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Editorial Comment

EDITORIAL COMMENT

Longer or shorter dual antiplatelet therapy in dialysis patients receiving a coronary drug-eluting stent? A rope game still ongoing

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ABSTRACT

In this issue of *Clinical Kidney Journal*, Park *et al.* presents the results of a nationwide population-based trial that included >5000 dialysis patients receiving a drug-eluting stent (DES). The main objective was to evaluate the effectiveness and the safety of prolonged dual antiplatelet therapy (DAPT). The primary outcome was a composite of mortality, non-fatal myocardial infarction, coronary revascularization and stroke, significantly lowered by a longer DAPT regimen at 12, 15 and 18 months, respectively. Longer DAPT tended to be correlated with higher bleeding events at all landmarks, with no statistical significance. An important element was that almost 75% of the index events were acute coronary syndromes. This study presents the first solid evidence for a significant benefit of prolonged DAPT in dialysis patients receiving a DES. We believe that end-stage renal disease is still in the middle of a rope game, being pulled to one side or another by other features, inclining towards a higher bleeding risk or towards higher ischaemic risk. The acute versus elective presentation seems to weigh in choosing the antiplatelet regimen. The 'one-size-fits-all strategy' is not suitable for this particular group. Probably in the future, practitioners will be provided with decision pathways generated by artificial intelligence algorithms yielding 'truly individualized' DAPT protocols for every single patient.

Keywords: coronary artery disease, DAPT, dialysis, drug-eluting stent, end-stage renal disease, evidence-based therapies

The high burden of coronary artery disease (CAD) in end-stage renal disease (ESRD) patients and the elevated mortality due to cardiovascular causes in this chronic kidney disease (CKD) population [1] have led to a great/increasing number of revascularization procedures [both coronary artery bypass grafting and percutaneous coronary interventions (PCIs)] [2]. Since nearly half of the patients starting dialysis present asymptomatic coronary artery stenosis [3] and Stage 5D CKD *per se* is associated with accelerated atherosclerosis and coronary calcifications, there is a huge mobilization of resources focused on improving quality of life and extending survival, especially in the acute setting of the CAD spectrum.

Currently, Stage 5D CKD patients receive fewer revascularization interventions than non-CKD populations [4], as

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the multivessel atherosclerosis, small diffuse obstructive disease combined with severe calcifications are highly prevalent in ESRD, thus hampering PCI outcomes [5]. However, importantly, a recent study from the USA including almost 900 000 patients admitted for acute coronary syndromes (ACSs) showed a significant upward trend in the use of PCIs in dialysis patients [6], with a marked reduction in mortality risk.

In addition, a recent robust meta-analysis [7] and a nationwide cohort study [8] concluded that implantation of drug-eluting stents (DESs) conferred a significant reduction in all-cause and cardiovascular mortality in dialysis patients over bare-metal stents. Looking closer, both trials were non-randomized and the first study included 60% of ESRD patients with ACS, while the second included only one-third of patients manifesting ACS. Nevertheless, the solid benefits of DES use in dialysis have been extended to non-acute patients. It seems a bit surprising, as recently presented at the 2019 American Heart Association Scientific Sessions, Philadelphia, November 2019, that the results of the only randomized trial (ISCHEMIA-CKD) involving stable angina patients with advanced CKD (therefore not just ESRD) failed to demonstrate a benefit of stenting over optimal medical therapy on mortality and anginal symptoms. It is obvious that not all DES procedures are associated with the same long-term thrombosis risk, but notably, the intervention arm of the ISCHEMIA-CKD study received only short-term dual antiplatelet therapy (DAPT).

The ISCHEMIA trial was conceived to answer questions left over from the 2007 Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, which found no benefit with PCIs over medical therapy in stable CAD. However, the COURAGE trial included only 16 patients with advanced CKD [9] and there is no evidence-based information to indicate what should be the optimal medical therapy for dialysis patients with CAD (as blood pressure and cholesterol targets, the benefits of the new antiplatelet agents, angiotensin-converting enzyme inhibitors/receptor blockers and the newer neutral endopeptidase inhibitors are still questionable and unstudied in randomized trials involving Stage G5D CKD).

In this issue of the *Clinical Kidney Journal* (*CKJ*), Park *et al.* [10] present the results of a nationwide population-based trial that included >5000 dialysis patients receiving a DES. The main objective of this study was to evaluate the effectiveness and safety of prolonged (compared with the standard 12 months) DAPT. The authors used three landmark points after the DES procedure: 12, 15 and 18 months. The primary outcome was major adverse cardiovascular events (MACES; a composite of mortality, non-fatal myocardial infarction, coronary revascularization and stroke), which was significantly lowered by a longer DAPT regimen. The safety outcome consisted of major bleeding events. Longer DAPT tended to be correlated with higher bleeding events at all landmarks, but the differences were not statistically significant.

It should be noted that even if it was not the objective of this study and even if there was not a control group without PCIs (as in ISCHEMIA-CKD trial), mortality and myocardial infarction after using a DES in this cohort were significantly lowered by PCIs (up to 18 months), supporting the conclusions of both studies mentioned above (the meta-analysis and nationwide cohort [7, 8]. In other words, there are considerable arguments that the use of DES in CKD Stage 5D patients generates a favourable impact on mortality and MACEs.

An important element of this trial was that almost 75% of the index events were ACSs. It would be useful in a *post hoc* analysis to evaluate the impact on mortality of DES implantation in the remaining 25% of stable dialysis patients, as all three subgroups (of the present study and of the ISCHEMIA-CKD medical/interventional arm) may be comparable in size. In addition, important inferences could be generated through a rough comparison between the long DAPT regimen group from this trial and the short DAPT group from ISCHEMIA-CKD. These suggestions could change the conclusions of ISCHEMIA-CKD, because the medical treatment of stable dialysis patients receiving a DES would include a longer DAPT (in other words, we were wondering whether stenting a stable Stage 5D CKD patient and administering a prolonged >12 months DAPT regimen could significantly reduce MACEs compared with medical therapy only).

Park *et al.* [10] focused on the benefits and risks of DAPT duration after DES implantation. Since the era of the '12 months after DES' dogma has passed, two divergent tendencies have emerged. In a recent excellent review study, Becker *et al.* [11] considered the question: 'Are at least 12 months of dual antiplatelet therapy needed for all patients with drug-eluting stents?' And offered the conclusion in the title: 'Not all patients with DES need at least 12 months of DAPT'. One can adjoin this statement with two (equally true, but divergent) answers: there are groups of patients that require a few months and other groups that need >12 months.

Given the haemorrhagic risk posed by DAPT in the already fragile population of ESRD patients (with a divergent coagulopathy [12]), all healthcare professionals involved in dialysis patients' management expect a clear answer: which duration is both efficient and safe, a shorter or a longer one? Unfortunately, the answer is still not so simple. It looks like a rope game with two strong opponents.

In the 2019 European Society of Cardiology guidelines for the diagnosis and management of chronic coronary syndromes [13], there is a standard clopidogrel plus aspirin 6 months recommendation (with a supplementary shortening indication to 1–3 months for high to very high risk of life-threatening bleeding). It should be noted that in Table 9 from the same guidelines, dialysis patients are included in the high risk for bleeding group. One can conclude, therefore, that a DAPT period of 1–3 months is sufficient for stable ESRD patients who receive a DES. Indeed, a nested case–control analysis of dialysis patients after DES implantation noted that a 6-month DAPT policy could be implemented safely in Stage 5D CKD [14]. However, this analysis stopped the follow-up at 12 months, ignoring the late and very late stent thrombosis events as well as subsequent ACS. Moreover, two-thirds of the patients included had stable angina. A recent meta-analysis by Mavrakanas *et al.* [15] endorsed such a shorter DAPT for (all) CKD populations. Again, readers should notice with caution that most of the trials included in the meta-analysis enrolled mostly stable CKD patients and fewer dialysis patients. In fact, the authors acknowledge that they lacked data to explore ACS patients ('given the potentially higher platelet reactivity among acute coronary syndrome patients with CKD, results might differ according to presentation') and did not had valid information regarding the generation of DESs [15]. In contrast, in the study published in this issue of *CKJ*, almost 75% of dialysis patients had ACS and 85% of them received a second-generation DES.

The 2017 European Society of Cardiology (ESC) focused update on DAPT in CAD introduced three scores to identify the

risk of intrastent thrombosis, new myocardial infarction and major bleeding with short- (3–6 months) or long-term DAPT (≥12 months) [16]. In another article, we criticised these scores regarding their usefulness and lack of validation in CKD populations (since all excluded ESRD patients from the studies) [17]. For example, as Stage G5D CKD patients have virtually no renal function, they start with a Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy score of 25, suggesting from the beginning a shorter DAPT (3–6 months).

At the other end of the rope game, one can find Table 5 from the same ESC update that there are high-risk features of stent-driven recurrent ischaemic events (which call for a longer DAPT strategy): longer stents, diffuse multivessel disease and advanced CKD. Probably most of the ESRD patients included in the study of Park *et al.* [2020] had a high risk of coronary thrombosis, as more than half of them were diabetics, 85% had hypertension and 60% had dyslipidemia. In addition, extended DAPT reduced events progressively in those patients with greater procedural complexity (complex PCI was defined elsewhere as having at least one of the following features: three vessels treated, three or more stents implanted, three or more lesions treated, bifurcation with two stents implanted, total stent length >60 mm or chronic total occlusion) [18]. Three other recent trials have advocated for a longer DAPT in advanced CKD patients with ACS [19–21].

All of these 'arbitrary assumptions' [22] are not, in fact, based on solid evidence but merely attempt to make clear recommendations for a topic that does not have the same rules as in the general population. This is why the study of Park *et al.* [2020] is so important: it presents the first solid evidence for a significant benefit of prolonged DAPT in dialysis patients receiving a DES, most of these patients having an ACS. The authors argue (and pull the rope in the game) that 'risk scores [should] weigh dialysis as a risk factor for ischaemia rather than bleeding'. It seems a bold statement, which will probably trigger criticism and another trial to prove the contrary.

Based on the results from several subgroup analyses from the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 trial, Howard *et al.* [23] mentioned few clinical characteristics that benefit from extended DAPT, placing ACS presentation first, followed by peripheral arterial disease, diabetes, renal dysfunction, current cigarette use, left ventricular ejection fraction <30%, increased procedure complexity, high CAD burden and stent diameter <3 mm. So we believe that ESRD is still in the middle of this rope game, being pulled to one side or another, by other serious features inclining towards a higher bleeding risk or towards higher ischaemic risk.

Given the delicate matter and unsolved issue of bleeding versus thrombosis in ESRD, one needs to consider that some G5D CKD patients may benefit from shorter DAPT and others may need a longer regimen (as Park *et al.* advocate). We recommend a judicious approach for each individual with ESRD since there could be arguments for a longer DAPT or reasons for limiting DAPT. Also, as the authors observed, the acute versus elective presentation seems to weigh in choosing the antiplatelet regimen. As Mavrakanas *et al.* [15] said, the 'one size fits all strategy' is not suitable for this particular group. Probably in the future, practitioners will be provided with decision pathways generated by artificial intelligence algorithms (and not by trials) that will yield 'truly individualized' DAPT protocols for every single patient, in a manner not possible by using present uidelinerecommendations [24].

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CONFLICT OF INTEREST STATEMENT

None declared.

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