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**Ticagrelor versus Prasugrel in Acute Coronary Syndrome: Sex-Specific Analysis from the
RENAMI Registry**

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ABSTRACT

Background: The use of potent P2Y12 inhibitors (ticagrelor & prasugrel) in acute coronary syndrome (ACS) patients undergoing percutaneous coronary interventions (PCI) is a class I recommendation. We performed a sex-specific analysis comparing the difference in efficacy and safety outcomes between ticagrelor and prasugrel in a real-world ACS population.

Methods: Data from the multicentre REgistry of New Antiplatelets in patients with Myocardial Infarction for 4424 ACS patients who underwent PCI and were treated with ticagrelor or prasugrel between 2012 to 2016 were analysed. Mean follow-up was 17 ± 9 months. **Results:** After propensity score matching, there was no significant difference in the occurrence of primary endpoint of net adverse cardiac events between the ticagrelor and prasugrel in men (HR: 0.94; 95% CI: 0.69-1.29; $p=0.71$), or women (HR: 1.17; 95% CI: 0.63-2.20; $p=0.62$; p interaction [sex] = 0.40). Similarly, no differences were found in the occurrence of any of the secondary endpoints (MACE, all cause death, re-infarction, stent thrombosis, BARC major bleeding and BARC any bleeding) between the two P2Y12 groups between men and women.

Conclusion: In this real-world ACS population, no relative difference in efficacy or safety outcomes were found between ticagrelor and prasugrel between sexes.

Keywords: Acute coronary syndrome, antiplatelet therapy, ticagrelor, prasugrel

Abbreviation

ACS: acute coronary syndrome

PCI: percutaneous coronary interventions

DAPT: dual antiplatelet therapy

NACE: net adverse cardiac events

MACE: major adverse cardiac events

BARC: Bleeding Academic Research Consortium

STEMI: ST segment elevation myocardial infarction

NSTEMI: non-ST segment elevation myocardial infarction

AMI: acute myocardial infarction

BMI: body mass index

PAD: peripheral artery disease

CAD: coronary artery disease

MI: myocardial infarction

CABG: coronary artery bypass grafting

1 INTRODUCTION

Patients presenting with an acute coronary syndrome (ACS) constitute a significant global health burden that is associated with high morbidity and mortality worldwide [1]. The use of potent P2Y₁₂ inhibitors (prasugrel and ticagrelor) in ACS patients has been shown to be superior to clopidogrel in reducing ischemic events but at the cost of increased bleeding risk [2, 3]. Both prasugrel and ticagrelor achieve a greater level of platelet inhibition and have a faster onset of action compared to clopidogrel [4, 5]. Current ACS guidelines recommend dual antiplatelet therapy (DAPT) using either prasugrel or ticagrelor, in the absence of contraindications as a class I recommendation [6, 7]. To date, two randomised controlled trials have directly compared the efficacy and safety of prasugrel versus ticagrelor in ACS patients and showed inconsistent results [8-10].

At the platelet level, both ticagrelor and prasugrel were found to have similar level of platelet aggregation inhibition despite different mode of action [11, 12]. Nonetheless, sex related disparity in platelet reactivity and clinical response to several antiplatelet agents including aspirin, clopidogrel and glycoprotein IIb/IIIa inhibitors has been previously described [13-17]. Thus, it is unclear if both drugs have similar safety and efficacy profile in men and women. Clinical trials are often underpowered for such subgroup analysis since women are generally underrepresented [18].

The international and multicentre REgistry of New Antiplatelets in patients with Myocardial Infarction (RENAMI) included consecutive real-world ACS patients who were treated with either ticagrelor or prasugrel after percutaneous coronary intervention (PCI) [19]. The aim of the present study was to perform a sex-specific analysis of clinical outcomes comparing ticagrelor and prasugrel in this real-world population.

2 METHODS

2.1 Study population

We analysed data from the retrospective RENAMI registry that included 4424 ACS patients who underwent coronary angiography and PCI, and were subsequently discharged on DAPT with aspirin and either ticagrelor 90mg twice daily or prasugrel 10mg once daily. A total of 11 European centres participated in this database between 2012 and 2016. Patients age \geq 18 years with informed consent were included in the registry. There were no exclusion criteria. Information regarding baseline clinical characteristics, interventional features, and follow-up data was collected by a study coordinator in each centre. Interventional procedures protocol and the choice of DAPT loading and timing was at the discretion of the treating physician and individual centre. The research was conducted in accordance with the Helsinki declaration, and it was approved by the local ethics committee in each centre [19].

2.2 Endpoints and definitions

The primary endpoint was the occurrence of net adverse cardiac events (NACE), defined as a composite of major adverse cardiac events (MACE) and major bleeding (type 3-5 on the Bleeding Academic Research Consortium [BARC] scale) during the follow-up period (17 \pm 9 months). Secondary endpoints included MACE, defined as a composite of death, re-infarction and stent thrombosis, single components of MACE, BARC major bleeding or BARC any bleeding (Type 2-5 on BARC scale). Acute coronary syndrome was defined as ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina based on clinical guidelines definitions [7, 20]. The diagnosis of acute myocardial infarction (AMI) was in keeping with the universal AMI definition [21]. Unstable angina was diagnosed based on the presence of suggestive symptom or objective

evidence of myocardial ischaemia along with significant coronary artery stenosis ($\geq 70\%$, or $\geq 50\%$ in the left main coronary artery).

2.3 Statistical analysis

Statistical analysis was performed using the R coding environment (v3.5.3 Open Source). We examined baseline and procedural characteristics of participants by antiplatelet status. Crude baseline comorbidities were explored using Chi-squared test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. We also carried out unadjusted Cox proportional hazard regression modelling to describe event-free survival of unadjusted outcome data.

Multiple imputations were carried out using the *mice* package to reduce potential bias from missing data, assuming missingness at random mechanisms. We used chained equations to impute the data for all variables with missing information and generated 5 datasets to be used in the analyses. For each sex, we carried out a propensity-score matching between prasugrel and ticagrelor cases. This was performed with the *MatchIt* package using a nearest neighbour method. Baseline variables used for the matching were age, sex, weight, body mass index (BMI), creatinine, length of DAPT, smoker status, diabetes mellitus, insulin status, hypertension, dyslipidaemia, peripheral artery disease (PAD), coronary artery disease (CAD), prior myocardial infarction (MI), prior PCI, prior coronary artery bypass grafting (CABG), prior stroke, prior bleeding, malignancy, STEMI presentation, left ventricular ejection fraction $<40\%$, use of oral anticoagulant, use of glycoprotein IIb/IIIa inhibitors, thrombolysis, radial access, stenting, CABG, left main disease, multivessel disease and complete revascularisation. Matches are chosen for each unit one at a time in a ratio of 1:1 (ticagrelor: prasugrel). At each matching step, the prasugrel case that is not yet matched but is closest to the ticagrelor case

on the propensity distance measure was matched from the smallest value of the distance measure to the largest. This ensured that the matched cohort had no significant differences in baseline characteristics.

To examine the influence of antiplatelet choice on adjusted outcomes, we carried out a Cox-proportional hazard regression model on the matched data to analyse event-free survival for NACE, MACE, death, re-infarction, stent thrombosis, BARC major bleeding and BARC any bleeding.

3 RESULTS

3.1 Baseline patients and interventional characteristics

In total, 4424 patients were included in the analysis with 3,503 men (79%) and 921 women (21%). Mean follow-up period was 17 ± 9 months.

Baseline patients' characteristics are listed in Table 1. A total of 1433 (32.3%) men and 266 (6.1%) women were treated with prasugrel at hospital discharge, and 2,070 men (46.8%) and 655 (14.8%) women were treated with ticagrelor. Patients in the ticagrelor group were older (61.1 ± 11.6 vs 58.1 ± 10.3 , $p < 0.001$, in men; and 66.1 ± 12 vs 62.5 ± 10.6 , $p < 0.001$ in women), and had a lower average body weight (80.9 ± 13.4 vs 84.2 ± 12.3 , $p < 0.001$ in men; and 71.3 ± 13.4 vs 73.5 ± 13.6 , $p < 0.001$ in women). Additionally, there was a higher prevalence of cardiovascular risk factors and other comorbidities in the ticagrelor group including; insulin dependent diabetes (9.6 % vs 2.9%, $p < 0.001$ in men; and 18% vs 4.5%, $p < 0.001$, in women), history of CAD (24.9% vs 17.4% $p < 0.001$ in men; and 26.7% vs 16.9%, $p = 0.002$ in women), prior stroke (6.8% vs 1.7% $p < 0.001$ in men; and 9% vs 1.5%, $p < 0.001$ in women), and prior PCI (19.8% vs 14.8% $p < 0.001$ in men; and 20.8% vs 13.2%, $p = 0.01$ in women). Moreover, STEMI presentation was more common in the prasugrel group in men (73.5% vs 49.4%, $p < 0.001$) and women (69.5% vs 47%, $p < 0.001$).

Baseline procedural characteristics are listed in Table 2.

3.2 Unadjusted clinical outcomes

At follow-up, no significant differences were found in the clinical endpoints (NACE, MACE, death, reinfarction, stent thrombosis and BARC major bleeding) between the P2Y12 inhibitor groups in men and women, except for a higher rate of BARC any bleeding in the ticagrelor

group in men (5.2% vs 3.4%, HR 1.56; 95% CI: 1.11-2.19; $p=0.014$) [Table S1 in the online supplementary material & Figure 1].

3.3 Clinical outcomes after propensity score matching

Baseline patients and interventional characteristics after propensity score matching are listed in Table S2 in the online supplementary material. After adjusting for baseline variables, 1433 patients were included in each P2Y12 inhibitor group in men, and 266 in women. After propensity score matching, there was no significant difference in the occurrence of the primary endpoint (NACE) between the two P2Y12 inhibitor groups in men (HR: 0.94; 95% CI: 0.69-1.29; $p=0.71$), and women (HR: 1.17; 95% CI: 0.63-2.20; $p=0.62$; p interaction [sex]=0.40). Additionally, no differences were found in any of the secondary endpoints between the two groups. [Table 3 & Figure 2].

4 DISCUSSION

In this real-world ACS population, patient sex did not influence outcomes in patients treated with ticagrelor compared with prasugrel, with no interaction between patient sex and the choice of P2Y12 inhibitor with respect to the occurrence of primary or secondary endpoints.

It has been demonstrated that women have higher baseline platelet count and higher level of on-treatment (aspirin and clopidogrel) platelet reactivity compared to men [22, 23]. The mechanism of which is not fully understood but it could be explained by the higher level of oestrogen in women, leading to increased platelet aggregation [24]. Moreover, women have higher prevalence of comorbidities, which are associated with increased platelet reactivity [16]. Nonetheless, a study by Breet reported no difference in clinical endpoints between men and women despite higher baseline platelet count and reactivity in women [22]. Thus, the clinical relevance of between sex difference in platelet reactivity remains unclear.

Sex related difference in clinical response to antiplatelets has been previously reported. In a meta-analysis of aspirin use in primary prevention, a reduction in composite of cardiovascular events was mainly driven by reduction in stroke in women and MI in men [13]. However, this difference was no longer significant after controlling for multiple comparisons in a subsequent meta-analysis of aspirin in primary and secondary prevention. Moreover, secondary prevention trials showed no sex related difference in this meta-analysis [25].

When glycoprotein IIb/IIIa use was compared to placebo in a meta-analysis of six randomised clinical trials, heterogeneity of treatment effect was observed with treatment benefit in men but potential harm in women. This heterogeneity of treatment effect was not evident when patients were stratified according to their baseline troponin level [17]. Furthermore, sex-specific meta-analyses of potent P2Y12 inhibitors showed similar safety and efficacy profile for P2Y12 inhibitors in men and women when compared to clopidogrel [26, 27]. To our knowledge, the study described herein is the first sex-specific analysis comparing the efficacy and safety of ticagrelor versus prasugrel in real-world population, and as in other settings, we observed no sex related difference in response to one versus the other.

Head to head comparison of these two P2Y12 inhibitors was performed in two randomised controlled trials [9, 10]. In the Prague 18 trial, no significant difference in the combined endpoint of cardiovascular death, MI or stroke was found between prasugrel and ticagrelor at one year. Nonetheless, the trial was underpowered with a significant number of patients switching to clopidogrel from the assigned protocol drug early post hospital discharge resulting in inconclusive comparison [9]. Later, the randomised open-label ISAR- REACT 15 trial unexpectedly demonstrated superiority for prasugrel in reducing ischaemic events without increase in bleeding risk. The results were consistent for both STEMI and NSTEMI patients. Notably, the trial tested two different DAPT strategies with no pre-treatment with prasugrel in NSTEMI patients compared to pre-treatment with ticagrelor. In addition, a reduced dose of prasugrel for those age above 75 years and weight < 60 kg was used [10]. In the overall RENAMI population, the incidence of NACE, MACE and BARC major bleeding were lower in the prasugrel group compared to ticagrelor at one year [19]. The present RENAMI sub-study however compared outcomes over a longer follow up period.

It has been well recognised that sex related difference in outcomes after ACS exist with worse prognosis reported in women [28, 29]. Older age at ACS presentation in addition to the higher prevalence of comorbidities like diabetes and hypertension in women are contributing factors to this difference in outcomes [30]. Furthermore, studies have shown that women were less likely to receive evidence-based treatment including DAPT, and more likely to be treated conservatively [29, 31]. Patient sex was also found to impact on antiplatelet choice with more women receiving lower intensity antiplatelet therapy compared to men [31]. In the current study, women were also less likely to be treated with prasugrel (28.9% versus 40.9%). The tendency to prescribe less potent antiplatelet may in part be caused by concerns regarding increased bleeding risk in women. However as in other component of coronary intervention such as arterial access, given the increased likelihood of comorbidities, women may be at greater recurrent ischaemic risk and thus more to gain from more potent P2Y12 inhibition [32]. Therefore, the choice of antiplatelet warrants careful balancing of the ischaemic versus bleeding risk irrespective of patient sex.

4.1 Limitations

There are several limitations to our study. Firstly, the non-randomised, retrospective observational nature of the registry makes it prone to selection bias and potential unmeasured confounders. Moreover, the lack of adjudication of clinically relevant endpoints and adverse events may result in investigators related variability. Nonetheless, this international multicentre registry represents real-world practise, and it includes patients with high risk features who would otherwise be excluded from clinical trials. Additionally, the sample size after propensity score matching was small particularly in the female group with

relatively lower event rate and broad confidence intervals around the estimates. Therefore, the results should be interpreted as hypothesis generating only, as the absence of sex related differences may be caused by lack of statistical power and insufficient sample size.

Finally, as this is a multicentre registry, differences in procedural protocol, medication loading, operator experience could not be accounted for.

5 CONCLUSIONS

The two potent P2Y₁₂ inhibitors ticagrelor and prasugrel showed no significant difference in efficacy and safety profile in treatment of ACS patients in men and women. Therefore, our findings do not support a differential treatment with those two antiplatelets in ACS based on patient sex.

6 DECLARATIONS

6.1 Availability of Data and Material

The dataset analysed is available from the corresponding author on reasonable request.

6.2 Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

6.3 Conflict of Interest

Sara Al Raisi, Majd Protty, Sergio Raposeiras-Roubín, Fabrizio D’Ascenzo, Emad Abu-Assi, Albert Ariza-Solé, Sergio Manzano-Fernández, Christian Templin, Lazar Velicki , Ioanna Xanthopoulou, Enrico Cerrato, Giorgio Quadri, Andrea Rognoni, Giacomo Boccuzzi, Andrea Montabone, Salma Taha, Alessandro Durante, Sebastiano Gili, Giulia Magnani, Michele Autelli, Alberto Grosso, Pedro Flores-Blanco, Ferdinando Varbella, María Cespón-Fernández, Diego Gallo, Umberto Morbiducci, Alberto Domínguez-Rodríguez, Ángel Cequier, Fiorenzo Gaita, Dimitrios Alexopoulos, Marco Valgimigli, Andrés Íñiguez-Romo and Tim Kinnaird have no conflict of interest.

6.4 Authors’ Contribution

SA and MP contributed equally. TK contributed to the conception and design and critically revised the manuscript. SA and MP contributed to the conception and design, analysis and interpretation and drafted the manuscript. SR,FD, EA, AA, SM, CT, LV, IX, EC, GQ, AR, GB, AM, ST, ADu, SG, GM, MA, AG, PF, FV, MC, DG, UM, Ado, AC, FG, DA, MV and AI, contributed to acquisition, analysis, interpretation and critically revised the manuscript. All authors gave

their final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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8 FIGURE CAPTIONS

- **Fig 1.** Unadjusted crude outcomes by patient sex and by P2Y12 inhibitor
- **Fig 2.** Forest plot of adjusted clinical outcomes and P2Y2 inhibitors (ticagrelor versus prasugrel) stratified by patient sex (n: Male: 2866, Female: 523)

9 TABLES

Table 1. Baseline patients characterises

Baseline characteristics	Men				Women			
	All (n=3503)	Prasugrel (n=1433)	Ticagrelor (n=2070)	p- value	All (n=921)	Prasugrel (n=266)	Ticagrelor (n=655)	p- value
Age years (mean±SD)	59 ± 11.2	58± 10.3	61± 11.6	0.000	65±11.8	62.5±10.6	66.1±12	0.000
Weight kg (mean±SD)	82.3 ± 13	84.2 ± 12.3	80.9 ± 3.4	0.000	71.9 ± 13.5	73.5 ± 13.6	71.3 ± 13.4	0.000
BMI kg/m ² (mean±SD)	27.5 ± 3.9	28.1 ± 3.6	27.2 ± 4	0.000	27.2 ± 4.9	28.2 ± 5	26.8 ± 4.8	0.016
Creat mg/dl (mean±SD)	1 ± 0.5	0.9 ± 0.4	1 ± 0.5	0.000	0.9 ± 0.4	0.8 ± 0.3	1 ± 0.4	0.000
DAPT duration months (mean±SD)	12 ± 3.8	12.9 ± 3.5	11.4 ± 3.8	0.000	11.6 ± 3.9	12.9 ± 3.6	11.1 ± 3.9	0.000
Aspirin (%)	3501 (99.9)	1433 (100)	2068 (99.9)	0.647	921 (100)	266 (100)	655 (100)	-
CAD (%)	766 (21.9)	250 (17.4)	516 (24.9)	0.000	220 (23.9)	45 (16.9)	175 (26.7)	0.002
DLP (%)	1877 (53.6)	725 (50.6)	1152 (55.7)	0.003	502 (54.5)	148 (55.6)	354 (54)	0.697
Diabetes (%)	981 (28)	381 (26.6)	600 (29)	0.131	342 (37.1)	81 (30.5)	261 (39.8)	0.010
Insulin (%)	241 (6.9)	42 (2.9)	199 (9.6)	0.000	130 (14.1)	12 (4.5)	118 (18)	0.000
HTN (%)	1821 (52)	695 (48.5)	1126 (54.4)	0.001	568 (61.7)	159 (59.8)	409 (62.4)	0.496
LVEF < 40 (%)	324 (9.2)	107 (7.5)	217 (10.5)	0.003	104 (11.3)	25 (9.4)	79 (12.1)	0.291
Malignancy (%)	142 (4.1)	50 (3.5)	92 (4.4)	0.212	57 (6.2)	11 (4.1)	46 (7)	0.131
OAC (%)	55 (1.6)	22 (1.5)	33 (1.6)	0.922	13 (1.4)	5 (1.9)	8 (1.2)	0.609
PAD (%)	79 (3.8)	49 (5)	30 (2.7)	0.008	12 (2.4)	0 (0)	12 (3.9)	-
Prior AMI (%)	568 (16.2)	193 (13.5)	375 (18.1)	0.000	160 (17.4)	38 (14.3)	122 (18.6)	0.141
Prior bleeding (%)	80 (2.3)	28 (2)	52 (2.5)	0.395	27 (2.9)	4 (1.5)	23 (3.5)	0.155
Prior CABG (%)	33 (0.9)	19 (1.3)	14 (0.7)	0.106	4 (0.4)	2 (0.8)	2 (0.3)	0.645
Prior PCI (%)	622 (17.8)	212 (14.8)	410 (19.8)	0.000	171 (18.6)	35 (13.2)	136 (20.8)	0.010
Prior stroke (%)	165 (4.7)	24 (1.7)	141 (6.8)	0.000	63 (6.8)	4 (1.5)	59 (9)	0.000
Smoking history (%)	1728 (59.2)	712 (61.8)	1016 (57.5)	0.023	358 (43.6)	101 (44.7)	257 (43.1)	0.744
STEMI (%)	2075 (59.2)	1053 (73.5)	1022 (49.4)	0.000	493 (53.5)	185 (69.5)	308 (47)	0.000

Abbreviations: BMI, body mass index; creat, creatinine; DAPT, dual antiplatelet therapy; CAD, coronary artery disease; DLP, dyslipidemia; HTN, hypertension; LVEF, left ventricular ejection fraction; OAC, oral anticoagulant; PAD, peripheral arterial disease; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction

Table 2. Interventional characteristics

Interventional features	Men				Women			
	All (n=3503)	Prasugrel (n=1433)	Ticagrelor (n=2070)	p-value	All (n=921)	Prasugrel (n=266)	Ticagrelor (n=655)	p-value
Thrombolysis (%)	53 (1.5)	28 (2)	25 (1.2)	0.08	3 (0.3)	1 (0.4)	2 (0.3)	1.000
GP IIb/IIIa (%)	495 (20.6)	226 (30.4)	269 (16.2)	0.000	115 (16.5)	22 (17.9)	93 (16.1)	0.723
Radial (%)	2676 (76.4)	1127 (78.6)	1549 (74.8)	0.010	700 (76)	214 (80.5)	486 (74.2)	0.054
Left main (%)	287 (8.2)	119 (8.3)	168 (8.1)	0.882	66 (7.2)	18 (6.8)	48 (7.3)	0.899
Multi vessel (%)	1614 (46.1)	610 (42.6)	1004 (48.5)	0.001	379 (41.2)	99 (37.2)	280 (42.7)	0.146
DES (%)	2261 (64.5)	848 (59.2)	1413 (68.3)	0.000	646 (70.1)	181 (68)	465 (71)	0.420
CABG (%)	4 (0.1)	4 (0.3)	0 (0)	-	1 (0.1)	1 (0.4)	0 (0)	-
Complete revasc (%)	2063 (79.3)	895 (76.8)	1168 (81.3)	0.006	555 (84.3)	172 (77.1)	383 (88)	0.000

Abbreviations: GPIIb/IIIa, glycoprotein IIb/IIIa; DES, drug eluting stent; CABG, coronary artery bypass graft; revasc, revascularization

Tables 3. Clinical outcomes after propensity score matching

Outcomes	Men		Women	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
NACE	0.94 (0.69–1.29)	0.71	1.17 (0.63–2.20)	0.62
MACE	0.80 (0.56–1.15)	0.22	0.91 (0.40–2.07)	0.81
Death	0.70 (0.41–1.20)	0.19	0.18 (0.02–1.49)	0.06
Re-infarction	1.05 (0.66–1.68)	0.83	1.61 (0.61–4.28)	0.34
Stent thrombosis	0.58 (0.29–1.14)	0.10	1.20 (0.25–5.65)	0.82
BARC major bleeding	1.49 (0.81–2.73)	0.20	1.47 (0.56–3.86)	0.43
BARC any bleeding	1.42 (0.98–2.05)	0.06	1.41 (0.69–2.88)	0.34

Abbreviations: HR, hazard ratio; CI, confidence interval; NACE, net adverse cardiac events; MACE, major adverse cardiac events; BARC, Bleeding Academic Research Consortium