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Review

Nonvalvular atrial fibrillation in patients undergoing chronic hemodialysis. Should dialysis patients with atrial fibrillation receive oral anticoagulation?

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ABSTRACT

Chronic kidney disease (CKD) is an independent risk factor for presenting atrial fibrillation (AF), which conditions an increased risk already present in CKD of suffering a thromboembolic event. And this risk is even higher in the hemodialysis (HD) population. On the other hand, in CKD patients and even more so in HD patients, the probability of suffering serious bleeding is also higher. Therefore, there is no consensus on whether or not to anticoagulate this population.

Taking as a model what is advised for the general population, the most common attitude among nephrologists has been to opt for anticoagulation, even though there is no randomized studies to support it.

Classically, anticoagulation has been done with vitamin K antagonists, at high cost for our patients: severe bleeding events, vascular calcification, and progression of nephropathy, among other complications.

With the emergence of direct-acting anticoagulants, a hopeful outlook was opened in the field of anticoagulation, as they were postulated as more effective and safer drugs than antivitamin K. However, in clinical practice, this has not been the case.

In this paper we review various aspects of AF and its anticoagulant treatment in the HD population.

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Fibrilación auricular no valvular en pacientes en hemodiálisis crónica. ¿Debemos anticoagular?

Palabras clave:
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Anticoagulación oral
Antagonistas de la vitamina K
Anticoagulantes orales de acción directa
Cierre percutáneo orejuela izquierda

RESUMEN

La enfermedad renal crónica (ERC) es un factor de riesgo independiente para presentar fibrilación auricular (FA) lo que condiciona un incremento del riesgo ya presente en la ERC de sufrir un evento tromboembólico; y este riesgo es mayor aún en la población en hemodiálisis (HD). Por otro lado, en estos pacientes también es mayor la probabilidad de sufrir una hemorragia grave. Por ello, decidir si se debe anticoagular o no a un paciente con FA en diálisis es motivo de controversia entre la comunidad nefrológica.

Tomando como modelo lo aconsejado para la población general, la actitud más común entre los nefrólogos ha sido la de optar por la anticoagulación, pese a que no haya estudios randomizados que lo apoyen.

Clásicamente la anticoagulación se ha hecho con antagonistas de la vitamina K, con alto coste para nuestros pacientes: eventos hemorrágicos graves, calcificación vascular y progresión de la nefropatía entre otras complicaciones.

Con el surgimiento de los anticoagulantes de acción directa, se abrió un panorama esperanzador en el campo de la anticoagulación, al postularse como fármacos más eficaces y seguros que los antivitamina K. Sin embargo, en la práctica clínica, esto no ha sido así.

En esta revisión repasamos diversos aspectos de la FA y de su tratamiento anticoagulante en la población en HD.

Key concepts

- In the HD population with AF, the high risk of mortality due to bleeding associated with oral anticoagulation may outweigh the risk of stroke in a substantial proportion of patients.
- The indication for anticoagulation in the HD population with AF should probably be more restrictive than it is currently.
- Given the lack of evidence, and pending definitive trials that support the efficacy and safety of warfarin in HD patients, the routine use of VKAs in patients with non-valvular AF is not recommended, except in highly selected cases, and always with the consent of the patient after being informed of the risks.
- Regarding the use of DOACs in HD patients with non-valvular AF, low doses of rivaroxaban or apixaban could be considered as an alternative to VKAs, being very carefully and in agreement with the patient. In Europe, the use of any DOAC is not approved for eGFR < 15 ml/min.
- In patients on dialysis, the risk of presenting complications that require an invasive procedure is increased, which makes the management of these patients anticoagulated with DOAC more complicated.
- Percutaneous left atrial appendage (LAA) closure could be a non-pharmacological option fornthromboembolic protection in dialysis patients with AF.

Introduction

Although there are multiple situations in which nephrologists should consider anticoagulation in our patients, the one that generates the most doubts is the presence of atrial fibrillation (AF) in patients on hemodialysis (HD). The doubts refer to both the prevalence of AF in this population with the possible consequences, and to the oral anticoagulant treatment.

Atrial fibrillation in hemodialysis

Prevalence

Although it is assumed that AF is more prevalent in HD than in the general population,[1] the reality is, the lack of strategies to search AF,[2] as well as the existing variability when defining AF, has determined that the rates of AF described in HD patients vary from one study to another.[3] The fact that AF episodes occur mainly during HD sessions,[4] and many times asymptomatically, makes it possible that the prevalence may be higher than documented.[2]

In the Dialysis Outcomes and Practice Patterns Study (DOPPS) with more than 17,000 dialysis patients,[5] the prevalence of AF at baseline was 12.5%, and the incidence of "de novo" AF during follow-up was 1.0 per 100 patients/year, similar to the values already reported in the United States Renal Data System (USRD).[6] The prevalence increased with age, and

was higher than that observed in the general population for the same age. A subsequent meta-analysis of 25 observational studies showed that in dialysis patients the incidence and prevalence of AF were 2.7 and 11.65 per 100 patients/year, respectively[7]; and in another cohort of 258,605 patients ≥ 67 years who started dialysis, the incidence rate of AF was 14.8 per 100 patients/year[8] with an increase of 11% between the years 1995–2007.

Causes of greater presence of atrial fibrillation in hemodialysis

The multiple comorbidities associated with chronic kidney disease (CKD)[9] such as alterations in the cardiac structure, endothelial dysfunction, vascular calcification, premature atherosclerosis or increased activity of the renin angiotensin system and the adrenergic system, among others, make CKD an independent risk factor for AF.[10,11] This risk increases as glomerular filtration rate (GFR) decreases and/or the presence of proteinuria[12–16] and HD[17] increases AF, due to its intermittent nature,[6,18] as well as hydroelectrolytic changes caused during the sessions,[4,19] could aggravate this risk.

Possible consequences of atrial fibrillation in hemodialysis

In the general population, cerebrovascular accident (CVA) is a common complication of AF,[1,20] and HD patients with AF have numerous additional risk factors for stroke or venous thromboembolism (VTE).[21] In many cases, they are elderly, diabetic, hypertensive, with anemia, hyperuricemia, metabolic bone disease, platelet abnormalities or endothelial dysfunction, all of which lead to increased thrombotic risk.[22,23] In fact, the association of AF and CKD carries a greater risk of stroke, VTE, and mortality than that described for each of these diseases individually.[7,10,13,24] In studies of the prevalence of AF on HD, an increase in overall mortality[25,26] (1.7–3.8 times) has been reported, as well as a higher rate of stroke[27] in patients with AF compared with those without AF. In the DOPPS study,[5] AF was associated with an increase in the adjusted rates of stroke and death. Even so, the authors themselves highlighted the limitations of the study, as it was observational and that the questionnaire did not distinguish between hemorrhagic and ischemic infarction, or that the INR values were not collected, or the use of warfarin together plus heparin. They also pointed out the confusion in the diagnosis of AF, since it did not distinguish between permanent or paroxysmal AF or the existence of valve disease, except for the presence of a valve prosthesis, which was excluded. Subsequent studies also described a higher risk associated with AF in the HD population. In a meta-analysis of 13 observational studies,[8] all-cause mortality and the rate of stroke in HD were higher in patients with AF than in patients without it. Similarly, it has been reported that in incident patients on HD,[28,29] the presence of AF increases the rate of ischemic stroke.

However, some previous studies[26,30] and other even more recent ones[31] have failed to demonstrate such an association. In a cohort of 1382 HD patients, AF was not significantly associated with stroke.[32] Nor did AF predict the onset of ischemic infarction in 20,969 incident elderly dialysis patients in the US,[33] nor in 380 Japanese dialysis patients not treated with oral anticoagulants.[34] In a cohort study of HD patients in Taiwan, the initially detected slight increase in ischemic stroke in patients with AF disappeared when death due to hospitalization was considered as a competing risk factor.[35] Taking into account these latest findings, and added to the possibility that the prevalence of AF on HD could be underdiagnosed because it is often asymptomatic, it has been theorized that the risk of stroke attributable to AF would be even lower in the population in HD than in the general population,[36] either as a consequence of the protective effect of the use of heparin during dialysis or because AF was actually a marker of underlying cardiovascular disease and not the cause of it.[36]

Wathever it is, and given the difficulty in carrying out studies designed and be reliable to see the prevalence, incidence, and consequences of AF on HD, the truth is that the most widespread practice has been to anticoagulate our patients, as an extrapolation of the clinical trials that support the use of oral anticoagulants in the general population[1,20,37] with AF, despite the fact that there are no specific studies that demonstrate a net benefit of this practice in the HD population, and the lack of consensus, as demonstrated by a medical survey carried out jointly by the European Heart Rhythm Association and the European Renal Dialysis Association.[38]

Table 1 – Atrial fibrillation in the hemodialysis population.

- AF appears as a highly prevalent complication in the hemodialysis population.
- The consequences of AF in the dialysis population are not clearly defined, not even its association with ischemic stroke or thromboembolic disease, since the studies provide conflicting data and there are no specific studies designed for this population.
- There is insufficient evidence to indicate anticoagulation in the HD population with AF.
- The scores used to grade the risk/benefit of anticoagulation in the HD population with AF have not been fully validated.

AF: atrial fibrillation; HD: hemodialysis.

Graduate the risk

An added difficulty when it comes to indicating anticoagulation in HD patients is stratifying the risk/benefit of this practice. None of the scores used in the general population to measure bleeding risk have proven to be useful in HD,[3,39] not even the most frequently used, the CHA_2 DS_2-VASc. In fact, according to this score, the entire population on HD with AF should be anticoagulated,[40,41] so it could be overestimating[42] the risk of stroke in this population and minimizing the high risk of bleeding.

Conclusions (Table 1).

Choice of anticoagulant drug

Let us now see what we have observed with the use of the different oral anticoagulant drugs currently available.

Vitamin K antagonists

High bleeding risk and lack of efficacy

CKD increases risk of bleeding associated with the use of vitamin K antagonists (VKAs).[43,44] Patients with GFR < 30 ml/min present more out-of-range INR episodes, greater difficulty in reversing anticoagulation, and greater risk of minor and severe bleeding (more than double)[45,46] than patients with higher GFR.

Furthermore, the use of VKAs in the HD population, in addition to increasing the risk of severe bleeding,[43] has not been shown to reduce the risk of ischemic stroke[47–49] or mortality,[50–52] and some authors have even reported the opposite effect. In an observational study[47] in 1671 incident patients on HD with AF, the use of VKAs compared to no anticoagulation doubled the risk of both hemorrhagic and ischemic stroke, multiplied by four the risk of death from stroke, and increased hospitalization by 89% for this cause. Similar findings have been found in various meta-analyses.[53–57] In addition, it has been observed that this risk increases with age[58]; Wizemann et al., in a work based on the DOPPS study,[5] found that in people over 75 years of age, the use of VKAs doubled the risk of stroke.

More recently, in a Spanish study based on daily clinical practice,[59] it was described that the use of acenocoumarol did not show a benefit in survival, increased the risk of total hospitalizations and cardiovascular events (CV), and was associated with a higher risk trend for recurrent total bleeding.

However, some authors have defended the beneficial effect of VKAs in this population.[32,60] A Danish cohort study concluded that treatment with warfarin was associated with a significant (56%) decrease in the risk of stroke and/or VTE in patients who required renal replacement therapy (RRT) (HR = 0.44; 0.26−0.74; $P = .002$), although with an increased risk of bleeding (HR = 1.33; 1.16–1.53; $P < .001$).[21] Similarly, another observational study[61] defended that warfarin was safe and reduced the risk of ischemic infarction in patients with CKD, including the dialysis population. However, these 2 studies have been widely criticized[62] since they included in the same cohort patients with very different degrees of renal impairment[61]; they examined together patients with different RRT modalities such as HD, peritoneal dialysis (PD) and kidney transplantation[21,61]; the RRT cohort were younger patients and had less comorbidity than the patients without RR[21]; and they did not provide information on the indication of warfarin, nor on the INR achieved.

Risk of vascular calcification

An important complication in the HD population is the high risk of vascular calcification (VC), which could be aggravated by the use of VKAs.[63–66] The association between the use of warfarin and VC has been described both experimentally in uremic rats[67] and *in vivo* in HD patients.[68] In a longitudinal study In the HD population,[68] it was observed that treatment with warfarin, after adjusting for confounding factors, was independently associated with the progression of aortic stiffness.[68]

It is known that vitamin K[22] acts as a cofactor for the carboxylation and, therefore, the activation of numerous proteins, some of them involved in vascular and bone health, the most important being the Gla matrix protein (MGP). MGP is a small protein produced by vascular smooth muscle cells (VSMC) and chondrocytes, and with an important capacity to inhibit VC.[69] The VKAs,[70] by inhibiting the vitamin K cycle, would prevent the activation of this MGP protein, as well as other vitamin K-dependent proteins such as osteocalcin,[71] or Gas6,[72] also involved in vascular/osseous processes. Given that the population on dialysis presents a prevalent and severe vitamin K[73] deficiency at baseline, the use of VKAs would increase the deleterious effects of this deficiency. In fact, vitamin K supplementation strategies have been proposed to achieve better control of warfarin treatment,[74] and even prevent induced calcification[66]; however, currently, vitamin K supplementation in patients treated with VKAs in the HD population is not recommended.[75]

For all these reasons, multiple authors[76–78] have warned about the need to reassess the net benefit of long-term VKA therapy in the HD population.

Nephropathy associated with the use of vitamin K antagonists

Another pernicious effect is the nephropathy associated with the use VKAs,[79] causing both acute renal failure and progression of existing renal disease, an undesirable effect even for patients already on dialysis since, maintaining residual renal function for as long as possible is a desired goal. Warfarin nephropathy was initially described in renal biopsies from patients treated with warfarin[80–83] and confirmed in a recent meta-analysis[84] of 1733 studies, which concluded that warfarin-associated nephropathy is an entity with clinical definition and histopathological documentation.[84] Renal damage has been related to the presence of microhemorrhages that cause tubular obstruction,[80–84] as well as the possible induced VC.[69,85]

Difficult to control the target anticoagulation level

Despite all that has been said above, there are authors who consider that VKAs could indeed provide a net benefit in the HD population, provided that a close and reliable control of the level of anticoagulation can be ensured[86–88]; however, in clinical practice, and as has been widely demonstrated,[24,89,90] achieving this optimal control is very difficult in these patients. The causes of these poor results could be found in the characteristics of the HD population. Many of them are malnourished patients (99% of the VKAs circulate bound to proteins); multipathological and with interrecurrent infectious processes and, therefore, with frequent need for antibiotics and other drugs that interfere with the metabolism of VKAs[45]; to this should be added the already mentioned vitamin K deficiency in the HD population[89,90]; associated platelet dysfunction; and the volume fluctuations characteristic of the HD patient. All this conditions a narrow therapeutic window of efficacy and safety, forcing continuous monitoring of INR values, and still, the rate of suboptimal INR in the HD population is very high, which triggers an excess or deficiency of anticoagulation.[89,90]

Table 2 – Vitamin K inhibitor anticoagulants in hemodialysis patients with atrial fibrillation.

- The routine use of VKAs for non-valvular AF in HD patients is not recommended, since their deleterious effects could outweigh their potential benefits.
- There is no evidence that they protect against the risk of thromboembolic disease in this population, but they do increase the risk of bleeding, including stroke of hemorrhagic origin.
- Its use has been associated with vascular calcification.
- A relationship with the progression of kidney disease has been found.
- Optimal control of the level of anticoagulation is not ensured.

VKA: vitamin K antagonists; AF: atrial fibrillation; HD: hemodialysis.

Table 3 – Advantages of direct-acting oral anticoagulants over vitamin K antagonists.

- Oral administration without requiring monitoring.
- Quick onset of action.
- No interaction with food.
- Similar efficacy and greater safety than anticoagulation with vitamin K antagonists.

Table 4 – Disadvantages of direct-acting oral anticoagulants in the patients with kidney disease.

- Active participation of the kidney in its pharmacokinetics/pharmacodynamics.
- They circulate bound to proteins.
- The presence of proteinuria and the reduction of the GFR significantly affect its efficacy and safety.
- Metabolization through cytochrome P450,[92] a metabolic pathway used by drugs commonly used for the management of CKD comorbidities, which may limit its use in this population.
- Difficulty of its pharmacological reversal in the face of frequent medical/surgical interventions in the CKD population (for example, central catheterization for HD, imminent kidney transplant, etc.)
- High risk of bleeding due to overdose in cases of sudden worsening of the GFR.

CKD: chronic kidney disease; GFR: glomerular filtration rate; HD: hemodialysis.

Currently there is a clinical trial underway in HD patients with AF that compares the use of VKA drugs versus no anticoagulation, in the cumulative incidence of severe bleeding and thrombosis. It is planned to recruit 855 participants and end in January 2023 (AVKDIAL 9 [NCT02886962]).

Conclusions (Table 2).

Direct acting oral anticoagulants

Introduction

With the appearance in 2010 of a new family of oral anticoagulants, initially called new direct-acting oral anticoagulants (NOACs), and we prefer to call direct-acting oral anticoagulants (DOACs), since they have been available for more than a decade, the landscape of oral anticoagulation changed completely due to the advantages offered by these drugs[91] (Table 3).

However, in the field of nephrology, these DOACs have not turned out to be the ideal anticoagulants,[92] as shown in Table 4.

Studies in chronic kidney disease

Mild-moderate chronic kidney disease. The studies[93] have shown that in patients with mild to moderate CKD (eGFR, 30–59 ml/min) and AF, DOACs as compared to warfarin show a reduction in major bleeding, although without differences in the rate of CV events. An added benefit as compared to warfarin is that in CKD patients the use of DOACs, specifically apixaban[94,95] and rivaroxaban,[96] seem not to favor VC[97] or atherosclerosis[98,99] and, therefore, do not accelerate the progression of CKD.[100] Even so, microscopic bleeding and kidney damage have also been described in patients treated with DOAC.[98–103]

Therefore, the use of DOACs in moderate CKD seems to be an alternative to VKAs as long as the recommended dose adjustments are followed for the different stages of CKD.[104–106]

Advanced chronic kidney disease. In the initial randomized studies comparing VKAs and DOACs in patients with non-valvular AF, as well as in subsequent meta-analyses,[107] patients with advanced CKD were systematically excluded.[108] The first meta-analysis on the safety and efficacy of DOACs versus warfarin in CKD patients,[107] is based on 8 studies in which 3 drugs with different renal excretion were analyzed together: dabigatran (renal excretion > 80%–85%); rivaroxaban (renal excretion > 36%) and apixaban (renal excretion > 25%); and all patients analyzed presented GFR > 30 ml/min, therefore, despite the good results shown, the authors of the article concluded that it was not advised the routine use of DOACs in patients with eGFR < 30 ml/min. Chang et al.[109] In a prospective cohort study of 3771 patients with AF and CKD stages 4–5 (25% on dialysis), the group receiving DOAC (mean GFR of 25 ml/min) was analyzed versus the group on warfarin (mean GFR of 17 ml/min) and were compared with the group that did not receive anticoagulation (mean GFR of 16 ml/min). They found that in the groups with DOAC or warfarin versus those not anticoagulated, the risk of stroke was similar and there was a significant increase in the number of bleeding episodes, so these data did not support anticoagulation in patients with AF and stage 4 CKD-5.

Therefore, the benefit of DOACs seems less evident for patients with GFR < 30 ml/min (CKD stages 4–5).

Hemodialysis. Initially, it was thought that the benefit-risk profile of DOACs could be extended to the HD population; but this is more a wish than a reality, at least so far. The first published studies, all observational, showed that only rivaroxaban and apixaban were considered suitable for dialysis patients, since they present the lowest degree of renal clearance and are not substantially removed by dialysis.[110,111]

Rivaroxaban. In a cohort of 8589 HD patients, bleeding complications requiring hospitalization and fatal bleeding were more frequent in patients using full-dose dabigatran or rivaroxaban than those treated with VKA,[112] but not with the reduced dose of rivaroxaban. In another retrospective study[113] comparing rivaroxaban versus warfarin, a significant reduction in the risk of severe bleeding was observed, but no improvement was observed in the risk of ischemic stroke or VTE. The last comparative study between ribaroxaban and warfarin is a randomized and prospective study with 2 years of follow-up[114];

it was observed that rivaroxaban at a dose of 10 mg/day compared to VKAs, significantly reduced fatal and non-fatal QOL events, as well as serious bleeding events Although, as the authors themselves acknowledge, by not including a placebo group, it could not be ascertained whether the result was a consequence of the pernicious effect of VKAs or the protective effect of rivaroxaban.

Apixaban. Apixaban has been the most widely used DOAC in CKD,[115] and it is apparently the safest in HD patients. This drug has the lowest renal excretion (25%–29%) of all DOACs,[111] and seems safer than VKAs in preventing stroke because it presents a lower risk of bleeding,[105,116,117] in addition it presents fewer drug interactions and it has anti-inflammatory effects.[118] A small observational study of 124 HD patients revealed a lower rate of bleeding events in patients treated with apixaban than those with VKA.[119] In a large retrospective cohort study[120] of 25,523 patients on chronic HD (a minority of patients on PD, n = 1377; 5.4%) and AF included in the US Renal Data Registry (USRDS), the use of warfarin was compared with apixaban. The standard dose of 5 mg twice daily versus VKA or the non-anticoagulated cohort showed no advantage in the risk of transient ischemic stroke (TIA) or thromboembolism, but of compared with the reduced dose (2.5 mg/12 h) there was a lower risk of stroke/systemic embolism and death was observed. Regarding bleeding risk, patients treated with the standard dose of apixaban were safer than those anticoagulated with VKA, but there were no differences if compared with patients treated with the reduced dose, and compared with those not anticoagulated, a clear higher incidence of infarction was observed. Haemorrhagic and fatal bleeding (apixaban [4.9 events/100 patient-years] versus no anticoagulation [1.6 events/100 patient-years]). However, patients who received the reduced dose (2.5 mg/2 times daily) did not have an increased risk of bleeding compared to patients who did not receive anticoagulation. Despite the relatively favorable data for apixaban versus VKAs in AF patients with end-stage CKD or on dialysis, the authors are uncertain about the net benefit of anticoagulation for stroke prevention in dialysis patients with AF, given that bleeding although mild, it can be very common and problematic in dialysis patients with a vascular access.

A more recent study[121] has not shown any advantages of apixaban compared to no anticoagulation in this population on HD with AF.

Dosage of direct-acting oral anticoagulants in chronic kidney disease

Over time we have learned that the initially indicated doses of DOAC for the different degrees of renal failure were inappropriately high.

Pharmacokinetic studies have shown that, in HD patients without residual renal function, the appropriate dose of rivaroxaban is 10 mg daily[122]; and for apixaban, the most accepted dose is that of 2.5 mg/2 times a day,[120,122] since the dose of 5 mg/2 times a day has been associated with supratherapeutic levels.[123] And choosing between rivaroxaban and apixaban could also be conditioned by the dosing regimen. Compared with the advantage of possible greater adherence to rivaroxaban as it requires a single dose per day, the administration of apixaban twice a day could lead to a more stable anticoagulant effect over the course of 24 h.[124]

It has recently been described that the time of drug administration with respect to the session influences its pharmacokinetics and, therefore, its efficacy and risks[125]; specifically, 5 mg of apixaban administered 30 min pre-HD would result in the same absorption as a single dose of 2.5 mg post-HD.

It must be emphasized that, although the excess risk of bleeding observed with DOACs in the population with advanced CKD could be a consequence of the use of excessively high doses,[106,109] in dialysis patients, even after dose adjustment, the presence of slight bleeding increases the possible complications of an invasive procedure and/or the need for rapid reversal of the anticoagulant effect (as the case of canalizing a new vascular access, kidney transplant...) and, although antidotes already exist for DOACs,[126–128] their use is still highly restricted and not validated in this population.

Recommendations from regulatory agencies

The 2018 KDIGO guidelines suggested a reduced dose of apixaban (2.5 mg/2 times daily) in the HD population[129]; however, in the opinion of a working group of European experts[38] "the KDIGO position regarding apixaban may be too conservative... In fact, in patients who can take the full dose of the drug, there are benefits in terms of thromboembolic events and mortality, in the absence of an increased risk of bleeding».[38]

The Food and Drug Administration (FDA), based on pharmacokinetic data, has approved the use[130] of apixaban 5 mg/twice daily in patients with advanced CKD, unless a dose reduction to 2.5 mg is indicated. /2 times a day if the patient is ≥80 years old and/or weighs ≤ 60 kg. The FDA also allows the use of rivaroxaban 15 mg/once daily in this population.

Recent guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) establish the use of apixaban in HD patients as "reasonable", although would be justified specific studies for this population.[131]

In 2019, the results of the first randomized trial (RENAL-AF)[132] (NCT02942407) of apixaban versus warfarin in HD patients with AF[133] were reported· The study was prematurely suspended in July 2019 due to lack of funding, and the initial objective of recruiting 760 patients could not be reached so the statistical power was limited. A total of 154 patients were randomized to receive apixaban (n = 82, of which 29% received a reduced dose of 2.5 mg/12 h) versus warfarin (n = 72, with a target INR of 2–3). After one year of follow-up, the trial showed that there were no differences in the rates of ischemic stroke, bleeding, or mortality between the groups studied. It could not be clarified whether the lower dose of apixaban (2.5 mg/12 h) might have resulted in less bleeding than warfarin.[133]

Two other randomized studies are currently being carried out with apixaban and VKA in the dialysis population:

- *AXADIA* (NCT02933697), a German study, which compares apixaban 2.5 mg/every 12 h against VKA phenprocoumon. Try to recruit 222 patients and follow them for 6–24 months. It is scheduled to finish in July 2023.
- *SAFE-D* (NCT03987711), compares VKA versus apixaban 5 mg/2 times daily (or 2.5 mg/2 times daily in selected

Table 5 – Direct-acting oral anticoagulants and CKD.

- The use of DOACs in moderate CKD seems to be an alternative to VKAs as long as the recommended dose adjustments are made for the different stages of CKD.
- The benefit of DOACs is less evident in patients with GFR < 30 ml/min (CKD stages 4–5).
- In HD patients with non-valvular AF, although the possible net benefit of anticoagulation with DOAC (apixaban) for stroke prevention compared with no anticoagulation remains unclear, low doses of rivaroxaban or apixaban could be considered as a alternative to VKAs if given very carefully and in agreement with the patient.
- In HD, the FDA has approved the use of apixaban 5 mg/2 times a day (or 2.5 mg/2 times a day if the patient is ≥80 years of age and/or weighs ≤ 60 kg) and rivaroxaban 15 mg/once daily.
- The European Medicines Agency has not approved the use of any DOAC if the eGFR is <15 ml/min.
- Pending the data derived from randomized studies, it seems reasonable to wait and be prudent in the use of DOACs in HD patients.

DOAC: direct-acting oral anticoagulants; VKA: vitamin K antagonists; CKD: chronic kidney disease; FDA: Food and Drug Administration; GFR: glomerular filtration rate; HD: hemodialysis.

patients), and with no anticoagulation. It is scheduled to end on December 31, 2022.

The European Medicines Agency (EMA) has not yet approved the use of any DOAC when the eGFR is <15 ml/min.[134]

In summary, although in HD patients with non-valvular AF It has not been possible to demonstrate a clear benefit of DOACs compared to no anticoagulation, since DOACs do not reduce the risk of ischemic stroke, TIA, or systemic VTE. But, low doses of rivaroxaban or apixaban could be considered as an alternative to VKAs, given very carefully and in agreement with the patient.[135,136]

Pending the data derived from the randomized studies, it seems reasonable to wait and be prudent in the use of DOACs in HD patients.

Conclusions (Table 5).

Percutaneous closure of the left atrial appendage

An alternative to anticoagulant therapy in HD patients with AF could be the use of percutaneous devices that block the left atrial appendage (LAA), the site of thrombus formation.[137,138]

In a meta-analysis aimed at examining the efficacy of this device in patients with CKD[139] and AF, it was observed that, despite the low number of patients and the heterogeneity of the studies analyzed, this technique could effectively and safely prevent the occurrence of stroke and TIA.

In dialysis, an Italian study carried out in 11 centers[140] examined 92 patients with AF who underwent LAA occlusion against two cohorts of patients, one on wafarin treatment (114 patients) and the other without treatment (148 patients). After 2-year follow-up, they found that in the cohort of patients who underwent the procedure compared with the warfarin and no treatment, the incidence of non-fatal CV events was significantly lower and 2-year survival was significantly higher. Regarding bleeding, the incidence was significantly higher in patients with warfarin compared to the other two cohorts. The study suggests that AAI occlusion is feasible and safe in dialysis patients, and that, in the long term, it is associated with a reduction in both thromboembolic events compared with untreated patients, and in bleeding events compared with patients taking warfarin. For all these reasons, it seems that atrial appendage closure could open the way to a non-pharmacological option for thromboembolic protection in dialysis patients with AF and high risk of bleeding.

A single-arm prospective study with the Watchman™ device in dialysis patients is ongoing and is scheduled to end in December 2022 (NCT03446794).

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Conflict of interests

The authors have no conflict of interest.

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