

EDITORIAL COMMENT

Benefits and Risks of Anticoagulation in Dialysis Patients With Nonvalvular Atrial Fibrillation

Navigating Through Darkness*

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The prescription of oral anticoagulants (OACs) to patients with nonvalvular atrial fibrillation (NVAf) who are treated with maintenance dialysis poses a challenging conundrum to clinicians. Despite a high prevalence of NVAF (1), dialysis patients were routinely excluded from trials that established the risk-benefit profiles of vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) (2,3). Consequently, clinical practice guidelines (4–6) can offer little definitive guidance resulting in a wide variability in clinical practice (1). Intuitively, clinicians may be tempted to administer OACs to dialysis patients with NVAF, impelled by the high incidence of ischemic stroke in this population (7). On the other hand, elevated bleeding rates in dialysis patients, most ominously the risk of hemorrhagic stroke, should dampen any tendency to casually extrapolate evidence from patients with preserved kidney function (8). Furthermore, the substantial competing risk of death may render moot any impact of OACs on ischemic stroke in dialysis recipients (9).

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In this issue of the *Journal*, Kuno et al. (10) present the results of a network meta-analysis of studies that compared the efficacy and safety of different OACs, both to each other and to no anticoagulation, in dialysis recipients with NVAF. The findings were based entirely on observational data, after reconfirming the absence of published randomized trials. The 16 studies selected for the analysis comprised 71,877 patients, the vast majority of whom were on hemodialysis. All except 2 studies were comparisons of warfarin to no anticoagulation. One study explored the association between apixaban, as compared with warfarin, and systemic thromboembolism and major bleeding, respectively. An additional study examined the association between dabigatran and rivaroxaban as compared with warfarin but was limited to bleeding endpoints. When compared with no anticoagulation, neither warfarin, apixaban 5 mg twice daily, nor apixaban 2.5 mg twice daily was associated with a reduction in the risk of stroke or systemic embolism though heterogeneity was high. As compared with warfarin, both apixaban doses were associated with a lower risk of bleeding.

This work provides an updated review of anticoagulation strategies for stroke prevention, and the inherent risks of these drugs, in dialysis patients with NVAF. By including recent studies involving DOACs, the reader is provided with an important glimpse at the emerging experience with these drugs in the dialysis population. Given their partial dependence on kidney metabolism, concerns about bioaccumulation and bleeding risk, and ultimately, the lack of broad regulatory approval for use in

advanced chronic kidney disease, clinicians are understandably reluctant to treat dialysis patients with DOACs (11). However, the Food and Drug Administration has approved the use of apixaban in dialysis patients. This appears to have had an impact on practice: the study by Siontis et al. (12), included in this meta-analysis, showed that >25% of dialysis patients who commenced oral anticoagulation in 2015 were prescribed apixaban. Though the role of OACs for NVAf remains unsettled, clinicians caring for dialysis patients should be attuned to the practical issues around prescribing and managing DOACs, which may prove to be viable alternatives to VKAs.

The current study provides a sobering reminder of the poor evidence base at clinicians' disposal when deciding on whether and how to anticoagulate dialysis patients with NVAf. The cohort studies that constituted the meta-analysis were generally derived from population datasets or databases of large dialysis organizations (10). Although such data sources have the advantage of providing "real-world" insights that are often lacking in randomized controlled trials, confounding by indication is an insurmountable shortcoming. A clinician's decision to initiate an OAC could have been driven by a perception of the patient being at higher risk of thromboembolic events; these same high-risk patients would be more likely to develop strokes and other thromboembolic phenomena as compared with nonanticoagulated patients, thereby distorting any true underlying benefit of anticoagulation. By the same token, clinicians could have selectively prescribed apixaban, as opposed to VKAs, to those less likely to experience adverse bleeding events. Consistent achievement of therapeutic international normalized ratio values is a prerequisite for the effective and safe administration of VKAs, and the studies did not provide any information about time spent in the therapeutic range. Additionally, the studies were unable to account for important confounders such as the concomitant use of antiplatelet agents and interacting medications that may alter warfarin and DOAC pharmacokinetics. Finally, definitions for critical events such as stroke and bleeding could have differed both within cohorts and across studies. Reliance on diagnostic codes likely led to some misclassification of key outcomes, thereby biasing the reported effect estimates.

In addition to the well-known shortcomings of VKAs, the theoretical risks of accelerated vascular calcification and calciphylaxis due to vitamin K depletion are a particular concern for dialysis patients and underscore the pressing need for a safe oral anticoagulant in this high-risk population. In the

network meta-analysis by Kuno et al. (10), apixaban emerged as both more efficacious and safer than VKAs, but information on apixaban emanated from a single study with a very short follow-up duration (average time on apixaban 105 days) (12). It is also notable that bleeding rates, though relatively lower with apixaban as compared with warfarin, were still substantially higher than bleeding rates in the landmark clinical trial that compared apixaban to warfarin (13).

Since completion of the meta-analysis by Kuno et al. (10), 2 trials have shed further light on the relative safety of DOACs and VKAs. De Vriese et al. (14) compared a VKA (target international normalized ratio 2 to 3) versus rivaroxaban 10 mg daily versus rivaroxaban 10 mg + vitamin K2 (intended to mitigate vascular calcification) in 132 hemodialysis recipients with NVAf. Over 18 months of follow-up, vascular calcification progression did not differ across the 3 groups. However, life-threatening and major bleeding were lower in the rivaroxaban groups compared with those receiving a VKA. The RENAL-AF (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation; [NCT02942407](#)) trial recently reported its findings but remains unpublished. The trial intended to randomize 760 hemodialysis recipients with NVAf to apixaban or warfarin but was halted due to slow recruitment and resource limitations. Among the 154 patients who were enrolled, major or clinically relevant bleeding was comparable in both groups in the range of 20% to 25% with about one-half of the events related to the hemodialysis access site. Another ongoing trial in Germany is comparing apixaban to warfarin and will enroll 222 dialysis patients with NVAf (Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation [AF] and End-Stage Kidney Disease [ESKD] [AXADIA]; [NCT02933697](#)) (15). The primary outcome is a composite of major or clinically relevant, nonmajor bleeding episodes or death with a maximum follow-up of 24 months. The small sample sizes and relatively short follow-up duration in these trials will ultimately limit inferences about the effect of oral anticoagulation on stroke and thromboembolism.

Though expanded knowledge about the use of DOACs in dialysis patients is welcome, the most fundamental question in this area still remains unanswered. Specifically, can oral anticoagulation in any format deliver a reduction in thromboembolic events, as compared with no anticoagulation, with an acceptable risk of bleeding? Crucial evidence may be forthcoming as the ongoing open-label multicenter AVKDIAL (Oral Anticoagulation in Haemodialysis

Patients; [NCT02886962](#)) trial in France will randomize 855 maintenance hemodialysis patients with NVAf to warfarin or no anticoagulation. The primary outcome is a composite of bleeding and thrombotic events.

The network meta-analysis by Kuno et al. (10) has highlighted once again the existing evidence vacuum for the provision of OAC to dialysis recipients with NVAf. For patients and their clinicians, this is especially distressing because the stakes of providing—or withholding—OACs are conceivably so high. Recently

completed and ongoing trials will hopefully advance the quality of evidence in this area with the ultimate goal of resolving one of the most vexing dilemmas faced by clinicians who care for patients on maintenance dialysis.

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REFERENCES

1. Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int* 2010;77:1098-106.
2. Harel Z, Chertow GM, Shah PS, et al. Warfarin and the risk of stroke and bleeding in patients with atrial fibrillation receiving dialysis: a systematic review and meta-analysis. *Can J Cardiol* 2017;33:737-46.
3. Ha JT, Neuen BL, Cheng LP, et al. Benefits and harms of oral anticoagulant therapy in chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2019;171:181-9.
4. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;74:104-32.
5. Verma A, Cairns JA, Mitchell LB, et al. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol* 2014;30:1114-30.
6. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-962.
7. Seliger SL, Gillen DL, Longstreth WT Jr., Kestenbaum B, Stehman-Breen CO. Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int* 2003;64:603-9.
8. Sood MM, Bota SE, McArthur E, et al. The three-year incidence of major hemorrhage among older adults initiating chronic dialysis. *Can J Kidney Health Dis* 2014;1:21.
9. Findlay M, MacIsaac R, MacLeod MJ, et al. The association of atrial fibrillation and ischemic stroke in patients on hemodialysis: a competing risk analysis. *Can J Kidney Health Dis* 2019;6:2054358119878719.
10. Kuno T, Takagi H, Ando T, et al. Oral anticoagulation for patients with atrial fibrillation on long-term hemodialysis. *J Am Coll Cardiol* 2020;75:273-85.
11. Jain N, Reilly RF. Clinical pharmacology of oral anticoagulants in patients with kidney disease. *Clin J Am Soc Nephrol* 2019;14:278-87.
12. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation* 2018;138:1519-29.
13. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92.
14. De Vriese AS, Caluwe R, Pyfferoen L, et al. Multicenter randomized controlled trial of vitamin K Antagonist replacement by rivaroxaban with or without vitamin K2 in hemodialysis patients with atrial fibrillation: the Valkyrie study. *J Am Soc Nephrol* 2019 Nov 8 [E-pub ahead of print].
15. Reinecke H, Jurgensmeyer S, Engelbertz C, et al. Design and rationale of a randomised controlled trial comparing apixaban to phenprocoumon in patients with atrial fibrillation on chronic haemodialysis: the AXADIA-AFNET 8 study. *BMJ Open* 2018;8:e022690.

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