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ORIGINAL ARTICLE
Acute coronary syndromes

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

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Aims The 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 (REgistry of New Antiplatelets in patients with Myocardial Infarction) and BLEEMACS (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) registries were stratified according to estimated glomerular filtration rate (eGFR) lower or greater than 60 mL/min/1.73 m^2. Death and myocardial infarction (MI) were the primary efficacy endpoints. Major bleedings (MBs), defined as Bleeding Academic Research Consortium bleeding types 3 to 5, constituted the safety endpoint. A total of 19 255 patients were enrolled. Mean age was 63 ± 12; 14 892 (77.3%) were males. A total of 2490 (12.9%) patients had chronic kidney disease (CKD), defined as eGFR <60 mL/min/1.73 m^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 multivariable analysis, potent P2Y12 inhibitors significantly reduced the mortality rate [hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.54–0.96; $P = 0.006$] and the risk of reinfarction (HR 0.53, 95% CI 0.30–0.95; $P = 0.033$) in CKD patients as compared to clopidogrel. The reduction of risk of reinfarction was confirmed in patients with preserved renal function. Potent P2Y12 inhibitors did not increase the risk of MB in CKD patients (HR 1.00, 95% CI 0.59–1.68; $P = 0.985$).

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.

Keywords 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 dual 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 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 35–40% 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 ischaemic 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, multicentre projects designed to compare ticagrelor and prasugrel in ACS patients and to develop a bleeding risk prediction tool in this scenario.[13,14]

The aim of the present study 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 multicentre, 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 15 401 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 multicentre 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 centre 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 ethics committee of each participating centre.

Variables

Clinical and interventional data were recorded, including burden of cardiovascular risk factors, clinical presentation, comorbidities, arterial

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

	Overall population ($n = 19\,255$)	eGFR >60 mL/min/1.73 m^2 ($n = 16\,765$)	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* (%)	11 086 (57.6)	9218 (55)	1868 (75)	**<0.0001**
Dyslipidaemia, *n* (%)	10 106 (52.8)	8811 (52.1)	1295 (52.4)	0.66
LVEF	53 ± 11	53 ± 10	50 ± 12	**<0.0001**
Haemoglobin	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, *n* (%)	90 ± 39	97 ± 37	45 ± 12	**<0.0001**
45–60		—	1498 (60.1)	
30–45		—	676 (27.1)	
15–30		—	230 (9.2)	
<15		—	86 (3.5)	
ACS, *n* (%)				
STEMI	11 216 (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	13 552 (81.9)	12 084 (82.9)	1468 (74.8)	**<0.0001**
ACE-I	12 582 (76.1)	11 188 (76.8)	1394 (71)	**<0.0001**
Statin	15 937 (93.7)	14 110 (94.2)	1827 (90)	**<0.0001**
OAC therapy	827 (4.2)	641 (3.8)	186 (7.5)	**<0.0001**
DAPT regimen				
Clopidogrel	13 561 (70.4)	11 803 (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

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

access, kind of CAD and treatment. Data collection and analysis was supervised by a trained study coordinator in each centre. Renal function was assessed by calculating the estimated glomerular filtration rate (eGFR) using the four-variable Modification of Diet in Renal Disease (MDRD) study equation.[15,16]

Cohorts of interest

Patients were classified into two categories based on eGFR greater or lesser than 60 mL/min/1.73 m^2. Chronic kidney disease was defined as eGFR <60 mL/min/1.73 m^2. Patients were then stratified according to the P2Y12 antagonist administration at discharge. Patients without DAPT,

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**
Dyslipidaemia, *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**
Haemoglobin	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, *n* (%)				
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**

Continued

Table 2 *Continued*

eGFR < 60 mL/min/1.73 m^2 (*n* = 2490)	Clopidogrel (*n* = 1758)	Ticagrelor (*n* = 540)	Prasugrel (*n* = 192)	*P*-value
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**
Femoral	945 (61.3)	171 (31.7)	77 (41.8)	**T vs. *P* = 0.01** **C vs. *P* < 0.0001**

Statistically significant values are in bold.
ACE-I, angiotensin converting enzyme-inhibitors; ACS, acute coronary syndrome; AMI, acute myocardial infarction; C, clopidogrel; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; DES, drug eluting stents; eGFR, estimated glomerular filtration rate calculated by the MDRD (Modification of Diet in Renal Disease) equation; HTA, arterial hypertension; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; OAC, oral anticoagulant therapy; P, prasugrel; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; T, ticagrelor; UA, unstable angina.

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 European Society of Cardiology (ESC) current universal definition of MI,[17] excluding peri-procedural MI, in CKD patients were the primary efficacy endpoint; major bleedings (MBs), 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 centre.

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, and 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 (HR) 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 analysed with a stratified log-rank test. Two-tailed *P*-value <0.05 was considered statistically significant.

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

Results

Out of 19 825 patients (4244 from RENAMI and 15 401 from BLEEMACS), 19 255 patients with complete baseline data and with at least one follow-up contact were considered for this analysis. Five hundred and seventy 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/1.73 m^2. A total of 2490 (12.9%) patients had baseline eGFR <60 mL/min/1.73 m^2; among CKD patients, 2174 (87.3%) had eGFR 30–60 mL/min/1.73 m^2, 230 (9.2%) had eGFR 15–30 mL/min/1.73 m^2, and 86 (3.5%) had eGFR

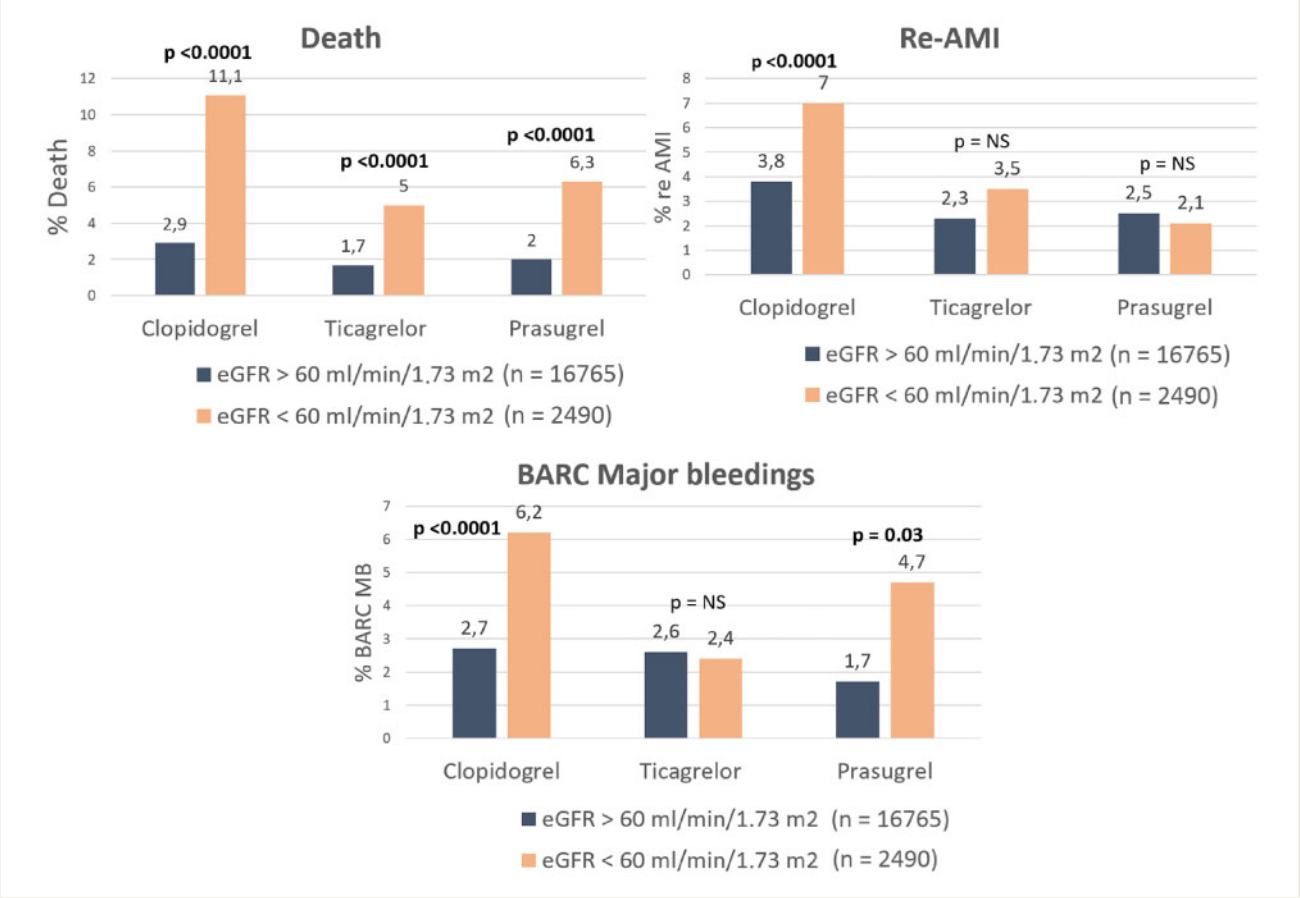

Figure 1 Long-term outcomes according to renal function and dual anti-platelet regimen. AMI, acute myocardial infarction; BARC, Bleeding Academic Research Consortium; eGFR, estimated glomerular filtration rate; NS, not significant.

<15 mL/min/1.73 m^2. Amongst CKD patients, 1758 (70.6%) were taking clopidogrel, 540 (21.7%) were on ticagrelor, and 192 (7.7%) received prasugrel. Chronic kidney disease 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

Figure 1 shows overall incidences of all-cause death, reinfarction, and BARC-MB rates divided according to renal function and antiplatelet regimen. 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 potent P2Y12 inhibitors (11% vs. 5.3%, $P < 0.0001$) as well as a higher incidence of reinfarction (7% vs. 3.1%, $P < 0.0001$) (*Figure 2*). Similar results were recorded by comparing individually the two potent P2Y12 inhibitors with clopidogrel (death 11.1% vs. 6.3%, $P = 0.04$, 11.1% vs. 5%, $P < 0.0001$ for clopidogrel vs. prasugrel and ticagrelor, respectively; reinfarction 7% vs. 2.1%, $P = 0.009$; 7% vs. 3.5%, $P = 0.04$, for clopidogrel vs. prasugrel and ticagrelor, respectively) (Supplementary material online, *Figure S1*). The Kaplan–Meier analysis also showed an overall survival benefit in patients with CKD on prasugrel or ticagrelor compared to patients on clopidogrel ($P < 0.00001$ at log-rank test) as shown in *Figure 3*. Multivariable adjustments for significant predictors of all-cause death (malignancy, multivessel CAD, complete revascularization, STEMI, diabetes mellitus, and left ventricular ejection fraction < 40%) highlighted an independent protective role of potent P2Y12 inhibitors in CKD patients either by merging ticagrelor and prasugrel as a unique category vs. clopidogrel [HR 0.82, 95% confidence interval (CI) 0.54–0.96; $P = 0.006$] (*Figure 4A*) or when comparing individually ticagrelor vs. clopidogrel (HR 0.45, 95%CI 0.21–0.99; $P = 0.047$) and prasugrel vs. clopidogrel (HR 0.34, 95% CI 0.13–0.88; $P = 0.026$) (*Figure 4B*). Significant predictors of outcome used in the multivariate model for reinfarction included complete revascularization, multivessel CAD, STEMI, prior MI, diabetes mellitus, and female sex. In patients with impaired renal function DAPT with potent P2Y12 inhibitors was an independent protective factor against reinfarction occurrence (HR 0.53, 95% CI 0.30–0.95;

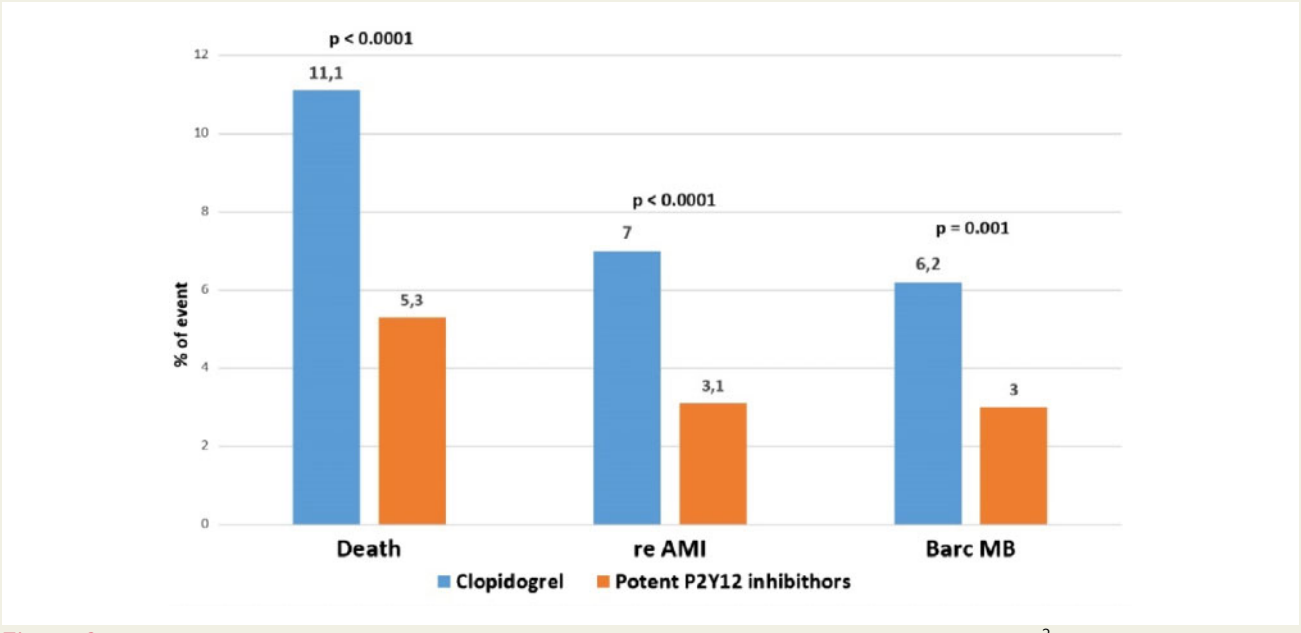

Figure 2 Outcomes in patients with impaired renal function (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) according to dual antiplatelet regimen (clopidogrel vs. potent P2Y12 inhibitors ticagrelor or prasugrel). AMI, acute myocardial infarction; BARC, Bleeding Academic Research Consortium.

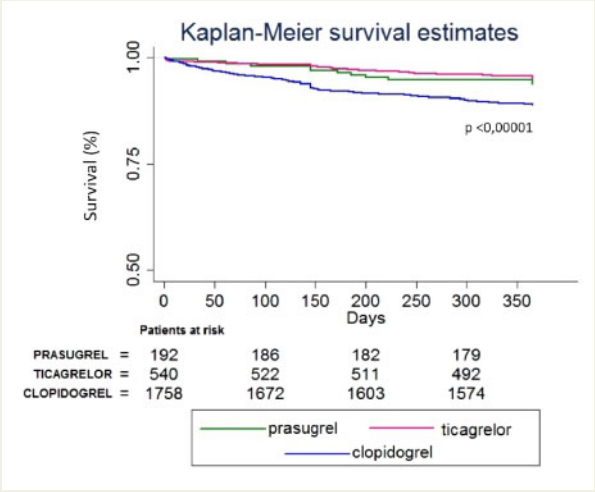

Figure 3 Survival estimates according to Kaplan–Meier analysis in patients with impaired renal function (estimated glomerular filtration rate ≤ 60 mL/min/1.73 m^2).

$P = 0.033$) (*Figure 5A*), this result being confirmed when comparing the two drugs individually against clopidogrel (HR 0.36, 95% CI 0.16–0.81; $P = 0.014$ for ticagrelor vs. clopidogrel and HR 0.07, 95% CI 0.01–0.54; $P = 0.01$ for prasugrel vs. clopidogrel) (*Figure 5B*).

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 (3% vs. 6.2%, $P = 0.001$) (*Figure 2*), 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%, $P = 0.4$) (Supplementary material online, *Figure S1*). The significant variables being considered for multivariable analysis for the safety endpoint were malignancy, prior stroke, peripheral artery disease, prior bleeding, STEMI, diabetes mellitus, and female sex. After multivariable adjustments, DAPT with either ticagrelor or prasugrel did not result in an increased risk of BARC-MB at follow-up in CKD patients (HR 1.00, 95% CI 0.59–1.68; $P = 0.985$) (*Figure 6A*). Similar results were obtained when comparing individual potent P2Y12 inhibitors vs. clopidogrel (HR 0.87, 95% CI 0.45–1.66; $P = 0.67$ for ticagrelor; HR 0.88, 95% CI 0.41–1.9; $P = 0.75$ for prasugrel) (*Figure 6B*).

Proportional hazard assumptions for all Cox multivariable analysis were tested and results are reported as Supplementary material online, *Tables S1–S3*.

Patients on oral anticoagulant therapy

A total of 186 CKD patients were on triple antithrombotic therapy with acetylsalicylic acid, warfarin, and either clopidogrel (165 patients) or ticagrelor (17 patients) or prasugrel (4 patients). Since the prevalence of concomitant anticoagulation therapy was higher among CKD patients treated with clopidogrel (9.4%) compared with ticagrelor (3.1%) and prasugrel (2.1%) we performed a sensitivity analysis relative to bleeding events excluding all patients on oral anticoagulant therapy (OAC); the overall bleeding risk in CKD patients was not affected by the exclusion of patients on OAC from the analysis (clopidogrel vs. potent P2Y12 inhibitors: HR 0.92, 95% CI 0.54–1.57; $P = 0.754$) (Supplementary material online, *Figure S2*).

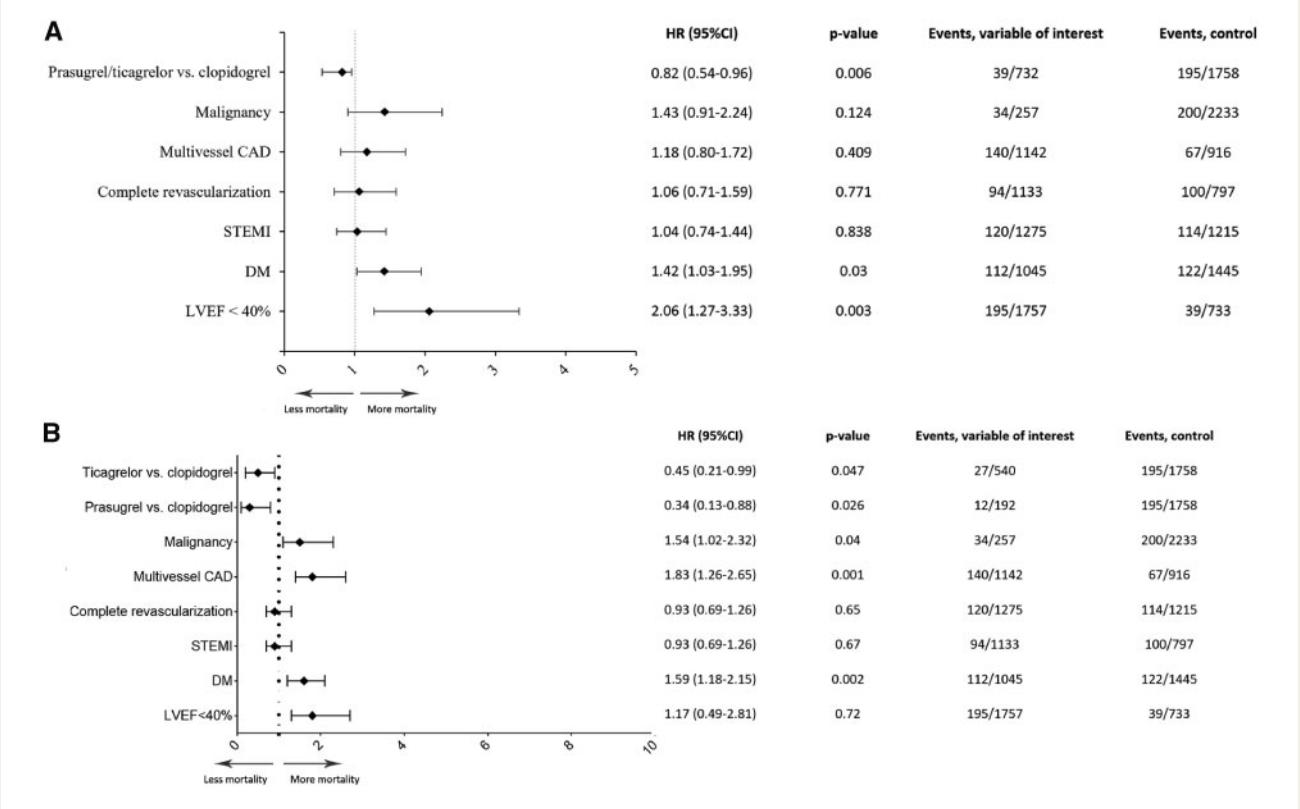

Figure 4 Independent predictors of mortality in patients with impaired renal function either by comparing prasugrel and ticagrelor combined vs. clopidogrel (above, *A*) or by considering each individual potent P2Y12 inhibitor vs. clopidogrel (below, *B*). Hazard ratios are reported next to each row, as well as the number of events and the number of subjects examined. CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; STEMI, ST-elevation myocardial infarction.

Moreover, the addition of OAC therapy as a covariate in the multivariable analyses did not affect the primary efficacy and safety endpoints (Supplementary material online, *Figures S3–S5*).

Supplementary data

Comparison of outcomes between patients with preserved renal function and patients with CKD are reported in the Supplementary material online, *Appendix*. In brief, patients with preserved renal function had overall better outcomes compared to patients with reduced eGFR, such as significantly lower incidence of all-cause mortality (2.6% vs. 9.4%, $P < 0.0001$), reinfarction (2.9% vs. 5.8%, $P < 0.0001$), and of MB (3% vs. 5.7%, respectively, $P < 0.0001$). A survival benefit of potent P2Y12 at Kaplan–Meier analysis was also evident for patients with preserved renal function (Supplementary material online, *Figure S6*), but this result was not confirmed after multivariable adjustments [HRs for mortality: 0.77 for ticagrelor vs. clopidogrel (95% CI 0.49–1.22, $P = 0.27$) and 0.81 for prasugrel vs. clopidogrel (95% CI 0.51–1.29, $P = 0.38$] (Supplementary material online, *Figure S7*). Both ticagrelor and prasugrel confirmed their independent protective role against MI recurrence as compared to clopidogrel in patients with eGFR >60 mL/min/1.73 m^2 (HR 0.48, 95% CI 0.35–0.65; $P < 0.0001$ and HR 0.38, 95% CI 0.27–0.55; $P < 0.0001$ for ticagrelor or prasugrel vs. clopidogrel, respectively) (Supplementary material online, *Figure S8*). Regarding the risk of bleeding, in patients with preserved renal function, ticagrelor was 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 0.60, 95% CI 0.46–0.88; $P = 0.01$) when compared with clopidogrel (Supplementary material online, *Figure S9*).

As a sensitivity analysis to support the reliability of the main results a propensity score analysis was performed; among patients with eGFR <60 mL/min/1.73 m^2 two propensity-matched cohorts 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 material online, *Tables S4* and *S5*. Outcomes in the propensity-matched cohorts were consistent with the ones of the main analysis (Supplementary material online, *Figure S10*). Further sub-analyses regarding outcomes in patients with eGFR <45 mL/min/1.73 m^2 and <30 mL/min/1.73 m^2 are reported in the Supplementary material online, *Figures S11* and *S12*.

Discussion

This multicentre, retrospective, observational study was conducted to explore the safety and efficacy of prasugrel and ticagrelor in CKD

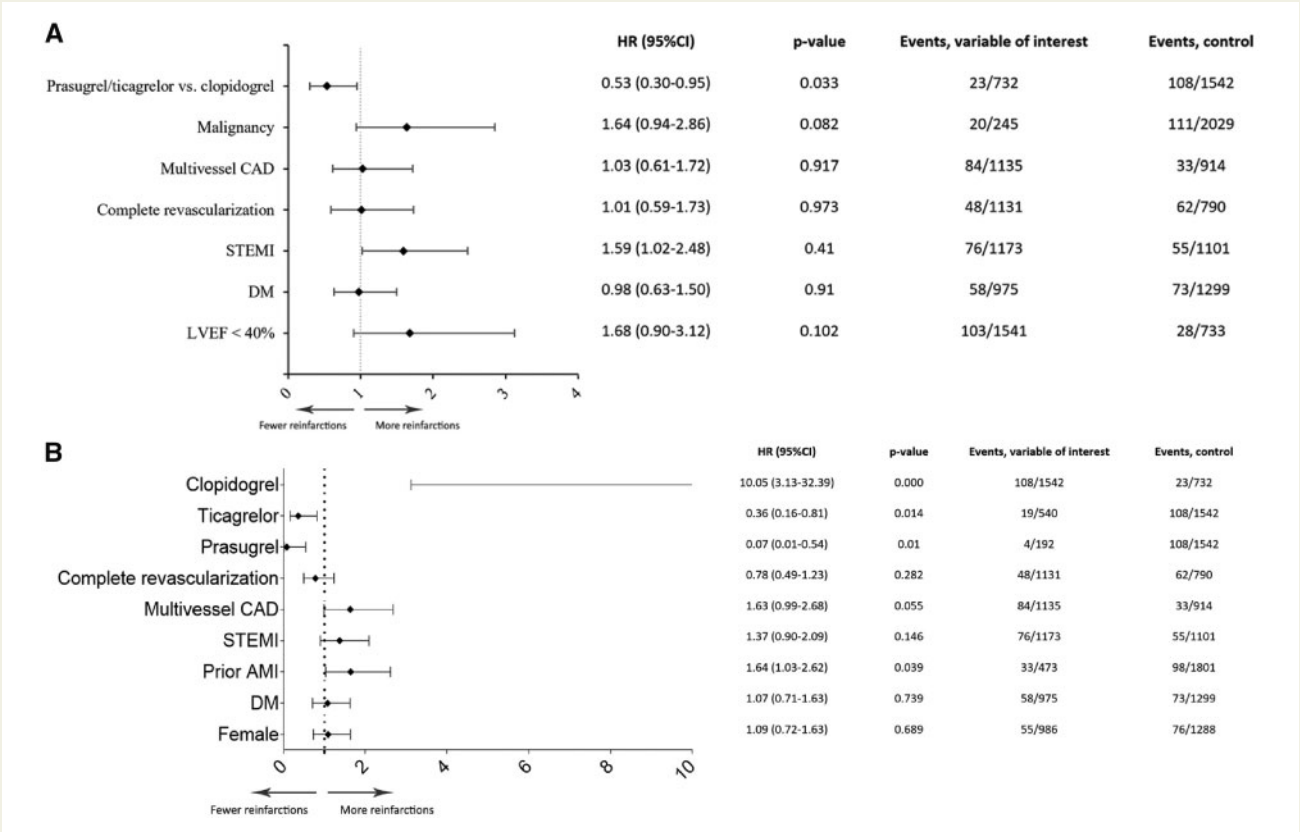

Figure 5 Independent predictors of reinfarction in patients with impaired renal function either by comparing prasugrel and ticagrelor combined vs. clopidogrel (above, *A*) or by considering each individual potent P2Y12 inhibitor vs. clopidogrel (below, *B*). Hazard ratios are reported next to each row, as well as the number of events and the number of subjects examined. AMI, acute myocardial infarction; CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; STEMI, ST-elevation myocardial infarction.

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 when 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 >60 mL/min/1.73 m^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 two RCTs and two prospective registries.[6,7,21,22] Patients with CKD and several comorbidities are often excluded from RCTs, which enroll highly selected populations.[12] Despite some observational registries previously approached the issue of administering DAPT in CKD patients, they 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-world cohort of unselected patients with CKD suffering from invasively managed ACS, aims to minimize these gaps in evidence.

Overall, the proportion of patients with eGFR <60 mL/min/1.73 m^2 in our cohort is low compared to that of the PLATO study (13% vs. 21%, respectively). In a PLATO sub-analysis by James *et al.*[23,24] 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. This fact could account for the lower proportion of CKD patients in our population. Chronic kidney disease patients developing ACS in our study were older and had more comorbidities, such as anaemia, 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 under-use of recommended therapies.[26] Our data highlight this latter phenomenon by documenting lower prevalence of optimal medical therapy administration and significant lower use of oral anticoagulants and prasugrel among CKD patients, thus suggesting that clinical decisions are often driven in the real-world setting by the perceived risk of bleeding harm. 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 < 60 mL/min), showing that ticagrelor

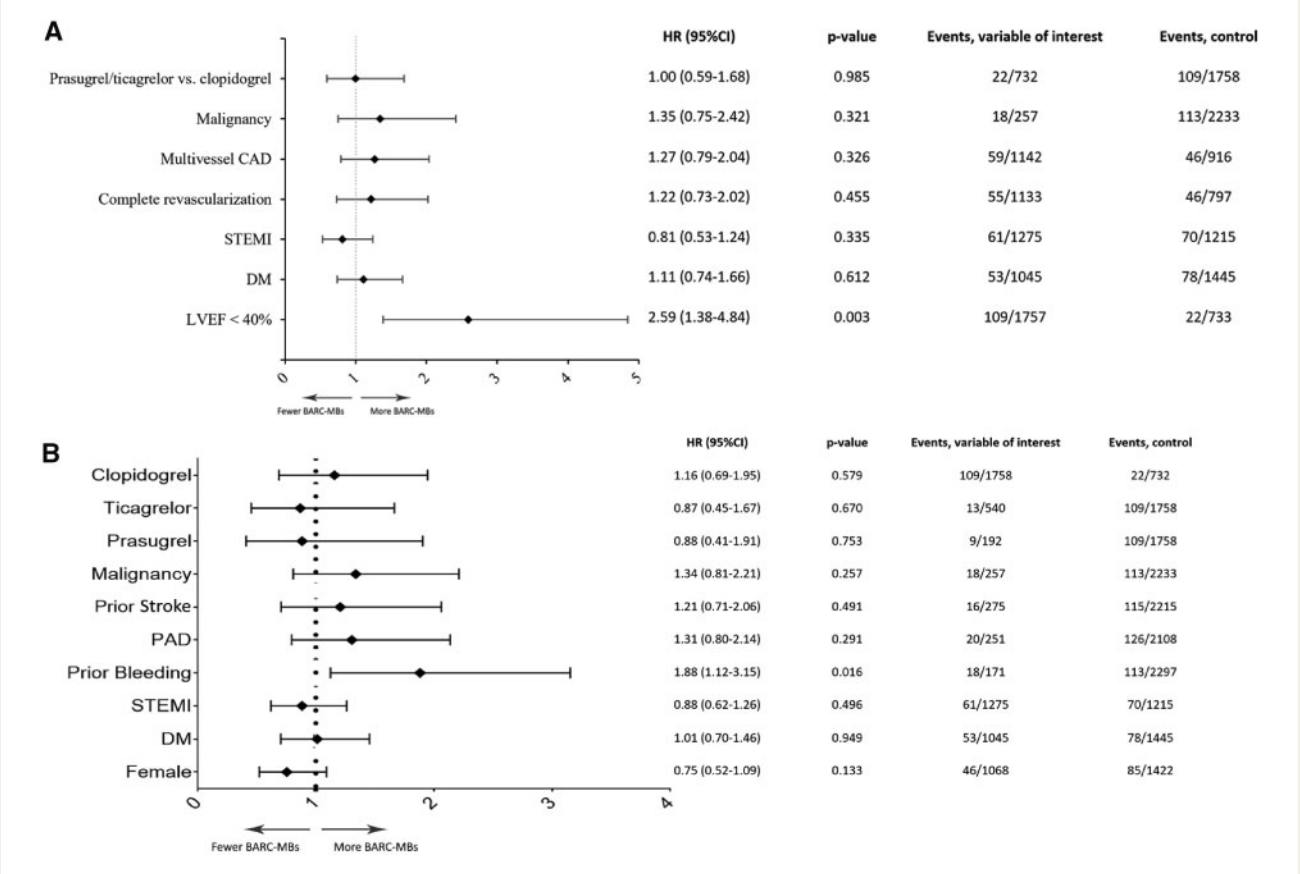

Figure 6 Independent predictors of BARC major bleedings (BARC-MBs) in patients with reduced renal function either by comparing prasugrel and ticagrelor combined vs. clopidogrel (above, *A*) or by considering each individual potent P2Y12 inhibitor vs. clopidogrel (below, *B*). Hazard ratios are reported next to each row, as well as the number of events and the number of subjects examined. CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; STEMI, ST-elevation myocardial infarction.

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/1.73 m^2, showed that the benefit of prasugrel over clopidogrel in this sub-population was similar to that of the overall population.[7] On the other hand, the PROMETHEUS observational study conducted by Baber *et al.*,[21] reported only a trend towards lower incidence of MI recurrences in CKD patients treated with prasugrel compared to clopidogrel at 1-year follow-up (6.3% vs. 8.1%, $P = 0.054$). We found a substantially lower incidence of reinfarction in CKD patients treated with prasugrel in the present study as compared to that reported by Baber *et al.*[21] These 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 agreement 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 favourable subgroup to demonstrate a benefit on hard but rare endpoints like mortality.[27]

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 uraemic 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 associated with 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 minimally depends on renal function,[28] whereas a study by Small *et al.*[29] observed that the levels of the active metabolites of prasugrel were not affected by moderate renal impairment. It is likely that the two-fold increase of the risk of BARC-MB in patients treated with clopidogrel as compared to ticagrelor, which

has never been reported in RCTs, 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 agreement with this hypothesis, multivariable adjustment for recognized predictors of bleeding did not confirm the unadjusted data. The present 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-analyses 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. However, the subgroup of patients with severely impaired renal function (eGFR < 15 mL/min/1.73 m^2) likely to receive an indication for chronic dialysis was limited to 86 patients, thus any further analysis would have been 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 results. Among CKD patients only 192 (7.7%) received prasugrel, thus limiting the strength of the analysis relative to this agent. Lastly, the eGFR cut-off value of 60 mL/min/1.73 m^2 to identify patients with renal dysfunction is somewhat arbitrary.[30] However, as already discussed, it was deliberately chosen since it was adopted by most of the prior studies exploring this subject.[7,23]

Conclusion

Patients with renal dysfunction who experience ACS are often undertreated and are at increased risk of recurrent ischaemic and bleeding events due to frequent comorbidities. Compared with clopidogrel, prasugrel, and ticagrelor were found to reduce MI recurrences and all-cause mortality in patients with ACS and impaired renal function undergoing PCI. Both agents were found to be safe in this set of patients, not increasing the risk of BARC-MB events on a long-term follow-up. Despite the limitations inherent to its retrospective design, our analysis, conducted in a large cohort of unselected patients with high rates of relevant prognostic features such as diabetes, dyslipidaemia, prior PCI, and index STEMI, endorses previous data and further extends their validity to a real-life setting.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

Conflict of interest: none declared.

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