Anticoagulation Management in Patients on Hemodialysis with Atrial Fibrillation

More Questions than Answers

By Fatima Ali, Mital Jhaveri, and Sheila Sarnoski-Brocavich

Is atrial fibrillation (AF) in patients on dialysis an actual effector of cardioembolic events, or is it a surrogate marker for cardiovascular disease?

Overall, direct oral anticoagulants (DOACs) have a superior benefit to a risk profile compared with vitamin K antagonists (VKAs), such as warfarin. When it comes to patients on hemodialysis (HD), however, the confusion lies in which, if any, anticoagulants are appropriate. Patients receiving maintenance HD have a high incidence of stroke, which typically warrants the use of anticoagulation. However, patients on HD also have an increased risk of bleeding because they are routinely heparinized three times each week and have platelet dysfunction (1). A meta-analysis of 13 studies among patients on HD reported a stroke rate of 5.2 per 100 patient-years with AF versus 1.9 per 100 patient-years without AF (2). This suggests that AF is a risk factor in patients on HD. Interestingly, in a cohort of 1382 patients on HD, AF was not significantly associated with new stroke (3). Potential reasons for this are the high competing risk of mortality in patients on HD, a possible protective effect of heparin administration during the dialysis procedure, and the high prevalence of subclinical AF in the "no AF" cohort in observational studies of patients on HD (4). As a result, the use of anticoagulation in patients on HD with AF remains controversial.

Although VKAs are the mainstay therapy for thromboembolic issues, there is a paucity of evidence to support a reduction of risk of stroke in patients on HD. Considering this and the increased risk of bleeding and calciphylaxis, the use of VKA in patients on HD should be questioned (4, 5). On the other hand, the dependence of DOACs on kidney clearance, bioavailability, and bleeding risk is a factor to consider when treating patients on HD with AF (6).

One major advantage of using direct oral agents…is that there is no need for measurement of INR levels or special dietary restrictions.

Should patients with kidney failure on HD with AF receive anticoagulants?

In a meta-analysis of 12 cohort studies comprising over 17,000 patients on HD with AF, VKAs had a non-significant (26%) reduction of ischemic stroke rate, no effect on total mortality, a 21% increase in total bleeding risk, and a doubling of the incidence of hemorrhagic stroke (7). On the other hand, in a meta-analysis of 15 studies that had more than 47,000 patients on HD with AF, the use of VKAs did not reduce ischemic stroke or all-cause mortality and increased risk of hemorrhagic stroke but did not affect overall risk of bleeding (8).

Overall, when compared with no anticoagulation, neither VKAs nor the DOAC apixaban (standard and reduced dose) were associated with a reduction in stroke or systemic embolism, although heterogeneity was high (9). In summary, the data are mixed, and we are still left with more questions than answers for stroke reduction using anticoagulation in patients on HD with AF.

Several randomized controlled trials assessing stroke and bleeding risk of oral anticoagulants versus VKAs or no anticoagulation in patients on HD with AF are currently ongoing and can provide better answers to this question (NCT02933697: AXADIA, NCT03987711: SAFE-D, and NCT03969953: TRACK).

Patients with AF on apixaban, a factor Xa inhibitor, qualify for either standard or reduced dosing. The standard dose for stroke risk reduction in patients with non-ventricular AF (NVAF) is typically 5 mg twice a day. A reduced dose of apixaban—2.5 mg twice daily—is warranted for patients meeting two of the three following criteria: ≥80 years old, serum creatinine ≥1.5 mg/dL, or weight ≤60 kg. The rationale for this dose adjustment is the greater risk of bleeding and mortality in patients with NVAF and in patients with at least two of the mentioned dose-adjustment criteria compared with patients with one or fewer of the criteria (10).

When it comes to bleeding events, the risk of fatal or intracranial bleeding increased in patients on apixaban (4.9 events/100 patient-years) versus those who received no anticoagulation (1.6 events/100 patient-years); this was true for apixaban 5 mg but not 2.5 mg twice a day. Apixaban at 2.5 mg twice a day dosing had a higher rate of myocardial infarction or ischemic stroke versus no anticoagulation. Apixaban resulted in lower all-cause mortality compared with those receiving no anticoagulation (11). Mortality risk is lowest with apixaban 5 mg compared with VKA, apixaban 2.5 mg, and no anticoagulation (11).

A study of 124 patients on HD found less bleeding in apixaban than VKAs (12). In a larger study of more than 25,000 patients on chronic HD with AF, 2351 were taking apixaban (44% on 5 mg twice a day and 56% on 2.5 mg twice a day), and 23,172 were taking VKAs; the risk of stroke and intracranial bleeding was identical between both agents. Apixaban showed fewer major bleeding events and a non-significant trend toward reduced mortality (13). At a dose of 5 mg, apixaban resulted in less major bleeding, lower risk of stroke, and a non-significant trend toward reduced mortality compared with VKAs. At a dose of 2.5 mg twice a day, there was a lower risk of bleeding without differences in stroke and death (13). Finally, a meta-analysis of five studies comprising more than 43,000 patients (combined chronic kidney disease and end stage kidney disease [ESKD]) demonstrated that apixaban was associated with lower risk of bleeding but similar risk of thromboembolic events when compared with VKA (14). Although the role of DOACs in patients on HD with AF remains ambiguous, apixaban is approved for use in dialysis and is a feasible alternative to VKA.

Data on the use of rivaroxaban for stroke risk reduction in patients with kidney failure and AF are limited. According to a study investigating the use of DOACs in HD patients with AF, the risk of bleeding is increased in DOACs, such as dabigatran and rivaroxaban, compared with apixaban (15). In addition, risk of hemorrhagic stroke was significantly lower in patients on dabigatran or rivaroxaban compared with VKAs, despite an overall increased bleeding risk (16). Only 33% of rivaroxaban is eliminated by the kidney with minimal dialyzability due to high protein binding. Currently, rivaroxaban can be used at a reduced dose of 15 mg in patients with reduced kidney function (creatinine clearance [CrCl] ≤50 mL/min). There are limited data for use of rivaroxaban in patients with kidney failure (15). Despite this, the renally impaired population is being exposed to both rivaroxaban and dabigatran. Further research is necessary to make a recommendation.

The Valkyrie study (5) looked at 132 patients on HD with AF who were randomized to VKAs with a target international normalized ratio (INR) of 2–3, rivaroxaban 10 mg daily, or rivaroxaban plus vitamin K2 for 18 months. The incidence of fatal and non-fatal cardiovascular events and of symptomatic limb ischemia was higher in VKAs than both rivaroxaban groups. Furthermore, death from any cause, cardiac death, and risk of stroke were not different between the groups. Life-threatening or major bleeding adjusted for competing risk of death was increased in VKAs compared with rivaroxaban (5). Overall, in patients on HD with AF, a lower dose of rivaroxaban (10 mg) showed fewer outcomes of fatal and non-fatal cardiovascular events and major bleeding complications compared with VKA (5). Trials are underway to reach more definitive conclusions.

What doses are used for direct oral agents in patients on HD?

Only rivaroxaban and apixaban are suitable for patients undergoing maintenance HD, as they have the least dependence on kidney clearance and are not substantially eliminated by HD. A pharmacokinetic study found that a 10-mg dose of rivaroxaban in HD patients without residual kidney function results in drug exposure, similarly as published for 20 mg in healthy volunteers (17). Table 1 lists the various anticoagulants used for AF and their dosage adjustments in HD patients.

Apixaban is approved for use in patients with ESKD. Dosing recommendations for apixaban are derived from limited studies. In one study, patients with ESKD received a one-time dose of apixaban 5 mg, resulting in 36% higher area under the curve (AUC) and no increase in the maximum concentration (Cmax) of the drug compared with healthy subjects (18). In addition, levels taken after the HD session show a 13% and 14% reduction of Cmax and AUC for apixaban, respectively (18). However, in another pharmacological study of apixaban in patients on HD, they received 5 mg twice daily, which resulted in supra-therapeutic levels that should be avoided. Meanwhile, the reduced dose (2.5 mg twice a day) in

patients on HD was comparable with the standard dose (5 mg twice a day) in patients with normal kidney function (19). This suggests that apixaban 2.5 mg twice a day may be a viable dose alternative for patients on HD. The Valkyrie study (5) does suggest safety of using rivaroxaban in patients on HD with AF at a 10-mg dose, but more data are needed to confirm the use of this agent in patients on HD.

In summary, the data surrounding the use of oral anticoagulation in patients on HD with AF are challenging to interpret. This is because no randomized clinical trial has definitively shown that oral anticoagulants provide protection against stroke, whereas a substantial amount of evidence reveals a significantly increased bleeding risk. ■

Fatima Ali, PharmD candidate, is with St. John's University College of Pharmacy and Health Sciences, Jamaica, NY. Mital Jhaveri, PharmD, CACP, is a clinical anticoagulation pharmacist, and Sheila Sarnoski-Brocavich, MS, PharmD, BCGP, is director of pharmacy services with NYC Health+ Hospitals, Queens, Jamaica, NY.

The authors report no conflicts of interest.

References

1. De Vriese AS, et al. The atrial fibrillation conundrum in dialysis patients. *Am Heart J* 2016; 174:111–119. doi: 10.1016/j.ahj.2016.01.010
2. Zimmerman D, et al. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. *Nephrol Dial Transplant* 2012; 27:3816–3822. doi: 10.1093/ndt/gfs416
3. Findlay MD, et al. Risk factors of ischemic stroke and subsequent outcome in patients receiving hemodialysis. *Stroke* 2015; 46:2477–2481. doi: 10.1161/STROKEAHA.115.009095
4. De Vriese AS, Heine G. Anticoagulation management in haemodialysis patients with atrial fibrillation: Evidence and opinion. *Nephrol Dial Transplant* [published online ahead of print February 27, 2021]. doi: 10.1093/ndt/gfab060; https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfab060/6153972?login=false
5. De Vriese AS, et al. Safety and efficacy of vitamin K antagonists vs rivaroxaban in HD patients with atrial fibrillation: A multicenter randomized controlled trial. *J Am Soc Nephrol* 2021; 32:1474–1483. doi: 10.1681/ASN.2020111566
6. Wald R, et al. Benefits and risks of anticoagulation in dialysis patients with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2020; 75:286–288. doi: 10.1016/j.jacc.2019.11.033
7. Van Der Meersch H, et al. Vitamin K antagonists for stroke prevention in hemodialysis patients with atrial fibrillation: A systematic review and meta-analysis. *Am Heart J* 2017; 184:37–46. doi: 10.1016/j.ahj.2016.09.016
8. Randhawa MS, et al. Association between use of warfarin for atrial fibrillation and outcomes among patients with end-stage renal disease: A systematic review and meta-analysis. *JAMA Netw Open* 2020; 3:e202175. doi: 10.1001/jamanetworkopen.2020.2175
9. Mookadam M, et al. Novel anticoagulants in atrial fibrillation: A primer for the primary physician. *J Am Board Fam Med* 2015; 28:510–522. doi: 10.3122/jabfm.2015.04.140297
10. Vu A, et al. Critical analysis of apixaban dose adjustment criteria. *Clin Appl Thromb Hemost* 2021; 27:10760296211021158. doi: 10.1177/10760296211021158
11. Mavrakanas TA, et al. Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. *Clin J Am Soc Nephrol* 2020; 15:1146–1154. doi: 10.2215/CJN.11650919
12. Reed D, et al. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. *Res Pract Thromb Haemost* 2018; 2:291–298. doi: 10.1002/rth2.12083
13. Siontis KC, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation* 2018; 138:1519–1529. doi: 10.1161/CIRCULATIONAHA.118.035418
14. Chokesuwattanaskul R, et al. Safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease: Meta-analysis. *Pacing Clin Electrophysiol* 2018; 41:627–634. doi: 10.1111/pace.13331
15. Kuno T, et al. Oral anticoagulation for patients with atrial fibrillation on long-term hemodialysis. *J Am Coll Cardiol* 2020; 75:273–285. doi: 10.1016/j.jacc.2019.10.059
16. Chan KE, et al. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. *Circulation* 2015; 13:972–979. doi: 10.1161/CIRCULATIONAHA.114.014113
17. De Vriese AS, et al. Dose-finding study of rivaroxaban in hemodialysis patients. *Am J Kidney Dis* 2015; 66:91–98. doi: 10.1053/j.ajkd.2015.01.022
18. Wang X, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *J Clin Pharmacol* 2016; 56:628–636. doi: 10.1002/jcph.628
19. Mavrakanas TA, et al. Apixaban pharmacokinetics at steady state in hemodialysis patients. *J Am Soc Nephrol* 2017; 28:2241–2248. doi: 10.1681/ASN.2016090980
20. Bohula EA, et al. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. *Circulation* 2016; 134:24–36. doi: 10.1161/CIRCULATIONAHA.116.022361

Table 1. Comparison of various anticoagulants available for atrial fibrillation and their use in patients on hemodialysis

Drug	MOA	Half-life	Atrial fibrillation dosing	Dose adjustment in reduced kidney function	% Kidney clearance	Hemodialysis	Atrial fibrillation hemodialysis dosing	Reversal agent	Reference
Dabigatran	Direct thrombin inhibitor	12–17 hours	CrCl >30 mL/min; 150 mg twice daily	CrCl 15 to ≤30 mL/min; 75 mg twice daily CrCl < 15 mL/min; avoid use	80%–85%	Dialyzable; 50%–60% eliminated in 4-hour treatment	Contraindicated	Idarucizumab	(1, 4, 7)
Rivaroxaban	Factor Xa inhibitor	5–9 hours	CrCl >50 mL/min; 20 mg daily with evening meal	CrCl 15 to ≤50 mL/min; 15 mg daily with evening meal CrCl <15 mL/min; avoid use	33%	Not dialyzable; 92%–95% protein bound	10 mg Daily (very limited evidence)	Andexanet alfa 4-Factor prothrombin complex concentrate (off label)	(5, 7)
Apixaban	Factor Xa inhibitor	8–15 hours	5 mg Q12H	2.5 mg Q12H If two of three of the following: age ≥80 y/o, wt ≤60 kg, or SCr ≥1.5 mg/dL	27%	Minimally dialyzed (AUC 14% decrease post-HD)	2.5 mg Q12h (approved for use)	Andexanet alfa 4-Factor prothrombin complex concentrate (off label)	(2, 4, 19)
Edoxaban	Factor Xa inhibitor	10–14 hours	CrCl >50–95 mL/min; 60 mg once daily	CrCl >95 mL/min; avoid use CrCl 15–50 mL/min; 30 mg once daily CrCl <15 mL/min; avoid use	50%	Not dialyzable	Contraindicated	4-Factor prothrombin complex concentrate (off label)	(20)
Warfarin	Vitamin K antagonist	40 hours	Based on INR	Based on INR	Extensively metabolized by CYP2C9	Not dialyzable; 97%–99% protein bound	Dosing based on INR (commonly used)	4-Factor prothrombin complex concentrate phytonadione (vitamin K)	(1–3)

AUC, area under the curve; CrCl, creatinine clearance; CYP2C9, cytochrome P450 family 2 subfamily C member 9; HD, hemodialysis; INR, international normalized ratio; MOA, mechanism of action; Q12H, every 12 hours; SCr, serum creatinine; wt, weight; y/o, years old.