thrombolysis Motovska et al showed that gender was not an independent predictor of outcome,(12) The recent PLATO trial showed concurred results but NSTEMI and STEMI patients were pooled in the gender analysis, despite the fact that the relationship between gender and outcome depends on the type of ACS.(20) Most of these studies do not reflect current treatment of STEMI patients. Despite evolving PCI techniques and novel pharmacological treatment, women still have worse short term outcome and special effort, with respect to their advanced age and comorbidities, to improve their outcomes are warranted.

Some well-known gender disparities in the concomitant management of STEMI patients remained unchanged. Women were less likely to be treated with GP IIb/IIIa inhibitors and thrombo-aspiration during PPCI despite lack of gender difference in protection from major adverse outcomes by GP IIb/IIIa inhibitors (21) and benefit of thrombo-aspiration at the time when the study was conducted.(22) Similar findings have been provided by large registries.(7, 8) Some of these lower rates of utilization may be “appropriate” given the higher TIMI 3 flow rates in the IRA pre-PPCI and lower rates of PPCI in women vs. men. Furthermore, physician’s concern for higher risk of bleeding in older women with STEMI has certainly contributed to the lower use of GP IIb/IIIa inhibitors in women.

Although the impact of early reperfusion on mortality in STEMI patients is now unquestionable,(23) patients’ delay from symptom onset to prehospital ECG was not an independent predictor of mortality in our study, in agreement with results from previous gender analyses.(24, 25) A plausible explanation is an assosiation between age and delay, and thus adjustment for age minimizes the relative impact of delay. Furthermore, in PPCI, female gender has been associated with similar or even smaller infarct size than that in male gender, due to longer prehospital delays, indicating that other factors than larger infarct size secondary to longer prehospital delay mainly contribute to the observed higher unadjusted short term mortality.(24) The proportion of 30 day mortality that occurred within 48 hours of admission was similar in women and men (38% vs 36% respectively) contrasting previous

data where gender differences in early mortality were accounted for by excess very early (within 24-48 hours) deaths in women with STEMI.(7, 26) Cardiogenic shock and hemodynamic instability were key exclusion criteria in the ATLANTIC trial which may have influenced these results. Cardiogenic shock has been shown to be more common in women and female gender has been highly associated with mortality in shock patients.(27)

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

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

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

The analysis of the effect of gender on outcomes dependent on the randomised treatment showed no statistically significant interactions. Pre-hospital administration of ticagrelor did not improve pre- or post-PCI coronary reperfusion as assessed by TIMI flow in IRA and

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

Strengths and limitations

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

Conclusion

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

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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.

J.A. reports receiving lecture fees from AstraZeneca.

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

A.C. reports that he 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.

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

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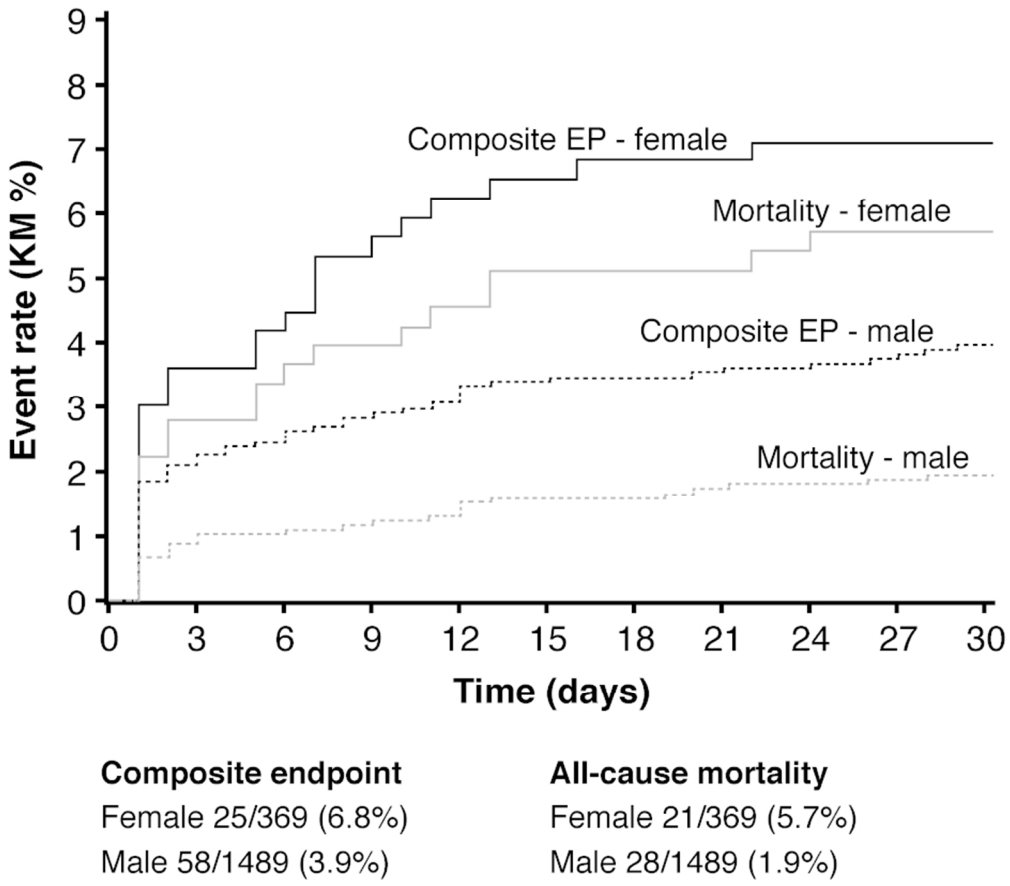
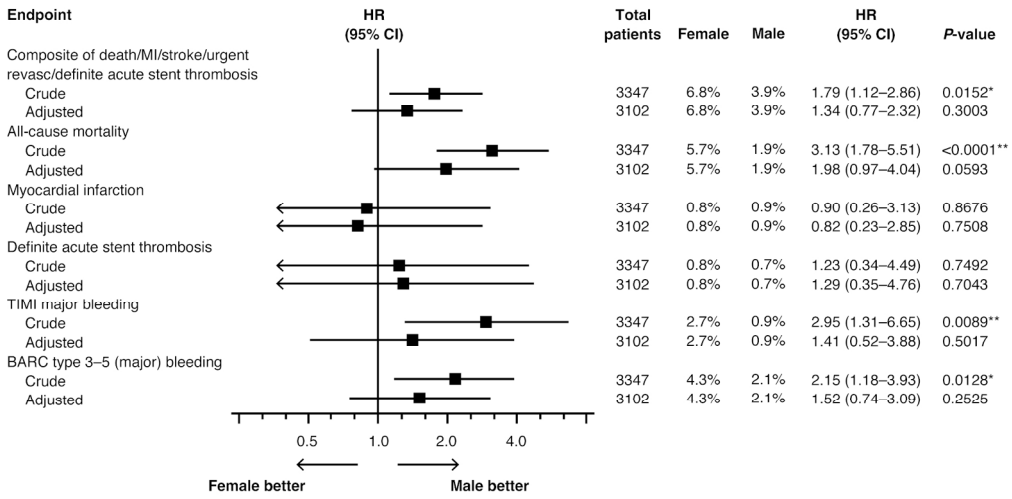


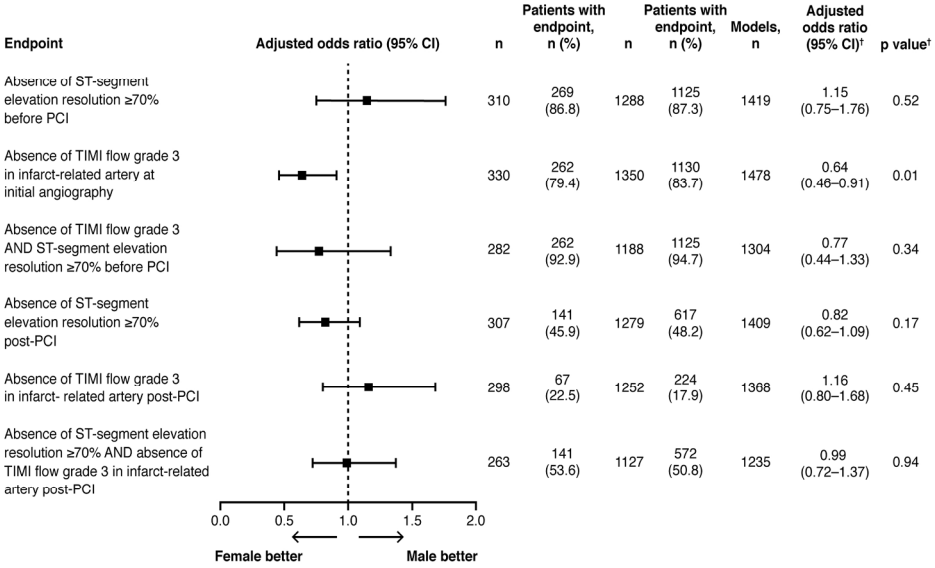
Figure 1. Cumulative Kaplan-Meier estimates of the incidence of the composite endpoint of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis and all-cause mortality at 30 days by gender.

79x70mm (300 x 300 DPI)



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

165x81mm (300 x 300 DPI)



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

228x140mm (300 x 300 DPI)

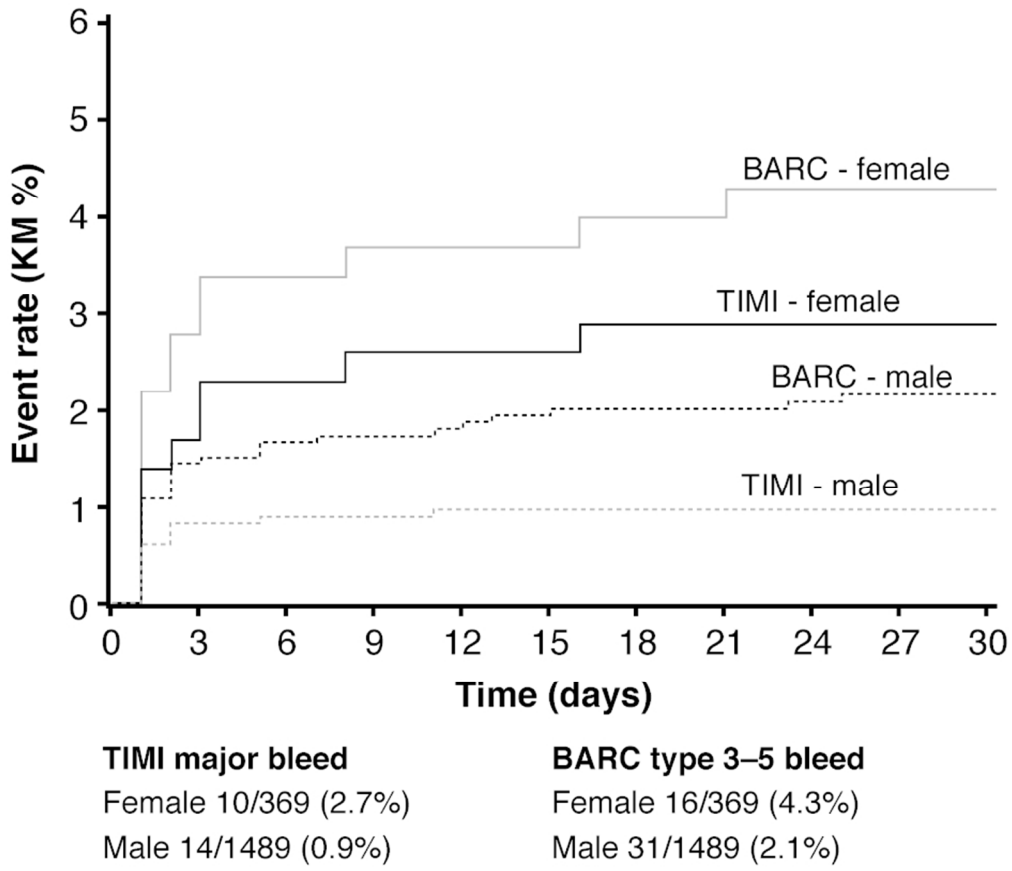


Figure 4. Cumulative Kaplan-Meier estimates of the incidence of the TIMI major bleeding and BARC type 3-5 bleeding at 30 days by gender.

79x69mm (300 x 300 DPI)

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)**	

≠ 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 KIIIip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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 endpoin, 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)**	

≠≠ 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

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)**	

≠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 KIIIip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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	4
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	NA (SEE PAGE 4)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, 8, 9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	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	9, 10, 11, 12
		(*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	
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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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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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 ≥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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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 incidence of bleeding complications in women could mainly be explained by older age and clustering of comorbidities..

CLINICAL TRIAL REGISTRATION: clinicaltrials.gov identifier: NCT01347580.

Strengths and limitations

- This is a prespecified analysis of an randomised control trial
- All patients were planned for primary PCI
- Current PCI techniques and novel antiplatelet therapy were used
- Appropriate statistical methods used to adjust for baseline differences between genders
- The large imbalance in the proportion of men and women included caused a reduced study power for definitely excluding significant differences in outcomes

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 standard clinical care. All patients were to subsequently receive ticagrelor 90 mg twice daily for 30 days, after which it was recommended that ticagrelor should be continued for up to 12 months. Pre-hospital administration of a GP IIb/IIIa inhibitor was left to the physician's

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discretion. Peri-procedural use of parenteral anticoagulants was also left to the physician's discretion, according to the local practice.

The proportion of patients who did not have ≥70% resolution of ST segment elevation before PCI and / or did not meet the criteria for TIMI flow 3 in the infarct related artery (IRA) at initial angiography was the primary outcome of the ATLANTIC trial. Secondary outcomes (clinical efficacy outcomes) included the composite of death, MI, stent thrombosis, stroke, or urgent revascularisation at 30 days and definite stent thrombosis at 30 days. Safety outcomes included major and minor bleeding over the 30-day treatment period. Bleeding risk was evaluated using the TIMI (The Thrombolysis In Myocardial Infarction), BARC (Bleeding Academic Research Consortium) and PLATO (Study of Platelet Inhibition and Patient Outcomes) bleeding definitions.(14)

The main objective of our analysis was to study the association between gender and primary and secondary outcomes of the main study with a special focus on the clinical efficacy and safety outcomes. The interaction of gender subgroups with randomised treatment effects was also investigated.

The trial design and protocol were approved by the national regulatory authorities in all the participating countries and by the local ethics committee or institutional review board at each participating site. All patients provided written informed consent.

Statistical analysis

Continuous variables are presented by their mean and standard deviation (SD) or median and 25th -75th percentiles as appropriate. Categorical variables are presented as counts and percentages. Baseline and peri-procedural characteristics were compared according to gender by chi-square tests for categorical variables and Student`s t-test or Mann Whitney U test for continuous variables, depending on if the variable of interest was normally distributed or not. A p-value <0.05 is considered to indicate statistical significance.

The incidence of events over time by gender is presented by Kaplan-Meier curves.

In order to study the association between gender and the clinical efficacy and safety outcomes, independent of randomised treatment as well as the possible interactions between gender and randomised treatment with respect to the outcomes, hazard ratios [HR] with 95% confidence intervals [CI] were derived from Cox proportional-hazards models. In the

unadjusted (crude) model, gender was the only explanatory variable whereas in the adjusted multivariable model, gender was forcibly included and the other variables were chosen by using a forward stepwise selection algorithm with a significant cut-off level of 0.05 for inclusion. Adjustment variables included age, weight, prior MI, prior PCI, history of diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-PCI electrocardiogram [ECG], admission Killip class (as a dichotomous variable 1 / >1), baseline hemoglobin, estimated glomerular filtration rate (eGFR) according to the MDRD formula, access site, use of GP IIIb/IIa inhibitor, bivalirudin and UFH, location of MI and revascularisation. To evaluate the importance of early mortality, a landmark analysis of the clinical efficacy outcomes was also performed from 48 hours after randomisation (arbitrarily defined) to the end of the study. In order to explore the importance of bleeding on the clinical efficacy outcomes, a separate analysis was also performed by censoring the patients who reported a PLATO major bleeding at the time of the onset of a bleeding event.
A comparable statistical process was used to compare gender differences in the effect of randomised treatment by constructing logistic regression models. Odds ratios [OR] with 95% CI are presented. The above process for Cox regression and logistic regression was also used to explore the interaction effect of gender and treatment.

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

All the analyses were performed using SAS® version 9.3.

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 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). Similar result was obtained after adjustment but the difference between genders did not reach statistically significance (HR 2.15, 95% CI 0.93-5.00).

Female gender was associated with lower risk for TIMI flow < 3 in the IRA at initial angiography (adjusted OR 0.67, 95% CI 0.47-0.96). The risk of incomplete ST-segment

elevation resolution (<70%) before PCI did not differ significantly between the genders (adjusted OR 1.11, 95% CI 0.73-1.71). 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**)

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=0.94 for all-cause mortality, p=0.55 for absence of TIMI flow grade 3 in the IRA at initial angiography, p=0.71 for absence of ≥70% resolution of pre-PCI ST segment elevation, and p=0.31 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 short term mortality and bleeding complications in women. After multivariable adjustment female gender remained an independent predictor of mortality whereas advanced age and comorbidities could mainly explain the higher incidence of bleeding complications in women.

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 was still significantly higher in women. The 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. Furthermore, a trend toward increased mortality with prehospital ticagrelor was observed in the ATLANTIC trial that was mainly attributed to a plausible imbalance between the two groups in terms of the severity of the presenting event. Given the low rate of all-cause mortality, unobserved confounders in elderly women with STEMI may have significantly contributed to our results and the findings of the main study. These factors may have a significant impact on the remaining higher adjusted risk for short-term mortality in women.

Previous observational studies in STEMI cohorts, without focus on PPCI treated patients have shown a higher risk for early mortality in women.(6, 16, 17) Significant differences in the rate of reperfusion therapy between genders and hidden confounders such as frailty in elderly women with STEMI may have influenced their results. Recent observational studies including patients treated with PPCI(4, 18, 19) and pre-specified gender analysis of RCTs(11, 12, 15, 20, 21) have shown that the impact of gender on mortality could mainly be explained by differences in age and comorbidities between genders.. On the contrary, an observational study and a meta-analysis have reported higher multivariable adjusted risk of early mortality in women with STEMI treated with PPCI.(22, 23) Differences in the population studied and in the covariates included in the multivariable analysis between studies may explain the conflicting results. Previous studies have clearly demonstrated the importance of body surface area and the eGFR on prognosis.(24, 25) In a meta-analysis, Berger et al showed that female gender was an independent predictor of early mortality in STEMI patients. However, 30-day mortality was not statistically significant different between genders after additional adjustment for angiographic disease severity.(26)

In the present study, women had a 2-3 times higher unadjusted risk for non-CABG related bleedings, depending on the definition used. After adjustment for baseline characteristics, no significant difference remained. Female gender has previously been associated with higher risk for bleeding complications in patients with ACS.(27-30) Known predictors of bleedings like advanced age, diabetes, hypertension, renal insufficiency and anemia, are usually more often encountered in women with STEMI.(31) Additionally, smaller body and vessel size, higher use of femoral access and overdosing of antithrombotic medication in women may

explain the higher observed risk for bleeding. Procedural-related improvement such as increased use of radial access or smaller femoral sheaths and careful dose adjustment of antithrombotic medication, have resulted in a significant decline in the risk of bleeding/vascular complication during cardiovascular interventions the last years and have probably contributed to our results.(32) The negative impact of bleedings on prognosis in patients with STEMI is well established. (31) Our data showed that even after excluding patients from further analysis at the time of a PLATO major bleeding, the HR for early mortality in women vs men remained unchanged, implying that reducing the rate of major bleeding in women may improve their prognosis but is not the main reason for the observed difference between genders in the early mortality.

Some well-known gender disparities in the concomitant management of STEMI patients remained unchanged. Women were less likely to be treated with GP IIb/IIIa inhibitors and thrombo-aspiration during PPCI despite lack of gender difference in protection from major adverse outcomes by GP IIb/IIIa inhibitors (33) and benefit of thrombo-aspiration at the time when the study was conducted.(34) Similar findings have been provided by large registries.(7, 8) Some of these lower rates of utilization may be “appropriate” given the higher TIMI 3 flow rates in the IRA pre-PPCI and lower rates of PPCI in women vs. men. Furthermore, physician’s concern for higher risk of bleeding in older women with STEMI have certainly contributed to the lower use of GP IIb/IIIa inhibitors in women.

Although the impact of early reperfusion on mortality in STEMI patients is now unquestionable,(35) patients’ delay from symptom onset to prehospital ECG was not an independent predictor of mortality in our study, in agreement with results from previous gender analyses.(36, 37) A plausible explanation is an assosiation between age and delay, and thus adjustment for age minimizes the relative impact of delay. Furthermore, in PPCI, female gender has been associated with similar or even smaller infarct size than that in male gender, due to longer prehospital delays, indicating that other factors than larger infarct size secondary to longer prehospital delay mainly contribute to the observed higher unadjusted short term mortality.(36) The proportion of 30 day mortality that occurred within 48 hours of admission was similar in women and men (38% vs 36% respectively) contrasting previous data where gender differences in early mortality were accounted for by excess very early (within 24-48 hours) deaths in women with STEMI.(7, 17) Cardiogenic shock and

hemodynamic instability were key exclusion criteria in the ATLANTIC trial which may have influenced these results. Cardiogenic shock has been shown to be more common in women and female gender has been highly associated with mortality in shock patients.(19)

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

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

Strengths and limitations

The present study has some important limitations. The ATLANTIC trial was not stratified by gender. The large imbalance in the proportion of men and women included, commonly encountered in a STEMI population, caused a reduced power for detecting or definitely excluding significant differences in some outcomes between the genders or to definitely exclude an interaction between gender and the randomised treatment.

The current study was planned as a pre-specified gender analysis in the randomised, controlled ATLANTIC trial. The most important strength of our analysis is that patients were treated according to the current guidelines of STEMI, with PPCI as the reperfusion strategy of choice, administration of the modern ADP receptor-blocker ticagrelor in addition to aspirin as soon as possible after the first medical contact, high use of radial access during catheterisation and adjuvant pharmacologic treatment during PPCI with UFH or bivalirudin. (38) Therefore our study provides important information about differences and similarities between genders in STEMI patients treated with current PCI techniques and pharmacologic treatment.

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.

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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.

J.A. reports receiving lecture fees from AstraZeneca.

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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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Figure legends

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.

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

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

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 IV	332 (90.0) 2 (0,5)	1349 (90.4) 3 (0.2)	0.82
TIMI risk score			
0-2 3-6 >6	119 (32.2) 231 (62.6) 19 (5.1)	1006 (67.4) 471 (31.5) 16 (1.1)	0.01
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 (25^{th}–75^{th} 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)	Adjusted hazard ratio (95%CI)*	P-value *
	Patients with endpoint, n (%)	Patients with endpoint, n (%)	(n included=1858)	(n included=1613)	
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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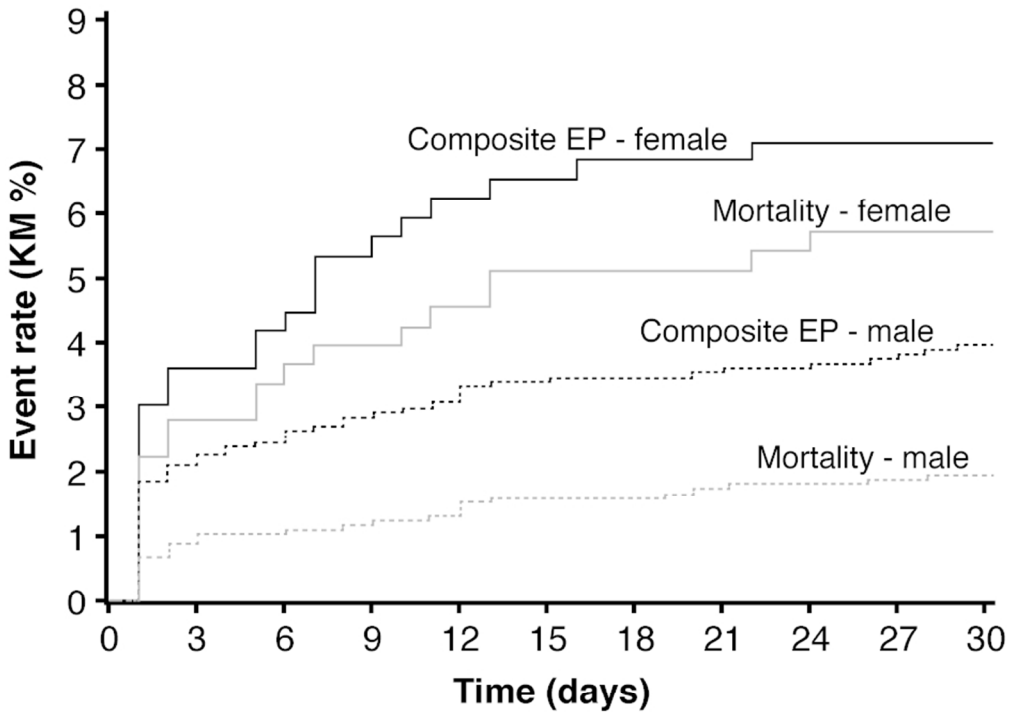
TIMI major or minor bleeding**	18 (4.9)	54 (3.6)	1.38 (0.81-2.35)	0.94 (0.51-1.74)	0.85
BARC type 3-5 (major) bleeding**	16 (4.3)	31 (2.1)	2.15 (1.18-3.93)	1.45 (0.72-2.91)	0.30
BARC type 2-5 (major or minor) bleeding**	20 (5.4)	56 (3.8)	1.48 (0.89-2.47)	1.03 (0.57-1.84)	0.93

*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 KIIIip 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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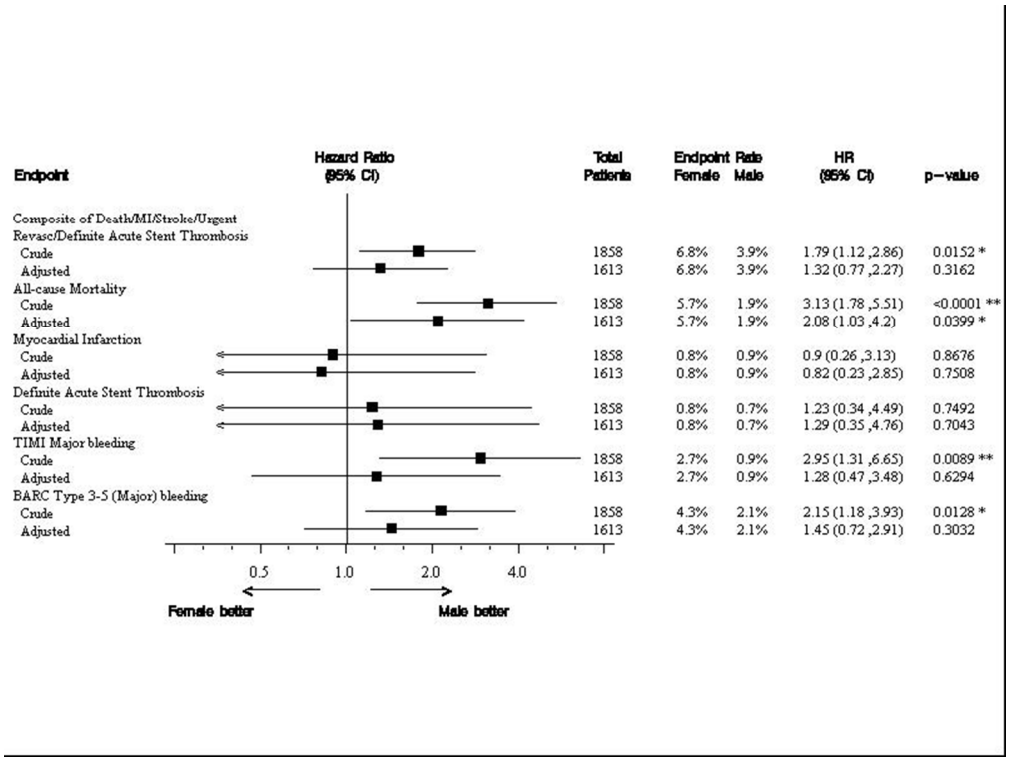

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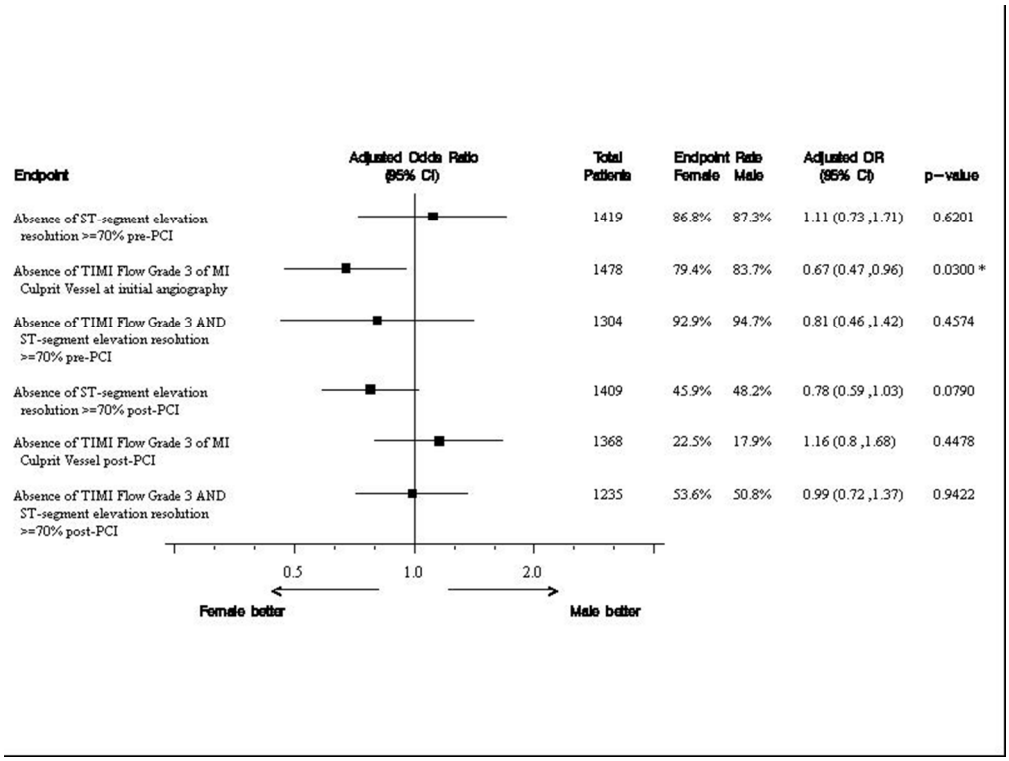

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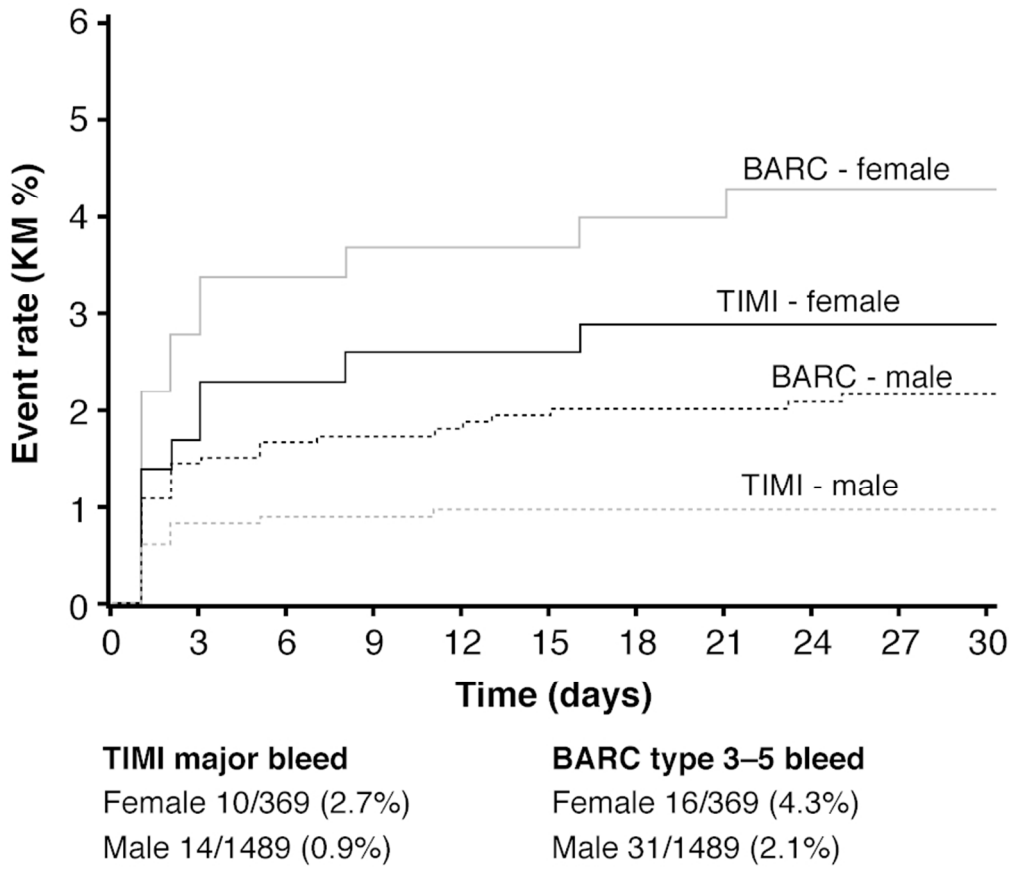

Caption : Figure 4. Cumulative Kaplan-Meier estimates of the incidence of the TIMI major bleeding and BARC type 3-5 bleeding at 30 days by gender.

79x69mm (300 x 300 DPI)

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)**	

≠ 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 KIIIip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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 endpoin, 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)**	

≠≠ 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

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)**	

≠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 KIIIip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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	4
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	NA (SEE PAGE 4)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, 8, 9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	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	9, 10, 11, 12
		(*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	
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 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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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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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 ≥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

incidence of bleeding complications in women could mainly be explained by older age and clustering of comorbidities.

CLINICAL TRIAL REGISTRATION: clinicaltrials.gov identifier: NCT01347580.

Strengths and limitations

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

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

standard clinical care. All patients were to subsequently receive ticagrelor 90 mg twice daily for 30 days, after which it was recommended that ticagrelor should be continued for up to 12 months. Pre-hospital administration of a GP IIb/IIIa inhibitor was left to the physician's discretion. Peri-procedural use of parenteral anticoagulants was also left to the physician's discretion, according to the local practice.

The proportion of patients who did not have ≥70% resolution of ST segment elevation before PCI and / or did not meet the criteria for TIMI flow 3 in the infarct related artery (IRA) at initial angiography was the primary outcome of the ATLANTIC trial. Secondary outcomes (clinical efficacy outcomes) included the composite of death, MI, stent thrombosis, stroke, or urgent revascularisation at 30 days and definite stent thrombosis at 30 days. Safety outcomes included major and minor bleeding over the 30-day treatment period. Bleeding risk was evaluated using the TIMI (The Thrombolysis In Myocardial Infarction), BARC (Bleeding Academic Research Consortium) and PLATO (Study of Platelet Inhibition and Patient Outcomes) bleeding definitions.(14)

The main objective of our analysis was to study the association between gender and primary and secondary outcomes of the main study with a special focus on the clinical efficacy and safety outcomes. The interaction of gender subgroups with randomised treatment effects was also investigated.

The trial design and protocol were approved by the national regulatory authorities in all the participating countries and by the local ethics committee or institutional review board at each participating site. All patients provided written informed consent.

Statistical analysis

Continuous variables are presented by their mean and standard deviation (SD) or median and 25th -75th percentiles as appropriate. Categorical variables are presented as counts and percentages. Baseline and peri-procedural characteristics were compared according to gender by chi-square tests for categorical variables and Student`s t-test or Mann Whitney U test for continuous variables, depending on if the variable of interest was normally distributed or not. A p-value <0.05 is considered to indicate statistical significance.

The incidence of events over time by gender is presented by Kaplan-Meier curves.

In order to study the association between gender and the clinical efficacy and safety outcomes, independent of randomised treatment as well as the possible interactions between gender and randomised treatment with respect to the outcomes, hazard ratios [HR] with 95% confidence intervals [CI] were derived from Cox proportional-hazards models. In the unadjusted (crude) model, gender was the only explanatory variable whereas in the adjusted multivariable model, gender was forcibly included and the other variables were chosen by using a forward stepwise selection algorithm with a significant cut-off level of 0.05 for inclusion. Selection of covariates included in the multivariable analysis was based on previous studies (3, 4, 6, 15) and clinical experience. Univariate analysis was not performed. However, this is a common practice in observational studies and we included 18 covariates in our multivariable analysis that, we believe, incorporated all possible predictors of adverse outcomes in a STEMI population.

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

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

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

All the analyses were performed using SAS® version 9.3.

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

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). Similar result was obtained after adjustment but the difference between genders did not reach statistically significance (HR 2.15, 95% CI 0.93-5.00).

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

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=0.94 for all-cause mortality, p=0.55 for absence of TIMI flow grade 3 in the IRA at initial angiography, p=0.71 for absence of ≥70% resolution of pre-PCI ST segment elevation, and p=0.31 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 short term mortality and bleeding complications in women. After multivariable adjustment female

gender remained an independent predictor of mortality whereas advanced age and comorbidities could mainly explain the higher incidence of bleeding complications in women.

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 was still significantly higher in women. The 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, 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. Furthermore, a trend toward increased mortality with prehospital ticagrelor was observed in the ATLANTIC trial that was mainly attributed to a plausible imbalance between the two groups in terms of the severity of the presenting event. Given the low rate of all-cause mortality, unobserved confounders in elderly women with STEMI may have significantly contributed to our results and the findings of the main study. These factors may have a significant impact on the remaining higher adjusted risk for short-term mortality in women.

Previous observational studies in STEMI cohorts, without focus on PPCI treated patients have shown a higher risk for early mortality in women.(6, 17, 18) Significant differences in the rate of reperfusion therapy between genders and hidden confounders such as frailty in elderly women with STEMI may have influenced their results. Recent observational studies including patients treated with PPCI(4, 19, 20) and pre-specified gender analysis of RCTs(11, 12, 16, 21, 22) have shown that the impact of gender on mortality could mainly be explained by differences in age and comorbidities between genders.. On the contrary, an observational study and a meta-analysis have reported higher multivariable adjusted risk of early mortality in women with STEMI treated with PPCI.(23, 24) Differences in the population studied and in the covariates included in the multivariable analysis between studies may explain the conflicting results. Previous studies have clearly demonstrated the importance of body surface area and the eGFR on prognosis.(25, 26) In a meta-analysis, Berger et al showed that female gender was an independent predictor of early mortality in STEMI patients. However,

30-day mortality was not statistically significant different between genders after additional adjustment for angiographic disease severity.(27)

In the present study, women had a 2-3 times higher unadjusted risk for non-CABG related bleedings, depending on the definition used. After adjustment for baseline characteristics, no significant difference remained. Female gender has previously been associated with higher risk for bleeding complications in patients with ACS.(28-31) Known predictors of bleedings like advanced age, diabetes, hypertension, renal insufficiency and anemia, are usually more often encountered in women with STEMI.(15) Additionally, smaller body and vessel size, higher use of femoral access and overdosing of antithrombotic medication in women may explain the higher observed risk for bleeding. Procedural-related improvement such as increased use of radial access or smaller femoral sheaths and careful dose adjustment of antithrombotic medication, have resulted in a significant decline in the risk of bleeding/vascular complication during cardiovascular interventions the last years and have probably contributed to our results.(32) The negative impact of bleedings on prognosis in patients with STEMI is well established. (15) Our data showed that even after excluding patients from further analysis at the time of a PLATO major bleeding, the HR for early mortality in women vs men remained unchanged, implying that reducing the rate of major bleeding in women may improve their prognosis but is not the main reason for the observed difference between genders in the early mortality.

Some well-known gender disparities in the concomitant management of STEMI patients remained unchanged. Women were less likely to be treated with GP IIb/IIIa inhibitors and thrombo-aspiration during PPCI despite lack of gender difference in protection from major adverse outcomes by GP IIb/IIIa inhibitors (33) and benefit of thrombo-aspiration at the time when the study was conducted.(34) Similar findings have been provided by large registries.(7, 8) Some of these lower rates of utilization may be “appropriate” given the higher TIMI 3 flow rates in the IRA pre-PPCI and lower rates of PPCI in women vs. men. Furthermore, physician’s concern for higher risk of bleeding in older women with STEMI have certainly contributed to the lower use of GP IIb/IIIa inhibitors in women.

Although the impact of early reperfusion on mortality in STEMI patients is now unquestionable,(35) patients’ delay from symptom onset to prehospital ECG was not an independent predictor of mortality in our study, in agreement with results from previous

gender analyses.(36, 37) A plausible explanation is an assosiation between age and delay, and thus adjustment for age minimizes the relative impact of delay. Furthermore, in PPCI, female gender has been associated with similar or even smaller infarct size than that in male gender, due to longer prehospital delays, indicating that other factors than larger infarct size secondary to longer prehospital delay mainly contribute to the observed higher unadjusted short term mortality.(36) The proportion of 30 day mortality that occurred within 48 hours of admission was similar in women and men (38% vs 36% respectively) contrasting previous data where gender differences in early mortality were accounted for by excess very early (within 24-48 hours) deaths in women with STEMI.(7, 18) Cardiogenic shock and hemodynamic instability were key exclusion criteria in the ATLANTIC trial which may have influenced these results. Cardiogenic shock has been shown to be more common in women and female gender has been highly associated with mortality in shock patients.(20)

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

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

Strengths and limitations

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

underrepresentation of women in clinical trials is a well recognised problem. Moreover, the study was conducted at several centers and countries increasing externa validity. Taken together our results should be applied to a real-world STEMI population with caution. Additionally, the ATLANTIC trial was not stratified by gender. The large imbalance in the proportion of men and women included, commonly encountered in a STEMI population, caused a reduced power for detecting or definitely excluding significant differences in some outcomes between the genders or to definitely exclude an interaction between gender and the randomised treatment.

The most important strength of our analysis is that patients were treated according to the current guidelines of STEMI, with PPCI as the reperfusion strategy of choice, administration of the modern ADP receptor-blocker ticagrelor in addition to aspirin as soon as possible after the first medical contact, high use of radial access during catheterisation and adjuvant pharmacologic treatment during PPCI with UFH or bivalirudin. (38) Therefore our study provides important information about differences and similarities between genders in STEMI patients treated with current PCI techniques and pharmacologic treatment.

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.

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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.

J.A. reports receiving lecture fees from AstraZeneca.

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

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

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

S.G.G. reports receiving research grants and speaker/consulting honoraria from AstraZeneca, Daiichi Sankyo, Eli Lilly, Sanofi, Bristol-Myers Squibb, Merck, and The Medicines Company.

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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.

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

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Figure legends

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.

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

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

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.

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 IV	332 (90.0) 2 (0,5)	1349 (90.4) 3 (0.2)	0.82
TIMI risk score			
0-2 3-6 >6	119 (32.2) 231 (62.6) 19 (5.1)	1006 (67.4) 471 (31.5) 16 (1.1)	0.01
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

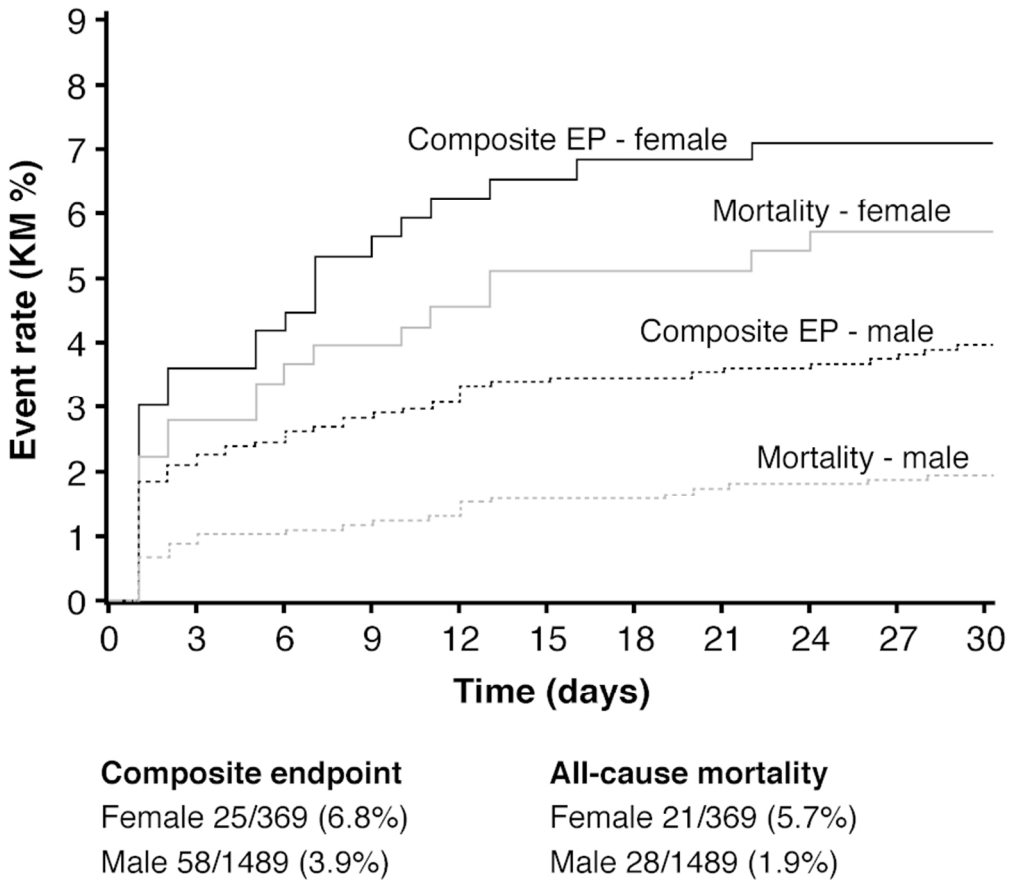
Variables presented as numbers (percentages) unless otherwise indicated.
BMI, body mass index; CABG, coronary artery bypass grafting; DES, drug-eluting stent; IQR, interquartile range (25^{th}–75^{th} percentile); PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, Thrombolysis In 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)	Adjusted hazard ratio (95%CI)*	P-value *
	Patients with endpoint, n (%)	Patients with endpoint, n (%)	(n included=1858)	(n included=1613)	
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

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 KIIIip 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



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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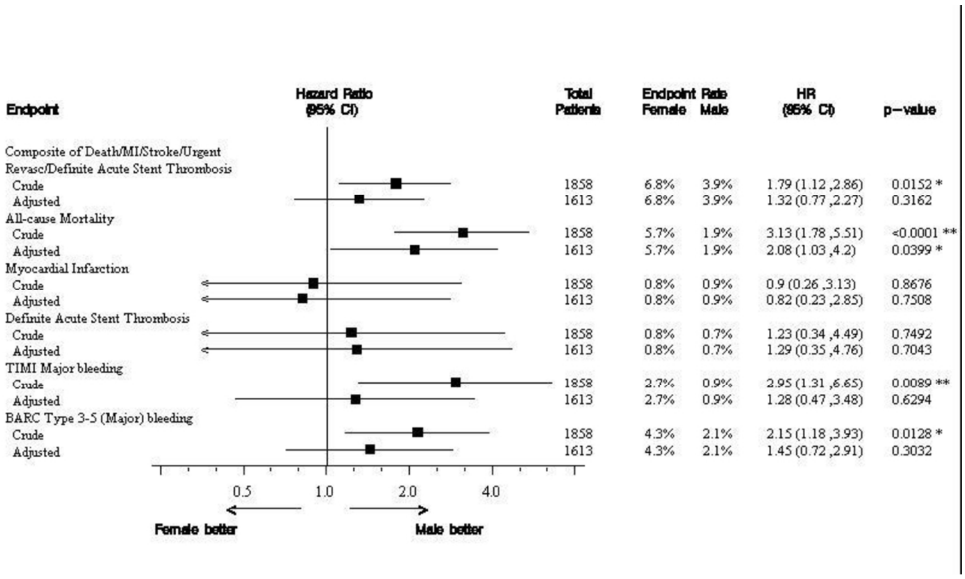

Figure 2. Association between gender and clinical efficacy and safety outcomes independent of randomised treatment.

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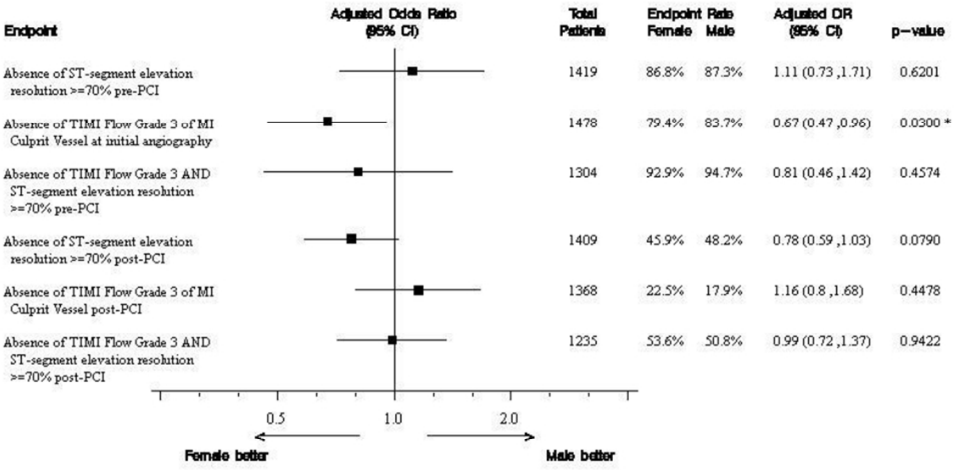

Figure 3. Association between gender and primary and secondary outcomes, independent of randomised treatment.

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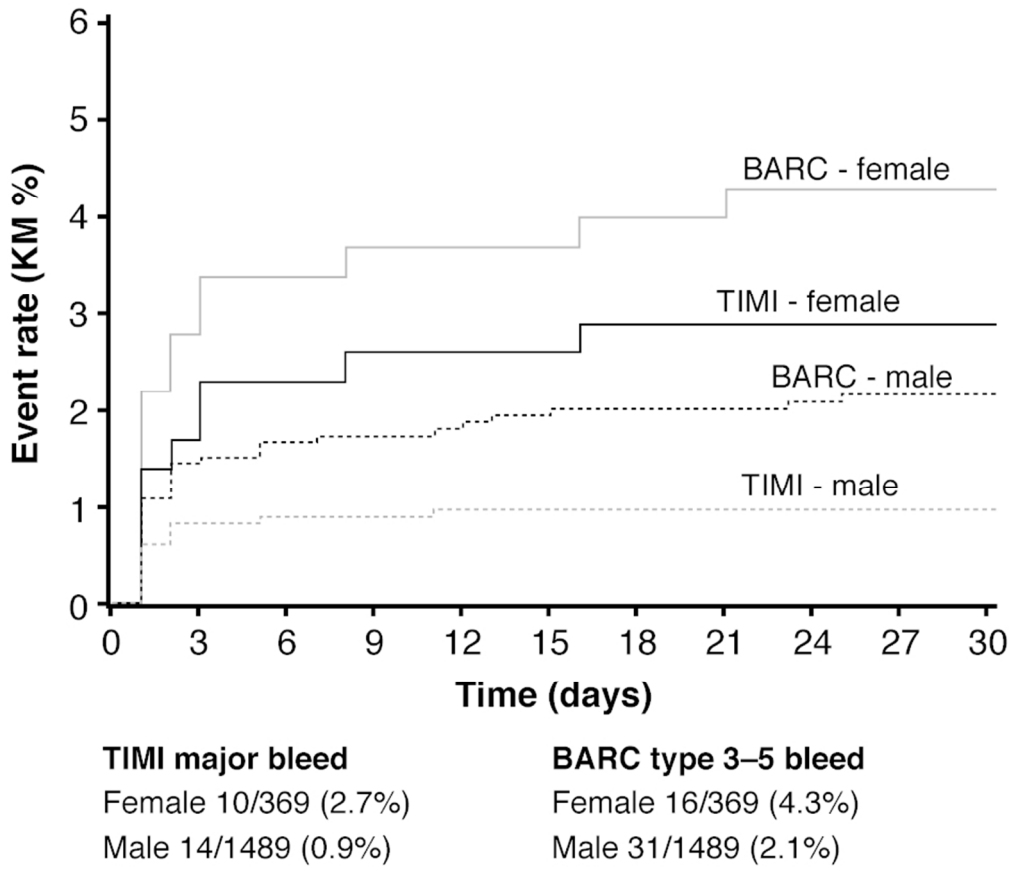

Caption : Figure 4. Cumulative Kaplan-Meier estimates of the incidence of the TIMI major bleeding and BARC type 3-5 bleeding at 30 days by gender.

79x69mm (300 x 300 DPI)

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)**	

≠ 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

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 endpoin, 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)**	

≠≠ 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

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)**	

≠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 KIIIip class, baseline hemoglobin, estimated glomerular filtration rate, glycoprotein IIb/IIIa inhibitor use during index procedure, location of myocardial infarction

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.