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Review

Direct Oral Anticoagulants in Patients on Chronic Dialysis and Concomitant Atrial Fibrillation: A Common Clinical Impasse

Nikolaos Ktenopoulos[1], Marios Sagris[2,*], Panagiotis Theofilis[2], Sophia Lionaki[3], Loukianos S. Rallidis[4]

[1]Internal Medicine Department, Konstantopoulio General Hospital, 14233 Athens, Attica Province, Greece
[2]1st Cardiology Clinic, 'Hippokration' General Hospital, National and Kapodistrian University of Athens, School of Medicine, 11527 Athens, Attica Province, Greece
[3]Nephrology Department & Attikon University Hospital, National & Kapodistrian University of Athens, 12462 Athens, Attica Province, Greece
[4]Second Department of Cardiology, University General Hospital, "Attikon", Athens, National and Kapodistrian University of Athens, 11527 Athens, Attica Province, Greece
*Correspondence: masagris1919@gmail.com (Marios Sagris)
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Abstract

The most frequent arrhythmia treated is atrial fibrillation (AF), which necessitates the use of oral anticoagulants (OACs) to reduce the risk of thromboembolism and stroke. Patients with chronic kidney disease are more likely to develop AF, with a 10% frequency among those on chronic dialysis. Warfarin is the most widely prescribed OAC for individuals with end-stage kidney disease (ESKD). On the other hand, direct OACs (DOACs) are generally safer than warfarin, with fewer fatal bleeding events and a fixed dose that does not require close international normalized ratio (INR) monitoring. For those patients, warfarin and apixaban appear to be FDA-approved, whereas dabigatran, rivaroxaban, and edoxaban are not recommended yet. Due to a lack of large randomized studies, data from major trials cannot be extended to dialysis patients. In this review, we summarize the available data and literature referring to patients on chronic hemodialysis with concomitant AF. Due to the scarcity of data, we try to assist clinicians in selecting the appropriate therapy according to the specific characteristics of each patient. Finally, future directions are provided in two key areas of focus: left atrial appendage closure therapies and genetic research.

Keywords: atrial fibrillation; chronic kidney disease; hemodialysis; DOACs; optimal management; future directions

1. Introduction

Atrial fibrillation (AF) [1–4] is the most common condition of abnormal heart rhythm treated, affecting millions of people worldwide. Thus, as was published by Williams *et al.* in 2017 [5], it is the source of a substantial rising burden for patients, physicians, and, of course, each country's healthcare system. Oral anticoagulants (OACs) are prescribed for AF to reduce the thromboembolic and stroke risk, notwithstanding the fact that renal function is still a limiting factor. Chronic kidney disease (CKD) [6,7] is a condition where there is gradual impairment of the kidney function, described as glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for more than 3 months or with albuminuria ($\geq$30 mg/day or equivalent). It can gradually reach severe end-stage kidney disease (ESKD) requiring renal replacement therapies, such as hemodialysis and peritoneal dialysis, or kidney transplant.

AF has already been associated with CKD; therefore, these two conditions may present simultaneously in several patients. Certain theories have been proposed in order to explain why AF is more common in patients with CKD. Renal impairment is linked to various arrhythmogenic substrates [8], all of which can lead to the onset of AF. For instance, some patients with CKD present, more frequently than those without CKD, with conditions such as left ventricular hypertrophy and atrial enlargement, which occur in response to stressors, becoming maladaptive over time. Not unexpectedly, left ventricular hypertrophy is significantly linked to atrial enlargement which, along with diastolic dysfunction, predispose to AF. Furthermore, increased circulating levels of angiotensin II are linked to atrial myocyte apoptosis and interstitial fibrosis with parallel activation of the renin-angiotensin-aldosterone pathway, which is also related to progressive renal failure. Myocardial fibrosis is frequent in those patients, offering a structural foundation that promotes atrial re-entrant excitation. Likewise, studies in individuals without CKD have discovered a link between inflammation markers and AF load [9], as well as an inverse connection between inflammation levels and the persistence of sinus rhythm after cardioversion [4]. Inflammatory indicators are also enhanced in patients with CKD, and the frequency of AF in individuals with CKD is greater when C-reactive protein is persistently elevated. Finally, patients with CKD have a higher rate of left atrial enlargement and diastolic dysfunction, which is linked to AF [4,5].

AF and CKD are well-studied risk factors for thromboembolic events, such as stroke. The concurrent existence of both conditions in the same individual is associated with increased morbidity rates, with an escalation of mortality in 66% among patients with CKD. In particular, individuals with ESKD, with or without renal replacement therapy, have almost a 2-times greater risk of thromboembolic events compared to patients without renal disease [1,2]. As a result, the objective of this review is to examine the existing evidence on DOACs as anticoagulants in patients with AF and ESKD on hemodialysis, as well as their implementation in daily practice.

2. Epidemiology and Clinical Scores

AF is a common condition and it is estimated to reach a number of 12.1 million patients in the United States of America (USA) since 2030. More than 454,000 patients are hospitalized each year for AF, with comorbidities such as cognitive impairment and heart failure [10], while this arrhythmia contributes to 158,000 deaths in the USA alone [2,3]. In 2019, Di Carlo *et al.* [11] appraised that in the European Union, the prevalence of AF will increase from 7.8% to 9.5% in the general population over 65 years old by 2060, which means an 89% increase in AF cases. On the other hand, researchers have calculated that more than one in seven people in the USA are estimated to have CKD, which is approximately 37 million people. As many as nine out of ten patients with CKD and two out of five patients with severe CKD are unaware of their condition [6,7]. Cardiac injury and arrhythmias, including AF, are also not uncommon in the current pandemic of the novel coronavirus disease 2019 (COVID-19). Since the virus is highly contagious revealing a close association with AF onset, management of these patients is quite challenging [4].

Moreover, AF has a high incidence in patients on hemodialysis, with an estimation of 148 per 1000 person-years [6]. In 2010, Wizemann *et al.* [12] calculated the incidence of developing AF in hemodialysis patients at 1.0 per 100 patients per year, associated with older age, non-black race, and higher facility mean dialysate calcium. The incidence of those two conditions has been increasing because of the aging of the population as well as the risk factors that they share, like diabetes mellitus and hypertension.

As previously mentioned, patients with AF have a high risk of stroke and systemic thromboembolic events. Thus, it is recommended, for this group of patients, to be treated with OACs, according to the AHA/ACC/HRS [13] and the ESC Guidelines [14] for the Management of Patients with AF. Since 2012, the $CHADS_2$ score and later the CHA_2DS_2-VASc score have been implemented in the guidelines and suggest that patients with a CHA_2DS_2-VASc score $\geq$2 in men or $\geq$3 in women start OACs. However, in research published in 2021 by Jong *et al.* [15], it was found that ischemic stroke risk scores for initiating anticoagulant medication in individuals with either early stages of CKD, i.e., with estimated GFR(eGFR) between 30–60 mL/min/1.73 m^2 or advanced CKD, i.e., eGFR $<$30 mL/min/1.73 m^2, have poor predictive performance. For this patient population, only the modified CHADS2 score fared well. Furthermore, different scores have been suggested for bleeding risk assessment, but only one of them was recently recommended by the ESC and Canadian guidelines [14,16]. The widely used HAS-BLED score suggests that patients with scores greater than 3 have a major bleeding risk [17]. CKD is a risk factor for bleeding due to platelet dysfunction and CKD has been incorporated in estimating the HAS-BLED score [18]. Moreover, in patients with ESKD, who are maintained on chronic dialysis, the interaction between anticoagulative agents used during hemodialysis (usually heparin) with antiplatelet medications and/or OAC are poorly prescribed concerning the potential bleeding risk. The medications that are currently available are vitamin K antagonists (VKAs) and DOACs, which include dabigatran, apixaban, rivaroxaban, and edoxaban [4,14,16].

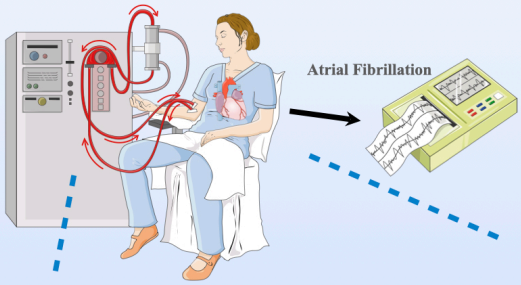
3. Vitamin K Antagonists as Anticoagulants in ESKD

VKAs are a group of medications that have traditionally been used as OACs, including coumarins (e.g., warfarin and acenocoumarol) and indandiones (e.g., fluindione and phenindione) [19]. Currently, warfarin and, secondly, acenocoumarol are the most widely used VKAs, while indandiones are scarcely prescribed. While the use of dicoumarin in hemodialysis patients with AF is debatable, Knoll *et al.* [20] stated in a 2012 study that coumarins may be less hazardous than previously believed in hemodialysis patients. However, Soriano *et al.* [21] revealed later in 2018, that oral anticoagulation with acenocoumarol did not improve survival and resulted in greater rates of admittions due to cardiovascular events and possibly increased bleeding risk. Furthermore, there is a paucity of randomized clinical trial evidence supporting the safety and efficacy of VKAs in AF patients with CKD, particularly ESKD. Warfarin, though, is the most studied VKA, and its conclusions may be generalized to other coumarin drugs [22].

Warfarin

Warfarin is the most commonly prescribed OAC among patients with ESKD, which is anticipated due to its pharmacokinetic and pharmacodynamic profile. Warfarin inhibits vitamin K epoxide reductase that reactivates vitamin K1 and is eliminated by hepatic metabolism with a minimal clearance (0.2 L/h/70 kg), almost negligible [23]. As such, warfarin might be a proper choice for patients with renal impairment. It is mostly bounded to proteins, appearing to be significantly efficient in hemodialysis since it cannot be filtered from the circulation.

On the other hand, it is hard to manage due to its narrow therapeutic range, unpredictable dose-response, and its



	DOACs [18]	Warfarin [18]
Pros	• Higher efficiency • Fewer fatal bleeding events • Fixed doses without close monitoring of the INR	• Secreted through the liver, proper for CKD • Highly bound to proteins, insusceptible to hemodialysis
Cons	• Only used in nonvalvular AF • Expensive	• Narrow therapeutic range • Unpredictable dose-response • Interaction with drugs/foods • Requires close monitoring (INR= 2- 3) • Calciphylaxis

Anticoagulation with ESKD on Dialysis					
	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
CHEST (2018)	Modified dose for INR 2-3	Not suggested	5 mg twice daily	Not suggested	Not suggested
KDIGO (2018)	Equipoise based on observational data and meta-analysis	Not suggested	2.5 mg twice daily - option consideration	Unknown	Not suggested
AHA/ACC/ HRS (2019)	Modified dose for INR 2-3	Not suggested	2.5 or 5 mg twice daily	Not suggested	Not suggested
ESC (2020)	Not documented	Not suggested	Not suggested	Not suggested	Not documented
CCS/CHRS (2020)	Lack of data - need for individualization	Not suggested	Lack of data - need for individualization	Not suggested	Not documented
EHRA (2021)	Lack of data - need for individualization	Lack of data - need for individualization	Lack of data - need for individualization	Lack of data - need for individualization	Lack of data - need for individualization

* ESKD: end-stage kidney disease

Fig. 1. Comparison between direct oral anticoagulants (DOACs) and Warfarin.

interaction with some foods (e.g., alcohol, leafy greens) and drugs (e.g., acetylsalicylic acid, ibuprofen, etc.), requiring close monitoring with international normalized ratio (INR) [target 2–3] to prevent major bleeding events [18] (Fig. 1 and Table 1 (Ref. [18,23])).

Finally, calciphylaxis is an uncommon but life-threatening condition, marked by vascular calcification of the medial layer of arterioles and small arteries, which reduce the blood flow, leading to luminal narrowing and occlusion. As a result, tissue ischemia and cutaneous necrosis occur [18]. Additionally, calcification in the coronary vascular bed may be associated with mortality in hemodialysis patients, as shown by Bellasi *et al.* in 2021 [24]. Attenuation of this deleterious process may be beneficial towards the survival of this patient population [24]. In a case of major bleeding, warfarin can be reversed using fresh frozen plasma, recombinant factor VIIa, or 4-factor prothrombin complex concentrate (4-factor PCC) administered with vitamin K (Tables 1 and 2 (Ref. [25–29])).

Several studies have investigated the association of warfarin with cardiovascular events protection in patients with AF and ESKD, but the results remain inconclusive [30,31]. In 2020, Randhawa *et al.* [32] published a systematic review and meta-analysis on the prevention of ischemic strokes using warfarin in patients with ESKD and AF. They showed that among 15 studies with 47,480 patients, warfarin administration appears to be related to no change in the incidence of ischemic stroke, while it appears to be linked to a greater risk of hemorrhagic stroke, without affecting the risk of bleeding or all-cause mortality. Alongside, in another meta-analysis, warfarin did not offer a decrease in deaths or thromboembolic events, while it increased the prevalence of bleeding events [33,34].

Dose-adjusted warfarin has been used, but observational data on safety and efficacy are conflicting. There were several cohort studies with opposing results, mainly showing no benefit for warfarin compared to no treatment for thromboembolic prevention in hemodialysis patients with AF, while it was associated with elevated bleeding risk [35]. So, as described in the literature and the latest guidelines (Fig. 1), in clinical practice warfarin in adjusted dose for target INR of 2–3 is a valid option for patients with AF and ESKD, requiring oral anticoagulation [36,37]. However, further research is forthcoming, ideally from large-scale randomized studies.

4. DOACs as a Treatment Option for Patients with AF on Hemodialysis

Direct OACs seem safer with higher efficiency than warfarin, causing fewer bleeding events [23]. Alongside, these medications have established set dosages and do not require close INR monitoring. The lack of efficient reversal agents was a disadvantage for their wide use until now. They recently received their own reversal agents avoiding events of severe bleeding, striking of vital organs, without the need to use other reversible conservative measures [23]. Although adverse bleeding events in DOACs treatment are very uncommon, they are only prescribed in non-valvular AF and their high cost, limit their use [23].

Table 1. Characteristics of oral anticoagulants.

Features	Dabigatran	Apixaban	Rivaroxaban	Edoxaban	Vitamin K antagonists (Coumarins-Warfarin) [23]
Mechanism of action [18]	Inhibition of IIa	Inhibition of Factor Xa	Inhibition of Factor Xa	Inhibition of Factor Xa	Inhibition of Vitamin K dependent clotting factors synthesis (II, VII, IX, X)
Duration to Peak Levels	1.5–3 h	1.5–3.5 h	2–4 h	1–2 h	1.5 h
Elimination Half-Time	12–17 h	12–15 h	5–13 h	10–14 h	36–42 h
Pro-drug	Yes	No	No	No	No
Normal Dosage [18]	150 mg twice/day	5 mg twice/day	20 mg once/day with the evening meal	60 mg once/day	INR adjusted once/day
Dosage for Renal Impairment [18]	• CrCl >30 mL/min: No dosage adj.	• Cr <1.5 mg/dL: No dosage adj. *unless* ≥80 years of age and body weight ≤60 kg, then 2.5 mg twice/day	• CrCl >50 mL/min: No dosage adj.	• CrCl >50 mL/min: No dosage adj.	INR adjusted once/day
		• Cr ≥1.5 mg/dL and *either* ≥80 years of age or body weight ≤60 kg: 2.5 mg twice/day	• CrCl 15 to 50 mL/min: 15 mg once daily with food	• CrCl 15 to 50 mL/min: Oral: 30 mg once daily	
	• CrCl ≤30 mL/min: Avoid use	• ESKD not on dialysis (CrCl <15 mL/min): 2.5 mg twice/day	• CrCl <15 mL/min: Avoid use	• CrCl <15 mL/min: Use not suggested	
		• Hemodialysis: No dosage adj. unless ≥80 years or body weight ≤60 kg, then 2.5 mg twice/day			
Non-Renal Clearance (e.g., hepatic with feces) [18]	20%	75%	65%	65%	Mainly through hepatic metabolism
Renal Clearance [18]	80%	25%	35%	35%	Negligibly excreted by the kidney
Plasma Protein binding	35%	87%	95%	55%	97%
Need for INR Monitoring	No	No	No	No	Yes
Food and Drugs Interactions	Dronedarone, Ketoconazole, Rifampin, Antacids, St. John's wort, Mifepristone, Cyclosporine, Cobicistat	Carbamazepine, Defibrotide, Dexamethasone, Fosphenytoin, Phenytoin, Rifampin	Clarithromycin, Cobicistat, Conivaptanf, Idelalisib, Indinavir	mifepristone	Foods rich in vitamin K1 (eg. grapefruit juice, mango, leafy green vegetables, fish oil)
					Various medications (eg. omeprazole)

INR, international normalized ratio; CrCl, creatinine clearance; adj., adjustment; ESRD, end-stage renal disease.

Table 2. List of all OACs' reversal agents.

OACs	Reversal agent	Dosage for IV administration	Dose adjustment for ESRD	Onset of action of Rev.Ag.
Dabigatran [25,26]	Idarucizumab (Praxbind)	5 g	Unknown	Less than 5 min
Apixaban Rivaroxaban Edoxaban [27–29]	Andexanet alfa (Andexxa)	• Rivaroxaban >10 mg, apixaban >5 mg, or dose unknown within 8 hours: 800 mg bolus at 30 mg/min and then 960 mg infusion at 8 mg/min for up to 120 min	Unknown	2–5 min
		• Rivaroxaban ≤10 mg or apixaban ≤5 mg, or ≥8 hours since latest dose: 400 mg bolus at 30 mg/min and then 480 mg infusion at 4 mg/min for up to 120 min		
	4- factor PCC (Kcentra, Beriplex P/N, Octaplex).	Fixed dose of 2000 units OR 25–50 units/kg	Unknown	Unknown
Warfarin [29]	Vitamin K	10 mg in slow infusion (e.g., 20–60 min)	Unknown	2 h

IV, intravenous; OACs, oral anticoagulants; ESRD, end-stage renal disease; PCC, prothrombin complex concentrate.

Direct OACs are not deeply studied agents in patients with AF and ESKD. Specifically, all major phase III trials that introduced DOACs as a standard treatment excluded patients with impaired renal function and creatinine clearance (CrCl) <25 mL/min [38–41]. Furthermore, there have been no adequate prospective studies to show the safety and efficacy of those agents in ESKD patients. Of all four DOACs, only apixaban and rivaroxaban have received FDA approval for patients on hemodialysis based on pharmacodynamic studies [42,43]. Table 3 (Ref. [39–41,44–47]) and Table 4 (Ref. [39–41,44–47]) summarize all the large-scale trials mentioned below.

4.1 Dabigatran

Dabigatran is a novel oral anticoagulant that directly inhibits thrombin with a half-life of 9 hours, which increases to 25–30 hours in patients with a CrCl of 30 mL/min or less. Its first approval was granted by the Food and Drugs Administration (FDA) in 2010, after evaluating the data extracted by the Randomized Evaluation of Long-Term Anticoagulant Therapy Trial (RE-LY Trial) [38], which showed equal or greater protection for dabigatran compared with warfarin in thromboembolic events (e.g., stroke), while maintaining the same or fewer bleeding events, and was first recorded for ESKD patients, 45 days after its initial approval. However, it is important to state that patients with CrCl <30 mL/min were excluded from this study. Its use for ESKD patients is not approved by the FDA, although it is prescribed off-label to some individuals with the above-mentioned profile. Its limited use can be attributed firstly to the high levels of drug accumulation in the kidneys (80%) and secondly to the lack of protein binding among the other DOACs (less than 20%) (Table 1). Furthermore, the last parameter poses one more concern. Due to its low percentage of protein binding, it can be affected by hemodialysis, leading to its removal from the circulation after the session, which can either increase the thromboembolic risk or vice versa bleeding risk if a session is missed [48].

In a study, Chan *et al.* [49] showed that dabigatran was more hazardous than warfarin, with more bleeding events. This study is one of the very few to include patients in chronic dialysis. They showed no statistically notable difference in thromboembolic events in the dabigatran group compared to warfarin, with the limitation of short follow-up times. Regarding the bleeding events, chronic dialysis patients receiving dabigatran had an elevated risk for major bleeding and no notable difference in minor bleeding compared to chronic dialysis patients receiving warfarin, resulting in subsequent higher mortality rates and hospitalizations. As a result, and according to the latest guidelines for the management of AF [7,13,14,16,50,51], dabigatran is not recommended in ESKD patients with AF. However, due to the lack of sufficient data, the clinician can tailor his decision, taking into consideration the existing data and the patient's profile [52].

4.2 Rivaroxaban

Rivaroxaban is another drug of the DOACs group, which directly inhibits the Xa factor. It was approved by the FDA in 2011, using data from the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF - Trial) [39]. In the same way with the RE-LY Trial, patients with CrCl <30 mL/min were also excluded from this study. This agent is primarily eliminated by the liver (66%) and 35% by the kidney. At the same time, it provides a half-life of approximately 8 hours, which increases minimally to 9.5 hours in individuals with severe kidney disease (CrCl <30 mL/min). Unlike dabigatran, rivaroxaban is approximately 95% bound to proteins, making it unable to be removed by dialysis. Rivaroxaban does not accumulate after many daily doses [53], and it is recommended that a 15- mg dosage should be used in this patient group, since comparable changes on pharmacokinetic and pharmacodynamic parameters were observed in individuals with moderate-to-severe renal im-

Table 3. List of large-scale trials with direct oral anticoagulants.

Study	Author/Year	N of patients	Medications	Main outcomes
The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) [44]	L Wallentin, 2010	18,113	Dabigatran vs Warfarin	Dabigatran had similar rates of stroke and embolism with warfarin and lower bleeding rates at 110 mg twice daily, while at 150 mg twice daily lower rates of stroke and systemic embolism and similar bleeding
The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF - Trial) [39]	Patel MR, 2011	14,264	Rivaroxaban vs Warfarin	Rivaroxaban was shown to be noninferior to warfarin in preventing stroke or systemic embolism. Although there was no significant difference in the risk of severe bleeding across groups, intracranial and fatal hemorrhage occurred less frequently in the rivaroxaban group.
The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial (the ARISTOTLE Trial) [40]	C B Granger, 2011	18,201	Apixaban vs Warfarin	Apixaban outperformed warfarin in terms of stroke and systemic embolism prevention, produced less bleeding, and resulted in decreased mortality
Edoxaban versus warfarin in patients with atrial fibrillation [41]	Giugliano RP, 2013	21,105	Edoxaban vs warfarin	Once-daily edoxaban was found to be noninferior to warfarin in terms of stroke and systemic embolism prevention, as well as significantly lower rates of bleeding and mortality from cardiovascular events
Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States [45]	K C Siontis, 2018	25,523	Apixaban vs Warfarin	Apixaban treatment may be related with a lower risk of bleeding in patients with ESKD on dialysis and AF compared to warfarin, with a conventional 5 mg twice daily dosage being associated with decreases in thromboembolic and mortality risk
Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation [46]	T A Mavrakanas, 2020	2082	Apixaban vs No Anticoagulation	Apixaban wasn't related with a decreased incidence of new stroke, TIA, or systemic thromboembolism in patients with CKD and nonvalvular AF, but it was associated with a greater rate of fatal or intracranial hemorrhage
Effectiveness and safety of rivaroxaban versus warfarin in Taiwanese patients with end-stage renal disease and nonvalvular atrial fibrillation [47]	Y C Lin, 2021	3358	Rivaroxaban vs Warfarin	Rivaroxaban may be linked with a comparable risk of bleeding but a decreased risk of thromboembolism in patients with ESRD and nonvalvular AF compared to warfarin. Further research is needed to determine the possible benefit of 10 mg of Riv/ban in this population.

AF, atrial fibrillation; TIA, transient ischemic attack; CrCl, creatinine clearance; ESRD, end-stage renal disease; CKD, chronic kidney disease.

pairment (CrCl: 15–50 mL/min) and in those on chronic hemodialysis [54]. Currently, it is not recommended for people with ESKD or on chronic dialysis, without randomized controlled trials to provide high-level evidence and specific recommendations. Yet, dabigatran and rivaroxaban are associated with a higher risk of hospitalization or death from bleeding than that of warfarin in this group [49].

However, similar to dabigatran, Chan *et al.* [49] showed in 2015 no significant difference in thromboembolic events and elevated incidence of bleeding events when comparing rivaroxaban with warfarin. Rivaroxaban may have a comparable risk of bleeding but a lower risk of thrombosis in Taiwanese patients with ESKD and AF when compared to warfarin [47]. Lin *et al.* [47] reported that administration of 10 mg of rivaroxaban might be beneficial in this group, while De Vriese *et al.* [53] proposed that even a lower dose of rivaroxaban could decrease the occurrence of cardiovascular and major bleeding events. As trials results are controversial, and according to the latest guidelines for the management of AF [7,13,14,16,50,51], rivaroxaban is not recommended in ESKD patients with AF. Nevertheless, in the light of lack of adequate data, each clinical practitioner may personalize this choice, taking into account all available recommendations.

4.3 Apixaban

Apixaban, along with rivaroxaban, inhibits the Xa factor and was introduced to the market in 2012, after the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial (the ARISTOTLE Trial) [40], which showed clear superiority over warfarin for thromboembolic events while having fewer bleeding events. As in the previous studies of the other DOACs, patients with significant impairment of renal function were not included in that study.

Table 4. List of large-scale trials focusing on the bleeding events.

Study	Medications	Specifics on CKD	Bleeding events
The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) [44]	Dabigatran vs Warfarin	Patients with CrCl <30 mL/min were excluded	Major bleeding: decrease in hemoglobin level of at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a crucial location or organ. Life-threatening bleeding: fatal bleeding, symptomatic cerebral bleeding, hemorrhage with a fall in hemoglobin level of at least 5 g/dL, bleeding needing transfusion of at least 4 units of blood or inotropic drugs, or bleeding demanding surgery. All other bruising was regarded as minor
The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF - Trial) [39]	Rivaroxaban vs Warfarin	Patients with CrCl <30 mL/min were excluded	Major bleeding: major, postoperative bleeding occurring after the first postoperative study dose; fatal bleeding; bleeding into a critical organ (retroperitoneal, intracranial, intraocular, intraspinal); overt bleeding necessitating treatment cessation; bleeding necessitating reoperation; clinically overt bleeding associated with a hemoglobin drop of 2 g/dL or more or necessitating a transfusion of 2 or more units of blood
The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial (the ARISTOTLE Trial) [40]	Apixaban vs Warfarin	Patients with CrCl <25 mL/min were excluded	Parameters for major bleeding in non-surgical patients: Fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dL) or more, or leading to transfusion of 2 or more units of whole blood or red cells
Edoxaban versus warfarin in patients with atrial fibrillation [41]	Edoxaban vs warfarin	Patients with CrCl <30 mL/min were excluded	Parameters for major bleeding in non-surgical patients: Fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dL) or more, or leading to transfusion of 2 or more units of whole blood or red cells
Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States [45]	Apixaban vs Warfarin	Included patients with ESKD	Bleeding was considered major when it was linked to a critical site code (such as intracranial), the necessity for blood product transfusion based on a procedure code during the same admission, or death
Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation [46]	Apixaban vs No Anticoagulation	Included patients with ESKD	Clinically important bleeding was considered any bleeding resulting in death; any bleeding at a critical site (intracranial, intraocular, retroperitoneal, intra-articular, pericardial, airway); or any gastrointestinal, urinary tract, or gynecologic bleeding necessitating hospitalization
Effectiveness and safety of rivaroxaban versus warfarin in Taiwanese patients with end-stage renal disease and nonvalvular atrial fibrillation [47]	Rivaroxaban vs Warfarin	Included patients with ESKD	Parameters for major bleeding in non-surgical patients: Fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dL) or more, or leading to transfusion of 2 or more units of whole blood or red cells

CrCl, creatinine clearance; ESKD, end-stage kidney disease; CKD, chronic kidney disease.

It is one of the most commonly used DOACs in CKD and ESKD since it is only 25% excreted by the kidney and it is not affected by dialysis, as was published by Wang *et al.* [55] in 2016. Specifically, only 6.7% of the drug may be removed after 4 hours of dialysis [55]. The FDA has approved the use of apixaban for patients with ESKD [56,57] on dialysis at 5 mg twice daily, reduced to 2.5 mg twice daily for patients 80 years old or with a bodyweight <60 kg [40]. Although this was written in 2014, resulting in further use of apixaban in ESKD patients, it was already used before the FDA approval, off-label in high percentages. There is no confirmed data on single- and multiple-dose apixaban in patients with AF and ESKD on dialysis, who have maintained their diuresis. In patients on chronic dialysis, apixaban exposure is affected not only by the medication dose but also by the timing of intake in relation to the hemodialysis

process. Van den Bosch *et al.* [58] suggested that the exposure and the concentration of apixaban were lower when the drug was administered 30 minutes before the hemodialysis session, which makes dialysis computable enough for the drug exposure.

In 2018, Siontis *et al.* [45] compared apixaban (5 mg vs 2.5 mg twice daily) and warfarin in patients with ESKD and AF. People taking standard-dose apixaban (5 mg) had a lower thromboembolic risk than those taking low-dose apixaban (2.5 mg) or warfarin illustrating a lower risk of death and major bleeding. Additionally, in 2020, Mavrakanas *et al.* [46] showed that when ESKD on chronic dialysis patients received 5 mg of apixaban twice daily for 8 days, it resulted in a similar drug concentration to healthy controls, with the observation of potentially higher, probably harmful levels of the drug in this group. Apixaban was related to a greater risk of fatal or cerebral hemorrhage rather than a reduced incidence of a new stroke, transient ischemic attack, or systemic thromboembolism. Nevertheless, this study had some limitations since it did not assess long-term clinical outcomes like bleeding. Although apixaban seems to have become a clear alternative to warfarin for ESKD on chronic dialysis and AF patients [59], further studies with high-quality data are needed to establish a high level of evidence.

4.4 Edoxaban

Edoxaban is the last Xa factor inhibitor with a 35% renal excretion, approved by the FDA in 2015 using data from the ENGAGE AF-TIMI 48 randomized trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) [41]. It was shown that edoxaban was not inferior to warfarin in terms of the occurrence of thromboembolic events, while it showed significant superiority in the avoidance of bleeding events. Currently, it is not approved for use in patients with ESKD or those with CrCl $<$30 mL/min or on chronic hemodialysis [7,13,14,16,50,51,60].

5. Guidelines and Practical Recommendations for the Anticoagulation in Concomitant AF and ESKD

Owing to the lack of randomized clinical data on OACs in ESKD patients, guidelines of major societies do not provide recommendations with a strong level of evidence for their use in this group of patients. The American College of Cardiology, the American Heart Association Task Force, and the Heart Rhythm Society (AHA/ACC/HRS) [13] and The American College of Chest Physicians (CHEST) [51] guidelines do not recommend dabigatran, rivaroxaban, and edoxaban in dialysis patients. The Kidney Disease Improving Global Outcomes (KDIGO) [7] guidelines do not discuss warfarin or apixaban for patients in chronic dialysis, and they do not recommend the other three OACs in those patients. According to the latest European Society of Cardiology (ESC) guidelines [14], there are no specific recommendations regarding anticoagulation in hemodialysis patients with AF. They support the notion that for patients with CrCl $<$29 mL/min, there is no sufficient data for treatment with OAC, warfarin, or DOACs since these patients were excluded from the major randomized clinical trials. Especially for patients with CrCl $<$15 mL/min or on hemodialysis, DOACs have not been approved in Europe. The unique RENAL-AF trial [61], which investigated apixaban versus warfarin in AF patients with ESKD on chronic dialysis, was never completed and its data were not specific on relative stroke and bleeding rates. In addition, the 2019 AHA/ACC/HRS Guidelines [13] for the Management of Patients With AF softly suggest patients with ESKD on hemodialysis using warfarin (dose adjustment for target INR: 2–3) or apixaban (without need for INR monitoring). However, they mention that further studies are needed to provide a high level of evidence. They provided a Class IIa indication to prescribe warfarin for patients with ESKD and AF and a CHA2DS2-VASc score of 2 or greater.

In studies comparing all the medications, it was shown that treatment with OAC was not linked to a higher risk of hospitalization for stroke or death, but it was linked to a higher risk of bleeding and cerebral hemorrhage [62,63]. Specifically, Kuno *et al.* [64] supported that when compared to apixaban and no anticoagulant, medication with warfarin, dabigatran, or rivaroxaban were linked to a considerably greater risk of bleeding. In Fig. 1, we present a comparison between DOACs and warfarin, while in Table 1 we summarize the characteristics of all available OACs.

Unfortunately, data from the large trials cannot be extrapolated to dialysis patients since there is no data from randomized studies in that population. Current data comes only from observational studies or registries. Specific corporations suggest its use but with no proper level of documentation in accordance with those trials. Despite the promising acceptable results, the data must be interpreted cautiously, given the risk of a potential confounding factor influencing their reliability. So, it is understood that patients on dialysis with AF should be informed of the lack of data, with uncertain benefit, and be aware of the potential risk of bleeding events. At the same time, further research is forthcoming, ideally from large-scale randomized studies.

6. Future Directions

AF is a common healthcare burdening condition requiring close monitoring and an established preventive approach [5]. Data is still hazy concerning the most appropriate anticoagulant strategy in CKD patients, especially in ESKD patients on chronic dialysis or not. Existing evidence appears to be promising for the future, with strategies focusing on two primary areas: left atrial appendage closure interventions and genomics. There are ongoing research efforts to develop modalities for individualizing therapeu-

tic management, as well as novel screening techniques for identifying high-risk patients [33].

6.1 Left Atrial Appendage Closure

Impaired kidney function has been associated with an increased risk of clot formation in the left atrial appendage in patients with concomitant AF [65]. So in cases with contraindication to OACs, left atrial appendage closure (LAAC) could be considered, because, as Zhang *et al.* [66] showed in their meta-analysis, it is safe and efficient in that population. As a result, percutaneous LAAC appears to be a promising treatment option for CKD patients with AF. In this regard, it appears that these patients had reduced risk of cerebrovascular events and bleeding events following LAAC interventions with appropriate devices (e.g., the WATCHMAN device) [67]. The observed stroke rate in a 189- patient trial was more than two- thirds lower than expected, and the bleeding risk was more than half lower [65]. Female patients, as well as those with severe renal impairment, i.e., CKD stages IV and V, exhibited a greater rate of device-related thrombi accumulation [65]. Furthermore, the ongoing German multi-center Left-Atrium-Appendage-Occluder Register-GErmany research (LAARGE, ClinicalTrials.gov Identifier: NCT02230748) [68] in 2021 added to the current evidence, by evaluating 299 patients who underwent LAAC interventions. In their publication Fastner *et al.* [68] suggested that despite CKD patients presenting a burdened cardiovascular risk profile, device implantation was safe with few complications, and LAAC was related to excellent stroke prevention across all CKD stages. It is worth noting that the first trial was not randomized, making it susceptible to associated bias, whereas the second was an observational study that collected data from a registry, with all of the limitations that entails.

6.2 Genomics

New evidence from patients with AF and CKD is establishing the molecular architecture of both conditions and their close pathophysiological connection. As a result, we would be able to comprehend the complex aspects of AF and CKD and bring them closer to clinical practice. Genetic research and the field of genomics appear to be quite promising and are garnering a lot of scientific attention [69]. There is insufficient data from trials to identify specific genes related to CKD, particularly ESKD, and AF. Saracyne *et al.* [70], in 2018, revealed a significant and independent association of AF occurrence in a Polish cohort of patients with ESKD on hemodialysis. They presented concurrent AF and a common genetic risk score that included 13 previously described single-nucleotide polymorphisms. The limitation of this study is the small number of patients leading to the need for more research on larger patient groups to validate the results. The gene analysis will bring us closer to precisive and individualized medicine under the precondition of becoming cost-effective in clinical practice [71,72]. A future target would be the assessment of telomeres length. As previously indicated, shorter leukocyte telomere length was independently associated with increased AF and CKD development in a community-based population [27].

7. Conclusions

In conclusion, clinical trial results and recommendations should not be easily and safely integrated into clinical practice for individuals with ESKD and AF. Due to the increased risk of thrombosis and bleeding, the use of OACs in CKD patients remains challenging. Thus, more randomized controlled studies are required to get a high level of evidence for OAC therapy in chronic dialysis patients with AF. According to the most recent recommendations, warfarin and apixaban appear to be FDA-approved for such individuals, while dabigatran, rivaroxaban, and edoxaban are not [7,13,14,16,50,51]. Although it is apparent that clinicians are currently prescribing these medicines either off-label, the recent FDA approval of DOAC antidotes [25,26,28,29,73] (and exanet alfa for apixaban, edoxaban, and rivaroxaban, and idarucizumab for dabigatran) may enhance their usage (Table 2). Clinicians demand more precise data to provide their patients with the best and most preferred treatment strategy. As a result, additional research will be conducted, ideally through large-scale randomized trials. Until then, each clinical practitioner can tailor his judgment according to the patient's profile, keeping in mind the increased risk of thrombosis and bleeding.

Author Contributions

All authors (NK, MS, PT, SL, LR) contributed to the conception of the review. NK and MS reviewed the literature and wrote and prepared the original draft. All authors (NK, MS, PT, SL, LR) contributed to revising it critically for intellectual content. All authors (NK, MS, PT, SL, LR) read and gave final approval of the version published.

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Conflict of Interest

The authors declare no conflict of interest.

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