Impaired platelet P2Y12 inhibition by thienopyridines in chronic kidney disease: mechanisms, clinical relevance and pharmacological options

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ABSTRACT

Patients with chronic kidney disease (CKD) represent an increasing proportion of the population undergoing percutaneous coronary intervention (PCI) and up to 40% of the patients treated for acute coronary syndrome (ACS). Several studies and registries in the setting of ACS and elective PCI have reported a negative association between CKD and mortality, stent thrombosis, post-procedural ischaemic events and bleeding events. Pharmacological inhibition of the adenosine diphosphate receptor by thienopyridines or ticagrelor and disruption of the cyclooxygenase pathway by aspirin constitute the current standards of care to prevent thrombotic complications following stent-based PCI. In CKD patients, the avoidance of anti-platelet therapy may be driven by the lack of clinical trial data to support its efficacy, by errors or omissions, or by a reluctance to use this therapy in a population characterized by its enhanced bleeding risk. However, there is growing evidence to suggest that a severely decreased glomerular filtration rate per se, independent of the presence of diabetes mellitus, is an important determinant of high residual platelet reactivity under a clopidogrel maintenance dose. Recent reports have emphasized that the impact of impaired platelet inhibition by thienopyridines is of paramount importance in CKD patients, with an enhanced mortality rate in low-responder patients. Pharmacodynamic studies indicate the phosphodiesterase 3 inhibitor, cilostazol, the third generation thienopyridine prasugrel and the reversible P2Y12 antagonist ticagrelor to be potent strategies to overcome this biological resistance. In clinical practice, platelet function testing should be considered in CKD patients undergoing PCI, especially in those who experience thrombotic events despite dual therapy. Newer agents should be contemplated in patients who display higher residual platelet aggregability after standard treatment. Among these, the non-thienopyridine P2Y12 receptor antagonist ticagrelor, which does not require biotransformation, could be the drug of choice in CKD patients with ACS. In this population, ticagrelor has been found to reduce mortality and ischaemic events with an acceptable bleeding risk.

INTRODUCTION

Patients with chronic kidney disease (CKD) represent an increasing proportion of the population undergoing percutaneous coronary intervention (PCI) and up to 40% of the patients treated for acute coronary syndrome (ACS) [1]. Several studies and registries in the context of ACSs and elective PCI have reported a negative association between CKD on the one hand and mortality, stent thrombosis, post-procedural ischaemic events and bleeding events on the other hand [1–5]. One year after successful PCI, the mortality was 5-fold higher in patients with moderate CKD and 12-fold
higher in patients with severe CKD than in those with normal renal functions [6]. In patients with acute myocardial infarction, the mortality rate at 1 year was 12.7% in moderate CKD patients when compared with 2.4% in individuals without CKD [3]. Recent data from a national registry show a very high mortality in patients with severe CKD and those on long-term dialysis, with nearly one in three (32.7%) and more than one half (52.0%), respectively, dying within 3 years [1].

The mechanisms through which CKD affects the clinical outcome are probably multifactorial and may include endothelial dysfunction, persistent micro-inflammation, coronary calcification, platelet activation and insufficient use of well-proven therapies. Pharmacological inhibition of the adenosine diphosphate (ADP) receptor (encoded by the P2RY12 gene) by thienopyridines or ticagrelor and disruption of the cyclooxygenase pathway by aspirin are the current standards of care to prevent thrombosis after stent-based PCI. CKD is usually a condition eliciting a more conservative approach with less revascularization and use of fewer drugs at lower doses [7]. The avoidance of cardioprotective medication including anti-platelet therapy may be driven by the lack of clinical trial data to support its efficacy, by errors or omissions, or by the reluctance to use this therapy in a CKD population characterized by an enhanced bleeding risk [2].

Due to the lack of sufficient studies, the American College of Cardiology and American Heart Association give no specific recommendations for patients with CKD. Since individuals with CKD have often been excluded from clinical trials, the clinical impact of more potent P2Y12 inhibition remains largely unexplored in this particular population with an increased bleeding risk. Very recently, two registry studies have emphasized the deleterious impact of hyporesponsiveness to thienopyridines, with a worsened cardiovascular (CV) outcome in CKD patients including an enhanced mortality rate [8, 9]. In line with these data, the Platelet Inhibition and Patient Outcomes (PLATO) trial demonstrated that more potent inhibition of the P2Y12 pathway by ticagrelor, a reversible antagonist, had a major effect in CKD patients and resulted in an improved CV outcome [10].

In this review, we will summarize the putative mechanisms involved in impaired P2Y12 inhibition by thienopyridines in CKD and highlight the evidence supporting the need for optimal platelet inhibition in CKD patients in primary and secondary cardioprotection. We will also discuss strategic options to overcome impaired P2Y12 inhibition in the setting of PCI.

**PLATELET FUNCTION IN CKD**

In addition to a higher incidence of atherosclerotic disease and CV comorbidities, several small studies have emphasized the existence of platelet dysfunction in CKD patients. Many pathways of platelet activation have been hypothesized to play a causative role in this increased thrombotic and bleeding risk. Alterations in primary haemostasis as a result of intrinsic platelet abnormalities and impaired platelet–vessel wall interactions have been described for a long time in CKD patients and speculatively associated with an enhanced bleeding risk. After vascular injury, shear-induced platelet aggregation, involving von Willebrand factor (vWF) and platelet glycoproteins (GP) Ia and IIb-IIIa, is a determinant process in primary haemostasis. In uraemic patients, part of the platelet dysfunction could be explained by decreased GP IIb-IIIa availability due to receptor occupancy by fibrinogen and vWF fragments [11] or uraemic toxins [12]. An impairment of cytoskeletal organization leading to decreased cell spreading was described at baseline in platelets from uraemic patients, an abnormality which was more evident after thrombin stimulation [13]. The activation of several platelet inhibition pathways has also been reported in uraemic patients. Uraemic platelets generated more NO than control platelets, whereas intraplatelet levels of cyclic guanosine monophosphate (the NO second messenger) were also higher in uraemic than in control cells [14, 15]. Both cytoskeletal abnormalities and the activation of inhibitory pathways could contribute to diminishing the secretory ability of these platelets, as testified by a decreased release of adenosine triphosphate and a reduced serotonin content in dense granules [16]. However, if mild differences in platelet function seem to exist, their clinical impact on the bleeding risk would appear to be limited. Thus, recent data have suggested that the skin bleeding time correlates poorly with measurements of platelet function, the elevated bleeding time in uraemic patients reflecting perturbations in platelet adhesion or secretion rather than aggregation [17].

Conversely, other studies support the hypothesis of an enhanced platelet activation in uraemic patients, which could be associated with the thrombotic risk. When assessing the exposure of phosphatidylserine, a hallmark of platelet stimulation, in the outer leaflet of the plasma membrane of uraemic platelets, Bonomini et al. [18] observed an intense membrane remodelling together with the exposure of procoagulant aminophospholipids. In line with this drastic platelet activation, the enzymatic activity of caspase 3, a protease involved in membrane remodelling, microparticle shedding and platelet ‘apoptosis’ [19], was found to be increased in platelets isolated from uraemic patients [18]. At the outer leaflet of stimulated platelets, phosphatidylyserine not only enables the assembly of the procoagulant enzymatic complexes tenase and prethrombinase, but also constitutes a recognition signal favouring the clearance of senescent cells by macrophages. Consistent with this view, CKD patients exhibit higher levels of various markers of platelet activation including P-selectin and CD40 ligand [20] or platelet-derived microparticles shed by stimulated platelets [21]. Accordingly, an enhanced expression of different markers of activation could be detected in the outer leaflet of the plasma membrane of platelets from patients with either mild or moderate CKD. In this study, the expression of various markers of platelet activation was inversely related to the estimated glomerular filtration rate (eGFR) [22]. In other work, the changes in platelet surface receptor activation, if they exist, appeared to be of limited extent [23]. Altogether, some degree of platelet activation probably occurs in CKD patients, and the subsequent clearance of stimulated cells could contribute to an increased platelet turnover, especially in haemodialyzed patients, who
are characterized by a low platelet count and elevated thrombopoietin levels [24].

**IMPACT OF CKD ON PLATELET INHIBITION BY THIENOPYRIDINES**

Recent findings from randomized trials have suggested that renal function could influence the clinical efficacy of clopidogrel (see below). Indeed, CV outcomes in patients receiving clopidogrel were found to be worse in the presence of CKD than in those with normal renal function [25, 26]. Whether CKD affects the pharmacokinetics of clopidogrel has not been conclusively clarified. In small cohorts, the extent of platelet inhibition by clopidogrel would appear to be comparable between CKD patients [27, 28], including those on maintenance haemodialysis [29] and individuals with normal renal function. There is on the other hand evidence that a lack of platelet responsiveness to clopidogrel may be more pronounced in patients with CKD. Several recent studies have shown that a low eGFR was associated with reduced antplatelet effects of clopidogrel, especially in patients with diabetes mellitus (Table 1).

A first insight into the deleterious impact of CKD on platelet responsiveness to clopidogrel was obtained by Park et al. [30]. In this study, a higher residual platelet reactivity was observed in a small cohort of patients with severely decreased eGFR (18 patients, 83% Stage 5 CKD). The percentage of P2Y12 inhibition by clopidogrel (75 mg/day) as assessed by the Verify Now assay, a semi-automated, cartridge-based platelet function assay in whole blood, which measures the agglutination of fibrinogen-coated beads by ADP-stimulated platelets, was 66% higher in patients without CKD (no CKD 35 ± 20 versus CKD 21 ± 16%; P = 0.013). Similarly, there was a significant negative relationship between serum creatinine and the percentage of platelet inhibition by clopidogrel (r = −0.363; P = 0.005). However, as the prevalence of diabetes mellitus, an important factor associated with impaired P2Y12 inhibition by clopidogrel, was much higher in the low eGFR group (72 versus 30%), no definite conclusion could be reached concerning the independent contribution of the latter to the alteration in clopidogrel pharmacodynamics.

In a larger cohort of diabetic patients, Angiolillo et al. [31] confirmed the deleterious effect of a decreased eGFR on platelet inhibition by clopidogrel. These authors observed higher ADP-induced (60 ± 13 versus 52 ± 15%; P = 0.001) and collagen-induced (49 ± 20 versus 41 ± 20%; P = 0.004) platelet aggregation in patients with moderate/severe CKD (n = 84) when compared with those without CKD (n = 222). After adjustment for potential confounders, CKD patients were more likely to have high post-treatment platelet reactivity (HPPR) upon stimulation by ADP (adjusted odds ratio [OR] 3.8; 95% confidence interval [CI] 1.7–8.5; P = 0.001) or collagen (adjusted OR 2.4; 95% CI 1.1–5.4; P = 0.001). In this work, consistent with a previous report by Park et al. [30], the proportion of HPPR after ADP stimulation was 71% higher among CKD patients (35.7 versus 20.8%; OR 2.1; 95% CI 1.2–3.7; P = 0.007) [31].

Since diabetes accounts for nearly one half of the end-stage renal failure cases in the USA [32] and is also associated with a high prevalence of HPPR [33, 34], this disease constitutes a major confounding factor when assessing the impact of a decreased eGFR on the extent of platelet inhibition. We therefore investigated whether a low eGFR per se alters the pharmacodynamics of clopidogrel independently of diabetes [35]. As the most severe cases are usually excluded from clinical trials, special attention was paid to including patients with end-stage renal failure. In this study, the extent of platelet inhibition by clopidogrel was evaluated using the platelet vasodilator-stimulated phosphoprotein flow cytometry test (VASP-FCT), specific for the P2Y12 ADP receptor pathway [36], and the Verify Now assay [35] in patients under clopidogrel treatment (75 mg/day) for at least 8 days. An inverse relationship was found between eGFR and platelet reactivity as assessed either by the VASP assay (r = −0.307; P < 0.001) or by the Verify Now assay (r = −0.485; P < 0.001). In this cohort, the proportion of patients with HPPR increased steadily from ∼20% in patients with Stage 1–2 CKD to 35% in those with Stage 3 or 4 CKD and up to >60% in Stage 5 CKD patients. Interestingly, no impact of the dialysis procedure on platelet reactivity could be substantiated. In a multivariate model with adjustment for diabetes mellitus, Stage 5 CKD was identified as an independent predictor of HPPR (adjusted prevalence ratio 2.82; 95% CI 1.09–8.71;...
P = 0.04). This finding is in agreement with several recent reports [9, 20]. As an example, in the PREDICT study (1092 patients), renal failure as defined by a serum creatinine of >1.5 mg/dL was an independent risk factor for high post-treatment platelet aggregation in PCI patients receiving clopidogrel [37]. Likewise, in a larger cohort (1567 patients), an ∼2-fold increase in the proportion of low responders to clopidogrel was observed in Stage 4–5 CKD when compared with Stage 1–2 CKD patients [9].

Overall, a growing body of evidence suggests that a severely decreased eGFR per se is an important determinant of high residual platelet reactivity, independently of diabetes mellitus, under a maintenance dose of clopidogrel.

**PUTATIVE MECHANISMS OF IMPAIRED CLOPIDOGREL PHARMACODYNAMICS IN CKD PATIENTS**

In analysing the potential mechanisms accounting for the poor efficacy of thienopyridines in CKD patients, it is pertinent to understand the complex metabolism of clopidogrel that can be altered in uraemia. Clopidogrel is a prodrug requiring hepatic conversion to exert its anti-platelet effect. After its intestinal absorption, which is limited by the P-GP efflux transporter encoded by the ABCB1 gene containing an adenosine triphosphate-binding cassette, also known as the multidrug resistance 1 (MDR1) gene, most of the absorbed clopidogrel (85%) is hydrolysed by esterase to an inactive metabolite, while the remaining 15% is rapidly metabolized by hepatic cytochromes in a two-step process. In this hepatic process, the thiophene ring of clopidogrel is oxidized to 2-oxo-clopidogrel, which is then hydrolyzed by the esterases PON-1 and PON-3 to a highly labile active metabolite, R-130964. Recent studies indicate that CYP2C19, CYP1A2 and CYP2B6 participate in the first metabolic step, whereas CYP2C19, CYP2C9, CYP2B6 and CYP3A are responsible for the second step. A number of lines of evidence strongly suggest that variable and insufficient active metabolite generation are the primary cause of the variability of the clopidogrel response and of non-responsiveness. In the setting of uraemia, every step could contribute to reduction of the bioavailability of clopidogrel. Limited absorption could be induced by the alteration of the intestinal microbial flora observed in end stage renal disease (ESRD) patients, by reduced expression of the organic anion transporter responsible for drug transport into enterocytes and hepatocytes or by coprescription of chelating drugs like calcium carbonate [37, 38]. Several esterase activities such as that of PON-1 can be altered in uraemia [39]. Finally, uraemia reduces the expression and activity of a variety of CYP450s, including CYP2C19 and CYP3A4, which are crucial for clopidogrel metabolism [38].

Therefore, challenging the current paradigm focusing on platelet hyperactivity in CKD [31], it cannot be excluded that the low platelet response to thienopyridines in these patients could result mainly from impaired drug absorption or metabolism [40, 41] and lower levels of circulating active metabolites. In line with this hypothesis, a previous study in a small cohort of ESRD patients revealed lower levels of the active metabolite of prasugrel [42], consistent with the concept of an altered metabolism of thienopyridine in CKD. The pharmacokinetics of clopidogrel in patients on haemodialysis or peritoneal dialysis are mostly unknown, as there are no data in the literature. The active metabolites are renally excreted, and a small proportion could theoretically be removed by dialysis. This mechanism is nevertheless unlikely to explain the alteration of clopidogrel pharmacodynamics observed in Stage 5 CKD, because both clopidogrel and its active metabolite are strongly bound to proteins (respectively, 98 and 94%) and this link is not saturable.

The precise mechanisms involved in the alteration of clopidogrel pharmacodynamics observed in CKD patients remain to be established. An alternative explanation is based on the accumulation of dinucleoside polyphosphates in uraemic patients [43]. Beyond their deleterious impact on the CV system including proatherogenic effects and an increase in arterial wall thickness, it has been shown that dinucleoside polyphosphates and, in particular, diadenosine tetraphosphate (Ap₄A), can act as partial agonists of the P2Y12 receptor [44]. In intact platelets from CKD patients, increased concentrations of dinucleoside polyphosphates were found in dense granules [45] and were released upon platelet activation [44]. Ex vivo, Ap₄A was found to be a weak agonist of P2Y12 causing a decrease in VASP phosphorylation and at the same time a partial antagonist of P2Y12 blocking the ADP-stimulated decrease in VASP phosphorylation [44]. Finally, we cannot exclude that an enhanced platelet turnover, as reflected by increased levels of thrombopoietin [24] and a low platelet count, could lead to insufficient P2Y12 inhibition by the available active metabolite of clopidogrel.

Whatever the exact mechanisms, there is converging evidence that end-stage renal failure patients constitute a specific population with a 2- to 3-fold increase in the prevalence of impaired P2Y12 inhibition under a routine clopidogrel regimen.

**CLINICAL IMPACT OF CKD ON THE EFFICACY OF CLOPIDOGREL**

Several studies have investigated the clinical benefit of thienopyridines in CKD patients. In the CREDO trial, patients with mild or moderate CKD had a 2- to 4-fold higher death rate and a 2-fold higher risk of myocardial infarction after PCI. CKD patients therefore have the potential to derive a greater benefit from intensive anti-platelet therapy. In this trial, in addition to aspirin therapy, the patients were randomly assigned to receive clopidogrel (300 mg) or placebo 3–24 h before PCI followed by clopidogrel (75 mg/day) directly after the procedure and once daily for 28 days. After 28 days, those who had been given the loading dose of clopidogrel continued to receive 75 mg/day for 1 year. Whereas long-term use of clopidogrel resulted in a significant reduction in major adverse CV events at 28 days and 1 year in patients with normal renal functions, its benefit was less apparent in mild CKD and vanished in moderate CKD [25]. In this
post hoc analysis of the CREDO trial, the relative and absolute bleeding risk associated with long-term clopidogrel therapy was less among moderate CKD patients than in those with mild or no CKD. Likewise in the CURE trial, clopidogrel therapy was not found to afford any significant improvement in outcome in the lowest eGFR tertile, but did result in a significant reduction in adverse events in the middle and upper tertiles [46]. Although the CREDO and CURE trials were not designed to provide pharmacokinetic insights, one possible explanation for the lack of efficacy of clopidogrel in moderate CKD patients could be the alteration of its metabolism and bioavailability in these patients as described above. As speculated by the authors, the dose requirement of clopidogrel may be greater in CKD patients, or it may take longer for the loading dose to adequately inhibit the P2Y12 pathway [25].

Apart from the clinical setting of ACS or PCI that was mainly investigated in the CURE and CREDO trials, another interesting subgroup of patients is those with established atherosclerotic disease (symptomatic) or multiple risk factors for atherosclerotic disease (asymptomatic). All CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management and Avoidance) patients (n = 15,603) were treated with aspirin and further stratified into three groups: non-diabetic patients, diabetic patients without nephropathy and diabetic patients with nephropathy. Within each group, outcomes were compared between patients randomly assigned to either clopidogrel or placebo. Patients with nephropathy who received clopidogrel displayed no difference in bleeding, but experienced significantly increased CV and overall mortality when compared with those receiving placebo. In the asymptomatic cohort, patients with nephropathy assigned to clopidogrel exhibited significantly increased overall and CV mortality when compared with those given placebo. Asymptomatic patients without nephropathy allocated to clopidogrel displayed no significant difference in mortality when compared with those receiving placebo [26]. In this study, the early increase in events detected in patients with nephropathy assigned to clopidogrel continued to rise with increasing duration of the therapy. This rise in mortality was nevertheless not accompanied by any significant increase in the bleeding risk in these patients, which would suggest an independent negative interaction.

If it is difficult to provide a pathophysiological explanation for the deleterious relationship between renal dysfunction and clopidogrel therapy, several hypotheses may be postulated. Diabetic nephropathy constitutes a prototype of advanced vascular damage, with atherosclerotic plaques characterized by the development of neo vaso-vasorum prone to bleeding. Intraplaque haemorrhage has indeed been reported to be an important factor in plaque vulnerability. Therefore, in patients on dual anti-platelet therapy, an increased incidence of intraplaque haemorrhage could paradoxically contribute to a higher rate of thrombotic events. However, since the rates of myocardial infarction and stroke were not significantly increased in patients with nephropathy assigned to clopidogrel in the CHARISMA trial [26], this hypothesis would appear highly unlikely.

Alternatively, the alteration of clopidogrel pharmacodynamics observed in CKD could explain why these patients may derive less benefit from the drug, although it does not explain why the drug could be harmful. Another interesting explanation involves the possible pleiotropic effects of clopidogrel on the inflammatory status. Several groups, including ours, have demonstrated the complex interplay between impaired platelet inhibition by clopidogrel, leukocytosis and fibrinogen levels, especially in diabetic patients [47–49]. P2Y12 inhibition by clopidogrel blunts the inflammatory response [50], and clopidogrel withdrawal is associated with proinflammatory and prothrombotic effects [51]. Other anti-inflammatory properties of clopidogrel could be due in part to its effect on the P2Y12 receptors expressed on leukocytes [52], which could blunt platelet–leukocyte interactions.

Whatever the precise mechanism, the clinical relevance of this interplay among leukocytes, inflammation and altered platelet inhibition by clopidogrel is supported by several large clinical trials. In the CAPRIE (clopidogrel versus placebo) trial, leukocyte count was a predictor of recurrent myocardial ischaemic events and stroke [53]. Interestingly, in STEMI patients of the CLARITY-TIMI 28 trial, clopidogrel reduced by 54% the adjusted OR of the primary endpoint only in patients with a neutrophil count below the median and was basically inefficient in those with a neutrophil count above the median [54]. Similarly, in patients of the secondary prevention subgroup of the CHARISMA trial, who received dual anti-platelet therapy with aspirin and clopidogrel, an increased neutrophil count was a significant predictor of death or myocardial infarction [55]. In this trial, another subgroup analysis of high risk patients showed that clopidogrel was ineffective in the presence of inflammation [56]. It is therefore tempting to speculate that, in CKD patients, the beneficial effects of clopidogrel may be reduced and outweighed by an enhanced inflammatory status, with a net increase in adverse outcomes [26].

**CLINICAL IMPACT OF IMPAIRED P2Y12 INHIBITION BY CLOPIDOGREL IN CKD PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION**

Besides the recent recognition of the existence of impaired P2Y12 inhibition in CKD, the real issue is how low responsiveness to clopidogrel could affect the CV outcome of CKD patients undergoing PCI. Two recent registries gave converging results [8, 9]. In our experience, at a mean follow-up of 9 ± 2 months post-PCI, all cause mortality, cardiac death and possible stent thrombosis were more frequent in CKD than in non-CKD patients [8]. In CKD patients, low responsiveness to clopidogrel as assessed by the VASP assay was associated with higher rates of all-cause mortality (25.5 versus 2.8%, P < 0.001), cardiac death (23.5 versus 2.8%, P < 0.001), all stent thrombosis (19.6 versus 2.7%, P = 0.003) and major adverse cardiac events (MACE, 33.3 versus 12.3%, P = 0.007). Conversely, the prognosis of CKD patients with a normal response to clopidogrel was similar to that of patients with a
normal eGFR. In patients with a normal eGFR, a low responder status did not substantially alter the CV outcome [8]. In a multivariate analysis, the combination of CKD and a low response to clopidogrel was found to be an important predictor of cardiac death (hazard ratio 11.96 [1.2–118.8], P = 0.033). Similarly, in the large registry published by the Tübingen group, the thienopyridine efficacy as measured by post-treatment platelet function was an important determinant of an increased risk of a short- or long-term adverse clinical outcome in CKD patients undergoing PCI [9]. The monitoring of platelet P2Y12 inhibition by thienopyridines would therefore appear to be useful in CKD and should be contemplated in every patient in order to tailor the antiplatelet therapy while carefully considering the bleeding risk.

**OVERCOMING IMPAIRED PLATELET P2Y12 INHIBITION IN CKD**

Since impaired P2Y12 inhibition constitutes an important risk factor for an adverse CV outcome following PCI, especially in CKD [8, 9], several studies have investigated the possible benefit of more potent P2Y12 inhibition in CKD patients (Table 2). The pharmacological options are represented by use of (i) a higher dose of clopidogrel, (ii) cilostazol, a selective and reversible phosphodiesterase 3 inhibitor, (iii) prasugrel, another thienopyridine affording irreversible and potent inhibition of the P2Y12 receptor or (iv) ticagrelor, a reversibly binding P2Y12 receptor antagonist that provides faster, stronger and more consistent P2Y12 inhibition than clopidogrel.

**Higher maintenance dose of clopidogrel**

In the past, it was found in a number of studies that increasing the maintenance dose of clopidogrel from 75 to 150 mg/day could elicit more intense platelet inhibition [57, 58]. Other studies in CKD patients nevertheless failed to demonstrate any such effect. Thus, in CKD patients, Park showed that impaired platelet inhibition by clopidogrel was not overcome by increasing the dosage (from 75 to 150 mg/day) [30].

Likewise, in the Piano-CKD 2 trial, in CKD patients on maintenance haemodialysis, a sustained high dose of clopidogrel (150 mg/day for 14 days) did not further suppress ADP-induced platelet aggregation [20].

**Cilostazol**

In the Piano-CKD 2 trial, the adjunction of cilostazol (100 mg twice daily, 14 days) to clopidogrel intensified the inhibition of platelet activation and significantly reduced the rate of HPPR in both the group assigned to clopidogrel 75 mg/day and that assigned to clopidogrel 150 mg/day (12 versus 46 and 32%, respectively, P < 0.05). Similarly, other markers of platelet activation such as CD40L or P-selectin exposure were significantly reduced in CKD patients on haemodialysis receiving clopidogrel and cilostazol [20].

**Prasugrel**

Another appealing strategy is the switch from clopidogrel to prasugrel, a third generation thienopyridine affording potent and irreversible P2Y12 inhibition. In patients with HPPR, the switch from clopidogrel to prasugrel can indeed provide effective platelet inhibition, as recently demonstrated in the TRIGGER PCI trial [59]. In the TRITON-TIMI 38 trial, in patients with ACS, intensive anti-platelet therapy with prasugrel resulted in fewer ischaemic events and less stent thrombosis when compared with standard clopidogrel therapy [60, 61]. In this trial, CKD was defined as an eGFR below 60 mL/min and was present in <12% of the cohort. In this study, the risk reduction of the primary end point afforded by prasugrel was of 14% in CKD patients (15.1 versus 17.5%) and of 20% (9.0 versus 11.1%) in non-CKD patients [60]. In the subgroup of patients treated by stenting, the reduction of definite and probable stent thrombosis using prasugrel instead of clopidogrel was even more pronounced in CKD patients (eGFR <60 mL/min: prasugrel 1.1% versus clopidogrel 3.9% [−70%]; eGFR >60 mL/min: prasugrel 1.1% versus clopidogrel 2.1% [−51%]) [61].

In the diabetic subgroup, the decrease in thrombotic events was similar in CKD (−32%) and non-CKD patients (−31%) [62]. In CKD patients on haemodialysis exhibiting Table 2: Overcoming impaired P2Y12 inhibition in CKD patients

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<th>Stage 5 CKD (%)</th>
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<td>Clopidogrel</td>
<td>75</td>
<td>Clopidogrel (75 mg/day)</td>
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<td>(150 mg/day)</td>
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<tr>
<td>Clopidogrel</td>
<td>100</td>
<td>Clopidogrel (75 mg/day)</td>
<td>32 versus 46</td>
<td>NS</td>
<td>[20]</td>
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<td>(150 mg/day)</td>
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<td>Clopidogrel + cilostazol</td>
<td>100</td>
<td>Clopidogrel (75 mg/day)</td>
<td>12 versus 46</td>
<td>&lt;0.05</td>
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<td>Prasugrel</td>
<td>100</td>
<td>Clopidogrel (150 mg/day)</td>
<td>19 versus 85.7</td>
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<td>Ticagrelor</td>
<td>100</td>
<td>Clopidogrel (75 mg/day)</td>
<td>10 versus 88.9</td>
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<td>(90 mg twice daily)</td>
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LR: low responder.
HPPR following standard clopidogrel therapy, prasugrel (10 mg/day) was found to be more efficient than doubling the dose of clopidogrel in achieving adequate platelet inhibition [63]. In this study, increasing the dosage of clopidogrel to 150 mg appears highly ineffective at reducing HPPR. Although prasugrel was much more efficient in achieving optimal platelet inhibition, this therapeutic option could not be viewed as ideal, a worrying level of prasugrel ‘resistance’ being observed in 19% of the cases [63]. It should further be emphasized that so far no studies have been dedicated to the clinical outcome in CKD patients receiving prasugrel.

**Ticagrelor**

Ticagrelor is a reversible, non-thienopyridine P2Y12 receptor antagonist; it is not a prodrug and does not require biotransformation. Ticagrelor provides faster, stronger and more consistent (interpatient) P2Y12 inhibition than clopidogrel [64]. Moreover, in a recent pharmacodynamic study in ACS patients with HPPR, ticagrelor afforded more potent platelet inhibition than prasugrel [65]. The PLATO trial in a broad population of individuals with ACS showed that the use of ticagrelor instead of clopidogrel substantially reduced the risk of death from vascular causes, myocardial infarction or stroke and decreased CV and total mortality at 12 months, without increasing the risk of major bleeding [66]. In a prespecified analysis of the PLATO trial, patients with CKD drew an impressive benefit from ticagrelor, with a 23% reduction in the relative risk of the primary ischemic end point (when compared with a non-significant 10% decrease in patients without CKD) and even more striking reductions of 4.0 and 28%, respectively, in the absolute and relative risks of all-cause mortality. These results translate into a number of patients who needed to be treated to prevent one death of 25 in the CKD subgroup and 200 in the non-CKD subgroup [7, 10]. In CKD patients, despite a higher level of platelet inhibition with ticagrelor when compared with clopidogrel, there was no increase in major bleeding as defined in the PLATO trial, in non-CABG-related major bleeding as defined in the TIMI trial or in fatal bleeding. The slight bleeding excess induced by ticagrelor in the overall population was of similar magnitude in the CKD and non-CKD subgroups [7, 10]. This study suggests that stronger antiplatelet therapy with ticagrelor could be of particular benefit in patients with CKD and reduce mortality and ischemic events at the price of a slight excess of bleeding, especially when considering spontaneous non-CABG bleeding [7]. Although the metabolism and excretion of ticagrelor depend minimally on renal function, one could imagine a specific effect in patients with CKD. Indeed, besides its ability to block the P2Y12 pathway, ticagrelor can also inhibit adenosine reuptake by erythrocytes and may improve myocardial perfusion [67]. Such an effect could be more important in patients with impaired renal function [7, 10]. Hence the relevance of this mechanism in CKD patients deserves further investigation. One recent study assessed the ability of ticagrelor to overcome a low response to clopidogrel in haemodialysis patients. In this work, ticagrelor drastically reduced the proportion of patients with HPPR from 88 on clopidogrel to 10% on ticagrelor (90 mg twice daily for 15 days) [68].

**CONCLUSIONS**

Renal dysfunction is a powerful independent predictor of both thrombotic and bleeding complications and consequently, of mortality. Owing to this enhanced bleeding risk, physicians have long been reluctant to use potent anti-platelet therapy in CKD patients. However, alongside other confounding factors such as diabetes, end-stage renal failure has now emerged as an important determinant of low platelet inhibition by thienopyridines, probably due to the reduced bioavailability of clopidogrel. Recent reports have emphasized the impact of impaired platelet inhibition by thienopyridines in CKD patients, with enhanced mortality rates following PCI in low-responder patients. In clinical practice, platelet function testing should be considered in CKD patients undergoing PCI, especially among those who experience thrombotic events despite dual therapy. Newer agents should be contemplated in patients who display higher residual platelet aggregability after standard treatment. Among these, ticagrelor, a non-thienopyridine P2Y12 receptor antagonist, which does not require biotransformation, could be the drug of choice for CKD patients with ACS. In this population, ticagrelor has been shown to reduce mortality and ischemic events with an acceptable bleeding risk.

**CONFLICT OF INTEREST STATEMENT**

None declared.

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