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Rethinking Anticoagulation in Kidney Disease and Kidney Transplantation

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ABSTRACT

Background

A clinical dilemma exists in patients with CKD, ESKD, and after kidney transplantation, as they face concurrent risks of both thromboembolic and hemorrhagic complications.

Objective

To review the literature on anticoagulant treatments in CKD, hemodialysis, and transplantation, with particular emphasis on pharmacology, safety, and clinical implementation.

Methods

Narrative review of scientific articles from PubMed, EMBASE, and Cochrane databases up to July 2025 inclusive using predefined search strategy. Observational studies, randomized trials, and major guidelines (KDIGO, AHA/ACC, ESC) were included.

Results

Despite its widespread use, warfarin has the disadvantage of bleeding and vascular calcification. Apixaban has the best data available among DOACs for use in CKD stage 5. The use of UFH is preferred in dialysis patients due to its reversibility properties. Other new drugs like factor XI inhibitors and LAAO are also very promising.

Conclusion

Anticoagulant therapy in patients with renal diseases needs personal risk assessment, proper selection of medications, and good management, especially during emergencies.

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INTRODUCTION

An intriguing hemostatic paradox exists in patients with CKD: both thrombotic and hemorrhagic complications arise from uremic changes affecting platelet function, coagulation pathways, endothelial cells, and vascular calcification [1–3]. This challenge is further magnified among ESKD patients on dialysis and in those receiving kidney transplantations, where additional variables — including extracorporeal circuits, perioperative stress, altered pharmacokinetics, and extensive drug-drug interactions attributable to immunosuppressant medications — complicate anticoagulation management [2, 3].

Within this context, this review critically analyzes the current literature on anticoagulation therapy in patients with CKD, on dialysis, and after kidney transplantation. This topic is clinically significant due to the increasing incidence of chronic kidney disease throughout the world and the increased use of DOACs, making an evidence-based strategy critical for efficacy and reduced bleeding complications [4].

EPIDEMIOLOGY

Patients with CKD face an established, progressively increased susceptibility to both thromboembolic and hemorrhagic events, including venous thromboembolism (VTE) and atrial fibrillation (AF). The degree of this susceptibility is proportionate to the severity of kidney function impairment and the impact of coexisting conditions like diabetes and high blood pressure [2–4]. The prothrombotic state is accompanied by a concurrent propensity for bleeding complications, arising from hemostatic abnormalities intrinsic to CKD. Patients with end-stage renal disease (ESKD) on dialysis face additional thrombotic and hemorrhagic risks related to frequent vascular access, extracorporeal circulation, dialysis-related anticoagulation, and uremia-induced platelet dysfunction [3–6]. Kidney transplant recipients constitute a further high-risk subgroup, in whom surgical trauma and ongoing immunosuppressive therapy contribute to an elevated early post-transplant risk of VTE [2, 7].

METHODS

This is a narrative review. It does not aim to conduct a systematic review; rather, it synthesizes available scientific evidence on anticoagulant therapy in patients with CKD, ESKD, dialysis, and kidney transplantation.

The literature search was conducted across PubMed, EMBASE, and the Cochrane Library from database inception through July 2025. Search terms were combined using Boolean operators (AND/OR) and included: "chronic kidney disease," "end-stage renal disease," "dialysis," "kidney transplant," "anticoagulation," "warfarin," "direct oral anticoagulants (DOACs)," "bleeding," "thrombosis," and "stroke."

Studies considered eligible comprised randomized controlled trials (RCTs) as well as observational, cohort studies, meta-analyses, and major international clinical practice guidelines (KDIGO, AHA/ACC, and ESC). Case reports, narrative commentaries without original data, and non-English publications were excluded.

Study selection was carried out in two phases: a preliminary review of titles and abstracts, followed by full-text assessment for relevance to the pharmacokinetics and clinical use of anticoagulants in CKD, dialysis, and transplantation populations. Given the known exclusion of patients with an estimated glomerular filtration rate (eGFR) <30 mL/min from most RCTs, the evidence base was anticipated to rely predominantly on observational studies and post-hoc subgroup analyses — a finding that was confirmed.

Qualitative data synthesis was performed through comparison of efficacy, bleeding risk, pharmacokinetics, and clinical applicability in both chronic and emergency settings.

PHARMACOKINETIC CONSIDERATIONS

Renal dysfunction significantly impacts drug distribution, protein binding, and metabolism; hence, thereby influencing anticoagulant pharmacodynamics. DOACs vary widely in their reliance on renal elimination; dabigatran is highly dependent, being primarily eliminated by the kidneys [4, 11]. For ESKD patients, available treatment options are restricted, as only a few anticoagulants — including warfarin and apixaban — have received FDA approval in this population [10–13]. Significant drug-drug interactions are also common in kidney transplant patients owing to concomitant use of immunosuppressants [7].

Results: Evidence Synthesis by Anticoagulant Class

Vitamin K Antagonists

Warfarin remains the most widely used anticoagulant in CKD and ESKD **(Table 1)** owing to its long clinical track record and reversibility. However, its use is limited by a narrow therapeutic index, frequent drug and food interactions, and increased risks of bleeding and vascular calcification, including calciphylaxis [8, 9]. Observational studies suggest no consistent reduction in stroke risk in dialysis populations, with a concurrent increase in major bleeding compared with non-CKD cohorts.

TABLE 1 - Pharmacologic Considerations of Vitamin K Antagonists in Kidney Disease

Parameter	Warfarin
Mechanism	Vitamin K epoxide reductase inhibition
Renal clearance	<3%
Dose adjustment in CKD	Required (lower doses in ESKD)
Monitoring	INR (target 2.0–3.0)
Half-life in ESKD	36–42 h
Major interactions	Food + drug (high burden)
Adverse effects	Bleeding, vascular calcification, calciphylaxis
Reversal	Vitamin K, Four-factor PCC, FFP

Footnotes: INR = International Normalized Ratio; FFP = Fresh Frozen Plasma; PCC = Prothrombin Complex Concentrate

Direct Oral Anticoagulants (DOACs)

DOACs offer more predictable pharmacokinetics and do not require routine monitoring compared with warfarin, although pharmacokinetic variation among agents is notable **(Table 2)**. Among DOACs, apixaban has the largest body of clinical evidence in patients with severe CKD and those on dialysis **[10–14]**. Observational studies consistently indicate that apixaban reduces the incidence of major bleeding and provides similar or superior antithrombotic efficacy compared with warfarin.

By contrast, dabigatran is primarily excreted renally, leading to drug accumulation in CKD; its use is therefore generally not recommended in severe CKD in this population. In addition, rivaroxaban and edoxaban have moderate renal clearance, and data on their use in ESKD patients remain limited.

Heparins and LMWH

Nevertheless, UFH remains the gold standard for anticoagulation during hemodialysis because of its short half-life and completely reversible action. While LMWHs exhibit superior pharmacokinetic behavior, their use should be strictly controlled since there is a possibility of their accumulation in patients with renal insufficiency **[5, 6]**. The pharmacology of these medications is described in **Table 3**.

Emerging Therapies

Novel anticoagulant strategies are summarized in **Table 4**. Antiplatelets may be used adjunctively in select transplant patients but increase bleeding risk **[16]**. Novel strategies such as Factor XI inhibitors and left atrial appendage closure are promising **[25, 26]**.

TABLE 2 - Direct Oral Anticoagulants in CKD and Dialysis

Parameter	Apixaban	Rivaroxaban	Dabigatran	Edoxaban
Mechanism	Factor Xa inhibitor	Factor Xa inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor
Renal clearance (%)	27	36	80	50
Use in ESKD	Allowed (cautious)	Limited data	Avoid	Limited data
Dialyzability	Minimal	Minimal	High	Minimal
Half-life (ESKD)	15–18 h	11–13 h	>24 h	10–14 h
Reversal agent	Andexanet alfa	Andexanet alfa	Idarucizumab	Andexanet alfa

Footnotes: CrCl = Creatinine Clearance; ESKD = End-Stage Kidney Disease

TABLE 3 - Heparins in Kidney Disease

Parameter	UFH	Enoxaparin	Dalteparin	Fondaparinux
Renal clearance	Minimal	Moderate	Low	High
Use in ESKD	Standard	Dose adjustment	Caution	Contraindicated
Monitoring	aPTT	Anti-Xa	Anti-Xa	Anti-Xa
Dialysis use	Yes	Limited	Limited	No
Reversal	Protamine	Partial	Partial	None

Footnotes: UFH = Unfractionated Heparin; aPTT = Activated Partial Thromboplastin Time

TABLE 4 - Emerging Anticoagulants and Non-Pharmacologic Strategies in CKD

Strategy	Mechanism	Evidence level	CKD applicability
Factor XI inhibitors	Intrinsic pathway inhibition	Phase II–III trials	Promising
LAAO	Mechanical exclusion of appendage	Observational + trials	High-risk AF patients
AI risk models	Predictive analytics	Early development	Future tool

Footnotes: AF = Atrial Fibrillation; CKD = Chronic Kidney Disease; LAAO = Left Atrial Appendage Closure

POPULATION-SPECIFIC CONSIDERATIONS

For patients undergoing hemodialysis, there is a need for achieving a balance between the timing of doses and the risk of vascular access complications as well as clot formation within the dialysis machine circuit. Peritoneal dialysis is relatively safe regarding the pharmacokinetic stability and decreased bleeding tendency. However, evidence supporting this remains limited. For patients receiving a kidney transplant, there are notable adverse drug interactions that may affect the pharmacologic efficacy of the drug, especially with regards to CYP3A4 and P-glycoprotein mechanisms [7, 16].

DISCUSSION

The management of anticoagulation therapy for those with CKD, dialysis, and kidney transplantation represents one of the most complex tasks owing to the risks of developing both thrombosis and bleeding. Research concerning this issue shows that there is a high degree of heterogeneity, while the majority of studies conducted are observational. Few randomized controlled trials have been conducted for advanced renal dysfunction. As far as warfarin is concerned, it is one of the most researched anticoagulants in CKD patients, although its application poses risks including increased chances of bleeding, need for regular monitoring, and vascular calcification. Among the DOACs, apixaban appears to be quite promising. Evidence grading across therapies highlights that high-quality RCT data are restricted to general atrial fibrillation populations with minimal inclusion of advanced CKD patients, moderate evidence stems from post-hoc or subgroup analyses of DOAC trials that remain underpowered for renal endpoints, and low to moderate evidence is dominated by observational studies, especially for apixaban, which consistently signals reduced bleeding compared with warfarin. Expert opinion and guideline-based recommendations reflect this uncertainty: KDIGO emphasizes insufficient evidence, whereas AHA/ACC and ESC guidelines cautiously support DOAC use in selected CKD patients [15–17]. With regards to the field of emergency medicine, the proper identification of the anticoagulant in question along with its reversal become particularly crucial in the situation of either bleeding or urgent procedures, which might involve the utilization of vitamin K and PCC as treatment strategies in managing bleeding due to warfarin, idarucizumab as a treatment strategy aimed at reversing the effects of dabigatran, and andexanet alfa as a treatment strategy used to reverse the action of factor Xa inhibitors, although, only with the modest efficiency of hemodialysis in the latter case and without having any impact on most of the factor Xa inhibitors. There is no applicability of the findings obtained from the existing research studies due to several factors: the lack of data obtained within the framework of randomized trials,

the involvement of individuals who have an estimated GFR below 30 mL/min, heterogeneous study designs, the insufficient representation of patients with transplants, and lack of consistency in defining the endpoint. In summary, although apixaban has been shown to be the safest of all anticoagulants through observational studies and heparin unfractionated still plays an important role in dialysis, there is still no certainty about which approach is superior in patients with advanced stages of CKD. Some of the areas that remain challenging and require further research include adequately powered RCTs among dialysis and transplanted patients [6, 17], improvement of risk stratification models accounting for specific uremia-related factors [17], and development of more tolerable medications including factor XI inhibitors [17]. Possible strategies to improve anticoagulation therapy among this population include increasing the availability of reversal agents for DOACs [13] and validation of other non-pharmacologic methods like left atrial appendage closure (LAAC) [18].

Recent Developments in Anticoagulation in CKD (2022–2025)

Recent developments (2022–2025) have contributed substantially to the scientific basis of anticoagulation in patients with chronic kidney disease (CKD), especially in dialysis, transplantation, and non-pharmacologic approaches.

Use of DOACs in Dialysis Populations

New insights gained from current meta-analyses and cohort studies show that DOACs, specifically apixaban, might offer a better safety profile when compared with VKAs in dialysis patients, mainly based on a reduced bleeding risk without compromising thromboembolism prevention [6, 13]. New systematic reviews from clinical trials and observational studies demonstrate that DOACs can decrease bleeding risk in dialysis patients, despite the limited number of participants and study heterogeneity [6]. Nonetheless, guidelines still recommend caution in view of the lack of large-scale randomized clinical trials in ESKD populations [17].

Factor XI Inhibitors (Newer Anticoagulants)

Newer factor XI inhibitors, among which there is abelacimab and milvexian, represent a novel anticoagulant class aiming to improve thromboprotection without increasing bleeding risks. Phase II and ongoing Phase III clinical studies indicate that the selective targeting of factor XI may be more beneficial for high-bleeding-risk individuals, such as CKD patients, owing to the minimal dependence on renal elimination [25]. However, at present, there is not enough randomized trial data about the use of factor XI inhibitors among dialysis patients.

Left Atrial Appendage Occlusion (LAAO)

The latest literature (2022–2025) highlights new evidence regarding the potential benefits of using left atrial appendage occlusion (LAAO) as a non-medication therapy modality for stroke prevention among atrial fibrillation patients who suffer from CKD and ESKD. According to modern findings, LAAO has been proven to have some advantages over long-term oral anticoagulation therapy concerning both decreased mortality rate and lower major bleeding rates [18, 26]. Moreover, observational registries in dialysis patients confirm satisfactory procedural safety, with no increased hemorrhagic events despite limited randomized comparison with DOACs [6, 26].

Anticoagulation in Kidney Transplant Recipients

In recent years, new research has shown the difficulty of anticoagulation among kidney transplant recipients, where interactions between drugs such as calcineurin inhibitors and mTOR inhibitors play a role in the pharmacokinetics of anticoagulants. According to recently updated cohort studies (2023–2025), apixaban and rivaroxaban can be safely administered among specific transplant patients, despite possible interactions with cytochrome P450 3A4 and P-glycoprotein [8]. While observational studies show the relative safety of DOACs among transplant recipients, more evidence is still needed from randomized controlled trials. Warfarin is thus a common choice for such patients [7].

Integrated Interpretation of Recent Evidence

As a whole, findings reported over the years 2022–2025 have supported the notion that there has been a relatively slow move toward increasing yet prudent administration of apixaban in dialysis patients, emergence of factor XI inhibitors as future safe anticoagulants, and further confirmation of LAAO as an effective approach in high-risk CKD patients. Simultaneously, the use of DOACs in renal transplant patients has become more prevalent but still highly restricted owing to various safety issues. Nevertheless, even with such advancements, it should be noted that most of the available evidence continues to come from observational studies, calling for randomized controlled trials involving advanced CKD, dialysis, and transplant patients.

LIMITATIONS

The current review is limited by its narrative approach and heterogeneous sources of information. The high number of observational studies and subgroup analyses increases the risk of bias and decreases the generalizability of findings. Moreover, the majority of

randomized clinical trials do not include patients with advanced kidney failure, which limits the level of the obtained evidence. The lack of information among kidney transplant recipients is another limitation.

FUTURE DIRECTIONS

Further studies should focus on RCTs involving dialysis and transplantation patients [6, 17]. The creation of new CKD-risk stratification models will be essential in achieving an optimal balance between thromboembolism and hemorrhagic complications [17]. New anticoagulants, especially that inhibiting factor XI, can be promising for future clinical practice [17]. Finally, the development of DOAC reversal agents and novel treatment modalities, such as LAA occlusion, needs to be considered [13, 18]. Future AI-based methods might become indispensable for personalized anticoagulation.

CONCLUSION

Despite the concurrent presence of a heightened risk for thrombosis and bleeding, anticoagulation therapy in CKD patients, dialysis, and kidney transplantation remains challenging. In clinical practice, warfarin is still largely used, while UFH is the preferred choice of anticoagulant in dialysis patients. When considering the DOACs, apixaban appears to have a favorable safety profile based on observational data as long as dosage modification is considered. In conclusion, for an ideal anticoagulation therapy, risk-benefit analysis, monitoring, and choosing the appropriate medication are all essential. More research studies using randomized controlled trials are recommended for the future.

Keywords

Anticoagulants, Warfarin, Chronic Renal Insufficiency, Renal Dialysis, Kidney Transplantation

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Author Contributions

AJZ conceived, drafted, critically reviewed and edited the manuscript. The author approved the final version.

Declarations

Ethical Approval

This review is based entirely on previously published studies and publicly available data. No individual patient data were collected or analyzed. Institutional review board approval was not required.

Informed Consent

No new human participants were involved in this review article; informed consent was not required.

Animal Research

This article does not contain any studies with animals performed by the author.

Conflict of Interest

The author declare that he has no conflicts of interest related to this work.

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Data Availability

All data underlying this article are derived from the published literature cited herein. No new datasets were generated or analyzed by the author.

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