Journal of Translational Critical Care Medicine **2026** vol. 8(1) | e00013
DOI: 10.1097/JTCCM-D-23-00013

Review Article

Anticoagulant Strategies in Atrial Fibrillation and Chronic Kidney Disease: From Pathophysiology to Clinical Practice

Luca Di Lullo[1*], Aldo Franculli[1], Pasquale Saporito[1], Andrea Dello Strologo[1], Laura Pedata[1], Vincenzo Barbera[2], Lorenzo D'Elia[2], Antonio Bellasi[3] and Paola Peverini[1]

[1]*Department of Nephrology and Dialysis, Nuovo Ospedale dei Castelli, Ariccia, Rome, Italy;* [2]*Department of Nephrology and Dialysis, Ospedale L. Parodi Delfino, Colleferro, Rome, Italy;* [3]*Service of Nephrology, Ospedale Regionale Di Lugano, Lugano, Ticino, Switzerland*

Received: November 17, 2023 | **Revised:** January 16, 2026 | **Accepted:** January 28, 2026 | **Published online:** March 30, 2026

Abstract

Atrial fibrillation and chronic kidney disease (CKD) frequently coexist, increasing thromboembolic and bleeding risks. This is a narrative review of pathophysiology and clinical evidence for anticoagulation strategies in CKD patients. Direct oral anticoagulants are preferred in CKD stages 1–4. Recent data suggest that the efficacy of apixaban and rivaroxaban is comparable to that of warfarin in end-stage renal disease. In advanced CKD, anticoagulation should be tailored with close monitoring.

Introduction

Definitions and classification of chronic kidney disease (CKD)

CKD is defined by the Kidney Disease: Improving Global Outcomes guidelines as abnormalities of the kidney structure or function persisting for more than 3 months.[1] The classification system incorporates the two key dimensions of estimated glomerular filtration rate (eGFR) and degree of albuminuria, providing a comprehensive framework for disease staging and prognosis (Table 1). In clinical practice, eGFR calculated from serum creatinine concentration and albuminuria assessment is the most commonly employed diagnostic tool.[2] Progressive decline through CKD stages G1-G5 (eGFR categories from > 90 to < 15 mL/min/1.73 m^2) reflects worsening clinical status, with patients reaching end-stage renal disease (ESRD; G5) potentially requiring renal-replacement therapy through dialysis or kidney transplantation.[1]

The bidirectional relationship between atrial fibrillation (AF) and CKD

The coexistence of AF and CKD is more than a simple comorbidity. These conditions share a bidirectional pathophysiological relationship that amplifies cardiovascular risk.[3] Approximately 50% of patients with AF demonstrate some degree of renal impairment, while one in five patients with CKD experience symptomatic AF.[4] This bidirectional association manifests through multiple mechanisms: kidney dysfunction increases AF incidence through electrolyte disturbances, volume overload, and neurohormonal activation, while AF accelerates CKD progression through hemodynamic instability and reduced renal perfusion.[3] Prospective studies have demonstrated that incident AF confers a threefold-increased risk of progression to ESRD during follow-up periods averaging 5.9 years.[5] The interconnection between these conditions extends beyond mere association because they share common risk factors, including advanced age, hypertension, diabetes mellitus, heart failure, obesity, and cardiovascular disease, supporting the hypothesis of shared abnormal molecular signaling pathways contributing to their pathogenesis.[4]

Impact on mortality and cardiovascular outcomes

The combined burden of CKD and AF substantially elevates the risks of ischemic stroke, bleeding complications, and mortality.[2]

Table 1. CKD stage according to GFR

GFR category	GFR (mL/min per 1.73 m^2)	Terms
G1	≥ 90	Normal to high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure or ESRD

CKD, chronic kidney disease; GFR, glomerular filtration rate; ESRD, end-stage renal disease.

Keywords: Chronic kidney disease; Anticoagulation; Apixaban; Rivaroxaban; Atrial fibrillation; Direct oral anticoagulants.

[*]**Correspondence to:** Di Lullo Luca, Department of Nephrology and Dialysis, Nuovo Ospedale dei Castelli, Via Nettunense Km 11/5, Ariccia 00040, Rome, Italy. ORCID: https://orcid.org/0000-0001-8285-5448. E-mail: dilulloluca69@gmail.com

How to cite this article: Di Lullo L, Franculli A, Saporito P, Strologo AD, Pedata L, Barbera V, *et al*. Anticoagulant Strategies in Atrial Fibrillation and Chronic Kidney Disease: From Pathophysiology to Clinical Practice. *J Transl Crit Care Med* 2026; 8(1):e00013. doi: 10.1097/JTCCM-D-23-00013.

© 2026 The Author(s). This article has been published under the terms of Creative Commons Attribution-Noncommercial 4.0 International License (CC BY-NC 4.0), which permits noncommercial unrestricted use, distribution, and reproduction in any medium, provided that the following statement is provided. "This article has been published in *Journal of Translational Critical Care Medicine* at https://doi.org/10.1097/JTCCM-D-23-00013 and can also be viewed on the Journal's website at https://www.xiahepublishing.com/journal/jtccm".

An inverse relationship exists between eGFR and adjusted hazard ratios (HRs) for all-cause mortality: patients with eGFR < 15 mL/min/1.73 m^2 face a nearly sixfold-increased mortality risk compared to those with eGFR > 60 mL/min/1.73 m^2.[6] In comprehensive systematic analyses, AF was found to be associated with a 46% higher risk of all-cause mortality.[7] The presence of both conditions creates a vicious cycle: CKD-related uremic milieu, platelet dysfunction, endothelial damage, and inflammation predispose to AF, while AF-induced hemodynamic compromise and reduced cardiac output impair renal perfusion, accelerating renal-function decline.[8] This bidirectional pathophysiology necessitates integrated management approaches that address both cardiac-rhythm control and renal-function preservation.

Age-related considerations and global epidemiology

Both AF and CKD predominantly affect elderly populations, with their prevalence increasing proportionally with advancing age.[9] The worldwide prevalence of CKD ranges from 8% to 16%, escalating dramatically to 23.4–35.8% in individuals beyond 64 years of age.[10] Similarly, AF prevalence rises progressively with age, with several studies demonstrating directly proportional correlations between age and CKD prevalence.[11] This demographic overlap has profound clinical implications as the global population ages, projecting substantial increases in the number of patients requiring complex management for concurrent AF and CKD. Elderly people with these conditions typically present with multiple comorbidities, polypharmacy, and increased frailty, further complicating anticoagulation decisions and necessitating individualized risk-benefit assessments.[12]

Pathophysiological mechanisms: Coagulation dysfunction in CKD and AF

The coagulation paradox in CKD

Patients with CKD, particularly those with an advanced stage of the disease, exhibit a paradoxical hemostatic state characterized by simultaneous prothrombotic and hemorrhagic tendencies.[2] This complex coagulation imbalance stems from multiple interconnected mechanisms that disrupt normal hemostatic equilibrium. Uremia-induced platelet dysfunction is a primary contributor to bleeding risk, manifesting through impaired platelet adhesion, aggregation, and release reactions.[13] Concurrently, patients with CKD demonstrate a hypercoagulable state driven by elevated levels of procoagulant factors (fibrinogen, factor VIII, and von Willebrand factor), reduced natural anticoagulant proteins (protein C, protein S, and antithrombin), and endothelial dysfunction with impaired nitric-oxide production.[2] The accumulation of uremic toxins further amplifies this imbalance by inducing chronic inflammation, oxidative stress, and vascular calcification, creating an environment that simultaneously predisposes to both thrombosis and bleeding.[9]

Inflammatory and endothelial dysfunction in the AF-CKD axis

Chronic low-grade systemic inflammation is a central pathophysiological mechanism linking AF and CKD.[2] CKD-associated inflammation manifests through elevated levels of pro-inflammatory cytokines (interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α], and C-reactive protein) that promote atrial structural and electrical remodeling, creating a substrate for AF initiation and maintenance.[14] Endothelial dysfunction, characterized by impaired nitric-oxide signaling, increased endothelin-1 production, and activation of the renin-angiotensin-aldosterone system (RAAS), contributes to atrial fibrosis and progressive kidney damage.[15] Studies have documented elevated levels of circulating endothelial/platelet microparticles in patients with AF and progressive renal dysfunction, demonstrating a significant correlation with declining eGFR ($P < 0.001$) and CKD stage progression.[8] This endothelial activation perpetuates a vicious cycle: renal dysfunction exacerbates endothelial damage through uremic-toxin accumulation, while endothelial dysfunction promotes further renal injury through microvascular dysfunction and impaired autoregulation.

Neurohormonal and hemodynamic contributions

RAAS activation plays a pivotal role in the pathophysiology of both AF and CKD progression.[15] In CKD, compensatory RAAS upregulation initially maintains glomerular filtration through efferent arteriolar vasoconstriction but subsequently drives intraglomerular hypertension, proteinuria, and progressive fibrosis.[16] Aldosterone excess promotes atrial fibrosis, ion channel remodeling, and electrical instability, predisposing to AF development.[17] Hemodynamic factors further contribute to this pathophysiological cascade: AF-related loss of atrial contraction and irregular ventricular response compromise cardiac output by 15–25%, reducing renal-perfusion pressure and activating compensatory mechanisms that paradoxically accelerate kidney damage.[3] Volume overload in CKD increases atrial stretch, promoting electrical remodeling and triggered activity through mechanosensitive ion channel activation.[4] This complex interplay of neurohormonal activation and hemodynamic compromise creates a self-perpetuating cycle that accelerates both AF progression and renal-function decline.

Mineral and bone disorder: impact on cardiovascular calcification

CKD-mineral and bone disorder is a unique pathophysiological link between kidney disease and cardiovascular complications.[18] Hyperphosphatemia, hyperparathyroidism, and vitamin D and Klotho deficiency characterize advanced CKD, promoting vascular calcification through multiple mechanisms, including the transformation of vascular smooth muscle cells into osteoblast-like cells.[18] This calcification process particularly affects the cardiac valves and coronary arteries, increasing stroke risk in patients with AF and complicating anticoagulation management.[19] Warfarin therapy paradoxically accelerates vascular calcification by inhibiting vitamin K–dependent matrix Gla protein, a critical inhibitor of vascular calcification, raising concerns about its use in advanced CKD.[20] There is emerging evidence that direct oral anticoagulants (DOACs) may offer advantages in this context by avoiding vitamin K antagonism, although definitive comparative studies remain limited.[1]

Pharmacology of anticoagulants: Mechanisms, pharmacokinetics, and renal considerations

Molecular mechanisms of DOACs: direct thrombin and factor Xa inhibition

The use of DOACs represents a paradigm shift in anticoagulation therapy through their targeted inhibition of specific coagulation cascade components.[21] Dabigatran functions as a selective, competitive, direct thrombin (factor IIa) inhibitor, blocking the final common pathway of coagulation and preventing fibrin formation.[22] In contrast, rivaroxaban, apixaban, and edoxaban act as direct factor Xa inhibitors, interrupting coagulation at an ear-

lier step, where both intrinsic and extrinsic pathways converge.[22] These agents demonstrate relatively short half-lives (5–17 h, depending on the specific DOAC and renal-function level), achieve peak plasma concentrations within 1–4 h after administration, and exhibit predictable pharmacodynamic responses without requiring routine laboratory monitoring.[23] The molecular selectivity of DOACs confers advantages over warfarin, which nonspecifically inhibits multiple vitamin K-dependent clotting factors (II, VII, IX, and X) and anticoagulant proteins (proteins C and S), resulting in variable anticoagulant effects and necessitating frequent International Normalized Ratio (INR) monitoring.[21]

Pharmacokinetics and renal-elimination pathways

The pharmacokinetic profiles of DOACs demonstrate critical differences in renal elimination that directly impact their use in patients with CKD.[24] Dabigatran exhibits the highest renal clearance (approximately 80%), necessitating significant dose adjustments or contraindications in advanced CKD.[25] Edoxaban demonstrates approximately 50% renal elimination, rivaroxaban approximately 33%, and apixaban 27% (the lowest), making apixaban theoretically the most favorable option for patients with severe renal impairment.[26] These agents also undergo varying degrees of hepatobiliary elimination and metabolism *via* cytochrome P450 enzymes (primarily CYP3A4) and P-glycoprotein (P-gp) transporter systems.[27] In patients with declining renal function, accumulation of the parent drug and active metabolites increases the anticoagulant effect and bleeding risk, necessitating dose adjustments based on creatinine clearance (CrCl) thresholds specific to each DOAC.[25] Pharmacokinetic studies have demonstrated that even in patients with severe renal impairment (CrCl < 30 mL/min), dose-adjusted apixaban and rivaroxaban maintain the therapeutic-drug levels within acceptable ranges, although individual variability remains substantial.[26]

Calculating renal function for DOAC dosing: importance of the Cockcroft-Gault formula

Accurate assessment of renal function is a critical prerequisite for safe DOAC prescribing in patients with CKD.[25] While multiple equations for calculating eGFR exist (including Modification of Diet in Renal Disease [MDRD] and CKD Epidemiology Collaboration [CKD-EPI]), the Cockcroft-Gault formula calculating CrCl using actual body weight was employed in all pivotal DOAC registration trials and remains the recommended method for DOAC dosing decisions.[28] This distinction carries significant clinical implications: the CKD-EPI and MDRD equations, which provide eGFR normalized to body surface area, often overestimate renal function compared to Cockcroft-Gault CrCl, potentially leading to inappropriate DOAC dosing and increased bleeding risk.[29] For example, a 75-year-old female weighing 50 kg with 1.2 mg/dL serum creatinine would have a CrCl (Cockcroft-Gault) of approximately 35 mL/min but an eGFR (CKD-EPI) of approximately 48 mL/min—a difference that could alter dose recommendations.[25] Regular monitoring of renal function remains essential, with experts recommending monitoring frequency (in months), calculated as CrCl divided by 10 (*e.g.*, for CrCl 40 mL/min, recheck every 4 months).[30]

Drug-drug interactions and P-gp modulation

DOACs demonstrate clinically significant interactions with medications affecting P-gp transport and CYP3A4 metabolism, which are particularly relevant in patients with CKD who typically receive multiple concurrent medications.[31] Strong dual inhibitors of both P-gp and CYP3A4 (including azole antifungals, human immunodeficiency virus [HIV] protease inhibitors, and dronedarone) substantially increase DOAC plasma levels, amplifying bleeding risk and necessitating dose reduction or alternative anticoagulation strategies.[32] Conversely, strong inducers (including rifampin, carbamazepine, phenytoin, and St. John's Wort) accelerate DOAC metabolism and elimination, potentially resulting in subtherapeutic anticoagulation and increased thrombotic risk.[33] Commonly prescribed medications for patients with CKD warrant particular attention: amiodarone and verapamil increase dabigatran levels through P-gp inhibition, clarithromycin and erythromycin increase rivaroxaban and apixaban exposure, and nonsteroidal anti-inflammatory drugs confer additive bleeding risk through antiplatelet effects.[34] Recent pharmacokinetic studies have demonstrated that even commonly prescribed statins (particularly atorvastatin and simvastatin, both CYP3A4 substrates) may modestly increase apixaban and rivaroxaban levels, although clinical significance remains unclear.[35] Systematic medication reviews at initiation and during DOAC therapy are essential safety measures for patients with CKD.[36]

Anticoagulation in CKD stages 1–4: Evidence, dosing, and comparative effectiveness

Evidence from pivotal trials: DOAC superiority in mild–moderate CKD

The landmark randomized controlled trials establishing DOAC efficacy in AF (RE-LY for dabigatran, ROCKET-AF for rivaroxaban, ARISTOTLE for apixaban, and ENGAGE AF-TIMI 48 for edoxaban) demonstrated non-inferiority or superiority compared to warfarin for stroke prevention, with prespecified subgroup analyses evaluating outcomes across renal-function strata.[37] In the collective evidence obtained from patients with CKD stages 1–3 (eGFR > 30 mL/min) in these trials, the use of DOACs showed a 19% reduction in stroke/systemic-embolism risk, a 51% reduction in hemorrhagic-stroke incidence, a 10% reduction in all-cause mortality, a 14% reduction in major bleeding cases, and a 52% reduction in intracranial-hemorrhage occurrence compared to warfarin.[38] Meta-analyses incorporating data from over 16,000 patients with CKD confirmed that these benefits extend consistently across CKD stages 1–3, with some analyses suggesting enhanced relative-risk reduction in patients with moderate renal impairment (eGFR 30–49 mL/min) compared to those with preserved renal function.[39] The safety advantages of DOACs appeared particularly pronounced for intracranial bleeding, with HRs decreasing progressively with declining renal function (a 6.2% decrease in HR per 10 mL/min decrease in CrCl), suggesting potential enhanced benefit-risk profiles in moderate CKD.[39]

Comparative effectiveness of individual DOACs in CKD

Direct head-to-head comparisons of DOACs in CKD populations are limited, with most of the existing evidence derived from network meta-analyses and real-world observational studies.[40] Among the four available DOACs, apixaban demonstrated the most favorable pharmacokinetic profile for advanced CKD due to its minimal renal-elimination rate (27%), with approval for use down to CrCl 15 mL/min in some jurisdictions.[41] The results of network meta-analyses evaluating comparative effectiveness across CKD stages suggest that apixaban and edoxaban rank highest for reducing stroke/systemic-embolism risk, while apixaban demonstrates a superior safety profile, with the lowest rates of major bleeding across all

Table 2. Dose selection criteria for DOACs

CrCl	Dabigatran	Rivaroxaban	Edoxaban	Apixaban
90 mL/min; 50 mL/min	150 mg BID; 110 mg BID[a]	20 mg	60mg[b]	5 mg BID
30 mL/min	110 mg BID[*]	15 mg	30 mg	2.5 mg BID[c]
15 mL/min	X	15 mg[*]	30 mg[*]	2.5 mg BID[*]
Dialysis	Contraindicated as per SmPCs; Limited data available for outcome; Multidisciplinary, individualized approach; Off-label situation			

[a]A 110 mg BID dose may be considered in patients with a high bleeding risk, in accordance with the SmPC. [b]Additional dose-reduction criteria may apply, including body weight ≤ 60 kg or concomitant therapy with potent P-gp inhibitors. For edoxaban, the EMA recommends use in patients with high creatinine clearance only after careful evaluation of the individual thromboembolic and bleeding risks. [c]Apixaban 2.5 mg twice daily should be used when at least two of the following criteria are present: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 µmol/L). [*]Situations requiring cautious use of the drug. BID, twice daily; CrCl, creatinine clearance; DOACs, direct oral anticoagulants; EMA, European Medicines Agency; P-gp, P-glycoprotein; SmPC, Summary of Product Characteristics.

CKD stages.[37] Rivaroxaban, despite a mere 33% renal-elimination rate, has shown effectiveness in patients with CKD stage 4 (eGFR 15–29 mL/min) in real-world studies, with reduced major bleeding compared to warfarin.[42] Dabigatran, with an 80% renal-elimination rate, generally requires avoidance in CKD stages 4–5 due to substantial drug accumulation and elevated bleeding risk, although a reduced 75 mg twice-daily dose received US Food and Drug Administration (FDA) approval based on pharmacokinetic modeling for CrCl 15–30 mL/min (not approved in Europe).[25] The results of comparative-effectiveness studies in CKD stages 3–4 suggest that apixaban and rivaroxaban demonstrate similar efficacy levels, but apixaban may offer modest safety advantages, with 20–30% lower major bleeding rates.[19]

Dose adjustments and regulatory guidance across CKD stages

Dose adjustment recommendations for DOACs vary by agent and differ between regulatory authorities (FDA *vs.* European Medicines Agency), creating potential confusion in clinical practice (Table 2).[43] For apixaban, the standard dosing is 5 mg twice daily, with a reduction to 2.5 mg twice daily recommended when two or more of the following criteria are met: age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine ≥ 1.5 mg/dL (≥133 µmol/L).[25] Notably, CrCl 15–29 mL/min alone mandates dose reduction to 2.5 mg twice daily regardless of other factors.[26] The rivaroxaban standard dosing of 20 mg once daily requires a reduction to 15 mg once daily for CrCl 15–49 mL/min in patients with AF, while edoxaban 60 mg once daily requires a reduction to 30 mg once daily for CrCl 15–50 mL/min, body weight ≤ 60 kg, or concomitant P-gp inhibitors.[44] Dabigatran dosing varies substantially between regions: FDA approved 75 mg twice daily for CrCl 15–30 mL/min based solely on pharmacokinetic data, while European guidelines contraindicate dabigatran for CrCl < 30 mL/min due to safety concerns.[25] Real-world studies have revealed concerning rates of inappropriate DOAC dosing (both under- and over-dosing), approaching 25–50% in CKD populations, emphasizing the need for improved clinician education and decision support tools.[45]

Monitoring requirements: renal-function and coagulation parameters

While DOACs do not require routine coagulation monitoring for dose titration, systematic assessment of renal function is a critical safety measure, particularly because renal function may fluctuate due to acute illness, volume depletion, or medication changes.[12] Evidence-based guidelines recommend baseline renal-function assessment before DOAC initiation, with the subsequent monitoring frequency tailored to CKD stage and clinical stability.[43] There is expert consensus that annual monitoring suffices for CrCl > 60 mL/min, with increasing frequency as renal function declines: every 6 months for CrCl 30–60 mL/min, every 3–4 months for CrCl 15–30 mL/min, and monthly to quarterly for dialysis patients.[29] The practical formula for monitoring frequency (frequency in months = CrCl/10) provides individualized guidance (*e.g.*, CrCl 40 mL/min warrants monitoring every 4 months).[30] Beyond renal function, assessment of hemoglobin, hepatic function, and clinical signs of bleeding or thrombosis should occur at each monitoring visit.[46] While routine measurement of DOAC drug levels or anti-Xa activity is not recommended for standard management, specific clinical scenarios may warrant testing, including suspected overdose, urgent surgery, active bleeding, thrombosis despite anticoagulation, or concerns about medication adherence.[47]

Advanced CKD and ESRD: Evidence, controversies, and emerging strategies

The evidence gap: Why patients with ESRD were excluded from pivotal trials

Patients with severe CKD (CrCl < 25–30 mL/min) and those requiring dialysis were systematically excluded from the pivotal DOAC registration trials, creating a substantial evidence gap for this high-risk population.[48] This exclusion stemmed from multiple concerns: unpredictable pharmacokinetics due to severely impaired renal elimination, elevated baseline bleeding risk from uremic-platelet dysfunction, concern for drug accumulation given prolonged half-lives in advanced renal failure, and ethical considerations regarding the benefit-risk balance in a population already experiencing high mortality.[49] Consequently, FDA and European Medicines Agency regulatory approvals for DOACs explicitly excluded or provided limited guidance for ESRD/dialysis populations, with most labels contraindicating use or stating "not recommended" for patients with CrCl < 15 mL/min.[50] Notable exceptions include FDA labeling for apixaban (5 mg twice daily can be used in patients with ESRD, including hemodialysis) and rivaroxaban (15 mg once daily can be considered, albeit with limited clinical data), while European labels remain more conservative.[51] This regulatory discrepancy reflects the paucity of prospective data and the reliance on pharmacokinetic modeling rather than clinical-outcome evidence.[50]

Concerns with warfarin in ESRD: Bleeding risk and vascular calcification

Despite being the traditional anticoagulant of choice for patients

with ESRD, warfarin use in this population is associated with significant concerns regarding both safety and mechanism-mediated toxicity.[20] Observational studies have demonstrated that warfarin significantly increases bleeding risk as CrCl declines, with HRs for major bleeding approaching twofold to threefold in patients with ESRD compared to patients with preserved renal function.[52] More concerning, warfarin induces vascular calcification through inhibition of matrix Gla protein, a vitamin K-dependent inhibitor of vascular calcification, potentially accelerating cardiovascular-disease progression in a population already burdened by CKD-mineral and bone disorder.[20] This warfarin-associated arteriopathy manifests as progressive calcification of the arterial media and intima, contributing to arterial stiffness, left ventricular hypertrophy, and increased cardiovascular mortality.[18] In extreme cases, warfarin can precipitate calciphylaxis (calcific uremic arteriolopathy), a rare but often fatal condition characterized by painful skin necrosis resulting from calcification and thrombosis of dermal arterioles.[51] Despite these concerns, observational studies evaluating the efficacy of warfarin versus no anticoagulation in patients with dialysis and AF have yielded conflicting results: some suggest a modest reduction in stroke risk with warfarin, others demonstrate no benefit or even increased harm, and nearly all show elevated bleeding risk.[52] This equipoise regarding warfarin's benefit-risk balance in ESRD has motivated the investigation of DOACs as potentially safer alternatives.

Randomized evidence in ESRD: The AXADIA-AFNET 8, RENAL-AF, and Valkyrie trials

Three landmark randomized controlled trials discussed in articles published in 2020–2023 have substantially advanced the evidence base for anticoagulation in ESRD patients with AF.[19] The AXADIA-AFNET 8 trial randomized 97 patients with AF undergoing chronic hemodialysis to apixaban 2.5 mg twice daily versus phenprocoumon (a vitamin K antagonist); apixaban did not meet the prespecified non-inferiority criteria for the composite safety/efficacy endpoint (International Society on Thrombosis and Haemostasis major bleeding or all-cause mortality), with similar rates between groups, but the trial was underpowered.[19] The RENAL-AF trial, which was prematurely terminated due to slow enrollment, compared apixaban (2.5 mg or 5 mg twice daily per FDA labeling) and warfarin in 154 patients undergoing hemodialysis. The major bleeding rates were numerically similar (apixaban 10% *vs.* warfarin 11%), although the cardiovascular mortality rate was unexpectedly higher with apixaban (apixaban 19% *vs.* warfarin 11%, HR 1.75, 95% confidence interval [CI]: 0.62–4.94).[19] The Valkyrie trial had more promising results. This three-arm study randomized 132 hemodialysis patients with AF to rivaroxaban 10 mg once daily, rivaroxaban 10 mg plus vitamin K2 supplementation, or warfarin and found significantly lower composite cardiovascular events and major bleeding with rivaroxaban compared to warfarin (HR 0.47, 95% CI: 0.24–0.93, $P = 0.03$).[19] Notably, vitamin K2 co-administration did not provide additional benefits beyond rivaroxaban alone.[19]

Meta-analyses of ESRD trials: Synthesizing the evidence

Two meta-analyses presented at the 2023 European Society of Cardiology Congress synthesized the randomized evidence obtained from the AXADIA-AFNET 8, RENAL-AF, and Valkyrie trials, encompassing approximately 380 patients with ESRD undergoing chronic hemodialysis.[19] They had concordant conclusions: there were no significant differences between DOACs (apixaban or rivaroxaban) and warfarin for cardiovascular mortality, all-cause mortality, ischemic stroke, or major/life-threatening bleeding.[19] The pooled estimates suggested that DOACs were at least as safe and effective as warfarin, although the CIs remained wide due to limited sample sizes and event rates.[19] Importantly, these meta-analyses highlighted the fact that despite anticoagulation with either DOACs or warfarin, patients with ESRD and AF retain a substantially elevated risk for adverse outcomes: annual rates of major bleeding approached 8–12%, stroke rates 2–4%, and all-cause mortality 15–25%, underscoring the high baseline risk in this population regardless of the anticoagulation strategy used.[19] These findings support the conclusion that DOACs are reasonable alternatives to warfarin in ESRD, potentially offering practical advantages (no INR monitoring and fewer drug interactions) without compromising safety or efficacy, although neither approach eliminates the substantial residual risk inherent in this vulnerable population.

Renal preservation and DOAC selection: Optimizing outcomes

Nephroprotective effects of DOACs: Beyond anticoagulation

There is emerging evidence that DOACs, particularly factor Xa inhibitors, may confer nephroprotective benefits beyond anticoagulant effects, contrasting with warfarin's potential to accelerate CKD progression.[1] Large observational cohorts have demonstrated that DOAC use is associated with lower rates of acute kidney injury, reduced incidence of CKD development, and slower eGFR decline compared to warfarin treatment.[53] Mechanistic studies have proposed several pathways through which DOACs may preserve renal function: reduction of renal microthrombi formation and ischemic injury, decreased glomerular endothelial activation and inflammation, mitigation of prothrombotic uremic milieu without inducing vascular calcification (which occurs with warfarin), and preservation of renal microcirculatory perfusion.[1] The XARENO registry, a prospective observational study of patients with AF and advanced CKD (CrCl 15–49 mL/min), demonstrated that rivaroxaban is associated with a 38% reduction in composite adverse kidney outcomes (eGFR decline to < 15 mL/min/1.73 m^2, need for dialysis, or acute kidney injury) compared to warfarin (HR 0.62, 95% CI: 0.43–0.88) over 2.1-year follow-up.[42] Similarly, the results of a large Korean national cohort data encompassing over 20,000 patients with AF showed that rivaroxaban conferred a 61% lower risk of kidney failure (defined as dialysis initiation or transplantation) compared to warfarin, with particular benefits in patients with baseline eGFR ≤ 60 mL/min (HR 0.389, 95% CI: 0.300–0.499).[42]

Rivaroxaban: Specific evidence for renal outcomes

Among DOACs, rivaroxaban has accumulated the most robust evidence for renal-preservation benefits, supported by data from mechanistic studies and large-scale clinical outcomes.[42] Pharmacokinetic studies have demonstrated that despite a mere 33% renal-elimination rate, rivaroxaban maintains favorable clearance characteristics even in severe renal impairment (CrCl 15–29 mL/min), with modest increases in drug exposure manageable through dose reduction to 15 mg once daily.[26] The nephroprotective mechanisms of rivaroxaban appear multifactorial: inhibition of factor Xa reduces protease-activated receptor signaling in the renal endothelium, potentially mitigating inflammation and fibrosis; prevention of fibrin deposition in glomerular capillaries preserves microvascular perfusion; and avoidance of vitamin K antagonism preserves

matrix Gla protein function, preventing vascular calcification.[1] Clinical evidence of particularly striking renal benefits was obtained from the XARENO study: among patients with severe renal impairment (CrCl < 30 mL/min) at baseline (comprising 20.8% of the cohort), rivaroxaban reduced adverse kidney outcomes by 38%, higher compared to warfarin, with an additional 24% reduction in all-cause mortality (HR 0.76, 95% CI: 0.59–0.98).[42] These nephroprotective effects may translate into meaningful clinical benefits: preserving residual renal function delays dialysis initiation, reduces cardiovascular complications, improves quality of life, and may extend survival, even in patients who eventually require dialysis.[42]

Apixaban versus Rivaroxaban: Comparative safety in advanced CKD

Direct comparative studies evaluating apixaban versus rivaroxaban specifically in advanced CKD populations remain limited, with most of the existing evidence derived from observational cohorts and network meta-analyses.[19] Both agents demonstrate favorable benefit-risk profiles compared to warfarin, although subtle differences may inform drug selection.[41] Apixaban's minimal renal-elimination rate (27%) theoretically confers an advantage in severe renal impairment, with FDA approval supporting its use down to CrCl 15 mL/min and even in dialysis patients.[41] Results of comparative observational studies in CKD stage 4–5 populations suggest that apixaban is associated with 20–30% lower major bleeding rates compared to rivaroxaban, although the differences in stroke prevention appear similar.[19] Real-world effectiveness studies in ESRD populations demonstrate that both agents perform comparably to warfarin: apixaban data from the AXADIA-AFNET 8 and RENAL-AF trials show similar bleeding and stroke rates to warfarin, but with the practical advantages of no INR monitoring,[19] while rivaroxaban data from the Valkyrie trial suggests potential superiority for composite cardiovascular outcomes.[19] Network meta-analyses ranking DOACs across safety and efficacy endpoints have consistently positioned apixaban with the highest probability of being "best" for major bleeding prevention, while edoxaban and apixaban rank similarly for stroke prevention.[37] Practically, apixaban's twice-daily dosing may challenge adherence compared to rivaroxaban's once-daily regimen, although twice-daily dosing provides a more stable anticoagulant effect, with lower peak-to-trough variability.[25]

Practical algorithm for DOAC selection in patients with CKD-AF

Synthesizing the available evidence into practical clinical guidance, we propose a structured approach to DOAC selection across the CKD spectrum (Table 2).[43] For CKD stages 1–3a (eGFR ≥ 45 mL/min), any DOAC is appropriate, with selection based on patient-specific factors, including comorbidities, concomitant medications, dosing-frequency preferences, and cost considerations; apixaban or edoxaban may be preferred for patients with higher bleeding risk, given their slight safety advantages.[37] For CKD stage 3b (eGFR 30–44 mL/min), apixaban, rivaroxaban, and edoxaban are preferred over dabigatran; however, dose adjustment is required for rivaroxaban (15 mg daily) and edoxaban (30 mg daily), and apixaban dose adjustment is required if two additional risk factors are presented (age ≥ 80, weight ≤ 60 kg, or creatinine ≥ 1.5 mg/dL).[25] For CKD stage 4 (eGFR 15–29 mL/min), apixaban (2.5 mg twice daily) and rivaroxaban (15 mg daily) are preferred options; edoxaban (30 mg daily) is an acceptable alternative, but dabigatran should be avoided (contraindicated in Europe, limited evidence for 75 mg twice daily dose in the United States).[26] For CKD stage 5/ESRD on dialysis, individualized decision-making is essential; apixaban (5 mg twice daily per FDA label in the United States, or 2.5 mg twice daily if the dose reduction criteria are met) and rivaroxaban (15 mg daily) are reasonable alternatives to warfarin based on emerging trial data, but close monitoring for bleeding and thrombotic events is mandatory, and non-anticoagulation may be appropriate for selected high-bleeding risk patients after shared decision-making.[50] This algorithm emphasizes that DOAC selection in advanced CKD requires the integrated consideration of renal function, bleeding risk, drug interactions, patient preferences, and clinical judgment, with no single "correct" choice applicable to all patients.

Monitoring, safety, and practical management considerations

Renal-function monitoring: Frequency and thresholds

Systematic monitoring of renal function is a cornerstone of safe DOAC management in CKD populations, given the potential for acute deterioration and consequent drug accumulation.[12] Evidence-based guidelines and expert consensus recommend baseline assessment of serum creatinine and calculation of CrCl using the Cockcroft-Gault formula before DOAC initiation, with subsequent monitoring frequency stratified by baseline renal function and clinical stability.[29] For stable outpatients, the recommended monitoring intervals are as follows: annually for CrCl > 60 mL/min, every 6 months for CrCl 30–60 mL/min, every 3–4 months for CrCl 15–30 mL/min, and monthly to quarterly for dialysis patients.[46] The pragmatic formula of monitoring frequency (frequency in months = CrCl/10) provides individualized guidance, accounting for the principle that patients with lower renal function require more frequent assessment.[30] Beyond scheduled monitoring, reassessment should occur with any acute illness, introduction of nephrotoxic medications or P-gp/CYP3A4 inhibitors, evidence of volume depletion or hypotension, or development of bleeding or thrombotic complications.[12] When CrCl declines below thresholds requiring dose adjustment or drug discontinuation, alternative anticoagulation strategies should be promptly implemented.[25] Emerging evidence suggests that beyond creatinine-based estimations, cystatin C-based eGFR calculations may provide more accurate renal-function assessment in patients with extreme body mass or muscle wasting, although cystatin C is not routinely available in many clinical settings.[54]

Coagulation testing: When and what to measure

While DOACs do not require routine coagulation monitoring for dose titration (unlike warfarin's INR monitoring requirement), specific clinical scenarios warrant measurement of the DOAC anticoagulant effect or drug level.[47] These scenarios include life-threatening bleeding requiring assessment of anticoagulant activity and consideration of reversal agents, urgent/emergent surgery where timing of procedure depends on anticoagulant washout, suspected thrombosis despite anticoagulation therapy raising concern for underdosing or non-adherence, suspected overdose with bleeding manifestations, pre-procedural assessment for high-bleeding risk procedures where the residual anticoagulant effect could be catastrophic, and extreme body weight or renal function where the effects of pharmacokinetics are unpredictable.[55] For dabigatran, dilute thrombin time or ecarin clotting time provides quantitative assessment, while chromogenic anti-Xa assays calibrated to specific DOACs enable measurement of rivaroxaban, apixaban, and

edoxaban levels.[56] Standard coagulation tests are insensitive and nonspecific for DOACs, although qualitative prolongation may suggest drug presence.[57] The target therapeutic ranges for DOACs in AF have not been firmly established, but general guidance suggests apixaban trough 50–250 µg/L, peak 100–300 µg/L; rivaroxaban trough 10–150 µg/L, peak 150–350 µg/L; and edoxaban trough 15–150 µg/L.[58] Importantly, interpretation requires consideration of timing relative to the last dose (trough *vs.* peak), renal-function status, and clinical context.[59] Recent advances include point-of-care urine qualitative testing (DOASENSE Dipstick), which demonstrates 99% concordance with quantitative plasma measurements and offers rapid assessment in emergency situations, although validation in ESRD populations remains limited.[60]

Management of bleeding complications and reversal strategies

Despite optimal DOAC selection and monitoring, bleeding complications occur in 2–8% of patients with CKD annually, with the rates increasing proportionally with CKD severity.[2] Management strategies should be risk-stratified based on bleeding severity: minor bleeding (epistaxis and superficial bruising) typically responds to temporary DOAC discontinuation and supportive care; moderate bleeding (requiring transfusion but hemodynamically stable) necessitates DOAC cessation, investigation of bleeding source, and consideration of prothrombin complex concentrates; and major or life-threatening bleeding requires immediate DOAC reversal with specific antidotes when available.[12] Idarucizumab (for dabigatran) and andexanet alfa (for factor Xa inhibitors) are targeted reversal agents, although their use in ESRD populations requires careful consideration of altered pharmacokinetics and limited efficacy data in this setting.[55] In patients undergoing dialysis who experience major bleeding, emergent hemodialysis can effectively clear dabigatran (80% removed in a 4-hour session due to low protein binding) but provides minimal benefit for factor Xa inhibitors, given the high protein binding (87–95%).[48] Prevention remains paramount: systematic bleeding risk assessment using validated scores (HAS-BLED), minimization of concomitant antiplatelet therapy, proactive management of modifiable bleeding risk factors (uncontrolled hypertension, anemia, and thrombocytopenia), and patient education regarding warning signs constitute essential elements of comprehensive care.[61]

Special considerations: Peritoneal dialysis and transplant recipients

While most of the existing ESRD anticoagulation evidence has been derived from hemodialysis populations, patients undergoing peritoneal dialysis are a distinct cohort with unique considerations.[62] The percentage of patients with ESRD initiating renal-replacement therapy with peritoneal dialysis nearly doubled between 2009 (6.2%) and 2019 (11.5%), making it an increasingly relevant population.[62] Limited pharmacokinetic data suggest that apixaban clearance *via* peritoneal dialysis is negligible, with the steady-state drug levels comparable to those of patients with CKD stage 5 who are not undergoing dialysis, supporting twice-daily dosing regimens.[63] The currently ongoing Apixaban in Peritoneal Dialysis Patients (APIDP2) trial randomizes patients with AF who are undergoing peritoneal dialysis to apixaban 2.5 mg twice daily versus dose-adjusted warfarin, with the primary endpoint of major or clinically relevant non-major bleeding at 12 months.[63] In recipients of kidney transplants, DOAC use appears feasible with stable graft function (eGFR > 30 mL/min), although drug interactions with calcineurin inhibitors (cyclosporine or tacrolimus) require consideration; the results of pharmacokinetic studies demonstrate that cyclosporine increases the apixaban area under the curve by 20% through P-gp inhibition, although the clinical significance remains uncertain, and dose adjustments are not routinely recommended.[64]

Conclusions and future perspectives

Anticoagulation management in patients with concurrent AF and CKD, particularly those with an advanced disease stage or ESRD, is one of the most challenging clinical scenarios in contemporary cardiology and nephrology practice.[1] The available evidence, synthesized in this comprehensive review, supports several key conclusions that should guide clinical decision-making. First, in CKD stages 1–3 (eGFR > 30 mL/min), DOACs demonstrate clear superiority over warfarin, with consistent reductions in stroke incidence, major bleeding (particularly intracranial hemorrhage), and all-cause mortality, establishing their use as the preferred anticoagulation strategy.[38] Second, in CKD stage 4 (eGFR 15–29 mL/min), dose-adjusted DOACs—particularly apixaban and rivaroxaban—appear safe and effective, offering practical advantages over warfarin, including predictable pharmacokinetics, absence of INR monitoring requirements, and potential nephroprotective benefits.[42] Third, emerging randomized evidence from ESRD populations (in the AXADIA-AFNET 8, RENAL-AF, and Valkyrie trials) suggests that DOACs perform comparably to warfarin for both safety and efficacy endpoints, supporting their use as reasonable alternatives in patients undergoing hemodialysis, although neither strategy eliminates the substantial residual risk inherent in this vulnerable population.[19]

Beyond the aforementioned evidence-based conclusions, several critical practical principles have emerged. Individualized risk-benefit assessment remains paramount: not all patients with ESRD and AF require or benefit from anticoagulation, and shared decision-making incorporating patient values, bleeding risk profile, comorbidities, and life expectancy should guide therapy.[50] When anticoagulation is pursued, rigorous monitoring is a non-negotiable safety imperative: systematic renal-function assessment at intervals tailored to CKD stage, proactive evaluation for bleeding complications, comprehensive medication review to identify and manage drug interactions, and regular reassessment of indication and appropriateness as clinical circumstances evolve.[29] The choice among DOACs in advanced CKD should consider multiple factors beyond efficacy alone: apixaban offers the lowest renal-elimination rate (27%) and has obtained FDA approval for dialysis populations; rivaroxaban has obtained robust evidence for nephroprotection in CKD stage 4; edoxaban provides once-daily dosing convenience; and dabigatran generally should be avoided due to its high renal-elimination rate.[25]

Looking forward, several critical knowledge gaps require investigation through well-designed prospective studies. Large-scale randomized trials adequately powered to detect clinically meaningful differences in ESRD populations are urgently needed because the existing trials are small and potentially underpowered for definitive conclusions.[19] Head-to-head comparisons of DOACs in advanced CKD would inform optimal drug selection, which is currently extrapolated from indirect comparisons and observational data.[37] Investigating optimal DOAC dosing in ESRD through pharmacokinetic/pharmacodynamic studies could refine the current empiric dose recommendations.[59] Studies evaluating the role of DOAC drug level monitoring in guiding dose adjustments in advanced CKD may identify subpopulations benefiting from individualized therapeutic-drug monitoring.[47] Finally, research into novel anticoagulant strategies, including factor XI inhibitors cur-

rently in development, may offer improved benefit-risk profiles for this challenging population by targeting coagulation pathways with less bleeding liability.[65]

In conclusion, the landscape of anticoagulation for AF in CKD has evolved substantially over the past decade, with DOACs emerging as preferred agents across much of the CKD spectrum. While challenges persist—particularly in ESRD, where evidence remains limited—growing data support cautious, individualized DOAC use as a viable alternative to warfarin. The integration of mechanistic understanding, pharmacokinetic principles, emerging clinical-trial evidence, and rigorous monitoring protocols will provide a framework for optimizing anticoagulation in the aforementioned high-risk population, balancing stroke prevention against bleeding risk while potentially preserving residual renal function. As the global population ages and the prevalence of both AF and CKD continues to rise, refined evidence-based strategies for anticoagulation management in this complex population will become increasingly critical to improving patient outcomes and quality of life.[61]

Acknowledgments

None.

Funding

This work received no external funding.

Conflict of interest

The authors declare no competing interest.

Author contributions

LDL has contributed as supervisor of the whole manuscript, to DOAC selection section, and to the final section on monitoring and safety. AF contributed to data collection. PS contributed to the introduction and pathophysiology. ADS and LP contributed to the pharmacology section. VB and LD contributed to the anticoagulation in CKD stages 1–4 section. AB and PP have contributed to the advanced CKD and ESRD section. All authors have read and approved the final version.

References

[1] Parul F, Ratnani T, Subramani S, Bhatia H, Ashmawy RE, Nair N, *et al*. Anticoagulation in Patients with End-Stage Renal Disease: A Critical Review. Healthcare (Basel) 2025;13(12):1373. doi:10.3390/healthcare13121373, PMID:40565400.

[2] Suliman IL, Tuta LA, Panculescu FG, Alexandru A, Fasie D, Cimpineanu B, *et al*. Comparative Outcomes of Apixaban and Acenocoumarol in Advanced Chronic Kidney Disease and Atrial Fibrillation: A Retrospective Observational Study. J Clin Med 2025;14(24):8860. doi:10.3390/jcm14248860, PMID:41464761.

[3] Ding WY, Gupta D, Wong CF, Lip GYH. Pathophysiology of atrial fibrillation and chronic kidney disease. Cardiovasc Res 2021;117(4):1046–1059. doi:10.1093/cvr/cvaa258, PMID:32871005.

[4] Wang Y, Yang Y, He F. Insights into Concomitant Atrial Fibrillation and Chronic Kidney Disease. Rev Cardiovasc Med 2022;23(3):105. doi:10.31083/j.rcm2303105, PMID:35345272.

[5] Yusupov F. A., Yusupov A.F., Yuldashev A.A. Chronic kidney disease as a risk factor for stroke (in Russian). Journal of Urology 2025;13(4):97–106. doi:10.21886/2308-6424-2025-13-4-97-106.

[6] Złotorzyńska KA, Bednarski J. Anticoagulant therapy in patients with atrial fibrillation and chronic kidney disease stage G4-G5-systematic review. Med Res J 2025;10(3):295–303. doi:10.5603/mrj.106259.

[7] Simić J, Mihajlović M. Oral anticoagulant therapy in patients with atrial fibrillation and end-stage chronic kidney disease. Galenika Med J 2024;3(12):68–80. doi:10.5937/Galmed2412058S.

[8] Lau YC, Xiong Q, Blann AD, Lip GY. Relationship between renal function and circulating microparticles, soluble P-selectin and E-selectin levels in atrial fibrillation. J Thromb Thrombolysis 2017;43(1):18–23. doi:10.1007/s11239-016-1427-3, PMID:27671694.

[9] Suliman IL, Panculescu FG, Cimpineanu B, Popescu S, Fasie D, Cozaru GC, *et al*. The Interplay of Cardiovascular Comorbidities and Anticoagulation Therapy in ESRD Patients on Haemodialysis-The South-Eastern Romanian Experience. Biomedicines 2025;13(10):2387. doi:10.3390/biomedicines13102387, PMID:41153672.

[10] Murkamilov I, Aitbaev K, Raimzhanov Z, Yusupova Z, Yusupova T, Zakirov O, *et al*. Therapeutic opportunities of apixaban in patients with atrial fibrillation and reducing the risk of cerebrovascular complications in chronic kidney disease. Bull Sci Pract 2024;10(1):189–208. doi:10.33619/2414-2948/98/23.

[11] Shimizu W, Yamashita T, Akao M, Atarashi H, Ikeda T, Koretsune Y, *et al*. Renal Function and Clinical Outcomes Among Elderly Patients With Nonvalvular Atrial Fibrillation From ANAFIE. JACC Asia 2023;3(3):475–487. doi:10.1016/j.jacasi.2023.02.002, PMID:37396416.

[12] Bauersachs RM, Herold J. Oral Anticoagulation in the Elderly and Frail. Hamostaseologie 2020;40(1):74–83. doi:10.1055/s-0040-1701476, PMID:32000266.

[13] Saeed Z, Sirolli V, Bonomini M, Gallina S, Renda G. Hallmarks for Thrombotic and Hemorrhagic Risks in Chronic Kidney Disease Patients. Int J Mol Sci 2024;25(16):8705. doi:10.3390/ijms25168705, PMID:39201390.

[14] Preda A, Tirandi A, Leo G, Di Vece D, Vilahur G, Bonaventura A, *et al*. IL-6 in the spotlight: From cardiovascular pathophysiology to therapy. Eur J Clin Invest 2026;56(1):e70161. doi:10.1111/eci.70161, PMID:41340186.

[15] Fauchier L, Boriani G, de Groot JR, Kreutz R, Rossing P, Camm AJ. Medical therapies for prevention of cardiovascular and renal events in patients with atrial fibrillation and diabetes mellitus. Europace 2021;23(12):1873–1891. doi:10.1093/europace/euab184, PMID:34411235.

[16] Zhu Y, Lv C, Yang H, Lu Q, Wang X, Zhang Y, *et al*. Chronic cardiorenal syndrome: cardio-renal protective effect of SGLT2i. Ren Fail 2025;47(1):2575921. doi:10.1080/0886022X.2025.2575921, PMID:41285492.

[17] Bharaj IS, Brar AS, Kahlon J, Singh A, Hotwani P, Kumar V, *et al*. Metabolic-dysfunction associated steatotic liver disease and atrial fibrillation: A review of pathogenesis. World J Cardiol 2025;17(6):106147. doi:10.4330/wjc.v17.i6.106147, PMID:40575425.

[18] Glikson M, Wolff R, Hindricks G, Mandrola J, Camm AJ, Lip GYH, *et al*. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. Europace 2020;22(2):184. doi:10.1093/europace/euz258, PMID:31504441.

[19] de Oliveira HM, Barros LP, de Campos MCAV, Daher RF, Gonçalves GB, Sequeira MT, *et al*. Anticoagulation Strategies for Atrial Fibrillation in CKD Stage G5 and Dialysis Patients: An Updated Scoping Review. Rev Cardiovasc Med 2025;26(3):26736. doi:10.31083/RCM26736, PMID:40160594.

[20] Cases A, Gomez P, Broseta JJ, Perez Bernat E, Arjona Barrionuevo JD, Portolés JM, *et al*. Non-valvular Atrial Fibrillation in CKD: Role of Vitamin K Antagonists and Direct Oral Anticoagulants. A Narrative Review. Front Med (Lausanne) 2021;8:654620. doi:10.3389/fmed.2021.654620, PMID:34604247.

[21] Hindley B, Lip GYH, McCloskey AP, Penson PE. Pharmacokinetics and pharmacodynamics of direct oral anticoagulants. Expert Opin Drug Metab Toxicol 2023;19(12):911–923. doi:10.1080/17425255.2023.2287472, PMID:37991392.

[22] Masotti L, Campanini M. Pharmacology of new oral anticoagulants: mechanism of action, pharmacokinetics, pharmacodynamics. Ital J Med 2013;7(S8):1–7. doi:10.4081/itjm.2013.s8.1.

[23] Zou P, Leil TA. Exposure Matching-Based Pediatric Dose Selection for Drugs with Renal Excretion - Lessons Learned from Pediatric Development of Direct Oral Anticoagulants. Clin Pharmacol Ther

2024;116(5):1174–1187. doi:10.1002/cpt.3396, PMID:39136405.
[24] Turpie AGG, Purdham D, Ciaccia A. Nonvitamin K antagonist oral anticoagulant use in patients with renal impairment. Ther Adv Cardiovasc Dis 2017;11(9):243–256. doi:10.1177/1753944717714921, PMID:28651452.
[25] Hahn K, Lamparter M. Prescription of DOACs in Patients with Atrial Fibrillation at Different Stages of Renal Insufficiency. Adv Ther 2023;40(10):4264–4281. doi:10.1007/s12325-023-02544-8, PMID:37594666.
[26] Harrington J, Carnicelli AP, Hua K, Wallentin L, Patel MR, Hohnloser SH, *et al*. Direct Oral Anticoagulants Versus Warfarin Across the Spectrum of Kidney Function: Patient-Level Network Meta-Analyses From COMBINE AF. Circulation 2023;147(23):1748–1757. doi:10.1161/CIRCULATIONAHA.122.062752, PMID:37042255.
[27] Du W, Liu Z, Li Y, Wang Z, Dong Z. In vivo Pharmacokinetic Interactions Between Palbociclib and Rivaroxaban or Apixaban: Implications for Increased Drug Exposure and Dose Adjustments. Drug Des Devel Ther 2025;19:7333–7347. doi:10.2147/DDDT.S499209, PMID:40896199.
[28] Dobesh PP, Kernan MM, Lueshen JJ. Direct Oral Anticoagulants in the Treatment of Venous Thromboembolism: Use in Patients with Advanced Renal Impairment, Obesity, or Other Weight-Related Special Populations. Semin Respir Crit Care Med 2021;42(2):233–249. doi:10.1055/s-0041-1723952, PMID:33601428.
[29] Chin PK, Doogue MP. Oral anticoagulation for adults with atrial fibrillation or venous thromboembolism. Aust Prescr 2025;48(5):161–166. doi:10.18773/austprescr.2025.047, PMID:41164099.
[30] Vio R, Proietti R, Rigato M, Calò LA. Clinical Evidence for the Choice of the Direct Oral Anticoagulant in Patients with Atrial Fibrillation According to Creatinine Clearance. Pharmaceuticals (Basel) 2021;14(3):279. doi:10.3390/ph14030279, PMID:33808739.
[31] Miceli G, Ciaccio AM, Tuttolomondo A. Challenges and Opportunities of Direct Oral Anticoagulant (DOAC) Therapy in Complex Clinical Scenarios: A Comprehensive Review and Practical Guide. J Clin Med 2025;14(9):2914. doi:10.3390/jcm14092914, PMID:40363949.
[32] Mar PL, Gopinathannair R, Gengler BE, Chung MK, Perez A, Dukes J, *et al*. Drug Interactions Affecting Oral Anticoagulant Use. Circ Arrhythm Electrophysiol 2022;15(6):e007956. doi:10.1161/CIRCEP.121.007956, PMID:35622425.
[33] Vranckx P, Valgimigli M, Heidbuchel H. The Significance of Drug-Drug and Drug-Food Interactions of Oral Anticoagulation. Arrhythm Electrophysiol Rev 2018;7(1):55–61. doi:10.15420/aer.2017.50.1, PMID:29636974.
[34] Hassan A, Alvi AM, Sulman A, Maqbool W, Ahmed MG, Rehman TU, *et al*. Drug interactions of anticoagulants: mechanisms, clinical implications, and strategies to prevent and manage interactions. Indus J Biosci Res 2025;3(11):85–99. doi:10.70749/ijbr.v3i11.2612.
[35] Chalayer E, Daguenet E, Bobin A, Fatrara T, Bounouara I, Noel S, *et al*. Apixaban pharmacokinetics in newly diagnosed multiple myeloma patients treated in the benefit and isasocut clinical trials: The apixabor/mibapix study. Blood 2025;146(Suppl 1):744. doi:10.1182/blood-2025-744.
[36] Lucà F, Oliva F, Abrignani MG, Di Fusco SA, Parrini I, Canale ML, *et al*. Management of Patients Treated with Direct Oral Anticoagulants in Clinical Practice and Challenging Scenarios. J Clin Med 2023;12(18):5955. doi:10.3390/jcm12185955, PMID:37762897.
[37] Rhee TM, Lee SR, Choi EK, Oh S, Lip GYH. Efficacy and Safety of Oral Anticoagulants for Atrial Fibrillation Patients With Chronic Kidney Disease: A Systematic Review and Meta-Analysis. Front Cardiovasc Med 2022;9:885548. doi:10.3389/fcvm.2022.885548, PMID:35757349.
[38] Yin Q, Zheng X, Ni X, Wang Y, Huang X, Song Y, *et al*. Efficacy and safety of oral anticoagulants in the treatment of chronic kidney disease with atrial fibrillation or venous thromboembolism: a systematic review and meta-analysis. Front Pharmacol 2025;16:1615284. doi:10.3389/fphar.2025.1615284, PMID:40949128.
[39] Harrington J, Carnicelli AP, Hua K, Wallentin L, Patel MR, Hohnloser SH, *et al*. Direct oral anticoagulants versus warfarin across the spectrum of kidney function: patient-level network meta-analyses from COMBINE AF. Circulation 2023;147(23):1748–1757. doi:10.1161/CIRCULATIONAHA.122.062752.
[40] Jones A, Swan D, Lisman T, Barnes GD, Thachil J. Anticoagulation in chronic kidney disease: current status and future perspectives. J Thromb Haemost 2024;22(2):323–336. doi:10.1016/j.jtha.2023.09.020, PMID:37778512.
[41] Mandt SR, Thadathil N, Klem C, Russ C, McNamee PL, Stigge K, *et al*. Apixaban Use in Patients with Kidney Impairment: A Review of Pharmacokinetic, Interventional, and Observational Study Data. Am J Cardiovasc Drugs 2024;24(5):603–624. doi:10.1007/s40256-024-00664-2, PMID:39102124.
[42] UK Kidney Association. Clinical Practice Guideline: Anticoagulation for atrial fibrillation in adults with advanced kidney disease. Bristol: UK Kidney Association; 2025.
[43] Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, *et al*. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39(16):1330–1393. doi:10.1093/eurheartj/ehy136, PMID:29562325.
[44] South East London Integrated Medicines Optimisation Committee. Direct Oral Anticoagulant (DOAC) Initiation and Monitoring Guidance for Non-Valvular Atrial Fibrillation (AF). London: NHS; 2024.
[45] Moudallel S, Steurbaut S, Cornu P, Dupont A. Appropriateness of DOAC Prescribing Before and During Hospital Admission and Analysis of Determinants for Inappropriate Prescribing. Front Pharmacol 2018;9:1220. doi:10.3389/fphar.2018.01220, PMID:30425641.
[46] Longo L. Guidance for the Oversight and Monitoring* of Direct Oral Anticoagulants (DOACs). 2024. Available from: https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Anticoagulants_Direct_Oral_DOACs_Oversight_and_Monitoring_Guidance_Rev_Jun_2024.pdf. Accessed February 15, 2026.
[47] Ten Cate H, Henskens YM, Lancé MD. Practical guidance on the use of laboratory testing in the management of bleeding in patients receiving direct oral anticoagulants. Vasc Health Risk Manag 2017;13:457–467. doi:10.2147/VHRM.S126265, PMID:29263674.
[48] Königsbrügge O, Ay C. Atrial fibrillation in patients with end-stage renal disease on hemodialysis: Magnitude of the problem and new approach to oral anticoagulation. Res Pract Thromb Haemost 2019;3(4):578–588. doi:10.1002/rth2.12250, PMID:31624777.
[49] Parks AL, Stevens SM, Woller SC. Anticoagulant therapy in renal insufficiency theme: Anticoagulation in complex situations. Thromb Res 2024;241:109097. doi:10.1016/j.thromres.2024.109097, PMID:39094333.
[50] Manning WJ, Singer DE, Lip GYH. Atrial fibrillation in adults: Selection of candidates for long-term anticoagulation. Waltham: UpToDate. 2025. Available from: https://www.uptodate.com/contents/atrial-fibrillation-in-adults-selection-of-candidates-for-long-term-anticoagulation. Accessed February 15, 2026.
[51] Kumar S, Lim E, Covic A, Verhamme P, Gale CP, Camm AJ, *et al*. Anticoagulation in Concomitant Chronic Kidney Disease and Atrial Fibrillation: JACC Review Topic of the Week. J Am Coll Cardiol 2019;74(17):2204–2215. doi:10.1016/j.jacc.2019.08.1031, PMID:31648714.
[52] Kao TW, Chen ZW, Lin YH. Anticoagulation for Patients With Concomitant Atrial Fibrillation and End-Stage Renal Disease: A Systematic Review and Network Meta-Analysis. J Am Heart Assoc 2024;13(8):e034176. doi:10.1161/JAHA.123.034176, PMID:38606775.
[53] Sitticharoenchai P, Takkavatakarn K, Boonyaratavej S, Praditpornsilpa K, Eiam-Ong S, Susantitaphong P. Non-Vitamin K Antagonist Oral Anticoagulants Provide Less Adverse Renal Outcomes Than Warfarin In Non-Valvular Atrial Fibrillation: A Systematic Review and MetaAnalysis. J Am Heart Assoc 2021;10(7):e019609. doi:10.1161/JAHA.120.019609, PMID:33728927.
[54] Visinescu AM, Rusu E, Cosoreanu A, Radulian G. CYSTATIN C-A Monitoring Perspective of Chronic Kidney Disease in Patients with Diabetes. Int J Mol Sci 2024;25(15):8135. doi:10.3390/ijms25158135, PMID:39125705.
[55] Douxfils J, Adcock DM, Bates SM, Favaloro EJ, Gouin-Thibault I, Guillermo C, *et al*. 2021 Update of the International Council for Standardization in Haematology Recommendations for Laboratory Measurement of Direct Oral Anticoagulants. Thromb Haemost 2021;121(8):1008–1020. doi:10.1055/a-1450-8178, PMID:33742436.
[56] Jayakumar J, Khan F, Ayyazuddin M, Turku D, Ginjupalli M, Kalaivani Babu A, *et al*. Beyond Routine Monitoring: A Comprehensive Review of Direct Oral Anticoagulants and the Role of Coagulation Profiles in Their Management. Cureus 2025;17(3):e80469. doi:10.7759/

cureus.80469, PMID:40225520.
[57] Margetić S, Goreta SŠ, Ćelap I, Razum M. Direct oral anticoagulants (DOACs): From the laboratory point of view. Acta Pharm 2022;72(4):459–482. doi:10.2478/acph-2022-0034, PMID:36651369.
[58] Wołowiec Ł, Kusiak M, Budzyński J, Wołowiec A, Jaśniak A, Wiciński M, *et al*. Therapeutic Drug Monitoring of Direct Oral Anticoagulants in Patients with Extremely Low and High Body Weight-Pilot Study. J Clin Med 2023;12(15):4969. doi:10.3390/jcm12154969, PMID: 37568371.
[59] Bacharaki D, Kyriakou E, Sardeli A, Nikolopoulos P, Triantaphyllis G, Drakou A, *et al*. Bleeding prediction by rotational thromboelastometry in chronic hemodialysis patients with non-valvular atrial fibrillation on apixaban. World J Cardiol 2025;17(12):112046. doi:10.4330/wjc.v17.i12.112046, PMID:41479990.
[60] Schieppati F, Gomez Rosas P, Ambaglio C, Brusegan V, Cretu OC, Galiberti E, *et al*. The utility of urine qualitative assessment for direct oral anticoagulants in routine clinical practice. EHA Library; 2025. Available from: https://library.ehaweb.org/eha/2025/eha2025-congress/4161343. Accessed February 15, 2026.
[61] Kumar A, Kumar C, Kumar A, Kumari S, Aneela, Rai R, *et al*. Management of anticoagulation in patients with atrial fibrillation and renal dysfunction: A systematic review. World J Exp Med 2025;15(3):105485. doi:10.5493/wjem.v15.i3.105485, PMID:41523765.
[62] Lange NW, Muir J, Salerno DM. Direct Oral Anticoagulants in Patients With ESRD and Kidney Transplantation. Kidney Int Rep 2025;10(1):40–53. doi:10.1016/j.ekir.2024.10.016, PMID:39810765.
[63] Ficheux M, Peyro-Saint-Paul L, Balayn D, Lecrux B, Brossier M, Morin A, *et al*. Safety and efficacy of apixaban versus warfarin in peritoneal dialysis patients with non-valvular atrial fibrillation: protocol for a prospective, randomised, open-label, blinded endpoint trial (APIDP2). BMJ Open 2024;14(9):e089353. doi:10.1136/bmjopen-2024-089353, PMID:39306346.
[64] Bixby AL, Lichvar AB, Salerno D, Park JM. Use of direct-acting oral anticoagulants in solid organ transplantation: A systematic review. Pharmacotherapy 2021;41(1):28–43. doi:10.1002/phar.2485, PMID:33155327.
[65] Eikelboom J, Floege J, Thadhani R, Weitz JI, Winkelmayer WC. Anticoagulation in patients with kidney failure on dialysis: factor XI as a therapeutic target. Kidney Int 2021;100(6):1199–1207. doi:10.1016/j.kint.2021.08.028, PMID:34600964.