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Should Oral Anticoagulation be used in ESKD Patients on Hemodialysis with Atrial Fibrillation? CON

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INTRODUCTION

Atrial fibrillation (AF) is common in patients with end-stage kidney disease (ESKD) and is associated with a high rate of mortality and stroke. In the general population, clinical trial data have demonstrated that anticoagulation is effective in decreasing rates of stroke without markedly increasing rates of bleeding[1]. However, existing data on the benefits and risks of anticoagulation for the prevention of AF related complications in the ESKD population are conflicting; thus current evidence does not support their use in hemodialysis patients. In this perspective, we will examine the relevant data and make the argument that anticoagulation should NOT be used in hemodialysis patients with AF. This assertion is supported by: the lack of definitive data showing an improvement in rates of stroke or all-cause mortality, the possible harm of oral anticoagulation, and the burden these medications incur on patients (**Box 1**).

LACK OF DEFINITIVE DATA SHOWING BENEFIT

In the general population, warfarin and direct oral anticoagulation (DOACs) medications are commonly used for anticoagulation in AF to prevent ischemic strokes. The data in hemodialysis patients on the use of warfarin are much more limited and based largely on observational (rather than clinical trial) data. While observational data are important, these data should be interpreted with caution due to possible confounding by indication, bias in patient selection and effect of residual confounders (e.g. comorbidity). Even with these considerations, the data from observational studies largely do not support use of warfarin for prevention of stroke in hemodialysis patients. For example, a recent meta-analysis of 15 observational studies including 47,480 ESKD patients with AF showed that as compared to no anticoagulation, warfarin use in ESKD did not improve rates of mortality (HR, 0.95; 95% CI, 0.83-1.09) or

ischemic stroke (HR, 0.96; 95% CI, 0.82-1.13).[2] This study is not alone; a previous meta-analysis of 20 observational studies involving 31,321 patients with ESKD and AF also showed no benefit to anticoagulation in terms of all-cause (relative risk 0.97, 95% CI 0.90 to 1.04) and cardiovascular mortality (relative risk 0.99, 95% CI 0.86 to 1.15). Indeed, the anticoagulated patients actually had a higher risk of stroke.[3] Until published randomized clinical trial become available, observational studies certainly do not support the use of warfarin in patients with ESKD and AF.

Data on the efficacy of DOACs for stroke prevention in patients with ESKD and AF are even more limited than that for warfarin. Unfortunately, all the randomized clinical trials of DOACs in the general population have excluded patients with ESKD. While there are ongoing trials of DOACs in ESKD (RENAL-AF; ClinicalTrials.gov identifier NCT02942407; SAFE HD; ClinicalTrials.gov identifier NCT03987711; AXADIA; ClinicalTrials.gov identifier NCT02933697), none are yet published. Observational data of DOACs in patients with ESKD have been inconclusive or have shown marginal benefit at best. In a retrospective cohort study of Medicare beneficiaries included in the United States Renal Data System, a matched analysis of apixaban and warfarin users reported no significant different in risk of stroke or systemic embolism between the two groups (HR, 0.88; 95% CI, 0.69-1.12).[4] In another observational study of hemodialysis patients, there was no difference in risk of stroke or systemic embolism in matched patients treated with warfarin vs. rivaroxaban (HR = 0.55, 95% CI = 0.27-1.10).[5] A systematic review also reported no difference in stroke outcomes between apixaban, dabigatran (RR 1.71, 95% CI 0.97-2.99) or rivaroxaban (RR 1.8, 95% CI 0.89-3.64) versus warfarin in hemodialysis patients.[6] It should be noted that none of these observational

studies compared DOAC use to no anticoagulation. In summary, current published data do not support the use of either warfarin or DOACs for stroke reduction in hemodialysis patients.

POTENTIAL FOR HARM

Oral anticoagulation can have devastating adverse effects, including major bleeding. Unfortunately, the dialysis population, although prothrombotic, is also uniquely susceptible to higher risk of bleeding[7] from biological factors (e.g. platelet dysfunction) and use of concurrent therapies (e.g. heparin during dialysis). Furthermore, repeated cannulation of arteriovenous fistulae (AVFs) in hemodialysis patients poses additional risks of hemorrhage, which can be fatal.[8]

Although clinical trial data are lacking, observational data suggests that warfarin is associated with higher risk of bleeding in hemodialysis patients. In a meta-analysis of 20 observational studies including 56,146 patients with AF and ESKD, warfarin use (vs. no warfarin use) was significantly associated with an increased risk of all-cause bleeding.[9] Another meta-analysis also demonstrated higher risk of hemorrhagic stroke among hemodialysis patients receiving warfarin compared to those not on anticoagulation (HR, 1.49; 95% CI, 1.03-1.94).[2] A study of patients from a Danish registry also reported an increased risk of bleeding in ESKD patients treated with warfarin compared to those not treated with warfarin.[7] In addition to increased risk of bleeding, another possible adverse effect related to warfarin use in dialysis patients is an increased risk of vascular calcification and calciphylaxis.

There are some published observational studies examining risks of bleeding in dialysis patients treated with DOACs versus those treated with warfarin, which have yielded differing results (perhaps due to varying pharmacologic properties of DOAC medications in dialysis

patients). Some studies have reported lower risk of bleeding with DOACs compared to warfarin;[4, 5] and others have reported higher risk.[6] For example, in a systematic review of observational studies, rivaroxaban and dabigatran were associated with increased risk of major bleeding compared with warfarin; while rates of bleeding were similar with apixaban versus warfarin.[6] There are no data which directly compare risk of bleeding in hemodialysis patients treated with DOACs versus no anticoagulation at all. Collectively, the current body of data does not provide reassurance on safety of oral anticoagulation in hemodialysis patients.

BURDEN OF THERAPY

The ESKD population faces a disproportionate pill burden compared to patients with other chronic comorbidities. One study of U.S. hemodialysis patients reported a median daily pill burden of 19 pills.[10] In addition to commonly prescribed medications such as phosphate binders, antihypertensives, and diabetes medications, hemodialysis patients with AF may be also prescribed rate or rhythm controlling medications. Should we be adding another medication to this pill burden with no clear benefit and possible harm with oral anticoagulation? Higher pill burden may lead to other unintended consequences as well, including higher risk of interactions with other medications, poor quality of life and lower adherence to medications overall due to "pill fatigue."

The burden of anticoagulation does not stop at simply taking a pill, however. Patients on warfarin have their INRs checked frequently, and dose adjustments are very common. INRs are also labile and therefore adequate time in therapeutic range (TTR) can be challenging to achieve in this population. Frequent dose adjustments are not only disruptive and difficult to fit into a schedule already calling for several dialysis sessions weekly, but can be mentally challenging as

well, as patients must constantly keep track of what dose of warfarin they need to take in any given week. Frequent dose changes can also lead to potentially life-threatening errors in dose administration. Warfarin also requires dietary changes, including restriction of foods rich in vitamin K, for example green leafy vegetables. Hemodialysis patients are already burdened with many dietary restrictions, including restrictions in potassium, phosphorus and sodium intake. Further restricting the diets of hemodialysis patients may contribute to the already poor nutrition of this patient population, portending worse outcomes. It should be noted that DOACs do not require the same monitoring, dose adjustments or dietary restrictions as warfarin and thus may be promising alternatives to warfarin pending more data. Taken in sum, the "toll" of oral anticoagulation on the quality of life in dialysis patients currently appears to be too high, particularly given the lack of clear benefit and potential harm.

CONCLUSIONS

In summary, we do not believe that the current body of literature supports the use of oral anticoagulation in hemodialysis patients. Thereare no definitive clinical trial data that shows clear reduction in stroke or mortality with use of oral anticoagulation versus no anticoagulation. Further, observational data suggest higher risk of devastating complications, including hemorrhagic strokes, with use of oral anticoagulation. Also, the hemodialysis population is quite heterogenous and it remains unknown whether the observed risks and lack of benefit apply to all hemodialysis patients; a more individualized approach may be necessary. Lastly, oral anticoagulation medications (particularly warfarin) also pose increased burden on patients by increasing pills counts, increased need for monitoring, and dietary restrictions, which may

further reduce quality of life. Weighing these risks versus benefits, hemodialysis patients with AF should NOT be anticoagulated for primary prevention of stroke.

DISCLOSURES

N. Bansal reports Scientific Advisor or Membership: CJASN, AJKD; Associate Editor – *Kidney360;* and is on the steering committee for the RENAL-AF clinical trial, sponsored by BMS/Pfizer Alliance. Dr. Bansal is supported by NHLBI R01 HL142834 (outside the submitted work). The remaining author has nothing to disclose.

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AUTHOR CONTRIBUTIONS

N Bansal: Conceptualization; Writing - original draft; Writing - review and editing

B Lidgard: Writing – original draft

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Box 1: Key Points: Current barriers to use of oral anticoagulation for treatment of atrial fibrillation in patients on hemodialysis

Lack of clear efficacy data	Possible harm	Greater patient burden
Largely observational data	Risk of bleeding, including dialysis access bleeding	Pill burden
Studies with conflicting findings	Risk of vascular calciphylaxis with warfarin	Frequent monitoring and dose adjustments
Limited studies on DOACs		Labile INRs
Heterogeneity of hemodialysis patients		Interactions with other medications
		Dietary restrictions