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Review

How to Safely Anticoagulate Patients With Renal Impairment

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Abstract

Chronic kidney disease (CKD), a highly prevalent condition worldwide, is associated with increased thrombotic and bleeding risks. Thrombotic risks include heightened cardiovascular risk and that of venous thromboembolism, driven by endothelial dysfunction, and inflammation. Conversely, platelet dysfunction and vascular abnormalities elevate the bleeding risk. This complex interplay of bleeding and thrombosis highlights the challenges faced in anticoagulant prescribing in CKD. Although warfarin and low-molecular-weight heparin are currently recommended in the guidelines, direct oral anticoagulants (DOACs) may offer a favourable profile in mild-to-moderate CKD based on the decreased incidence of thrombotic events and lower bleeding risk reported in studies. There remains a paucity of studies on DOAC use in severe CKD and end-stage renal disease (ESRD). In this article we discuss different options of anticoagulant use in the setting of CKD for venous thromboembolism (VTE) treatment and prophylaxis in atrial fibrillation (AF), highlighting the need for further clinical trials in this patient population.

Keywords: CKD; ESRD; anticoagulation; haemorrhage; anti-Xa

1. Introduction

Chronic kidney disease (CKD) affects around 850 million people worldwide, with rising rates attributed to an aging population alongside increasing cardiovascular risk factors, particularly hypertension and diabetes mellitus [1,2]. The Kidney Disease: Improving Global Outcomes (KDIGO) defines CKD as abnormalities of kidney structure or function, present for a minimum of 3 months with implications for health [3]. Management is complex and focuses on controlling modifiable risk and managing complications such as anaemia and electrolyte abnormalities [3,4]. Severity of CKD is graded by the KDIGO system, based on the estimated glomerular filtration rate (eGFR) and the presence or absence of albuminuria. End-stage renal disease (ESRD) describes patients with an eGFR of <15 mL/min/1.73 m^2 or those requiring renal replacement therapy [3]. It is important to note that most direct oral anticoagulant (DOAC) studies use creatinine clearance (CrCl) rather than eGFR to stratify patients [3,5]. CKD is often multifactorial, and patients typically have comorbidities that may contribute to both bleeding and thrombosis risk in this population. In this article, we will review the pathophysiology of both bleeding and thrombosis in CKD and discuss how these risks impact anticoagulant prescribing in CKD.

2. Thrombotic Risk in CKD

Around 50% of deaths in CKD are attributable to cardiovascular disease (CVD), particularly stroke or myocardial infarction [6,7]. Falling glomerular filtration rate (GFR) is associated with greater CVD risk, with the highest incidence seen in patients requiring dialysis [7]. Dialysis patients also have 2–3 times the risk of venous thromboembolism (VTE) of the general population [8], with an incidence of VTE of nearly 4% reported [9].

Chronic inflammation and endothelial dysfunction occurring in advanced CKD and ESRD result in increased circulating levels of pro-coagulants, such as Factor VIII and Von Willebrand factor (VWF). Inflammatory markers and pro-inflammatory molecules, including C-Reactive Protein and interleukin-6, are also increased, contributing to the elevated thrombotic potential [10,11]. Conversely, natural anticoagulants such as Antithrombin III (AT-III) are depleted in CKD, particularly in those with evidence of the nephrotic syndrome [12]. Tissue factor, an initiator of the extrinsic coagulation pathway, has been found to be closely linked to uraemic toxins expressed in CKD patients [13]. Additionally, increased levels of plasminogen activator inhibitor 1 promote hypofibrinolysis by blocking tissue plasminogen activator, required for the conversion of plasminogen into plasmin [10,11]. Collectively, these processes promote thrombosis, as summarized in Fig. 1.

3. Bleeding Risk in CKD

Paradoxically, declining eGFR (especially <30 mL/min/1.73 m^2) is also associated with increased bleeding risk [5]. In fact, patients with ESRD have up to

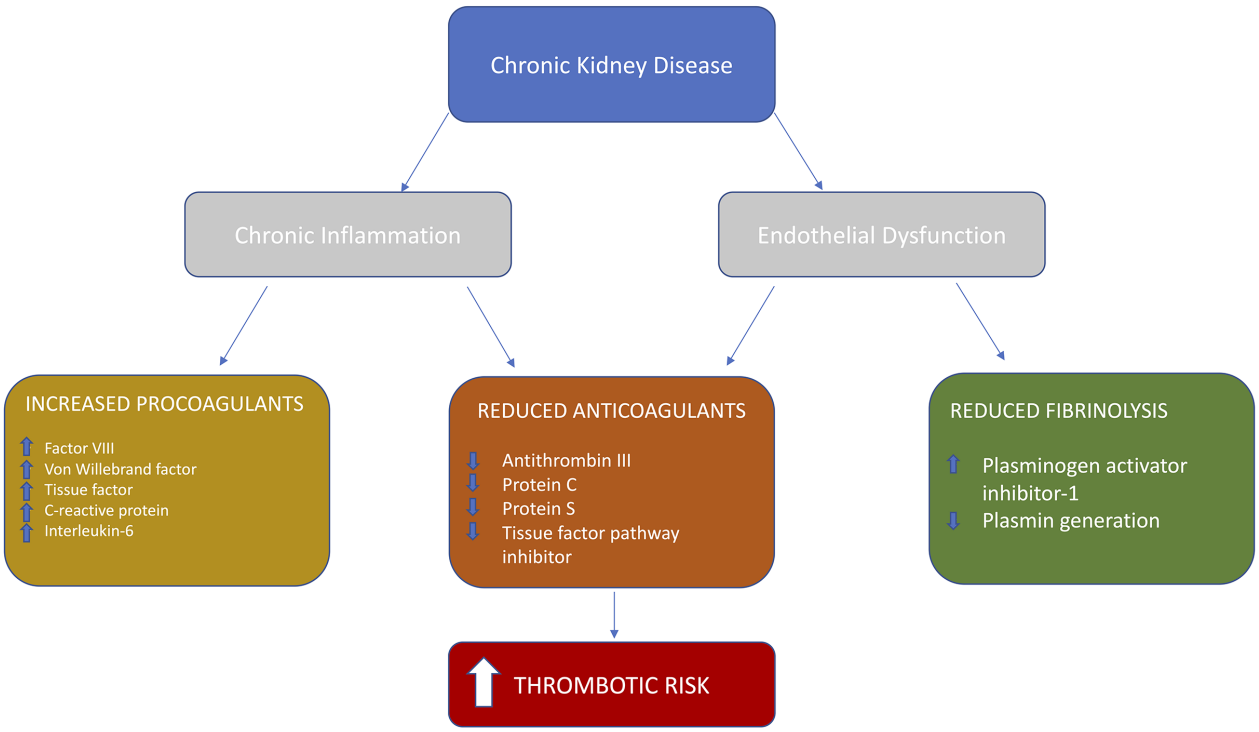

Fig. 1. Simplified schematic illustrating the changes in procoagulant and anticoagulant pathways in chronic kidney disease. Created by the authors using Microsoft PowerPoint Version 15.39 (2017) (Microsoft Corporation, Redmond, WA, USA).

a 100-fold increased risk of gastrointestinal bleeding as compared to the general population [14]. CKD is also associated with intracerebral haemorrhage, with a stronger magnitude in ESRD [15]. There are several mechanisms for this, including thrombocytopaenia, platelet dysfunction, and abnormal platelet-vessel wall interactions [16]. Uraemia and dialysis both contribute to thrombocytopaenia, via underproduction/overconsumption and complement activation leading to platelet clearance, respectively [16]. Platelet dysfunction is multifactorial. An acquired storage pool disorder occurs with reduced levels of pro-aggregatory substances such as adenosine diphosphate and 5-hydroxytryptamine (serotonin) found in the dense granules, and reduced thromboxane A2 levels due to defective cyclooxygenase activity [11,17]. Furthermore, the number of glycoprotein (GP) Ib and GP IIb/IIIa receptors, responsible for adhesion and aggregation respectively, is reduced in uraemia [11]. There are also increased levels of anti-aggregatory substances such as cyclic guanosine monophosphate (released from nitric oxide), cyclic adenosine monophosphate, and prostacyclin (see Fig. 2) [16]. Abnormal vessel wall interactions typically occur due to impaired binding of VWF and fibrinogen to platelets due to toxic substance accumulation present in uraemic plasma [16]. Renal anaemia, a common occurrence in CKD, may also contribute to bleeding risk [5,16]. Erythrocytes normally concentrate platelets peripherally along blood vessel walls. Reduced erythrocyte concentration in anaemia allows platelets to migrate away from the periphery, reducing potential platelet-vessel wall interactions [10]. This is summarized in Fig. 2.

4. Should We Anticoagulate Patients With CKD?

Not only is VTE more prevalent in the CKD population, but it also confers a higher morbidity and mortality compared to the general population, with poorer outcomes in ESRD reported [18,19]. Similarly, rates of CVD are enriched in the CKD population, with a striking association between CVD mortality and heart failure seen as eGFR falls [20]. Atrial fibrillation (AF) is more prevalent in CKD patients than in the general population [18,21], with higher rates of ischaemic stroke and systemic embolism seen in the CKD AF cohort [22]. Subgroup analysis fromthe ENGAGE AF-TIMI 48 trial demonstrated increasing rates of stroke and systemic embolism in CKD patients with AF as kidney function declined [23], and another group reported that the risk of stroke increased 7% for every 10 mL/min/1.73 m^2 decline in eGFR [18,21].

Given the high rates of CVD and VTE seen in patients with CKD, appropriate anticoagulation is required to optimise patient care and minimise associated morbidity and mortality. In the following sections, we discuss the available anticoagulants and their evidence base in renal impairment.

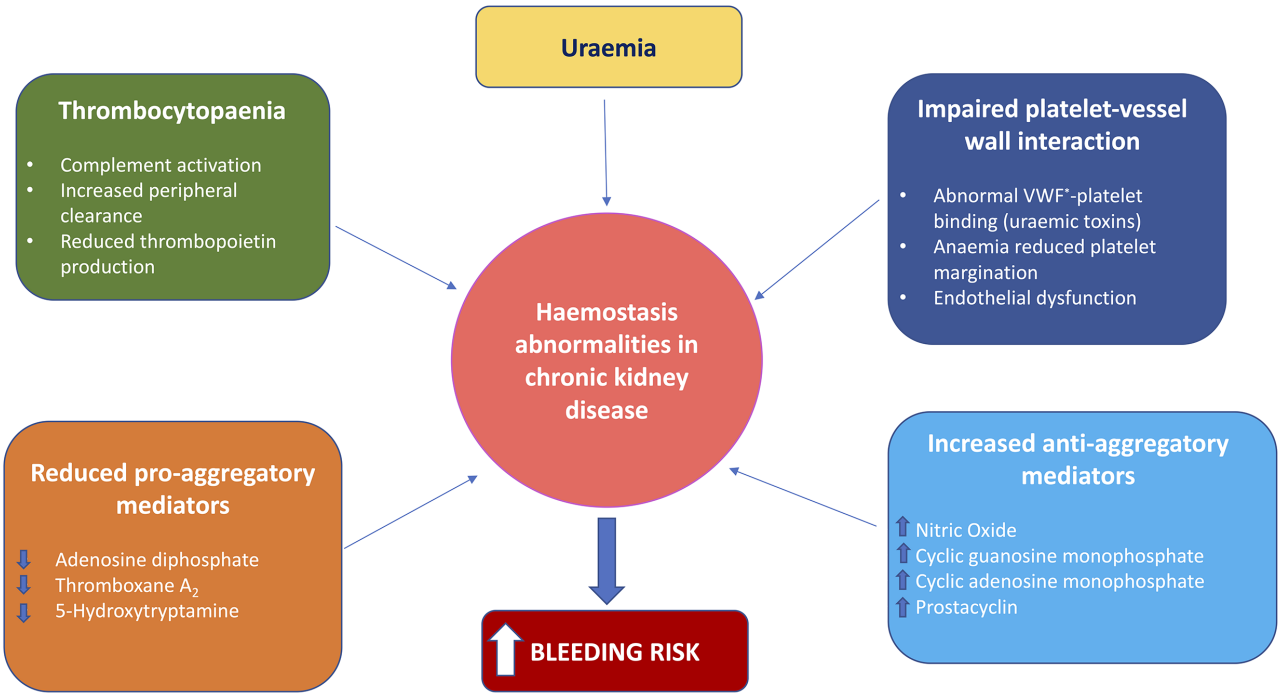

Fig. 2. Summarizing the mechanisms leading to increased bleeding risk in chronic kidney disease. VWF*, Von Willebrand factor. Created by the authors using Microsoft PowerPoint Version 15.39 (2017) (Microsoft Corporation, Redmond, WA, USA).

5. Anticoagulation in CKD – Warfarin

The vitamin K epoxide reductase inhibitor warfarin inhibits synthesis of factors II, VII, IX, and X to produce its anticoagulant effect. Warfarin is monitored via the international normalized ratio (INR) to ensure therapeutic levels and minimise the risk of bleeding [24]. Warfarin is metabolised almost exclusively by hepatic cytochrome P450 enzymes with minimal renal clearance [18,24]. However, INR levels tend to fluctuate more in CKD than in the general population, and it can therefore be harder to maintain patients within a safe therapeutic range [18], with lower doses often required in severe CKD [25]. Bleeding events are also more likely in the event of supratherapeutic INRs in CKD compared to the general population [26]. A retrospective analysis of over 15,000 patients on warfarin reviewed the rate of warfarin-related nephropathy (WRN) in patients who had an INR of greater than 3 within the prior week. WRN occurred around twice as frequently in patients with CKD compared with those without (33% vs. 16.5%) and was associated with a 65% increased risk of death [10,27].

A systematic review of 47,480 patients with ESRD and AF across 15 mostly retrospective studies compared outcomes in those taking warfarin (22%) compared with non-anticoagulated patients [28]. The authors identified no significant difference in the incidence of ischaemic stroke (hazard ratio [HR] 0.96, 95% confidence interval [CI] 0.82–1.13), major bleeding (HR 1.20, 0.99–1.47) or mortality (HR 0.95, 0.83–1.09), but observed an increased incidence of haemorrhagic stroke in patients on warfarin (HR 1.49, 1.03–1.94). Other studies have shown conflicting results [18]. Warfarin use in CKD is also associated with a 3–13 times higher risk of calciphylaxis than in the general population. Calciphylaxis is a rare but painful and potentially dangerous complication of warfarin therapy and poses another serious complication for CKD patients requiring anticoagulation [18,29]. To summarise, due to the increased incidence of WRN, calciphylaxis, and subtherapeutic INR, warfarin carries many risks when prescribed in CKD.

6. Anticoagulation in CKD – Heparins

Heparins are commonly prescribed anticoagulants in VTE prophylaxis and initial treatment of VTE prior to initiation of oral anticoagulants [30]. They are classified according to molecular weight: unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). UFH binds to AT-III with high affinity, equally inhibiting thrombin and Factor Xa. At lower doses, UFH is predominantly metabolised by the reticuloendothelial system; however, as doses increase, this mechanism becomes saturated, and clearance becomes increasingly reliant upon renal excretion [31]. This produces a non-linear relationship between dose administered and plasma concentration, with a disproportionate rise in anticoagulation as doses increase. Monitoring using the activated partial thromboplastin time (APTT) is therefore mandatory in all patients. This is particularly relevant to CKD patients who are more prone to over-anticoagulation once reticuloendothelial clearance has become saturated.

UFH has a short half-life, requiring administration via infusion to achieve therapeutic levels. However, this short

half-life alongside UFH's ability to be fully reversed by protamine sulphate is advantageous for patients with CKD, especially those at higher risk of bleeding [32]. In addition to its unpredictable dose-response and need for APTT monitoring, UFH also confers a higher risk of heparin-induced thrombocytopaenia (HIT) than LMWH [33], which can be life-threatening. Given the risk of over-anticoagulation in CKD, an initial dose reduction of 33% has been recommended by some groups, with subsequent rate adjustments to target an APTT of between 1.5 and 2.5 in most situations [32,34].

LMWHs, synthesised from depolymerization of UFH, have shorter heparin chains, with a mean molecular weight of 4000–6000 Da. These shorter fragments retain their ability to inhibit Factor Xa; however, they cannot bind to thrombin [35]. There is a lower incidence of immune events such as HIT with LMWHs and a more predictable anticoagulation response due to reduced non-specific binding to plasma proteins, which means that monitoring of plasma levels is only needed in certain circumstances. However, unlike UFH, LMWH is metabolised almost exclusively by renal clearance, with a risk of accumulation in patients with CKD, affecting the lower weight LMWHs more-so [34]. This was demonstrated by pharmacokinetic analysis of patients receiving 1 mg/kg or 1.25 mg/kg twice daily subcutaneous injections of enoxaparin for the treatment of unstable angina or non-ST-elevation myocardial infarction. The authors reported that patients with a creatinine clearance (CrCl) of 30 mL/min had a 27% reduction in clearance of enoxaparin compared with those with a CrCl of 88 mL/min, which was associated with increased bleeding risk [36]. Another group also reported reduced enoxaparin clearance in moderate CKD (CrCl 30–49 mL/min) [37]. When comparing LMWH to warfarin in VTE treatment in a cancer cohort with CKD, LMWHs had higher major and fatal bleeding events, especially in patients with an eGFR <30 mL/min/1.73 m^2 [38].

These data suggest that therapeutic doses of LMWH must be used with caution in patients with CKD and highlight the potential role for anti-Xa monitoring to avoid over-accumulation in serum [38]. The American College of Chest Physicians (CHEST) guidelines from 2012 suggest anti-Xa monitoring in VTE treatment if CrCl <30 mL/min to reduce risk of accumulation in serum, and a dose reduction of 50% if enoxaparin is used, with no specific recommendations on other LMWHs [39]. However, the updated guideline from 2016 considers therapeutic doses of LMWH to be contra-indicated in patients with severe CKD (CrCl <30 mL/min) [40]. The European Society of Cardiology 2019 guideline on the management of acute pulmonary embolism (PE) also recommends against LMWH in severe CKD, favouring UFH, and suggests use of adapted LMWH dosing if this is considered in patients with a CrCl of 15–30 mL/min [41]. Anti-Xa monitoring can be of assistance in patients with CKD receiving LMWHs [42]. However, this is an area of contention, with uncertainty regarding whether trough or peak dose levels are most important, and the optimal therapeutic range to target [43]. Some authors recommend against anti-Xa levels, instead suggesting dose reductions based on renal function; however inter-patient variation may limit this approach for all patients [44].

To summarise, UFH may be preferred to LMWH in CKD due to easy monitoring, easy reversibility and lower renal clearance; however, it carries a higher risk of HIT.

7. Anticoagulation in CKD – DOACs

Direct oral anticoagulants (DOACs) are the first-line choice in the majority of settings for the treatment of VTE and for stroke prophylaxis in patients with AF. Apixaban, rivaroxaban and edoxaban all inhibit Factor Xa, whereas dabigatran inhibits thrombin (Factor IIa). Due to more predictable anticoagulation profiles than warfarin, DOACs do not routinely require any monitoring [18], and may be associated with a lower risk of anticoagulant-related nephropathy. Dabigatran, edoxaban, rivaroxaban, and apixaban are all eliminated by the kidneys to variable degrees (80%, 50%, 35%, and 27%, respectively) [18]. Kidney function can affect the suitability and dosage of direct oral anticoagulants (DOACs), but recommended regimens can vary significantly depending on the drug, indication, and regional product information.

7.1 DOACs in the Setting of VTE

There are no randomised data concerning the use of DOACs in patients with VTE and severe CKD. Evidence for their use in mild-to-moderate renal impairment comes from subgroup analyses from a number of randomised controlled trials (RCTs) comparing DOACs with warfarin in VTE, namely AMPLIFY for apixaban, EINSTEIN for rivaroxaban, RE-COVER for dabigatran, and Hokusai for edoxaban. These trials all excluded patients with CrCl <30 mL/min (or <25 mL/min in the case of AMPLIFY). 5–7% of patients enrolled had a CrCl <50 mL/min, with similar outcomes in favour of DOACs seen in the CKD cohorts to those without renal impairment [45,46,47,48]. Across these studies, there were no planned dose reductions in CKD, apart from in Hokusai, where the dose of edoxaban was reduced to 30 mg in those with a CrCl between 30 and 50 mL/min [18]. Importantly, these subgroup analyses were not pre-planned, and none of these studies are powered to assess outcomes in moderate CKD.

Studies of extended duration anticoagulation have also largely excluded patients with renal impairment. The RENOVE study compared apixaban at 5 mg twice daily (BD) or 2.5 mg BD and rivaroxaban at 20 mg once daily (OD) or 10 mg OD; EINSTEIN CHOICE compared rivaroxaban 20 mg, rivaroxaban 10 mg and aspirin, and AMPLIFY EXT compared apixaban 5 mg BD, apixaban 2.5 mg BD and placebo. 3–6% of participants had a CrCl <50 mL/min, with no evidence of superiority of one regimen over another reported [49,50,51].

Table 1. Suggested doses of the maintenance phase of DOACs in VTE.

Suggested DOAC dosing in VTE for CKD patients based on available evidence and local labelling					
CrCl (mL/min)	>80	50–79	30–49	15–29	<15
Apixaban*	Loading then 5 mg BD	Loading then 5 mg BD	Loading then 5 mg BD	Loading then 5 mg BD	Consider
Rivaroxaban**	Loading then 20 mg OD	Loading then 20 mg OD	Loading then 20 mg OD	Loading then 20 mg OD	Contra-indicated
Edoxaban	60 mg OD	60 mg OD	30 mg OD	30 mg OD	Contra-indicated
Dabigatran	150 mg BD	150 mg BD	150 mg/110 mg BD	Contra-indicated	Contra-indicated

CrCl, creatinine clearance; DOACs, direct oral anticoagulants; VTE, venous thromboembolism; CKD, chronic kidney disease; BD, twice daily; OD, once daily.

Dosing recommendations are based on available clinical trial data, published reviews, and commonly used guideline summaries, but should be interpreted with caution. Evidence supporting DOAC use in patients with severe CKD (CrCl <30 mL/min) and end-stage renal disease remains limited, and recommendations may vary according to regional regulatory approvals, local prescribing guidance, and individual drug labelling. Most trials used moderate to severe CKD as an exclusion criterion, leading to limited evidence in this clinical setting. Treatment decisions should therefore be individualised according to patient characteristics, bleeding risk, thrombotic risk, and local clinical guidance.

*Apixaban loading: 10 mg BD for 7 days.

**Rivaroxaban loading: 15 mg BD for 21 days.

Edoxaban and dabigatran require at least 5 days of parenteral anticoagulation before initiation and maintenance dosing. The table is adapted from Jones et al. [5] with permission.

There is even less data concerning severe CKD. Two retrospective studies comparing apixaban to warfarin in severe CKD demonstrated lower bleeding rates in both studies and a lower VTE recurrence rate in one, in apixaban's favour [52,53]. A recent meta-analysis of studies of anticoagulation in patients with ESRD included 5 studies in VTE and 7 in which there were multiple indications for anticoagulation, including VTE. DOACs were associated with numerically lower rates of VTE recurrence than warfarin among the 15,582 patients with CKD Stage 5 requiring renal replacement therapy (odds ratio [OR] 0.66, 95% CI 0.38–1.16), although this difference did not reach statistical signifiance. DOACs were also not significantly different from warfarin in patients with eGFR <30 mL/min/1.73 m^2 overall [54]. These results are encouraging, but further randomised data are required in ESRD. A dosing strategy for the maintenance phase of DOAC usage in the management of VTE is shown in Table 1 (Ref. [5]).

7.2 DOACs in the Setting of AF

Similar to VTE, the majority of data concerning the use of DOACs as stroke prophylaxis in patients with AF and mild-to-moderate CKD, comes from subgroup analysis of the major RCTs comparing the DOACs with warfarin. These were ARISTOTLE (apixaban), ROCKET-AF (rivaroxaban), ENGAGE AF-TIMI 48 (edoxaban) and RELY (dabigatran). In ENGAGE AF-TIMI 48, approximately 20% of participants had a CrCl <50 mL/min, although patients with severe renal impairment were excluded from the trial [55]. Outcomes in patients with CKD were not significantly different from those without renal impairment, showing non-inferiority of DOACs versus warfarin, and a better safety profile. In ARISTOTLE, for example, while apixaban was associated with less major bleeding than warfarin in all patients, this was more pronounced in those with a CrCl <50 mL/min (HR 0.50, 95% CI 0.38–0.66) [56].

Unfortunately for patients with severe CKD or ESRD, there is a paucity of RCT data from which to draw conclusions [56]. The VALKYRIE trial randomised 132 dialysis-dependent patients to warfarin or rivaroxaban 10 mg daily with or without vitamin K2. The primary endpoint, a composite or fatal and non-fatal cardiovascular events, occurred significantly less frequently in both the rivaroxaban arms compared with the warfarin group (HR 0.41, 95% CI 0.25–0.68 rivaroxaban; HR 0.34, 95% CI 0.19–0.61 rivaroxaban and vitamin K2). Life-threatening and major bleeding was also significantly reduced in both rivaroxaban groups (HR 0.44, 95% CI 0.23–0.85) [57]. Two RCTs for apixaban use did not show inferiority compared to warfarin; however, these were not adequately powered due to recruitment issues and sample size. The AXADIA-AFNET study randomised 48 patients to apixaban 2.5 mg BD and 49 to warfarin, with no difference in mortality, major bleeding or thrombotic events observed [58]. The SAFE-D (strategies for the management of AF in patients receiving dialysis) trial (NCT03987711) recruited 151 patients, 51 of whom were randomised to apixaban 5 mg BD, 52 to warfarin and 48 to no anticoagulation. Major bleeding events occurred in two in the apixaban arm, four in the warfarin arm and two in the no anticoagulation arm [59].

There is, however, a growing body of evidence from meta-analyses in this area. A retrospective study of over 25 thousand Medicare beneficiaries with ESRD and AF, receiving either apixaban or warfarin, reported that 5 mg twice daily apixaban was superior to both warfarin (HR 0.64, 95% CI 0.42–0.97) and reduced dose apixaban (HR 0.61, 95% CI 0.37–0.98) in terms of rates of ischaemic stroke or systemic embolism. The apixaban cohort overall was also associated with less major bleeding than warfarin (HR 0.72, 95% CI 0.59–0.87) [60]. On the other hand, there are conflicting reports, with another meta-analysis finding no benefit of DOACs in reducing VTE events in severe

Table 2. Suggested doses of DOACs in AF.

Suggested DOAC dosing in AF for CKD patients based on available evidence and local labelling					
CrCl (mL/min)	>80	50–79	30–49	15–29	<15
Apixaban	5 mg BD	5 mg BD	5 mg BD	5 mg/2.5 mg BD	5 mg/2.5 mg BD
Rivaroxaban	20 mg OD	20 mg OD	15 mg OD	15 mg OD	Contra-indicated
Edoxaban	60 mg OD	60 mg OD	30 mg OD	30 mg OD	Contra-indicated
Dabigatran	150 mg BD	150 mg BD	110 mg BD	75 mg BD*	Contra-indicated

CrCl, creatinine clearance; AF, atrial fibrillation; BD, twice daily; OD, once daily.

Dosing recommendations are based on available trial data and commonly used guideline summaries but are simplified for illustrative purposes. DOAC dosing in atrial fibrillation is dependent on multiple factors, including renal function, age, body weight, concomitant medications, and varies according to regional regulatory approvals and individual drug labels. The values presented should therefore not be interpreted as a direct linear relationship with CrCl alone. Clinicians should consult local prescribing guidelines and product-specific labelling when determining appropriate dosing, particularly in patients with severe CKD (CrCl <30 mL/min) or end-stage renal disease.

*Dabigatran 75 mg BD is approved in the United States but not widely used in other regions.

No loading dose is required for apixaban or rivaroxaban in the setting of atrial fibrillation. The table is adapted from Jones et al. [5] with permission.

CKD, and an increased bleeding risk compared to no anticoagulant in ESRD [61]. A dosing strategy for DOACs in the management of AF is shown in Table 2 (Ref. [5]).

7.3 DOAC Monitoring

DOACs do not require routine monitoring; however, plasma levels may correlate with risk of thrombosis and bleeding. Analysis of DOAC levels in the ENGAGE AF-TIMI 48 study reported an association between low edoxaban trough levels and thrombotic events, and a corresponding association between high levels and bleeding. Of note, CrCl 30–50 mL/min was significantly associated with major bleeding events at both the 60 mg and 30 mg edoxaban doses [62]. Similar results were reported from post-hoc analysis of dabigatran levels in RE-LY [63]. While it seems likely that plasma levels do correlate with outcomes, interpretation of results is hampered by a lack of laboratory standardisation, inter- and intra-patient variability, and a lack of a clear concentration threshold to delineate increased bleeding or thrombosis risk. The clinical setting in which DOAC levels may be of most benefit in CKD is within peri-operative management. The PAUSE (perioperative management of patients with AF receiving a DOAC) study provided a simple strategy to approach DOAC cessation prior to surgery, with strong evidence of safety reported in patients with a CrCl of >30 mL/min [64]. Based on the findings of this study, CHEST recommends that the anti-Xa inhibitors be stopped one day prior to a low-moderate bleeding risk procedure or two days prior to a high bleeding risk procedure. Dabigatran cessation follows this pattern for patients with a CrCl >50 mL/min, whereas for patients with CrCl 30–50 mL/min, dabigatran should be ceased two days before a low-moderate bleeding risk procedure and four days before a high bleeding risk procedure [65]. This approach resulted in DOAC levels of <50 ng/mL pre-operatively in the vast majority of patients, a threshold considered to be associated with a minimal risk of significant bleeding [66]. However, patients with severe CKD were excluded from PAUSE (CrCl <30 mL/min for rivaroxaban and dabigatran, CrCl <25 mL/min for apixaban), with no consensus guidelines available [65,66]. As such, optimal management of these patients in the peri-operative setting remains unclear, resulting in considerable variation in clinical practice [67]. DOAC levels may play a role in this setting; however, further evidence is required before this approach can be recommended routinely [68].

8. Future Considerations

CKD is a global issue, with rising rates reported and increasing numbers of patients suffering from ESRD. These patients are at increased risk of both thrombo-embolic and cardiovascular disease, frequently requiring the use of anticoagulants, but are also at increased risk of bleeding. Currently available risk assessment tools for the prediction of thrombo-embolic events or bleeding in patients with AF merely identify CKD as a risk factor, without providing useful predictive information for these patients. Current studies suggest that DOACs are as safe as warfarin in mild-to-moderate CKD, and possibly safer than warfarin in severe CKD; however, further randomised data are required. Based on current evidence, apixaban is the only DOAC that may be cautiously considered in patients with ESRD. Recent appraisals of the evidence have similarly concluded that there is insufficient evidence to support the use of rivaroxaban or edoxaban in such cohorts [69,70]. Furthermore, the randomised COBRRA trial (comparison of bleeding risk between rivaroxaban and apixaban) reported a significant increase in bleeding events in patients without renal impairment receiving rivaroxaban, raising further concerns regarding safety in the CKD population [71]. There may also be a role for drug monitoring in severe CKD to guide optimal dosing and peri-operative safety, but this lacks stan-

dardisation. Novel anti-thrombotic agents targeting factor XI (FXI) are also of interest for patients with ESRD, with a number of initial reports suggesting that these agents may not increase bleeding rates in this population [72]. Whether FXI inhibitors prove to be efficacious remains to be determined in phase 3 randomised controlled trials but remains an active area of interest.

Key questions for future research include:

Is anticoagulation superior to no anticoagulation in patients with ESRD, and if so, what is the optimal dosing strategy for arrhythmias versus VTE?

Can DOAC management in the peri-operative setting be standardised for patients with ESRD?

Can DOAC levels be used in the peri-operative setting in ESRD to determine whether it is safe to proceed with the required surgery/invasive procedure?

Are factor XI inhibitors effective and safe in ESRD?

9. Conclusion

To conclude, DOACs can be used in appropriately selected patients with mild-to-moderate CKD for VTE treatment and in AF. They offer a favourable profile in comparison with vitamin K antagonists (VKAs) and heparins.

More studies are required for the use of DOACs in severe CKD for both VTE and AF. In this cohort, selected DOACs—particularly apixaban—may be considered cautiously in appropriate patients after individualised assessment, dose adjustment according to indication and local labelling, and careful evaluation of bleeding risk.

Key Points

• Patients with kidney failure are at an increased risk of thrombosis and also have an increased risk of bleeding.

• Historically, patients with chronic kidney disease requiring anticoagulation, were treated with warfarin.

• Emerging evidence supports the use of DOACs in selected patients with CKD, particularly apixaban.

• More trials are needed in end-stage renal disease to draw evidence-based conclusions.

Availability of Data and Materials

Not applicable.

Author Contributions

NA: Conceptualisation, Methodology, Reference collection and analysis, Writing—original draft, Project administration. RH: Conceptualisation, Reference collection and analysis. JT: Conceptualisation, Reference collection and analysis, Supervision. DS: Conceptualisation, Reference collection and analysis. All authors contributed to revising the manuscript critically for important intellectual content, approved the final version for publication, and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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