



Impact of renal function on clinical outcomes after PCI in ACS and stable CAD patients treated with ticagrelor: a prespecified analysis of the GLOBAL LEADERS randomized clinical trial

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Abstract

Background Impaired renal function (IRF) is associated with increased risks of both ischemic and bleeding events. Ticagrelor has been shown to provide greater absolute reduction in ischemic risk following acute coronary syndrome (ACS) in those with versus without IRF.

Methods A pre-specified sub-analysis of the randomized GLOBAL LEADERS trial ($n = 15,991$) comparing the experimental strategy of 23-month ticagrelor monotherapy (after 1-month ticagrelor and aspirin dual anti-platelet therapy [DAPT]) with 12-month DAPT followed by 12-month aspirin after percutaneous coronary intervention (PCI) in ACS and stable coronary artery disease (CAD) patients stratified according to IRF (glomerular filtration rate < 60 ml/min/1.73 m²).

Results At 2 years, patients with IRF ($n = 2171$) had a higher rate of the primary endpoint (all-cause mortality or centrally adjudicated, new Q-wave myocardial infarction [MI]) (hazard ratio [HR] 1.64, 95% confidence interval [CI] 1.35–1.98, $p_{\text{adj}} = 0.001$), all-cause death, site-reported MI, all revascularization and BARC 3 or 5 type bleeding, compared with patients without IRF. Among patients with IRF, there were similar rates of the primary endpoint (HR 0.82, 95% CI 0.61–1.11, $p = 0.192$, $p_{\text{int}} = 0.680$) and BARC 3 or 5 type bleeding (HR 1.10, 95% CI 0.71–1.71, $p = 0.656$, $p_{\text{int}} = 0.506$) in the experimental versus the reference group. No significant interactions were seen between IRF and treatment effect for any of the secondary outcome variables. Among ACS patients with IRF, there were no between-group differences in the rates of the primary endpoint or BARC 3 or 5 type bleeding; however, the rates of the patient-oriented composite endpoint (POCE) of all-cause death, any stroke, MI, or revascularization ($p_{\text{int}} = 0.028$) and net adverse clinical events (POCE and BARC 3 or 5 type bleeding) ($p_{\text{int}} = 0.045$), were lower in the experimental versus the reference group. No treatment effects were found in stable CAD patients categorized according to presence of IRF.

Conclusions IRF negatively impacted long-term prognosis after PCI. There were no differential treatment effects found with regard to all-cause death or new Q-wave MI after PCI in patients with IRF treated with ticagrelor monotherapy.

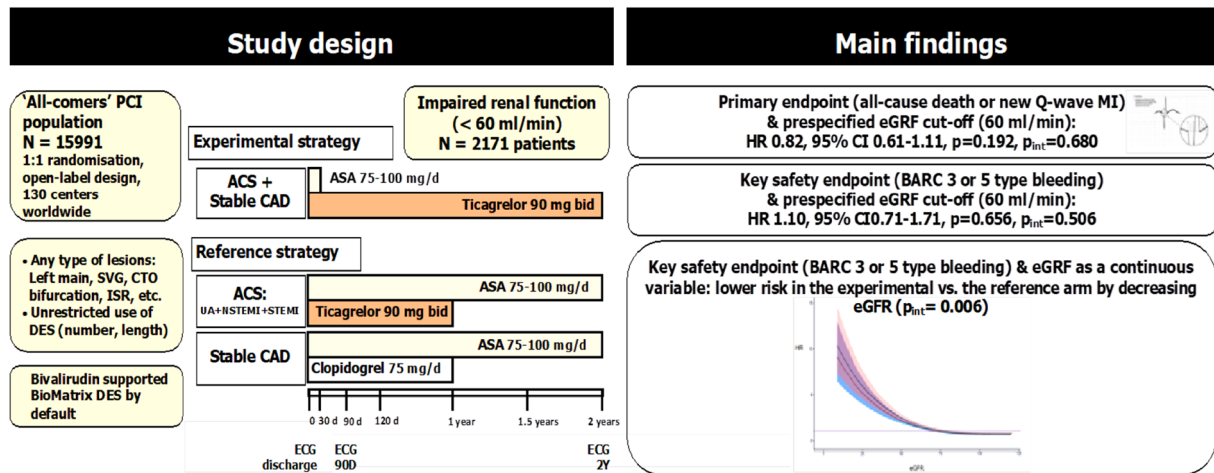
Clinical trial registration The trial has been registered with ClinicalTrials.gov, number NCT01813435.

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Graphic abstract



Keywords Impaired renal function · Percutaneous coronary intervention · DAPT · Ticagrelor · Chronic kidney disease · Aspirin-free antiplatelet strategies

Background

Impaired renal function (IRF) is an independent predictor of ischemic and bleeding events [1–6]. Despite registries suggesting a progressive increase in the number of patients with IRF, these patients still tend to be under represented or excluded from clinical trials, and undertreated in real life [1, 2]. Antiplatelet treatment in patients with IRF is, therefore, complex because IRF can effect thrombocyte function and coagulation [7], and this is further complicated by the change in drug pharmacokinetics in chronic kidney disease [2, 7, 8]. In the PLATO study, the combination of ticagrelor with aspirin substantially reduced cardiovascular death, myocardial infarction (MI), or stroke compared with clopidogrel plus aspirin in patients with acute coronary syndrome (ACS), with a consistent relative risk reduction in patients with and without IRF and a greater absolute risk reduction for patients with IRF [9]. This benefit was not associated with a significant increase in major bleeding; however, numerically more non-procedure-related bleeding events were observed among patients with IRF [9].

In an attempt to mitigate bleeding risk whilst preserving ischemic efficacy, aspirin-free antiplatelet regimens utilizing more potent P2Y₁₂ antagonists have been advocated [10]. The first and largest trial to date evaluating this concept—GLOBAL LEADERS—failed to show superiority of ticagrelor monotherapy starting one month post percutaneous coronary intervention (PCI), compared to standard dual antiplatelet therapy (DAPT) followed by aspirin

monotherapy in an all comer patient population [11]. Nevertheless, understanding the impact of IRF on long-term outcomes after PCI in this large all-comer contemporary trial is of clinical interest.

Given this background, we report the results of this pre-specified analysis according to an estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73 m² and the five major categories of renal impairment, defined by the Kidney Disease: Improving Global Outcomes (KDIGO) classification [12]. In addition, as the randomization in this trial was stratified according to clinical presentation (ACS vs. stable coronary artery disease [CAD]), we assessed the experimental treatment effects in relation to baseline renal function specifically in ACS and stable CAD patients.

Methods and patients

This is a pre-specified subgroup analysis of the GLOBAL LEADERS trial (NCT01813435). GLOBAL LEADERS was an investigator-initiated, randomized, multi-center, open-label trial designed to evaluate two strategies of antiplatelet therapy after PCI using uniformly bivalirudin and biolimus A9-eluting stents (Biomatrix) in an all-comers population [13, 14]. In the experimental treatment strategy, patients received aspirin 75–100 mg once daily in combination with ticagrelor 90 mg twice daily for one month; followed by ticagrelor 90 mg twice daily alone for 23 months (irrespective of the clinical presentation). In the reference treatment strategy, patients received aspirin 75–100 mg daily in combination

with either clopidogrel 75 mg once daily in patients with stable CAD or ticagrelor 90 mg twice daily in patients with ACS for 1 year; followed by aspirin 75–100 mg once daily alone for the following 12 months (from 12 to 24 months after PCI).

The trial was approved by the institutional review board at each participating institution. All patients provided informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practices. An independent data and safety monitoring committee oversaw the safety of all patients.

In the present analyses, patients were stratified according to an eGFR cut-off of 60 ml/min/1.73 m², calculated according to the MDRD equation [15], as pre-specified in the trial protocol. In addition, exploratory analyses were performed stratifying the overall population, and specifically the ACS and stable CAD subgroups, according to the KDIGO classification with chronic kidney disease stage I, II, III, IV, and V defined as respective eGFRs of ≥ 90 , 60–89, 44–59, 15–29 and < 15 ml/min/1.73 m² [12].

Patients were followed up at 30 days and 3, 6, 12, 18, and 24 months after the index procedure. Electrocardiogram (ECG) was obtained at discharge, 3-month and 2-year follow-up and during the follow-up if there was suspected ischemic event or repeat revascularization. All ECGs were analyzed at the core laboratory (Cardialysis, Rotterdam, Netherlands) by technicians who were blinded to the treatment assignments.

Study endpoints

The primary endpoint of the present study was the composite of all-cause mortality and new Q-wave myocardial infarction (MI) within 2 years after the index procedure. The survival status of the patients lost to follow-up or those who withdrew their consent was obtained via public civil registries in all but eight patients; complete vital status at 2 years was available in 99.95% [11]. Minnesota classification was used to define the new Q-wave MI which was centrally adjudicated by an independent ECG core lab [16]. The key secondary safety endpoint was investigator-reported bleeding academic research consortium (BARC) type 3 or 5 [17]. Further secondary endpoints included the following: individual components of the primary endpoint (all-cause death, new Q-wave MI), individual components of key secondary safety endpoint (BARC defined bleeding type 3 and type 5) any stroke, site-reported MI, any revascularization, target vessel revascularization (TVR), definite stent thrombosis (ST) and the composite of the definite or probable ST, defined according to the Academic Research Consortium criteria [18].

Finally, the patient-oriented composite endpoint (POCE)—advocated by academic research consortium

(ARC)-2, and net adverse clinical events (NACE) were analyzed up to 2 years [17, 19, 20]. The POCE was defined as the composite of all-cause death, any stroke, site-reported MI (including periprocedural or spontaneous with ST elevation MI [STEMI] or non-ST-segment elevation MI [NSTEMI]) and any revascularization (re-PCI or coronary artery bypass graft surgery [CABG] in the target or non-target vessel) [19], whereas NACE combined POCE and BARC 3 or 5 type bleeding [21, 22].

The trial was monitored for event under-reporting and event definition consistency. There were seven on-site monitoring visits performed at individual sites, with 20% of reported events checked against source documents. There was no independent adjudication of clinical events [11, 13].

Statistical analysis

All the analyses were performed on the intention-to-treat population. Continuous variables are expressed as mean \pm standard deviation and were compared using independent t test. Categorical variables are presented as counts and percentage and were compared using Chi square test. Kaplan–Meier method was used to estimate the cumulative rates of events and Log-rank test was performed to examine the differences between groups. The effect of IRF on the outcomes was assessed in the univariable and multivariable Cox proportional hazards model. The covariates in the multivariable model included age, gender, diabetes, presentation of ACS, diabetes mellitus, hypertension, hypercholesterolemia, history of stroke, MI, PCI, peripheral vascular disease, COPD and previous major bleeding and current smoking. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from the model and interaction test was performed to evaluate the differences in the treatment effect of antiplatelet strategy in IRF and non-IRF patients. A schematic summary of the performed analyses in the overall cohort and specifically among stable CAD and ACS patients is presented in Table 1. No procedures were prespecified for multiple testing for subgroup analyses of the trial and, therefore, all presented findings should be considered as exploratory. Analyses were performed in SPSS 25. A two-sided p value less than 0.05 was considered as statistical significance.

Results

Study population

The GLOBAL LEADERS trial recruited and randomly assigned 15,991 participants; as 23 patients subsequently withdrew consent and requested deletion of their data from the database, a total of 15,968 patients remained in the study

[11]; of these, 15,883 patients (99.5%) had a baseline serum creatinine level available.

There were 2171 patients with IRF identified using MDRD-derived eGFR threshold of 60 ml/min/1.73 m² in this study (Suppl. Figure 1). Patients with IRF were older, were more often female, diabetic, hypertensive or hypercholesterolemic, more often had a history of prior stroke, prior PCI or CABG, prior MI, COPD, or peripheral vascular disease or a history of previous major bleeding and were less frequently smoking. Patients with IRF presented more often with stable CAD (Table 2). Patients with IRF had more often left main coronary artery treated and had a larger number of stents implanted. Direct stenting and aspiration thrombectomy were performed less often in patients with IRF, compared with patients without IRF (Table 3).

The baseline clinical characteristics were balanced between the experimental and the reference arm for both IRF and non-IRF subgroups, except for a higher proportion of hypertensive patients in the IRF subgroup receiving the experimental strategy, and lower proportion of patients with peripheral vascular disease among non-IRF patients in the experimental arm (Suppl. Table 1).

Patients with IRF had a consistently lower treatment adherence at each follow-up visit (Suppl. Table 2). At 1 year, among IRF patients 769 out of 1013 (75.9%) versus 828 out of 969 (85.4%) adhered to the experimental and reference strategy, respectively. Among non-IRF patients, these proportions were 5372 out of 6684 (82.7%) versus 5863 out of 6527 (89.8%), respectively. At 2 years, 718 out of 999 (71.9%) versus 859 out of 949 (90.5%) patients with IRF, and 5062 out of 6445 (78.5%) versus 6092 out of 6513 (93.5%) non-IRF patients adhered to the experimental and reference strategies, respectively (Suppl. Table 3).

Table 2 Baseline clinical characteristics

	Non-IRF (<i>n</i> =13,712)		IRF (<i>n</i> =2171)		<i>p</i> value
	<i>N</i>	(%)	<i>N</i>	(%)	
Age > 75 years	1726	12.6	827	38.1	0.001
Sex (female)	2873	21.0	823	37.9	0.001
Acute coronary syndrome	6495	47.4	967	44.5	0.014
UA	1730	26.6	288	29.8	0.005
NSTEMI	2908	44.8	449	46.4	
STEMI	1857	28.6	230	23.8	
Diabetes mellitus	3189	23.3	838	38.6	0.001
Insulin-treated diabetes mellitus	869	6.4	352	16.2	0.001
Hypertension	9774	71.5	1889	87.1	0.001
Hypercholesterolemia	9197	69.2	1513	72.1	0.008
Previous stroke more than 30 days ago	329	2.4	92	4.2	0.001
Previous MI	3081	22.5	613	28.3	0.001
Previous PCI	4358	31.8	843	38.8	0.001
Previous CABG	743	5.4	198	9.1	0.001
Peripheral vascular disease	753	5.5	247	11.5	0.001
COPD	664	4.9	155	7.2	0.001
Previous major bleeding or predisposition to bleeding	77	0.6	21	1.0	0.025
Current smoker	3825	27.9	318	14.6	0.001

IRF—impaired renal function, *CABG*—coronary artery bypass grafting, *CAD*—coronary artery disease, *COPD*—chronic obstructive pulmonary disease, *MI*—myocardial infarction, *NSTEMI*—non-ST segment elevation myocardial infarction, *PCI*—percutaneous coronary intervention, *SD*—standard deviation, *STEMI*—ST-segment elevation myocardial infarction, *UA*—unstable angina

Table 1 Schematic summary of clinical outcome analyses performed in the overall cohort and in the subgroups according to clinical presentation

Overall population	
Analyses according to prespecified eGFR cut-off of 60 ml/min Figure 1, Tables 4 and 5, Suppl. Table 4	
Analyses according to KDIGO-defined eGFR subgroups (5 major categories) Suppl. Figure 2	
Analyses with eGFR treated as a continuous variable Fig. 2	
Stable coronary artery disease	Acute coronary syndrome
Analyses according to prespecified eGFR cut-off of 60 ml/min Fig. 3	Analyses according to prespecified eGFR cut-off of 60 ml/min Fig. 3
Analyses according to KDIGO-defined eGFR subgroups (5 major categories) Suppl. Table 5	Analyses according to KDIGO-defined eGFR subgroups (5 major categories) Suppl. Table 5

eGFR estimated glomerular filtration rate

Clinical outcomes in relation to renal function

Patients with IRF had a significantly higher rate of the primary endpoint (HR 1.64, 95% CI 1.35–1.98, p adjusted = 0.001), all-cause death (HR 1.82, 95% CI 1.46–2.26, p adjusted = 0.001), MI (HR 1.55, 95% CI 1.22–1.96, p adjusted = 0.001), all revascularization (HR 1.19, 95% CI 1.02–1.37, p adjusted = 0.023), TVR (HR 1.22, 95% CI 1.01–1.49, p adjusted = 0.044), BARC type 3 bleeding (HR 1.45, 95% CI 1.09–1.92, p adjusted = 0.012), BARC type 3 or 5 bleeding (HR 1.40, 95% CI 1.07–1.85, p = 0.016), and BARC type 2,3,5 bleeding (HR 1.22, 95% CI 1.03–1.44, p adjusted = 0.019) (Table 4).

Clinical outcomes in relation to renal function and randomized treatment strategy

At 2 years, among patients with IRF, the primary endpoint occurred in 79 patients (7.2%) in the experimental arm and in 93 patients (8.7%) in the reference group (HR 0.82, 95% CI 0.61–1.11, p = 0.192, p_{int} = 0.680). Among patients with IRF there were no significant between-group differences in the rates of all-cause death (HR 0.76; 95% CI 0.55–1.06; p = 0.105), POCE (HR 0.86, 95% CI 0.71–1.04, p = 0.128), NACE (HR 0.89, 95% CI 0.74–1.07, p = 0.228) and BARC type 3 or 5 type (HR 1.10, 95% CI 0.71–1.71, p = 0.656) (Table 5). No significant interactions were found between IRF and treatment effect for any of the outcome variables at 1- and 2-year follow-up (Fig. 1, Suppl. Figure 2, Suppl. Table 4). However, when treating eGFR as a continuous variable, there was a differential treatment effect with

Table 3 Angiographic and procedural characteristics in patients categorized according to baseline function using a prespecified eGFR cut-off of 60 ml/min (n = 15,883)

	Non-IRF (n = 13,712)	IRF (n = 2171)	p value
Patient level			
Index PCI attempted	13,639	2160	0.878
Lesion treated at index PCI			0.474
One lesion	10,148 (74.7)	1588 (73.7)	
Two lesions	2719 (20.0)	456 (21.2)	
Three or more lesions	712 (5.2)	111 (5.2)	
Lesion level [‡]			
Number of lesion treated	17,884	2854	
Vessel treated			0.001
Left main coronary artery	308 (1.7)	78 (2.7)	
Left anterior descending artery	7510 (42.0)	1115 (39.1)	
Left circumflex artery	4350 (24.3)	703 (24.6)	
Right coronary artery	5548 (31.0)	906 (31.7)	
Bypass graft	168 (0.9)	52 (1.8)	
Number of stent per lesion, mean \pm SD	1.19 \pm 0.53	1.22 \pm 0.58	0.019
Mean stent length, mean \pm SD	24.76 \pm 13.79	25.15 \pm 15.07	0.193
Mean stent diameter, mean \pm SD	2.99 \pm 0.47	2.97 \pm 0.46	0.101
Direct stenting	5826 (33.1)	819 (29.2)	0.001
Bifurcation PCI	2176 (12.2)	330 (11.6)	0.357
Aspiration thrombectomy	936 (5.2)	95 (3.3)	0.001
TIMI pre			0.001
0 or 1	2315 (13.7)	290 (10.6)	
2	1983 (11.7)	367 (13.5)	
3	12,616 (74.6)	2068 (75.9)	
TIMI post			0.771
0 or 1	65 (0.4)	8 (0.3)	
2	83 (0.5)	13 (0.5)	
3	17,187 (99.1)	2765 (99.2)	

Data shown are n (%), unless otherwise indicated

SD standard deviation

[‡]Calculated per lesion and analyzed with general or generalized linear mixed-effects models with a random effect for patients to account for multiple lesions treated within patient

regard to rates of BARC 3 type ($p_{\text{int}}=0.019$) and BARC 3 or 5 type bleeding ($p_{\text{int}}=0.006$), being less frequently observed in the experimental than in the reference arm by decreasing eGFR (Fig. 2).

Clinical outcomes in relation to extent of renal dysfunction and randomized treatment strategy

The experimental treatment strategy was associated with a lower rates of the primary endpoint, all-cause mortality, any revascularizations, TVR, POCE and NACE versus the reference treatment, with progressively decreasing point estimates of the HR with decreasing cut-off values of eGFR from 90 to 15 ml/min; however, no significant interactions were found between KDIGO defined eGFR categories and treatment effect for any of the outcome variables (Suppl. Figure 2).

Clinical outcomes in ACS and stable CAD patients with impaired renal function

Among ACS patients, individuals with impaired renal function had similar rates of the primary endpoint (HR 0.71; 95% CI 0.47–1.06; $p=0.094$, $p_{\text{int}}=0.305$) and BARC 3 or 5 type bleeding (HR 0.68; 95% CI 0.36–1.27; $p=0.227$; $p_{\text{int}}=0.841$) in both treatment groups, but there was a lower rate of POCE (HR 0.71, 95% CI 0.53–0.93, $p=0.014$, $p_{\text{int}}=0.028$) and NACE (0.71, 95% CI 0.54–0.92, $p=0.010$, $p_{\text{int}}=0.045$) in the experimental arm (Fig. 3). No treatment effects were seen in stable CAD patients categorized according to presence of IRF (Fig. 3). The results of KDIGO-stratified analysis of clinical outcomes in the experimental versus the reference group in the overall population and specifically for stable CAD and ACS patients are presented in the Suppl. Figure 2 and Suppl. Table 5.

Table 4 Two year clinical outcomes in relation to baseline renal function impairment using a prespecified cut-off of 60 ml/min according to the MDRD equation ($n=15,883$)

	Non-IRF ($n=13,712$)		IRF ($n=2171$)		Unadjusted HR 95% CI	p value	Adjusted HR 95% CI	p value
	N	(%)	N	(%)				
Primary endpoint	479	3.5	172	7.9	2.32 (1.95–2.76)	0.001	1.64 (1.35–1.98)	0.001
All-cause death	334	2.4	141	6.5	2.73 (2.24–3.32)	0.001	1.82 (1.46–2.26)	0.001
New Q-wave MI	154	1.1	32	1.5	1.34 (0.92–1.96)	0.130	1.05 (0.70–1.59)	0.801
BARC 3 or 5	250	1.8	81	3.7	2.10 (1.64–2.70)	0.001	1.40 (1.07–1.85)	0.016
BARC 3	232	1.7	76	3.5	2.13 (1.64–2.76)	0.001	1.45 (1.09–1.92)	0.012
BARC 5	33	0.2	13	0.6	2.54 (1.34–4.82)	0.004	1.41 (0.70–2.84)	0.337
Stroke*	125	0.9	37	1.7	1.92 (1.33–2.77)	0.001	1.18 (0.79–1.76)	0.410
MI (site reported)	392	2.9	105	4.8	1.74 (1.40–2.16)	0.001	1.55 (1.22–1.96)	0.001
Revascularization	1278	9.3	242	11.1	1.24 (1.08–1.42)	0.003	1.19 (1.02–1.37)	0.023
Target vessel revascularization	686	5.0	138	6.4	1.31 (1.09–1.57)	0.004	1.22 (1.01–1.49)	0.044
Definite ST	109	0.8	19	0.9	1.12 (0.69–1.82)	0.652	1.25 (0.73–2.11)	0.415
Definite/probable ST	134	1.0	30	1.4	1.44 (0.97–2.13)	0.074	1.50 (0.97–2.31)	0.069
POCE	1755	12.8	413	19.0	1.55 (1.39–1.72)	0.001	1.33 (1.19–1.50)	0.001
NACE	1910	13.9	458	21.1	1.59 (1.43–1.76)	0.001	1.34 (1.20–1.49)	0.001
Additional bleeding endpoints								
BARC 2	644	4.7	136	6.3	1.37 (1.14–1.64)	0.001	1.15 (0.94–1.40)	0.181
BARC 2, 3 or 5	853	6.2	202	9.3	1.54 (1.32–1.80)	0.001	1.22 (1.03–1.44)	0.019

Hazard ratio (HR) adjusted, when appropriate, for age, sex, clinical presentation with ACS, diabetes mellitus, hypertension, hypercholesterolemia, previous myocardial infarction, percutaneous coronary intervention or stroke, history of previous major bleeding, peripheral vascular disease, chronic obstructive pulmonary disease, current smoking, and randomized treatment. The primary endpoint was a composite of 2-year all-cause mortality or nonfatal, centrally adjudicated, new Q-wave myocardial infarction (MI). Patient-oriented composite endpoint (POCE) included all-cause mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE, bleeding academic research consortium (BARC)-defined bleeding type 3 or 5 type

HR—hazard ratio, 95% CI—95% confidence interval, ST—stent thrombosis, MDRD—modification of diet in renal disease

*Not including transient ischemic attack

Table 5 Two year clinical outcomes in relation to baseline renal function impairment (using prespecified cut off of 60 ml/min according to MDRD equation) and the randomized treatment ($n = 15,883$)

	Non-IRF ($n = 13,712$)				IRF ($n = 2,171$)				<i>p</i> value	<i>p</i> interaction			
	Reference ($n = 6877$)		Experimental ($n = 6835$)		Reference ($n = 1072$)		Experimental ($n = 1099$)						
	<i>N</i>	(%)	<i>N</i>	(%)	<i>N</i>	(%)	<i>N</i>	(%)					
Primary endpoint	255	3.7	224	3.3	0.88 (0.74–1.06)	0.170	93	8.7	79	7.2	0.82 (0.61–1.11)	0.192	0.680
All-cause death	173	2.5	161	2.4	0.94 (0.76–1.16)	0.545	79	7.4	62	5.6	0.76 (0.55–1.06)	0.105	0.300
New Q-wave MI	88	1.3	66	1.0	0.75 (0.55–1.04)	0.082	15	1.4	17	1.5	1.09 (0.55–2.18)	0.807	0.339
BARC 3 or 5	130	1.9	120	1.7	0.93 (0.73–1.19)	0.575	38	3.5	43	3.9	1.10 (0.71–1.71)	0.656	0.506
BARC 3	123	1.8	109	1.6	0.89 (0.69–1.16)	0.396	35	3.3	41	3.7	1.14 (0.73–1.80)	0.560	0.354
BARC 5	16	0.2	17	0.2	1.07 (0.54–2.12)	0.840	8	0.7	5	0.5	0.61 (0.20–1.85)	0.379	0.393
Stroke*	62	0.9	63	0.9	1.03 (0.72–1.46)	0.883	20	1.9	17	1.5	0.83 (0.43–1.58)	0.564	0.562
MI (site reported)	198	2.9	194	2.8	0.99 (0.81–1.21)	0.926	51	4.8	54	4.9	1.04 (0.71–1.52)	0.859	0.841
Revascularization	662	9.6	616	9.1	0.94 (0.84–1.05)	0.242	127	11.8	115	10.5	0.88 (0.68–1.13)	0.302	0.633
Target vessel revascularization	361	5.2	325	4.8	0.91 (0.78–1.05)	0.204	79	7.4	59	5.4	0.72 (0.51–1.01)	0.056	0.216
Definite ST	52	0.8	57	0.8	1.11 (0.76–1.61)	0.594	12	1.1	7	0.6	0.57 (0.22–1.44)	0.231	0.191
Definite/probable ST	64	0.9	70	1.0	1.11 (0.79–1.55)	0.563	18	1.7	12	1.1	0.65 (0.31–1.34)	0.242	0.193
POCE	908	13.2	847	12.4	0.94 (0.86–1.03)	0.181	219	20.4	194	17.7	0.86 (0.71–1.04)	0.128	0.434
NACE	993	14.4	917	13.4	0.93 (0.85–1.02)	0.098	239	22.3	219	19.9	0.89 (0.74–1.07)	0.228	0.724

The *p*-value for interaction for the various endpoints derives from the dichotomized analysis with the pre-specified cut-off of 75 years. The primary endpoint was a composite of 2-year all-cause mortality or nonfatal, centrally adjudicated, new Q-wave myocardial infarction (MI). Patient-oriented composite endpoint (POCE) included all-cause mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE. Bleeding Academic Research Consortium (BARC)-defined bleeding type 3 or 5 type

HR—hazard ratio, *95% CI*—95% confidence interval, *ST*—stent thrombosis, *MDRD* modification of diet in renal disease

*Not including transient ischemic attack

eFR (MDRD)	Experimental Treatment	Reference Treatment	Hazard Ratio [Exp/Reference] (95% CI)		p-value for interaction	
Primary endpoint					0.680	
< 60 ml/min	79/1099	93/1072	0.82 (0.61-1.11)			
≥ 60 ml/min	224/6835	255/6877	0.88 (0.74-1.06)			
All-cause death						0.300
< 60 ml/min	62/1099	79/1072	0.76 (0.55-1.06)			
≥ 60 ml/min	161/6835	173/6877	0.94 (0.76-1.16)			
Stroke						0.562
< 60 ml/min	17/1099	20/1072	0.83 (0.43-1.58)			
≥ 60 ml/min	63/6835	62/6877	1.03 (0.72-1.46)			
Myocardial infarction						0.841
< 60 ml/min	54/1099	51/1072	1.04 (0.71-1.52)			
≥ 60 ml/min	194/6835	198/6877	0.99 (0.81-1.21)			
Revascularization						0.633
< 60 ml/min	115/1099	127/1072	0.88 (0.68-1.13)			
≥ 60 ml/min	616/6835	662/6877	0.94 (0.84-1.05)			
BARC 3 or 5 bleeding						0.506
< 60 ml/min	43/1099	38/1072	1.10 (0.71-1.71)			
≥ 60 ml/min	120/6835	130/6877	0.93 (0.73-1.19)			
POCE					0.434	
< 60 ml/min	194/1099	219/1072	0.86 (0.71-1.04)			
≥ 60 ml/min	847/6835	908/6877	0.94 (0.86-1.03)			
NACE					0.724	
< 60 ml/min	219/1099	239/1072	0.89 (0.74-1.07)			
≥ 60 ml/min	917/6835	993/6877	0.93 (0.85-1.02)			

Fig. 1 Two-year clinical outcomes in patients stratified according to presence of impaired renal function* and randomized treatment. The primary endpoint was a composite of 2-year all-cause mortality or nonfatal, centrally adjudicated, new Q-wave myocardial infarction (MI). Patient-oriented clinical outcome (POCE) included all-cause

mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC 3 or 5 type bleeding. *ST*—stent thrombosis. * based on modification of diet in renal disease (MDRD) equation, using a prespecified cut-off of 60 ml/min

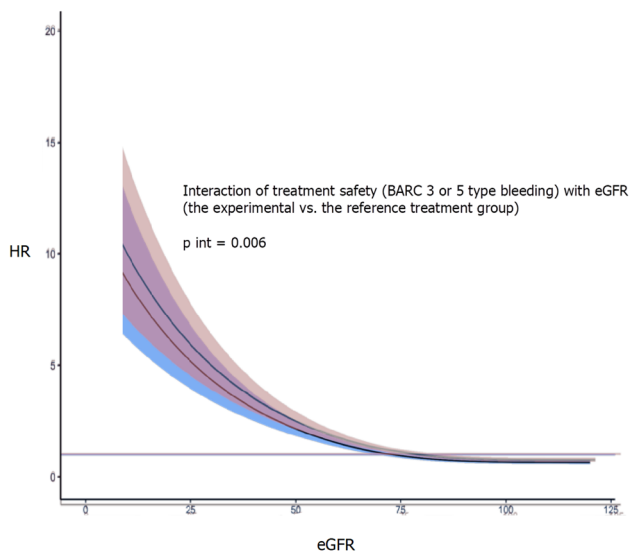


Fig. 2 Interaction of treatment safety (BARC 3 or 5 type bleeding) with baseline eGFR (the experimental vs. the reference treatment group). The line represents the hazard ratios, the colored areas represent the 95% confidence intervals. The *p* value denotes the interaction term between the randomized treatment effects on BARC 3 or 5 type bleeding and the estimated glomerular filtration rate, treated as a continuous variable. Cox proportional hazard model was used. Blue line/area—the experimental treatment, Red line/area—the reference treatment

Discussion

The main findings of this prespecified sub-analysis of the GLOBAL LEADERS trial can be summarized as follows:

- (1) The incidence of IRF in this large, contemporary, unselected patient population undergoing PCI, was 13.7% (13% in patients undergoing PCI for ACS and 14.3% in patients undergoing PCI for stable CAD).
- (2) Among patients undergoing PCI, any degree of IRF is associated with a higher risk of mortality, ischemic and bleeding events.
- (3) In the overall population, there was no differential treatment effect on safety or efficacy with long-term ticagrelor monotherapy after 1-month DAPT among patients with and without IRF. Nevertheless, post hoc exploratory analyses including eGFR as a continuous variable showed a differential treatment effect on BARC 3 or 5 type bleeding, with less BARC 3 or 5 type bleeding in the experimental group.

This study is currently the largest baseline eGFR-stratified analysis of ischemic and bleeding outcomes in PCI patients receiving monotherapy with a potent P2Y₁₂ antagonist, following 1 month DAPT.

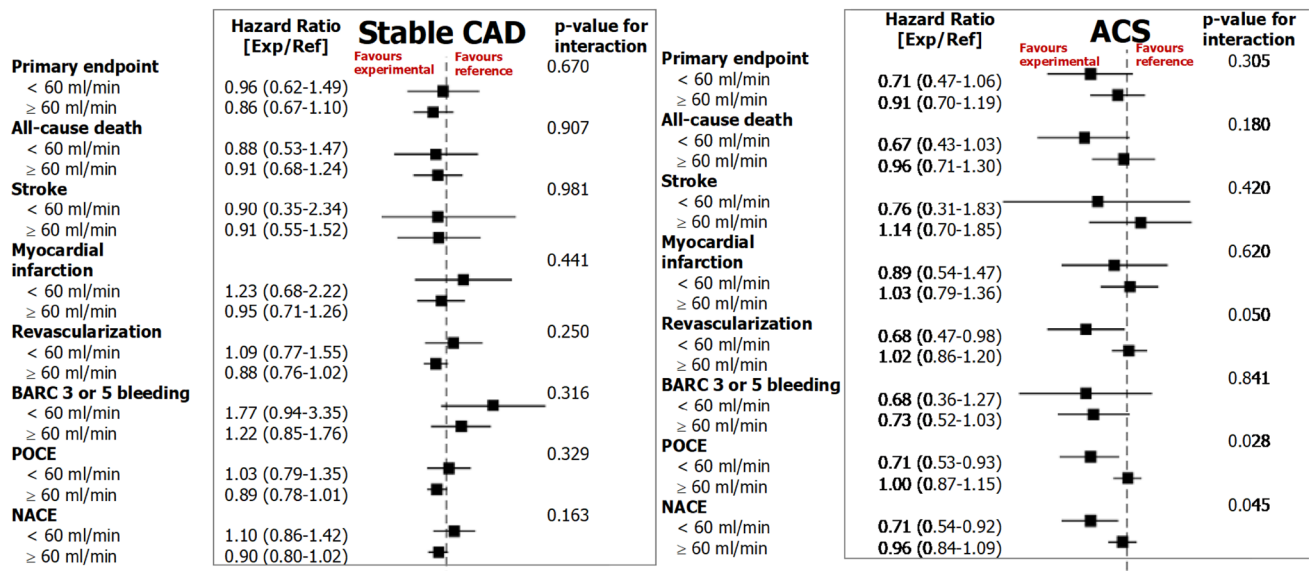


Fig. 3 Impact of the randomized treatment on 2-year clinical outcomes according to prespecified eGFR cut off of 60 ml/min (according to MDRD equation) in stable CAD and ACS patients. The primary endpoint was a composite of 2-year all-cause mortality or nonfatal, centrally adjudicated, new Q-wave myocardial infarction

(MI). Patient oriented clinical outcome (POCE) included all-cause mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC 3 or 5 type bleeding. *ST*—stent thrombosis, *MDRD*—modification of diet in renal disease

Based on the PLATO study, which demonstrated ticagrelor’s superiority over clopidogrel in patients with ACS regardless of baseline renal function, and its increasing advantage in reducing major adverse cardiac events in cohorts with worsening renal dysfunction, it was of interest to evaluate whether similar findings could be replicated with ticagrelor monotherapy after 1 month of DAPT in an unselected patient population undergoing PCI. Indeed, compared to the reference treatment, the experimental treatment group had non-significantly lower rates of the primary endpoint and all-cause mortality, with progressively decreasing point estimates of the HR with decreasing cutoff values of eGFR from 90 to 30 ml/min. However, no significant interaction term was detected between the randomized treatment and IRF for any of the outcomes. The safety profile of ticagrelor in this large contemporary PCI cohort may facilitate better informed clinical decisions on the use of the more potent P2Y₁₂ antagonists in patients with IRF undergoing PCI. Further research may also establish whether the experimental treatment strategy represents a good alternative in selected patients with IRF, such as those in whom standard DAPT is contra-indicated due to expected excess bleeding risk. Of note, IRF is considered as a major or minor bleeding risk criterion based on the degree of renal dysfunction, as described in the recent consensus document from the Academic Research Consortium for High Bleeding Risk [23].

However, neither the analysis stratifying patients according to baseline IRF status nor the KDIGO categories were powered to detect between-group differences or

treatment-by-subgroup interactions. Thus, the present analysis should be considered strictly exploratory, and interpreted in the context of the neutral primary analysis of the parent trial [11] and the limitations inherent to subgroup analyses [24].

Reported clinical outcomes, in particular bleeding rates, should also be interpreted in light of the lower adherence to the randomized treatment in the experimental arm, in particular among patients with IRF who had a consistently lower attendance at each follow-up visit. Importantly, however, discontinuation rates in GLOBAL LEADERS were comparable to other trials evaluating ticagrelor [25, 26].

Reassuringly, there was no excess in bleeding risk related to the experimental therapy among patients with moderate IRF (eGFR = 30–59 ml/min/1.73 m²; n = 2055); however, in patients with an eGFR of < 30 ml/min/1.73 m² (n = 116) BARC 3 or 5 type bleeding occurred in 4 out of 61 patients in the experimental arm and in 1 out of 55 patients in the reference arm; all but one event occurred in patients presenting with stable CAD.

This corresponds with previous pharmacodynamic studies showing that exposure to ticagrelor was approximately 20% lower, and exposure to the active metabolite approximately 17% higher, in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m²) compared to subjects with normal renal function.

Exploratory analyses suggested that the potential net clinical benefit of the experimental strategy in ACS patients with IRF was mainly observed in patients with grade 3 renal

impairment (eGFR = 30–59 ml/min/1.73 m²). A plausible explanation is that the selection of chronic kidney disease patients is an effective way to identify high-risk patients with high event rates, and the subgroup with moderate renal impairment has the greatest reduction in ischemic events, without a corresponding increased bleeding risk [2, 7]. This further underscores the prominent role of IRF as a component of ischemia and bleeding prediction scores used for antiplatelet therapy planning [4, 11, 27].

The present results obtained in the ACS population are very consistent with the PLATO data in showing the excess risk in IRF patients [(19.0% IRF vs. 12.8% no IRF, for POCE in GLOBAL LEADERS) vs. (19.7% vs. 8.4% for death/MI/stroke in PLATO)] with incremental risk with more severe renal dysfunction. In the two studies also, there was a greater absolute all-cause mortality risk reduction found among IRF patients, as compared to that of patients with normal renal function [9]. In both studies also, the bleeding excess with ticagrelor appears to be of similar magnitude in IRF and no IRF patients. This leads to a favorable net clinical benefit with ticagrelor in the two sub-studies. The combined effect of IRF and ACS on ischemic outcomes appears to benefit from ticagrelor use, probably related to the inadequate platelet inhibition achieved with earlier generation P2Y₁₂ inhibitors (e.g., clopidogrel) in patients having both conditions [3, 8]. Whether this is ticagrelor-specific is uncertain as close findings have been reported with prasugrel [28] and in a metaanalysis [29]. In addition, recently among patients who presented with ACS with or without ST-segment elevation enrolled in the randomized open-label ISAR REACT 5 trial, the incidence of death, myocardial infarction, or stroke was significantly lower in the group receiving prasugrel, compared with the group treated with ticagrelor, and the incidence of major bleeding (bleeding BARC 3, 4 or 5 type) was not significantly different between the two groups [30]. Nevertheless, among the elderly ≥ 70 years of age being treated for a non-ST-segment elevation ACS the results of POPular AGE trial showed that clopidogrel was associated with less bleeding and similar ischemic events versus more potent P2Y₁₂ inhibitors (ticagrelor or prasugrel) [31].

The poorer long-term prognosis of patients with IRF is possibly explained by more prevalent pre-existing cardiovascular disease, more extensive atherosclerosis, more frequent high-risk presentations of ACS, lower rates of complete revascularization, and underutilization of guideline-recommended therapies [2, 32]. Renal disease can alter thrombocyte function, coagulation and cause endothelial dysfunction [7, 33, 34]. In this context, it is noteworthy that among patients with ACS, ticagrelor monotherapy, after 1-month DAPT, reduced the rates of POCE and NACE among patients with IRF, without an

increase in BARC 3 or 5 type bleeding, compared to standard 12-month DAPT after PCI.

In the present analysis, stable CAD patients with IRF had a similar rate of ischemic events, and a non-significantly higher relative risk of BARC 3 or 5 type bleeding in the experimental versus the reference group. In the PEGASUS-TIMI 54 trial, ticagrelor was associated with an increase in Thrombolysis in Myocardial Infarction (TIMI) major bleeding in stable outpatients with prior MI¹². Nevertheless, as GLOBAL LEADERS also enrolled patients with acute MI, and a generally lower cardiovascular risk, as demonstrated by the overall all-cause mortality, the presented findings cannot be directly compared to prior studies evaluating ticagrelor in relation to baseline renal function. A patient cohort with a risk profile which is higher than GLOBAL LEADERS, and comparable to PEGASUS-TIMI 54, has been recently evaluated in the TWILIGHT trial, in which presence of chronic kidney disease was one of the enrichment factors according to the trial protocol [35]. In TWILIGHT, comparing ticagrelor monotherapy following 3-month event-free period of DAPT after PCI with DAPT strategy, a significant reduction of the composite primary endpoint of bleeding BARC 2, 3 or 5 type (HR 0.56, 95% CI 0.45–0.68, $p_{\text{for superiority}} < 0.001$) has been demonstrated in the experimental group versus the reference group 15 months after PCI (12 months after randomization) [36]. The trial also showed non-inferiority of the experimental treatment with regard to the composite secondary endpoint of all-cause death, non-fatal MI, or stroke (HR 0.99, 95% CI 0.78–1.25, $p_{\text{for non-inferiority}} < 0.001$), with the caveat of a higher than anticipated drop-out in the first 3 months after the index procedure, leading to a lower rate of this endpoint and potential bias of the results towards null hypothesis [36, 37].

Limitations

This study has several limitations. Given that two antiplatelet strategies did not differ significantly with respect to the rates of the primary endpoint in the overall trial [11], all presented findings have to be considered exploratory and hypothesis-generating. The randomization in GLOBAL LEADERS study was not stratified for renal function; thus some imbalance between the randomized groups may exist among patients with IRF. Importantly, this was a prespecified subgroup analysis based on prespecified cut-off points of renal function at admission. Creatinine data were not available in 85 patients (0.5%); however, this rate of missing creatinine data is significantly lower, compared to prior trials on antiplatelet agents in context of renal dysfunction [9].

GLOBAL LEADERS was an open label trial; however, to minimize bias, the primary endpoint included solid components of all-cause mortality—not requiring adjudication, and a core lab adjudicated new-Q wave MI. No central adjudication of investigator-reported secondary clinical outcomes was performed. Bias and misclassification can, therefore, not be excluded. This limitation should be considered in particular when interpreting bleeding event rates. However, the trial was monitored for event definition consistency and event under-reporting, with as many as seven on-site monitoring visits done at individual sites and one-fifth of events verified based on the source documentation [11, 38]. Use of site-reported endpoints is a valid methodology in clinical research, especially involving large cohorts and well-defined and restricted categories within a classification (e.g. BARC-defined bleeding type 3–5 as compared with type 1 and 2) are expected to provide higher concordance among sites than a central clinical event adjudication committee, as well as higher reproducibility.

Conclusions

IRF is associated with worse short- and long-term clinical outcomes after PCI. There were no differential treatment effects found with regard to all-cause death or new Q-wave MI after PCI in patients with IRF treated with ticagrelor monotherapy after 1-month dual therapy with aspirin. In ACS patients with IRF, the experimental strategy may be associated with less ischemic events and similar bleeding rates, compared to standard DAPT after PCI.

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Compliance with ethical standards

Conflict of interest Dr. Tomaniak reports lecture fee from Astra Zeneca, outside the submitted work. Dr. Chichareon reports Grants from biosensors, outside the submitted work. Dr. Modolo reports Grants from Biosensors, outside the submitted work. Dr. Curzen reports Grants and personal fees from Boston Scientific, Grants and personal fees from Heartflow, Grants and personal fees from Haemonetics, outside the submitted work. Dr. Haude reports institutional Grant/research support from Biotronik AG, Abbott Vascular, Cardiac Dimensions, Volcano, Lilly and consultant/speaker's bureau: Biotronik AG, Abbott Vascular, Cardiac Dimensions. Dr. Montalescot has received research Grants to the institution or consulting/lecture fees from Abbott, Amgen, Actelion, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Brigham Women's Hospital, Cardiovascular Research Foundation, Daiichi-Sankyo, Idorsia, Lilly, Europa, Elsevier, Fédération Française de Cardiologie, ICAN, Medtronic, Journal of the American College of Cardiology, Lead-Up, Menarini, Merck Sharp & Dohme,

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