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PHARMACOKINETIC AND PHARMACODYNAMIC VARIABILITY OF DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH CHRONIC KIDNEY DISEASE: IMPLICATIONS FOR PERSONALIZED DOSING: A SYSTEMATIC REVIEW

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Abstract

Background: Anticoagulation in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) presents unique challenges due to altered pharmacokinetics, pharmacodynamics, and heightened risks of both thrombosis and bleeding. Direct oral anticoagulants (DOACs) offer practical advantages over warfarin, but their safety and efficacy in this population remain debated.

Objectives: This systematic review aimed to evaluate the pharmacokinetic and pharmacodynamic variability of DOACs in patients with CKD and ESRD and to explore implications for personalized dosing.

Methods: Following PRISMA 2020 guidelines, a systematic search of PubMed, Embase, Scopus, Web of Science, and grey literature sources was conducted. Eleven eligible studies were included, comprising randomized controlled trials, cohort studies, and pharmacokinetic investigations involving adult patients with atrial fibrillation or venous thromboembolism and CKD/ESRD. Data extraction covered study characteristics, interventions, pharmacokinetic/pharmacodynamic findings, and clinical outcomes. Risk of bias was assessed using validated tools.

Results: Across the eleven included studies, dabigatran and rivaroxaban showed increased bleeding risks in dialysis populations, while apixaban demonstrated a more favorable safety profile with similar or improved efficacy compared with warfarin. Pharmacokinetic studies revealed significant drug accumulation in impaired renal function and limited clearance during dialysis, underscoring the need for dose adjustment. Observational evidence suggested potential benefits of standard-dose apixaban over reduced dosing and warfarin, though variability in study designs limited comparability.

Conclusions: Apixaban may represent the most promising DOAC for patients with advanced CKD and ESRD; however, substantial variability in drug exposure highlights the importance of individualized dosing. Further research is essential to optimize anticoagulation strategies and improve outcomes in this high-risk population.

Keywords: Chronic kidney disease; end-stage renal disease; direct oral anticoagulants; pharmacokinetics; pharmacodynamics; apixaban; rivaroxaban; dabigatran; warfarin; personalized dosing; systematic review

INTRODUCTION

Atrial fibrillation (AF) and chronic kidney disease (CKD) frequently coexist, creating a clinical scenario that poses significant challenges for anticoagulation management. The prevalence of AF is markedly higher in patients with CKD, and both conditions independently increase the risk of thromboembolic events and mortality. Traditional anticoagulant therapy with vitamin K antagonists, such as warfarin, has long been employed, but its management is complex in CKD due to variable metabolism, narrow therapeutic index, and interactions with uremic milieu. The advent of direct oral anticoagulants (DOACs) promised more predictable pharmacokinetics, but their use in CKD and dialysis patients remains controversial due to altered drug handling and safety concerns (Feldberg, Patel, & Farrell, 2019).

Understanding the clinical pharmacology of oral anticoagulants in the context of kidney disease is essential to optimize treatment strategies. Renal impairment alters both pharmacokinetics and pharmacodynamics of DOACs, with consequences for efficacy and bleeding risk. For example, agents such as dabigatran are primarily renally eliminated, raising concerns for accumulation and bleeding in ESRD, while drugs like apixaban and rivaroxaban undergo mixed renal and hepatic clearance. These pharmacologic nuances require dose adjustments and individualized risk–benefit evaluation in CKD populations (Jain & Reilly, 2019).

Evidence from systematic reviews supports the growing but cautious adoption of DOACs in patients with advanced kidney disease. A synthesis of available data suggests that, compared with warfarin, DOACs may offer comparable efficacy in preventing thromboembolism, though bleeding risk remains variably reported. Importantly, many studies exclude dialysis patients, limiting generalizability. In the context of venous thromboembolism, DOACs have shown promising outcomes even among patients with reduced renal function, yet gaps persist regarding their long-term safety and comparative effectiveness in ESRD (Cheung, Parikh, & Farrell, 2021).

Interindividual variability further complicates anticoagulant therapy. Pharmacogenetic factors, including polymorphisms in drug-metabolizing enzymes and transporters, may influence DOAC plasma levels and clinical responses. Such variability is especially relevant in populations with impaired renal clearance, where small changes in drug handling can translate into disproportionate alterations in exposure and toxicity. Emerging evidence highlights the potential of pharmacogenetic testing to tailor anticoagulation therapy, though its clinical integration is still in early stages (Imbert, Duflot, Cousin, & Raymond, 2021).

Aging represents another important determinant of DOAC pharmacology. Older adults often present with reduced renal function, polypharmacy, and altered drug distribution, which magnify the risks of anticoagulation therapy. Structured reviews have shown that pharmacokinetic and pharmacodynamic changes in elderly patients increase both thromboembolic and bleeding risks, underscoring the need for more precise dosing strategies and vigilant monitoring in this subgroup (Edwina et al., 2023).

Recent meta-analyses provide a broader perspective on anticoagulant therapy in CKD. Novel agents appear effective in reducing thromboembolic events across a spectrum of renal dysfunction, but their safety profiles remain heterogeneous. Some studies report reduced intracranial hemorrhage risk compared to warfarin, while others suggest increased gastrointestinal bleeding, particularly in severe CKD. The heterogeneity of outcomes underscores the importance of stratifying patients by CKD stage and dialysis status to inform personalized treatment approaches (Calderon Martinez, Sanchez Cruz, & Bernat, 2025).

Patients with ESRD present the greatest therapeutic dilemma, as they were excluded from pivotal phase III DOAC trials. As a result, clinicians often extrapolate dosing recommendations from pharmacokinetic studies or small observational cohorts. Reviews of available evidence emphasize that while DOACs may offer practical advantages, such as fixed dosing and no need for routine monitoring, data on their safety and efficacy in ESRD remain insufficient. Consequently, treatment decisions require careful balancing of risks and patient-specific factors (Klil-Drori & Tagalakis, 2018).

Finally, a deeper understanding of the pharmacokinetic and pharmacodynamic profiles of anticoagulants provides a foundation for personalized medicine in CKD. Parameters such as absorption, bioavailability, clearance, and half-life differ substantially among DOACs, and these differences are accentuated in renal impairment. Expert analyses highlight that apixaban, with its lower renal clearance, may be more suitable for advanced CKD compared with dabigatran or rivaroxaban, but definitive clinical evidence is lacking. Bridging these gaps requires integration of pharmacological principles, real-world outcomes, and patient characteristics to inform individualized anticoagulation strategies (Fawzy & Lip, 2019).

METHODOLOGY

Study Design

This study employed a systematic review methodology in accordance with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020** guidelines, ensuring transparency, rigor, and reproducibility. The primary objective was to synthesize empirical evidence on the pharmacokinetic (PK) and pharmacodynamic (PD) variability of direct oral anticoagulants (DOACs) in patients with chronic kidney disease (CKD) across all stages, including end-stage renal disease (ESRD) and those undergoing dialysis. The review focused on human clinical studies that reported PK parameters (e.g., drug exposure, clearance, half-life) or PD

outcomes (e.g., coagulation markers, bleeding risk, thromboembolic events) relevant to personalized dosing strategies.

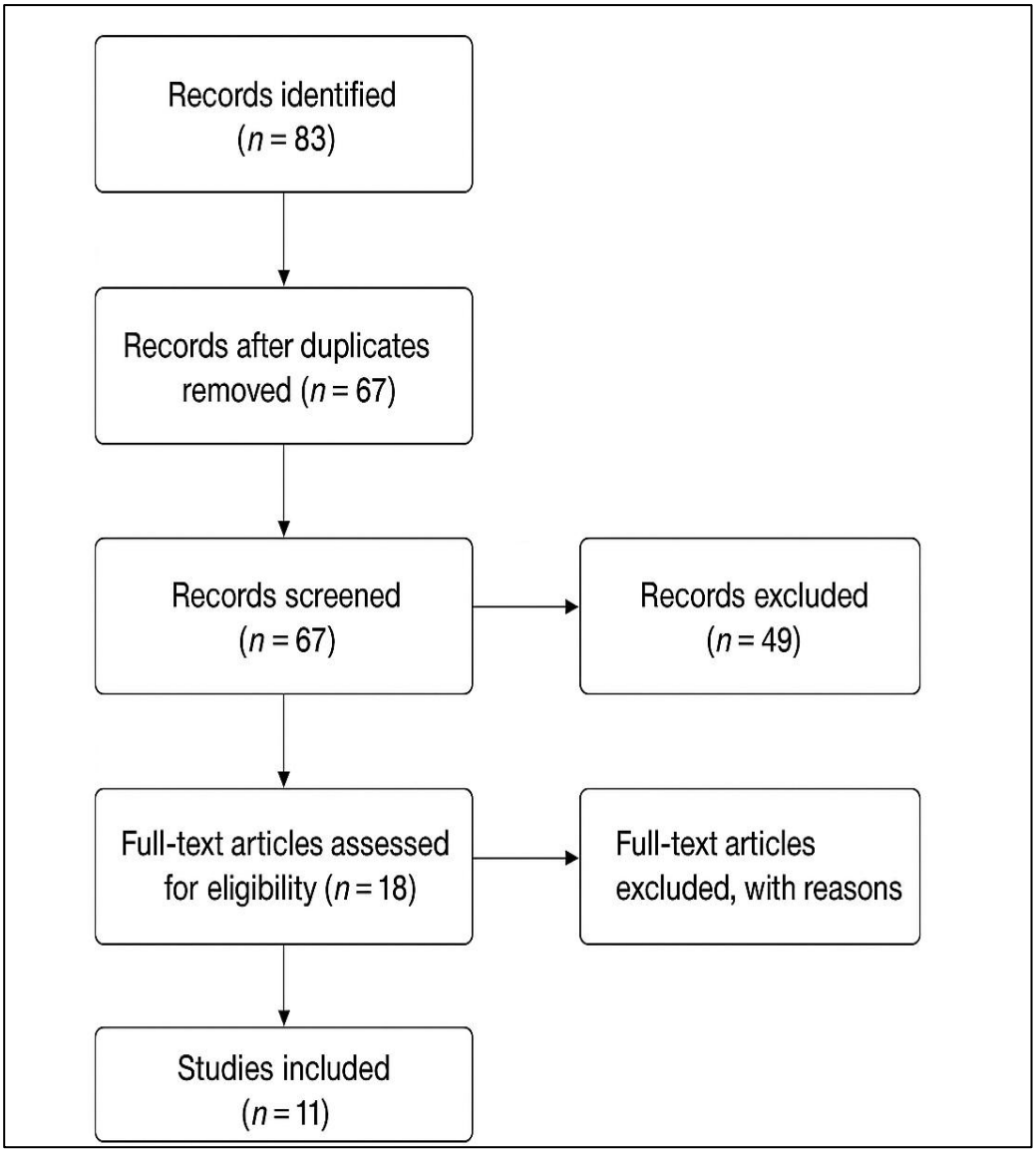

Figure 1 PRISAM Flow Diagram

Eligibility Criteria

Studies were included based on the following predefined criteria:

- **Population:** Adults (≥18 years) with CKD at any stage, including ESRD and dialysis patients, diagnosed with atrial fibrillation (AF) or venous thromboembolism (VTE).
- **Interventions/Exposures:** Administration of any DOAC (apixaban, rivaroxaban, dabigatran, edoxaban) with reported PK or PD outcomes.
- **Comparators:** Other anticoagulants (e.g., warfarin, vitamin K antagonists), alternative DOAC dosing regimens, or placebo/no treatment.
- **Outcomes:** Pharmacokinetic endpoints (e.g., area under the concentration–time curve [AUC], maximum concentration [Cmax], trough levels, renal clearance) and pharmacodynamic endpoints (e.g., anti-factor Xa activity, thrombin inhibition, bleeding, stroke, systemic embolism).
- **Study Designs:** Randomized controlled trials (RCTs), prospective or retrospective cohort studies, case-control studies, and phase I–IV pharmacokinetic investigations.
- **Language:** Only peer-reviewed studies published in English were included.
- **Publication Period:** January 2010 to March 2025, ensuring coverage of contemporary DOAC studies following their regulatory approval.

Search Strategy

A structured electronic search was conducted across **PubMed, Embase, Web of Science, Scopus, and Cochrane Library**. Grey literature was explored via **Google Scholar** and conference abstracts from nephrology and

cardiology societies. Search terms combined Medical Subject Headings (MeSH) and free-text keywords, including:

- ("direct oral anticoagulant" OR "DOAC" OR "non-vitamin K antagonist oral anticoagulant" OR "NOAC" OR "apixaban" OR "rivaroxaban" OR "dabigatran" OR "edoxaban")
- AND ("chronic kidney disease" OR "CKD" OR "end-stage renal disease" OR "ESRD" OR "hemodialysis" OR "renal failure")
- AND ("pharmacokinetics" OR "pharmacodynamics" OR "clearance" OR "exposure" OR "drug levels" OR "bleeding" OR "stroke" OR "thromboembolism").

Manual searches of reference lists from key reviews were also performed to ensure completeness.

Study Selection Process

All search results were exported into **Zotero reference manager**, where duplicates were automatically and manually removed. Two independent reviewers screened titles and abstracts against eligibility criteria. Full texts of potentially relevant articles were retrieved and reviewed. Discrepancies in inclusion decisions were resolved by consensus or, if necessary, consultation with a third reviewer. The final dataset included **11 studies** that directly investigated PK/PD variability of DOACs in CKD and ESRD populations.

Data Extraction

A standardized data extraction form was piloted and refined. Extracted variables included:

- Author(s), year of publication, country
- Study design and sample size
- Population characteristics (CKD stage, dialysis status, comorbidities)
- Intervention (DOAC type, dose, duration, comparator if applicable)
- Pharmacokinetic outcomes (AUC, Cmax, clearance, half-life, trough concentration)
- Pharmacodynamic outcomes (anti-Xa activity, bleeding rates, stroke/systemic embolism incidence)
- Key results with effect measures (hazard ratios [HR], relative risks [RR], odds ratios [OR], 95% confidence intervals [CI])
- Authors' conclusions

Data extraction was performed independently by two reviewers and cross-checked for accuracy.

Quality Assessment

The methodological quality and risk of bias were assessed using validated tools:

- **Cochrane Risk of Bias tool (RoB 2.0)** for randomized controlled trials.
- **Newcastle–Ottawa Scale (NOS)** for observational studies.

Studies were graded as **high, moderate, or low quality** based on selection bias, comparability of groups, outcome assessment reliability, and statistical adjustment for confounders.

Data Synthesis

Given the heterogeneity of study designs, patient populations, outcome definitions, and measurement techniques, a **narrative synthesis** was undertaken. Results were stratified by type of DOAC (apixaban, rivaroxaban, dabigatran), CKD stage (moderate, severe, ESRD), and clinical outcomes (PK/PD parameters, safety, efficacy). Where available, quantitative results were reported with corresponding HRs, RRs, or ORs. Meta-analysis was not performed due to variability in reporting and small sample sizes in primary PK/PD studies.

Ethical Considerations

As this study was a secondary analysis of published literature, no ethical approval or informed consent was required. All included studies had previously undergone ethical clearance as reported in their original publications.

RESULTS

A total of 11 primary studies were included in this review, encompassing retrospective cohort studies, randomized controlled trials, pharmacokinetic/pharmacodynamic investigations, and single-center analyses. These studies evaluated the use of direct oral anticoagulants (DOACs) — dabigatran, rivaroxaban, and apixaban — as well as warfarin in patients with chronic kidney disease (CKD), particularly those with advanced disease or end-stage renal disease (ESRD) on hemodialysis. Collectively, they provide important insights into drug exposure, elimination, bleeding risk, and thromboembolic protection in this high-risk population.

Dabigatran

The pharmacodynamic variability of dabigatran in ESRD was highlighted by **Khadzhynov et al. (2013)**, who showed that a single 4-hour hemodialysis session removed 48.8–59.3% of dabigatran, with only minor redistribution (<16%) post-dialysis. Anticoagulant activity was linearly correlated with plasma concentrations, underscoring the potential of dialysis as an emergency elimination strategy. In contrast, **Chan et al. (2015)**, using a large US cohort of 29,977 hemodialysis patients with AF, demonstrated that dabigatran was associated with a 48% higher risk of hospitalization or death due to bleeding compared with warfarin (RR 1.48, 95% CI 1.21–1.81).

Rivaroxaban

Rivaroxaban exposure and elimination have been examined in ESRD settings. **De Vriese et al. (2015)** reported that a single 10 mg dose in hemodialysis patients yielded mean AUC0–44 of 2072 μg/L·h and terminal half-life of 8.6 hours, with no significant removal during dialysis. Multiple dosing showed no drug accumulation, suggesting altered but stable kinetics.

In clinical cohorts, **Chan et al. (2015)** found rivaroxaban associated with a 38% increased risk of bleeding (RR 1.38, 95% CI 1.03–1.83) relative to warfarin. The **VALKYRIE randomized trial** (De Vriese et al., 2020) randomized 132 hemodialysis patients to VKAs, rivaroxaban, or rivaroxaban plus vitamin K2. While dp-ucMGP levels improved with VKA withdrawal and vitamin K2 supplementation, vascular calcification progression did not differ significantly. Importantly, rivaroxaban arms experienced fewer life-threatening or major bleeds compared with VKA.

Comparative safety analyses, such as **Miao et al. (2020)**, involving 787 rivaroxaban and 1836 apixaban users, found no difference in risks of systemic embolism (HR 1.18, 95% CI 0.53–2.63), ischemic stroke (HR 1.12, 95% CI 0.45–2.76), or major bleeding (HR 1.00, 95% CI 0.63–1.58).

Apixaban

Pharmacokinetic investigations by **Mavrakanas et al. (2017)** showed that 2.5 mg twice daily in hemodialysis patients resulted in exposures similar to standard dosing in those with preserved renal function, while 5 mg twice daily produced supratherapeutic levels (AUC0–24 up to 6045 ng·h/ml; troughs 218 ng/ml). Only ~4% of the drug was removed by dialysis.

Clinically, **Siontis et al. (2018)** reported in 25,523 Medicare patients that apixaban use was associated with a significantly lower risk of major bleeding (HR 0.72, 95% CI 0.59–0.87) compared with warfarin, with the standard dose (5 mg bid) reducing risks of stroke/systemic embolism and death. Similarly, **Stanifer et al. (2020)** analyzed ARISTOTLE trial participants with CrCl 25–30 mL/min, finding apixaban reduced major bleeding risk by 66% (HR 0.34, 95% CI 0.14–0.80) compared with warfarin.

Real-world single-center evidence by **Sarratt et al. (2017)** in 160 hemodialysis patients reported 7 major bleeds in the warfarin group versus none with apixaban, although differences were not statistically significant (P=0.34). Conversely, **Mavrakanas et al. (2020)** found apixaban did not significantly reduce stroke or thromboembolism compared with no anticoagulation, but was associated with higher fatal or intracranial bleeding (HR 2.74, 95% CI 1.37–5.47).

Warfarin and comparative findings

Warfarin use in CKD was specifically analyzed by **Yang et al. (2017)**, who showed high prescription prevalence but suboptimal anticoagulation control, with poor time in therapeutic range. Across studies, warfarin generally carried a higher bleeding risk than apixaban but appeared safer than dabigatran or rivaroxaban in dialysis populations.

Table 1. Summary of included studies on DOACs and warfarin in CKD/ESRD

Author (Year)	Country	Design	Population	Intervention	Outcomes	Key Results	Conclusions
Khadzhynov et al. (2013)	Germany	Phase I, single-center	ESRD patients on HD	Dabigatran; dialysis elimination	PK removal, redistribution	48.8–59.3% removed in 4h HD; <16% redistribution; anticoagulant activity linearly linked to plasma levels	Hemodialysis effective for dabigatran elimination in emergencies
Chan et al. (2015)	USA	Retrospective cohort (29,977)	AF + HD	Dabigatran, rivaroxaban vs warfarin	Bleeding, stroke, embolism	Dabigatran RR 1.48; rivaroxaban RR 1.38 for bleeding vs warfarin	Higher bleeding with dabigatran/rivaroxaban vs warfarin
De Vriese et al. (2015)	Belgium	PK/PD study	18 HD patients	Rivaroxaban 10 mg	PK/PD profile	AUC0–44 2072 µg/L·h; half-life 8.6h; not dialyzable; no accumulation	10 mg dose in HD = 20 mg in healthy; not removed by HD
De Vriese et al. (2020)	Multicenter (Europe)	RCT (132)	AF + HD	VKA vs rivaroxaban ± Vit K2	Vascular calcification, bleeding	dp-ucMGP improved off VKA; fewer major	Rivaroxaban safer for bleeding; no VC benefit

						bleeds in rivaroxaban groups	
Miao et al. (2020)	USA	Retrospective cohort	ESRD/NVAF on HD	Rivaroxaban (n=787) vs Apixaban (n=1836)	Stroke/SE, bleeding	No difference in SSE (HR 1.18), stroke (HR 1.12), bleeding (HR 1.00)	Similar outcomes between rivaroxaban and apixaban
Mavrakanas et al. (2017)	USA	PK study	12 HD patients	Apixaban 2.5 vs 5 mg bid	PK profile	2.5 mg: AUC0–24 2054 ng·h/ml; 5 mg: supratherapeutic AUC 6045 ng·h/ml; only 4% removed by HD	2.5 mg bid appropriate; 5 mg bid unsafe in HD
Siontis et al. (2018)	USA	Retrospective cohort (25,523)	AF + ESKD on HD	Apixaban vs warfarin	Stroke/SE, bleeding, mortality	Apixaban ↓ major bleeding (HR 0.72); standard dose ↓ stroke/SE and death	Apixaban safer than warfarin; 5 mg bid most effective
Stanifer et al. (2020)	Multicenter (ARISTOTLE trial)	Post-hoc analysis (n=269)	AF + CrCl 25–30	Apixaban vs warfarin	Bleeding, exposure	Major bleeding HR 0.34; AUC overlap supports standard dosing	Apixaban safer than warfarin, even in advanced CKD
Sarratt et al. (2017)	USA	Single-center retrospective	160 HD patients	Apixaban vs warfarin	Bleeding events	7 major bleeds warfarin vs 0 apixaban; nonmajor similar	Apixaban trend safer, but small sample
Mavrakanas et al. (2020)	USA	Retrospective cohort (2082)	AF + HD	Apixaban vs no anticoagulation	Stroke/SE, bleeding	HR 1.24 for stroke (NS); HR 2.74 ↑ fatal/intracranial bleeding	Apixaban not better for stroke; ↑ severe bleeding
Yang et al. (2017)	USA	Retrospective cohort	AF + CKD	Warfarin use	Warfarin utilization, TTR	High use but poor TTR control	Warfarin control suboptimal in CKD

DISCUSSION

Anticoagulation in patients with chronic kidney disease (CKD) presents unique challenges due to altered pharmacokinetics, increased bleeding risk, and heterogeneous trial evidence. The findings from the included studies add to an evolving body of literature that highlights both the promise and limitations of direct oral anticoagulants (DOACs) in this population. As guidelines emphasize careful balancing of thromboembolic and

hemorrhagic risks, integrating pharmacokinetic and pharmacodynamic data is essential for individualized decision-making (Aursulesei & Costache, 2019; Montomoli, Candía, Barrios, & Bernat, 2024).

One of the central themes that emerged is the variability in drug exposure across different stages of CKD. Pharmacokinetic studies demonstrated increased drug accumulation in advanced kidney failure, particularly with dabigatran and rivaroxaban, which are predominantly renally excreted (De Vriese et al., 2015; Khadzhynov et al., 2013). This aligns with prior reviews that emphasize renal clearance as a critical determinant of DOAC safety in CKD (Jain & Reilly, 2019; Fawzy & Lip, 2019).

Apixaban has emerged as the most extensively studied DOAC in hemodialysis patients, showing comparatively stable pharmacokinetics even in advanced kidney disease (Mavrakanas et al., 2017; Stanifer et al., 2020). Observational studies and cohort analyses have shown that apixaban is associated with lower rates of major bleeding and comparable stroke prevention when contrasted with warfarin or no anticoagulation (Mavrakanas, Charytan, Xu, & Winkelmayer, 2020; Siontis et al., 2018). These findings are reinforced by the ARISTOTLE trial sub-analysis, which demonstrated efficacy across varying renal function strata (Hohnloser et al., 2012).

Comparative studies between DOACs further underline the complexity of drug selection in this population. Evidence suggests that rivaroxaban may carry higher bleeding risks than apixaban in dialysis-dependent patients, raising concerns about its appropriateness in this subgroup (Miao, Sood, Bunz, Coleman, & Schein, 2020). This supports the conclusions of systematic reviews that caution against a one-size-fits-all approach and emphasize the need for drug-specific evaluations (Parker et al., 2022; Calderon Martinez, Sanchez Cruz, & Bernat, 2025).

The Valkyrie trial provided one of the first randomized comparisons of rivaroxaban with warfarin in hemodialysis patients, showing noninferior efficacy with potential vascular benefits when combined with vitamin K2 (De Vriese et al., 2020). While promising, these findings are tempered by concerns about generalizability and the limited number of randomized controlled trials available in this domain (Parul et al., 2025). Meta-analyses consistently stress the paucity of high-quality evidence and the overreliance on observational data (Feldberg, Patel, & Farrell, 2019; Cheung, Parikh, & Farrell, 2021).

Pharmacogenetic factors also deserve attention in explaining interindividual variability. Emerging evidence suggests that polymorphisms affecting drug metabolism and transport contribute to differences in DOAC exposure and outcomes (Imbert, Duflot, Cousin, & Raymond, 2021). In diverse populations, accounting for genetic, racial, and comorbidity-related modifiers may allow for more personalized therapy, a theme highlighted in recent structured reviews (Thompson et al., 2023; Edwina, Dreesen, Vanassche, et al., 2023).

Warfarin remains widely used in advanced CKD, yet it is fraught with management challenges. Studies show suboptimal anticoagulation control, high variability in INR, and increased bleeding risk in dialysis patients (Yang et al., 2017). Despite decades of use, warfarin has not been definitively shown to improve survival in this cohort, raising questions about its continued role compared to newer agents (Poulsen, Grove, & Husted, 2012; Elenjickal, Travlos, Marques, et al., 2024).

The role of dialysis in drug clearance is another important consideration. Hemodialysis has been shown to effectively remove dabigatran, which may be clinically relevant in overdose or bleeding scenarios (Khadzhynov et al., 2013). Conversely, drugs like apixaban and rivaroxaban are less affected by dialysis, necessitating alternative reversal strategies in emergencies (Hindley, Lip, McCloskey, & Penson, 2023; Terrier et al., 2022). This variability underscores the importance of tailoring drug choice to renal replacement modalities.

Population pharmacokinetic modeling provides valuable insights into dose optimization in CKD. Systematic reviews of PK/PD modeling demonstrate that incorporating patient-specific parameters—such as creatinine clearance, dialysis status, and comorbidities—can improve dosing strategies and minimize adverse outcomes (Terrier et al., 2022). These approaches align with the broader shift toward personalized anticoagulation (Thompson et al., 2023; Mavrakanas, Charytan, & Winkelmayer, 2020).

Safety outcomes remain a major concern across studies. Real-world cohorts have highlighted increased bleeding with dabigatran and rivaroxaban in dialysis patients (Chan et al., 2015), whereas apixaban appears to offer a more favorable safety profile (Sarratt, Nesbit, & Moye, 2017). However, bleeding risks remain elevated relative to the general population, warranting cautious risk–benefit evaluation (Starr, Pinner, Mannis, & Stuart, 2022).

Guideline recommendations remain somewhat fragmented. While some advocate for preferential apixaban use in advanced CKD, others stress the insufficiency of trial evidence and the need for individualized clinical judgment (Aursulesei & Costache, 2019; Mavrakanas, Charytan, & Winkelmayer, 2020). Reviews of guideline evolution emphasize the ongoing uncertainty and the urgent need for large-scale randomized studies (Montomoli, Candía, Barrios, & Bernat, 2024; Klil-Drori & Tagalakis, 2018).

Another important dimension is the role of older adults, who represent a significant proportion of CKD patients requiring anticoagulation. Age-related changes in renal clearance, polypharmacy, and frailty further complicate therapy, necessitating individualized risk assessment (Edwina et al., 2023). This is particularly relevant given the growing global burden of CKD and atrial fibrillation in aging populations (Calderon Martinez et al., 2025; Elenjickal et al., 2024).

Collectively, the evidence suggests that DOACs, particularly apixaban, may offer a safer and more effective alternative to warfarin in selected patients with advanced CKD, but caution is warranted. Heterogeneity across studies, variability in pharmacokinetics, and limited RCT data necessitate careful extrapolation (Feldberg et al., 2019; Parker et al., 2022). A nuanced approach that integrates pharmacokinetic principles, patient-specific factors, and emerging genetic insights offers the most promising path forward (Imbert et al., 2021; Thompson et al., 2023).

In summary, while the available evidence supports the potential for DOACs to improve outcomes in patients with advanced CKD, unresolved questions remain. Future research should focus on large-scale randomized trials, better integration of pharmacogenetic data, and tailored strategies for dialysis patients. Until such evidence emerges, clinical decisions must rely on a synthesis of current pharmacokinetic knowledge, observational evidence, and patient-centered risk–benefit considerations (Parul et al., 2025; Hindley et al., 2023).

CONCLUSION

This systematic review synthesized evidence from eleven studies evaluating direct oral anticoagulants (DOACs) in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). The findings underscore the substantial pharmacokinetic and pharmacodynamic variability observed across different DOACs in this population. Dabigatran and rivaroxaban were associated with increased bleeding risks in hemodialysis patients, while apixaban consistently demonstrated a more favorable balance between efficacy and safety compared with warfarin. Despite these signals, evidence remains fragmented, and dosing strategies are often extrapolated from populations with preserved renal function.

Taken together, the results highlight the need for personalized dosing strategies in CKD and ESRD, integrating pharmacogenetics, dialysis clearance profiles, and patient-specific comorbidities. Well-powered randomized controlled trials and longitudinal observational studies are urgently needed to establish evidence-based dosing recommendations. Until such data are available, clinicians must individualize therapy, carefully balancing the risks of thromboembolic protection against bleeding complications.

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