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

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56 **ABSTRACT**

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

59 **Methods and results.** **All consecutive patients from** RENAMI and BLEEMACS registries
60 were stratified according to estimated glomerular filtration rate (eGFR) lower or greater than
61 60mL/min/1.73m². Death and myocardial infarction (MI) were the primary efficacy
62 endpoints. Major bleedings (**MB**), defined as Bleeding Academic Research Consortium
63 bleeding types 3 to 5, constituted the safety endpoint.

64 19255 patients were enrolled. **Mean age was 63 ± 12; 14892 (77.3%) were males.** 2490
65 (12.9%) patients had chronic kidney disease (CKD), defined as eGFR<60mL/min/1.73m².
66 Mean follow-up was 13±5 months. Mortality was significantly higher in CKD patients (9.4%
67 vs 2.6%, p<0.0001), as well as the incidence of reinfarction (5.8% vs 2.9%, p<0.0001) and
68 MB (5.7% vs 3%, p<0.0001). At Cox multivariate analysis both prasugrel (HR=0.34,
69 p=0.026) and ticagrelor significantly reduced the mortality rate (HR=0.45, p=0.047) in CKD
70 patients as compared to clopidogrel. Prasugrel and ticagrelor compared to clopidogrel were
71 associated with decreased risk of reinfarction both in CKD patients (HR=0.07, p=0.01;
72 HR=0.36, p=0.01, respectively) and in those with preserved renal function (HR 0.38,
73 p<0.0001; HR 0.48, p<0.0001, respectively). Potent P2Y12 inhibitors did not increase the
74 risk of MB in CKD patients, the hazard ratios being 0.87 for ticagrelor (p=0.67) and 0.88 for
75 prasugrel (p=0.75).

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

78

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

81 **INTRODUCTION**

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

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

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

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

108

109 **METHODS**

110 **Study population.**

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

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

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

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

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

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

130

131 **Variables.**

132 Clinical and interventional data were recorded, including burden of cardiovascular risk
133 factors, clinical presentation, comorbidities, arterial access, kind of CAD and treatment. Data
134 collection and analysis was supervised by a trained study coordinator in each center. Renal
135 function was assessed by calculating the estimated glomerular filtration rate (eGFR) using the
136 4-variable Modification of Diet in Renal Disease (MDRD) study equation.[15,16]

137

138 **Cohorts of interest.**

139 Patients were classified into 2 categories based on eGFR greater or lesser than 60
140 ml/min/1.73m². CKD was defined as eGFR < 60 ml/min/1.73m². Patients were then stratified
141 according to the P2Y12 antagonist administration at discharge. Patients without DAPT,
142 crossovers between groups and patients whose baseline data necessary for eGFR calculation
143 were unavailable were excluded from the present analysis.

144

145 **Endpoints and follow-up.**

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

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

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

156 **Statistical analysis.**

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

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

173

174 **RESULTS**

175 **Out of 19825 patients (4244 from RENAMI and 15401 from BLEEMACS), 19255**
176 **patients with complete baseline data and with at least one follow-up contact were**
177 **considered for this analysis. 570 patients were excluded because baseline serum**
178 **creatinine value was not available and therefore eGFR could not be estimated.** Mean
179 eGFR was 90 ± 39 ml/min/1.73m². 2490 (12.9%) patients had baseline eGFR < 60
180 ml/min/1.73m²; **among CKD patients, 2174 (87.3%) had eGFR 30-60 ml/min/1.73m², 230**
181 **(9.2%) had eGFR 15-30 ml/min/1.73m² and 86 (3.5%) had eGFR < 15 ml/min/1.73m².**
182 **Amongst CKD patients, 1758 (70.6%) were taking clopidogrel, 540 (21.7%) were on**
183 **ticagrelor and 192 (7.7%) received prasugrel.** CKD patients were significantly older and
184 had higher prevalence of all major cardiovascular risk factors and high-risk features for MI
185 recurrence and bleeding complications. Moreover, CKD patients had lower rate of complete
186 revascularization and optimal medical therapy administration compared to patients with
187 preserved renal function. Clinical and interventional features of the study population are
188 shown in Table 1.

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

193

194 **Efficacy endpoints**

195 After a mean follow-up of 13 ± 5 months (**median 12 months**), significantly higher unadjusted
196 death-rate was observed in CKD patients treated with clopidogrel as compared to those on
197 prasugrel (11% vs 6.3%, p=0.04) or ticagrelor (11% vs 5%, p<0.0001) and a similar trend
198 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/1.73m² 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

224 clopidogrel with regard to re-MI was confirmed in those with preserved renal function (HR
225 3.3, 95%CI 2.4-4.4, $p<0.0001$) (**Figure 4, panel B**).

226 Overall, patients with CKD presented worse outcomes compared to patients with preserved
227 renal function, such as significantly higher incidence of all-cause mortality (9.4% vs 2.6%,
228 $p<0.0001$) and re-infarction (5.8% vs 2.9%, $p<0.0001$). Higher mortality rates were observed
229 in all subgroups of CKD patients, regardless of their DAPT regimen; re-infarction incidence
230 on clopidogrel was significantly higher in patients with CKD than in those with preserved
231 kidney function (3.8% vs 7%, $p<0.0001$), but this difference was not observed in patients on
232 potent P2Y12 inhibitors. **Figure 5** shows all-cause death, reinfarction and BARC-MB rates
233 divided according to renal function and anti-platelet regimen.

234

235 **Safety endpoint**

236 The overall rate of MB in patients with impaired renal function was 5.7%. At univariate
237 analysis, DAPT with potent P2Y12 inhibitors was associated with lower rates of MB, the
238 difference being statistically significant between clopidogrel and ticagrelor (6.2% vs. 2.4%,
239 $p=0.01$) but not between clopidogrel and prasugrel (6.2% vs. 4.7%, $p=0.4$) (**Figure 1**). **The**
240 **significant variables being considered for multivariate analysis for the safety endpoint**
241 **were malignancy, prior stroke, peripheral artery disease, prior bleeding, STEMI,**
242 **diabetes mellitus and female sex.** After multivariate adjustments, DAPT with either
243 ticagrelor or prasugrel did not result in an increased risk of BARC-MB at follow-up in CKD
244 patients, the hazard ratios being 0.87 for ticagrelor (95%CI 0.45-1.66, $p=0.67$) and 0.88 for
245 prasugrel (95%CI 0.41-1.9, $p=0.75$) (**Figure 6, panel A**). In patients with preserved renal
246 function, ticagrelor was instead associated with a moderate but significant higher risk of
247 BARC-MB (HR 1.43, 95%CI 1.09- 1.89, $p=0.009$), whereas treatment with prasugrel resulted

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

251

252 **Patients with preserved renal function**

253 Patients with eGFR > 60 mL/min/1.73m² had an overall lower rate of MB compared to
254 patients with impaired renal function (3% vs 5.7% respectively, p<0.0001). As shown in
255 **Figure 5**, these difference was mainly driven by higher rates of MB in CKD patients on
256 prasugrel or clopidogrel (6.2% vs 2.7%, p<0.0001; 4.7% vs 1.7%, p=0.03, respectively),
257 whereas similar rates of the safety outcome were recorded among CKD and non-CKD
258 patients on ticagrelor (2.4% vs 2.6%, p= NS).

259

260 **Supplementary data**

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

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

275

276 **DISCUSSION**

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

296 **Overall, the proportion of patients with eGFR<60ml/min/1.73m² in our cohort is low**
297 **compared to that of the PLATO study (13% vs 21% respectively). In a PLATO**
298 **subanalysis by James *et al.* CKD was defined as serum creatinine clearance < 60 ml/min**
299 **as calculated by the Cockcroft-Gault formula, which is known to underestimate eGFR**
300 **in older patients.[23-24] We think that the smaller number of CKD patients in our study**
301 **might be due to the fact that the Cockcroft-Gault formula might have underestimated**
302 **eGFR in the PLATO sub-analysis (median age 74 in CKD patients vs 60 in patients with**
303 **creatinine clearance > 60 ml/min), thus resulting in an increased proportion of CKD**
304 **patients in that population as compared to ours.**

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

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

321 SWEDHEART registry by Edfors *et al.*[22] As for prasugrel, the subgroup analysis of the
322 TRITON-TIMI38 trial, including 1490 patients with eGFR<60 mL/min/1.73m², showed that
323 the benefit of prasugrel over clopidogrel in this sub-population was similar to that of the
324 overall population.[7] This finding was not confirmed by the results of the PROMETHEUS
325 observational study conducted by Baber *et al.*, who reported a non-significantly different
326 albeit lower incidence of MI recurrences in CKD patients treated with prasugrel compared to
327 clopidogrel at 1-year follow-up (6.3% vs. 8.1%, p=0.054).[21] Our results are in line with the
328 TRITON-TIMI38 sub-analysis while disagreeing with those of the PROMETHEUS study.
329 Moreover, the incidence of reinfarction in CKD patients treated with prasugrel in the present
330 study was substantially lower compared to that reported by Baber *et al.*[25] These
331 controversial results might be due to differences existing between the baseline features of the
332 study populations, the limited sample size of both observational studies, the diverse
333 geographic reference area and the different equation used to calculate eGFR (CKD-EPI
334 formula was applied by Baber *et al.*). However, it must be acknowledged that, to date, the
335 PROMETHEUS registry represents the largest report of CKD patients treated with prasugrel.

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

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

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

358 **Limitations**

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

371 **chronic dialysis was limited to 86 patients, thus any further analysis would have been**
372 **anyway scarcely informative. Peri-PCI MI could not be investigated due to change in MI**
373 **definitions throughout recent years and the retrospective nature of the study. Moreover,**
374 **data about DAPT duration was not available for the BLEEMACS registry and**
375 **consequently a sensitivity analysis for DAPT duration could not be performed. Despite**
376 **in both registries DAPT duration was prescribed according current European guidelines**
377 **and all the safety and efficacy outcomes reported in this study regarded patients being**
378 **still on DAPT, we acknowledge a possible impact of this missing information on the**
379 **presented results. 1758 (70.6%) CKD patients were taking clopidogrel, while only 192**
380 **(7.7%) received prasugrel; albeit this might be due to physicians' fear of administering**
381 **potent P2Y12 inhibitors in CKD patients, as previously discussed, the numerical**
382 **disproportion between these two populations may have affected the study results.**
383 **Proportional hazard assumptions were not violated (Supplementary Tables S6-S8).**
384 Lastly, the eGFR cut-off value of 60ml/min/1.73m² to identify patients with renal dysfunction
385 is somewhat arbitrary.[30] However, as already discussed, it was adopted by most of the prior
386 studies exploring this subject.[7,23] Its selection was mainly driven by the idea to have
387 comparable results with already existing literary data.

388

389 **Conclusion**

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

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

400

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404

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406

407

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Table 1. Baseline and interventional features of the study population according to renal function.				
	Overall population (n=19255)	eGFR > 60 ml/min/1.73 m² (n=16765)	eGFR < 60 ml/min/1.73 m² (n=2490)	p-value
<i>Baseline features</i>				
<i>Age</i>	63±12	62±12	73±11	<0.0001
<i>Female gender n (%)</i>	4363 (22.7)	3295 (19.6)	1068 (42.8)	<0.0001
<i>Diabetes Mellitus n (%)</i>	4920 (25.6)	3875 (23.1)	1045 (42)	<0.0001
<i>HTA n (%)</i>	11086 (57.6)	9218 (55)	1868 (75)	<0.0001
<i>Dyslipidemia n (%)</i>	10106 (52.8)	8811 (52.1)	1295 (52.4)	0.66
<i>LVEF</i>	53±11	53±10	50±12	<0.0001
<i>Hemoglobin</i>	14±1.6	14±1.6	13±1.9	<0.0001
<i>Malignancy</i>	1102 (5.7)	845 (5)	257 (10.3)	<0.0001
<i>Prior AMI n (%)</i>	2498 (13)	1990 (11.9)	508 (20.4)	<0.0001
<i>Prior PCI n (%)</i>	2615 (13.7)	2129 (12.8)	486 (19.7)	<0.0001
<i>Prior CABG n (%)</i>	526 (2.7)	406 (2.4)	120 (4.8)	<0.0001
<i>Prior stroke n (%)</i>	1116 (5.8)	841 (5)	275 (11)	<0.0001
<i>Prior bleeding n (%)</i>	873 (4.6)	702 (4.2)	171 (6.9)	<0.0001
<i>Kidney function</i>				
<i>eGFR</i>	90±39	97±37	45±12	<0.0001

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

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

544

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

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554

555

Table 2. Baseline and interventional features of patients with impaired renal function.				
eGFR < 60 ml/min/1.73 m² (n=2490)	Clopidogrel (n=1758)	Ticagrelor (n=540)	Prasugrel (n=192)	p-value
<i>Baseline features</i>				
<i>Age</i>	74±11	69±11	67±10	C vs T<0.0001 T vs P=0.01 C vs P<0.0001

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

				C vs P=0.09
<i>Prior PCI n (%)</i>	266 (15.3)	172 (32)	48 (25)	C vs T<0.0001 T vs P=0.07 C vs P=0.001
<i>Prior CABG n (%)</i>	114 (6.5)	5 (0.9)	1 (0.5)	C vs T<0.0001 T vs P=0.59 C vs P=0.001
<i>Prior stroke n (%)</i>	202 (11.5)	68 (12.6)	5 (2.6)	C vs T=0.5 T vs P<0.0001 C vs P<0.0001
<i>Prior bleeding n (%)</i>	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 (%)				
<i>STEMI</i>	898 (51.1)	267 (49.9)	110 (57.3)	p=NS
<i>NSTEMI/UA</i>	860 (48.9)	273 (50.6)	82 (42.7)	
Therapy				
<i>Beta blockers</i>	1271 (73)	98 (89)	99(89)	C vs T<0.0001 T vs P=0.98 C vs P<0.0001
<i>ACE-I</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
<i>Statin</i>	1547 (88.8)	144 (98.6)	136 (95.8)	C vs T<0.0001 T vs P=0.14

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

556

557 **Table 2.** Characteristics of patients with impaired renal function according to their respective

558 DAPT regimen. C: clopidogrel; T: ticagrelor; P: prasugrel. Other abbreviations as in Table 1.

559

560 **FIGURE LEGENDS**

561 **Figure 1:** Long-term outcomes in patients with impaired renal function (eGFR<60 ml/min/1.73 m²)
562 based on dual anti-platelet regimen. AMI: acute myocardial infarction; eGFR: estimated glomerular
563 filtration rate; BARC: Bleeding Academic Research Consortium; NS: not significant.

564 The statistical significance of each comparison is as follows:

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

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

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

571

572 **Figure 2: Survival estimates according to Kaplan-Meier analysis in patients with impaired renal**
573 **function (eGFR ≤ 60mL/min/1.73 m²).**

574

575 **Figure 3: Independent predictors of mortality in patients with impaired renal function (above,**
576 **panel A) and in patients with preserved renal function (below, Panel B). Hazard ratios are**
577 **reported next to each row, as well as the number of events and the number of subjects examined.**

578 **AMI: acute myocardial infarction; CAD: coronary artery disease; DM: diabetes mellitus;**
579 **STEMI: ST-elevation myocardial infarction; CI: confidence interval.**

580

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

585

586

587 **Figure 5:** Long-term outcomes according to renal function and dual anti-platelet regimen.

588 Abbreviations as in Figure 1.

589

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

594