Atrial Fibrillation and Anticoagulant Treatment in End-Stage Renal Disease Patients: Where Do We Stand?

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Abstract
The frequent coexistence in daily clinical practice of chronic kidney disease (CKD) and atrial fibrillation (AF), especially in the elderly, represents a conundrum for physicians, mainly related to the management of anticoagulant therapy. The reduction of estimated glomerular filtration rate (eGFR) impairs anticoagulant clearance, increasing bleeding propensity. Moreover, dysfunctional responses of endothelial cells and inflammatory systems both trigger thromboembolic status. Those mechanisms pose an increased risk of adverse events for AF patients with CKD. While several data suggested the use of direct oral anticoagulants (DOACs) over warfarin as preferred anticoagulant strategy in patients with Stage 3A to Stage 4 CKD (eGFR range of 15–49 mL/min/1.73 m\textsuperscript{2}), less is known about the optimal anticoagulation management in patients with end-stage renal disease (ESRD) or on renal replacement therapy (RRT). Furthermore, a pivotal feature to be considered when choosing the anticoagulant drug in CKD patients is represented by nephroprotective capability. Indeed, anticoagulant therapy with warfarin showed detrimental effects on kidney function, whereas DOACs demonstrated a beneficial effect on renal function preservation. Mounting data showed that, when pharmacological treatment cannot be pursued due to contraindication to anticoagulation, left atrial appendage occlusion (LAAO) may represent a valid alternative. This brief review outlines the current knowledge regarding anticoagulation therapy in ESRD/RRT patients, reporting new lines of evidence on the nephroprotective effect of oral anticoagulants and on the use of LAAO as a non-pharmacological alternative to oral anticoagulation.

Introduction
Chronic kidney disease (CKD) is frequently diagnosed in clinical practice and its prevalence is expected to increase in the next decades due to population aging and diffusion of risk factors for CKD in the general population, such as systemic arterial hypertension [1]. It is well known that CKD is associated with poor outcomes, with

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an inverse relationship among estimated glomerular filtration rates (eGFRs) and adjusted risk ratios for death from any cause: patients with end-stage renal disease (ESRD) and eGFR <15 mL/min/1.73 m² have an almost 6-fold increased risk of mortality as compared to patients with eGFR >60 mL/min/1.73 m² [2]. Unfortunately, CKD not only increases mortality from any cause but also the incidence of cardiovascular diseases, such as atrial fibrillation (AF). On the one hand, the prevalence and incidence of AF increase with decreasing renal function due to the association of renal dysfunction with proinflammatory state, systemic arterial hypertension, endothelial dysfunction, and left ventricular hypertrophy [3]. Reduced eGFR and elevated urine albumin-to-creatinine ratio were significantly associated with higher risk of incident AF [4]. As a result, AF and CKD frequently coexist: up to 20% of CKD patients present AF and 40–50% of AF patients suffer from CKD [5]. Since all direct oral anticoagulants (DOACs) are partly eliminated by the kidneys, the coexistence of CKD and AF represents a unique challenge in clinical daily practice due to the synergic increase of thromboembolic and bleeding events risk [6, 7], especially for patients with ESRD (Fig. 1, 2). In patients with moderately to severely reduced renal function (glomerular filtration rate below 60 mL/min/1.73 m²), the risk of thromboembolic events is increased due to the higher plasma levels of coagulation factors and the reduced excretion of anticoagulant and antiplatelet drugs.
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Current guidelines recommend DOACs as preferred anticoagulant strategy over warfarin [5, 8]. Indeed, in this category of CKD patients, several studies have demonstrated the superiority of DOACs, as compared to warfarin, in reducing AF-related thromboembolic complications and bleeding events [9–13]. Moreover, in moderate to severe CKD, DOACs showed mortality benefit and a greater renoprotective effect as compared to warfarin [14–16]. Fewer data have been published in literature on the use of DOACs in patients with severely reduced renal function and ESRD or on renal replacement therapy (RRT). In patients with severe CKD (eGFR of 15–29 mL/min/1.73 m²), new observational data suggest a favorable efficacy and safety profile of reduced dose regimen of rivaroxaban, apixaban, and edoxaban compared to warfarin [17–20]. As a result, 2020 AF ESC guidelines and 2021 EHRA practical guide on the use of DOACs in patients with AF allow a cautionary use of Factor Xa inhibitors in patients with severe CKD [5, 8]. Even less is known about the best anticoagulant strategy in patients with AF and eGFR <15 mL/min/1.73 m² or on RRT, due to the few observational and conflicting studies that have been published so far. Although ESRD portends the highest thromboembolic and bleeding propensity across the whole CKD spectrum, recent evidence showed that DOACs may be not only safer but also more effective than warfarin in this subgroup of patients, suggesting that DOACs may be suitable for ESRD patients or for patients on RRT [7].

Renoprotection and DOACs

A cornerstone of CKD patients’ management is represented by nephroprotection, especially in early stages of the disease and in high-risk patients as those with diabetes and heart failure. In these subgroups of patients, new oral hypoglycemic drugs such as glyfoxizines or GLP-1 agonists have shown a favorable renoprotective effect [5]. The maintenance of renal function is particularly important in patients with coexistent AF because anticoagulation is associated with renal function decline [14]. In patients with AF and CKD, renal function declines faster in those with warfarin exposure versus no warfarin exposure [1]. Warfarin nephrotoxicity, also called “warfarin-related nephropathy,” was suggested for the first time in 2009 by Brodsky et al. [14], as a result of two main pathophysiological processes: the disruption of the glomerular filtration...
tion barrier causing bleeding into Bowman’s space and the aggregation of red blood cells, forming casts in the tubules, which lead to their obstruction and ischemia. Moreover, the inhibition of the vitamin-K-dependent matrix gamma-carboxyglutamate protein is responsible of vascular calcifications leading to renal microcirculatory injuries, decline in eGFR, and increased mortality rate [21].

Conversely, the use of DOACs in AF patients is associated with a protective effect in terms of slowing the progression of kidney disease and evolution towards ESRD. In a large US administrative database including almost 10,000 patients, Yao et al. [22] showed that, as compared to warfarin, dabigatran, rivaroxaban, and apixaban were associated with lower rates of adverse renal outcomes, such as greater than or equal to 30% reduction in glomerular filtrate compared to baseline, the incidence of acute kidney injury, or the doubling, compared to baseline, of serum creatinine levels. These results were confirmed and expanded in a new paper published in 2020, documenting nephroprotective effects of rivaroxaban and dabigatran also in patients with advanced stages of CKD [23].

Di Lullo et al. [24, 25] showed that in a cohort of patients with moderate to severe CKD the use of rivaroxaban was associated with an improvement/stabilization in eGFR and cardiac valve calcifications as compared to warfarin. These results seem to be related to the significant reduction of cytokines levels observed in rivaroxaban arm: since higher cytokines levels were associated with reduction of eGFR and augmented severity of cardiac valve calcifications, the anti-inflammatory effects of rivaroxaban may be responsible of the delay in kidney disease progression and of the decrease in the density of cardiovascular calcifications [24, 25].

Recently, a population-based study from the UK found that in patients with AF and baseline preserved renal function (eGFR >50 mL/min/1.73 m²), an anticoagulation strategy based on rivaroxaban markedly reduced the risk and rate of renal decline as compared to a warfarin-based strategy [26]. On the basis of these data on the nephroprotective effects of DOACs, it is therefore interesting to see what happens in patients with eGFR values below 15 mL/min/1.73 m² and in those undergoing hemodialysis treatment.

DOACs and ESRD

Increased bleeding risk and lack of safe evidence for an effective risk/benefit ratio are the main reasons for the limited use of anticoagulants in patients with CKD, especially those undergoing RRT [27]. On the one hand, drug clearance is strictly dependent on molecule size, plasma protein-bound rates, and physicochemical properties of the dialysis filter, so that warfarin and DOACs are both poorly cleared by dialysis clearance in patients undergoing RRT (Table 1). On the other hand, conflicting results have been published on the effectiveness of anticoagulation in ESRD patients. A large meta-analysis including 47,480 patients showed that warfarin did not reduce the incidence of ischemic stroke in ESRD patients but increased rates of hemorrhagic stroke [28]. While the superiority of DOACs over warfarin is well documented in patients with preserved renal function or moderate CKD, there is a lack of currently available data for DOACs in patients with severe CKD or ESRD that may lead to an increased risk of bleeding [29]. Since all landmark studies on DOACs have excluded patients with eGFR <30 mL/min/1.73 m² (except for a few patients on apixaban with eGFR 25–30 mL/min/1.73 m²), there are no data from randomized controlled trials on the use of DOACs for stroke prevention in AF patients with severe CKD or on RRT [30–34].

Few pieces of evidence are available on the use of DOACs in patients on RRT. The main studies assessed pharmacokinetics features associated with the use of DOACs in patients on dialysis. Dabigatran 110 or 150 mg twice daily was associated with 1.5- to 3.3-fold increase in area under the curve than in standard RE-LY patients, whereas the use of dabigatran 75 or 110 mg once daily produced exposures similar to those measured in RE-LY patients. These results suggest that the lower-dose regimen may be more suitable for hemodialysis patients [29, 35].

More detailed information on the pharmacokinetic characteristics of apixaban is available. Apixaban 2.5 mg b/day administered to RRT patients resulted in drug exposure similar to that of the standard dose (5 mg b/day) in patients with preserved renal function, whereas apixaban 5 mg twice daily is associated with supratherapeutic levels in ESRD [36, 37]. In addition, apixaban is highly protein-bound, and in the event of a bleeding event, reversal of anticoagulant activity with a prothrombin complex concentrate should be attempted instead of dialysis.

Similarly, rivaroxaban 10 mg/day in hemodialysis patients resulted in drug exposure similar to that of the standard dose (20 mg/day) in patients with normal renal function [38]. Surprisingly, deterioration of renal function from severe CKD to ESRD does not appear to have a significant impact on rivaroxaban pharmacokinetics and anticoagulant effect compared with changes observed with moderate or severe renal impairment [39].
Table 1. Pharmacodynamic and pharmacokinetic features of oral anticoagulants

| Characteristics                        | Warfarin                                                                 | Rivaroxaban     | Apixaban         | Edoxaban       | Dabigatran     |
|----------------------------------------|---------------------------------------------------------------------------|-----------------|------------------|----------------|----------------|
| Mechanism of action                    | Inhibition of vitamin K dependent clotting factors (II, VII, IX, X)       | Factor Xa inhibition | Factor Xa inhibition | Factor Xa inhibition | Factor IIa (thrombin) inhibition |
| Dosing                                 | Variable (INR monitoring) OD                                              | Fixed 20/15 mg OD | Fixed 5/2.5 mg BID | Fixed 60/30 mg OD | Fixed 150/110 mg BID |
| Protein binding, %                     | 99                                                                        | 90              | 87               | 40–59          | 35             |
| Metabolism                             | Extensive metabolism by CYP2C9                                             | Metabolized in the liver by CYP3A4/2J2 (65%) | Metabolized in the liver by CYP3A4 (75%) | Metabolized in the liver by CYP3A4 (50%) | Esterase mediated hydrolysis (no CYP450) |
| Interactions                           | Multiple food-drug and drug-drug                                          | CYP3A4/2J2 P-gP | CYP3A4 P-gP      | P-gP           | P-gP           |
| Renal excretion, %                     | <1                                                                        | 35              | 25               | 50             | 80–85          |
| C_{max}, h                             | 72–96                                                                     | 2–4             | 3–4              | 1–2            | 1–2            |
| t1/2, h                                | 40                                                                        | 6–13            | 12               | 10–14          | 12–14          |
| Dialyzable                             | No                                                                        | No              | Small            | No             | Yes            |
| Recommendation in severe renal impairment (eGFR = 15–29 mL/min/1.73 m²) | Strict INR monitoring                                                      | Dose adjustment (15 mg QD) | No action until at least 2 criteria fulfilled (age ≥80 years; weight ≤60 kg; creatinine ≥1.5 mg/dL) | Dose adjustment (30 mg QD) | Contraindicated (EU)/dose adjustment (75 mg BID [US]) |
| Recommendation in ESRD or RRT (eGFR <15 mL/min/1.73 m²) | Strict INR monitoring                                                      | Dose adjustment (15 mg QD [US])/individualized multidisciplinary approach (EU) | No action until at least 2 criteria fulfilled (age ≥80 years; weight ≤60 kg; creatinine ≥1.5 mg/dL [US])/individualized multidisciplinary approach (EU) | Contraindicated (US)/individualized multidisciplinary approach (EU) | Contraindicated |

BID, twice a day; C_{max}, peak concentration; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; OD, once a day; P-gP, P glycoprotein transporter involved in absorption and renal clearance; t1/2, half-life.
Promising data on the efficacy and safety of DOACs in ESRD have been recently published [40]. In a retrospective cohort study, apixaban as compared to warfarin proved to be superior in ESRD patients in terms of both safety and efficacy; both the standard (5 mg/bd) and reduced (2.5 mg/bd) doses of apixaban were associated with lower risks of major bleeding, but only the standard dose (5 mg/bd) was associated with lower thromboembolic events and mortality [41]. Miao et al. [42] did not find any difference in thromboembolic and bleeding events comparing rivaroxaban and apixaban in ESRD patients; however, compared with warfarin, rivaroxaban appeared safer, with greater reduction in bleeding [43]. In addition, a meta-analysis enrolling 71,877 long-term dialysis patients with AF showed a significantly lower risk of mortality in patients receiving apixaban 5 mg twice daily than those receiving apixaban 2.5 mg twice daily, warfarin, or no anticoagulant and a lower risk of bleeding as compared to those taking warfarin, dabigatran, or rivaroxaban [44]. Overall, among patients with advanced CKD and ESRD, apixaban seems a promising anticoagulant strategy, reducing the risk of major bleeding compared with warfarin and preventing systemic embolism [45–48].

Extremely interesting data come from the Valkyrie study, conducted with rivaroxaban, in which three different therapeutic intervention strategies were compared in patients undergoing hemodialysis treatment [49]. A first arm of patients was treated with vitamin K antagonists (VKAs) with the therapeutic target of international normalized ratio (INR) between 2 and 3, a second arm was treated with rivaroxaban at a dosage of 10 mg/day, and a third arm was treated with combination therapy rivaroxaban 10 mg/day and vitamin K2. The results of the study, although conducted on a sample of only 117 patients, showed, once again, the superiority of direct anticoagulant therapy over VKAs. More specifically, in patients treated with rivaroxaban or with the combination of rivaroxaban and vitamin K2, a clear increase in 5-year survival was observed together with a decrease in the composite outcome of fatal and nonfatal cardiovascular events and major bleeding complications compared to VKA.

Randomized trials comparing DOACs and warfarin in ESRD are eagerly awaited to clarify which is the safest and most effective long-term stroke prevention therapy in ESRD and AF patients (Table 2). Similar rates of clinically relevant major and nonmajor bleeding events were reported in the RENAL-AF study in which patients were randomized to apixaban 5 mg/bd or warfarin...
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Although limited, the aforementioned data foster the use of DOACs in patients with ESRD or on RRT. Nowadays, rivaroxaban 15 mg/day and apixaban 5 mg/bd (reduced dose 2.5 mg/bd in patients 80 years of age or older who weigh 60 kg or less) are approved by the Food and Drug Administration as a long-term oral anticoagulant in ESRD patients. Moreover, a novelty that is far from negligible, the latest EHRA Practice Recommendations 2021 foresee, for patients with glomerular filtration values ≤15 mL/min/1.73 m², to evaluate the possibility of an off-label use of DOACs in this subgroup of patients [8]. The same KDIGO nephrology guidelines begin to contemplate the possibility of using rivaroxaban (15 mg/day) or apixaban (2.5 mg twice daily) in patients with eGFR ≤15 mL/min/1.73 m² or under hemodialysis treatment [55]. On the other hand, emerging lines of evidence have been raised concerning an increased risk of fatal intracranial hemorrhages in a USRDS large cohort of apixaban-treated hemodialysis patients [56].

Other Anticoagulant Approaches in ESRD Patients

If treatment with DOACs cannot be practiced and the only option available is VKAs, which is not very recommendable given the difficulty in managing this therapy in this particular patient population (excessive fluctuations in INR values, poor patient compliance), one possibility is the surgical approach with closure of the left atrial appendage. The latter has emerged as a potential alternative to lifelong oral anticoagulation because 90% or more of the thrombi during AF are located in the left atrial appendage, a remnant of the primordial left atrium [56]. The main indication for LAAO is reserved for patients with a high thromboembolic and bleeding risk who are not eligible for long-term OACs. However, the use of LAAO is likely to grow tremendously in the future due to the relatively low periprocedural thromboembolic and bleeding complications, especially in high-risk subgroups of patients such as ESRD patients and on RRT [57–65]. Indeed, in patients with advanced CKD, percutaneous LAAO appears to have a similar risk of periprocedural complications compared with patients without significant renal impairment [66, 67].

In addition, recent studies have explored its efficacy for thromboembolic prevention in patients with ESRD [67–71]. Although not yet confirmed in large studies, these preliminary results are very promising. We believe that LAAO could be a viable alternative to lifelong anticoagulation in patients with advanced CKD with AF, thus providing effective thromboembolic prevention without increasing the risk of life-threatening bleeding events.
The main disadvantage of endocardial LAAO is the risk of possible thrombus formation on the occlusion device. Several antithrombotic strategies have been empirically adopted in clinical practice to avoid this worrisome complication [67–71]. To date, the most common approach relies on the use of aspirin, initially with clopidogrel and then alone, to prevent the activation of platelets contacting the atrial surface of the device until complete endothelialization [67–71]. Randomized clinical trials are needed to identify the best antithrombotic therapy to prevent device-related thrombosis and to explore the efficacy of LAAO in high-risk populations with a reduced margin of safety between stroke prevention and bleeding risk (e.g., end-stage CKD, elderly).

Conclusions

Patients with CKD, especially with ESRD already on RRT, needing long-term anticoagulant therapy represent a challenging population due to the increase propensity of adverse effects related to anticoagulation. Growing data suggest that DOACs may be a better alternative to warfarin in terms of reduction in thromboembolic and bleeding risk, preserving renal function with better risk/benefit ratio although some negative reports have been recently published. LAAO has emerged as a promising alternative to life-long anticoagulation, also in patients with significant renal impairment.

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