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Clinical Insights

Stroke prevention in atrial fibrillation patients with end-stage renal disease: how far from Ithaca after a long Odyssey?

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Atrial fibrillation (AF) and chronic kidney disease (CKD) are closely interlinked clinical entities that frequently coexist [1–3] . CKD predisposes to AF through structural, inflammatory and neurohormonal mechanisms including hypertension, atrial enlargement, and systemic inflammation[4]. Conversely, AF may contribute to CKD progression by reducing renal perfusion and promoting neurohormonal activation[4]. Patients with both conditions carry a disproportionately high risk of stroke, bleeding, cardiovascular events, and all-cause mortality [1]. Oral anticoagulant (OAC) therapy is considered a cornerstone of stroke prevention in patients with AF. However, treating patients with AF and end stage renal disease (ESRD) - e.g. CKD stages 4–5 or on dialysis - remains particularly challenging, as CKD significantly increases both thromboembolic and haemorrhagic risk[1]. Therefore, weighing the risks-benefits profile of OAC therapy in this scenario is complex and requires making difficult decisions, also considering the difficulties in the prediction of bleeding events in AF patients[5].

This clinical insight aims to summarise the current evidence on the interaction between AF and CKD, with a focus on the role and challenges of OAC therapy in ESRD individuals, and to explore the potential future options in the management of this complex scenario.

1. Bleeding and thrombosis

The coexistence of AF and ESRD results in a complex risk profile, because of elevated thromboembolic risk and, simultaneously, an increased risk of major bleeding compared to the general population[4]. ESRD is an independent risk factor for incident stroke as there is a linear relationship between the reduction of estimated glomerular filtration rate (eGFR) and the increase of stroke risk[3]. Several factors contribute to the increased thromboembolic risk in patients with CKD; this is partly due to a chronic inflammatory state, which increases oxidative stress, fibrinogen, factor VIII, and von Willebrand factor, all contributing to endothelial dysfunction and thrombotic risk [4].

At the same time, bleeding occurs in up to 50 % of patients with ESRD including a 5-to-10-fold increase in the rate of intracranial bleeding compared with the general population[6]. Dialysis in an independent risk factor for bleeding, particularly intracranial and gastrointestinal, with rates up to 100 times higher than in the general population[6]. The bleeding risk is multifactorial and is due to factors such as platelet dysfunction, thrombocytopenia, chronic anaemia, uraemia and the frequent need for antiplatelet and/or anticoagulant medications[6].

2. The Odyssey of stroke prevention in ESRD individuals with AF

Anticoagulation is the cornerstone for stroke prevention in patients with AF[7,8]. The perilous journey of anticoagulation in ESRD originally started with Vitamin K Antagonists (VKAs, Fig. 1). Traditionally VKAs

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have been the treatment of choice for anticoagulation in ESRD and patients on dialysis[7]. The use of VKAs in this setting, however, has been problematic: their narrow therapeutic range, numerous drug interactions, unpredictable response, accelerated vascular calcification and anticoagulant-related nephropathy have posed significant challenges for clinicians[9]. Considering all these factors, balancing thromboembolic and haemorrhagic risks has proven particularly difficult. Indeed, there is no randomized controlled trial (RCT) derived evidence supporting a favourable benefit-risk ratio for VKA in patients with ESRD and AF. The AVKDIAL trial (Oral Anticoagulation in Haemodialysis Patients, NCT02886962) was the first and only RCT assessed to evaluate the efficacy and safety of VKAs compared with no anticoagulation in dialysis patients, but it was stopped prematurely due to under recruitment (50 patients enrolled versus target of 850). Indeed, a large pooled meta-analysis of 20 observational studies (56,146 patients) evaluated the associations between VKA use and clinical outcomes (stroke, bleeding and mortality) in patients with ESRD and AF[10]. Nineteen studies compared VKAs use to no VKAs use, while two studies also compared VKA use to aspirin and one study compared VKA use to dabigatran and rivaroxaban. The results of the meta-analysis showed no significant difference in stroke prevention (Hazard Ratio [HR] 1.01, 95 % confidence interval [CI], 0.81–1.26) but a higher risk of bleeding (HR 1.21, 95 % CI 1.01–1.44) associated with VKA therapy[10].

In the early 2010s, direct oral anticoagulants (DOACs) were introduced into clinical practice, based on evidence from four pivotal phase III RCTs (Fig. 1). All these trials demonstrated the non-inferiority of DOACs versus warfarin in patients with Cockroft–Gault estimated creatinine clearance (eCrCl) of 30–50mL/min (25–50mL/min for apixaban), with an improved safety profile and fewer major bleeding events, particularly regarding intracranial haemorrhagic events[11]. In patients with mild-to-moderate CKD, DOACs have proven to be superior to VKAs and have been incorporated into routine clinical practice. However, given that the renal system plays a key role in the clearance of these agents and that dose adjustments are largely dependent on renal function, their effects in ESRD remain unclear, as these patients and patients on dialysis were systematically excluded from the landmark trials[11]. For this reason, efforts have been made to evaluate the efficacy and safety of DOACs compared to VKAs in ESRD patients.

The journey of stroke prevention continued with 3 RCT comparing DOACs versus VKAs in ESRD (Fig. 1)[12–14]. Apixaban and rivaroxaban were the two studied agents, primarily due to their more favourable pharmacokinetic profiles. Two small and largely under-powered RCTs compared apixaban versus VKAs in ESRD[12,13].

The RENAL-AF[12] trial evaluated apixaban 5 mg twice daily (2.5 mg in patients aged 80 years or older and/or who weighed 60 kg or less) versus adjusted dose warfarin (target INR 2.0–3.0), but was stopped prematurely because of slow enrolment, after randomizing only 154 patients. There were no significant differences in the rates of major or clinically relevant non-major bleeding (HR 1.20, 95 % CI, 0.63–2.30), stroke or systemic embolism (3.0 % and 3.3 % respectively in apixaban and VKAs groups) between the groups.

Similarly, the AXADIA-AFNET[13] trial enrolled 97 patients comparing apixaban 2.5 mg twice daily versus adjusted-dose phenprocoumon (target INR 2.0–3.0). The primary outcome was a composite of all-cause death, major bleeding events, and clinically relevant non-major bleeding. Secondary outcomes was a composite of ischemic stroke, death, myocardial infarction, deep vein thrombosis, or pulmonary embolism. Composite primary safety outcome events occurred in 22 patients (45.8 %) on apixaban and in 25 patients (51.0 %) on VKA (HR 0.93, 95 % CI, 0.53–1.65). Composite primary efficacy outcome events occurred in 10 patients (20.8 %) on apixaban and in 15 patients (30.6 %) on VKA which was not statistically significant ($P = 0.51$). Both RCTs failed to demonstrate significant differences in terms of efficacy or safety outcomes, reporting comparably high rates of thrombo-embolic and bleeding events in both groups, suggesting that patients remain at high risk of cardiovascular events despite OAC.

A small three-arm Valkyrie pilot trial[14] enrolled 132 dialysis patients with AF and were randomize 1:1.1 to receive VKAs (target INR

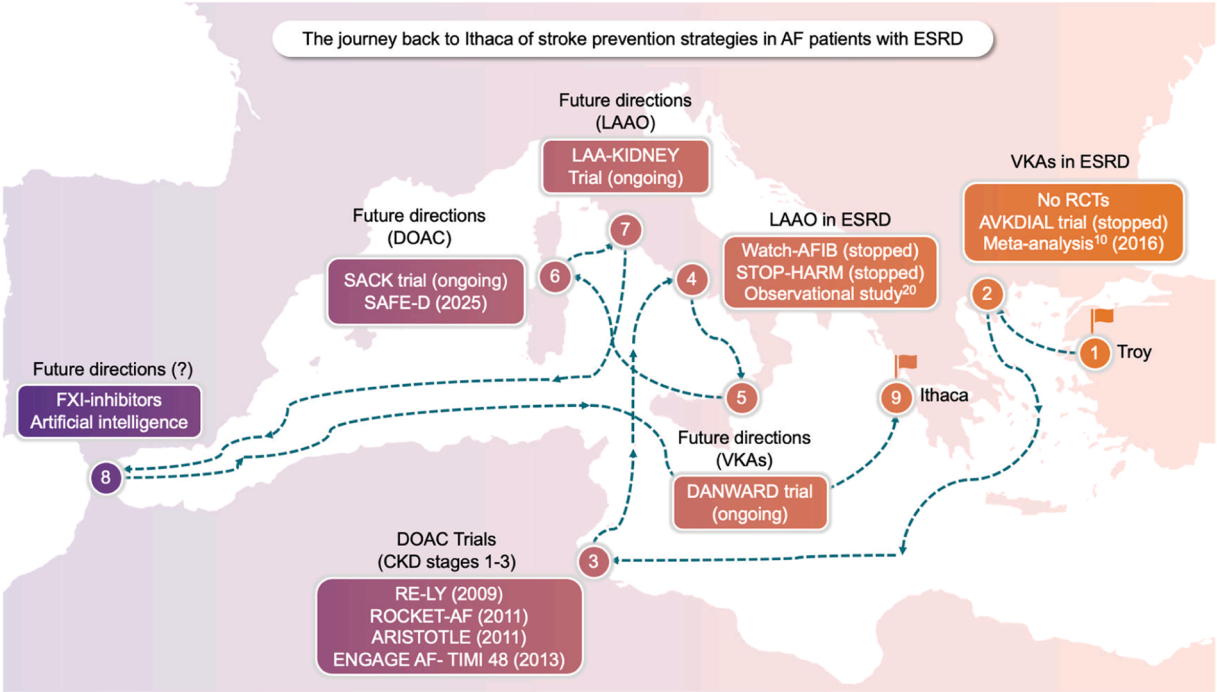

Fig. 1. The Odyssey serves as a metaphor for the challenges in identifying an optimal strategy for stroke prevention in the complex interplay between atrial fibrillation (AF) and end-stage renal disease (ESRD). Each stage of the journey represents a key clinical study or trial that has contributed evidence toward this evolving therapeutic landscape.

Legend. AF, atrial fibrillation; DOAC, direct oral anticoagulants; ESRD, end-stage renal disease; FXI, factor eleven; LAAO, left atrial appendage occlusion; RCT, randomized control trial; VKA, vitamin K-antagonist.

2.0–3.0), rivaroxaban (10 mg once daily), or rivaroxaban 10 mg plus 2000 μg menaquinone-7 three times weekly. The study was not designed or powered to address the comparative benefits of DOACs versus VKAs with respect to stroke prevention and bleeding complications. Nevertheless, all cause death, stroke and cardiovascular event rates were similar between the groups. Bleeding outcomes were not significantly different, except for a lower number of life-threatening and major bleeding episodes in the rivaroxaban arms versus the VKA arm. Pending further evidence, the authors suggest that rivaroxaban 10 mg once daily can be used safely and effectively in patients on haemodialysis.

A recently published meta-analysis evaluated the efficacy and safety of DOACs versus VKAs in patients with AF and ESRD[15]. The authors included a total of 6 studies, three RCTs and three observational studies, with overall 21,692 patients (3225 on DOACs and 18,467 on VKAs). The meta-analysis showed no significant differences in thromboembolic events prevention (Risk ratio [RR] 0.65, 95 % CI 0.38–1.10) and no significant differences in bleeding events (RR 0.79, 95 % CI 0.49–1.28) with high heterogeneity (I^2 91 %) between DOACs and VKAs. Taken together, these results suggest that despite DOACs and VKAs have comparable effects in this setting, the absolute risk of both major bleeding and thromboembolic events in ESRD patients remains markedly high, ranging from 10 % to over 30 % annually. This confirms the difficult profile to handle with significant problems in terms of OAC therapy in this population, with the risks of such therapy not adequately balanced by the benefits.

Indeed, in the absence of robust RCT evidence, findings from observational studies on the efficacy and safety of anticoagulation for stroke prevention in patients with AF and ESRD are conflicting and there is insufficient high-quality evidence to recommend warfarin or DOACs in this population. Therefore, guideline recommendations based on solid data are lacking: there are no specific recommendations in the ESC guidelines for the use of OAC in ESRD, while the American guidelines provide a Class IIb recommendation to prescrive warfarin (target INR 2.0–3.0) or apixaban in patients with AF and ESRD (CrCl <15 ml/min or on dialysis)[16–18]. In this context the decision to start OAC therapy is often challenging and requires a tailored approach to every single individuals based on the personal balance between thromboembolic and bleeding risk.

Subsequently, left atrial appendage occlusion (LAAO) has emerged as a possible non-pharmacological alternative (Fig. 1). The LAA is believed to be the site of thrombus formation for most AF-related cardioembolic strokes[19]. LAAO is an efficacious non-pharmacological, device-based therapy that reduces stroke/systemic embolism in high-risk patients, and it is an available alternative to OAC (both VKA and DOAC) in patients with contraindications to long-term OAC due to high haemorrhagic risk[19]. Unfortunately, few studies to date have evaluated the efficacy of LAAO in patients with ESRD. Over the last decade, 2 open multicentre RCTs (STOP-HARM, NCT02885545 and Watch-AFIB, NCT02039167) evaluating the safety of LAAO versus OAC therapy (respectively LAAO vs OAC and LAAO vs VKA) in patients with ESRD (eGFR <30 ml/min per 1.73m2 > 90 days or on dialysis >90 days) had to be prematurely terminated as a result of slow enrollment, thus underling the challenges of studying this group of patients. Besides these two RCTs, other observational studies have attempted to investigate the efficacy and safety of this procedure. The largest of these studies is a multicentre italian prospective observational study that enrolled 106 dialysis patients with AF and assessed the cumulative incidence of thromboembolic and bleeding events following LAAO[20]. For comparative purposes, the authors compared this group of patients with a historical cohort of dialysis patients with AF, meeting the same inclusion criteria as the LAAO cohort, deriving from a previous prospective study - albeit with limited statistical validity due to the non-contemporaneous and observational nature of the comparison [20]. These patients were divided according to anticoagulant therapy in two groups, one treated with VKAs and the other not treated with any OAC[20]. The authors concluded that LAAO is a safe procedure associated with lower percentage of thromboembolic events at five years compared with warfarin (HR 0.19, 95 % CI 0.04–0.96; $P = 0.045$) and compared with no-OAC (HR 0.16, 95 % CI 0.04–0.66; $P = 0.011$), with lower bleeding events (HR 0.37, 95 % CI 0.16–0.83; $P = 0.017$) compared with warfarin. There were no significant differences between the incidence of bleeding in the LAAO cohort and the no- OAC cohort (HR 0.51, 95 % CI 0.23–1.12; $P = 0.094$). However, the limitations of the study must be acknowledged, primarily its observational design and the fact that outcomes were compared with a cohort from a separate study.

Up to date, there is lack of solid evidence supporting the preferential use of LAAO in ESRD compared to VKA or other strategies**.** RCTs are required to assess the long-term efficacy and cost-effectiveness of this approach[21], but in the meantime use of LAAO in patients under dialysis is increasing in many centers [19,20].The interpretation of outcome data after LAAO implant in advanced renal disease and dialysis is also dependent on post-implant antithrombotic regiment, which may include a single- or a dual-antiplatelet drug[19]. Additionally, outcome assessment post LAAO implant must consider that dialysis patients have a significantly higher burden of comorbidities, that independently predispose to cerebrovascular events and bleeding [22,23], as well as a higher risk of all-casue mortality[24]. The European multicentre LAA-KIDNEY (Left Atrial Appendage closure in patients with non-valvular AF and end stage chronic KIDNEY disease; NCT05204212) is the next step in the journey back to Ithaca (Fig. 1). It is a RCT designed to systematically examine the clinical benefits of interventional LAAO compared with best medical care in AF patients with ESRD. It is expected to provide data helping to determine the best treatment for stroke prevention in this high-risk group of patients, potentially offering an alternative strategy for those in whom systemic anticoagulation is contraindicated or poorly tolerated.

Another field of investigations involve new pharmacological strategies, able to overcome the limitations of DOACs in patients with advanced renal function. Indeed, the Odyssey is continuing with several ongoing trials (Fig. 1), aiming to fill these gaps in knowledge. The ongoing DANWARD trial (Danish Warfarin-Dialysis, NCT03862859) aims to investigate the safety and efficacy of VKAs (INR target 2.0–3.0) compared with no-OAC in a group of 718 chronic dialysis patients with AF, while the ongoing European multicentre SACK trial (Stroke Prophylaxis With Apixaban in CKD stage 5 Patients With Atrial Fibrillation, NCT05679024) is investigating the safety and efficacy in stroke prevention of reduced-dose apixaban (2.5 mg twice daily) compared with no-OAC in ESRD (dialysis patients or eGFR <20 ml/min/1.73 m2). Lastly, the recently published multicentre, open-label, pilot RCT SAFE-D [25] (Strategies for the Management of Atrial Fibrillation in Patients Receiving Dialysis, NCT03987711) enrolled 151 dialysis patients randomized 1:1:1 to receive apixaban 5 mg twice daily ($n = 51$), dose-adjusted warfarin ($n = 52$), or no OAC ($n = 48$). The primary endpoint was adherence, defined as >80 % of randomized patients remaining on the assigned treatment strategy at the end of follow-up, which the study successfully demonstrated (83 %). However, the trial was underpowered to detect differences in stroke or bleeding events.

Among emerging pharmacological strategies, a new family of OAC agents, direct inhibitors of factor XIa (FXI) have gained particular interest. FXI inhibitors hold the theoretical advantage of reducing thromboembolic risk while minimizing bleeding complications[26] (Fig. 1). Ongoing phase III trials include OCEANIC-AF (NCT05643573) with asundexian, LILAC-TIMI 76 (NCT05712200) and AZALEA TIMI-71 (NCT04755283) with abelacimab and LIBREXIA-AF (NCT05757869) with milvexian. These trials are comparing Factor XI inhibitors against DOACs or placebo. However, OCEANIC-AF has been terminated prematurely for lack of asundexian efficacy when compared with apixaban [27]. On the other hand, the AZALEA TIMI-71 trial was also terminated prematurely but because there were substantially fewer bleeding events with abelacimab than with rivaroxaban[28].

Early-phase clinical studies have suggested a favourable safety profile of FXI inhibitors in dialysis patients[26]. However, comprehensive

data on their efficacy in preventing ischemic stroke and systemic embolism are still needed before their integration into clinical practice can be considered.

In parallel, artificial intelligence (AI) is increasingly being explored in the field of cardiovascular medicine, with potential applications in risk prediction, therapeutic decision-making, and personalized care [29, 30]. In the context of ESRD, where stroke prevention often involves difficult clinical trade-offs, AI-driven models may support clinicians in identifying optimal strategies tailored to individual patient profiles, as well as predict the risk of worsening renal function. Further research is warranted to validate and integrate such approaches into routine clinical practice.

3. Conclusion

Stroke prevention in patients with AF and ESRD remains a major clinical challenge due to the dual risk of thrombosis and bleeding, so the search for an optimal treatment in this setting still constitute a long Odyssey, with uncertainty about the final destiny. Current evidence does not support a clear benefit of VKAS or DOACs in this population, and robust randomized data are lacking. LAAO is emerging as a promising alternative, but definitive evidence is still awaited. Ongoing trials and novel agents, such as factor XI inhibitors, may represent a potential safer and more effective alternative. Until then, treatment decisions must be individualized, balancing risks and benefits through close collaboration between cardiologists and nephrologists.

Declaration of competing interests

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The other authors do not have conflict of interests to report

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