

Anticoagulation in Atrial Fibrillation and Chronic Kidney Disease: A Critical Review and Future Perspectives in Peritoneal Dialysis

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Abstract

Atrial fibrillation (AF) and chronic kidney disease (CKD) are two closely related pathophysiologically interconnected conditions, sharing common risk factors and resulting in poor clinical outcomes when coexisting. In patients with end-stage renal disease (ESRD) on renal replacement therapy, AF significantly complicates clinical management, as these patients have a doubled risk of death, stroke, and bleeding. Choosing the optimal anticoagulant strategy remains a major challenge, with direct oral anticoagulants (DOACs) emerging as a potentially superior alternative to vitamin K antagonists (VKAs), especially due to their renoprotective profile. However, data in patients on peritoneal dialysis (PD) remain sparse, constituting a significant gap in the scientific literature. This review examines the current state of evidence on anticoagulation in patients with AF and advanced CKD, with a particular focus on new therapeutic perspectives in the PD population.

Keywords: Atrial fibrillation; Chronic kidney disease; Peritoneal dialysis; Direct oral anticoagulants; Warfarin; Nephroprotection

Introduction

The prevalence of atrial fibrillation (AF) in the general popula-

tion is around 0.5–1%, reaching 8% in patients over 80 years of age. However, in specific pathological conditions, this prevalence increases considerably, particularly in chronic kidney disease (CKD) and especially in patients undergoing renal replacement therapy [1].

The prevalence ranges from approximately 15–20% in patients with CKD stages 3–4 to 15–27% in patients with end-stage renal disease (ESRD) on dialysis [2].

A direct and independent relationship exists between the degree of CKD and the prevalence of AF. An epidemiological study conducted in Japan on approximately 41,000 people demonstrated that, although age is a relevant factor in the prevalence of AF, the severity of CKD plays an independent predictive role, with increasing prevalence in subgroups with lower glomerular filtration rate (GFR) [3]. This association is also confirmed in patients on hemodialysis treatment, where the length of treatment is associated with a progressive increase in the prevalence of AF over time [4].

The clinical consequences of this coexistence are significant: the meta-analysis by Zimmerman et al showed that mortality in dialysis patients with AF is more than doubled compared to those without atrial arrhythmia [4]. Furthermore, the analysis of a Danish registry of 132,000 patients with non-valvular AF revealed that with the progression of CKD there is a simultaneous increase in both the risk of thromboembolism/stroke and the risk of bleeding, creating a complex therapeutic dilemma [5].

Pathophysiology of the AF–CKD connection

The pathophysiological connection between AF and CKD is multidimensional and involves shared hemodynamic, inflammatory, and neurohormonal mechanisms. Activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system (RAAS), volume retention, increased oxidative stress, and pro-inflammation represent the “vicious cycle” that fuels the reciprocal progression of the two diseases.

Hypertension plays a pivotal role in the high incidence of AF in patients with kidney disease, acting as both a consequence and a contributor to the AF–CKD connection. Chronic hypertension leads to left ventricular hypertrophy and increased left atrial pressure, promoting atrial fibrosis and struc-

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tural remodeling that create the substrate for AF.

Simultaneously, hypertension accelerates nephrosclerosis and glomerular damage, worsening renal function. The resulting volume overload and neurohormonal activation further elevate blood pressure, perpetuating a vicious cycle. Moreover, hypertension-induced arterial stiffness reduces vascular compliance, increasing cardiac afterload and atrial wall stress, which facilitates the development and persistence of atrial arrhythmias. This bidirectional relationship underscores why hypertension management is crucial in breaking the AF-CKD cycle [6].

At the cardiac level, CKD causes valvular calcification, ventricular remodeling with heart failure, and alterations in atrial function. At the renal level, vascular remodeling progresses with nephrosclerosis and proteinuria. Both processes also generate rhythm alterations with deleterious hemodynamic consequences: the rapid irregular ventricular rate and the loss of atrial systole cause a reduction in cardiac output and renal hypoperfusion, perpetuating organ damage [7].

The Therapeutic Dilemma: Thromboembolic Risk vs. Hemorrhagic Risk

Increased thromboembolic risk

Patients with CKD and AF are at particularly high risk of thromboembolism. All elements of Virchow's triad are abnormal: abnormalities in blood flow (reduced atrial flow velocity), vessel wall (vascular stiffness, accelerated atherosclerosis), and blood constituents (prothrombotic state).

A reduced estimated glomerular filtration rate (eGFR) is an independent predictor of low contractility and left atrial appendage flow velocity, resulting in blood stasis and dense spontaneous echocardiographic contrast. CKD patients also present with elevated endogenous endothelin-1 levels and platelet alterations, accompanied by increased inflammatory and coagulation biomarkers (VII, VIII, fibrinogen, von Willebrand factor, lipoprotein (a)) [8].

Paradoxical hemorrhagic risk

Counterintuitively, patients with CKD and AF also have an unexpectedly high bleeding risk, especially those on dialysis. Platelet dysfunction is the predominant feature, with reduced intracellular adenosine diphosphate (ADP), impaired alpha granule release, increased intracellular cyclic adenosine monophosphate (cAMP), and abnormalities in arachidonic acid metabolism. Uremic toxins further impair blood flow and increase erythropoietin deficiency. A significant percentage of patients with eGFR < 30 mL/min are at significant bleeding risk due to this platelet dysfunction [9].

A critical issue is that the commonly used risk calculators (HAS-BLED and CHA₂DS₂-VASc) do not adequately consider parameters related to renal dysfunction, making accurate risk stratification in this population difficult.

Vitamin K Antagonists (VKAs): Limited Effectiveness and New Risks

Warfarin-related nephropathy (WRN)

In 2011, Brodsky et al introduced the concept of "WRN", identifying a specific form of acute kidney injury (AKI) with no apparent underlying cause, found in patients on supratherapeutic anticoagulation with warfarin [10]. Renal biopsies in patients with WRN showed a diffuse and dysmorphic pattern of red blood cell accumulation in the tubules and glomeruli, with tubular obstruction and consequent ischemia. The two main pathophysiological mechanisms are: 1) breakdown of the glomerular filtration barrier with hemorrhage into Bowman's space, and 2) aggregation of red blood cells with formation of tubular cylinders that obstruct the tubules [9].

In a large retrospective cohort from a single academic medical center, 15,258 adult patients who initiated warfarin therapy between 2005 and 2009 were identified through the hospital information warehouse, irrespective of the indication for anticoagulation or kidney biopsy findings. Among the 4,006 patients who experienced at least one episode of international normalized ratio (INR) > 3.0 with serum creatinine measured within 3 months before and 1 week after the INR elevation and without evidence of overt hemorrhage, a presumptive diagnosis of WRN was made when serum creatinine increased by ≥ 0.3 mg/dL, occurring in 20.5% of the entire cohort and in 33.0% of patients with CKD. The 1-year mortality rate was 31.1% in patients with WRN versus 18.9% in those without WRN, corresponding to a 65% increased risk of death [10, 11].

An important clinical question arises: since direct oral anticoagulants (DOACs) also work through anticoagulation mechanisms, could they cause a similar nephropathy due to bleeding into the kidney? To date, there have been no reported cases of a "DOAC-related nephropathy" analogous to WRN. In fact, the evidence suggests the opposite: DOACs demonstrate a nephroprotective profile rather than nephrotoxic effects. Unlike warfarin, which can cause glomerular hemorrhage at supratherapeutic levels, DOACs have more predictable pharmacokinetics and do not require the same degree of monitoring, reducing the risk of excessive anticoagulation. Moreover, the absence of vitamin K inhibition with DOACs prevents the vascular calcification pathway that contributes to chronic kidney damage with warfarin therapy [12].

Vascular calcifications and renal damage

A study by Han and O'Neill demonstrated that warfarin use was associated with a 44% higher prevalence of peripheral arterial calcification (30.2% versus 20.9% in controls), limited to a medial calcification pattern and primarily in distal arteries (ankle and foot) [12]. The prevalence of medial arterial calcification was 49% higher in warfarin patients than in controls, but did not differ on radiographs obtained before initiation of warfarin therapy. This effect is mediated by inhibition of vitamin K-dependent carboxylation of matrix Gla protein (MGP), a major

endogenous inhibitor of vascular calcification produced by vascular smooth muscle cells. The absence of MGP causes medial arterial calcification in both animals and humans [13].

Warfarin-induced vascular calcifications have important clinical consequences: they are associated with worse cardiovascular outcomes, predispose to critical limb ischemia, and may perpetuate the vicious cycle of renal damage in the setting of advanced CKD.

DOACs: A New Era of Renal Protection

Nephroprotection superior to VKAs

A systematic meta-analysis by Sitticharoenchai et al highlighted that DOACs exert a significant protective effect in terms of renal outcome, determining a lower risk of both AKI and CKD progression itself, not only as a pharmacological class but also when analyzed individually [14].

Data from Yao et al on large, heterogeneous cohorts of patients with AF revealed that DOAC treatment is associated with a lower incidence of worsening renal function (defined as a $\geq 30\%$ decline in eGFR, doubling of serum creatinine, or AKI) compared with warfarin [15]. These findings persist even when patients are stratified by GFR levels, with greater benefit in the rivaroxaban and dabigatran subgroups.

An Italian group has also documented how rivaroxaban not only slows the progression of cardiac valve calcifications but also preserves renal function, probably through an anti-inflammatory action documented by the impact on serum levels of inflammatory cytokines [16].

The advantages of DOACs compared to VKAs are well-established in the general population, including reduced risk of intracranial hemorrhage, more predictable pharmacokinetics, and no need for routine monitoring. However, these benefits appear to be amplified in patients with CKD. In the CKD population, DOACs offer additional advantages beyond those seen in patients with normal renal function. The nephroprotective effects of DOACs, including reduced progression of kidney disease and lower incidence of AKI, represent benefits specific to the CKD population. Furthermore, the prevention of WRN and vascular calcifications provides substantial additional value in CKD patients, where these complications can accelerate both cardiovascular and renal deterioration. Studies have shown that the relative risk reduction for major bleeding and stroke with DOACs versus warfarin is maintained or even enhanced across declining levels of kidney function, making the therapeutic advantage particularly significant in advanced CKD stages [14–17].

Renal metabolism and dose limits

DOACs exhibit variable rates of renal elimination, which initially led to restrictions on their use in patients with advanced CKD. However, apixaban and rivaroxaban have the least renal dependence and are the only ones for which dosages have been proposed in dialysis patients.

Apixaban

ESRD results in a modest increase (36%) in area under the curve (AUC) with no increase in peak concentration. Apixaban 2.5 mg bid administered to patients on hemodialysis results in drug exposure similar to that of the standard dose (5 mg bid) in patients with preserved renal function [18].

Rivaroxaban

Deterioration of renal function from severe to ESRD does not appear to have a significant impact on the pharmacokinetics and anticoagulant effect compared to the changes observed with moderate/severe renal impairment. Rivaroxaban 10 mg/day in patients on hemodialysis maintains similar exposure to rivaroxaban 20 mg/day in patients with normal renal function [19].

Efficacy and safety in ESRD

Although data on the efficacy and safety of DOACs in ESRD have been limited, recent studies are very encouraging. Apixaban was found to be superior in ESRD patients in terms of both safety and efficacy compared to warfarin. A meta-analysis of 71,877 patients on long-term dialysis with AF showed that those receiving apixaban 5 mg bid had a significantly lower risk of mortality than those receiving apixaban 2.5 mg bid, warfarin, or no anticoagulant, with a lower risk of bleeding than those taking warfarin, dabigatran, or rivaroxaban [19, 20].

To date, apixaban 5 mg twice daily (with reduced dose of 2.5 mg twice daily in patients meeting at least two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL) is approved by the FDA for use in ESRD patients on hemodialysis. Rivaroxaban is not FDA-approved for ESRD patients on dialysis, although pharmacokinetic studies support the use of reduced doses (10–15 mg/day) in this population. The increased mortality observed with VKAs in ESRD patients compared to DOACs can be attributed to multiple mechanisms. First, WRN represents a direct cause of accelerated renal function decline and increased mortality risk, with a 65% higher 1-year mortality rate in patients who develop WRN. Second, the acceleration of vascular calcifications induced by warfarin through inhibition of MGP leads to increased cardiovascular events, vascular stiffness, and critical limb ischemia. Third, the difficulty in maintaining stable INR levels in dialysis patients results in frequent episodes of both under-anticoagulation (increasing thrombotic risk) and over-anticoagulation (increasing bleeding risk) [10]. Studies have shown that ESRD patients on warfarin spend a significantly lower percentage of time in therapeutic range compared to patients with normal renal function. Finally, the hemorrhagic complications associated with warfarin in the setting of uremic platelet dysfunction contribute to increased mortality, with major bleeding events representing a leading cause of death in this population. These combined mechanisms explain why warfarin is associated with worse survival outcomes compared to DOACs in the ESRD population [11].

The Therapeutic Void in Peritoneal Dialysis (PD)

Lack of evidence in PD

While data on DOACs in ESRD patients on hemodialysis have progressively increased, those on PD patients remain virtually nonexistent. The first significant evidence of inclusion of PD patients with AF on anticoagulant therapy comes from the study published in *Nephrology Dialysis Transplantation* in 2024 by Laville et al [21]. In this study, nearly 9,000 patients with AF receiving anticoagulant therapy on replacement therapy underwent a safety and efficacy comparison between VKAs and DOACs (specifically, apixaban and rivaroxaban). After a follow-up of approximately 18 months, apixaban and rivaroxaban emerged as superior in terms of thromboembolic risk, while the bleeding risk was lower, although not statistically significant.

The crucial innovation lies in the fact that, for the first time, a subpopulation of PD patients was included. Although the numbers were limited and did not allow definitive conclusions to be drawn, these data represent a fundamental starting point.

Pharmacokinetic studies in PD

Research in PD patients had initially focused on apixaban, mainly in terms of pharmacokinetic studies. Ficheux et al conducted a first pharmacokinetic study comparing serum concentration curves of apixaban in 10 PD patients treated with a dose of 2.5 mg versus the upper and lower concentration limits in healthy patients treated with a dose of 5 mg bid [18].

Concentration values at the 2.5 mg bid dose did not exceed the safety limits observed in healthy subjects, suggesting the possibility of safe dose titration in patients on PD [22].

First randomized trial in PD

Following pharmacokinetic studies, a prospective, randomized, open-label study with a hidden endpoint (APIDP2) was initiated to evaluate the safety and efficacy of PD patients with non-valvular AF treated with apixaban 2.5 mg bid compared to warfarin [18]. This study, which concludes in 2027, represents the first randomized trial dedicated to the evaluation of DOACs in the PD population with AF.

Mechanisms of Nephroprotection of DOACs

Beyond calcification inhibition

The benefit of DOACs is not limited to the prevention of vascular calcifications due to MGP inhibition. Rivaroxaban, in particular, appears to provide nephroprotection through multiple mechanisms: 1) reduction of vascular inflammation, through inhibition of PAR-1 and PAR-2 signaling; 2) systemic

anti-inflammatory effect, documented by reduction of serum levels of inflammatory cytokines; 3) preservation of renal function: independent of simple anticoagulation control diabetic patients with AF treated with rivaroxaban had a lower incidence rate of hospitalization for AKI, progression to CKD stage 5, or need for hemodialysis compared to patients on warfarin [23]. In the *post-hoc* analysis of the ROCKET AF study, rivaroxaban showed improved safety and efficacy compared to warfarin in patients with AF and diabetes mellitus.

Protection in diabetes

Diabetic patients with AF and CKD represent a particularly challenging population. Metabolic abnormalities predispose the arteries to atherosclerosis, increasing platelet reactivity and blood clotting. Progressive deterioration of kidney function is associated with increased rates of AF and a greater risk of bleeding.

An Italian study by Magnocavallo et al followed up a cohort of diabetic patients undergoing renal replacement therapy, documenting a significant advantage of treatment with rivaroxaban not only in terms of preservation of renal function but also in slowing the progression of cardiovascular calcifications [16].

Pharmacological Alternatives: Left Atrial Closure

Left atrial appendage occlusion (LAAO) as a complementary strategy

Given the difficulty of managing VKA therapy and the higher mortality rate in patients treated with warfarin, ESRD patients requiring anticoagulation may benefit from interventional procedures. Percutaneous LAAO has emerged as a potential alternative to lifelong oral anticoagulation, as 90% or more of thrombi during AF originate in the left atrial appendage.

Currently, this strategy is limited to patients at high thromboembolic and bleeding risk who are not suitable for long-term oral anticoagulants. Based on available data, the use of LAAO will grow enormously in the coming years, as the rate of major periprocedural adverse events is very low even in patients with multiple comorbidities and high thromboembolic/hemorrhagic risk [24].

In patients with advanced CKD, percutaneous LAAO appears to have a similar risk of periprocedural complications compared to patients without significant renal impairment. Recent studies have explored its efficacy for thromboembolic prevention in patients with ESRD, with very promising preliminary results, although not yet confirmed in large trials [24].

Transplant perspective

For patients undergoing renal transplantation, the prevention of vascular calcifications with DOACs (rather than VKAs) is particularly important. Systemic vascular calcifications sig-

nificantly worsen transplant outcomes and are an independent risk factor for graft loss. The reduced incidence of calcifications with DOACs therefore represents a significant additional benefit in this population.

Current Clinical Recommendations

ESC 2024 guidelines

The ESC 2024 guidelines recommend anticoagulant therapy for patients with AF at high thromboembolic risk. Thromboembolic risk stratification is performed using the CHA₂DS₂-VA score (Congestive heart failure, Hypertension, Age ≥ 75 years (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74 years, Sex category (female)). Oral anticoagulation is recommended (class I recommendation, level of evidence A) for males with a CHA₂DS₂-VA score ≥ 2 and females with a score ≥ 3 . DOACs are preferred to VKAs in patients with non-valvular AF (class I recommendation, level of evidence A), and LAA closure is recommended in addition to anticoagulant therapy in selected high-risk patients who have contraindications to long-term anticoagulation (class IIa recommendation, level of evidence B) [7].

Specific recommendations based on renal function include: 1) eGFR ≥ 60 mL/min/1.73 m²: standard DOAC dosing; 2) eGFR 30–60 mL/min/1.73 m²: dose-adjusted DOACs preferred over VKAs (class I); 3) eGFR 15–30 mL/min/1.73 m²: reduced DOAC dosages with caution; apixaban and rivaroxaban may be considered (class IIb, level of evidence C); 4) eGFR < 15 mL/min/1.73 m² or patients on RRT: use contraindicated according to most technical data sheets, though emerging evidence supports cautious use of reduced-dose apixaban or rivaroxaban in selected patients with multidisciplinary evaluation (class IIb, level of evidence C).

The guidelines emphasize that anticoagulation decisions in advanced CKD and dialysis patients should be individualized, considering both thromboembolic risk (CHA₂DS₂-VASc) and bleeding risk, recognizing that standard bleeding risk scores may underestimate risk in this population.

Clinical reality in PD

In the clinical practice of PD, this dilemma remains unresolved. Patients with AF and ESRD undergoing PD do not receive adequate anticoagulation assessments, leading to the underuse of effective antithrombotic strategies. At the same time, when warfarin is prescribed, the risks of WRN and vascular calcifications remain high.

Discussion and Future Perspectives

The emerging role of DOACs in PD

The current evidence base strongly suggests that DOACs may

represent a superior alternative to warfarin even in patients on PD. The documented mechanisms of nephroprotection, the lower incidence of vascular calcifications, and encouraging data from hemodialysis studies support this conclusion.

However, the extremely limited data available on PD represents a significant obstacle. The high prevalence of AF in dialysis patients, combined with the lack of robust evidence specific to PD, creates a significant gap in clinical practice.

Need for future research

As highlighted in De Vriese's recent editorial in *JASN*, there is a real "call to arms" [24]. What we know to date about the best anticoagulation strategy is mainly the result of observational studies and expert opinion. In light of the documented benefits, it would be appropriate to proceed with more robust trials specifically involving patients on peritoneal renal replacement therapy.

The ongoing studies represent an important step: AXA-DIA: Results published in 2023. In 97 hemodialysis patients with AF, apixaban 2.5 mg bid showed similar safety and efficacy to VKA therapy, with composite safety outcomes of 45.8% versus 51.0% and efficacy outcomes of 20.8% versus 30.6% respectively. Although the trial did not meet prespecified non-inferiority criteria due to lower-than-expected enrollment, the findings support the clinical use of apixaban in this population. RENAL-AF: Compare apixaban 5 mg bid with warfarin in dialysis patients (prematurely discontinued). Valkyrie: Comparison of warfarin, rivaroxaban 10 mg/day, and rivaroxaban + vitamin K2 in ESRD with encouraging results. APIDP2: First trial dedicated to PD, with completion in 2027.

A multidisciplinary approach

Anticoagulation management in patients with AF and ESRD on PD should be multidisciplinary, involving nephrologists, cardiologists, and, when appropriate, interventional cardiac surgeons. The individualized risk/benefit assessment should consider: 1) accurate stratification of thromboembolic and hemorrhagic risk; 2) residual renal function and PD clearance; 3) vascular calcification status and transplant eligibility; 4) social factors and therapeutic adherence; 5) availability of interventional procedures (LAAO).

Conclusions

AF in patients with advanced CKD, particularly those undergoing PD, represents a complex and largely unresolved therapeutic challenge. Current evidence suggests that DOACs, particularly apixaban and rivaroxaban at reduced doses, may offer significant advantages over VKAs in terms of nephroprotection, reduction of vascular calcifications, and a better safety profile. However, the near-total lack of specific data in the PD population represents a significant knowledge gap that hinders the clinical adoption of these strategies. Ongoing stud-

ies, particularly the APIDP2 study on PD, represent a crucial opportunity to fill this gap. In the meantime, a pragmatic approach based on the best available evidence, considering the possibility of using reduced-dose DOACs with close clinical and laboratory monitoring, could represent a reasonable option for many patients. Percutaneous LAA closure remains a valid alternative in patients at very high risk of bleeding or in those who refuse oral anticoagulation. Finally, it is appropriate for the nephrology community to continue with rigorous research and randomized trials specifically involving PD patients, thus providing the necessary evidence to optimize anticoagulation management in this complex and often overlooked population.

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Conflict of Interest

The authors declare no competing interests relevant to the contents of this article.

Author Contributions

Aldo Franculli: conceptualization, literature review, drafting of the manuscript, and coordination of the work. Luca Di Lullo: conceptual input, critical revision of the manuscript for important intellectual content. Pasquale Saporito: literature review and contribution to manuscript drafting. Eleonora Bernabei: data collection, literature analysis, and manuscript editing. Laura Pedata: literature review and contribution to specific sections of the manuscript. Vincenzo Barbera: data interpretation and critical manuscript revision. Lorenzo D'Elia: contribution to discussion and future perspectives sections; manuscript review. Antonio Bellasi: scientific supervision and critical revision for intellectual content. Paola Peverini: Literature analysis and manuscript editing. Andrea Dello Strologo: study supervision, critical revision, and final approval of the manuscript. All authors read and approved the final version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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