Circulation

IN DEPTH

P2Y$_{12}$-ADP Receptor Blockade in Chronic Kidney Disease Patients With Acute Coronary Syndromes

Review of the Current Evidence

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ABSTRACT: Because of its high prevalence, chronic kidney disease (CKD) remains a major health hazard throughout the world. Patients with CKD have a high prevalence and incidence of acute coronary syndromes (ACS). Despite decades of improved care, their higher risk profile persists and cardiovascular diseases remain their leading cause of death. Along with the reduction of glomerular filtration rate, several physiological processes are impacted and participate in the pathophysiology of ischemic and bleeding events. CKD is associated with an accelerated and severe course of atherothrombotic disease, and this relates to a modified vascular milieu with alterations on the level of the coagulation cascade and platelet aggregation. In addition, pharmacokinetics of several drugs, in particular antithrombotics, are altered and differ from that of non-CKD patients. Patients with CKD therefore represent a challenging population for both physicians and researchers. In addition to these perturbations of physiological processes, CKD patients face 2 major issues. First, there is a clear gap in scientific research as they are commonly underrepresented or excluded from major clinical trials. This is particularly true regarding antithrombotic treatment during ACS. Second, there is a gap in offering evidence-based treatment for these patients including state-of-the art options for revascularization and modern antiplatelet treatment, both of which are commonly underused. During the last decade, new potent oral P2Y$_{12}$-ADP receptor antagonists, prasugrel and ticagrelor, which are more potent antiplatelet agents compared with clopidogrel, were introduced for ACS treatment. However, despite the fact that CKD patients represent a large proportion of those experiencing an ACS and are considered at high risk, there is a lack of dedicated trials and we are left with subgroup analysis of large randomized clinical trials were stage 4 and dialysis patients were rare. In the present review we summarize the mechanisms involved in the high ischemic and bleeding risk of CKD patients and the risk–benefit ratio of potent antiplatelet drugs during ACS.

Key Words: acute coronary syndrome ■ antiplatelet agents ■ chronic kidney disease ■ P2Y12 receptor

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Chronic kidney disease (CKD) patients make-up a significant proportion (between 20% and 40%) of those admitted for an acute coronary syndrome (ACS).[1–5] In contrast, CKD patients are often underrepresented or excluded from major randomized, clinical trials (RCTs) including those on ACS patients undergoing percutaneous coronary intervention (PCI).[6] In addition, underuse of recent therapeutic advances contributes to the poorer outcome of these patients despite the fact that they are considered at high risk.[7,8] Kidney dysfunction results in perturbation of physiological processes leading to an accelerated atherosclerosis, heightened thrombotic risk, and a reduced impact of therapeutic interventions with increased risk of side effects of the utilized antithrombotic agents. Thus, their management remains difficult.

ACS patients, especially those who undergo invasive management, require a dual antiplatelet treatment (DAPT) regimen for up to 12 months in most cases.[9,10] In conjunction with aspirin, clopidogrel was the standard of treatment in the past decade and is still among the options for ACS patients with and without CKD.[9,10] Clopidogrel has several pharmacological shortcomings, including delayed onset of action, large response variability, and on average modest $P2Y_{12}$-inhibition, with high on-treatment platelet reactivity (HPR) in a substantial proportion of patients.[11–14] These limitations are particularly relevant to ACS patients with CKD, as comparatively high HPR rates were reported for this high-risk cohort and the benefit of clopidogrel was often debated.[15–17] Prasugrel and ticagrelor are potent $P2Y_{12}$-ADP receptor antagonists overcoming the limitations of clopidogrel (Table 1).[18,19] These drugs have an improved clinical efficacy in intermediate risk ACS. In the PLATO trial (Study of Platelet Inhibition and Patient Outcomes), ticagrelor reduced the rate of major adverse cardiovascular events (MACE) in patients treated either by PCI, coronary artery bypass graft (CABG), or medically managed. On the other hand, to date in these patients prasugrel showed efficacy in patients treated with PCI.[3,4] However, in some of these trials the number of CKD patients was limited, and stage 4 CKD and end-stage kidney failure patients' were either rare or excluded. For example, in the PLATO trial the proportion of CKD patients was 21.3% but dialysis was an exclusion criteria. In the TRITON TIMI 38 trials (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) on the other hand the proportion of CKD patients was 15.1% in those randomized to prasugrel but patients with stage >4 CKD were rare (Table 2). In the overall patient population, the reduction in ischemic events achieved by the potent $P2Y_{12}$-ADP receptors antagonists compared with clopidogrel came at the price of increased major bleedings.[3,4] Therefore, the risk–benefit ratio of new these potent drugs appears of particular importance in CKD patients in relation to their high risk profile for ischemic and bleeding events. In the present review, we aim to summarize the pathophysiological processes at the interface of CKD and antiplatelet drugs as well as the available evidence for potent $P2Y_{12}$-

Table 1. Available Oral $P2Y_{12}$ Receptor Antagonists for Use in Patients With Acute Coronary Syndrome With and Without Chronic Kidney Disease

	Clopidogrel	Prasugrel	Ticagrelor
Basic drug properties and dosing			
Receptor inhibition	Irreversible	Irreversible	Reversible
Drug class	Thienopyridine	Thienopyridine	Cyclopentyltriazolo-pyrimidine
Prodrug	Yes	Yes	No
Onset of action	2–8 h	30 min to 4 h	30 min to 4 h
Half-life	6 h	<5 min	6–12 h
Offset of action	5 days	7 days	2 days
Dose (loading dose/maintenance dose)	600 mg/75 mg	60 mg/10 or 5 mg	180/90/60 mg twice per day
Bioactivation	Yes, prodrug, Cytochromes P450 dependent, 2 steps	Yes, prodrug, Cytochromes P450 dependent, 1 step	No
Mode of antagonism	Competitive	Competitive	Noncompetitive
Characteristics related to renal function			
Elimination	50% renal	68% renal	1% renal
High on-treatment platelet reactivity (%)	20% to 50%	<10%	<10%
Dialysis	Lack of data	Lack of data	Lack of data
Impact on kidney function	None	None	Increase in creatinine level during therapy
Dose reduction in patients with chronic kidney disease	No	No	No

Table 2. Ischemic and Bleeding Risk in Patients With CKD in Contemporary Trials and Registries

Study	Setting	Total No. of Patients	No. of Patients With CKD (%)	Definition of CKD	Ischemic Risk		Hazard Ratio for Ischemic Risk Potent P2Y12 Versus Clopidogrel and *P* for Interaction	Bleeding Risk		Hazard Ratio for Bleeding Risk Potent P2Y12 Versus Clopidogrel and *P* for Interaction
					Patients With CKD	Patients Without CKD	Patients With CKD	Patients With CKD	Patients Without CKD	
PLATO[3]	Randomized comparison of ticagrelor vs clopidogrel in patients with ACS	15 202	3237 (21.3)	CrCl < 60 mL/min CGF	17 vs 22%	7.9 vs 8.9%	0.77 (0.65–0.9); *P*=0.13	4.8 vs 3.9%	2.2 vs 1.7%	1.28 (0.88–1.85) *P*=0.98
TRITON-TIMI 38[4]	Randomized comparison of prasugrel vs clopidogrel in patients with ACS	13 608	1490 (10.9)	CrCl < 60 mL/min CGF	15.1 vs 17.5%	9.0% vs 11.1%	0.86 (0.67–1.1); *P*=ns	NA	NA	NA
TRILOGY-ACS[5]	Randomized comparison of prasugrel vs clopidogrel in medically patients with ACS	8953	2924 (32.7)	CrCl < 60 mL/min CGF	CrCl [30–60]: 22.7 vs 23.7% CrCl <30: 28.1 vs 47.5%	11.9 vs 13.6%	CrCl [30–60]: 1.14 (0.88–1.49) CrCl <30: 0.68 (0.33–1.41) *P*=0.17	Overall population CrCl [30–60]: 3.1% CrCl <30: 3.8%	Overall population 1.8%	NA
PROMETHEUS[1]	ACS registry of clopidogrel and prasugrel treated patients	19 832	5613 (28.3)	CrCl < 60 mL/min/1.73m^2 CKD epi	19.3 vs 26.5%	10.9 vs 17.9%	1 (0.8–1.25); *P*=0.2	CrCl [30–60]:0.82 (0.7–0.97) CrCl <30: 6 vs 7.4%	2.6 vs 3.5%%	1.04 (0.7–1.53) *P*=0.4
SWEDEHEART[2]	Retrospective cohort study for patients hospitalized with ACS and discharged with ticagrelor or clopidogrel	45 206	11 538 (25.5)	CrCl < 60 mL/min/1.73m^2 CKD epi	CrCl [30–60]: 18 vs 33% CrCl <30: 48 vs 64%	7% vs 11%	CrCl [30–60]: 0.82 (0.7–0.97) CrCl <30: 0.95 (0.69–1.29) *P*=0.55	CrCl [30–60]: 7.4 vs 5.6% CrCl <30: 15 vs 9.1%	3.7 vs 3.2%	CrCl [30–60]: 1.13 (0.84–1.51) CrCl <30:1.79 (1–3.2) *P*=0.3

CGF indicaets Cockroft-Gault formula; CKD, chronic kidney disease; CKD epi, CKD Epi equation; and CrCl, creatinin clearance.

ADP receptor inhibition. Based on the available data we also aim to provide guidance with risk–benefit assessment and future steps to be taken in this important and interesting field of clinical research.

DEFINITION AND EPIDEMIOLOGY OF CKD

To assess kidney function, several formulas are available including the Cockcroft and Gault formula, the Modification of Diet in Renal Disease Study equation, or the Chronic Kidney Disease Epidemiology Collaboration equation. The latter represents the best assessment to predict end-stage renal disease and the risk for mortality and should be preferred in future research.[20] CKD is defined according to the presence of kidney damage and the level of kidney function, irrespectively of the underlying kidney disease. Based on the estimated glomerular filtration rate, 5 CKD stages can be differentiated from kidney damage with normal estimated glomerular filtration rate (stage 1) up to stage 5, which is characterized by an estimated glomerular filtration rate<15 mL/min/1.73 m^2 or hemodialysis.[21] The overall prevalence of CKD, which had increased from the late 1990s to the early 2000s, has since then remained stable in the U.S. at ≈17%.[22] CKD burden is increasing in some parts of the world while it is decreasing in Europe.[23] CKD is common among patients with ACS (20% to 40%).[1–5] In parallel, coronary artery disease is common in patients with CKD, and cardiovascular events are responsible for up to 50% of deaths[24,25] (Table 2). Conversely, the prevalence of CAD and history of ACS is higher in patients with versus without CKD;

for example, 15.1% of CKD patients >66 years of age in the U.S. had acute myocardial infarction compared with 6.4% of those without.[26]

Direct and indirect costs attributable to CKD and end-stage renal disease varies between studies, with most of the evidence focusing on direct renal failure–related costs, but the high burden of cardiovascular events and mortality is a large indirect cost driver for this specific population.[27]

Despite therapeutic advances which overall improved the clinical outcome, CKD patients with ACS still experience a higher rate of recurrent ischemic events including a higher mortality and reinfarction rates.[3,4,28–30] In parallel, these patients also carry a higher risk of bleeding.[3,25,29,31] Therefore, there is a need to specifically assess the net clinical benefit of drugs or therapeutic strategies in this population.[32] It must be underlined that the risk of events diminishes if kidney function is re-established in the advent of kidney transplant. On the other hand, hemodialysis is unable to reverse the complex modifications of the vascular milieu associated with CKD and is therefore still associated with a higher ischemic risk profile[33,34] (Table 2). However, when considering the factors responsible for an increased cardiovascular mortality with increasing levels of renal dysfunction, it should be underlined that in end-stage CKD sudden death and arrhythmias become the main cause of cardiovascular mortality instead of atherosclerotic disease.[35]

THERAPEUTIC AND RESEARCH GAPS

Major concerns and issues regarding CKD patients are obvious gaps in research and treatment concepts. In a dedicated study, Charytan et al[6] observed that in the early 2000s, CKD patients were excluded from ≈75% of clinical trials, highlighting the huge research gap. In addition, they are commonly deprived from the benefit of some therapeutic improvements by not receiving guideline-recommended treatment.[8,36]

PATHOPHYSIOLOGY OF THROMBOSIS AND BLEEDING IN CKD PATIENTS

Ischemic Risk

There seems to be a gradient in the level of ischemic risk which parallels that of CKD stage.[20,23,24,30] In fact, Go et al[37] demonstrated a stepwise relationship between the level of CKD and cardiovascular events or mortality with adjusted hazard ratio ranging from 1.4 for moderate CKD to 3.4 for end-stage renal disease compared with non-CKD patients. This higher risk profile persists after adjustment for comorbidities even in the case of mild CKD[37,38] (Table 2).

Mechanisms Responsible for the Ischemic Risk

There are several pathophysiological pathways responsible for the increased risk of thrombosis in CKD patients. Figure 1 illustrates the multifactorial mechanisms commonly involved and contributing to the excess risk.

The coagulation cascade is affected by CKD, and studies have reported that the concentration of prothrombotic factors within the coagulation cascade are increased including fibrinogen and tissue factor but also inflammatory markers such as interleukin 6 or C reactive protein.[39,40] In particular, the concentration of coagulation factors XIIa and VIIa are increased while antithrombin activity is reduced, thus promoting a procoagulant phenotype.[41–43] In addition, plasminogen activator inhibitor levels are also increased, which further inhibits the activation of the fibrinolytic system.[44]

Platelets are also involved in the overall thrombotic risk. They have an increased susceptibility to thrombin and contain higher levels of P-selectin and of fibrinogen receptor PAC-1, resulting in increased platelet-leukocyte aggregates formation and increased platelet reactivity.[44–46]

The endothelium is the third actor which participates in the thrombotic risk. The endothelial injury associated with CKD favors the loss of the antithrombotic properties of the endothelial layer, including decreased release

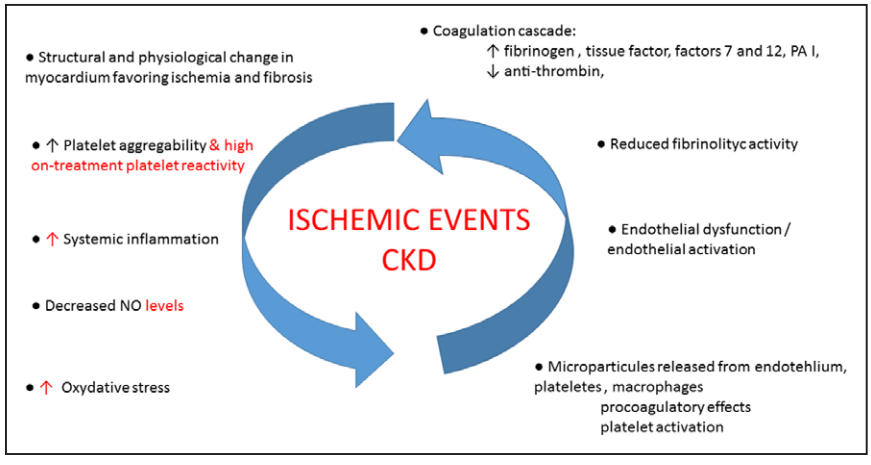

Figure 1. The mechanisms involved in ischemic events in chronic kidney disease (CKD) patients include platelet, endothelial, and coagulation cascade behavior modifications.

of t-PA and the loss of secretion of factors modulating the coagulation cascade.[47,48]

Mediators of the thrombotic phenotype of CKD patients also include microparticles. These vesicles issued from the endothelium or from platelets represent a mechanism of communication recently characterized. In CKD, microparticles have an increased level and express procoagulant phenotype[49,50] (Figure 1).

All of these factors contribute to a more diffuse coronary artery disease with more vulnerable plaques and higher tendency for thrombosis.[51,52] Baber et al[53] observed that CKD patients with ACS had more extensive and severe coronary plaques with larger necrotic core and reduced fibrous tissue. Likewise, histology and immunohistochemistry analysis of carotid endarterectomy plaques showed that CKD patients had more unstable and ruptured plaques than non-CKD patients, highlighting the changes in component associated with CKD in atherosclerotic disease.[54]

Risk Patterns for Bleeding in CKD Patients

Bleeding Risk

In parallel to a higher ischemic risk, CKD patients have an increased risk of bleeding both spontaneously but also with the use of anticoagulants and antiplatelet agents.[3,31,32,44] It should be underlined that major bleeding events have a similar prognostic impact on patient´s overall mortality rates when compared with nonfatal ischemic events, and this observation is particularly true for ACS patients undergoing PCI.[55–57] Overall, the bleeding risk is estimated to double with CKD based on the pivotal randomized trials and recent large-scale registries[3,5,56] (Table 2).

Mechanisms of Bleeding

The mechanisms responsible for the high rate of bleeding are multiple and interconnected (Figure 2).

Platelets are key drivers for the observed increased bleeding risk in CKD patients.[57] This is related to several factors including disturbance of α-granules, deregulated arachidonic acid and prostaglandin metabolism, and reduced ADP release. These altered pathways of platelet function result in reduced adhesion and aggregation.[58,59] In addition, circulating fibrinogen fragments interfere by competitive binding to the glycoprotein IIb/IIIa receptor, resulting in decreased adhesion and aggregation.[60,61] Changes in intraplatelet calcium flux are responsible for abnormal responses to stimuli together with function defects in von Willebrand factor–platelet interaction and insufficient binding of von Willebrand factor and fibrinogen to platelets which are responsible for a decreased glycoprotein IIb/IIIa complex function.[62–64] Furthermore, anemia induced by CKD results in an increased NO level. All of these factors translate into a reduction of platelet aggregation.[65,66]

In addition to the direct effects of CKD and uremic toxin described above, the increase in bleeding risk is related to modified drug interactions.[67] These modifications can result from the modified pharmacokinetic or pharmacodynamic profiles of the drugs in this milieu but also from the presence of uremic toxins.[68,69]

Recent studies have observed that the higher bleeding risk in this population persists despite the use of bleeding avoidance strategies such as drug dose-adjustment or radial route for PCI.[9] There are, to date, no therapeutic means to specifically reduce the bleeding risk associated with CKD.

The alteration of key factors of vascular homeostasis, including blood platelets, coagulation factors, and the vascular wall itself, participates in the higher thrombotic and bleeding risk. As described above, platelets are key actors contributing to the higher risks of CKD patients. It is therefore of utmost importance and difficulty to adequately evaluate the balance between ischemic risk reduction and bleeding risk increase with potent antiplatelet agents.

CLOPIDOGREL PHARMACODYNAMICS AND CLINICAL EFFICACY

Clopidogrel is commonly used in patients with CKD, and dose-adjustment to creatinine clearance is not re-

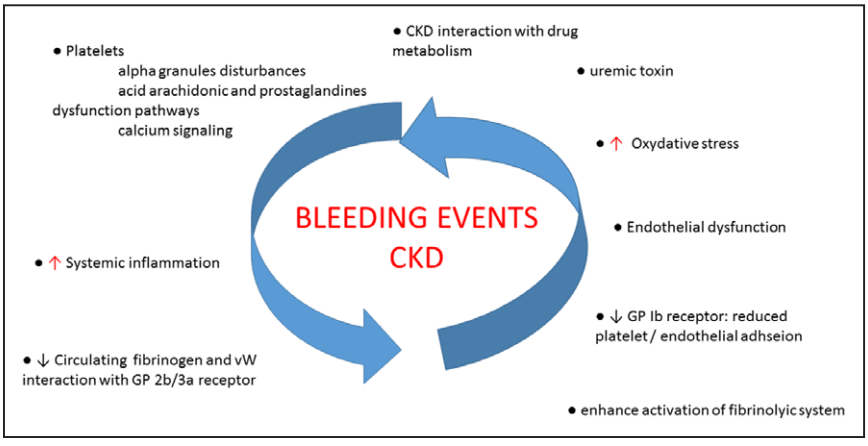

Figure 2. The multifactorial pathophysiology of bleeding events in chronic kidney disease (CKD) patients.

quired because only the inactivated derivate of clopidogrel passes through the kidneys.[70] Despite similar active metabolite generation from clopidogrel, on-treatment platelet reactivity seems to be increased with a higher rate of HPR in CKD patients compared with non-CKD patients[71–74] (table 3).

Although this effect of CKD on platelet function was not always observed,[75,76] the current evidence suggest a higher baseline platelet reactivity but also the presence of a gradual association between worsening renal dysfunction and HPR.[71,72,75,76] Data from the ADAPT-DES registry (Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents) including 8582 patients were used to compare platelet function in patients with and without CKD. The registry adjusted for various confounding risk factors and analyzed ischemic and bleeding events in relation to platelet and renal function. In the unadjusted analyses, CKD patients had higher platelet reactivity than the non-CKD counterparts, and the prevalence of HPR increased with worsening renal function. Interestingly, this association between CKD and HPR disappeared after multiple adjustments.[74] This finding suggests that the comorbidities associated with these serious conditions participate in HPR in this population. The impact of comorbidities in CKD patients was also highlighted by studies of Angiolillo and coworkers which observed that diabetic patients with CKD had markedly elevated platelet reactivity with a reduced response to the active metabolite of clopidogrel suggesting altered $P2Y_{12}$-mediated signaling.[71,76,77]

HPR on clopidogrel was strongly associated with the risk of ischemic recurrence in ACS patients undergoing PCI.[13] In addition, Morel et al[78] observed that the higher rate of low response to clopidogrel in CKD patients was responsible for their increased risk of MACE and death. In summary, most pharmacodynamic studies suggest that high rates of HPR in CKD patients participate in their increase ischemic risk. Table 3 summarizes the pharmacodynamic studies investigating the association between CKD and platelet function.

Indirect evidence in support of these PD findings arise from post hoc analyzes of two major RCTs and a meta-analysis. Subgroup analysis from the CREDO trial (Clopidogrel for the Reduction of Events During Observation) showed that clopidogrel in mild or moderate CKD patients may not have the same beneficial effect as it does in patients with normal renal function. In this study, patients with normal kidney function who received 1 year of clopidogrel had a marked reduction in death, myocardial infarction, or stroke compared with those who received placebo, whereas patients with CKD did not have a significant difference in outcomes with clopidogrel therapy versus placebo.[79] There was, on the contrary, a strong trend toward worse outcome in patients with moderate CKD assigned to clopido-

Table 3. Pharmacodynamic Studies Investigating the Association Between CKD and Platelet Function

First Author	Year	No. of Patients	Patient Population	Clopidogrel Dose	Platelet Function Assay	Results
Park[73]	2009	59	CKD vs non-CKD	No CKD: 75 mg CKD group I: 75 mg CKD group II: 150 mg	VerifyNow P2Y12	Sign. higher PRU in CKD vs no CKD No diff. in CKD between 75 vs 150 mg clopidogrel
Angiolillo[71]	2010	306	Patients with diabetes mellitus with and without CKD stage 3/4	Clopidogrel 75 mg	LTA ADP 20 umol/L and collagen 6 μg/mL Flow cytometry for P-selectin and GPIIbIIIa expression	Significantly higher ADP and collagen-induced aggregation and surface expression in patients with CKD
Tello Montoliu[76]	2013	60	Patients without diabetes mellitus with and without CKD stage 3/4	Clopidogrel 600 mg	LTA ADP 5 and 20 umol/L VASP	No difference in platelet reactivity at baseline and 24 h after 600 mg clopidogrel
Gremmel[72]	2013	316	Patients with and without CKD stage 3/4	Clopidogrel 75 mg	LTA with ADP 10umol/L and AA VerifyNow P2Y12 and ASA Flow cytometry for surface GPIIbIIIa	Significantly higher ADP and AA-induced aggregation, VerifyNow PRU and surface expression in patients with CKD
Mangiacapra[75]	2014	800	Patients with and without CKD stage 3/4	Clopidogrel 75 mg	VerifyNow P2Y12	No difference in PRU between CKD and no CKD
Baber[74]	2015	8410	Patients with and without CKD stage 3/4	600 mg clopidogrel <6 h testing, 300 mg <12 h before testing, or ≥75 mg for at least 5 days before testing	VerifyNow P2Y12	The prevalence of HPR increased in a graded fashion with worsening renal function. After multivariable adjustments, these associations were no longer significant.

AA indicates acid arachidonic; ACS, acute coronary syndrome; CKD, chronic kidney disease; HPR, high platelet reactivity; and PRU, platelet reactivity unit.

grel (*P* for interaction = 0.07). Similar findings were obtained in a post hoc analysis of the CHARISMA trial (Clopidogrel and Aspirin Versus Aspirin Alone for the Prevention of Atherothrombotic Events). In this analysis patients with diabetes mellitus and CKD who received clopidogrel experienced increased cardiovascular and overall mortality compared with those assigned to placebo (*P* for interaction 0.019).[80] As a synthesis of the available evidence, Palmer and colleagues[81] showed, in a meta-analysis involving 9969 persons with ACS or after PCI, that administration of glycoprotein IIb/IIIa inhibitors or clopidogrel compared with standard of care alone had little or no effect on all-cause or cardiovascular mortality or on myocardial infarction but increased bleeding. Although there was no dedicated prospective, RCT designed to test clopidogrel in CKD patients with ACS, both the pharmacodynamic and the clinical efficacy of clopidogrel seem impaired in these patients compared with those with normal kidney function.

PHARMACOKINETIC AND PHARMACODYNAMICS DATA FOR POTENT P2Y12-ADP RECEPTOR ANTAGONISTS IN CKD

The pharmacodynamics and pharmacokinetics of the potent oral P2Y12-ADP receptor antagonists were investigated in a number of dedicated PK/PD studies in CKD patients. Many of those mechanistic studies included comparisons with clopidogrel, and details of the studies are summarized in Table 4.

In a small single-center study enrolling non ST-elevation myocardial infarction patients with CKD, Wang et al[82] observed significantly lower PRU values in patients treated with ticagrelor versus clopidogrel. However, in a linear regression analysis, the authors of one study observed no association between renal function and platelet reactivity within the group of clopidogrel (*r*=–0.04, *P*=0.52) or ticagrelor (*r*=0.006, *P*=0.92) treated patients.[83] Further on, in small randomized studies ticagrelor showed a more rapid and greater platelet inhibition than clopidogrel and was able to overcome HPR in in 90% of clopidogrel-resistant patients undergoing maintenance hemodialysis.[84,85] Interestingly, in a head-to-head comparison of the w potent oral antiplatelet agents, ticagrelor exhibited higher levels of platelet inhibition when compared with prasugrel in CKD patients.[86]

In a series of smaller investigations, prasugrel pharmacokinetics and pharmacodynamics were assessed in subjects with CKD showing no difference in PK/PD responses in relation to renal function contrarily to clopidogrel.[87–89]

In summary, published data from PK/PD studies with ticagrelor or prasugrel show the superiority of the potent P2Y12 receptor antagonists over clopidogrel in CKD patients (Table 4). These potent agents were as-

Table 4. Pharmacodynamic Studies Including Potent $P2Y_{12}$ Inhibitors (Prasugrel or Ticagrelor)

Study	Year	No. of Patients	Patient Population	$P2Y_{12}$ Inhibitors	Platelet Function Assay	Key Results
Wang et al[82]	2017	60	Patients with CKD with NSTE-ACS (randomized 1:1 to ticagrelor vs clopidogrel)	Ticagrelor Clopidogrel	VerifyNow P2Y12	Lower PRU in patients treated with ticagrelor vs clopidogrel at 30 days (32.6±11.29 vs 203.7±17.92; *P*<0.001) as well as at 2 h, 8 h, and 24 h after loading dose (*P*<0.001)
Nishi et al[87]	2016	53	Patients with and without CKD with stable CAD	Clopidogrel Low-dose (3.75 mg) Prasugrel	VerifyNow P2Y12	Platelet inhibition is lower for clopidogrel but not for prasugrel in patients with CKD. Lower platelet reactivity levels with prasugrel regardless of the presence of mild to moderate CKD
Barbieri et al[83]	2015	537	Patients with CKD with ACS and DAPT (nonrandomized)	Ticagrelor Clopidogrel	Multiplate analyzer	In patients with DAPT, CKD did not influence platelet reactivity levels with either ticagrelor or clopidogrel
Deharo et al[86]	2015	703	Patients with ACS with and without CKD (nonrandomized)	Prasugrel Ticagrelor	VASP	Lower PRU values in patients treated with ticagrelor vs prasugrel. Similar findings in the subgroup of all patients with CKD (16.7%±1.4 vs 25.0%±0.8; *P*<0.0001) and for moderate to severe patients with CKD (16.7% ± 2.8 vs 25.4% ± 1.8; *P*<0.001)
Jeong et al[84]	2015	25	Patients with CKD with hemodialysis (randomized crossover study)	Ticagrelor Clopidogrel	VerifyNow P2Y12	Faster and greater platelet inhibition in ticagrelor vs clopidogrel treated patients
Alexopoulos[85]	2012	20	Patients with CKD with hemodialysis (nonrandomized)	Ticagrelor Clopidogrel	VerifyNow P2Y12	Ticagrelor maintenance dose effectively reduces platelet reactivity in hemodialysis patients who are clopidogrel poor responders

ACS indicates acute coronary syndrome; and CKD, chronic kidney disease.

sociated with substantially lower levels of platelet reactivity, and on clopidogrel HPR could be overcome by a switch to potent agents in the majority of CKD patients. These results were independent of the level of kidney function. These biological findings offer promise in order to reduce the ischemic burden of CKD patients.

CLINICAL OUTCOME WITH POTENT P2Y12-ADP RECEPTOR ANTAGONISTS IN CKD PATIENTS WITH ACS

As underlined above, the biological efficacy of the potent $P2Y_{12}$-ADP receptor antagonists, prasugrel and ticagrelor, compared to clopidogrel was well demonstrated in patients with ACS.[18,19] Subsequently to their superior biological efficacy, in the overall population of RCT, potent P2Y12-ADP receptor antagonists translated into a benefit on MACE with a 15 to 20% risk reduction compared to clopidogrel in patients with ACS (prasugrel versus clopidogrel: relative ischemic risk reduction of 19%; ticagrelor versus clopidogrel: relative ischemic risk reduction of 16%). In parallel, an increase in non-CABG related TIMI major bleedings was noted (for ticagrelor versus clopidogrel: 2.8 versus 2.2%; *P*=0.03 and 2.4 versus 1.8%; *P*=0.03 for prasugrel versus clopidogrel).[3,4]

Although there are no dedicated trials for the CKD population, the clinical impact of these potent P2Y12-ADP antagonists can be evaluated by subgroup analysis of recent trials and registries as described below and in Table 2 and Figure 3.

ACS Patients Managed With Coronary Artery Bypass Surgery

The current guidelines on antiplatelet therapy in ACS patients managed surgically support clopidogrel or ticagrelor in association with aspirin.[9,10] This is based on the subgroup analysis of the PLATO trial. In this trial, 1261 patients received coronary revascularization with CABG within 7 days after the last study drug uptake. The overall benefit of ticagrelor compared to clopidogrel on MACE was similar to the whole trial (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.6–1.16; *P*=0.29) without excess in CABG major related bleedings (59.3 versus 57.6%; *P*=0.5). No significant interaction between CABG and treatment groups (p for interaction not available) was observed. In this sub group analysis CKD patients however did only represent ≈5% of patients and no specific analysis is available.[3,90]

ACS Patients With Medical Management

Currently the guidelines for antiplatelet therapy in medically-managed ACS support ticagrelor or clopidogrel in addition to aspirin.[9,10]

The TRILOGY ACS trial (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) was a randomized study comparing prasugrel and clopidogrel over 30 months in combination to aspirin in medically-managed ACS patients (Table 4). In the main cohort, the primary end point of cardiovascular death, myocardial infarction, and stroke

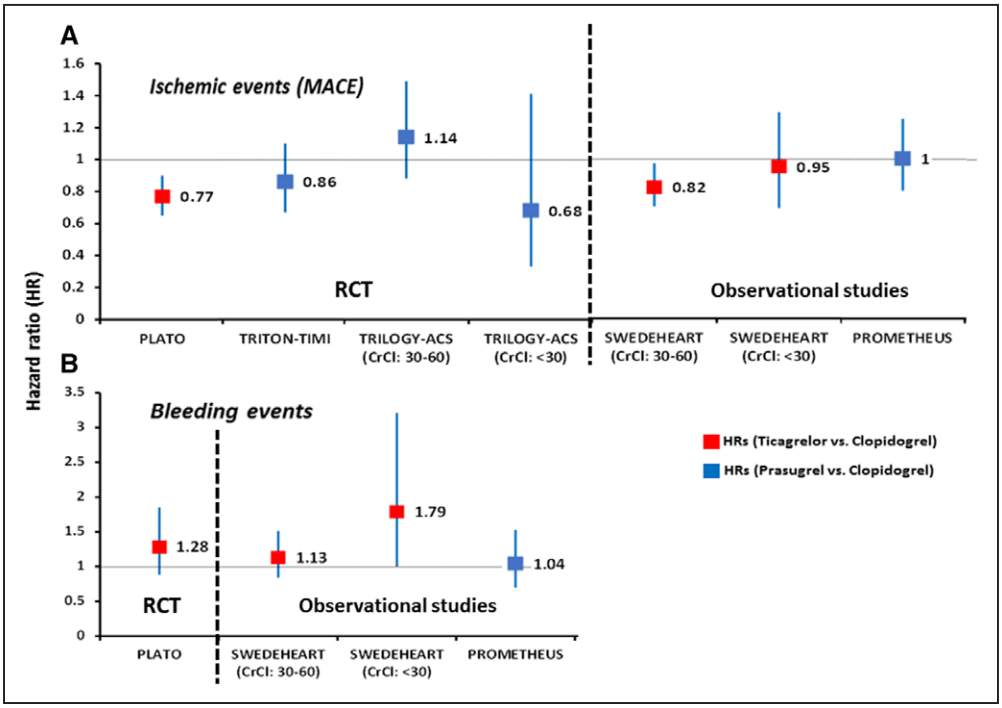

Figure 3. Hazard ratios of ischemic and bleeding events comparing potent P2Y12-ADP receptor antagonists and clopidogrel in chronic kidney disease (CKD) patients with acute coronary syndrome (ACS) in randomized, clinical trials (RCTs) and observational studies.[1–5]
A, Ischemic events (major adverse cardiovascular events [MACE]). **B**, Bleeding events. CrCl indicates creatinine clearance

was not improved with prasugrel compared with clopidogrel (13.9 versus 16.0%; *P*=0.20). The rates of severe and intracranial bleeding were similar in the 2 groups (TIMI major 2.1 versus 1.5%; *P*=0.27). In a prespecified subgroup analysis, the authors observed that patients with moderate or severe CKD had an excess in the risk of both ischemic and bleeding events. However, no differences were observed between prasugrel and clopidogrel on outcomes in these subgroups. This result was reinforced by the lack of interaction between outcome and treatment groups (*P* value for interaction 0.46 for ischemic and 0.30 for bleedings; Figure 3).[5,89] Based on these results prasugrel seems to offer no benefit over clopidogrel in medically managed ACS patients.

However, the available evidence draws a more complex picture for ticagrelor. Overall in the PLATO trial, which compared ticagrelor and clopidogrel in ACS patients, 3143 of 18 624 patients were managed noninvasively. Ticagrelor reduces the rate of ischemic events compared with clopidogrel (HR, 0.85; 95% CI, 0.73–1.00; *P*=0.04). No difference was observed regarding major bleeding in these patients (HR, 1.3; 95% CI, 0.95–1.77).[91] Regarding the subgroup of patients with CKD, the risk reduction was similar to that of the overall trial population. No interaction was noted between treatment and CKD suggesting a similar risk-benefit ratio in CKD compared to non-CKD patients (ticagrelor versus clopidogrel [odds ratio (OR) for MACE, 0.77; 95% CI, 0.65–0.90; *P* for interaction =0.13]; OR for TIMI major non-CABG–related bleedings, 1.28; 95% CI, 0.88–1.85; *P*=0.98]). However, the number of medically-managed patients in the CKD subgroup was small with ≈40% of the cohort (n=1306). This is particularly true for patients with a creatinine clearance <30 mL/min, which was composed of 214 patients.[92]

Overall subgroup analyses suggest a favorable risk benefit ratio of ticagrelor in medically managed ACS patients with CKD and a creatinine clearance above 30 mL/min.

ACS Patients With Invasive Management

ACS patients with and without CKD are mostly treated invasively by PCI.[9,10] Interestingly, registries, including contemporary ones, observed that invasive management was underused in patients with CKD and that such underuse contributes to their poorer outcome.[8,93] Optimal platelet inhibition during and after PCI is crucial to prevent acute and subacute stent thrombosis which can lead to a dramatic outcome. In general, CKD patients exhibit a higher risk of stent thrombosis in line with their procoagulant state and higher rate of HPR under clopidogrel.[94] Thus, potent $P2Y_{12}$-ADP antagonists are expected to be particularly beneficial in CKD patients because these patients exhibit both a reduced efficacy of clopidogrel and an overall increased ischemic risk.

Available Subgroup Analyses of RCT

Comparisons of potent $P2Y_{12}$-ADP receptor antagonists and clopidogrel in CKD patients with ACS undergoing PCI are available with outcome data in the subgroup analysis of the 2 RCTs (TRITON TIMI 38 and PLATO studies) and 2prospective dedicated registries (Prometheus and SWEDEHEART; Figure 3).[1–4,8,92–95]

In the TRITON TIMI 38 trial, 13 608 patients undergoing PCI for an ACS were randomized to prasugrel or clopidogrel. In the subgroup analysis, which included 1490 patients with a creatinine clearance <60 mL/min, the benefit of prasugrel compared with clopidogrel was similar to that of the overall population as illustrated by the lack of significant interaction between treatment groups and CKD. Unfortunately, bleeding end points are not available for this subgroup of patients, but, in the overall trial population, prasugrel increased the rate of major non-CABG related TIMI bleeding[4] (Figure 3).

In the PLATO trial, which compared ticagrelor to clopidogrel in intermediate and high-risk ACS patients, the CKD group was composed of 3237 patients followed over a mean of 9 months. In invasively managed patients, ticagrelor reduced the rate of MACE compared to clopidogrel with a HR of 0.84 (95% CI, 0.75–0.94), without excess in TIMI major non-CABG related events with a HR of 1.28 (95% CI, 0.88–1.85).[3,95] No interaction was noted between CKD and treatment groups suggesting a similar risk–benefit ratio in patients with compared with patients without CKD (*P*=0.13). However, interestingly, all-cause mortality was lower in the ticagrelor group, with a 36% reduction (3.9 versus 5%; *P*=0.01) compared with a nonsignificant reduction in non CKD patients.[95] In addition, Silvain et al,[96] when analyzing the data using the Modification of Diet in Renal Disease formula instead of the Cockcroft and Gault formula, to better classify CKD, observed a significant interaction between CKD and treatment, suggesting a larger benefit of ticagrelor in patients with CKD compared to those without.

In these 2 large clinical trials, patients with CKD undergoing PCI for an ACS had a major clinical benefit of the use of potent $P2Y_{12}$-ADP receptors antagonists compared with clopidogrel on ischemic events. The risk–benefit ratio of ticagrelor in invasively managed ACS was positive with a reduction of ischemic events without increased bleeding.

However, it must be acknowledged that the number of patients with stage ≥4 CKD was limited. Therefore, no conclusions can be drawn for this latter group of patients.

Available Observational Studies

Recently, 2 registries compared the potent oral $P2Y_{12}$-ADP receptors antagonists with clopidogrel in contem-

porary PCI of ACS patients with CKD. They provide data from routine clinical practice to further delineate the net clinical benefit of $P2Y_{12}$-ADP receptor antagonists in this population.

Baber and colleagues[1] recently reported the results of the PROMETHEUS registry which was a prospective multicenter observational study. They enrolled ACS patients undergoing PCI under clopidogrel or prasugrel. Among the 19 832 patients included, 28.3% had CKD defined by a creatinine clearance <60 mL/min using the Chronic Kidney Disease Epidemiology Collaboration formula. These patients were less frequently prescribed prasugrel despite their higher risk profile. Regarding clinical outcome, after propensity adjustment prasugrel was not superior to clopidogrel with respect to the incidence of a composite of end point consisting of death, myocardial infarction, stroke, and urgent revascularization at 1 year in the CKD subgroup (adjusted HR, 1.0; 95%, CI 0.8–1.25) and similar bleedings (adjusted HR, 1.04; 95% CI, 0.7–1.53).[1]

Edfors and colleagues[2] analyzed the SWEDEHEART database to provide a comparison of ticagrelor and clopidogrel in CKD patients undergoing PCI for an ACS. This registry compared potent P2Y12-ADP receptor antagonists and clopidogrel in invasively managed CKD patients with ACS. In this registry, 11 538 patients had CKD defined as a creatinine clearance <60 mL/min according to the Chronic Kidney Disease Epidemiology Collaboration formula. These patients were further divided into moderate CKD (30–60 mL/min) and severe CKD (<30 mL/min). Patients with moderate CKD had lower rates of death, myocardial infarction, and stroke at 1-year follow-up when treated with ticagrelor compared with clopidogrel (adjusted HR, 0.82; 95% CI, 0.7–0.97). No benefit was observed for patients with severe CKD (adjusted HR, 0.95; 95% CI, 0.69–1.29). Of note, there was no interaction between treatment and kidney function (P_{int}=0.55). The database captured rehospitalization for bleeding, which did not differ between groups in moderate CKD (OR, 1.13; 95% CI, 0.84–1.51), but a trend was observed toward higher bleeding rates in severe CKD (adjusted HR, 1.79; 95% CI, 1.00–3.21). Again, there was significant interaction (P_{int}=0.30).[2]

Overall, the subgroup analyses of the PLATO trial and the SWEDEHEART registry suggest that ticagrelor reduces ischemic events without increasing bleeding in CKD patients undergoing PCI for an ACS compared with clopidogrel. The large absolute risk reduction further strengthens the potential benefit of ticagrelor in this population. However, it must be underlined that the relative risk reduction was similar to non-CKD patients, suggesting that optimal P2Y12-ADP receptor blockers did not alter the pathophysiological processes at play in the increased ischemic risk associated with CKD. For prasugrel, the benefit observed in TRITON-TIMI 38 was not confirmed in a large registry, and the bleeding risk remains not fully elucidated (Figure 3).

These results should not be extrapolated to patients with stage ≥ 4 CKD.

END-STAGE RENAL DISEASE AND HEMODIALYSIS

Patients with ESRD undergoing hemodialysis represent a small subset of patients. Although they have the highest cardiovascular mortality mortality, the cause differs from that of patients with lower CKD stage.[37] In fact, in this subgroup of patients, cardiovascular mortality mortality is mainly related to nonatherosclerosis disease. Thus, the potential benefit of improved care of acute coronary syndromes and in particular optimized antiplatelet therapy may be reduced in these patients. Consistently the limited evidence available in the SWEDEHEART study points to a potential harm of increased PR inhibition with the potent P2Y12-ADP receptor antagonists.[2]

OPTIMAL ANTIPLATELET TREATMENT IN CKD ACS PATIENTS AND FUTURE PERSPECTIVES

Despite improvements in the care of ACS patients, including latest generation drug-eluting stents that reduce restenosis and stent thrombosis, together with improved antiplatelet agents, the higher ischemic risk of CKD patients persists[20,25] (Table 2). It is likely related to the complex alterations of the vascular milieu in the context of altered kidney function. Apart from reestablishing complete kidney function, alternate means of restoring a more physiological vascular milieu may be necessary to further improve the clinical outcome of these patients.

Regarding the case of P2Y12-ADP receptor antagonists, prasugrel and ticagrelor have demonstrated their clinical efficacy in ACS. Despite a higher bleeding risk, these drugs have a positive risk benefit ratio thanks to a greater ischemic risk reduction in high-risk patients such as those with CKD. In medically managed CKD patients, there seems to be a benefit of ticagrelor in mild to moderate CKD although the evidence remains limited. In invasively managed CKD, ticagrelor provides clinical benefit over clopidogrel. For prasugrel, there is some uncertainty since bleeding data are not available and the Prometheus study did not confirm the ischemic benefit. Finally, in patients with stage ≥ 4, evidence is lacking to support one P2Y12 inhibitor over the others (Table 5). In fact, there is an increased risk of recurrent ischemic events,

Table 5. Proposed Algorithm for P2Y12-ADP Receptor Selection Depending on Management and Stage of Kidney Failure Based on Available Literature

Chronic Kidney Disease Type	Creatinine Clearance, mL/min	Acute Coronary Syndrome					Coronary Artery Bypass Surgery	
		Managed Medically		Managed Invasively				
No chronic kidney disease	≥90	Clopidogrel	Ticagrelor	Prasugrel		Ticagrelor	Ticagrelor	Clopidogrel
Mild	60–89	Clopidogrel	Ticagrelor	Prasugrel		Ticagrelor	Ticagrelor	Clopidogrel
Moderate	30–60	Clopidogrel	Ticagrelor	Prasugrel		Ticagrelor	Ticagrelor	Clopidogrel
Severe	15–29	Clopidogrel		Clopidogrel	Prasugrel	Ticagrelor	Clopidogrel	
End-stage chronic kidney disease or dialysis	<15 or kidney replacement therapy	Clopidogrel		Clopidogrel			Clopidogrel	

but also increased risk of drug side effects and safety hazard with worsening CKD.

A number of additional therapeutic strategies may help optimize outcomes of CKD patients. First, beyond optimized concepts on antiplatelet treatment in CKD patients, device-based approaches like the use of polymer-free drug-eluting stents in high bleeding risk patients (which include most of the CKD patients), which can come along with a shorter DAPT course of 1 month, may help to mitigate CKD patients´ bleeding risk although this as yet to be adequately assessed in this specific population.[97] Second, results from the large ADAPT DES registry have highlighted that bleeding risk is not uniform but varies by the level of platelet reactivity in non-CKD but also in CKD patients.[98] A platelet function testing guided approach and especially a guided DAPT de-escalation, as it was investigated in the TROPICAL-ACS trial,[99] may prove useful in the complex cohort of CKD patients by reducing bleeding risk without increasing the risk of ischemic complications. Dedicated studies and analyses are however needed to explore this hypothesis. Third, a number of algorithms and risk scores (PARIS score, DAPT score, PRECISE-DAPT score) have been published and promoted to inform clinical decisions on DAPT duration and regarding thrombotic and bleeding risk. The value of such scoring systems warrants specific investigation in CKD patients.

Dedicated trials or appropriate inclusion of CKD patients' in future randomized trials should be encouraged. A specific research program is required to not only test new therapies in the ACS field but also to evaluate therapies targeting the specific pathophysiology of ischemic and bleeding events in this population. Development of biomarkers to evaluate the ischemic and bleeding risk could help tailor therapy and improve the clinical outcome in these patients. Specific studies are required for patients with stage ≥4 CKD who represent an even more understudied cohort of patients. Improved awareness of physician are required to further reduce under treatment in these patients and promote up-to-date care.

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Disclosures

Dr Bonello reports the following relationships: research grants from AstraZeneca, Boston, Abbott, and Biosensors; and lecture fees from AstraZeneca, Medtronic, and Abbott. Dr Angiolillo reports receiving payments as an individual for: consulting fee or honorarium from Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Janssen, Merck, PLx Pharma, Pfizer, Sanofi, and The Medicines Company; participation in review activities from CeloNova and St. Jude Medical; institutional payments for grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, and Renal Guard Solutions. In addition, Dr Angiolillo is recipient of a funding from the Scott R. MacKenzie Foundation and the National Institutes of Health/National Center for Advancing Translational Science Clinical and Translational Science Award to the University of Florida UL1 TR000064 and National Institutes of Health/National Human Genome Research Institute U01 HG007269, outside the submitted work. Dr Aradi has received lecture fees from Daiichi Sankyo/Lilly, Roche Diagnostics, AstraZeneca, Bayer, Pfizer, and Merck Sharp & Dohme Corp. Dr Sibbing reports grants from Roche Diagnostics, grants from Daiichi Sankyo; personal fees from Bayer AG, personal fees from Daiichi Sankyo, personal fees from Eli Lilly, personal fees from Roche Diagnostics, personal fees from Merck Sharp & Dohme Corp, personal fees from Pfizer, personal fees from Astra Zeneca, outside the submitted work.

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