

REVIEW ARTICLE

Atrial fibrillation in patients with end-stage renal disease on hemodialysis: Magnitude of the problem and new approach to oral anticoagulation

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Abstract

Atrial fibrillation (AF) is a frequent comorbid condition in patients with end-stage renal disease on hemodialysis (HD) with a prevalence of up to 27%. The incidence rate of stroke in AF patients on HD is approximately 5%. The AF-associated risk of stroke is a major clinical challenge because current evidence for anticoagulation in HD patients with AF is based on observational data. Results from these observational studies is largely contradictory because they do not show a clear benefit of vitamin K antagonists over no treatment in terms of stroke prevention, and they show an increased risk of hemorrhage associated with anticoagulation treatment in HD patients. HD patients were not included in randomized trials of the direct oral anticoagulants (DOACs), and therefore there is no evidence to support efficacy and safety of DOACs compared to vitamin K antagonists in HD patients. The pharmacological characteristics of DOACs are of particular interest in the HD setting. The factor Xa inhibitors rivaroxaban, apixaban, and edoxaban are not predominantly eliminated via the kidneys. The thrombin inhibitor dabigatran is 80% eliminated via the kidneys but is dialyzable due to its low protein binding. In this narrative review, we examine the current state of evidence regarding the prevalence of AF in patients on HD, the associated risk of stroke, and the efficacy and safety of anticoagulation for stroke prevention in the HD setting. Further, based on the pharmacokinetic properties of DOACs, we discuss their potential use in patients on HD and ongoing randomized trials.

KEYWORDS

anticoagulation, atrial fibrillation, bleeding, chronic stroke, factor Xa inhibitors, kidney failure, renal dialysis

1 | INTRODUCTION

Atrial fibrillation (AF) is associated with increased risk of stroke and systemic thromboembolism.¹ Long-term oral anticoagulation is the treatment of choice for prevention of stroke and thromboembolism and superior to any other antithrombotic treatment.^{2,3} For many

decades vitamin K antagonists were the only orally available anticoagulation agents.⁴ The drug class of anticoagulants have been introduced in several indications for the treatment and/or prevention of thromboembolic disorders. These include prevention and treatment of deep vein thrombosis and pulmonary embolism, and also stroke prevention in AF.⁴ Patients with end-stage renal disease (ESRD)

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have increased risk of AF,⁵ but a definitive indication for anticoagulation treatment in ESRD patients with AF was never established,^{6,7} because the risk-benefit profile of anticoagulation in patients with ESRD is unclear.^{8,9} The population of patients with ESRD on hemodialysis (HD) treatment were not included in any trials on stroke prevention and treatment of venous thromboembolism and have therefore not profited from the introduction of direct oral anticoagulants (DOACs).¹⁰ These direct anticoagulation agents are small molecules and act via direct factor inhibition,^{11,12} and are therefore classified as DOACs. The members of the DOAC drug class differ with respect to their pharmacokinetic properties. Differences between DOACs include renal elimination, oral bioavailability, protein binding, and plasma half-life.

The aim of this narrative review is to examine and discuss current evidence on AF, stroke occurrence, and prevention in patients with ESRD on HD as well as the opportunities of DOAC use in this clinically challenging setting.

2 | LITERATURE SEARCH STRATEGY

Combinations of key words related to ESRD (eg, renal failure, dialysis, chronic kidney disease), atrial fibrillation (eg, arrhythmia, af, afib), and anticoagulation (eg, oral anticoagulation, DOAC, NOAC, antithrombotics) were used to search the MEDLINE database. The last search was performed in March 2019. The retrieved literature was carefully checked, focusing on primary data on epidemiology of AF in the HD population, risk of stroke associated with AF in patients with HD, and data on the efficacy and safety of anticoagulation in patients with HD with AF. The authors selected the most relevant articles to give a narrative review of the literature.

3 | ATRIAL FIBRILLATION IN PATIENTS ON HEMODIALYSIS AND RISK OF STROKE AND THROMBOEMBOLISM

The risk of cardiovascular diseases increases with decreasing kidney function, reaching its peak in patients with ESRD on HD.¹³ Among cardiovascular diseases in HD patients, the risk of ischemic stroke in particular is increased,¹⁴ and AF represents a well-known risk factor for ischemic stroke.¹ The incidence rate of stroke in AF patients on HD is reported to be between 4.8 and 5.6 per 100 person-years.^{15,16} The incidence of cardioembolic strokes in patients with AF in the non-ESRD population can be significantly reduced with anticoagulation treatment, as established and confirmed by randomized controlled trials comparing warfarin, a vitamin K antagonist, to antiplatelet agents such as aspirin or placebo.^{2,3,17,18} In these pivotal, practice-changing studies, patients with ESRD were not included. Therefore, no hard evidence for the use of anticoagulation agents exists in patients with ESRD on maintenance HD treatment. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guideline for the management of patients with AF

recommends the use of warfarin with target international normalized ratio (INR) of 2.0 to 3.0 for patients with nonvalvular AF with a CHA₂DS₂-VASc score of ≥ 2 ,⁶ while the 2016 European Society of Cardiology/European Society for Cardio-Thoracic Surgery guidelines for the management of AF refrain from giving a recommendation.⁷

4 | PREVALENCE OF ATRIAL FIBRILLATION IN PATIENTS ON HEMODIALYSIS

The epidemiologic evidence in fact indicates a high prevalence of AF in HD patients that has been underestimated for quite some time. In the multinational Dialysis Outcomes and Practice Patterns Study (DOPPS) of 17 513 randomly sampled HD patients, 2188 had a prevalent diagnosis of AF.¹⁹ The overall prevalence in DOPPS was 12.5%, but varied from 5.6% in Japan to 24.7% in Belgium. The large variability of AF prevalence across different countries observed in the DOPPS registry may be attributed to ethnic differences, but methodology of diagnosis confirmation may have also played a role.^{19,20} Among the highest prevalences of AF in observational studies are one prospective cohort study with 27% in a province of northern Italy²¹ and results from our own research project, a population-based cross-sectional cohort from Vienna, Austria, with a prevalence of 26.5%.²² The results of these 2 studies confirm that the prevalence of AF may be underestimated in large registries, which obtained the AF diagnosis from national or health care provider databases.^{21,22} The prevalence of AF in patients on HD also appears to be increasing over time. In the United States Renal Data System registry from 1989 to 2006, including 2 483 199 patients over a 15-year time period, the prevalence of AF increased more than 3-fold, from 3.5% to 10.7%.⁵ The high AF prevalence in patients with ESRD on HD should, however, also be regarded with respect to detection bias due to increased exposure of this patient population to health care.²³

5 | THE ASSOCIATION OF ATRIAL FIBRILLATION AND RISK OF STROKE IN PATIENTS ON HEMODIALYSIS

The risk of stroke in patients on HD is increased compared to the general population.^{14,24} The overall high frequencies of comorbidities such as hypertension, diabetes, and vascular disease may increase the risk of stroke significantly without AF being of significance. In fact, a retrospective study on hemodialysis patients from Austria showed that there was no significant difference in the incidence of strokes between patients with AF and those without the arrhythmia (1.0/100 patient-years in AF vs. 2.8/100 patient-years in non-AF; $P = 0.220$).²⁵ It is noteworthy that this was a retrospective cohort with 22% of patients on antithrombotic therapy, but the end point stroke included both ischemic and hemorrhagic strokes.²⁵ In patients with AF not receiving anticoagulation, another study indicated that the risk of stroke is not elevated compared to patients without AF on HD.²⁶ One prospective cohort

study also did not report significantly increased risk of stroke for AF patients.²⁷ Therefore, it may be necessary to take a closer look at the pattern of AF present in patients with HD, that is, first-diagnosis, paroxysmal, persistent, long-standing persistent, and permanent.⁷ A large epidemiologic study, powered to calculate the association of permanent AF on the risk of stroke, found a significantly increased risk of stroke compared to HD patients without permanent AF.²⁸ In the general population, patients with AF of different patterns are similarly treated regarding anticoagulation,⁷ but the same level of evidence does not exist for patients with ESRD on HD. Paroxysmal AF in patients with HD may therefore not have the same risk of stroke in HD patients as it has in the general population. Another discussion-worthy issue is whether patients with prevalent AF at beginning of HD treatment are at the same risk of stroke as patients who develop incidental AF after HD treatment commencement. A well-conducted analysis of the Taiwanese National Health Insurance Research Database showed that incidental AF did not significantly increase the risk of stroke compared to absence of AF in patients with HD.²⁹ Incidental AF may be an epiphenomenon that occurs during an HD session as a result of fluid and electrolyte shifts³⁰ and may not be associated with increased risk of stroke. Recent results indicate the opposite. In a large US registry of patients with ESRD, patients with incidental AF after initiating HD treatment had a 2-fold increased risk of ischemic stroke (hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.6-2.7) during the first 30 days after AF diagnosis.³¹ In the authors' opinion, the risk of stroke in patients with HD should ideally be assessed with a score that is specific to the HD population taking into account the pattern of AF, comorbidities, and prior history of stroke or thromboembolism. Such an HD-specific score is currently not available.

6 | STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION ON HEMODIALYSIS

There are currently no results from randomized trials on the efficacy and safety of anticoagulation for stroke prevention in patients with AF with ESRD on HD treatment.⁸ In the absence of hard evidence, large registries and observational studies were used to compare the efficacy and safety of anticoagulation agents. An overview of selected studies is provided in Table 1. The majority of studies were retrospective cohort studies comparing the occurrence of the clinical outcomes stroke, bleeding, or death in warfarin users to nonusers. Among these, Chan and colleagues¹⁵ were the first to publish findings on their investigation of the use of warfarin in incident HD patients with prevalent AF (N = 1671) in a large data set from an HD provider in North America. They found a significantly increased risk for stroke in warfarin users compared to nonusers (HR, 1.93; 95% CI, 1.29-2.90). This surprising finding was most notably contradicted by 3 retrospective cohort studies by Olesen et al,¹⁶ Carrero et al,³² and Shen et al,³³ who all showed

reduced risk of ischemic stroke in patients with AF on warfarin treatment and at the same time did not find increased risk of bleeding in warfarin users compared to nonusers.

The safety end point of bleeding occurrence is of special significance in the HD setting because bleeding complications are common in HD patients, and it is of little surprise, therefore, that findings by Shah et al³⁴ and Yoon et al³⁵ showed increased risk of bleeding in warfarin users compared to nonusers in the respective retrospective cohort studies.^{34,35}

Ultimately, patients with ESRD have multiple comorbid conditions and a reduced life expectancy.³⁶ With regard to the mortality outcome in warfarin users compared to nonusers, findings, where provided in observational studies, were not conclusive (Table 1).

The study design and data quality of these retrospective studies is very heterogeneous and therefore limitations have to be addressed. In the publication by Olesen and colleagues,¹⁶ the analysis of the data set from the Danish National Registry did distinguish patients with ESRD into ones receiving HD, peritoneal dialysis, and patients after kidney transplantation; thus, HD patients were not specifically addressed. In the comprehensive analysis of stroke outcomes in prevalent HD patients by Shen and colleagues, the finding of a reduced risk of ischemic stroke in warfarin users (HR, 0.68; 95% CI, 0.47-0.99) may be limited by the high warfarin discontinuation rate of 70% within the first year of treatment.³³

The only prospective observational cohort study investigating warfarin use and nonuse in patients with AF on HD, by Genovesi and colleagues,³⁷ reported occurrence of stroke, bleeding, and mortality in a cohort of 290 patients. In multivariable regression analysis, there was no conclusive result regarding the use of warfarin on occurrence of the composite end point of stroke and pulmonary embolism (HR, 0.12; 95% CI, 0.00-3.59; $P = 0.2$), partially due to low event rates. Patients on warfarin treatment, however, had increased risk of hemorrhage (HR, 3.96; 95% CI, 1.15-13.68; $P = 0.03$).³⁷

In light of these results from nonrandomized studies, the overall efficacy and safety of warfarin or other vitamin K antagonists for stroke prevention in AF in the HD setting is not confirmed.^{38,39} The emergence of DOACs as new treatment options for stroke prevention in AF raised hope that new evidence in the setting of patients with ESRD with AF would become available. The hope that the trials of DOACs for stroke prevention in AF would include patients with ESRD was not fulfilled. The DOACs proved to be noninferior to vitamin K antagonists for several indications including stroke prevention in AF, treatment of venous thromboembolism, and prevention of venous thromboembolism after orthopedic surgery.⁴⁰⁻⁴² In these trials, creatinine clearance was assessed during screening of potential trial patients and implemented as exclusion criteria according to different cutoffs (Table 2). Consequentially, DOACs were not approved for use in patients with ESRD on hemodialysis by the European Medicines Agency, but only to the criteria set forth in the exclusion criteria of the phase 3 trials. The US Food and Drug Administration (FDA), however, approved the use of apixaban for patients with estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m². This surprising expansion of the apixaban licensing gave Siontis et al⁴³ and Sarrat et al⁴⁴ the opportunity to retrospectively

TABLE 1 Overview of observational studies investigating the use of anticoagulation in patients with ESRD with AF

First author, journal, publication year	Cohort	Study design	Comparison	Efficacy	Safety	Death
Voskamp, NDT, 2018	1718 incident dialysis patients (not exclusively patients with AF)	Prospective cohort study	244 patients on vitamin K antagonists, 1474 patients without vitamin K antagonists	Not provided	Not provided	Increased risk of all-cause death in vitamin K antagonist users
Siontis, Circulation, 2018	25 523 patients with ESRD and AF on dialysis (HD and PD)	Retrospective cohort study	2351 patients on apixaban and 23 172 patients on warfarin	No significant difference	Reduced risk of major bleeding in apixaban users	Borderline reduced risk of death in apixaban users
Yoon, Stroke, 2017	9974 HD patients with AF	Retrospective, population-based cohort study	Warfarin users versus nonusers	No significant difference	Significantly increased risk of hemorrhagic stroke in warfarin users; bleeding risk overall not provided	Not provided
Genovesi, Journal of Nephrology, 2017	290 HD patients with AF	Prospective observational cohort study	Warfarin users versus nonusers	Intention-to-treat: no difference As-treated: nonsignificant decrease of thromboembolic events in warfarin users	Intention-to-treat: no difference As-treated: nonsignificant increase in bleeding in warfarin users	Intention-to-treat: no difference As-treated: significant reduction in the risk of total and cardiovascular mortality in warfarin users
Kai, Heart Rhythm, 2017	4286 patients with AF on HD	Retrospective, population-based cohort study	Warfarin vs. no warfarin	Reduced risk of ischemic stroke in warfarin users	No significant difference in risk of hemorrhagic stroke or gastrointestinal bleeding	Decreased risk of all-cause death in warfarin users
Sarrat, Annals of Pharmacotherapy, 2017	160 HD patients with AF or venous thromboembolism	Retrospective cohort study	120 warfarin patients and 40 apixaban patients	Not provided	No significant difference	Not provided
Chan, Circulation, 2015	8064 HD patients on warfarin, 281 HD patients on dabigatran, 244 patients on rivaroxaban	Population based retrospective cohort study	Rivaroxaban vs. warfarin and dabigatran vs. warfarin	Adjusted analysis not provided, unadjusted no significant difference	Dabigatran and rivaroxaban associated with an increased risk of major bleeding	Not provided
Shen, AJKD, 2015	12 284 prevalent HD patients with newly diagnosed AF	Retrospective cohort study	Warfarin vs. no warfarin	Reduced risk of ischemic stroke in warfarin users	No significant difference	No significant difference

(Continues)

TABLE 1 (Continued)

First author, journal, publication year	Cohort	Study design	Comparison	Efficacy	Safety	Death
Carrero, JAMA, 2014	478 patients with AF and acute myocardial infarction and eGFR < 15 mL/min/1.73 m ²	Prospective observational cohort study	Warfarin vs. no warfarin	Reduced risk of composite end point (death, stroke, myocardial infarction, and bleeding) in warfarin users	No significant difference	Nonsignificant reduction in death in warfarin users
Shah, Circulation, 2014	1626 dialysis patients with AF	Retrospective population-based cohort study	Warfarin vs. no warfarin	No significant difference	Increased risk of bleeding events in warfarin users	Not provided
Olesen, NEJM, 2012	901 patients with AF requiring renal-replacement therapy	Retrospective population-based cohort study	Warfarin versus no antithrombotic agent	Reduced risk of stroke or systemic embolism in warfarin users	No significant difference	Not provided
Chan, JASN, 2009	1671 incident hemodialysis patients with preexisting AF	Retrospective cohort study	Warfarin vs. no warfarin	Increased risk of stroke in warfarin users	Not provided	No significant difference

AF, atrial fibrillation; e GFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis; PD, peritoneal dialysis.

TABLE 2 Renal insufficiency criteria for DOAC dose reduction in phase 3 trials⁷⁵⁻⁷⁸ and in ESC recommendation⁷

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Trial dose reduction criteria	Dose reduction randomly assigned	If CrCl 30-49 mL/min	If 2 criteria applied: 1) age ≥ 80, 2) body weight ≤ 60 kg, or 3) serum creatinine level ≥ 1.5 mg/dL	If any 1 criterion applied: CrCl 30-50 mL/min, body weight ≤ 60 kg or use of verapamil/quinidine/dronedronarone
Trial exclusion criteria	CrCl < 30 mL/min	CrCl < 30 mL/min	Serum creatinine level > 2.5 mg/dL or CrCl < 25 mL/min	CrCl < 30 mL/min
Dose reduction criteria in ESC recommendation	CrCl < 50 mL/min	CrCl < 50 mL/min	Same as trial dose reduction criteria	CrCl ≤ 50 mL/min

CrCl, creatinine clearance according to the Cockcroft-Gault formula; DOAC, direct oral anticoagulant; ESC, European Society of Cardiology.

analyze the risk of stroke and bleeding in apixaban users compared to warfarin users on HD. In a data set of 25 523 patients with ESRD and AF on dialysis, of whom 2351 patients were taking apixaban and 23 172 patients were taking warfarin, Siontis and colleagues⁴³ found no significant difference in the risk of stroke between the 2 groups, a reduced risk of major bleeding and a reduced risk of death in apixaban users. Given that the patients were not randomized to either treatment greatly limits the power of interpretation due to selection bias.

Using a health care provider national registry of patients with ESRD, Chan and colleagues further provided outcome data on the

off-label use for rivaroxaban and dabigatran in HD patients in the United States.⁴⁵ The use of dabigatran and rivaroxaban in HD patients increased as soon as the drugs were licensed for use in the non-ESRD population. The authors found that dabigatran users (relative risk, 1.48; 95% CI, 1.21-1.81; *P* = 0.0001) and rivaroxaban users had an increased risk of hospitalization or death from bleeding compared to warfarin users but no significant difference in stroke or thromboembolism outcome due to low event rates.⁴⁵ The findings have to be regarded critically because they were obtained outside of the approved licensing for rivaroxaban and dabigatran and treatment

allocation was not controlled, so the analysis may be biased in multiple ways.

Regardless of the above discussion, DOACs may yet prove useful for stroke prevention in patients with ESRD to be viable candidates for use in ESRD patients. There are currently 3 ongoing randomized trials of stroke prevention in patients with AF on HD (Table 3): the AXADIA trial⁴⁶ comparing apixaban 2.5 mg twice daily to phenprocoumon (vitamin K antagonist target INR, 2-3), the AVKDIAL trial⁴⁷ comparing vitamin K antagonists (target INR, 2-3) to no treatment, and the RENAL-AF trial⁴⁸ comparing apixaban 5 mg twice daily to warfarin (target INR, 2-3).

Given the contradictory evidence from nonrandomized studies regarding efficacy and safety in warfarin users compared to non-users, the results of the AVKDIAL trial will be of great interest, especially as it is the only trial that appears to be powered for the net clinical benefit of anticoagulation treatment with a composite end point of thromboembolism and bleeding. Given the high bleeding complication rate in HD patients, it is of further note that apixaban was selected to be investigated in the AXADIA and RENAL-AF trials, which are addressing safety as their primary end point. In the non-ESRD population, apixaban had the best safety profile of the DOACs in stroke prevention in AF and has a lower percentage of renal elimination than dabigatran, rivaroxaban, and edoxaban (Table 4). Positive results of these trials, especially with regard to a net clinical benefit, may achieve a real practice change for stroke prevention among HD patients with AF. A closer look at the pharmacokinetic properties of anticoagulation agents in the HD setting is nevertheless warranted.

7 | COMPLICATIONS OF VITAMIN K ANTAGONIST USE IN HD PATIENTS

In patients with ESRD on HD treatment, management of vitamin K antagonist treatment is difficult because maintaining a stable INR is hindered by the downregulation of cytochrome P450 isoenzymes in chronic uremic conditions.⁴⁹ Further, HD patients generally have several comorbid conditions and comedications with potential for drug interactions. In fact, with declining kidney function, the dose of

vitamin K antagonists required to achieve and maintain therapeutic INR levels decreases.⁵⁰

A further effect of vitamin K antagonists in patients with ESRD to be considered is the progression of vascular calcification. Patients with ESRD suffer from calcium overload, which in turn leads to loss of vascular smooth muscle cells.⁵¹ The result is vascular calcification, particularly of the arterial tunica media and preexisting intimal atherosclerotic plaques.⁵¹ Both types of calcification are associated with increased mortality in patients with ESRD.⁵² The physiologic antagonist of the vascular calcification process is the matrix Gla protein (MGP), which requires vitamin K for its carboxylation.⁵³ Most HD patients are inherently vitamin K deficient,⁵³ but conditions that further decrease vitamin K, such as in vitamin K antagonist treatment, may accelerate the process.⁵⁴ Whether the progression of vascular calcification through vitamin K antagonist treatment outweighs the antithrombotic benefits remains to be seen. In the authors' opinion, the risk of progression of vascular calcification has to be weighed against the benefits of antithrombotic treatment as part of an HD-specific individualized treatment approach.

The most dreaded complication of vascular calcification is calciphylaxis. Although the pathomechanism of calciphylaxis is not entirely understood, vitamin K deficiency, vitamin K antagonist use, and uncarboxylated MGP are all associated with the disease.⁵⁵ Fortunately, calciphylaxis is rare, but affected patients have a 1-year survival rate of only 45%.⁵⁶ This is why the mortality end point should be addressed in studies of anticoagulation agents in HD patients.

8 | PHARMACOLOGY OF DOACS IN THE HD SETTING

Owing to the widespread success of DOACs in the prevention of stroke in patients with AF without ESRD, numerous investigations have dedicated significant efforts to explore the pharmacokinetics of the drug class with special regards to changes in renal function.

While vitamin K antagonists have a long half-life of 36 to 42 hours,¹¹ DOACs have a relatively short half-life of 5 to 14 hours in

TABLE 3 Overview of currently ongoing randomized trials investigating the use of anticoagulation for stroke prevention in HD patients with AF (taken from www.clinicaltrials.gov)

Trial name and sponsor	Planned N	Study design	Intervention arm	Comparator arm	Primary outcome measure	Status
AXADIA, Atrial Fibrillation Network, Germany	222	Randomized open label	Apixaban 2.5 mg bid	Phenprocoumon (vitamin K antagonist) adjusted to target INR 2-3	Incidence of major and clinically relevant, nonmajor bleeding	Recruiting
AVKDIAL, University Hospital, Strasbourg, France	855	Randomized open label	No oral anti-coagulation	Vitamin K antagonists adjusted to target INR 2-3	Cumulative incidence of severe bleedings and thrombosis	Recruiting
RENAL-AF, Duke University, United States	155	Randomized open label	Apixaban 5 mg bid	Warfarin adjusted to target INR of 2-3	Time to occurrence of major or clinically relevant nonmajor bleeding	Active, not recruiting

AF, atrial fibrillation; HD, hemodialysis; INR, international normalized ratio.

TABLE 4 Clinical pharmacology of oral anticoagulants^{11,57-60}

	Phenprocoumon ^a	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Vitamin K antagonist	Direct FIIa inhibitor	Direct FXa inhibitor	Direct FXa inhibitor	Direct FXa inhibitor
Prodrug	No	Yes	No	No	No
Standard dose for stroke prevention in AF (reduced dose)	INR guided	150 mg twice daily (110 mg twice daily)	20 mg once daily (15 mg once daily)	5 mg twice daily (2.5 mg twice daily)	60 mg once daily (30 mg once daily)
Time to maximum plasma concentration	~4 h	0.5-2 h	2-4 h	3-4 h	1-2 h
Oral bioavailability	~99%	~6.5%	80%-100%	~50%	~62%
Food interaction	Several dietary restrictions	No	Yes, uptake with food recommended	No	No
Renal elimination	<15% unchanged	85%	~33% unchanged	~27% unchanged	50%
Median plasma half-life in non-HD patients	36-42 h	12-14 h	5-9 h in young 11-13 h in elderly	~12 h	10-14 h
Known pharmacokinetic interactions	CYP2C9, 3A4	P-gp	CYP3A4, P-gp	CYP3A4, P-gp	P-gp
Protein binding	99%	35%	92%-95%	87%	55%

^aIn comparison warfarin has a time to maximal plasma concentration of 90 min and a plasma half-life of 36 to 42 h.

AF, atrial fibrillation; CYP, cytochrome P450; FIIa, factor IIa; FXa, factor Xa; HD, hemodialysis; INR, international normalized ratio; P-gp, P-glycoprotein.

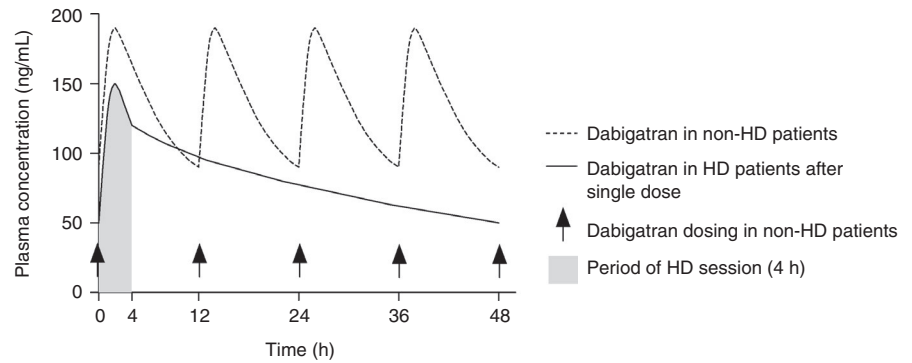
renally healthy individuals.¹¹ The half-life increases with decreasing kidney function due to the renal elimination of the DOACs but greatly differs between DOAC substances (Table 4). The direct thrombin inhibitor dabigatran is eliminated renally to up to 80%, while the factor Xa inhibitors are renally eliminated 25% to 50%.⁵⁷⁻⁶⁰ An immediate clinical consequence is the handling of perisurgical anticoagulation according to kidney function to reduce the risk of bleeding.^{61,62} Another particularly important aspect of DOAC pharmacokinetic characteristics in the HD setting is the protein-binding property. While rivaroxaban, apixaban, and edoxaban exhibit high protein binding, dabigatran is dialyzable due to its low protein-binding characteristic.^{63,64} The potential implications of the ability to dialyze dabigatran were explored for the emergency setting of dabigatran-associated bleeding or overdose.⁶⁵⁻⁶⁷ Dedicated pharmacokinetic studies further explored the characteristic of dabigatran elimination during HD sessions. When dabigatran was administered in the 110-mg dose at the beginning of the dialysis session, the maximum plasma concentration reached was significantly lower than in non-HD patients, but the area under the curve (AUC) of dabigatran elimination during a 48-hour interval was greater in the HD patients.⁶⁸ By administering dabigatran at the beginning of the HD session, very high plasma concentrations and the associated risk of bleeding can possibly be avoided,⁶⁹ while the patient maintains a low but steady dabigatran concentration during the 48 hours until the next HD session. The resultant plasma concentration curve was estimated based on the pharmacokinetic data and displayed in Figure 1. Further, the risk of long-term accumulation is lower than in post-HD administration.

The properties of the factor Xa inhibitors in the HD setting may be different. A phase 1 trial of rivaroxaban showed a significant 56%

increase in AUC but no significant difference between pre- and post-HD administration after single dose of 15 mg.⁷⁰ A 10-mg dose of rivaroxaban in HD patients without residual kidney function resulted in drug exposure similar to findings published for 20 mg in healthy volunteers.⁷¹ The authors conclude that rivaroxaban is not significantly eliminated by dialysis.⁷¹

In addition, the clearance of the factor Xa inhibitor edoxaban did not differ significantly between the on- and off-HD days in patients with ESRD.⁷² The reduced kidney function, however, does have an impact on the plasma concentration of factor Xa inhibitors. After 8 days of twice-daily administration of apixaban 2.5 mg, the AUC of apixaban concentrations over time increased 2- to 5.4-fold despite HD treatment.⁷³ Although the renal elimination fraction of apixaban is stated as approximately 25%,⁵⁹ there is a risk of accumulation over time in patients with ESRD.²³ Inconsistent with these findings, the drug administration of apixaban 5 mg in one pharmacokinetic study significantly increased AUCs compared to healthy controls when given at the end of an HD session, and 6.7% of the apixaban dose was recovered in the dialysate.⁷⁴ The FDA approval for apixaban 5 mg twice daily for stroke prevention in AF patients with ESRD is based on these findings. In the authors' opinion, the license of apixaban for patients with ESRD based on limited pharmacokinetic and not data on efficacy and safety was premature and has to be regarded critically. Patients with ESRD are a population of patients with limited evidence regarding treatment with anticoagulants, but it is our firm conviction that evidence should not be generated on an ipso facto basis of giving apixaban and observing the outcomes in nonrandomized studies. Therefore, if DOACs were to be considered for stroke prevention in AF for HD patients in

FIGURE 1 Hypothesized dosing regimen of dabigatran for stroke prevention in AF for patients on thrice-weekly HD treatment based on data from dedicated pharmacokinetic studies on the use of dabigatran in HD patients^{68,79}



future trials, the appropriate dosage of DOACs for stroke prevention in AF in the HD setting would have to be evaluated in dedicated dose-finding studies first. A dose adjustment of the factor Xa inhibitors may still be necessary to avoid accumulation and overdose. The thrombin inhibitor dabigatran, on the other hand, must

be administered in relation to the HD procedure. Giving dabigatran at the beginning of the HD session would have the advantage of creating lower spikes in the plasma concentration and less chance of overdose.⁶⁹ The elimination of dabigatran during the off-HD period is slow enough to maintain sufficient concentration. The efficacy

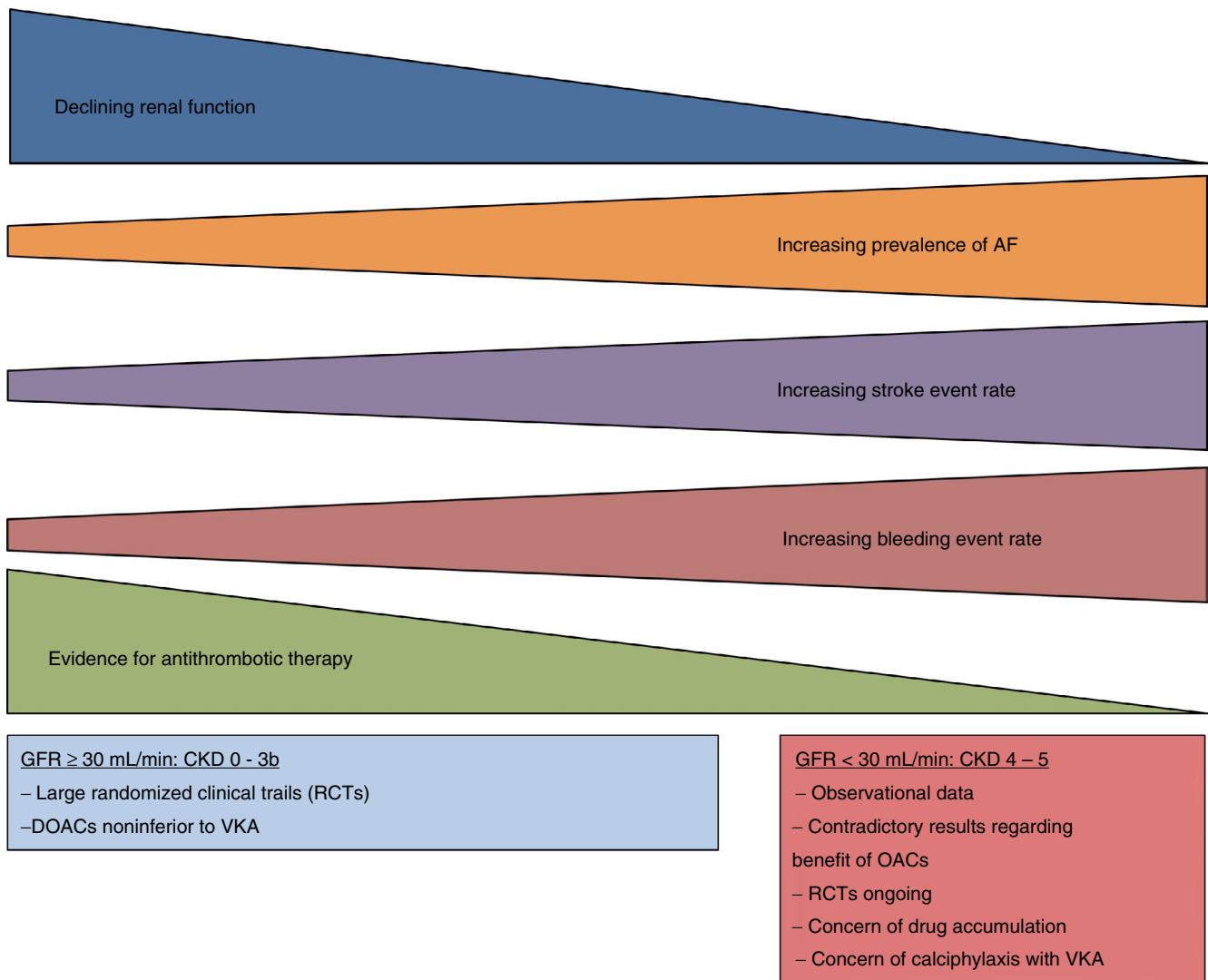


FIGURE 2 With declining renal function, the event rates of stroke and bleeding increase in patients with CKD. The evidence for antithrombotic therapy, however, decreases with the renal function. CKD, chronic kidney disease; DOACs, direct oral anticoagulants; GFR, glomerular filtration rate; VKA, vitamin K antagonist

and safety of these administration regimens would have to be evaluated in trials (Figure 2).

9 | CONCLUSION

Patients with ESRD on HD maintenance treatment are at increased risk of ischemic stroke and systemic thromboembolism. The high prevalence of AF among other cardiovascular risk factors may be a pivotal reason for the increased thromboembolic risk. While there is no hard evidence on the efficacy and safety of oral anticoagulation drugs in patients with AF on HD, observational evidence on the use of warfarin and other vitamin K antagonists indicates that we should be cautious because of the high risk of bleeding in HD patients and uncertain efficacy. The DOACs have not been tested in randomized trials including patients with ESRD on HD and are therefore not licensed for use in this setting outside of the United States. Specific pharmacokinetic properties of DOACs may make them viable candidates in patients with ESRD. Currently ongoing randomized trials in HD patients with AF may provide new evidence in this neglected population of patients.

RELATIONSHIP DISCLOSURE

The authors have no conflicts of interest or financial relationships to any commercial entities related to the subject of the paper to disclose.

AUTHOR CONTRIBUTIONS

OK and CA screened literature for relevant content, OK drafted the manuscript, and CA revised the manuscript and provided critical appraisal of intellectual content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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