

EDITORIAL COMMENT

# When Oral Anticoagulation Becomes Difficult\*



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Oral anticoagulation in patients with atrial fibrillation and impaired renal function is challenging and not based on high levels of evidence. Although patients with chronic kidney disease hold an increased risk of thromboembolism, they also experience an increased risk of bleeding. The large-scale randomized trials investigating efficacy and safety of oral anticoagulation have never included patients with severe chronic kidney disease, including both the older trials comparing vitamin K antagonist with placebo and the newer trials comparing nonvitamin K antagonist with vitamin K antagonist. Clinical decision-making regarding anticoagulation for patients with atrial fibrillation and impaired renal function is based on case reports and observational studies. Hopefully, the future will bring more light to this important subject, because the patient population is growing and frail. Recently, the RENAL-AF (Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients With Atrial Fibrillation; [NCT02942407](#)), which compared apixaban and warfarin, was stopped early after including only 154 patients during 3.5 years of enrollment, illustrating how difficult randomized trials are in a dialysis population. AXADIA-AFNET 8 (A Safety Study Assessing Oral Anticoagulation with Apixaban versus Vitamin-K Antagonists in Patients with Atrial Fibrillation [AF] and End-Stage Kidney Disease [ESKD] on

Chronic Hemodialysis Treatment) (1) will also compare apixaban and a vitamin K antagonist, and the combined results of the 2 trials will hopefully settle the role of apixaban as an anticoagulant among patients with hemodialysis. The burning question, however, is whether patients on dialysis with atrial fibrillation should receive anticoagulation at all. Only the DANWARD (Danish Warfarin-Dialysis Study-Safety and Efficacy of Warfarin in Patients With Atrial Fibrillation on Dialysis; [NCT03862859](#)), which aims to include 718 dialysis patients, will compare anticoagulation against no anticoagulation, but several years will pass before results from this study will be presented, and decisions regarding oral anticoagulation among patients with hemodialysis will be based on observational evidence during the following years.

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When decision making relies on observational studies, it is unfortunate that the observational studies draw different conclusions. In this issue of the *Journal*, Pokorney et al. (2) report results on patients with atrial fibrillation and end-stage renal disease retrieved from a 5% sample of Medicare fee-for-service beneficiaries in the United States from 2006 to 2013. They found oral anticoagulation (99% warfarin) was associated with an increased risk of bleeding and has no association with stroke or death. This result is in line with 2 previous meta-analyses of observational studies (3,4). Since these meta-analyses from 2015 and 2016, respectively, several studies have investigated the quality of warfarin treatment in patients with chronic kidney disease and creatinine clearance <30 ml/min (5-7). The results are clear: observational studies report decreased time in therapeutic range with decreasing renal function. However, none of the studies report time in therapeutic range for patients with end-stage renal disease, and

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one could speculate that warfarin would be even more difficult to control in these patients. As expected, reduced time in therapeutic range was associated with worse outcomes and reduced renal function was associated with worse outcomes (6,7), but interestingly, no effect modification was observed between time in therapeutic range and renal function (6), indicating that a longer time in therapeutic range is as important in this population as in the general atrial fibrillation population, although much more rarely achieved.

In conclusion, it remains to be determined if warfarin is associated with a positive or negative net clinical benefit in patients with atrial fibrillation and severe chronic kidney disease, especially in

end-stage renal disease. Thus, it seems clear that well-controlled warfarin treatment is difficult to achieve in these patients, and when warfarin is chosen, more efforts should be put into monitoring of the patient than usual. The use of nonvitamin K antagonists or left atrial appendage occlusion in end-stage renal disease has potential; however, for now, the evidence for these options is even more questionable.

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## REFERENCES

1. Reinecke H, Jürgensmeyer 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.
2. Pokorney SD, Black-Maier E, Hellkamp AS, et al. Oral anticoagulation and cardiovascular outcomes in patients with atrial fibrillation and end-stage renal disease. *J Am Coll Cardiol* 2020;75:1299-308.
3. Liu G, Long M, Hu X, et al. Effectiveness and safety of warfarin in dialysis patients with atrial fibrillation: a meta-analysis of observational studies. *Medicine (Baltimore)* 2015;94:e2233.
4. Wong CX, Odutayo A, Emdin CA, Kinnear NJ, Sun MT. Meta-analysis of anticoagulation use, stroke, thromboembolism, bleeding, and mortality in patients with atrial fibrillation on dialysis. *Am J Cardiol* 2016;117:1934-41.
5. Pokorney SD, Simon DN, Thomas L, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: results from ORBIT-AF registry. *Am Heart J* 2015;170:141-8.e1.
6. Szummer K, Gasparini A, Eliasson S, et al. Time in therapeutic range and outcomes after warfarin initiation in newly diagnosed atrial fibrillation patients with renal dysfunction. *J Am Heart Assoc* 2017;6:e004925.
7. Bonde AN, Lip GYH, Kamper A-L, et al. Effect of reduced renal function on time in therapeutic range among anticoagulated atrial fibrillation patients. *J Am Coll Cardiol* 2017;69:752-3.

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