Editorial

Prolonged dual antiplatelet therapy in renal failure: a challenging trade-off

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Patients with renal failure and coronary artery disease (CAD) represent a complex and delicate cohort. Obviously, their management can be challenging and requires attention and expertise. Globally, the prevalence of chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 and/or the presence of albuminuria, seems to constantly increase with CKD now having evolved as a global public health issue (1,2). Nowadays, the most important factors promoting the development of CKD worldwide include aging, obesity, diabetes, hypertension and atherosclerotic disease (1-3). Renal failure is not only the consequence of manifold systemic diseases, but also has systemic adverse effects and is related to high morbidity and mortality, even at an early stage (4,5). Among patients with established cardiovascular disease, CKD is related to a higher rate of adverse events, including atherothrombotic manifestations and hemorrhagic events (3). Taken together, those factors contribute to the massive increase in mortality in patients with both CAD and CKD (6).

With this background, Siddiqi *et al.* aimed to shed some light on this field. By analyzing administrative data from the Veterans Affairs Healthcare System, they assessed the role of prolonged clopidogrel therapy among an all-comer cohort with CKD undergoing percutaneous coronary intervention (PCI) and stenting. According to their findings, extended dual antiplatelet therapy (DAPT) after stenting might reduce risk for myocardial infarction (MI) or death in certain patients with renal failure. Moreover, the authors found no difference in rates of relevant bleedings between those patients with normal and those with impaired renal function.

Pursuant to a recent analysis from the U.S. EVENT Registry, approximately 40% of all patients undergoing PCI have an impaired renal function (7). In comparison to those with normal renal function, PCI among individuals with CKD is related to higher rates of procedural and other complications, including restenosis and future ischemic events (3,7). CKD additionally represents an important predictor for bleedings, both in the specific case of PCI as well as in general (7,8).

However, DAPT after PCI is supposed to prevent stent thrombosis during the healing phase and atherothrombotic events stemming from lesions beyond the stented segment (9,10). Recently, prolonged DAPT after PCI gained much attention as several landmark studies have been published in that field (9-11). In summary, they reported that DAPT beyond one year after MI with or without stenting, reduced the risk of cardiovascular events in comparison to aspirin alone, but increased the risk for bleedings (9,11). Since patients with CKD were underrepresented among those trials, more robust data is needed. Hence, the study by Siddiqi *et al.* addresses an important and incompletely covered subject.

While the *Dual Antiplatelet Therapy (DAPT) Trial* did not provide any information about the number of individuals with CKD, about one fourth of all patients included in the Prevention of Cardiovascular

Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS-TIMI 54) trial had an eGFR <60 mL/min/1.73 m^2 (11). Additionally, a subgroup analysis of PEGASUS-TIMI 54 trial showed that patients with non-end stage renal dysfunction on either 60 mg or 90 mg ticagrelor twice daily had a better outcome in comparison to those on placebo (11). Nevertheless, DAPT with ticagrelor was related to higher bleeding risk, irrespective of underlying renal function (11). Although these data must be interpreted cautiously, it may highlight the fact that patients with renal dysfunction represent a vulnerable cohort that has a further benefit from a more intensive antiplatelet management. In addition, one of the main findings of the DAPT study was that recipients of paclitaxel-eluting stents, i.e., a first generation drug eluting stent, had the greatest benefits from extended thienopyridine therapy with regards to the reduction of atherothrombotic events (9). That finding implied that the suggested advantages of prolonged DAPT might partially rely on the implanted stent-type. Since Siddiqi *et al.* analyzed only patients with first generation drug eluting stents, their findings point toward the same direction. Taken together, a growing body of evidence indicates that prolonged DAPT may be beneficial in selected patients. However, establishing DAPT reflects a challenging trade-off, in particular among those with renal failure.

Regarding the interaction between CKD and antiplatelet therapy, it is important to note that renal disease can be related to complex enzymatic coagulation, platelet dysfunction and endothelial abnormalities (12,13). In renal failure, coagulopathies with decreased levels of protein C and elevated levels of plasminogen activator inhibitor-1, fibrinogen, thrombin–antithrombin complexes, and von Willebrand factor (vWF) multimers are found. Furthermore, platelet dysfunction with a decreased production of thromboxane A2 and other platelet transmitters, abnormal intracellular calcium handling, and activation-dependent binding of glycoprotein llb/llla to vWF represent important issues. Finally, enhanced endothelial dysfunction itself promotes atherosclerosis and atherothrombosis (13). This background may partially emphasize the changes and mechanisms contributing to the clash of atherothrombotic and bleeding events in patients with CAD and impaired renal function (3).

The handling of antiplatelet therapies is complicated not only by altered thrombocyte function and plasmatic coagulation, but also by changed pharmacokinetics of drugs when used in CKD (3). Of note, patients with severe or end stage renal failure are either underrepresented or excluded in major cardiovascular trials studying the P2Y12 receptor antagonists (12). Therefore, data analyzing the role of P2Y12 receptor antagonists are limited and their prolonged administration in CKD conflicting (3,14). The Clopidogrel for the Reduction of Events during Observation (CREDO) and the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trials have implied that renal function may affect the clinical efficacy of clopidogrel and therefore outcomes (15,16). In those studies, patients with CKD treated with clopidogrel had worse outcomes in comparison to those with normal renal function (15,16). The use of clopidogrel significantly reduced the rate of major cardiovascular adverse events in patients with preserved renal function, but this benefit was less obvious among individuals with mild CKD and even vanished in moderate CKD (16).

Due to the nature of the data and the analyses performed, some questions and limitations remain unmet by Siddiqi *et al*. and may establish the fundament for future research. First, it is not possible to draw definitive conclusions based on the nature of that analysis. Second, the applied exclusion criteria may have resulted in a selection bias. Third, bleedings in CKD patients with PCI seem to be more common than reported here (7,8). In the DAPT study, BARC type 2, 3, or 5 bleedings were met in roughly 5% in the intervention arm (9). Thus, this retrospective analysis with less reported bleedings should be interpreted with caution—it may not reflect the real world, and more prospective data are warranted. Fourth, within the last decade, there were tremendous advances in PCI and stent technology. From this perspective, it would therefore be of interest to know how the use of the latest stent generations (e.g., coated with mTOR inhibitors or biodegradable polymers) impacts the outcome of CKD patients. Fifth, the association between eGFR and cardiovascular events is not linear but rather exponential. Hence, the dichotomized classification applied by the authors, which groups individuals either to an eGFR value of below <60 mL/min per 1.73 m^2 or beyond and normal, may oversimplify that relationship and excludes potentially relevant subgroups. Sixth, since the analyzed data stem from administrative data including almost only male individuals, the gender aspect

had inevitably to be excluded by the authors. Nonetheless, one needs to take in account that the underlying gender influences the outcome of cardiovascular diseases and sex-specific disparities in thrombotic and bleeding risks may play a fundamental role (17).

What should we learn and take along from that study?—patients with CKD have a markedly higher risk for recurrent ischemic events and death. Among those patients, the trade-off between benefits and risks of prolonged DAPT will remain challenging, since an adequately powered randomized trial is still missing. In patients with CKD undergoing PCI, a thorough assessment and balancing of bleeding and ischemic risks is mandatory. Prolonging DAPT among renal failure patients that received a first generation drug eluting stent seems to be reasonable with regards to the beneficial long-term outcomes with those stents. This is of special interest, since the number of patients treated with those stents and returning for recurrent ischemic events is growing in the near future, specifically in patients with CKD.

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Footnote

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