

Use of Oral Anticoagulation for Patients with ESRD on Hemodialysis with Atrial Fibrillation: Verdict 1

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In this issue of the *Clinical Journal of the American Society of Nephrology*, McCullough *et al.* (1) and Keskar *et al.* (2) present compelling perspectives for both the pros and cons of anticoagulation use in patients with ESRD and atrial fibrillation (AF). Patients with ESRD uniquely have increased risk for thromboembolism and a paradoxical increased risk of bleeding, which makes decisions on anticoagulation challenging in this vulnerable population. This is clearly a complex discussion, which has led to confusion and inconsistency among providers. I applaud both groups for providing a comprehensive review of both sides of this important clinical question.

Patients with ESRD and AF are at greater risk for stroke (3,4); however, it remains unclear whether anticoagulation decreases this risk (5–9). There are significant limitations in the available data to effectively guide decision making on appropriate anticoagulation in the fragile ESRD population. Risk prediction scores for stroke and risk of bleeding have not performed well in ESRD populations. Rather than adapt current tools to patients with ESRD, development of dialysis-specific scores are needed, which may better account for the unique considerations in patients on dialysis, such as the high competing risk of death from infections and access-related complications for example. These data would help determine the risk-to-benefit ratio of anticoagulation in the short- and long-term in patients on dialysis with AF.

Review of the observational literature presented by both McCullough *et al.* (1) and Keskar *et al.* (2) suggests that risks of warfarin may outweigh the benefits. As both sides point out, the risks of warfarin are significant and include major hemorrhage from out of range International Normalized Ratio values, possibly from vitamin K deficiency from malnutrition, frequent antibiotic exposure, and chronic illness seen in patients with ESRD (10). Warfarin has a narrow therapeutic window and requires frequent monitoring. There are also numerous drug and food interactions, which can commonly occur in a patient population with a heavy pill burden and a myriad of dietary restrictions (10). Furthermore, warfarin use has also been associated with calciphylaxis (11). There is clearly a need for warfarin alternatives in patients with ESRD.

Both sides agree that novel oral anticoagulants (NOACs) are promising warfarin alternatives (12–15). These novel anticoagulants include two direct

thrombin inhibitors (ximelagatran and dabigatran) and two factor Xa inhibitors (apixaban and rivaroxaban) and have the benefit of not requiring regular anticoagulation monitoring and frequent dose adjustments. Several NOACs have been approved for clinical use and shown to be noninferior or superior to adjusted dose warfarin for stroke prevention, and in some patients, they reduced risk of major hemorrhagic complications. Keskar *et al.* (2) raise important points regarding the ability to extrapolate to patients with ESRD from clinical trials that have included a very modest number of patients with CKD (and none with ESRD). However, I do think that the data from subgroup analyses of clinical trial participants of patients with CKD are compelling. In a subanalysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial (which randomized patients to either apixaban or warfarin), apixaban was more effective than warfarin in preventing stroke and decreasing mortality, independent of level of kidney function (16). Moreover, the apixaban group had fewer bleeding events, and the greatest benefit was seen in patients with moderate kidney disease. In the AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) (which randomized patients to apixaban versus aspirin), a subgroup analysis reported that, among patients with kidney disease, apixaban significantly reduced risk of stroke compared with aspirin without significantly increasing the risk of hemorrhage (17).

In contrast to this clinical trial literature, Keskar *et al.* (2) cite an observational study that reported that patients on NOACs had significantly higher risk of complications compared with warfarin users (18). However, there are limitations to this study—the number of patients on NOACs was small, and the patients who were prescribed NOACs were more likely to have a history of bleeding compared with warfarin users. Thus, the findings in part may be due to bias from confounding by indication.

There are also concerns about possible renal clearance of NOACs. McCullough *et al.* (1) present interesting pharmacokinetic/pharmacodynamics data. In one study, apixaban exposure was only modestly higher in patients with ESRD compared with healthy subjects (19). Another study showed that, in patients

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with ESRD, rivaroxaban was not eliminated by dialysis, but there was no accumulation after multiple doses (20). With these data, I would not be quick to dismiss the potential use of these agents in patients on dialysis.

In conclusion, both groups of authors made convincing arguments. Without well conducted clinical trials specifically in patients with ESRD, it is impossible to definitely rule out anticoagulation for patients with ESRD and AF. I agree with Keskar *et al.* (2) that the risks of warfarin seem to outweigh the benefits on the basis of the current observational data. However, McCullough *et al.* (1) have provided a strong case for cautious optimism for the potential use of NOACs in patients with ESRD. I await more definitive evidence from clinical trials of NOACs in patients with ESRD to shed light on this important clinical issue.

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Disclosures

N.B. is on the steering committee of the RENnal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF) Trial, which is comparing the safety of apixaban with that of warfarin in patients with ESRD and nonvalvular atrial fibrillation.

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