## **The role of anticoagulation in patients with coexisting chronic kidney disease and atrial fibrillation**

## ***JACC Review Topic of the Week***

## **Running title:** Anticoagulation in patients with coexisting AF and CKD

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**Abstract**

Atrial fibrillation (AF) and chronic kidney disease (CKD) often coexist as they share multiple risk factors including hypertension, coronary artery disease and diabetes mellitus. Whilst there is irrefutable evidence supporting oral anticoagulation in AF in the general population, these data may not be transferable to the setting of CKD, where the decision to commence anticoagulation poses a conundrum. In this cohort, there is a progressively increased risk of both ischemic stroke and hemorrhage as renal function declines, complicating the decision to initiate anticoagulation. No definitive clinical guidelines derived from randomized controlled trials exist to aid clinical decision-making, and the findings from observational studies are conflicting. In this review, we outline the pathophysiological mechanisms at play and summarize the limited existing data related to anticoagulation in those with concomitant CKD and AF. Finally, we suggest how to approach the decision of whether and how to use oral anticoagulation in these patients.

**Abbreviations:**

American Heart Association Task Force/Americal College of Cardiology/Heart Rhythm Society = AHA/ACC/HRS)

Atrial fibrillation = AF

Chronic kidney disease = CKD

Direct oral anticoagulant = DOAC

European Heart Rhythm Association = EHRA

European Society of Cardiology = ESC

Kidney Disease: Improving Global Outcomes (KDIGO)

Oral anticoagulant therapy = OAT

Renin-angiotensin-aldosterone-system = RAAS

**Condensed abstract**

Evidence from large-scale randomized controlled trials supports using oral anticoagulant therapy (OAT) for stroke thromboprophylaxis in high-risk patients with atrial fibrillation (AF). However, in patients with concomitant chronic kidney disease (CKD) and AF, OAT does not rest on firm evidence. CKD patients exhibit both increased thrombosis and bleeding, and conventional scores to estimate stroke and bleeding risk are unreliable. There is a paucity of studies upon which to infer guidance, and conflicting findings are reported in observational cohorts. Here, we review the pathophysiology and existing data, before suggesting an approach to OAT in patients with coexistent AF and CKD.

**Keywords:**

Atrial fibrillation (AF), Chronic kidney disease (CKD), Warfarin, Direct oral anticoagulant (DOAC), Vitamin K antagonist (VKA), Stroke, Hemorrhage

**Highlights**

* The decision to initiate oral anticoagulant therapy (OAT) poses a clinical conundrum in patients with coexisting atrial fibrillation (AF) and chronic kidney disease (CKD).
* In CKD, several pathophysiological factors result in a progressively increased risk of both ischemic stroke and hemorrhage as renal function declines, irrespective of OAT.
* The limited available data suggests that DOACs should generally be favoured over VKAs in view of their probable increased safety and efficacy in CKD, with a lower risk of vascular calcification and anti-coagulant associated nephropathy.
* Until dedicated RCTs are completed to define optimal management, clinical decision-making should be informed by the limited data available, which necessitates individualization and physician-patient collaboration.

**Introduction**

Atrial fibrillation (AF), the most commonly occurring sustained arrhythmia worldwide, is associated with an increased risk of thromboembolic stroke and all-cause mortality. In the general population with AF at increased risk for thromboembolic complications, oral anticoagulant therapy (OAT) for stroke thromboprophylaxis is universally recommended in clinical guidelines (1-5).

Chronic kidney disease (CKD), affecting up to 15% of adults worldwide, is associated with increased cardiovascular disease (CVD) risk and age-standardised all-cause mortality, independent of other known risk factors (6,7) (Figure 1). It is not necessarily the case that therapeutic interventions, whose efficacy and safety profiles are well-understood in the non-CKD setting, can be utilised in CKD patients with a similar risk-to-benefit ratio. Indeed, there are situations where it has been shown to be incorrect to extrapolate from non-CKD to CKD cohorts e.g. statins do *not* reduce mortality in patients with stage 5 CKD (8). To date, the few large observational studies that have specifically studied the outcomes of OAT in patients with coexisting CKD and AF have yielded conflicting results, in both non-dialysis (9-12) and end-stage renal disease (ESRD)cohorts (13-18). Interestingly, some series have reported a paradoxical increase in ischemic stroke in non-ESRD (12) and hemodialysis patients with AF treated with OAT (16). This highlights the compelling need for adequately powered RCTs to provide clarity on this issue.

It is the purpose of this review to address the evidential gap of whether, when, and how to attempt OAT in patients with concomitant AF and CKD to safely reduce the risk of subsequent stroke.

**Arrhythmias in CKD**

Arrhythmias including AF, atrial flutter, ventricular arrhythmias and sudden cardiac death are frequent in patients with advanced CKD (19). They are associated with stroke, vascular dementia, myocardial infarction, heart failure, progressive CKD and death. Population-based studies suggest that AF occurs in around one in five patients with CKD not receiving dialysis (20), and about one in three patients undergoing dialysis (21,22). Although the prevalence of AF is reported to be up to 10-fold higher in patients with CKD aged less than 55 years compared with age-matched non-dialysis patients, it is in those over the age of 60 years that the prevalence of AF is the highest (21). As renal function declines, the prevalence of AF increases; among 235,818 subjects followed for 6 years, AF prevalence increased by 57% for those with an eGFR <30 compared with 32% for those with an eGFR of 30-59 mL/min per 1.73m2 (23).

A number of mechanisms have been proposed to account for why AF is more common in CKD patients. CKD is associated with a number of arrhythmogenic substrates which can result in the development of AF **(Table 1).** Activation of the renin-angiotensin-aldosterone-system (RAAS), occurring in CKD and associated with progressive renal disease, increases circulating levels of angiotensin II which contribute to atrial myocyte apoptosis and interstitial fibrosis (24). Studies in patients without CKD have found a correlation between markers of inflammation and AF burden (25), and an inverse relationship between levels of inflammation and maintenance of sinus rhythm following cardioversion (26). Similarly, inflammatory markers are elevated in CKD patients, and the prevalence of AF in patients with CKD is higher in the presence of a chronically elevated level of CRP (27). Left atrial enlargement and diastolic dysfunction are more common in patients with than without CKD, (28) and this is associated with AF (20). Myocardial fibrosis is common in CKD, and this may provide a structural substrate which enhances atrial re-entrant excitation (29).

AF in CKD is associated with stroke, heart failure, progressive CKD, death, as well as the potential adverse consequences of stroke risk prophylaxis using OAT. In a study of over 116,000 patients with CKD (eGFR<60 ml/min per 1.73 m2), new-onset AF was associated with a higher incidence of both stroke and death (30). AF is not only an independent predictor of death, but also a marker of underlying CVD and its associated impact (19). In a study of 206,229 patients with CKD, developing of AF was associated with a 67% enhanced risk of progression to end-stage renal disease (ESRD) at 5 years follow-up (31).

**Clotting and Bleeding in CKD**

Renal dysfunction causes alterations in hemostatic systems that may result in both a prothrombotic state and a bleeding diathesis **(Figures 2 and 3).** Changes in coagulation are influenced by the various pathophysiological mechanisms that cause CKD and also differ in acute kidney injury (AKI) versus CKD, and in patients undergoing dialysis. The pathophysiological mechanisms related to the effect of uremic toxins on various aspects of blood coagulation are poorly understood and many of the studies which tried to address this experimentally were performed when dialysis was in its infancy, and thus would benefit from repetition with modern dialysis patients and practices (32). The interactions between anticoagulation used for hemodialysis (typically heparin), and simultaneous use of one or more anti-platelet agents, and OAT, are poorly characterised in the dialysis population with the risk of increased bleeding (33).

**AF and Stroke in CKD Patients**

CKD is an independent risk factor for incident stroke (34). There is a linear relationship between GFR and risk of stroke increasing by 7% for every 10 mL/min/1.73 m2 GFR decrease (35). Albuminuria is also independently associated with stroke and cognitive impairment. The presumed etiology of these pathologies in CKD is multifactorial **(Figure 3).**

Both CKD and stroke share common traditional risk factors such as diabetes mellitus, smoking, hypertension, hypercholesterolemia and AF. Disorganized atrial contraction with a reduction in atrial blood flow, atrial fibrosis, endothelial and endocardial injury and dysfunction, augmented expression of tissue factor and von Willebrand factor, amplified platelet activation and fibrinolysis may all predispose to thrombus formation and systemic embolization in CKD patients with AF (34).

**Challenges of quantifying loss of renal function on an individual patient basis**

The most commonly used renal function estimation equations based on serum creatinine concentration and demographic variables are the Cockcroft-Gault formula (CG), the Modification of Diet in Renal Disease Study (MDRD) and the most recent equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Table 1, Figure 1) (36). While most nephrologists favour the latest CKD-EPI equation for diagnosing and classifying CKD, there is no consensus about the best formula to use for guiding drug dose choices; medical regulatory requirements still mandate the use of the dated CG formula despite it no longer being used in clinical practice. This is a significant concern as there is the potential for drug dosing errors; many commonly used medications in patients with AF or heart failure require dose adjustment according to renal function. There can be striking differences between the derived GFR values using these different equations (36).

**The utility of bleeding and clotting scoring schemes in CKD**

In the general population with AF, OAT is supported by guidelines that mandate the use of scoring systems to estimate thromboembolic and bleeding risk, most commonly through the CHA2DS2-VASc and HAS-BLED scores, respectively (5). Other scores include [CHADS2](https://www.sciencedirect.com/topics/medicine-and-dentistry/chads2-score), R2CHADS2, ABC, GARFIELD and ATRIA (to estimate stroke risk) and ABC, ATRIA, GARFIELD, ORBIT, HEMORRAGES (to estimate hemorrhage risk) (37). Although these scoring systems have been studied in a range of populations, their transferability to the setting of CKD is largely untested.

The most commonly used score for predicting stroke risk, CHA2DS2-VASc, was superior to [CHADS2](https://www.sciencedirect.com/topics/medicine-and-dentistry/chads2-score) in predicting the risk of ischemic stroke in a Taiwanese cohort of patients with ESRD requiring dialysis. Nevertheless, both of these scoring systems do not take account of loss of renal function (38). Moreover, R2CHADS2, which does incorporate a measure of renal status in the form of eGFR or creatinine clearance <60 ml/min has not yet been validated at creatinine clearances <30 ml/min. ATRIA has a single risk inflection point at an eGFR less than 45 ml/min/1.73 m2 and does not further subdivide severity of renal impairment or take in to consideration the different renal replacement therapy modalities which patients may be receiving.

While the commonly used scores to estimate bleeding (HAS-BLED, ATRIA, ORBIT, HEMORRAGES) attempt to reflect kidney function, they do not utilise eGFR thresholds and fail to differentiate between patients receiving different forms of renal replacement therapy. Current bleeding scoring systems are unreliable when applied to dialysis patients (39).

**Oral Anticoagulants in CKD**

**Vitamin K antagonists**

Vitamin K antagonists (VKAs) interfere with the synthesis of functional coagulation factors through inhibition of the vitamin K epoxide reductase. Management with VKAs is challenging due to their narrow therapeutic range, unpredictable dose-response, and interactions with drugs and food, which necessitate the close monitoring of the prothrombin time (International Normalized Ratio, INR) (40). The benefits of warfarin in AF patients with mild and moderate CKD to reduce stroke is firmly established (41). However, robust data on the benefits and risks in patients with severe CKD and ESRD are lacking.

In patients with severe CKD, the proportion of time in the INR target range (TTR) is lower than in patients with milder or no CKD (42). Low TTR is associated with an increased risk for stroke, bleeding and death (43).Even though warfarin is metabolized hepatically, patients with CKD require a lower dose of warfarin compared to patients with lesser or no renal impairment, typically 20% lower in severe CKD (42). Patients with CKD have a more labile INR and an increased risk for supratherapeutic INRs, especially during initiation.

Another important consideration of VKA in CKD is the risk of enhanced vascular calcification (44). Vascular calcification is inhibited by Matrix Gla Protein (MGP), a protein that also requires vitamin K dependent carboxylation to interact with calcium similarly to the vitamin K dependent coagulation factors. Uncarboxylated MGP may further enhance vascular calcification, a specific concern in CKD patients who have the burden of excess calcium and phosphate body deposition (45).

CKD patients who receive OAT are susceptible to anticoagulant-related nephropathy, which manifests as AKI secondary to glomerular hemorrhage and renal tubular obstruction as a consequence of excessive anticoagulation (46). Notably, in AF patients treated with warfarin, biopsy-proven anticoagulant-related nephropathy occurred twice as frequently in those with CKD compared to patients without underlying renal disease (47).

**Direct oral anticoagulants**

There are several direct oral anticoagulants (DOACs) currently approved for clinical use in AF which act as direct inhibitors of factor Xa (apixaban, edoxaban and rivaroxaban) or of thrombin (dabigatran). RCTs have demonstrated a benefit of DOACs compared with warfarin, including in patients with mild to moderate CKD (48). A recent systematic review and meta-analysis of over 78,000 patients with non-dialysis CKD and AF found that DOACs had a superior safety and efficacy profile to VKA, reducing stroke consistently with fewer major bleeding events (49). Indeed, contemporary evidence-based guidelines currently recommend DOACs over VKAs if OAT is judged appropriate, including those with CKD stages 1-3 (1-5). However, the situation in CKD stages 4 and 5 is more nuanced, mainly because these patients have been largely excluded from all of the registration and post-registration trials.

Relevant drug characteristics of DOACs are summarized in **table 3** (3). There is concern about drug/metabolite accumulation in patients with severe CKD. While there is a dose-response relationship for drug levels and bleeding (50,51), ideal therapeutic ranges of drug concentrations are not yet clearly established (3). Post-hoc analyses of the RCTs have revealed that DOACs, particularly dabigatran and rivaroxaban, are associated with reduced loss of GFR compared to warfarin (52,53). More trials with these outcomes as their primary focus are urgently required, particularly as there are currently inconsistencies in the prescribed doses of DOACs in routine clinical practice (54).

**Oral anticoagulant therapy in CKD**

In patients with **mild/moderate CKD** (eGFR 30-59 ml/min or stage 3a and 3b), present evidence on OAT suggests that it can be used safely and confers benefit . In this category of patients, both VKAs and DOACs have shown similar efficacy. In the majority of studies on DOACs, their safety profile seems to be at least non-inferior or even superior to VKAs (55-57). Interestingly, only when using the CKD-EPI equation was there an interaction between dabigatran and renal function in terms of risk of bleeding (58). It must be conceded, however, in the RE-LY study, the dose of dabigatran was not titrated to reflect the degree of CKD. Furthermore, in a recent systematic review and meta-analysis of 5 RCTs including 13878 AF patients with moderate CKD, DOAC use was associated with reduced risk of stroke/systemic embolism (OR 0.79; 95 % C.I. 0.67-0.94) and lower incidence of major bleeding (OR 0.74, 95% CI 0.65-0.86) (59). In this context, OAT is recommended by the European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA) and in the US guidelines, by the American Heart Association Task Force/Americal College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS), American College of Chest Physicians (CHEST guideline) and Kidney Disease: Improving Global Outcomes (KDIGO) conference reports – 2018) **(Table 4)** (1-5).

In individuals with CKD stage 4, all guidelines allow the use of warfarin, even though the net-benefit OAT itself has never been prospectively assessed in an RCT in this patient population. Additionally, AHA/ACC/HRS guidelines suggest treatment for patients with nonvalvular AF and moderate-to-severe CKD with CHA2DS2VASc scores of 2 or greater, using reduced doses of dabigatran and rivaroxaban (CrCl 30 - 49 ml/min), or apixaban (if CrCl between 25-29 ml/min) - CLASS IIb, level of Evidence: C. Whilst the EHRA/KDIGO guidelines do not formally recommend the use of DOACs in this category of patients, they do suggest that they can be considered for use (**Table 4**).

Although there are limited efficacy and safety outcome data, both the FDA and EMA have approved reduced doses of apixaban, edoxaban and rivaroxaban in patients with an eGFR 15-30 mL/min; the FDA has also approved the use of a specific low dose dabigatran (75 mg bid), based solely on pharmacokinetic data, for these patients **(Table 5).**

In patients with **CKD stage 5** and AF, there is no RCT-derived evidence that OAT has a favourable benefit–risk ratio. In this context, the EHRA did not provide specific recommendations regarding anticoagulation in HD, underlining the absence of RCTs for both VKAs and DOACs, and the contradictory results of observational studies reporting stroke prevalence. The KDIGO recommendations (2018) concluded that there is insufficient high-quality evidence to recommend VKAs for prevention of stroke in CKD stage 5 patients with AF, especially when balancing the significant risks of bleeding, accelerated vascular calcification, and calcific uremic arteriopathy associated with VKA therapy. Most recently, there was an updated 2019 AHA/ACC/HRS focused update guideline for the management of patients with AF; in this report there was a soft recommendation for using OAT with either warfarin or low-dose apixaban with the caveat “but further study is warranted” (5).

**No RCTs, but what about Registries and Regulators**?

A meta-analysis of 43,850 patients from five observational cohort studies including CKD stage 4-5 or 5D found that the use of apixaban was associated with lower risk of major bleeding compared to warfarin and to be relatively effective with no excess risk of thromboembolic events (60). A recent systematic review including 10 observational studies (3 with patients with eGFR < 25 ml/min or on dialysis) found that in dialysis patients there was no difference in stroke risk between apixaban, dabigatran [relative risk (RR) 1.71, 95% CI 0.97–2.99] or rivaroxaban (RR 1.8, 95% CI 0.89–3.64) versus warfarin (59). In hemodialysis patients, rivaroxaban and dabigatran were associated with an increased major bleeding risk (RR 1.45–1.76), whereas there was no major bleeding difference with apixaban compared to warfarin. A retrospective cohort study of Medicare beneficiaries included in the US Renal Data System (2,351 patients on apixaban and 23,172 patients on warfarin) found that apixaban use may be associated with lower risk of major bleeding compared with warfarin, with a standard 5 mg twice a day dose also associated with reductions in thromboembolic and mortality risk in ESRD (14). A retrospective series of AF patients with CKD stage 4 and 5 compared outcomes of 1,896 and 4,848 patients treated with rivaroxaban and warfarin, respectively, using MarketScan data. Rivaroxban was associated with fewer major bleeding events than warfarin, although neither anticoagulant reduced stroke or systemic embolism (61).

Though the FDA does mention OAT usage, it is crucial to understand that while both VKAs and DOACs have a recommended dosing for dialysis patients with AF (Tables 5 and 6), the FDA itself has not endorsed this indication for use in this population. Both labels indicate, “it is not known whether these concentrations will lead to similar stroke reduction and bleed risk in patients with ESRD on dialysis as was seen in ROCKET-AF/ARISTOTLE,” respectively. These decisions appear to be underpinned by very limited pharmacokinetic and pharmacodynamic studies (62-65). The European Medical Agency has not yet conformed with this approach.

**Non-anticoagulative approaches**

Other options such as left atrial appendage occlusion (LAAO) closure or excision may be a viable alternative to OAT in patients at risk of both cardioembolic stroke related to AF and life-threatening or recurrent major bleeding. Those with advanced CKD and AF comprise the most at-risk group. One LAAO device is approved in the USA and two are available in Europe; the technique is recommended in major guidelines (1,5) and reviewed elsewhere (66,67).

**How to approach OAT in patients with CKD and AF**

Presently, there is no RCT-based evidence regarding the benefit of OAT in patients with AF and CKD **(Table 4).** A suggested approach is provided in the **central illustration.** A rigorous discussion of the risk and benefits of OAT, taking into account patients’ characteristics and preferences is crucial to inform the decision. If it is deemed appropriate to use OAT, DOACs should generally be favoured in view of the limited efficacy and safety data available, along with the increased risk of vascular calcification, calciphylaxis and anti-coagulant associated nephropathy (glomerular haemorrhage) associated with VKAs. If OAT is not initiated, the viability of a non-pharmacological treatment such as LAAO should be considered or whether in fact no therapy is the most prudent choice.

**Conclusions**

Clinical trial and real-world clinical data from the non-CKD setting cannot be reliably and safely extrapolated into clinical practice for patients with significant/dialysis-requiring CKD. Initiating OAT in CKD patients is contentious due to their increased propensity to both thrombosis and bleeding. Furthermore, conventional scoring systems for estimating bleeding and clotting risk are not validated in CKD patients and cannot be relied upon alone for clinical decision-making. Until dedicated RCTs are undertaken, the decision of whether and how to initiate OAT in patients with concomitant CKD and AF requires an individualized approach with physician-patient collaboration.

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**Figure 1.** Stages of chronic kidney disease. Colors depict risk of progression, morbidity and mortality. Green (low risk), Yellow (moderate risk), Orange (high risk) and Red (very high risk). ACR - Albumin-to-creatinine ratio, GFR - glomerular filtration rate

**Figure 2.** Pathophysiology of the increased thrombotic risk in coexistent CKD and AF. Alterations in the three components of Virchow’s triad contribute to the increased risk of thromboembolism in coexistent CKD and AF. Altered pro-thrombotic blood constituents and increased platelet activity create a hypercoagulable state. Alterations in atrial anatomy and contractility, activation of the renin - angiotensin - aldosterone system and altered vessel wall contractility secondary to inflammation result in deranged hemodynamics. Injury and dysfunction of the cardiac muscle and vascular endothelium predisposes to thrombus formation. There is significant interplay between the individual effectors and the components of the triad.

**Figure 3.** The pathophysiology of hemorrhage in chronic kidney disease. Platelet dysfunction which is common in CKD can degrade hemostasis facilitating a pro-hemorrhagic state. Altered composition of α-granules, abnormal calcium mobilisation, dysregulation of arachidonic acid metabolism and increased oxidative stress all conspire to alter platelet function and activation. Proteolysis of platelet GPIIb receptors and defective interactions with vWF reduces adhesion to denuded endothelium. Platelet aggregation is compromised through competitive inhibition of the GPIIb/IIIa receptor complex by circulating fibrinogen fragments present in uremia and through altered receptor function. Coexistent anemia alters platelet function through a variety of indirect mechanisms. Many common medications used in the context of CKD treatment can act on the coagulation pathway; there are a number of regular dialysis and other procedures which mandate blood vessel wall breach with consequential hemorrhage.

**Central illustration.** Proposed approach to stroke thromboprophylaxis in a patient with concomitant CKD and AF.

\* References 1-5
\*\* Existing scoring systems are not validated in this setting
\*\*\* Please refer to tables 4 and 5 for current dosage recommendations

**Table 1.** Why does CKD predispose to AF?

**Table 2.** The most commonly used equations for the derivation of GFR from serum creatinine and a number of other parameters. A detailed discussion of this complex topic is beyond the scope of this article but readers are directed to reference 38. SCr - serum creatinine (mg/dL), IDMS - isotope-dilution mass spectrometry

**Table 3:** Absorption and metabolism of the different DOACs. Adapted from Steffel et al, European Heart Journal (3).

**Table 4:** DOAC Dosing and Oral Anticoagulation Medical Guidelines (2016 onwards) for AF in CKD

**Table 5:** EMA/FDA recommendation for CKD stages 4 and 5(D) patients