Defining the Link Between Chronic Kidney Disease, High Platelet Reactivity, and Clinical Outcomes in Clopidogrel-Treated Patients Undergoing Percutaneous Coronary Intervention

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Dual antiplatelet therapy with aspirin and an antagonist of the platelet adenosine diphosphate P2Y$_{12}$, receptor is pivotal for the treatment of ischemic events, particularly stent thrombosis, in patients undergoing percutaneous coronary intervention (PCI). Despite the availability of newer and more potent agents, namely prasugrel and ticagrelor, clopidogrel is still the most widely used P2Y$_{12}$ receptor antagonist and is the only agent currently approved for patients with stable coronary artery disease undergoing PCI. However, clopidogrel is characterized by high interindividual response variability. Notably, patients with high platelet reactivity (HPR) while on clopidogrel therapy are at increased risk of ischemic recurrences, in particular stent thrombosis. Clopidogrel response variability has a multifactorial etiopathogenesis, which includes genetic (ie, cytochrome P450 polymorphisms), cellular (ie, accelerated platelet turnover, reduced cytochrome P450 metabolic activity, or upregulation of P2Y$_{12}$ pathway), and clinical (ie, poor absorption, drug-drug interactions, acute coronary syndrome, diabetes mellitus [DM], obesity, chronic kidney disease [CKD]) factors. However, the relative contribution of each of these factors to HPR status and adverse atherothrombotic events remains poorly defined.

See Article by Baber et al

CKD is a pandemic public health problem, with >500 million people worldwide estimated to have some form of kidney injury and with a prevalence of 13.1% in the United States. Key factors contributing to the increased prevalence of CKD include the aging population and the growing burden of DM. In particular, patients with DM are found to have CKD in about one third of cases, with diabetic nephropathy as the most common cause of renal impairment. Moreover, although in patients with coronary artery disease the presence of either DM or CKD is associated with a similar enhanced risk of long-term cardiovascular events, when DM and CKD coexist, the risk is further increased, suggesting a synergistic effect of these clinical disorders. However, patients with all stages of CKD are also at increased risk of atherothrombotic disease manifestations, independent of common risk factors. Studies have reported an increased risk of mortality and post-procedural ischemic events, including stent thrombosis, in patients with CKD. One year after successful PCI, mortality was shown to be 5-fold higher in patients with moderate CKD and 12-fold higher in patients with severe CKD than in those with normal renal function.

Several mechanisms have been advocated to explain the enhanced cardiovascular risk carried by renal function impairment. First of all, patients with CKD presenting with an acute coronary syndrome are less likely to receive evidence-based therapies, which lead to higher mortality rate. Endothelial dysfunction, persistent microinflammation, coronary calcification, platelet activation, and reduced response to oral anti-platelet therapies also play a contributing role. Subgroup analysis of major clinical trials have shown a reduced benefit of clopidogrel in patients with CKD. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Clopidogrel for Reduction of Events During Observation (CREDO) trials, clopidogrel compared with placebo reduced atherothrombotic events in patients with normal or subnormal renal function, but the benefit of clopidogrel was not apparent in patients with mild or moderate renal dysfunction. Similarly, an analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial suggested that clopidogrel may even be harmful in patients with diabetic nephropathy. Even though registry data have shown clopidogrel to be associated with improved outcomes in patients with non–end-stage CKD, in adjusted and propensity analyses the benefit of clopidogrel was no longer significant in patients with CKD, indicating a key role of confounding factors in heterogeneous study populations.

High levels of circulating procoagulant factors, increased thrombin generation, abnormalities of nitric oxide synthesis, upregulation of the P2Y$_{12}$ signaling pathway, and poor bioavailability of clopidogrel’s active metabolite have been proposed to explain platelet hyper-reactivity and HPR among patients with renal dysfunction. In particular, platelets from patients with CKD are exposed to higher levels of dinucleoside polyphosphates, which can act as agonists of the P2Y$_{12}$ receptor causing a decrease in phosphorylation...
of VASP (a key intraplatelet mediator of P2Y_{12}-mediated signaling) and therefore increased platelet reactivity.^{9} Furthermore, CKD is associated with reduced activity of the hepatic cytochrome P450 system, a key mediator of clopidogrel metabolism, which can translate into reduced generation of clopidogrel’s active metabolite.^{9} However, to date pharmacodynamic studies have shown discordant results on the independent role of CKD as a determinant of impaired response to clopidogrel.^{11–14} Indeed, the limited sample size of these studies, composed of heterogeneous patient cohorts, may have contributed to these observations.

In this issue of Circulation: Cardiovascular Interventions, Baber et al^{15} elegantly report the results of a post hoc analysis of the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study, exploring the associations among CKD, HPR, and ischemic and bleeding events in a cohort of patients undergoing PCI with drug-eluting stents treated with aspirin and clopidogrel. ADAPT-DES is the largest individual registry linking platelet reactivity and clinical events reported to date; for this analysis, only patients with valid platelet function and creatinine values were included (n=8410). Platelet reactivity was assessed after successful PCI with VerifyNow P2Y12 at least 6 hours after a 600-mg loading dose of clopidogrel, 12 hours after a 300-mg loading dose or after at least 5 days of 75-mg clopidogrel maintenance therapy. HPR was defined as P2Y12 reaction units >208, according to consensus definition.^{15} CKD was defined as creatinine clearance (CrCl) <60 mL/min, assessed using the Cockcroft–Gault formula, and patients were stratified into 3 groups: CrCl <30 mL/min (n=119), 30 to 60 mL/min (n=1248), and ≥60 mL/min (n=7043). However, because of the small number of patients with CrCl <30 mL/min, ischemic and bleeding events were analyzed comparing patients with or without CKD.

Patients with CKD were characterized by an increased baseline risk profile compared with patients without CKD, including higher rates of DM and high-risk angiographic features. The authors found that platelet reactivity and rates of HPR progressively increased with worsening renal function, with an ≈2-fold higher rate of HPR among those with a CrCl <30 mL/min compared with those without CKD. However, after adjusting for multiple variables, this difference was strongly attenuated, resulting in the absence of significant associations between CKD status and HPR, and suggesting that confounding risk factors may account for the reduced platelet inhibition among patients with CKD. At 2 years, patients with CKD experienced higher rates of adverse ischemic events and clinical relevant bleeding. Overall, ischemic event rates, including stent thrombosis, were higher, and bleeding events were lower among patients with HPR when compared with those with adequate response to clopidogrel, in both CKD and non-CKD patients. Therefore, HPR showed to be a significant independent risk factor for thrombotic events irrespective of renal function, with the highest risk among patients with both CKD and HPR and the lowest risk among those with no CKD and no HPR. No interaction was observed between CKD and HPR on ischemic and bleeding events.^{15}

The major strength of the study is the large number of patients analyzed, which, with >1000 patients with CKD, make this investigation the largest report to date on the association between kidney function and platelet reactivity. With their results, the authors confirmed previous data showing a higher prevalence of HPR in patients with CKD. Furthermore, they showed for the first time that HPR independently increase the long-term risk of thrombotic events irrespective of renal function, with a significant additive effect of CKD and HPR.

However, there are important considerations that need to be taken into account when interpreting these findings. First of all, the authors measured platelet reactivity only with 1 assay and at a single time point in the early phases after starting clopidogrel therapy. Since it is well-known that response to clopidogrel may significantly vary over time, not only as absolute platelet reactivity values but also as HPR status, and that values tend to stabilize after several weeks of treatment, the number of patients with persistent HPR status could have been different.^{2,16} Furthermore, there is wide variability in the early pharmacodynamic response after a loading dose of clopidogrel, especially in patients with acute coronary syndrome (=50% of the study population), where 6 hours are not necessarily enough to achieve a consistent level of platelet inhibition in all patients, and with P2Y12 reaction unit levels similar to those achieved in the maintenance phase of treatment.^{2} Therefore, the authors may have over- or underestimated the number of patients with HPR. Indeed, repeated pharmacodynamic measurements over time, or use of >1 assay to corroborate findings, could have led to better stratification for HPR status of the patient population. Second, the authors assessed CKD according to the Cockcroft–Gault formula calculated on a single creatinine measurement performed pre PCI. Although in the sensitivity analysis the authors stratified CKD status also according to the CKD Epidemiology Collaboration formula, current guidelines recommend that albumin:creatinine ratio should also be considered in the definition of CKD, in addition to glomerular filtration rate preferably estimated with the CKD Epidemiology Collaboration or Modification of Diet in Renal Disease formula. Moreover, expert recommendations also state that kidney function should be stable for >3 months to define CKD.^{17} Thus, this is another source of variability in patients’ stratification, which may have influenced study findings. Third, in the present analysis, Baber et al^{15} did not report the results of the VerifyNow aspirin test, which were collected in the ADAPT-DES study. Although the role of aspirin resistance is to date still a matter of debate, large registries, including ADAPT-DES itself, have reported a role of response to aspirin in predicting long-term ischemic or bleeding events.^{18} Indeed, the presence of these data could have provided additional insights toward interpreting the study findings. Finally, based on the lack of association between CKD and HPR at the multivariable analysis, the authors suggest that renal dysfunction is not a direct determinant of impaired response to clopidogrel but rather is a marker of baseline comorbidities, such as DM or older age, that affect clopidogrel’s pharmacodynamic profile. However, the small number of patients in the group of patients with severe CKD
(CrCl <30 mL/min), which had the higher unadjusted odds for HPR, may have accounted for the lack of significance at the multivariable analysis.

Several pharmacodynamic studies have been reported exploring the link between CKD and response to clopidogrel, which have shown mixed results. In particular, although studies have shown that, in patients with type 2 DM, impaired renal function is associated with reduced clopidogrel-induced antiplatelet effects and higher rates of HPR, other studies performed in patients without DM have yielded inconsistent results. Therefore, the higher levels of platelet reactivity shown among patients with DM and CKD may be because of a synergistic effect of the 2 pathophysiological pathways, which may explain the enhanced risk of cardiovascular events when DM and CKD coexist. Also, differences in distribution of genetic variants within patient cohorts can modulate antiplatelet drug effects, leading to differences in outcomes also among patients with similar baseline risk profile. Nevertheless, it could also be hypothesized that including only diabetic patients simply reduces heterogeneity and confounding factors, which play a crucial role in the interpretation of data from large-scale registries and post hoc analyses. To this extent, a sub-analysis of the study by Barber et al on the subgroup of patients with DM would have been of interest.

These limitations, however, do not undermine the key finding of this study: CKD and HPR are both markers of an increased risk of atherothrombotic events in patients on clopidogrel therapy after coronary stenting, they are frequently associated and they provide additive effects when combined. Overall, these data help identifying an extremely high-risk population where more potent P2Y$_{12}$ receptor inhibiting strategies are warranted. Prasugrel and ticagrelor are 2 novel potent P2Y$_{12}$ receptor inhibitors with important pharmacological advantages over clopidogrel, which translate into better clinical outcomes in patients with acute coronary syndrome. Furthermore, the benefit of prasugrel over clopidogrel was consistent in patients with or without CKD, and the benefit of ticagrelor seemed even enhanced in patients with impaired kidney function. Therefore, the use of prasugrel and ticagrelor is an appealing strategy in this high-risk population, especially when HPR is present. Since routine broad scale use of ticagrelor or prasugrel is neither feasible nor warranted because of cost issues, adverse effects, relative contraindications, and increased bleeding, identifying markers of risk to better select their use is of key importance. Although randomized clinical trials evaluating the use of platelet function testing to tailor antiplatelet therapy have failed to demonstrate any benefit, the main limitation of all these studies was the inclusion of low-risk populations. The results of the study by Barber et al clearly identify a subset of patients where further risk-markers may potentially help stratify patients to optimize antithrombotic therapy. Indeed, additional prospective studies are needed to better evaluate this hypothesis.

Disclosures
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