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ABSTRACT.

Introduction. Safety and efficacy of prasugrel and ticagrelor in patients with Diabetes Mellitus (DM) presenting with Acute Coronary Syndrome (ACS) and treated with PCI remain to be assessed.

Methods. All DM patients admitted for ACS and enrolled the REgistry of New Antiplatelets in patients with Myocardial Infarction (RENAMI) were compared before and after propensity score with matching. Net Adverse Cardiovascular Events (NACE; composite of death, stroke, myocardial infarction [MI] and BARC 3-5 bleedings), and Major Adverse Cardiovascular Events (MACEs-composite of death, stroke and myocardial infarction), were the co-primary end points. Single components of primary endpoints were secondary ones.

Results. Among 4424 patients enrolled in the RENAMI registry, 462 and 862 diabetics treated with prasugrel and ticagrelor respectively, were considered. After propensity score with matching, 386 patients from each group were selected. At 19±5 months, MACE and NACE were similar in prasugrel and ticagrelor group (5.4% vs. 3.4%, p= 0.16 and 6.7% vs. 4.1 %, p=0.11 respectively). Ticagrelor was associated with a lower risk of death and BARC 2-5 bleeding when compared to prasugrel (respectively: 2.8% vs. 0.8%, p=0.031 and 6.0% vs. 2.6%, p 0.02) and a clear, but not significant trend for a reduction of BARC 3-5 bleeding (2.3% vs. 0.8%, p 0.08). There were no significant differences in MI recurrence and stent thrombosis.

Conclusion. Diabetic patients admitted for ACS seem to benefit equally in terms of MACE from ticagrelor or prasugrel use. Ticagrelor was associated with a significant reduction in all cause death and bleedings, without differences in recurrent ischemic events which should be confirmed in dedicated RCTs.

INTRODUCTION

Patients with diabetes mellitus (DM) are at increased risk of ischemic events post-acute coronary syndromes (ACS) (1,2). Although the augmented atherothrombotic risk in this population is multifactorial (3), the increased aggregation of platelets in DM is a main risk factor (4) asking for more effective platelet inhibiting therapeutic strategies as the ones based on ticagrelor and prasugrel. To complete the picture, DM patients often present from one side with a more severe and diffuse coronary disease (5,6), while from the other they are at increased risk of bleeding, mainly as consequence of a reduced renal function. The ultimate fallout is a sparse DAPT (Dual Antiplatelet Therapy) time duration distribution for those patients (7,8).

It has been observed that both ticagrelor and prasugrel improve outcomes when compared with clopidogrel (9,10). These results have been shown to be even more solid among diabetic patients particularly using prasugrel (10). However, ticagrelor has been proven to exert similar or more marked inhibition of ADP-induced platelet reactivity in comparison with prasugrel, in patients with ACS (11).

Here, outcomes of real life patients with ACS and DM receiving prasugrel or ticagrelor are compared using data from the large multicenter, international RENAMI registry.

METHODS.

Study population.

The study population was selected from the RENAMI registry (https://renami.000webhostapp.com/) which extends from 2012 to 2016, including 12 European centers. All patients gave oral and/or written informed consent to be enrolled in the registry and consented to be contacted for telephonic and/or onsite follow-up visit.

All patients underwent coronary angiography for ACS (ST-Segment Elevation Myocardial Infarction [STEMI], not ST-segment elevation myocardial infarction [NSTEMI] or Unstable Angina [UA]) and were treated with double antiplatelet therapy (DAPT) based on ticagrelor or prasugrel.

Cohort of interest.

Among the whole RENAMI cohort, patients with diabetes were selected and analyzed. Diabetic status and whether or not on insulin treatment were assessed at the time of enrollment. Patients were divided in two groups according to the applied DAPT strategy at discharge (aspirin and prasugrel vs. aspirin and ticagrelor). Prasugrel and ticagrelor doses were chosen according current guidelines: 5 or 10 mg/die and 90 mg bid respectively.

Clinical variables.

Diabetic status was assessed at discharge so to include during hospitalization de novo diagnosis. All clinical characteristics (burden of cardiovascular risk factors and clinical presentation) as well as interventional (access site, kind of coronary disease and treatment) and outcome data, were collected with the supervision of a trained study coordinator in each center participating to RENAMI. The institutional review board of each center approved participation in RENAMI registry. For patients with multivessel disease, completeness of revascularization during index PCI or staged was left at physicians' discretion.

End-point and follow-up.

Net Adverse Cardiovascular Events (NACE- a composite and mutual exclusive end-point of all cause death, stroke, myocardial infarction and BARC 3-5 bleeding) was the primary end point, while Major Adverse Cardiovascular Events (MACE-a composite and mutual exclusive end point of death, stroke and MI) the secondary one. Single components of NACE and MACE were considered as co-secondary end points, along with stent thrombosis, and BARC 2-5 bleeding. Follow up was censored for each patient at the end of the DAPT. All events were adjudicated in each center by dedicated physicians through clinical examination.

Statistical analysis.

Continuous variables are presented as mean ± standard deviation or median with the interquartile range (IQR), categorical variable are presented in terms of frequency (%). Categorical variables were compared with the Fisher's exact test. Parametric distribution of continuous variables was tested graphically and with Kolmorogov Smirnov, and the appropriate analyses were used in accordance with the results. Propensity score with matching analysis was performed as follows: first, logistic regression analysis was carried out on all baseline features that differed between prasugrel and ticagrelor, and matching was computed after division into quintiles and the application of the method of nearest neighbor on the estimated propensity score (12). Calibration was assessed by applying the Hosmer-Lermeshow test, and accuracy was assessed using the Area Under the Curve (AUC) approach. Standardized differences were evaluated before and after matching to evaluate the performance of the model. The cumulative incidences of NACE and MACE were calculated using the Kaplan-Meier method using DAPT time duration as median follow up analysis and differences among groups were analyzed using a stratified log-rank test. Statistical analysis

was performed using the statistical software package SPSS version 21.0. Differences were considered statistically significant at α=0.05.

RESULTS.

Of the 4424 patients enrolled in the RENAMI registry, 1324 (30%) presented with diabetes at the time of enrollment. Of them, 462 (34.9%) patients were discharged on aspirin and prasugrel, and 862 (63.1%) on aspirin and ticagrelor **(see Figure S1, Web appendix only).**

Baseline and procedural characteristics are summarized in **Table S1**. Compared to the group treated with ticagrelor, patients treated with prasugrel were significantly younger (61.8 vs 65.3, p=0.001), less frequently female (17.5% vs 30.4%, p=0.001), with higher Body Max Index (BMI) (29.1 vs 26.8, p= 0.001), lower serum creatinine (0.99 vs 1.13, p=0.001), and were less insulin dependent diabetes mellitus (IDDM) (11.7% vs 36.9%, p=0.001). It was also observed that rates of previous Acute Myocardial Infarction ([AMI]19.8% vs 28.1%, p=0.001), previous CABG (21.9% vs 32.1%, p=0.001) and previous stroke (3.5% vs 15.5%, p=0.001) were lower in the prasugrel than ticagrelor group. On the contrary, Left Ventricle Ejection Fraction (LVEF) lower than 40% was observed to be less common (11.5% vs 15.9%, p=0.029) in prasugrel group, while STEMI diagnosis (58.7% vs 47%, p=0.001) as as well as higher Killip classes (5.2% vs 2.1%, p=0.004) at presentation were more frequent in prasugrel than ticagrelor treated patients. Left main disease and Drug Eluted Stents (DES) use were observed to be lower in prasugrel group (5.6% vs 9.2%, p=0.023 and 64.5% vs 79.5%, p=0.001, respectively), that was also characterized by longer DAPT time duration (13.1 vs 11.6 months, p=0.001).

After 18±6 months, rate of the primary composite outcome did not differ between prasugrel vs ticagrelor-treated patients. NACE and MACE occurred in 6.5% vs 6.4% (p=0.94) and 5.4% vs 4.8% (p= 0.60) of the prasugrel and ticagrelor population, respectively **(see Table S2).** Single components of NACE and MACE occurred with similar frequency in the prasugrel and ticagrelor groups.

Matched study cohort after propensity score analysis

After propensity score with matching analysis, 386 patients treated with Prasugrel and 386 treated with Ticagrelor with similar clinical presentation, baseline risk factors and interventional features were selected **(Table 1).**

After 19±5 months, NACE rates were similar in Prasugrel group vs Ticagrelor one (6.7% vs. 4.1%, p=0.11), with similar MACE incidence (5.4% vs 3.4%, p= 0.16, see **Table 2**). Ticagrelor reduced risk of death (2.8% vs. 0.8%, p=0.031) and BARC 2-5 Bleeding (6.0% vs. 2.6%, p 0.02) with a clear, but not significant trend for less BARC 3-5 Bleeding (2.3% vs. 0.8%, p 0.08). No relevant differences in AMI,stroke and ST were observed between the two groups. Kaplan Meier analysis highlighted similar incidence of NACE, MACE and BARC 3-5 Bleeding in both groups (log rank p=0.26, 0.54 and 0.37 respectively) and a statistically significant higher mortality in the prasugrel group (log rank p=0.029) **(Figures 1-2 and S2-S3 web appendix only).**

DISCUSSION

To the best of our knowledge this is the largest prospective and propensity matched investigation on patients with ACS and DM comparing prasugrel versus ticagrelor.

The main findings we observed are:

1) diabetic patients with ACS receiving prasugrel or ticagrelor differed in general and procedural features at baseline;

2) NACE and MACE were similar in patients treated with prasugrel or ticagrelor;

3) patients treated with ticagrelor reported a lower incidence of mortality and of bleeding.

Type 2 Diabetes mellitus is strongly related to increased risk of adverse cardiovascular events and mortality in patients treated for ACS (1,2). Coronary lesions complexity is often challenging for both interventional cardiology and cardiac-surgeons (13,14). The pathophysiology of these reports can be found in several cardio-metabolic risk factors linked to DM such as hyperglycemia, hyperlipidemia, Chronic Kidney Disease (CKD) and particularly the inflammatory and pro-thrombotic environment typical of this type of patients (4,15). It is therefore mandatory to optimize antithrombotic strategy considering the well known higher platelet reactivity of DM patients (16,17) and the prognostic implication even when treated with antiplatelet agents (18). Newer P2Y12 inhibitors have shown more benefit in terms of strong cardiovascular outcome than clopidogrel (19,20), even in DM setting (9,10) with an apparent superiority of prasugrel in this subset (10).

Baseline characteristics of ACS patients treated with prasugrel or ticagrelor were different in our real life observational study. Prasugrel cohort was younger, with a lower burden of previous cardiovascular events (stroke and AMI), a better renal function and LVEF compared to Ticagrelor one. These differences are a consequence of guidelines recommendations (21,22), originated by safety consideration from TRITON TIMI Trial (20)

from the evidence of an unfavorable net clinical benefit in patients with previous stroke, older than 75 y.o. and with a lower BMI. For these reasons, patients that receive Prasugrel often have a lower ischemic and hemorrhagic risk profile. In the absence of direct randomized comparison, our analysis with propensity matching tends to reduce the impact of this baseline heterogeneity, so that less ambiguous, more solid conclusions can be drawn in terms of efficacy-safety profile of these two antiplatelet agents, particularly for a high risk population as the one under study here.

No significant differences emerged in terms of NACE and MACE in our study after propensity adjustment. Since now, only PRAGUE-18 trial (23) tested in a direct and randomized comparison prasugrel and ticagrelor in ACS patients showing neutral results at one year follow-up both in terms of ischemic as well as bleeding incidence. However, apart from some methodological limitations, the sample size was largely underpowered for hard outcome conclusions and economically driven downgrading to clopidogrel therapy was consistent (more than 40%) because of absence of drug reimbursement to enrolled patients. Furthermore, Motovska and colleagues did not focus on real high risk population as we did, even if a subanalysis on the small diabetic group did not show significant interaction on trial main conclusions. Apart from this RCT, an adjusted indirect meta-analysis of pivotal RCTs (24) showed a substantial equivalence between prasugrel and ticagrelor in ACS. More recently, Watti et al. (25) published another systematic revision on this issue, matching both randomized and observational studies comparing the new P2Y12 inhibitors and concluding for a slight better profile of prasugrel, mainly driven by observational and not always adjusted data. Nevertheless, all previous cited papers, lack for specific conclusion on diabetic patients. Two sub-analysis from the main trials have been published on this subset (9,10). In the sub study of TRITON TIMI (10), prasugrel benefit seemed to increase in diabetic patients

compared to non-diabetic ones, with a clear net clinical benefit also considering bleeding events. On the other side, James et al. reported a substantial reproducibility of results of ticagrelor also in DM cohort, without reaching a statistical significance, probably because of lack of requested power (9).

Different studies demonstrated clopidogrel poorer outcome in diabetic patients, depending on pharmacokinetic and pharmacodynamical considerations, particularly on the above mentioned higher platelet reactivity in DM (17,18). Prasugrel and ticagrelor have shown their superiority against clopidogrel in terms of faster and stronger platelet inhibitions (26,27). If a real difference exists between these two drugs, the ability to inhibit platelets aggregation must be the central element. In a pharmacodynamics study, Franchi et al. (11) observed that ticagrelor has similar or even greater ability of platelet aggregation inhibition versus prasugrel, supporting our result in a clinical setting.

Patients treated with ticagrelor were associated with a lower mortality incidence, mainly driven by less bleedings rates, compared to prasugrel-treated ones. In addition to its main action of P2Y12 receptors block, ticagrelor has shown to reduce adenosine intracellular uptake with a consequent increase in its circulating levels (28). This collateral action could explain the not so rare induction of dyspnea, as well as some pleiotropic activities such as vasodilatation and furthermore inflammatory modulation with the potential for cardiovascular prognosis improvement (29). An elegant study by Jeong et al. (30) compared, in a randomized manner, prasugrel vs. ticagrelor in diabetic patients interested by NSTE-ACS and treated with PCI and stenting. A significant reduction of inflammatory markers was evident in ticagrelor group, stressing the idea of a possible clinical benefit in this population. Despite this, due to reduced sample size, dedicate and powered RTCs on this high risk population are needed. Moreover, In the present registry an overall low risk of adverse events were noted,

especially when compared with the data presented by Sahlen et al. All patients in our registry were treated with PCI which demonstrated to reduce mortality in ACS patients potentially explaining the present results."

The result of our analysis partially contrasts previous findings that seem to suggest a better performance for prasugrel among diabetics (31). Larger sample size and direct randomized comparison are desirable to definitively put light on this shadow.

LIMITATIONS

The main limitation of our study is the small sample size so that our conclusion on a secondary outcome with low incidence such as death must be considered as hypothesis generating only. The reduced sample size may from one side generate a type II statistical error explaining the lack of difference in primary and secondary end-points and from the other may lead to a type I error being related to the difference in death rates. Moreover, as all observational studies our general analysis suffers of selection and adjudication biases even if it directly reflects real life practice. Our Propensity Score with matching futhermore, even if not comparable to a randomized controlled trial, showed a good accuracy (AUC of 0.78) and discrimination (p 0.8, test of Hosmer-Lermeshow). Lack of detailed data on each single BARC class and on fatal bleeding incidence did not allow a more comprehensive analysis of bleeding burden between the two investigated cohort. Nevertheless, the composite BARC 2-5 and BARC 3-5 classes allow a reliable interpretation. No data on incidence of switching between different P2Y12 Inhibitors during acute phase in index hospitalization were available, even if analysis was conducted on discharge prescribed therapy.

CONCLUSION

Diabetic patients interested by ACS seem to benefit equally in terms of MACE and NACE from ticagrelor or prasugrel use. Ticagrelor was associated with a significant reduction in all

cause death and bleedings, without differences in recurrent ischemic events which should be confirmed in dedicated RCTs.

Declaration of conflicting interests:

The authors declare that there is no conflict of interest inherent to the present study.

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