P2Y12 inhibitors in acute coronary syndrome patients with renal dysfunction: an analysis from the RENAMI and BleeMACS projects

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ABSTRACT

Aims. Aim of the present study was to establish the safety and efficacy profile of prasugrel and ticagrelor in real-life acute coronary syndrome (ACS) patients with renal dysfunction.

Methods and results. **All consecutive patients from** RENAMI and BLEEMACS registries were stratified according to estimated glomerular filtration rate (eGFR) lower or greater than 60mL/min/1.73m^2. Death and myocardial infarction (MI) were the primary efficacy endpoints. Major bleedings **(MB)**, defined as Bleeding Academic Research Consortium bleeding types 3 to 5, constituted the safety endpoint.

19255 patients were enrolled. **Mean age was 63 ± 12; 14892 (77.3%) were males.** 2490 (12.9%) patients had chronic kidney disease (CKD), defined as eGFR<60mL/min/1.73m^2. Mean follow-up was 13±5 months. Mortality was significantly higher in CKD patients (9.4% vs 2.6%, p<0.0001), as well as the incidence of reinfarction (5.8% vs 2.9%, p<0.0001) and MB (5.7% vs 3%, p<0.0001). At Cox multivariate analysis both prasugrel (HR=0.34, p=0.026) and ticagrelor significantly reduced the mortality rate (HR=0.45, p=0.047) in CKD patients as compared to clopidogrel. Prasugrel and ticagrelor compared to clopidogrel were associated with decreased risk of reinfarction both in CKD patients (HR=0.07, p=0.01; HR=0.36, p=0.01, respectively) and in those with preserved renal function (HR 0.38, p<0.0001; HR 0.48, p<0.0001, respectively). Potent P2Y12 inhibitors did not increase the risk of MB in CKD patients, the hazard ratios being 0.87 for ticagrelor (p=0.67) and 0.88 for prasugrel (p=0.75).

Conclusion. In ACS patients with CKD, prasugrel and ticagrelor are associated with lower risk of death and recurrent MI without increasing the risk of MB.

Key-words: acute coronary syndromes; acute myocardial infarction; P2Y12 inhibitors; chronic kidney disease.

INTRODUCTION

Acute coronary syndromes (ACS) represent the most common clinical presentation of patients with coronary artery disease (CAD) with high mortality and morbidity.[1,2] Percutaneous coronary intervention (PCI) with stent deployment and administration of double antiplatelet therapy (DAPT) with acetylsalicylic acid and oral P2Y12 receptor inhibitor represent the standard of care for ACS patients, with either ticagrelor or prasugrel being the preferred P2Y12 antagonist in this setting.[3-8] However, based on the results of the PLATO and TRITON-TIMI trials, both ticagrelor and prasugrel are associated with higher risk of bleeding not related to coronary artery bypass graft surgery (CABG) compared to clopidogrel.[6,7] In this context, individual bleeding risk plays an important role in the choice of optimal DAPT regimen.

Furthermore, chronic kidney disease (CKD) represents a common concern among physicians who care for patients with ACS, with clinical trials suggesting that 35% to 40% of ACS patients have some degree of renal impairment.[9] CKD is associated with prolongation of bleeding time and platelet dysfunction leading to increased bleeding risk and ischemic events.[10] The American College of Cardiology and American Heart Association acknowledge the lack of sufficient studies to make specific recommendations for patients with CKD,[11] due to the exclusion of patients with renal dysfunction from most of the published randomized controlled trials (RCTs).[12] The BleeMACS (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) and the RENAMI (REgistry of New Antiplatelets in patients with Myocardial Infarction) registries were two retrospective, observational, multi-center projects designed to compare

ticagrelor and prasugrel in ACS patients and to develop a bleeding risk prediction tool in this scenario.[13,14]

Aim of the present work was to establish the efficacy and safety profile of prasugrel and ticagrelor compared with clopidogrel in patients with renal dysfunction enrolled in the aforementioned registries on a long-term follow-up.

METHODS

Study population.

The study population of this multicenter, retrospective, observational study was selected from the BleeMACS and RENAMI registries.[13,14]

The BleeMACS registry was conducted between 2003 and 2014 from 15 tertiary hospitals in European, Asian and North and South American countries, enrolling 15401 consecutive patients discharged alive after admission for ACS, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina, who had undergone **PCI** and had been started on DAPT with acetylsalicylic acid and either clopidogrel or ticagrelor or prasugrel.[13] **The BleeMACS registry excluded patients who died during hospitalization or those who did not undergo in-hospital PCI.**

The RENAMI registry was a multi-center European registry extending from 2012 to 2016 and including 4425 adult patients (≥ 18 years old) with NSTEMI or STEMI who had undergone **PCI** for ACS and were treated with DAPT using acetylsalicylic acid and either ticagrelor or prasugrel.[14] **No specific exclusion criteria were considered for the RENAMI registry.**

The institutional review board of each center approved participation in the BleeMACS and RENAMI registries, which were performed according to the principles of the Declaration of

Helsinki. **All patients provided written informed consent at admission for their data collection and utilization for future anonymous studies**.

The present study was approved by the ethical committee of each participating center.

Variables.

Clinical and interventional data were recorded, including burden of cardiovascular risk factors, clinical presentation, comorbidities, arterial access, kind of CAD and treatment. Data collection and analysis was supervised by a trained study coordinator in each center. Renal function was assessed by calculating the estimated glomerular filtration rate (eGFR) using the 4-variable Modification of Diet in Renal Disease (MDRD) study equation.[15,16]

Cohorts of interest.

Patients were classified into 2 categories based on eGFR greater or lesser than 60 ml/min/1.73m^2. CKD was defined as eGFR < 60 ml/min/1.73m^2. Patients were then stratified according to the P2Y12 antagonist administration at discharge. Patients without DAPT, crossovers between groups and patients whose baseline data necessary for eGFR calculation were unavailable were excluded from the present analysis.

Endpoints and follow-up.

Clinical assessment, ECG recordings and further instrumental evaluation (when required) were performed periodically in every patient. Death from any cause and myocardial infarction (MI), defined according to the ESC fourth universal definition of myocardial infarction,[17] excluding peri-procedural MI, **in CKD patients** were the primary efficacy endpoint; major bleedings (MB), defined as Bleeding Academic Research Consortium (BARC) type 3 to 5

bleedings,[18] were the primary safety endpoint. **Death from any cause, MIs and MBs in patients with preserved renal function were secondary endpoints. Both the efficacy and the safety endpoints were assessed at each center.**

Follow-up was censored at **death occurrence** or at last contact with the patient, be it either clinical or by telephone.

Statistical analysis.

Continuous variables were reported as mean (standard deviation) or median (interquartile range) when appropriate. Categorical variables were represented as percentage. One-way Analysis of Variance (ANOVA) was used to assess differences in baseline, procedural and clinical variables between patients with preserved or impaired renal function in the three-treatment groups (clopidogrel, prasugrel, ticagrelor) for continuous variables, while Fisher's exact test was adopted for categorical variables. All significant clinical and procedural variables associated with follow-up primary and secondary endpoints were incorporated into Cox multivariate analysis.[19] Considering primary and secondary endpoints as time-to-event outcomes (survival outcomes), Cox regression analysis was used to estimate the hazard ratio between different treatments. **Proportional hazard assumptions were tested using variables adjusted for time. Comparison between potent P2Y12 and clopidogrel was also performed by propensity score analysis in patients with impaired renal function. The cumulative incidences of all-cause death were calculated using the Kaplan–Meier method and differences among groups were analyzed using a stratified log-rank test.** Two-tail p-value < 0.05 was considered statistically significant.

Statistical analysis was performed using SPSS 24 (IBM Corporation, Armonk, NY, USA).

RESULTS

Out of 19825 patients (4244 from RENAMI and 15401 from BLEEMACS), 19255 patients with complete baseline data and with at least one follow-up contact were considered for this analysis. **570 patients were excluded because baseline serum creatinine value was not available and therefore eGFR could not be estimated.** Mean eGFR was 90±39 ml/min/1.73m^2. 2490 (12.9%) patients had baseline eGFR < 60 ml/min/1.73m^2; **among CKD patients, 2174 (87.3%) had eGFR 30-60 ml/min/1.73m^2, 230 (9.2%) had eGFR 15-30 ml/min/1.73m^2 and 86 (3.5%) had eGFR < 15 ml/min/1.73m^2**. **Amongst CKD patients, 1758 (70.6%) were taking clopidogrel, 540 (21.7%) were on ticagrelor and 192 (7.7%) received prasugrel.** CKD patients were significantly older and had higher prevalence of all major cardiovascular risk factors and high-risk features for MI recurrence and bleeding complications. Moreover, CKD patients had lower rate of complete revascularization and optimal medical therapy administration compared to patients with preserved renal function. Clinical and interventional features of the study population are shown in Table 1.

Patients taking potent P2Y12 inhibitors were younger and had greater prevalence of prior PCI and less frequent history of bleeding as compared to patients on clopidogrel. The characteristics of patients with renal dysfunction divided according to their respective DAPT regimen are summarized in Table 2.

Efficacy endpoints

After a mean follow-up of 13±5 months **(median 12 months)**, significantly higher unadjusted death-rate was observed in CKD patients treated with clopidogrel as compared to those on prasugrel (11% vs 6.3%, p=0.04) or ticagrelor (11% vs 5%, p<0.0001) and a similar trend emerged for the incidence of re-infarction (7% vs 2.1%, p=0.009; 7% vs 3.5%, p=0.04,

199 respectively). A comparison of mortality, re-infarction and BARC-MB rates in CKD patients
200 according to their respective DAPT regimen is displayed **in Figure 1**. **Kaplan-Meier**
201 **analysis also showed an overall survival benefit in patients with CKD on prasugrel or**
202 **ticagrelor compared to patients on clopidogrel (p<0.00001 at log-rank test) as shown in**
203 **Figure 2**. Multivariable adjustments for significant predictors of all-cause death **(malignancy,**
204 **multivessel CAD, complete revascularization, STEMI, diabetes mellitus and LVEF <**
205 **40%) highlighted an** independent protective role of potent P2Y12 inhibitors in CKD patients
206 when comparing ticagrelor vs clopidogrel (HR 0.45, 95%CI 0.21-0.99, p=0.047) and
207 prasugrel vs clopidogrel (HR 0.34, 95%CI 0.13-0.88, p=0.026) (**Figure 3 panel A**). **A**
208 **survival benefit of potent P2Y12 was also evident for patients with preserved renal**
209 **function (Supplementary figure S1), but this result was not confirmed after**
210 **multivariable adjustments which showed** adjusted HRs for the mortality endpoint of 0.77
211 for ticagrelor vs clopidogrel (95%CI 0.49-1.22, p=0.27) and 0.81 for prasugrel vs clopidogrel
212 (95%CI 0.51-1.29, p=0.38) in this population **(Figure 3, panel B)**. **Significant predictors of**
213 **outcome used in the multivariate model for re-infarction included complete**
214 **revascularization, multivessel CAD, STEMI, prior MI, diabetes mellitus and female sex.**
215 An increased risk of re-infarction was detected in patients with impaired renal function treated
216 with clopidogrel (HR 10.05: 95%CI 3.1-32.3, p<0.0001). In this population DAPT with
217 potent P2Y12 inhibitors was instead an independent protective factor against re-infarction
218 occurrence (HR 0.36, 95%CI 0.16-0.81, p=0.01 for ticagrelor vs clopidogrel and HR 0.07,
219 95%CI 0.01-0.54, p=0.01 for prasugrel vs clopidogrel) **(Figure 4, panel A)**. The protective
220 role of potent P2Y12 receptor antagonists against MI recurrence was confirmed in patients
221 with eGFR > 60 mL/min/1.73m^2 for both ticagrelor (HR 0.48, 95%CI 0.35-0.65, p<0.0001)
222 and prasugrel (HR 0.38: 95%CI 0.27-0.55, p<0.0001) **(Figure 4, panel B)**. On the other hand,
223 similarly to patients with impaired renal function, the increased risk of DAPT with

clopidogrel with regard to re-MI was confirmed in those with preserved renal function (HR 3.3, 95%CI 2.4-4.4, p<0.0001) **(Figure 4, panel B)**.

Overall, patients with CKD presented worse outcomes compared to patients with preserved renal function, such as significantly higher incidence of all-cause mortality (9.4% vs 2.6%, p<0.0001) and re-infarction (5.8% vs 2.9%, p<0.0001). Higher mortality rates were observed in all subgroups of CKD patients, regardless of their DAPT regimen; re-infarction incidence on clopidogrel was significantly higher in patients with CKD than in those with preserved kidney function (3.8% vs 7%, p<0.0001), but this difference was not observed in patients on potent P2Y12 inhibitors. **Figure 5** shows all-cause death, reinfarction and BARC-MB rates divided according to renal function and anti-platelet regimen.

Safety endpoint

The overall rate of MB in patients with impaired renal function was 5.7%. At univariate analysis, DAPT with potent P2Y12 inhibitors was associated with lower rates of MB, the difference being statistically significant between clopidogrel and ticagrelor (6.2% *vs.* 2.4%, p=0.01) but not between clopidogrel and prasugrel (6.2% *vs.* 4.7%, p=0.4) (**Figure 1**). **The significant variables being considered for multivariate analysis for the safety endpoint were malignancy, prior stroke, peripheral artery disease, prior bleeding, STEMI, diabetes mellitus and female sex.** After multivariate adjustments, DAPT with either ticagrelor or prasugrel did not result in an increased risk of BARC-MB at follow-up in CKD patients, the hazard ratios being 0.87 for ticagrelor (95%CI 0.45-1.66, p=0.67) and 0.88 for prasugrel (95%CI 0.41-1.9, p=0.75) (**Figure 6, panel A**). In patients with preserved renal function, ticagrelor was instead associated with a moderate but significant higher risk of BARC-MB (HR 1.43, 95%CI 1.09- 1.89, p=0.009), whereas treatment with prasugrel resulted

in a risk reduction (HR 0.6, 95%CI 0.88-0.46, p=0.01) and clopidogrel was uninfluential **when compared to potent P2Y12 inhibitors** (HR 1.0, 95%CI 0.78-1.43, p=0.99) (**Figure 6, panel B).**

Patients with preserved renal function

Patients with eGFR > 60 mL/min/1.73m^2 had an overall lower rate of MB compared to patients with impaired renal function (3% vs 5.7% respectively, p<0.0001). As shown in **Figure 5**, these difference was mainly driven by higher rates of MB in CKD patients on prasugrel or clopidogrel (6.2% vs 2.7%, p<0.0001; 4.7% vs 1.7%, p=0.03, respectively), whereas similar rates of the safety outcome were recorded among CKD and non-CKD patients on ticagrelor (2.4% vs 2.6%, p= NS).

Supplementary data

In order to avoid possible biases related to the low sample size of patients with impaired renal function treated with prasugrel, further analyses were performed by considering ticagrelor and prasugrel as a combined class of potent P2Y12 inhibitors (Supplementary Figures S2-S4). After multivariable adjustments, P2Y12 inhibitors confirmed their independent protective role against all-cause mortality (HR 0.82, 95% CI 0.54-0.96, p=0.006) and MI recurrence (HR, 0.53, 95% CI 0.3-0.95, p=0.03) compared to Clopidogrel (Supplementary Tables S1 and S2). Moreover, as for the main analysis, the risk of major bleeding at follow-up was not significantly increased by potent P2Y12 inhibitors (HR 0.99, 95% CI 0.59-1.68, p= 0.98) (Supplementary Table S3). As a sensitivity analysis to support the reliability of the main results a propensity score analysis was performed; two propensity-matched cohorts of patients were obtained

according to their respective DAPT regimen (clopidogrel vs potent P2Y12 inhibitors). Baseline features of the pre- and post-propensity matched groups are reported in the supplementary appendix (Supplementary Tables S4 and S5).

DISCUSSION

This multicenter, retrospective, observational study was conducted to explore the safety and efficacy of prasugrel and ticagrelor in CKD patients presenting with ACS. Our work showed that independently of renal function both ticagrelor and prasugrel reduced the risk of MI recurrence in ACS patients as compared with clopidogrel; moreover, a DAPT regimen with potent P2Y12 antagonists, compared with standard DAPT with clopidogrel, resulted in lower all-cause mortality rate in CKD patients but not in subjects with eGFR>60mL/min/1.73m^2; lastly, ticagrelor and prasugrel did not significantly increase the risk of MB over a long-term follow up in patients with renal dysfunction. The small body of literature evaluating prasugrel and ticagrelor in ACS patients with CKD was recently resumed in an elegant work by Bonello *et al.*[20] and outcome data in this scenario are available from the post-hoc analysis of 2 RCTs and two prospective registries.[6,7,21,22]. **Patients with CKD and several co-morbidities are often excluded from RCTs, reporting outcomes of highly selected populations.[12] Despite some observational registries previously faced the issue of administering DAPT in CKD patients, they sometimes led to controversial results as compared to the aforementioned RCT sub-analyses, thus leaving some relevant issues unsolved such as the risk of bleeding associated with potent P2Y12 receptor inhibition in such a high-risk population.[21,22] The present study, reporting outcomes of a large real-word cohort of unselected patients with CKD suffering from invasively managed ACS, comes to help minimizing these gaps in evidence.**

Overall, the proportion of patients with eGFR<60ml/min/1.73m^2 in our cohort is low compared to that of the PLATO study (13% vs 21% respectively). In a PLATO subanalysis by James *et al.* CKD was defined as serum creatinine clearance < 60 ml/min as calculated by the Cockgroft-Gault formula, which is known to underestimate eGFR in older patients.[23-24] We think that the smaller number of CKD patients in our study might be due to the fact that the Cockgroft-Gault formula might have underestimated eGFR in the PLATO sub-analysis (median age 74 in CKD patients vs 60 in patients with creatinine clearance > 60 ml/min), thus resulting in an increased proportion of CKD patients in that population as compared to ours.

CKD patients developing ACS in our study were older and had more comorbidities, such as anemia, diabetes, prior revascularization and history of stroke and bleeding. Previous studies reported that even mild and moderate renal dysfunction increases the risk of MI across the spectrum of ACS,[25] probably due to greater oxidative stress burden, accelerated atherosclerosis and the underuse of recommended therapies.[26] Our data highlight this latter phenomenon by documenting inferior prevalence of optimal medical therapy administration and significant lower use of oral anticoagulants and prasugrel among CKD patients, thus suggesting that clinical decisions largely depend on the balance between potential for bleeding harm and therapeutic efficacy.

Based on the results of the present research, potent P2Y12 receptor antagonists reduced the risk of MI recurrences and all-cause mortality in CKD patients. The PLATO sub-analysis by James *et al.* evaluated the efficacy and safety of ticagrelor in CKD patients (estimated Creatinine Clearance < 60ml/min), showing that ticagrelor compared to clopidogrel significantly reduced the primary composite endpoint of cardiovascular death, MI and stroke at 12 months in ACS patients with CKD,[23] with greater absolute risk reduction in patients with reduced kidney function. These results were confirmed by an analysis of the

SWEDEHEART registry by Edfors *et al*.[22] As for prasugrel, the subgroup analysis of the TRITON-TIMI38 trial, including 1490 patients with eGFR<60 mL/min/1.73m^2, showed that the benefit of prasugrel over clopidogrel in this sub-population was similar to that of the overall population.[7] This finding was not confirmed by the results of the PROMETHEUS observational study conducted by Baber *et al.*, who reported a non-significantly different albeit lower incidence of MI recurrences in CKD patients treated with prasugrel compared to clopidogrel at 1-year follow-up (6.3% *vs.* 8.1%, p=0.054).[21] Our results are in line with the TRITON-TIMI38 sub-analysis while disagreeing with those of the PROMETHEUS study. Moreover, the incidence of reinfarction in CKD patients treated with prasugrel in the present study was substantially lower compared to that reported by Baber *et al*.[25] These controversial results might be due to differences existing between the baseline features of the study populations, the limited sample size of both observational studies, the diverse geographic reference area and the different equation used to calculate eGFR (CKD-EPI formula was applied by Baber *et al.*). However, it must be acknowledged that, to date, the PROMETHEUS registry represents the largest report of CKD patients treated with prasugrel.

Interestingly, our study showed that all-cause mortality rate was not significantly reduced by DAPT with potent P2Y12 receptor antagonists compared to clopidogrel in patients with preserved renal function, in accordance with the results of the aforementioned PLATO sub-analysis.[23] A likely explanation of this finding is that patients with CKD are a high-risk category with frequent event rates and, as such, they create a favorable subgroup to demonstrate a benefit on hard but rare endpoints like mortality.[26]

Several factors are thought to be involved in the increased risk of bleeding in patients with CKD, such as an abnormal expression of platelets glycoproteins, altered release of adenosine phosphate from platelet alpha-granules and the action of uremic toxins.[10] The most striking finding of our analysis was that the reduction of MI recurrences with prasugrel and ticagrelor

in CKD subjects was not related to an increase of MB. This result is consistent with previously reported data.[21,22,26] The risk of overdosing due to impaired renal clearance is averted from available pharmacokinetic data. Ticagrelor pharmacokinetics indeed depends on renal function,[28] whereas a study by Small *et al.* observed that the levels of the active metabolites of prasugrel were not affected by moderate renal impairment.[29] It could be argued that the two-fold increase of the risk of BARC-MB in patients treated with clopidogrel as compared to ticagrelor has never been reported in RCTs and suggests a selection bias caused by physicians choosing clopidogrel for patients with a high-perceived bleeding risk possibly related to unmeasured confounding factors (i.e. frailty). In accordance, multivariable adjustment for recognized predictors of bleeding did not confirm such unadjusted data. The here presented results further validate the BleeMACS bleeding risk score in a larger population.[13]

Limitations

The results of the present work should be interpreted in the context of several potential limitations. The main one is that BleeMACS and RENAMI were retrospective registries, thus carrying all the limitations of this type of studies. Therefore, although our results mostly agree with previously published data, they should be considered as hypothesis-generating and prompt further definitive trials on this matter. Specific sub-analysis and risk stratification according to angiographic (index lesion and its complexity) and interventional features were not performed and were beyond the scope of this research. Unknown and unmeasured known confounders (access to care, therapy adherence, concomitant use of drugs like non-steroid anti-inflammatory drugs) could have affected the analysis, but this limitation is shared by all previous studies on this matter. **Data about need for dialysis were not systematically collected and then not available. However, the subgroup of patients with severely impaired renal function (eGFR < 15 mL/min/1.73m2) likely to receive an indication for**

chronic dialysis was limited to 86 patients, thus any further analysis would have been anyway scarcely informative. Peri-PCI MI could not be investigated due to change in MI definitions throughout recent years and the retrospective nature of the study. Moreover, data about DAPT duration was not available for the BLEEMACS registry and consequently a sensitivity analysis for DAPT duration could not be performed. Despite in both registries DAPT duration was prescribed according current European guidelines and all the safety and efficacy outcomes reported in this study regarded patients being still on DAPT, we acknowledge a possible impact of this missing information on the presented results. 1758 (70.6%) CKD patients were taking clopidogrel, while only 192 (7.7%) received prasugrel; albeit this might be due to physicians' fear of administering potent P2Y12 inhibitors in CKD patients, as previously discussed, the numerical disproportion between these two populations may have affected the study results. Proportional hazard assumptions were not violated (Supplementary Tables S6-S8). Lastly, the eGFR cut-off value of 60ml/min/1.73m^2 to identify patients with renal dysfunction is somewhat arbitrary.[30] However, as already discussed, it was adopted by most of the prior studies exploring this subject.[7,23] Its selection was mainly driven by the idea to have comparable results with already existing literary data.

Conclusion

Patients with renal dysfunction who experience ACS are often undertreated and are at increased risk of recurrent ischemic and bleeding events due to frequent comorbidities**.** In the present research, prasugrel and ticagrelor confirmed their efficacy in reducing MI recurrences and all-cause mortality rate in patients with ACS and impaired renal function undergoing PCI. Both potent P2Y12 inhibitors proved to be safe in this set of patients, as they did not increase

the risk of BARC-MB events on a long-term follow-up. Despite the limitations inherent to its retrospective design, our analysis endorses previous existing data and further extends their validity to a real-life setting, as it was conducted in a large cohort of unselected patients with high rates of relevant prognostic features such as diabetes, dyslipidemia, prior PCI and STEMI diagnosis on admission.

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543 **TABLES**

Table 1. Baseline and interventional features of the study population according to renal function.

	Overall population (n=19255)	**eGFR > 60 ml/min/1.73 m^2 (n=16765)**	**eGFR < 60 ml/min/1.73 m^2 (n=2490)**	**p-value**
Baseline features				
Age	63±12	62±12	73±11	**<0.0001**
Female gender n (%)	4363 (22.7)	3295 (19.6)	1068 (42.8)	**<0.0001**
Diabetes Mellitus n (%)	4920 (25.6)	3875 (23.1)	1045 (42)	**<0.0001**
HTA n (%)	11086 (57.6)	9218 (55)	1868 (75)	**<0.0001**
Dyslipidemia n (%)	10106 (52.8)	8811 (52.1)	1295 (52.4)	0.66
LVEF	53±11	53±10	50±12	**<0.0001**
Hemoglobin	14±1.6	14±1.6	13±1.9	**<0.0001**
Malignancy	1102 (5.7)	845 (5)	257 (10.3)	**<0.0001**
Prior AMI n (%)	2498 (13)	1990 (11.9)	508 (20.4)	**<0.0001**
Prior PCI n (%)	2615 (13.7)	2129 (12.8)	486 (19.7)	**<0.0001**
Prior CABG n (%)	526 (2.7)	406 (2.4)	120 (4.8)	**<0.0001**
Prior stroke n (%)	1116 (5.8)	841 (5)	275 (11)	**<0.0001**
Prior bleeding n (%)	873 (4.6)	702 (4.2)	171 (6.9)	**<0.0001**
Kidney function				
eGFR	90±39	97±37	45±12	**<0.0001**

eGFR 45-60 n (%)			**1498 (60.1)**	
eGFR 30-45 n (%)			**676 (27.1)**	
eGFR 15-30 n (%)			**230 (9.2)**	
eGFR < 15 n (%)			**86 (3.5)**	
ACS n (%)				
STEMI	11216 (58.2)	9941 (59.3)	1275 (51.2)	**<0.0001**
NSTEMI/UA	8039 (41.8)	6824 (40.7)	1215 (48.8)	**<0.0001**
Therapy				
Beta-blockers	13552 (81.9)	12084 (82.9)	1468 (74.8)	**<0.0001**
ACE-I	12582 (76.1)	11188 (76.8)	1394 (71)	**<0.0001**
Statin	15937 (93.7)	14110 (94.2)	1827 (90)	**<0.0001**
OAC therapy	827 (4.2)	641 (3.8)	186 (7.5)	**<0.0001**
DAPT regimen				
Clopidogrel	13561 (70.4)	11803 (70.4)	1758 (70.6)	0.83
Ticagrelor	3349 (17.4)	2809 (16.8)	540 (21.7)	**<0.0001**
Prasugrel	2347 (12.2)	2155 (12.9)	192 (7.7)	**<0.0001**
Interventional features				
Thrombolysis n (%)	294 (1.5)	268 (1.6)	26 (1)	**0.03**
Stent DES n (%)	8772 (45.6)	7620 (45.5)	1152 (46.3)	0.45
Multivessel n (%)	7290 (47.5)	6148 (46.2)	1142 (55.5)	**<0.0001**
Complete revascularization n (%)				

	9531 (64.6)	8398 (65.5)	1133 (58.7)	**<0.0001**
Vascular access n (%)				
Radial	9016 (50.2)	7944 (50.6)	1072 (47.3)	**0.03**
Femoral	8942 (49.8)	7749 (49.4)	1193 (52.7)	0.45

Table 1. Characteristics of the study population according to renal function. HTA: arterial hypertension; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate calculated by the MDRD (Modification of Diet in Renal Disease) equation; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; ACS: acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; UA: unstable angina; ACE-I: angiotensin converting enzyme-inhibitors; OAC: oral anticoagulant therapy; DAPT: dual antiplatelet therapy; DES: drug eluting stents.

Table 2. Baseline and interventional features of patients with impaired renal function.

eGFR < 60 ml/min/1.73 m^2 (n=2490)	**Clopidogrel (n=1758)**	**Ticagrelor (n=540)**	**Prasugrel (n=192)**	**p-value**
Baseline features				
Age	74±11	69±11	67±10	**C vs T<0.0001** **T vs P=0.01** **C vs P<0.0001**

Female gender n (%)	736 (41.9)	258 (47.8)	74 (38.5)	**C vs T=0.01** **T vs P=0.03** C vs P=0.37
Diabetes Mellitus n (%)	660 (37.5)	288 (53.3)	97 (50.5)	**C vs T<0.0001** T vs P=0.5 **C vs P<0.0001**
HTA n (%)	1372 (78)	359 (66.5)	137 (71.4)	**C vs T<0.0001** T vs P=0.21 **C vs P=0.03**
Dyslipidemia n (%)	883 (50.7)	302 (56.5)	110 (57.3)	**C vs T=0.02** T vs P=0.81 C vs P=0.08
LVEF	51±13	48±11	49±11	**C vs T<0.0001** T vs P=0.34 C vs P=0.14
eGFR	45±13	45±12	47±11	C vs T=0.5 T vs P=0.13 **C vs P=0.04**
Hemoglobin	12.7±2	13.5±1.3	13.3±1.8	**C vs T<0.0001** T vs P=0.13 **C vs P<0.0001**
Malignancy	203 (11.5)	42 (7.8)	12 (6.3)	**C vs T=0.01** T vs P=0.49 **C vs P=0.03**
Prior AMI n (%)	307 (17.5)	158 (29.3)	43 (22.4)	**C vs T<0.0001** T vs P=0.07

				C vs P=0.09
Prior PCI n (%)	266 (15.3)	172 (32)	48 (25)	**C vs T<0.0001** T vs P=0.07 **C vs P=0.001**
Prior CABG n (%)	114 (6.5)	5 (0.9)	1 (0.5)	**C vs T<0.0001** T vs P=0.59 **C vs P=0.001**
Prior stroke n (%)	202 (11.5)	68 (12.6)	5 (2.6)	C vs T=0.5 **T vs P<0.0001** **C vs P<0.0001**
Prior bleeding n (%)	136 (7.8)	28 (5.2)	7 (3.6)	**C vs T=0.04** T vs P=0.39 **C vs P=0.04**
ACS n (%)				
STEMI	898 (51.1)	267 (49.9)	110 (57.3)	p=NS
NSTEMI/UA	860 (48.9)	273 (50.6)	82 (42.7)	
Therapy				
Beta blockers	1271 (73)	98 (89)	99(89)	**C vs T<0.0001** T vs P=0.98 **C vs P<0.0001**
ACE-I	1207 (69.3)	90 (81.8)	97 (87.4)	**C vs T=0.006** T vs P=0.25 **C vs P<0.0001**
Statin	1547 (88.8)	144 (98.6)	136 (95.8)	**C vs T<0.0001** T vs P=0.14

				C vs P=0.01
OAC	165 (9.4)	17 (3.1)	4 (2.1)	**C vs T<0.0001** T vs P=0.45 **C vs P=0.001**
Interventional features				
Thrombolysis n (%)	19 (1.1)	5 (0.9)	2 (1)	p=NS
Stent DES n (%)	665 (37.8)	381 (70.6)	106 (55.2)	**C vs T<0.0001** **T vs P<0.0001** **C vs P<0.0001**
Multivessel n (%)	784 (58.8)	261 (48.3)	97 (52.7)	**C vs T<0.0001** T vs P=0.3 C vs P=0.12
Complete revascularization n (%)	734 (51)	294 (87.8)	105 (67.3)	**C vs T<0.0001** **T vs P<0.0001** **C vs P<0.0001**
Vascular access n (%)				
Radial	596 (38.7)	369 (68.3)	107 (58.2)	**C vs T<0.0001** **T vs P=0.01** **C vs P<0.0001**
Femoral	945 (61.3)	171 (31.7)	77 (41.8)	

Table 2. Characteristics of patients with impaired renal function according to their respective DAPT regimen. C: clopidogrel; T: ticagrelor; P: prasugrel. Other abbreviations as in Table 1.

FIGURE LEGENDS

Figure 1: Long-term outcomes in patients with impaired renal function (eGFR<60 ml/min/1.73 m^2) based on dual anti-platelet regimen. AMI: acute myocardial infarction; eGFR: estimated glomerular filtration rate; BARC: Bleeding Academic Research Consortium; NS: not significant.

The statistical significance of each comparison is as follows:

Death: clopidogrel vs ticagrelor p<0.0001; prasugrel vs ticagrelor p=0.5; clopidogrel vs prasugrel p=0.04

Re-AMI: clopidogrel vs ticagrelor p=0.04; prasugrel vs ticagrelor p=0.33; clopidogrel vs prasugrel p=0.009

BARC MB: clopidogrel vs ticagrelor p=0.01; prasugrel vs ticagrelor p=0.11; clopidogrel vs prasugrel p=0.4

Figure 2: Survival estimates according to Kaplan-Meier analysis in patients with impaired renal function (eGFR ≤ 60mL/min/1.73 m^2).

Figure 3: Independent predictors of mortality in patients with impaired renal function (above, panel A) and in patients with preserved renal function (below, Panel B). Hazard ratios are reported next to each row, as well as the number of events and the number of subjects examined. AMI: acute myocardial infarction; CAD: coronary artery disease; DM: diabetes mellitus; STEMI: ST-elevation myocardial infarction; CI: confidence interval.

Figure 4: Independent predictors of reinfarction in patients with impaired renal function (above, Panel A) and preserved renal function (below, Panel B). Hazard ratios are reported next to each row, as well as the number of events and the number of subjects examined. MI: myocardial infarction; other abbreviations as in Figure 3.

Figure 5: Long-term outcomes according to renal function and dual anti-platelet regimen. Abbreviations as in Figure 1.

Figure 6: Independent predictors of BARC major bleedings (BARC-MBs) in patients with reduced renal function (above, Panel A) and preserved renal function (below, Panel B). Hazard ratios are reported next to each row, as well as the number of events and the number of subjects examined. PAD: peripheral artery disease; other abbreviations as in Figure 3.