

Should Oral Anticoagulation Be Used in ESKD Patients on Hemodialysis with Atrial Fibrillation?: COMMENTARY

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The debate in this issue of *Kidney360* addresses the question of oral anticoagulation for stroke prevention in patients with atrial fibrillation (AF) and ESKD on hemodialysis. This is an important topic that remains a considerable source of debate.

AF is highly prevalent among patients on hemodialysis. The annual incidence of subclinical new-onset AF is 19%, whereas the annual incidence of new-onset or recurrent AF may be as high as 26% in this population (1). In addition, AF is associated with higher morbidity and mortality in patients with advanced CKD, compared with patients with preserved kidney function, with an overall mortality rate up to 40% at 2 years (2).

Although use of oral anticoagulants is highly beneficial for stroke prevention in the general population or patients with moderate CKD and AF, there is a lack of high-quality randomized data in patients with advanced CKD or ESKD. Therefore, available evidence comes from retrospective observational studies that are notoriously unreliable to estimate treatment effects. Let us see what our debaters have to say about one of the most difficult conundrums for the experts.

On the pro side of the debate, Devabhaktuni and Mounsey highlight the results from a nationwide registry in Denmark, including 907 patients on maintenance hemodialysis. In this study, published in the *New England Journal*, patients treated with warfarin had a lower risk of stroke or systemic embolism, compared with patients who did not receive any antithrombotic therapy (3). In addition, Devabhaktuni and Mounsey discuss observational data from a prevalent dialysis population with AF from the United States Renal Data system, showing apixaban may be associated with a lower incidence of major bleeding compared with warfarin, and may therefore constitute a reasonable alternative in this population (4). They also highlight a potential mortality benefit from apixaban compared with no anticoagulation identified in a retrospective cohort study from the United States Renal Data system with an incident dialysis population with new-onset AF (5).

On the con side of the debate, Bansal and Lidgard discuss the important limitations of observational studies

due to selection bias and confounding by indication. They present results from a meta-analysis including 20 observational studies, showing that patients treated with oral anticoagulation have a higher incidence of any stroke and major bleeding compared with no anticoagulation (6). Bansal and Lidgard also highlight how challenging it is to achieve adequate time in the therapeutic range for patients on hemodialysis treated with warfarin. Indeed, according to preliminary results from the RENAL-AF trial (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation) presented at the American Heart Association 2019 meeting, time in therapeutic range was only 44% with a significant proportion of patients in the subtherapeutic range. The reason for this variability in the intensity of anticoagulation is not entirely clear, and it might be due, at least in part, to kidney disease-specific dietary restrictions.

So, what should nephrologists caring for patients with AF on maintenance dialysis take away from this debate? In my opinion, use of warfarin for stroke prevention in this setting is hard to justify for most patients, unless another compelling indication exists, such as venous thromboembolism or a metallic valve. Although available observational studies may have underestimated treatment effects, there is accumulating evidence that warfarin may be harmful in this setting. In addition to a higher incidence of bleeding complications, of particular importance is calciphylaxis, a life-threatening syndrome of vascular calcification that is 3–13 times as common among warfarin users, probably due to the warfarin-induced deficiency of vitamin K–dependent calcification inhibitors (7). Moreover, any potential benefit may be hard to obtain because it proves very difficult to achieve adequate time in the therapeutic range for most patients, even in the well-monitored setting of a randomized trial, as mentioned above.

If warfarin is not an option for patients on hemodialysis with AF, should direct oral anticoagulants (DOACs) be considered in this setting? There are several important points that have to be discussed with respect to use of these agents in patients with severely impaired kidney function.

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First, all DOACs are not the same. These agents have different mechanisms of action or different degrees of renal elimination, and they should not be grouped together in observational studies or meta-analyses. Second, if these agents were ever to be widely used in patients on hemodialysis, some degree of dose adjustment would probably prove to be necessary, as suggested by pharmacokinetic studies with repeated administration of rivaroxaban and apixaban in this population (8–9). Dose adjustment is also supported by differential treatment effect with standard and reduced doses of rivaroxaban and apixaban in this setting (5,10), and by a recently published randomized trial comparing rivaroxaban at the dose of 10 mg daily with warfarin (11). Unfortunately, results from single-dose pharmacokinetic studies have been widely diffused and cited, despite the fact that these studies are unable to account for drug accumulation occurring with repeated administration. Third, mortality benefit with apixaban in observational studies has to be interpreted with caution. This is most likely due to selection bias not accounted for by propensity score matching. This was acknowledged by the authors of the study showing this finding, who also report a numerically lower risk for outcomes that should not be influenced by anticoagulation, such as hospital admission for pneumonia or hip fracture, with apixaban compared with no anticoagulation (5). Fourth, careful selection of patients that may benefit from anticoagulation is necessary and requires more accurate prognostic scores for stroke and bleeding risk than we currently have (12). Fifth, relevant outcomes have to be carefully selected. If any benefit from ischemic stroke reduction is offset by a higher incidence of intracranial or fatal bleeding in this population, a composite outcome of ischemic or hemorrhagic stroke may be more relevant than the traditionally selected outcome of ischemic stroke or thromboembolism. It does not really matter to our patients if their hemiplegia or aphasia is due to a blood clot or an intraparenchymal hematoma. In addition, dialysis access bleeding is a clinically relevant complication that has not been adequately studied. Sixth, antiplatelet agents may have to be discontinued in patients who will be started on oral anticoagulation (12). Last, but not least, rivaroxaban or apixaban have to be compared in a randomized trial with no anticoagulation, and not with warfarin. Warfarin may significantly increase bleeding in the control arm and mask potential harm with DOACs in this setting. In a recently published observational study, apixaban was not associated with a lower incidence of stroke, but was associated with a higher incidence of fatal or intracranial bleeding compared with no anticoagulation (5).

For all reasons mentioned above, in my view, it is also hard to justify use of rivaroxaban or apixaban for stroke prevention for the majority of patients on hemodialysis with AF. Randomized data are necessary before such a recommendation can be made. However, if this approach is selected for a patient on hemodialysis because they are considered to be at very high risk of stroke, I would suggest using the reduced dose of 2.5 mg twice a day for apixaban or 10 mg daily for rivaroxaban, and consider obtaining a factor Xa trough level a couple of weeks after drug initiation. Although the target range remains largely unknown for these agents, overtly subtherapeutic or supratherapeutic levels would probably be identified. A thrombosis specialist might be involved for the interpretation of drug trough levels. This strategy should

not be widely implemented, at least for now, and may be considered only in selected patients after careful assessment of risks and benefits.

The SAFE-D trial (Strategies for the Management of Atrial Fibrillation in Patients Receiving Dialysis) (NCT03987711) is a randomized study that will compare different anticoagulation strategies (apixaban, warfarin, and no anticoagulation) in patients with AF on maintenance dialysis. Although at a pilot stage for now, this trial shows the way to proceed, and the investigators should be complimented for their effort. A phase 3 trial will ultimately be needed to answer this critical question, and such a study will have to be investigator initiated and will require international collaboration to be completed. The need for randomized trials of anticoagulation in end-stage kidney disease has been highlighted, at least since 2014 (13). Almost a decade later, the challenge for the nephrology community is still ahead.

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Author Contributions

T.A. Mavrakanas conceptualized and wrote the original draft.

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