Nephrol Dial Transplant, 2024, 39, 1248–1257
https://doi.org/10.1093/ndt/gfae121
Advance access publication date: 30 May 2024

TREATMENT STANDARD

Treatment strategies of the thromboembolic risk in kidney failure patients with atrial fibrillation

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ABSTRACT

The incidence and prevalence of atrial fibrillation (AF) in patients affected by kidney failure, i.e. glomerular filtration rate <15 ml/min/1.73 m^2, is high and probably underestimated. Numerous uncertainties remain regarding how to prevent thromboembolic events in this population because both cardiology and nephrology guidelines do not provide clear recommendations. The efficacy and safety of oral anticoagulant therapy (OAC) in preventing thromboembolism in patients with kidney failure and AF has not been demonstrated for either vitamin K antagonists (VKAs) or direct anticoagulants (DOACs). Moreover, it remains unclear which is more effective and safer, because estimated creatinine clearance <25–30 ml/min was an exclusion criterion in the randomized controlled trials (RCTs). Three RCTs comparing DOACs and VKAs in kidney failure failed to reach the primary endpoint, as they were underpowered. The left atrial appendage is the main source of thromboembolism in the presence of AF. Left atrial appendage closure (LAAC) has recently been proposed as an alternative to OAC. RCTs comparing the efficacy and safety of LAAC versus OAC in kidney failure were terminated prematurely due to recruitment failure. A recent prospective study showed a reduction in thromboembolic events in haemodialysis patients with AF and undergoing LAAC compared with patients taking or not taking OAC. We review current treatment standards and discuss recent developments in managing the thromboembolic risk in kidney failure patients with AF. The importance of shared decision-making with the multidisciplinary team and the patient to consider individual risks and benefits of each treatment option is underlined.

Keywords: atrial fibrillation, kidney failure, left atrial appendage closure, oral anticoagulant therapy, thromboembolism

Received: February 17, 2024; Editorial decision: April 30, 2024

In a nutshell

1. The incidence and prevalence of AF in patients affected by kidney failure is high and probably underestimated.
2. Numerous uncertainties still remain regarding how to prevent thromboembolic events in this population and both cardiology and nephrology guidelines do not provide clear recommendations.
3. There are no RCTs available that provide evidence of efficacy and safety in kidney failure patients for either VKAs or DOACs compared to no-therapy.
4. The left atrial appendage is the main source of thromboembolism in the presence of AF. LAAC has recently been proposed as an alternative to OAC for the prevention of thromboembolic events in patients with AF.
5. RCTs in patients with AF and preserved kidney function, without contraindication to OAC, showed a non-inferiority of LAAC in the prevention of thromboembolic events compared to both warfarin and apixaban. A recent prospective study showed a reduction in thromboembolic events in patients with CKD G5D and AF undergoing LAAC compared to patients taking or not taking OAC.

INTRODUCTION

The glomerular filtration rate (GFR) is defined as severely reduced when it decreases to <15 ml/min/1.73 m^2. This stage of chronic kidney disease (CKD) is defined as kidney failure and identified as CKD G5 if the patient is not on dialysis or CKD G5D if the patient is on dialysis [1]. The prevalence of atrial fibrillation (AF) in kidney failure patients is high [2, 3] and probably underestimated due to the high rate of intradialytic AF episodes that often remain undiagnosed [4]. In fact, haemodialysis (HD) session may be a trigger of arrhythmias due to the large and abrupt HD-related volume and electrolyte changes [5]. In 2020 the United States Renal Data System (USRDS) reported a prevalence of AF of 21% in patients on HD and 13% in those undergoing peritoneal dialysis. A meta-analysis including 25 studies conducted in HD patients showed that ≈12% (range 4.5–27%) of the patients had AF [2, 3].

The presence of AF among patients with kidney failure is associated with an increase in all-cause mortality {hazard ratio [HR] 1.65 [95% confidence interval (CI) 1.18–2.31]} and cardiovascular mortality [HR 2.15 (95% CI 1.27–3.64)] [6] compared with patients without AF. The USRDS registry reports a 2-year mortality rate of 45% in HD patients with AF and 28% in those without AF [2].

The major concern for all patients with AF is the increased risk of embolic stroke, and this also applies to HD patients. A recently published Scottish study showed that in patients receiving kidney replacement therapy between January 1996 and December 2016, the incidence of stroke was 2- to 4-fold higher compared with the general population and was associated with a poor prognosis [7]. A more than doubled prevalence of stroke (5.2 versus 1.9 events/100 patients/year) [3] and an adjusted odds ratio (OR) of 1.5 for new-onset cerebral infarction were demonstrated in CKD G5D patients with AF [8] compared with patients without AF. Older age, diabetes mellitus, higher blood pressure, malnutrition and inflammatory markers were the factors most strongly associated with ischaemic stroke.

Oral anticoagulant therapy (OAC) is considered the main therapeutic pillar in patients with AF [9]. However, this treatment is associated with a risk of bleeding. Patients with kidney failure and AF constitute a challenging population to treat, as advanced kidney disease is associated with a pronounced increase in both the thromboembolic and haemorrhagic risk—these patients often fulfil most criteria in commonly used thromboembolic and bleeding risk scores, e.g. CHA2DS2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischaemic attack (doubled), vascular disease, age 65–74, female] [10] and HAS-BLED [hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio (INR), elderly, drugs or alcohol] [11] scores—therefore weighing the risks and benefits of OAC prophylaxis is not straightforward. Pro-thrombotic factors (endothelial dysfunction and hypercoagulability) and factors that promote bleeding (abnormal platelet adhesion, aggregation and release reactions) are simultaneously present (Fig. 1) [12]. Moreover, this population is particularly susceptible to bleeding events owing to a high risk of falls, malnutrition, gastroduodenal disease and poorly controlled hypertension. The high concomitant use of antiplatelet therapy for coronary and arterial disease further amplifies the risk of bleeding.

TREATMENT STANDARDS

Assessment of the thromboembolic and bleeding risk in AF

Assessment of thromboembolic risk in AF is mandatory to guide effective anticoagulation strategies. The CHA_2DS_2-VASc score provides a framework for stratifying stroke risk [10]. However, its utility must be tempered by the recognition of the bleeding risk, necessitating an individualized approach to OAC selection and dosing. While the CHA_2DS_2-VASc score informs the assessment of thromboembolic risk, the HAS-BLED score [11] provides complementary insights into bleeding risk, facilitating a comprehensive evaluation of the risk–benefit profile of anticoagulant therapy [13]. Both risk scores (CHA_2DS_2-VASc and HAS-BLED) are long-established tools in predicting cerebrovascular and bleeding events in the general population with AF. However, their ability in predicting outcomes in kidney failure patients is questionable. The scores were developed and validated in populations not on dialysis. External validation of CHA_2DS_2-VASc showed weak predictive performance of ischaemic stroke models in incident dialysis patients [14]. The same observation was made for the HAS-BLED score [15]. A retrospective study conducted in HD patients showed that the CHA_2DS_2-VASc score was significantly associated with stroke, but with a modest predictive value [area under the curve (AUC) = 0.63]. The HAS-BLED score had a significant association with haemorrhagic events, with an AUC of 0.76 [16]. However, a large validation study in a cardiology population also showed relatively modest performance of the two scores (AUC = 0.67 for CHA_2DS_2VASc and AUC = 0.60 for HAS-BLED) [17]. Some newer scores in kidney failure patients have been developed. The Dialysis Risk Score was recently proposed by De Vriese and Heine [18]. However, this score has not yet been validated. The BLEED-HD risk score has been developed and validated, although questions remain about its generalizability [19]. Given the inadequacy of current scores, further development of new risk assessment tools tailored specifically for kidney failure patients is necessary.

Guideline recommendations

European and US cardiology guidelines recommend prescribing OACs in all individuals in the general population with

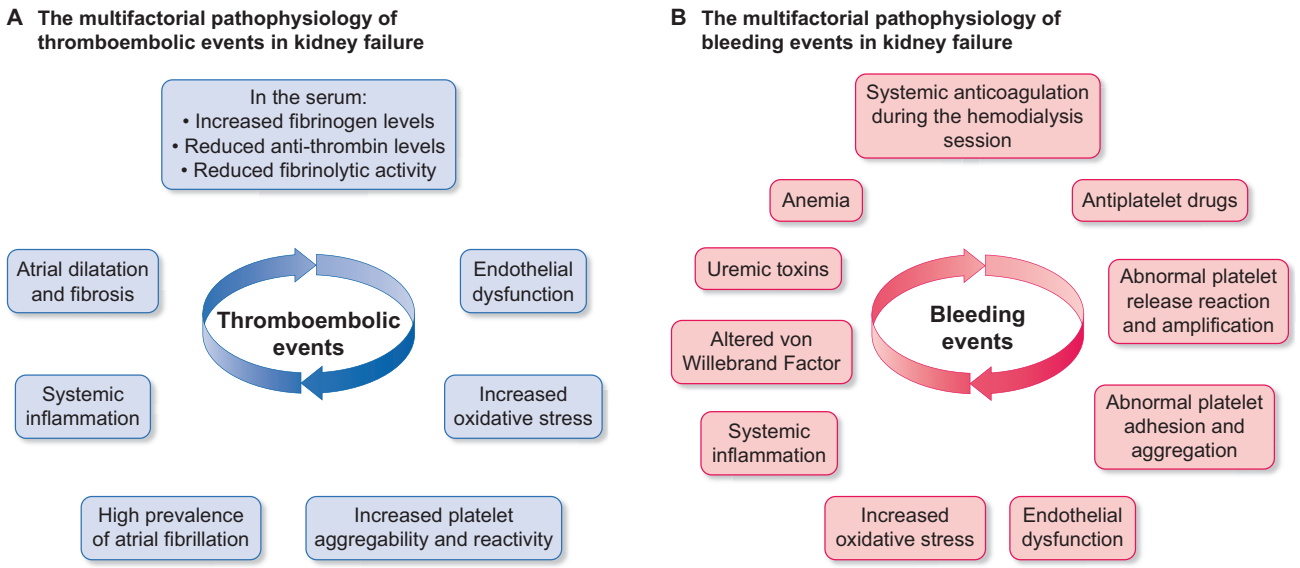

Figure 1: **(A)** Thromboembolic and **(B)** bleeding risk in kidney failure.

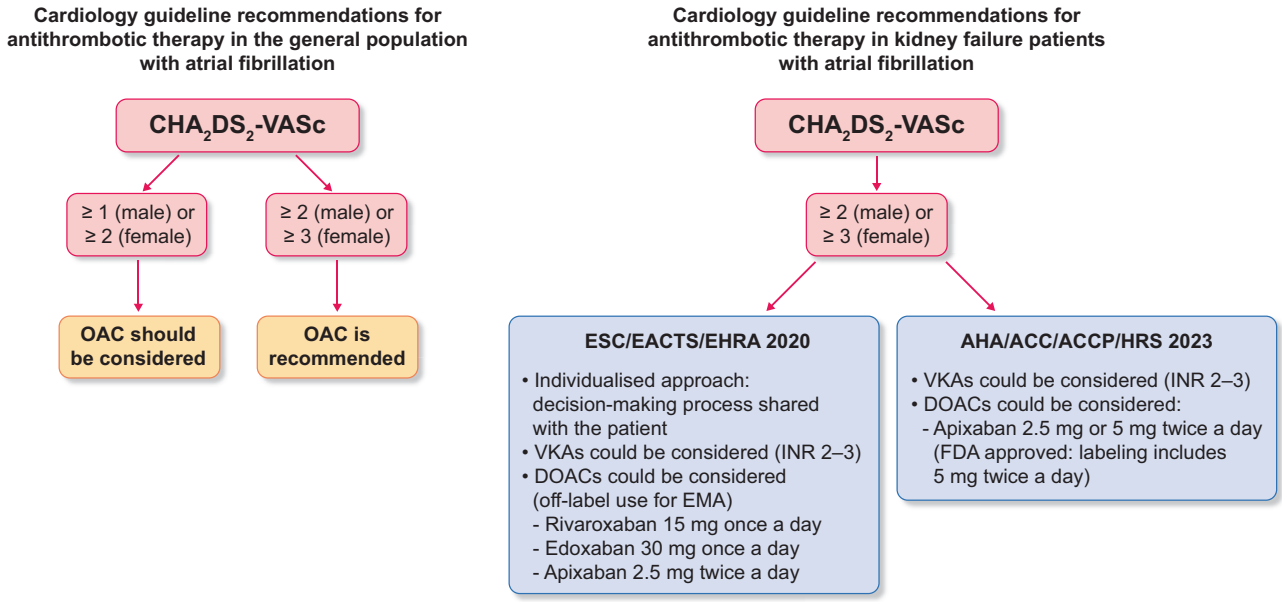

Figure 2: Flow chart of the standard treatment algorithm for the prevention of thromboembolic events in the general population with AF and in patients with kidney failure and AF, according to the most recent cardiology guidelines. ACC: American College of Cardiology; ACCP: American College of Clinical Pharmacy; AHA: American Heart Association; EACTS: European Association of Cardio-Thoracic Surgery; ESC: European Society of Cardiology; EHRA: European Heart Rhythm Association; HRS: Heart Rhythm Society.

documented AF having a thromboembolic score (CHA_2DS_2-VASc score) ≥2 in males or ≥3 in females, regardless of whether the AF pattern is paroxysmal, persistent, long-standing persistent or permanent [9, 20] (Fig. 2). Regarding the choice of anticoagulant, direct anticoagulants (DOACs) should be preferred over vitamin K antagonists (VKAs). This recommendation also applies to patients with CKD, however, dosage adjustment is required for specific molecules, as the estimated creatinine clearance (eCrCl) decreases. Dabigatran is not recommended when the eCrCl is <30 ml/min, while rivaroxaban, apixaban and edoxaban can be used down to 15 ml/min [9, 20]. Things become more complicated when a patient reaches kidney failure. Neither European nor US cardiology guidelines take a well-defined position here, stating that the use of VKAs with a target INR between 2 and 3 'can be taken into consideration'. The use of DOACs (rivaroxaban, apixaban and edoxaban) is accepted at reduced doses by European guidelines, but not clearly suggested. The use of apixaban is accepted by US guidelines, although not suggested.

It should be noted that the European Medicines Agency (EMA) (https://www.ema.europa.eu) considers all DOACs off-label in kidney failure patients, while the US Food and Drug Administration (FDA) (https://www.fda.gov) accepts the use of apixaban, even at full dosage in the absence of a second risk factor (such as advanced age or low body weight) in addition to CKD. Both guidelines underline the importance of shared decision-making with the multidisciplinary team and the patient,

considering the individual risks and benefits of the treatment (Fig. 2).

Regarding anticoagulation therapy in patients with kidney failure and AF, the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the evaluation and management of CKD [21] did not modify the previous position of the KDIGO Controversies Conference document on CKD and arrhythmias [22]. In patients with an eCrCl <15 ml/min or in patients undergoing dialysis, the use of dabigatran and edoxaban is discouraged; as regards warfarin, it is stated that the equipoise is based only on observational data and meta-analysis and the possibility of prescribing apixaban (2.5 mg twice daily) or rivaroxaban (15 mg once daily) is mentioned, even if it is clarified that the reported doses 'do not currently have any clinical or efficacy data'.

The position of these guidelines makes the nephrologist's therapeutic choices difficult when faced with a patient with kidney failure and AF.

VKAs

When a decision is made to start OACs for the prevention of thromboembolic events in a patient with kidney failure and AF, nephrologists have been prescribing VKAs for decades, even in the absence of randomized controlled trials (RCTs). To date, however, evidence that the prescription of VKAs in patients with kidney failure is associated with a reduction in the incidence of ischaemic stroke is inconsistent, while numerous studies highlight excess bleeding risk, in particular due to intracranial haemorrhage [23, 24]. The main factor associated with the possibility of undergoing a haemorrhagic event is previous bleeding [25, 26]. The high risk of bleeding associated with VKAs in patients with kidney failure is also due to the difficulty in maintaining the INR between 2 and 3 (the therapeutic range recommended by the cardiology guidelines) [27, 28], especially because of the high rate of hypoalbuminaemia (99% of warfarin is bound to albumin) and drug interactions. Other concerns in addition to the risk of bleeding have been raised regarding the possible side effects of VKAs in patients with kidney failure. Warfarin has been associated with an increased risk of vascular calcifications, as vitamin K is an essential cofactor for the activation of several extracellular matrix proteins that inhibit vascular calcium deposition [29, 30]. However, an RCT designed to verify whether the use of DOACs in HD patients was associated with a reduction in the number of aortic, coronary and cardiac valvular calcifications compared with warfarin showed no significant differences [31]. Finally, warfarin-related nephropathy [32] remains a potential threat in patients taking VKAs, although less relevant for individuals on maintenance dialysis. Noteworthy cases of acute kidney injury due to a similar mechanism have also been described in patients taking DOACs [33].

DOACs

DOACs are convenient for patients, having no requirement for INR monitoring and frequent dose adjustments, and have profoundly changed the management of thromboembolic risk in patients with AF. These drugs have been shown to have at least the same efficacy as VKAs and equal or greater safety in the general population [34–37]. This also applies to patients with CKD up to stage G4, in which DOACs are more effective than VKAs in reducing thromboembolic events, with an advantage in reduced bleeding [38]. As is often the case in nephrology, patients with an eCrCl <25–30 ml/min were excluded from RCTs investigating this issue [34–37]. Two RCTs in HD patients with AF, aiming to compare DOACs (apixaban) and VKAs in terms of efficacy and safety in preventing thromboembolism, were terminated prematurely due to insufficient recruitment. Both studies were unable to demonstrate differences between the two classes of drugs in either the incidence of thromboembolic or haemorrhagic events [39, 40]. A third RCT comparing rivaroxaban and VKAs in HD patients showed a reduction in fatal and non-fatal cardiovascular events in the arm taking rivaroxaban, but no reduction in strokes. In this trial, the number of major bleeding events was higher in patients taking VKAs than in those taking rivaroxaban [41]. However, several meta-analyses that put together the data from the three trials concluded that no significant difference was observed between DOACs and VKAs in cardiovascular mortality, all-cause mortality, ischaemic stroke, transient ischaemic attack and major bleeding, probably due to the low number of patients recruited in the three studies [42–44].

Observational studies in patients with kidney failure and AF taking DOACs have produced conflicting results. Chan *et al.* [45] described an increase in major bleeding and mortality in US HD patients taking dabigatran and rivaroxaban compared with VKAs, while Siontis *et al.* [46] demonstrated a reduction in mortality without an increase in bleeding events in a population of HD patients treated with apixaban compared with warfarin. It should be noted, however, that in the study by Chan *et al.*, patients who were taking the full dosage of dabigatran or rivaroxaban had a higher risk of major bleeding than patients who were prescribed a lower dose of the drug. Moreover, rivaroxaban was associated with significantly less major bleeding compared with warfarin among patients with AF and kidney failure [47] and a French study [48] showed that in a population of ≈9000 dialysis patients initiating an OAC, the off-label use of DOACs was associated with a significantly lower risk of thromboembolic events and a similar risk of bleeding compared with VKA use. However, a recent meta-analysis including both RCTs and observational studies concluded that the risk of ischaemic stroke, bleeding and all-cause mortality was similar in HD patients with AF treated with DOACs or VKAs [49].

More robust are the data provided by studies investigating the progression of kidney disease in CKD patients taking DOACs compared with those treated with VKAs. Both the worsening of kidney function and the incidence of acute kidney injury were significantly lower in patients treated with DOACs [50]. In particular, the incidence of kidney failure decreased by 18% [hazard ratio 0.82 (95% CI 0.78–0.86)] [51]. Recent data from the Xareno study confirmed this positive outcome in patients with advanced CKD and AF treated with rivaroxaban compared with those taking VKAs [52]. These findings suggest that, in patients with CKD G3–G4 and AF, DOACs should be preferred to VKAs for the prevention of thromboembolic events, as well as to slow progression of kidney failure.

Particular attention should be paid to the dosage of DOACs. Compared with on-label dosing, off-label underdosing of DOACs increased the risk of thromboembolic events but did not reduce the risk of bleeding in the general population with AF [53]. In the case of kidney failure patients, the problem arises especially for apixaban. The FDA recommended dose of apixaban is 2.5 mg taken orally twice a day in patients with at least two of the following characteristics: age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5 mg/dl. Therefore, according to the FDA, in the absence of a very low body weight or older age, the full dosage (5 mg twice a day) should be used in kidney failure patients. In subjects with reduced kidney function not undergoing kidney replacement therapy, inappropriate dose reduction of apixaban has been associated with an ≈5-fold increase in the risk of stroke [54], while

DOAC overdosing can lead to excessive bleeding [55]. The analysis of pooled data from the four major RCTs dealing with DOACs [34–37] showed that standard doses of DOACs, defined as the standard dose used in ROCKET AF (NCT00403767) [35] or ARISTOTLE (NCT00412984) [36], with trial protocol–specified dose adjustment based on age, weight and kidney function, and as the higher dosing regimen in RE-LY (NCT00262600) [34] or ENGAGE AF-TIMI 48 (NCT00781391) [37], with dose adjustment in patients meeting trial criteria, are safer and more effective than VKA in patients with an eCrCl down to 25 ml/min, while lower doses of DOACs do not reduce the incidence of bleeding but increase the incidence of thromboembolic events [38]. However, we do not know whether these observations may also be applicable to patients with CKD G5 and G5D. A pharmacological study showed that in HD patients the apixaban dose of 5 mg twice daily resulted in supratherapeutic levels of the drug [56]. Moreover, a recent retrospective cohort study showed that 5 mg versus 2.5 mg twice a day of apixaban was associated with a higher risk of bleeding in patients with AF and CKD G4–G5 [57]. A pharmacokinetic study conducted in HD patients suggested that taking rivaroxaban 10 mg once daily was sufficient to achieve plasma concentrations similar to taking rivaroxaban 20 mg in healthy volunteers [58]. However, there is no evidence showing that this dosage is effective in reducing thromboembolic events compared with VKAs in kidney failure patients with AF [41].

From the above, it is evident that there is great uncertainty about how to treat kidney failure patients with AF. It should also be underlined that beyond the therapeutic choice between VKAs and DOACs, the question remains whether there is an advantage to prescribing OAC in this population. Mavrakanas *et al.* [59] described an increase in the number of intracranial haemorrhages with no reduction in ischaemic strokes in a large sample of HD patients with AF taking OAC compared with no-OAC patients, and Kuno *et al.* [60] found no difference in the incidence of stroke in patients undergoing HD treated with either warfarin or apixaban compared with those not taking OAC. In that study, apixaban prescription was not associated with increased bleeding compared with no OACs, but this risk was increased with warfarin. A recent meta-analysis including 42 studies and 185 864 subjects showed that no anticoagulation was a non-inferior alterative to DOACs and that VKAs were associated with the worst outcomes [61]. Several RCTs directly comparing the efficacy and safety of OAC to no OAC are ongoing [AVKDIAL (NCT02886962), DANWARD (NCT03862859) and SACK (NCT05679024)] and we are waiting for the results of the already concluded SAFE-D trial (NCT03987711). We hope these studies will provide us with important information. In the absence of clear evidence in favour of the efficacy of anticoagulant drugs, it remains doubtful whether one can consider not starting OAC in patients with kidney failure and AF with very high bleeding risk.

NEW DEVELOPMENTS

Factor XIa inhibitors

Recently, new drugs that act by inhibiting the activity of activated factor XI (XIa) have been proposed as a new option for anticoagulation therapy. The cumulative safety data from two phase 3 trials of a factor XI inhibitor (asundexian) showed improved safety of asundexian compared with apixaban and similar safety compared with placebo in AF patients [62]. However, the OCEANIC-AF trial (NCT05643573), performed in a large population of patients with AF, was prematurely stopped because asundexian showed inferior efficacy compared with apixaban [63]. Furthermore, two small phase 2 RCTs employing factor XI inhibitors demonstrated reduced factor XI activity, dialyzer clotting and thrombin–antithrombin complex formation in HD patients without AF [64, 65]. The main study using an inhibitory factor XIa antibody (osocimab) in patients with kidney failure is a phase 2 RCT [the CONVERT trial (NCT04523220)] performed in 686 HD patients, of which only 46 had AF. The study aimed to test the safety of osocimab in this population and showed that it was associated with a low risk of bleeding in patients undergoing HD [66]. Finally, a recent phase 2 RCT evaluated the dose response of fesomersen, an inhibitor of factor XI expression, versus placebo for bleeding and atherothrombosis in 307 patients with kidney failure undergoing HD. Fesomersen produced a dose-dependent reduction in factor XI levels associated with similar rates of major bleeding compared with placebo. No difference was observed in atherothrombotic events [67]. In view of this evidence, we believe it is premature to propose factor XI inhibitors in patients with kidney failure and AF, as there are no studies that have proved the efficacy of factor XI inhibitors in thromboembolism prevention in patients with AF, with or without CKD.

Closure of the left atrial appendage

It has been shown that most atrial thrombi in patients with non-valvular AF arise in the left atrial appendage [68]. 'Extra-appendage' atrial thrombosis is a rare condition usually associated with prosthetic valves or thrombophilia [69]. Therefore, left atrial appendage closure (LAAC) has been proposed as an alternative to OAC for the prevention of thromboembolic events in patients with AF. The combined 5-year outcomes of two RCTs, the PREVAIL (NCT01182441) and the PROTECT AF (NCT00129545) trials, demonstrated that LAAC provides stroke prevention in AF comparable to VKA, with reduction in major bleeding, haemorrhagic stroke, cardiovascular death and all-cause mortality [70]. Subsequently, the PRAGUE-17 RCT (NCT02426944), with >4 years of follow-up, showed non-inferiority of LAAC versus DOACs (predominantly apixaban) versus a composite primary endpoint of cardioembolic events, cardiovascular death and clinically significant bleeding [71]. However, an eCrCl <30 ml/min was an exclusion criterion. Cardiology guidelines provide a weak recommendation for LAAC as an alternative to OAC, as the patients involved in these three trials had no contraindications to VKAs or DOACs [9, 20]. An international consensus paper was recently published that highlighted the importance for nephrologists, neurologists, haematologists and gastroenterologists who deal with populations at high risk of bleeding to consider LAAC in case of AF [72].

Several observational studies, derived mainly from registry data, have confirmed the results of the PRAGUE-17, PREVAIL and PROTECT AF trials, demonstrating the efficacy and safety of LAAC in the general population with AF [73, 74].

Patients with kidney failure and AF represent a population that could benefit from the procedure, given the uncertainties and difficulties related to the use of OAC. However, data on this topic are scarce and fragmentary and, above all, limited to a comparison of efficacy and safety of LAAC between patients with preserved kidney function and patients with advanced CKD. A recent meta-analysis that analysed data derived from the main available observational studies showed an increase in in-hospital adverse outcomes: in-hospital mortality [OR 8.61 (95% CI 5.9–12.5)], major bleeding [OR 1.63 (95% CI 1.33–2.01)] and pericardial effusion/tamponade [OR 1.54 (95% CI 1.17–2.03)] in kidney failure patients compared with non-kidney failure patients [75]. This finding is not surprising, as an increased risk of complications has

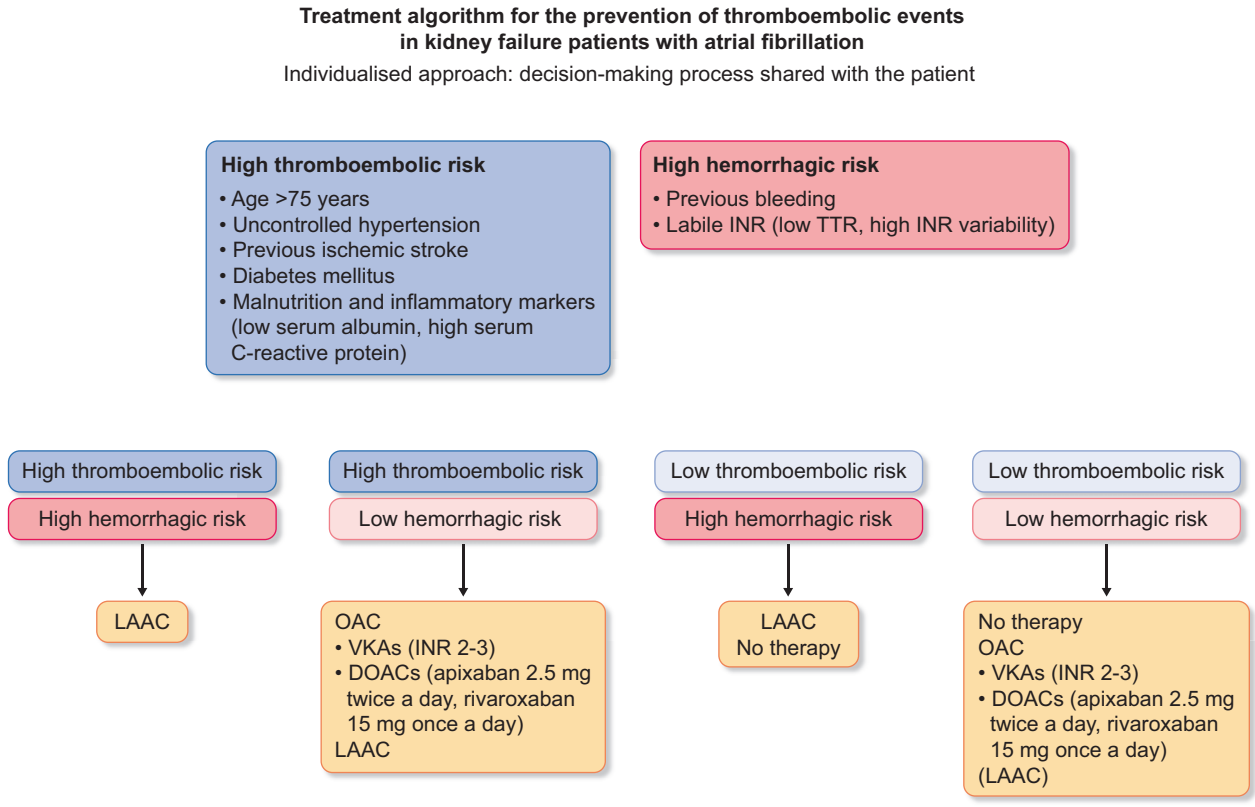

Figure 3: Proposal for a new treatment algorithm for the prevention of thromboembolic events in patients with kidney failure and AF. TTR: time in therapeutic range.

also been described with other invasive cardiologic procedures in kidney failure patients [76]. Information on long-term outcomes after LAAC showed a comparable incidence of stroke between patients with CKD at any stage and those with preserved kidney function [OR 1.33 (95% CI 0.53–3.34)]. As expected, the incidence of bleeding [OR 1.67 (95% CI 1.45–1.92)] and mortality [OR 3.45 (95% CI 2.01–5.92)] was higher in patients with CKD [75]. Some studies comparing the safety and efficacy of the procedure in patients with kidney failure versus populations with preserved or otherwise improved kidney function have come to encouraging conclusions, demonstrating comparable procedural safety and clinical efficacy in patients with kidney failure and patients without advanced CKD [77–79].

Two RCTs designed to evaluate the safety (primary outcome: first episode of major bleeding) of LAAC versus VKAs in patients with an estimated GFR (eGFR) <30 ml/min/1.73 m^2 (CKD G4, G5 and G5D) were terminated prematurely due to lack of recruitment [Watch-AFIB (NCT02039167) and STOP-ARM (NCT02885545)] [80]. A third RCT including only patients with an eGFR <15 ml/min/1.73 m^2 and comparing LAAC with best medical care, with a primary composite outcome of first stroke, systemic embolism, cardiovascular or unexplained death or major bleeding, is ongoing [LAA-Kidney trial (NCT05204212)]. Currently, only one observational prospective study is available comparing three groups of dialysis patients with AF in which three different intervention strategies were implemented for thromboembolism prevention [81]. By 4 years of follow-up, both multivariate analysis of the Cox model and propensity score analysis demonstrated a significant reduction in thromboembolic events in patients in the LAAC group compared with patients in the VKA group and those in the no-OAC group. The incidence of major bleeding was significantly lower in patients undergoing LAAC compared with those treated with warfarin. Interestingly, nearly half of all bleeding events occurred within the first 3 months following the procedure, when most patients were on dual antiplatelet therapy (DAPT). This observation raises the important issue of post-procedure antithrombotic therapy. At the moment there are no precise indications on the optimal drug prescription, but most cardiology centres prescribe at least 3 months of DAPT. The risks and benefits may need to be reconsidered in patients who are particularly prone to bleeding, e.g. by reducing the DAPT period or administering only one drug or even none. More evidence is required on this topic.

The proposal of a new treatment algorithm for the prevention of thromboembolic events in patients with kidney failure and AF is shown in Fig. 3. The algorithm aims to balance the thromboembolic and haemorrhagic risk of the patient to decide which antithrombotic prophylactic therapy to prescribe. Although the thromboembolic CHA_2DS_2-VASc score has limited predictor ability in kidney failure patients, some studies have shown that an increase in the score was associated with an increase in the occurrence of thromboembolic events [16, 82]. Moreover, in addition to the classic thromboembolism-associated factors that are part of the CHA_2DS_2-VASc score (older age, previous stroke, diabetes mellitus and high blood pressure), factors characterizing malnutrition–inflammation–atherosclerosis syndrome (high C-reactive protein and low serum albumin values) seem to play an important role in increasing the risk of cerebral thrombotic events in this population [8]. Interestingly, the study by Genovesi *et al.* [81] reported that the number of thromboembolic events was lower than predicted by the CHA_2DS_2-VASc score not only in HD patients undergoing LAAC or taking warfarin, but also in patients

not taking OAC (4.9 versus 8.4 per 100 patients/year). This finding might indirectly suggest that perhaps partial protection from the risk of thromboembolism is afforded by the anticoagulation occurring during the thrice-weekly dialysis regimen. It should also be emphasized that dialysis-related AF episodes [4, 5] are not an indication for OAC, as they are self-limited phenomena and occur when the patient is already anticoagulated with heparin. On these points, ongoing RCTs comparing OAC with no anticoagulation therapy will be fundamental in giving us an answer. Regarding the risk of bleeding, evidence shows that previous bleeding and INR lability (low time in therapeutic range values and high INR variability) are the factors most associated with bleeding events [25–27]. All these elements should be taken into account in treatment decisions.

CONCLUSIONS

The prescription of OAC for thromboembolic risk in patients with kidney failure and AF remains challenging and uncertain. RCTs comparing the efficacy of VKAs versus DOACs in preventing thromboembolic events in this population are lacking, as patients with an eCrCl <25–30 ml/min have been excluded from the major cardiology studies [34–37]. RCTs comparing VKAs and DOACs in dialysis patients with AF failed to provide convincing answers [39–41], therefore neither cardiology nor nephrology guidelines provide clear recommendations. Since the left atrial appendage is the main source of thromboembolism in the presence of AF, LAAC represents a valid non-pharmacological alternative for the treatment of AF [70, 71]. Some observational data suggest that the procedure may also be similarly effective and safe in patients on dialysis as in patients with preserved kidney function [77–79, 81]. However, RCTs comparing the efficacy and safety of LAAC versus OAC in kidney failure were terminated prematurely due to a lack of recruitment.

The difficulties and uncertainties in treating the common problem of AF in kidney failure underline the importance of shared decision-making with the multidisciplinary team and the patient to consider individual risks and benefits of each treatment option.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

AUTHORS' CONTRIBUTIONS

S.G. and C.B. conceptualized and designed the review, drafted the initial manuscript, and reviewed and revised the manuscript; A.C., A.B., V.Li. and G.A. prepared the tables; B.M., V.Lu., C.F. and C.C. performed the literature search; A.J.C. reviewed and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

S.G. has received consulting and speaker fees from Boston Scientific. A.J.C. has received personal fees from Abbott, Boston Scientific, Medtronic and Sanofi. B.M. has received grant support from BMS in relation to the topics of this article. C.B. has received consulting fees from Boston Scientific. The other authors declare no conflicts of interest.

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Received: February 17, 2024; Editorial decision: April 30, 2024