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

Benjamin Lidgard and Nisha Bansal

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Introduction
Atrial fibrillation (AF) is common in patients with 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, the evidence does not support their use in patients on hemodialysis. In this perspective, we will examine the relevant data and make the argument that anticoagulation should NOT be used in patients with AF on hemodialysis. 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 (Table 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 patients on hemodialysis and the use of warfarin are much more limited, and based largely on observational (rather than clinical trial) data. Although 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 patients on hemodialysis. For example, a recent meta-analysis of 15 observational studies including 47,480 patients with ESKD and AF showed that, compared with no anticoagulation, warfarin use in ESKD did not improve rates of mortality (hazard ratio [HR], 0.95; 95% confidence interval [95% CI], 0.83 to 1.09) or ischemic stroke (HR, 0.96; 95% CI, 0.82 to 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 [RR], 0.97; 95% CI, 0.90 to 1.04) and cardiovascular mortality (RR, 0.99; 95% CI, 0.86 to 1.15). Indeed, the anticoagulated patients had a higher risk of stroke (3).

Until published randomized clinical trials 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 of the randomized clinical trials of DOACs in the general population have excluded patients with ESKD. Although there are ongoing trials of DOACs in ESKD (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation [RENA-L-AF], ClinicalTrials.gov identifier NCT02942407; Strategies for the Management of Atrial Fibrillation in Patients Receiving Dialysis [SAFE-D], ClinicalTrials.gov identifier NCT03987711; Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation and End-stage Kidney Disease [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 to 1.12) (4). In another observational study of patients on hemodialysis, there was no difference in risk of stroke or systemic embolism in matched patients treated with warfarin versus rivaroxaban (HR, 0.55; 95% CI, 0.27 to 1.10) (5). A systematic review also reported no difference in stroke outcomes between apixaban, dabigatran (RR, 1.71; 95% CI, 0.97 to 2.99) or rivaroxaban (RR, 1.8; 95% CI, 0.89 to 3.64) versus warfarin in patients with hemodialysis (6). It should be noted that none of these observational studies compared DOAC use to no anticoagulation. In summary, published data do not support the use of either warfarin or DOACs for stroke reduction in patients on hemodialysis.

Potential for Harm
Oral anticoagulation can have devastating adverse effects, including major bleeding. Unfortunately, the
Table 1. Key points: Barriers to use of oral anticoagulation for treatment of atrial fibrillation in patients on hemodialysis

<table>
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<th>Lack of Clear Efficacy Data</th>
<th>Possible Harm</th>
<th>Greater Patient Burden</th>
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<td>Largely observational data</td>
<td>Risk of bleeding, including dialysis access and bleeding</td>
<td>Pill burden</td>
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<tr>
<td>Studies with conflicting findings</td>
<td>Risk of vascular calciphylaxis with warfarin</td>
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<td>Limited studies on DOACs</td>
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DOAC, direct oral anticoagulation; INR, international normalized ratio.

dialysis population, although prothrombotic, is also uniquely susceptible to higher risk of bleeding (7) from biologic factors (e.g., platelet dysfunction) and use of concurrent therapies (e.g., heparin during dialysis). Furthermore, repeated cannulation of arteriovenous fistulae in patients on hemodialysis poses additional risks of hemorrhage, which can be fatal (8).

Although clinical trial data are lacking, observational data suggest warfarin is associated with higher risk of bleeding in patients on hemodialysis. 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 patients on hemodialysis receiving warfarin compared with those not on anticoagulation (HR, 1.49; 95% CI, 1.03 to 1.94) (2). A study of patients from a Danish registry also reported an increased risk of bleeding in patients with ESKD treated with warfarin compared with those not treated with warfarin (7). In addition to increased risk of bleeding, another possible adverse effect related to warfarin use in patients on dialysis is an increased risk of vascular calcification and calciphylaxis.

There are some published observational studies examining risks of bleeding in patients on dialysis treated with DOACs versus those treated with warfarin, which have yielded differing results (perhaps due to varying pharmacologic properties of DOAC medications in patients on dialysis). Some studies have reported lower risk of bleeding with DOACs compared with 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, although rates of bleeding were similar with apixaban versus warfarin (6). There are no data that directly compare risk of bleeding in patients on hemodialysis treated with DOACs versus no anticoagulation at all. Collectively, the body of data does not provide reassurance on safety of oral anticoagulation in patients on hemodialysis 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 also lead to other unintended consequences, 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 extends beyond the pill burden. Patients on warfarin have their international normalized ratios checked frequently, and dose adjustments are very common. International normalized ratios are also labile and therefore achieving adequate time in the therapeutic range can be challenging in this population. Frequent dose adjustments are disruptive and difficult to fit into the rigorous dialysis schedule, and can be mentally challenging as patients need to meticulously track the 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. Patients on hemodialysis are already burdened with many dietary restrictions, including restrictions in potassium, phosphate, and sodium intake. Further restricting the diets of patients on hemodialysis 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 patients on dialysis appears too high, particularly given the lack of clear benefit and potential harm.

In summary, we do not believe the current body of literature supports the use of oral anticoagulation in patients on hemodialysis. There are no definitive clinical trial data that show a 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 the use of oral anticoagulation. Also, the hemodialysis population is heterogenous, and it remains unknown whether the observed risks and lack of benefit apply to all patients on hemodialysis; 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

Burden of Therapy

The ESKD population faces a disproportionate pill burden compared with patients with other chronic comorbidities. One study of US patients on hemodialysis reported a median daily pill burden of 19 (10). In addition to commonly prescribed medications, such as phosphate binders, antihypertensives, and diabetes medications, patients on hemodialysis...
these risks versus benefits, patients on hemodialysis with AF should NOT be anticoagulated for primary prevention of stroke.

Disclosures
N. Bansal reports being a scientific advisor of CJASN and *American Journal of Kidney Diseases*, and Associate Editor of Kidney360; and is on the steering committee for the RENAL-AF clinical trial, and is sponsored by Bristol Myers Squibb/Pfizer Alliance. The remaining author has nothing to disclose.

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Author Contributions
N. Bansal conceptualized this study and reviewed and edited the manuscript; and both authors wrote the original draft.

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