KI REPORTS
KIReports.org

CKD Effects on Platelets: Implications for Cardiovascular Risk

Constance C.F.M.J. Baaten[1,2], Claudio Rigatto[3,4] and Heidi Noels[1,2]

[1]Institute for Molecular Cardiovascular Research (IMCAR), University Hospital RWTH Aachen, Aachen, Germany; [2]Department of Biochemistry, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, the Netherlands; [3]Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada; and [4]Chronic Disease Innovation Centre, Seven Oaks General Hospital, Winnipeg, Manitoba, Canada

Kidney Int Rep (2022) **7,** 2126–2128; https://doi.org/10.1016/j.ekir.2022.08.005

See Clinical Research on Page 2242

Platelets are crucial to prevent and stop bleeding, a process referred to as hemostasis. They do so by adhering to the damaged vascular wall, triggering platelet activation and the subsequent growth of a thrombus through an increasing accumulation of platelets and thrombin-generated fibrin. Platelets, however, also contribute to the occurrence of cardiovascular events by stimulating the formation and progression of atherosclerotic lesions and through their crucial involvement in the formation of thrombi triggered by vascular dysfunction, atherosclerotic plaque rupture, or plaque erosion.[1] Subsequent narrowing or blocking of a coronary artery or its branches can trigger myocardial ischemia and infarction, whereas narrowing or blocking of the arteries supplying the extremities underlies peripheral artery disease (PAD). Of note, PAD is associated with a higher risk of coronary artery disease and worse cardiovascular outcomes. For example, patients with symptomatic PAD have a 70% higher risk of cardiovascular events and a 80% higher risk of death compared with patients without PAD.[2]

It is well known that patients with chronic kidney disease (CKD) are at higher risk of cardiovascular events. Heart disease in patients with CKD results from a complex interplay between the following 3 distinct processes: atherosclerosis, arteriosclerosis, and left ventricular growth and dysfunction (reviewed by P. Pun[3]). Approximately 50% of cardiovascular events in CKD are directly attributable to atherosclerosis,[4] and this proportion is likely higher among patients with concomitant PAD. Atherosclerotic disease, coronary artery disease, and PAD are prevalent in CKD, and CKD severity modifies the lethality of underlying atherosclerotic disease: patients presenting with both PAD and moderate CKD had a 32% increased risk of death within 1 year of follow-up compared with patients with PAD with normal or mildly reduced kidney function. This risk increased to almost 3-fold for patients with PAD with severe CKD or kidney failure.[5]

Given the central role of platelets in atherothrombotic events, in this issue of *KI Reports*, Cofer *et al.*[6] evaluated the hypothesis that CKD-associated changes in platelet activity may explain the higher rate of cardiovascular outcomes in patients with PAD undergoing lower extremity revascularization. Patients were classified into the following 2 groups: those with normal or mildly decreased kidney function (glomerular filtration rate $\geq$ 60 ml/min/1.73 m^2) versus those with moderately decreased kidney function or worse (glomerular filtration rate $<$ 60 ml/min/1.73 m^2). Within this latter group, 63% had moderate CKD (CKD3) and 37% severe to end-stage kidney disease (CKD4–CKD5), of which 60% of patients with CKD4 to CKD5 were on maintenance dialysis. Platelet aggregation was analyzed by light transmission aggregometry after stimulation with a broad range of platelet agonists and doses, certainly contributing to the value of this study. Overall, the authors observed higher platelet activity in patients with PAD with CKD compared with PAD controls upon a stimulation with submaximal concentrations of adenosine diphosphate, serotonin, and epinephrine. Risk of cardiovascular events over a median follow-up time of 18 months was higher in the CKD group, in line with expectations, and the increased platelet aggregation responses were calculated to contribute to 7% to 26% of the excess risk of myocardial infarction, death,

Correspondence: Heidi Noels, Institute for Molecular Cardiovascular Research (IMCAR), University Hospital Aachen, RWTH Aachen University, Pauwelsstraße 30, 52074 Aachen, Germany. E-mail: hnoels@ukaachen.de

major adverse cardiovascular events, or major adverse cardiovascular events with limb events. This study is the first to report such a comprehensive analysis of platelet contribution to cardiovascular risk in CKD, supporting its scientific value.

Platelet studies in CKD have been performed before, but the results have been highly variable.[7] Most of the studies of nondialysis patients with CKD revealed decreased platelet aggregation and reduced thromboxane production in CKD.[7] A meta-analysis also revealed maximal aggregation upon stimulation with collagen to be significantly reduced in patients with CKD.[8] In contrast, others reported unaltered or increased platelet aggregation responses in CKD.[7] Nonetheless, bleeding time was mostly prolonged in patients with CKD.[7]

Patient heterogeneity in terms of disease severity could have contributed to these conflicting findings in platelet responses in literature. CKD is a progressive disease, and cardiovascular risk increases with increasing kidney dysfunction,[3] as confirmed by Cofer *et al.*[6] Modest, significant negative correlations were observed by the authors between estimated glomerular filtration rate and platelet aggregation upon stimulation with the aforementioned agonists at specific doses. Yet, when directly comparing patients in CKD stages 4 to 5 (estimated glomerular filtration rate < 30) with patients in CKD stage 3, patients with CKD4 to CKD5 did not present a higher platelet aggregatory response to most of the investigated agonists.[6] Huang *et al.*,[9] however, previously reported increased platelet aggregatory responses upon adenosine diphosphate stimulation in nondialysis CKD5 compared with controls and patients with CKD3, but not in patients with CKD3 or CKD4 compared with controls. Potential factors contributing to this variability in results could include differences in studied patient cohorts in terms of comorbidities or therapy. The study in this issue focused specifically on patients with PAD undergoing revascularization and included patients with CKD4 to CKD5 of whom 60% were on dialysis,[6] whereas Huang *et al.*[9] studied nondialysis patients only. Although only a small number of patients were diagnosed with having diabetes in the study of Huang *et al.*[9] (5% of controls vs. 11% of nondialysis CKD5), a significantly higher number of patients with CKD in the study of Cofer *et al.*[6] also had diabetes (69%; compared with only 41.9% in the non-CKD group), with diabetes associated with a higher platelet reactivity.[1]

Furthermore, most patients in the study of Cofer *et al.*[6] were on antiplatelet therapy, with 79.6%/82.6% on aspirin and 37.2%/44.2% on clopidogrel for CKD and control patients, respectively, without significant differences between both groups. Although clopidogrel is an irreversible antagonist of P2Y12 as receptor for adenosine diphosphate, aspirin inhibits thromboxane A2 production. Despite highly frequent antiplatelet therapy of both the CKD and control group investigated by Cofer *et al.*,[6] platelets from patients with CKD PAD displayed increased aggregation responses upon stimulation with arachidonic acid, especially in the presence of a saturating dose of aspirin *ex vivo*. The latter was suggestive of a less complete platelet inhibitory effect of aspirin therapy in patients with CKD, with high on-treatment platelet reactivity also reported to be associated with increased cardiovascular risk after revascularization. Of note, for the PAD cohort studied by Cofer *et al.*,[6] it would have been interesting to also compare platelet responses in patients with versus without CKD with specific subdivision of patients either treated with antiplatelet therapy or not, the latter to investigate inherent effects of CKD on platelets in the absence of a potential impact of altered efficacy of antiplatelet therapy between both groups.

In summary, Cofer *et al.*[6] present in this issue solid evidence that platelet aggregation responses in patients with PAD are increased in patients with moderate-to-severe CKD compared with those with normal or mildly decreased kidney function, as detected by light transmission aggregometry analysis. Future studies should provide further insights into the source of the high heterogeneity of current findings on platelet responses in CKD, with either CKD etiology, stage, comorbidities, or antiplatelet treatment of the investigated patient cohort, and differential readouts of platelet activity as potential contributing factors. Moreover, as recently summarized, the causes of altered platelet activity in CKD are multifactorial and yet incompletely understood, with a suggested role for uremic toxin accumulation, low-grade inflammation, reduced vascular integrity, and hypercoagulability in CKD.[7] Increased insights into the mechanisms underlying altered platelet responses in CKD may contribute to the optimization of current antiplatelet treatment strategies for patients with CKD.

DISCLOSURE

CCFMJB is supported by the Dutch Heart Foundation (2020T020) and by the START-Program of the

Faculty of Medicine at the RWTH Aachen University (105/20). HN is supported by the German Research Foundation (DFG; Project-ID 322900939-SFB/TRR219) and the Else Kröner-Fresenius-Stiftung (Project 2020_EKEA.60). CR declared no competing interests.

REFERENCES

1. van der Meijden PEJ, Heemskerk JWM. Platelet biology and functions: new concepts and clinical perspectives. *Nat Rev Cardiol*. 2019;16:166–179. https://doi.org/10.1038/s41569-018-0110-0
2. Grenon SM, Vittinghoff E, Owens CD, et al. Peripheral artery disease and risk of cardiovascular events in patients with coronary artery disease: insights from the Heart and Soul Study. *Vasc Med (London, England)*. 2013;18:176–184. https://doi.org/10.1177/1358863X13493825
3. Pun PH. The interplay between CKD, sudden cardiac death, and ventricular arrhythmias. *Adv Chronic Kidney Dis*. 2014;21:480–488. https://doi.org/10.1053/j.ackd.2014.06.007
4. Bittencourt MS, Hulten EA, Ghoshhajra B, et al. Incremental prognostic value of kidney function decline over coronary artery disease for cardiovascular event prediction after coronary computed tomography. *Kidney Int*. 2015;88:152–159. https://doi.org/10.1038/ki.2014.426
5. O'Hare AM, Bertenthal D, Shlipak MG, et al. Impact of renal insufficiency on mortality in advanced lower extremity peripheral arterial disease. *J Am Soc Nephrol*. 2005;16:514–519. https://doi.org/10.1681/ASN.2004050409
6. Cofer LB, Soomro QH, Xia Y, et al. Platelet activity and cardiovascular risk in chronic kidney disease and peripheral artery disease. *Kidney Int Rep*. 2022;7:2242–2250. https://doi.org/10.1016/j.ekir.2022.07.169
7. Baaten C, Schröer JR, Floege J, et al. Platelet abnormalities in CKD and their implications for antiplatelet therapy. *Clin J Am Soc Nephrol*. 2022;17:155–170. https://doi.org/10.2215/CJN.04100321
8. Baaten C, Sternkopf M, Henning T, et al. Platelet function in CKD: a systematic review and meta-analysis. *J Am Soc Nephrol*. 2021;32:1583–1598. https://doi.org/10.1681/ASN.2020101440
9. Huang MJ, Wei RB, Wang Y, et al. Blood coagulation system in patients with chronic kidney disease: a prospective observational study. *BMJ Open*. 2017;7:e014294. https://doi.org/10.1136/bmjopen-2016-014294