

## Review

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

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### ARTICLE INFO

#### Article history:

Received 11 January 2022

Accepted 16 January 2022

#### Keywords:

Atrial fibrillation

Haemodialysis

Oral anticoagulation

Vitamin K antagonists

Direct acting oral anticoagulants

Oral anticoagulant therapy

Left atrial appendage occlusion

### 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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DOI of original article:

<https://doi.org/10.1016/j.nefro.2022.01.005>.

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

### R E S U M E N

#### Palabras clave:

Fibrilación auricular  
Hemodiálisis  
Anticoagulación oral  
Antagonistas de la vitamina K  
Anticoagulantes orales de acción directa  
Cierre percutáneo orejuela izquierda

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 antivitaminas 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.

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### 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 for thromboembolic 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,<sup>1</sup> the reality is, the lack of strategies to search AF,<sup>2</sup> 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.<sup>3</sup> The fact that AF episodes occur mainly during HD sessions,<sup>4</sup> and many times asymptotically, makes it possible that the prevalence may be higher than documented.<sup>2</sup>

In the Dialysis Outcomes and Practice Patterns Study (DOPPS) with more than 17,000 dialysis patients,<sup>5</sup> 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 (USRDR).<sup>6</sup> 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<sup>7</sup>; and in another cohort of 258,605 patients  $\geq$  67 years who started dialysis, the incidence rate of AF was 14.8 per 100 patients/year<sup>8</sup> 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)<sup>9</sup> 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.<sup>10,11</sup> This risk increases as glomerular filtration rate (GFR) decreases and/or the presence of proteinuria<sup>12–16</sup> and HD<sup>17</sup> increases AF, due to its intermittent nature,<sup>6,18</sup> as well as hydroelectrolytic changes caused during the sessions,<sup>4,19</sup> could aggravate this risk.

### **Possible consequences of atrial fibrillation in hemodialysis**

In the general population, cerebrovascular accident (CVA) is a common complication of AF,<sup>1,20</sup> and HD patients with AF have numerous additional risk factors for stroke or venous thromboembolism (VTE).<sup>21</sup> 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.<sup>22,23</sup> 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.<sup>7,10,13,24</sup> In studies of the prevalence of AF on HD, an increase in overall mortality<sup>25,26</sup> (1.7–3.8 times) has been reported, as well as a higher rate of stroke<sup>27</sup> in patients with AF compared with those without AF. In the DOPPS study,<sup>5</sup> 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,<sup>8</sup> 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,<sup>28,29</sup> the presence of AF increases the rate of ischemic stroke.

However, some previous studies<sup>26,30</sup> and other even more recent ones<sup>31</sup> have failed to demonstrate such an association. In a cohort of 1382 HD patients, AF was not significantly associated with stroke.<sup>32</sup> Nor did AF predict the onset of ischemic infarction in 20,969 incident elderly dialysis patients in the US,<sup>33</sup> nor in 380 Japanese dialysis patients not treated with

**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.

oral anticoagulants.<sup>34</sup> 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.<sup>35</sup> 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,<sup>36</sup> 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.<sup>36</sup>

Whatever 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<sup>1,20,37</sup> 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.<sup>38</sup>

### **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,<sup>3,39</sup> not even the most frequently used, the CHA<sub>2</sub> DS<sub>2</sub>-VASc. In fact, according to this score, the entire population on HD with AF should be anticoagulated,<sup>40,41</sup> so it could be overestimating<sup>42</sup> 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).<sup>43,44</sup> 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)<sup>45,46</sup> than patients with higher GFR.

Furthermore, the use of VKAs in the HD population, in addition to increasing the risk of severe bleeding,<sup>43</sup> has not been shown to reduce the risk of ischemic stroke<sup>47-49</sup> or mortality,<sup>50-52</sup> and some authors have even reported the opposite effect. In an observational study<sup>47</sup> 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.<sup>53-57</sup> In addition, it has been observed that this risk increases with age<sup>58</sup>; Wizemann et al., in a work based on the DOPPS study,<sup>5</sup> 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,<sup>59</sup> 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.<sup>32,60</sup> 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;  $P < .001$ ).<sup>21</sup> Similarly, another observational study<sup>61</sup> 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<sup>62</sup> since they included in the same cohort patients with very different degrees of renal impairment<sup>61</sup>; they examined together patients with different RRT modalities such as HD, peritoneal dialysis (PD) and kidney transplantation<sup>21,61</sup>; the RRT cohort were younger patients and had less comorbidity than the patients without RR<sup>21</sup>; 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.<sup>63-66</sup> The association between the use of warfarin and VC has been described both experimentally in uremic rats<sup>67</sup> and *in vivo* in HD patients.<sup>68</sup> In a longitudinal study in the HD population,<sup>68</sup> it was observed that treatment with warfarin, after adjusting for confounding factors, was independently associated with the progression of aortic stiffness.<sup>68</sup>

It is known that vitamin K<sup>22</sup> 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.<sup>69</sup> The VKAs,<sup>70</sup> 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,<sup>71</sup> or Gas6,<sup>72</sup> also involved in vascular/osseous processes. Given that the population on dialysis presents a prevalent and severe vitamin K<sup>73</sup> 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,<sup>74</sup> and even prevent induced calcification<sup>66</sup>; however, currently, vitamin K supplementation in patients treated with VKAs in the HD population is not recommended.<sup>75</sup>

For all these reasons, multiple authors<sup>76-78</sup> 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 of VKAs,<sup>79</sup> 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<sup>80-83</sup> and confirmed in a recent meta-analysis<sup>84</sup> of 1733 studies, which concluded that warfarin-associated nephropathy is an entity with clinical definition and histopathological documentation.<sup>84</sup> Renal damage has been related to the presence of microhemorrhages that cause tubular obstruction,<sup>80-84</sup> as well as the possible induced VC.<sup>69,85</sup>

### 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<sup>86-88</sup>; however, in clinical practice, and as has been widely demonstrated,<sup>24,89,90</sup> 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<sup>45</sup>; to this should be added the already mentioned vitamin K deficiency in the HD population<sup>89,90</sup>; associated platelet dysfunction; and the volume fluctuations characteristic of the HD patient. All these 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.<sup>89,90</sup>

**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,<sup>92</sup> 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<sup>91</sup> (Table 3).

However, in the field of nephrology, these DOACs have not turned out to be the ideal anticoagulants,<sup>92</sup> as shown in Table 4.

#### Studies in chronic kidney disease

**Mild-moderate chronic kidney disease.** The studies<sup>93</sup> 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<sup>94,95</sup> and rivaroxaban,<sup>96</sup> seem not to favor VC<sup>97</sup> or atherosclerosis<sup>98,99</sup> and, therefore, do not accelerate the progression of CKD.<sup>100</sup> Even so, microscopic bleeding and kidney damage have also been described in patients treated with DOAC.<sup>98–103</sup>

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.<sup>104–106</sup>

**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,<sup>107</sup> patients with advanced CKD were systematically excluded.<sup>108</sup> The first meta-analysis on the safety and efficacy of DOACs versus warfarin in CKD patients,<sup>107</sup> 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.<sup>109</sup> 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.<sup>110,111</sup>

**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,<sup>112</sup> but not with the reduced dose of rivaroxaban. In another retrospective study<sup>113</sup> 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 rivaroxaban and warfarin is a randomized and prospective study with 2 years of follow-up<sup>114</sup>;

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,<sup>115</sup> and it is apparently the safest in HD patients. This drug has the lowest renal excretion (25%–29%) of all DOACs,<sup>111</sup> and seems safer than VKAs in preventing stroke because it presents a lower risk of bleeding,<sup>105,116,117</sup> in addition it presents fewer drug interactions and it has anti-inflammatory effects.<sup>118</sup> A small observational study of 124 HD patients revealed a lower rate of bleeding events in patients treated with apixaban than those with VKA.<sup>119</sup> In a large retrospective cohort study<sup>120</sup> 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<sup>121</sup> 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<sup>122</sup>; and for apixaban, the most accepted dose is that of 2.5 mg/2 times a day,<sup>120,122</sup> since the dose of 5 mg/2 times a day has been associated with supratherapeutic levels.<sup>123</sup> 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.<sup>124</sup>

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<sup>125</sup>; 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,<sup>106,109</sup> 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,<sup>126–128</sup> 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<sup>129</sup>; however, in the opinion of a working group of European experts<sup>38</sup> “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.”<sup>38</sup>

The Food and Drug Administration (FDA), based on pharmacokinetic data, has approved the use<sup>130</sup> 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  $\geq 80$  years old and/or weighs  $\leq 60$  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.<sup>131</sup>

In 2019, the results of the first randomized trial (RENAL-AF)<sup>132</sup> (NCT02942407) of apixaban versus warfarin in HD patients with AF<sup>133</sup> 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.<sup>133</sup>

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 an 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.<sup>134</sup>

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.<sup>135,136</sup>

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.<sup>137,138</sup>

In a meta-analysis aimed at examining the efficacy of this device in patients with CKD<sup>139</sup> 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<sup>140</sup> examined 92 patients with AF who underwent LAA occlusion against two cohorts of patients, one on warfarin 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).

### Financing

This research has not received specific support from public sector agencies, the commercial sector or non-profit entities.

### Conflict of interests

The authors have no conflict of interest.

### REFERENCES

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation ed European Heart Rhythm Assoon the risk of death. The Framingham Heart Study. *Circulation*. 1998;98:946–52, <http://dx.doi.org/10.1161/01.cir.98.10.946>.
2. Roberts PR, Stromberg K, Johnson LC, Wiles BM, Mavrakans TA, Charytan DM. A systematic review of the incidence of arrhythmias in hemodialysis patients undergoing long-term monitoring with implantable loop recorders. *Kidney Int Rep*. 2021;6:56–65, <http://dx.doi.org/10.1016/j.ekir.2020.10.020>, eCollection 2021.
3. De Vriese AS, Caluwe R, Raggi P. The atrial fibrillation conundrum in dialysis patients. *Am Heart J*. 2016;174:111–9, <http://dx.doi.org/10.1016/j.ahj.2016.01.010>.
4. Buiten MS, De Bie MK, Rotmans JI, Gabreels BA, van Dop W, Wolterbeek R, et al. The dialysis procedure as a trigger for atrial fibrillation: new insights in the development of atrial fibrillation in dialysis patients. *Heart*. 2014;100:685–90, <http://dx.doi.org/10.1136/heartjnl-2013-305417>.
5. Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int*. 2010;77:1098–106, <http://dx.doi.org/10.1038/ki.2009.477>.
6. Abbott KC, Trespalacios F, Taylor AJ, Agodoa LY. Atrial fibrillation in chronic dialysis patients in the United States: risk factors for hospitalization and mortality. *BMC Nephrol*. 2003;4:1, <http://dx.doi.org/10.1186/1471-2369-4-1>.
7. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM, et al. Systematic review and metaanalysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. *Nephrol Dial Transplant*. 2012;27:3816–22, <http://dx.doi.org/10.1093/ndt/gfs416>.
8. Goldstein BA, Arce CM, Hlatky MA, Turakhia M, Setoguchi S, Winkelmayer WC. Trends in the incidence of atrial fibrillation in older patients initiating dialysis in the United

- States. *Circulation*. 2012;126:2293–301, <http://dx.doi.org/10.1161/CIRCULATIONAHA.112.099606>.
9. Bansal N, Hsu CY, Go A. S Intersection of cardiovascular disease and kidney disease: atrial fibrillation. *Curr Opin Nephrol Hypertens*. 2014;23:275–82, <http://dx.doi.org/10.1097/01.mnh.0000444820.80249.56>.
  10. Nelson SE, Shroff GR, Li S, Herzog CA. Impact of chronic kidney disease on risk of incident atrial fibrillation and subsequent survival in medicare patients. *J Am Heart Assoc*. 2012;1:e002097, <http://dx.doi.org/10.1161/JAHA.112.002097>.
  11. Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. *Circulation*. 2013;127:569–74, <http://dx.doi.org/10.1161/CIRCULATIONAHA.112.123992>.
  12. Ohyama Y, Imai M, Kurabayashi M. Estimated glomerular filtration rate and proteinuria are separately and independently associated with the prevalence of atrial fibrillation in general population. *PLoS One*. 2013;8:e79717, <http://dx.doi.org/10.1371/journal.pone.0079717>, eCollection 2013.
  13. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. *Am Heart J*. 2009;158:629–36, <http://dx.doi.org/10.1016/j.ahj.2009.06.031>.
  14. Liao JN, Chao TF, Liu CJ, Wang KL, Chen SJ, Lin YJ, et al. Incidence and risk factors for newonset atrial fibrillation among patients with end-stage renal disease undergoing renal replacement therapy. *Kidney Int*. 2015;87:1209–15, <http://dx.doi.org/10.1038/ki.2014.393>.
  15. Suzuki S, Sagara K, Otsuka T, Kanou H, Matsuno S, Uejima T, et al. Estimated glomerular filtration rate and proteinuria are associated with persistent form of atrial fibrillation: analysis in Japanese patients. *J Cardiol*. 2013;61:53–7, <http://dx.doi.org/10.1016/j.jjcc.2012.07.016>.
  16. McManus DD, Corteville DC, Shlipak MG, Whooley MA, Ix JH. Relation of kidney function and albuminuria with atrial fibrillation (from the Heart and Soul Study). *Am J Cardiol*. 2009;104:1551–5, <http://dx.doi.org/10.1016/j.amjcard.2009.07.026>.
  17. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123:2946–53, <http://dx.doi.org/10.1161/CIRCULATIONAHA.111.020982>.
  18. Ansari N, Manis T, Feinfeld D. Symptomatic atrial arrhythmias in haemodialysis patients. *Ren Fail*. 2001;23:71–6, <http://dx.doi.org/10.1081/jdi-100001285>.
  19. Vincenti A, Passini E, Fabbrini P, Luise MC, Severi S, Genovesi S. Recurrent intradialytic paroxysmal atrial fibrillation: hypotheses on onset mechanisms based on clinical data and computational analysis. *Europace*. 2014;16:396–404, <http://dx.doi.org/10.1093/europace/eut346>.
  20. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age, distribution and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med*. 1995;155:469–73.
  21. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367:625–35, <http://dx.doi.org/10.1056/NEJMoa1105594>.
  22. Tran L, Pannier B, Lacolley P, Serrato T, Benetos A, London GM, et al. A case-control study indicates that coagulation imbalance is associated with arteriosclerosis and markers of endothelial dysfunction in kidney failure. *Kidney Int*. 2021;99:1162–72, <http://dx.doi.org/10.1016/j.kint.2020.12.011>.
  23. Jeong JC, Kim JE, Ryu JW, Joo KW, Kim HK. Plasma haemostatic potential of haemodialysis patients assessed by thrombin generation assay: hypercoagulability in patients with vascular access thrombosis. *Thromb Res*. 2013;132:604–9, <http://dx.doi.org/10.1016/j.thromres.2013.09.002>.
  24. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–603, <http://dx.doi.org/10.1161/CIR.0000000000000485>.
  25. Vázquez E, Sánchez-Perales C, Borrego F, García-Cortés MJ, Lozano C, Guzmán M, et al. Influence of atrial fibrillation on the morbido-mortality of patients on haemodialysis. *Am Heart J*. 2000;140:886–90, <http://dx.doi.org/10.1067/mhj.2000.111111>.
  26. Genovesi S, Vincenti A, Rossi E, Pogliani D, Acquistapace I, Stella A, et al. Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysis patients. *Am J Kidney Dis*. 2008;51:255–62, <http://dx.doi.org/10.1053/j.ajkd.2007.10.034>.
  27. To AC, Yehia M, Collins JF. Atrial fibrillation in haemodialysis patients: do the guidelines for anticoagulation apply? *Nephrology (Carlton)*. 2007;12:441–7, <http://dx.doi.org/10.1111/j.1440-1797.2007.00835.x>.
  28. Wetmore JB, Ellerbeck EF, Mahnken JD, Phadnis M, Rigler SK, Mukhopadhyay P, et al. Atrial fibrillation and risk of stroke in dialysis patients. *Ann Epidemiol*. 2013;23:112–8, <http://dx.doi.org/10.1016/j.annepidem.2012.12.011>.
  29. Wetmore JB, Ellerbeck EF, Mahnken JD, Phadnis MA, Rigler SK, Spertus JA, et al. Stroke and the “stroke belt” in dialysis: contribution of patient characteristics to ischemic stroke rate and its geographic variation. *J Am Soc Nephrol*. 2013;24:2053–61, <http://dx.doi.org/10.1681/ASN.2012111077>.
  30. Wiesholzer M, Harm F, Tomasec G, Barbieri G, Putz D, Balcke P. Incidence of stroke among chronic haemodialysis patients with nonrheumatic atrial fibrillation. *Am J Nephrol*. 2001;21:35–9, <http://dx.doi.org/10.1159/000046216>.
  31. Toida T, Sato Y, Nakagawa H, Komatsu H, Uezono S, Yamada K, et al. Risk of cerebral infarction in Japanese hemodialysis patients: Miyazaki Dialysis Cohort Study (MID study). *Kidney Blood Press Res*. 2016;41:471–8, <http://dx.doi.org/10.1159/000443448>.
  32. Findlay MD, Thomson PC, Fulton RL, Solbu MD, Jardine AG, Patel RK, et al. Risk factors of ischemic stroke and subsequent outcome in patients receiving hemodialysis. *Stroke*. 2015;46:2477–81, <http://dx.doi.org/10.1161/STROKEAHA.115.009095>.
  33. Murray AM, Seliger S, Lakshminarayan K, Herzog CA, Solid CA. Incidence of stroke before and after dialysis initiation in older patients. *J Am Soc Nephrol*. 2013;24:1166–73, <http://dx.doi.org/10.1681/ASN.2012080841>.
  34. Mitsuma W, Matsubara T, Hatada K, Imai S, Tamura M, Tsubata Y, et al. Atrial fibrillation had less impact on the risk of ischemic stroke in non-anticoagulated patients undergoing hemodialysis: insight from the RAKUEN study. *Intern Med*. 2018;57:2295–300, <http://dx.doi.org/10.2169/internalmedicine.0021-17>.
  35. Shih CJ, Ou SM, Chao PW, Kuo SC, Lee YJ, Yang CY, et al. Risks of death and stroke in patients undergoing hemodialysis with new-onset atrial fibrillation: a competing-risk analysis of a nationwide cohort. *Circulation*. 2016;133:265–72, <http://dx.doi.org/10.1161/CIRCULATIONAHA.115.018294>.
  36. De Vriese AS, Heine G. Anticoagulation management in haemodialysis patients with atrial fibrillation: evidence and opinion. *Nephrol Dial Transplant*. 2021;fgab060, <http://dx.doi.org/10.1093/ndt/fgab060>.



37. American College of Cardiology; American Heart Association Task Force on Performance Measures; Physician Consortium for Performance Improvement; ACC/AHA/Physician Consortium 2008 Clinical Performance Measures for Adults with Nonvalvular Atrial Fibrillation or Atrial Flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and the Physician Consortium for Performance Improvement (Writing Committee to Develop Clinical Performance Measures for Atrial Fibrillation) Developed in Collaboration with the Heart Rhythm Society. *J Am Coll Cardiol.* 2008;51:865–84, <http://dx.doi.org/10.1016/j.jacc.2008.01.006>.
38. Potpara TS, Ferro C, Lip GYH, Dan GA, Lenarczyk R, Mallama C, et al. Management of atrial fibrillation in patients with chronic kidney disease in clinical practice: a joint European Heart Rhythm Association (EHRA) and European Renal Association/European Dialysis and Transplantation Association (ERA/EDTA) physician-based survey. *Europace.* 2020;22:496–505, <http://dx.doi.org/10.1093/europace/euz358>.
39. Ocak G, Ramspek C, Rookmaaker MB, Blankestijn PJ, Verhaar MC, Willem JWB, et al. Performance of bleeding risk scores in dialysis patients. *Nephrol Dial Transplant.* 2019;34:1223–31, <http://dx.doi.org/10.1093/ndt/gfy387>.
40. Pokorney SD, Black-Maier E, Hellkamp AS, Friedman DJ, Vemulapalli S, Granger CB, et al. Oral anticoagulation and cardiovascular outcomes in patients with atrial fibrillation and end-stage renal disease. *J Am Coll Cardiol.* 2020;75:1299–308, <http://dx.doi.org/10.1016/j.jacc.2020.01.019>.
41. Königsbrügge O, Posch F, Antlanger M, Kovarik J, Klausner-Braun R, Kletzmayer J, et al. Prevalence of atrial fibrillation and antithrombotic therapy in hemodialysis patients: cross-sectional results of the Vienna Investigation of Atrial Fibrillation and Thromboembolism in Patients on Hemodialysis (VIVALDI). *PLoS One.* 2017;12:e0169400, <http://dx.doi.org/10.1371/journal.pone.0169400>, eCollection 2017.
42. Dzeshka MS, Lane DA, Lip GY. Stroke and bleeding risk in atrial fibrillation: navigating the alphabet soup of risk-score acronyms (CHADS2, CHA2 DS2 -VASc, R2 CHADS2, HAS-BLED, ATRIA, and more). *Clin Cardiol.* 2014;7:634–44, <http://dx.doi.org/10.1002/clc.22294>.
43. Fabbian F, Catalano C, Lambertini D, Tarroni G, Bordin V, Squerzanti R, et al. Clinical characteristics associated to atrial fibrillation in chronic haemodialysis patients. *Clin Nephrol.* 2000;54:234–9.
44. Genovesi S, Pogliani D, Faini A, Valsecchi MG, Riva A, Stefani F, et al. Prevalence of atrial fibrillation and associated factors in a population of long-term hemodialysis patients. *Am J Kidney Dis.* 2005;46:897–902, <http://dx.doi.org/10.1053/j.ajkd.2005.07.044>.
45. Limdi NA, Beasley TM, Baird MF, Goldstein JA, McGwin G, Arnett DK, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. *J Am Soc Nephrol.* 2009;20:912–21, <http://dx.doi.org/10.1681/ASN.2008070802>.
46. Limdi NA, Nolin TD, Booth SL, Centi A, Marques MB, Crowley MR, et al. Influence of kidney function on risk of supratherapeutic international normalized ratio-related hemorrhage in warfarin users: a prospective cohort study. *Am J Kidney Dis.* 2015;65:701–9, <http://dx.doi.org/10.1053/j.ajkd.2014.11.004>.
47. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol.* 2009;20:2223–33, <http://dx.doi.org/10.1681/ASN.2009030319>.
48. Wakasugi M, Kazama JJ, Tokumoto A, Suzuki K, Kageyama S, Ohya K, et al. Association between warfarin use and incidence of ischemic stroke in Japanese hemodialysis patients with chronic sustained atrial fibrillation: a prospective cohort study. *Clin Exp Nephrol.* 2014;18:662–9, <http://dx.doi.org/10.1007/s10157-013-0885-6>.
49. Yodogawa K, Mii A, Fukui M, Iwasaki YK, Hayashi M, Kaneko T, et al. Warfarin use and incidence of stroke in Japanese hemodialysis patients with atrial fibrillation. *Heart Vessels.* 2016;31:1676–80, <http://dx.doi.org/10.1007/s00380-015-0777-7>.
50. Shen JJ, Montez-Rath ME, Lenihan CR, Turakhia MP, Chang TI, Winkelmayer WC. Outcomes after warfarin initiation in a cohort of hemodialysis patients with newly diagnosed atrial fibrillation. *Am J Kidney Dis.* 2015;66:677–88, <http://dx.doi.org/10.1053/j.ajkd.2015.05.019>.
51. Knoll F, Sturm G, Lamina C, Zitt E, Lins F, Freistätter O, et al. Coumarins and survival in incident dialysis patients. *Nephrol Dial Transplant.* 2012;27:332–7, <http://dx.doi.org/10.1093/ndt/gfr341>.
52. Chen JJ, Lin LY, Yang YH, Hwang JJ, Chen PC, Lin JL. Anti-platelet or anti-coagulant agent for the prevention of ischemic stroke in patients with end-stage renal disease and atrial fibrillation—a nation-wide database analyses. *Int J Cardiol.* 2014;177:1008–11, <http://dx.doi.org/10.1016/j.ijcard.2014.09.140>.
53. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. *Chest.* 2016;149:951–9, <http://dx.doi.org/10.1378/chest.15-1719>.
54. Tan J, Liu S, Segal JB, Alexander GC, McAdams-DeMarco M. Warfarin use and stroke, bleeding and mortality risk in patients with end stage renal disease and atrial fibrillation: a systematic review and meta-analysis. *BMC Nephrol.* 2016;17:157, <http://dx.doi.org/10.1186/s12882-016-0368-6>.
55. Randhawa MS, Vishwanath R, Rai MP, Wang L, Randhawa AK, Abela G, et al. Association between use of warfarin for atrial fibrillation and outcomes among patients with end-stage renal disease: a systematic review and meta-analysis. *JAMA Netw Open.* 2020;3:e202175, <http://dx.doi.org/10.1001/jamanetworkopen.2020.2175>.
56. Harel Z, Chertow GM, Shah PS, Harel S, Dorian P, Yan AT, et al. Warfarin and the risk of stroke and bleeding in patients with atrial fibrillation receiving dialysis: a systematic review and meta-analysis. *Can J Cardiol.* 2017;33:737–46, <http://dx.doi.org/10.1016/j.cjca.2017.02.004>.
57. Van Der Meersch H, De Bacquer D, De Vriese AS. Vitamin K antagonists for stroke prevention in hemodialysis patients with atrial fibrillation: a systematic review and meta-analysis. *Am Heart J.* 2017;184:37–46, <http://dx.doi.org/10.1016/j.ahj.2016.09.016>.
58. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. *Clin J Am Soc Nephrol.* 2011;6:2662–8, <http://dx.doi.org/10.2215/CJN.04550511>.
59. Sánchez Soriano RM, Albero Molina MD, Chamorro Fernández CI, Juliá-Sanchís R, López Menchero R, Del Pozo Fernández C, et al. Impacto pronostico a largo plazo de la anticoagulación en los pacientes en hemodiálisis con fibrilación auricular. *Nefrología (Engl Ed).* 2018;38:394–400, <http://dx.doi.org/10.1016/j.nefro.2017.11.026>.
60. Genovesi S, Rossi E, Gallieni M, Stella A, Badiali F, Conte F, et al. Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation. *Nephrol Dial Transplant.* 2015;30:491–8, <http://dx.doi.org/10.1093/ndt/gfu334>.

61. Bonde AN, Lip GY, Kamper AL, Hansen PR, Lamberts M, Hommel K, et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. *J Am Coll Cardiol*. 2014;64:2471–82, <http://dx.doi.org/10.1016/j.jacc.2014.09.051>.
62. Schlieper G, Floege J. Challenging the use of warfarin in patients on dialysis with atrial fibrillation. *Nat Rev Nephrol*. 2015;11:450, <http://dx.doi.org/10.1038/nrneph.2015.87>.
63. Chatrou M, Winckers K, Hackeng TM, Reutelingsperger CP, Schurgers LJ. Vascular calcification: the price to pay for anticoagulation therapy with vitamin K-antagonists. *Blood Rev*. 2012;26:155–66, <http://dx.doi.org/10.1016/j.blre.2012.03.002>.
64. Krueger T, Westenfeld R, Ketteler M, Schurgers LJ, Floege J. Vitamin K deficiency in CKD patients: a modifiable risk factor for vascular calcification? *Kidney Int*. 2009;76:18–22, <http://dx.doi.org/10.1038/ki.2009.126>.
65. Garza-Mayers AC, Shah R, Sykes DB, Nigwekar SU, Kroshinsky D. The successful use of apixaban in dialysis patients with calciphylaxis who require anticoagulation: a retrospective analysis. *Am J Nephrol*. 2018;48:168–71, <http://dx.doi.org/10.1159/000491881>.
66. Caluwé R, Pyfferoen L, De Boeck K, De Vriese AS. The effects of vitamin K supplementation and vitamin K antagonists on progression of vascular calcification: ongoing randomized controlled trials. *Clin Kidney J*. 2016;9:273–9, <http://dx.doi.org/10.1093/ckj/sfv146>.
67. McCabe KM, Booth SL, Fu X, Shobeiri N, Pang JJ, Adams MA, et al. Dietary vitamin K and therapeutic warfarin alter the susceptibility to vascular calcification in experimental chronic kidney disease. *Kidney Int*. 2013;83:835–44, <http://dx.doi.org/10.1038/ki.2012.477>.
68. Mac-Way F, Poulin A, Utescu MS, De Serres SA, Marquis K, Douville P. The impact of warfarin on the rate of progression of aortic stiffness in hemodialysis patients: a longitudinal study. *Nephrol Dial Transplant*. 2014;29:2113–20, <http://dx.doi.org/10.1093/ndt/gfu224>.
69. Cozzolino M, Fusaro M, Ciceri P, Gasperoni L, Cianciolo G. The role of vitamin K in vascular calcification. *Adv Chronic Kidney Dis*. 2019;26:437–44, <http://dx.doi.org/10.1053/j.ackd.2019.10.005>.
70. Kaesler N, Magdeleyns E, Herfs M, Schettgen T, Brandenburg V, Fliser D, et al. Impaired vitamin K recycling in uremia is rescued by vitamin K supplementation. *Kidney Int*. 2014;86:286–93, <http://dx.doi.org/10.1038/ki.2013.530>.
71. Booth SL, Broe KE, Peterson JW, Cheng DM, Dawson-Hughes B, Gundberg CM, et al. Associations between vitamin K biochemical measures and bone mineral density in men and women. *J Clin Endocrinol Metab*. 2004;89:4904–9, <http://dx.doi.org/10.1210/jc.2003-031673>.
72. Son BK, Kozaki K, Iijima K, Eto M, Kojima T, Ota H, et al. Statins protect human aortic smooth muscle cells from inorganic phosphate-induced calcification by restoring Gas6-Axl survival pathway. *Circ Res*. 2006;98:1024–31, <http://dx.doi.org/10.1161/01.RES.0000218859.90970.8d>.
73. Fusaro M, D'Alessandro C, Noale M, Tripepi G, Plebani M, Veronese N, et al. Low vitamin K1 intake in haemodialysis patients. *Clin Nutr*. 2017;36:601–7, <http://dx.doi.org/10.1016/j.clnu.2016.04.024>.
74. Mahtani KR, Heneghan CJ, Nunan D, Roberts NW. Vitamin K for improved anticoagulation control in patients receiving warfarin. *Cochrane Database Syst Rev*. 2014;5, <http://dx.doi.org/10.1002/14651858>.
75. Theuvsen E, Teunissen KJ, Spronk HM, Hamulyák K, Ten Cate H, Shearer MJ, et al. Effect of low-dose supplements of menaquinone-7 (vitamin K 2) on the stability of oral anticoagulant treatment: dose-response relationship in healthy volunteers. *J Thromb Haemost*. 2013;11:1085–92, <http://dx.doi.org/10.1111/jth.12203>.
76. Bennett WM. Should dialysis patients ever receive warfarin and for what reasons? *Clin J Am Soc Nephrol*. 2006;1:1357–9, <http://dx.doi.org/10.2215/CJN.01700506>.
77. Reinecke H, Brand E, Mesters R, Schäbitz WR, Fisher M, Pavenstädt H, et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. *J Am Soc Nephrol*. 2009;20:705–11, <http://dx.doi.org/10.1681/ASN.2007111207>.
78. Lo DS, Rabbat CG, Clase CM. Thromboembolism and anticoagulant management in hemodialysis patients: a practical guide to clinical management. *Thromb Res*. 2006;118:385–95, <http://dx.doi.org/10.1016/j.thromres.2005.03.031>.
79. Brodsky S, Eikelboom J, Hebert LA. Anticoagulant-related nephropathy. *J Am Soc Nephrol*. 2018;29:2787–93, <http://dx.doi.org/10.1681/ASN.2018070741>.
80. Abt AB, Carroll LE, Mohler JH. Thin basement membrane disease and acute renal failure secondary to gross hematuria and tubular necrosis. *Am J Kidney Dis*. 2000;35:533–6, [http://dx.doi.org/10.1016/s0272-6386\(00\)70209-5](http://dx.doi.org/10.1016/s0272-6386(00)70209-5).
81. Kabir A, Nadasdy T, Nadasdy G, Hebert LA. An unusual cause of gross hematuria and transient ARF in an SLE patient with warfarin coagulopathy. *Am J Kidney Dis*. 2004;43:757–60, <http://dx.doi.org/10.1053/j.ajkd.2003.08.050>.
82. Brodsky SV, Satooskar A, Chen J, Nadasdy G, Eagen JW, Hamirani M, et al. Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. *Am J Kidney Dis*. 2009;54:1121–6, <http://dx.doi.org/10.1053/j.ajkd.2009.04.024>.
83. Brodsky SV, Collins M, Park E, Rovin BH, Satooskar AA, Nadasdy G, et al. Warfarin therapy that results in an International Normalization Ratio above the therapeutic range is associated with accelerated progression of chronic kidney disease. *Nephron Clin Pract*. 2010;115:c142–6, <http://dx.doi.org/10.1159/000312877>.
84. Aquino Moura KB, Behrens PMP, Pirolli R, Sauer A, Melamed D, Veronese FV, et al. Anticoagulant-related nephropathy: systematic review and meta-analysis. *Clin Kidney J*. 2019;12:400–7, <http://dx.doi.org/10.1093/ckj/sfy133>.
85. Nigwekar SU, Zhao S, Wenger J, Hymes JL, Maddux FW, Thadhani RI, et al. A nationally representative study of calcific uremic arteriolopathy risk factors. *J Am Soc Nephrol*. 2016;27:3421–9, <http://dx.doi.org/10.1681/ASN.2015091065>.
86. Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J*. 2015;36:297–306, <http://dx.doi.org/10.1093/eurheartj/ehu139>.
87. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–962, <http://dx.doi.org/10.1093/eurheartj/ehw210>.
88. Sjögren V, Grzymala-Lubanski B, Renlund H, Friberg L, Lip GY, Svensson PJ, et al. Safety and efficacy of well managed warfarin. A Rep. from Swedish Qual. Register Auricula. *Thromb Haemost*. 2015;113:1370–7, <http://dx.doi.org/10.1160/TH14-10-0859>.
89. Bonde AN, Lip GY, Kamper AL, Staerk L, Torp-Pedersen C, Gislason GH, et al. Effect of reduced renal function on time in therapeutic range among anticoagulated atrial fibrillation patients. *J Am Coll Cardiol*. 2017;69:752–3, <http://dx.doi.org/10.1016/j.jacc.2016.11.031>.
90. Yang F, Hellyer JA, Than C, Ullal AJ, Kaiser DW, Heidenreich PA, et al. Warfarin utilisation and anticoagulation control in patients with atrial fibrillation and chronic kidney disease. *Heart*. 2017;103:818–26, <http://dx.doi.org/10.1136/heartjnl-2016-309266>.

91. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with nonvalvular atrial fibrillation. *Europace*. 2015;17:1467–507, <http://dx.doi.org/10.1093/eurpace/euv309>.
92. Derebail VK, Rheault MN, Kerlin BA. Role of direct oral anticoagulants in patients with kidney disease. *Kidney Int*. 2020;97:664–75, <http://dx.doi.org/10.1016/j.kint.2019.11.027>.
93. Ashley J, McArthur E, Bota S, Harel Z, Battistella M, Molnar AO, et al. Risk of cardiovascular events and mortality among elderly patients with reduced GFR receiving direct oral anticoagulants. *Am J Kidney Dis*. 2020;76:311–20, <http://dx.doi.org/10.1053/j.ajkd.2020.02.446>.
94. Stanifer JW, Pokorney SD, Chertow GM, Hohnloser SH, Wojdyla DM, Garonzik S, et al. Apixaban versus warfarin in patients with atrial fibrillation and advanced chronic kidney disease. *Circulation*. 2020;141:1384–92, <http://dx.doi.org/10.1161/CIRCULATIONAHA.119.044059>.
95. Wetmore JB, Yan H, Herzog CA, Weinhandl E, Reyes JL, Roetke NS. CKD progression in medicare beneficiaries with nonvalvular atrial fibrillation treated with apixaban versus warfarin. *Am J Kidney Dis*. 2021;78:180–9, <http://dx.doi.org/10.1053/j.ajkd.2020.12.004>.
96. Hernandez AV, Bradley G, Khan M, Fratoni A, Gasparini A, Roman YM, et al. Rivaroxaban versus warfarin and renal outcomes in non-valvular atrial fibrillation patients with diabetes. *Eur Heart J Qual Care Clin Outcomes*. 2020;6:301–7, <http://dx.doi.org/10.1093/ehjqcco/qcz047>.
97. Rattazzi M, Faggini E, Bertacco E, Nardin C, Pagliani L, Plebani M, et al. Warfarin, but not rivaroxaban, promotes the calcification of the aortic valve in ApoE<sup>-/-</sup> mice. *Cardiovasc Ther*. 2018;36:e12438, <http://dx.doi.org/10.1111/1755-5922.12438>.
98. Schurgers LJ, Spronk HM. Differential cellular effects of old and new oral anticoagulants: consequences to the genesis and progression of atherosclerosis. *Thromb Haemost*. 2014;112:909–17, <http://dx.doi.org/10.1160/TH14-03-0268>.
99. Hara T, Fukuda D, Tanaka K, Higashikuni Y, Hirata Y, Nishimoto S, et al. Rivaroxaban, a novel oral anticoagulant, attenuates atherosclerotic plaque progression and destabilization in ApoE-deficient mice. *Atherosclerosis*. 2015;242:639–46, <http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.023>.
100. De Vriese AS, Heine G. Anticoagulation management in haemodialysis patients with atrial fibrillation: evidence and opinion. *Nephrol Dial Transplant*. 2021;1–8, <http://dx.doi.org/10.1093/ndt/gfab060>.
101. Brodsky SV, Mhaskar NS, Thiruveedi S, Dhingra R, Reuben SC, Calomeni E, et al. Acute kidney injury aggravated by treatment initiation with apixaban: another twist of anticoagulant-related nephropathy. *Kidney Res Clin Pract*. 2017;36:387–92, <http://dx.doi.org/10.23876/j.krcp.2017.36.4.387>.
102. Jansky L, Mukkamala P, Jebakumar D, Rao A, Goldson TM, Forjuoh SN. Acute kidney injury and undiagnosed immunoglobulin A nephropathy after dabigatran therapy. *Proc (Bayl Univ Med Cent)*. 2018;31:321–3, <http://dx.doi.org/10.1080/08998280.2018.1463036>, eCollection 2018.
103. Escoli R, Santos P, Andrade S, Carvalho F. Dabigatran-related nephropathy in a patient with undiagnosed IgA nephropathy. *Case Rep Nephrol*. 2015;2015:298261, <http://dx.doi.org/10.1155/2015/298261>.
104. Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. *Cochrane Database Syst Rev*. 2017;11:CD011373, <http://dx.doi.org/10.1002/14651858.CD011373>.
105. Ha JT, Neuen BL, Cheng LP, Jun M, Toyama T, Gallagher MP, et al. Benefits and harms of oral anticoagulant therapy in chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2019;171:181–9, <http://dx.doi.org/10.7326/M19-0087>.
106. Feldberg J, Patel P, Farrell A, Sivarajahkumar S, Cameron K, Ma J, et al. A systematic review of direct oral anticoagulant use in chronic kidney disease and dialysis patients with atrial fibrillation. *Nephrol Dial Transplant*. 2019;34:265–77, <http://dx.doi.org/10.1093/ndt/gfy031>.
107. Harel Z, Sholzberg M, Shah PS, Pavenski K, Harel S, Wald R, et al. Comparisons between novel oral anticoagulants and vitamin K antagonists in patients with CKD. *J Am Soc Nephrol*. 2014;25:431–42, <http://dx.doi.org/10.1681/ASN.2013040361>.
108. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–92, <http://dx.doi.org/10.1056/NEJMoa1107039>.
109. Chang SH, Wu CV, Yeh YH, Kuo CF, Chen YL, Wen MS, et al. Efficacy and safety of oral anticoagulants in patients with atrial fibrillation and stages 4 or 5 chronic kidney disease. *Am J Med*. 2019;132:1335–43, <http://dx.doi.org/10.1016/j.amjmed.2019.06.006>, e6.
110. Dias C, Moore KT, Murphy J, Ariyawansa J, Smith W, Mills RM, et al. Pharmacokinetics, pharmacodynamics, and safety of single-dose rivaroxaban in chronic hemodialysis. *Am J Nephrol*. 2016;43:229–36, <http://dx.doi.org/10.1159/000445328>.
111. Frost C, Wang J, Nepal S, Schuster A, Barrett YC, Mosqueda-Garcia R, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics, and food effect in healthy subjects. *Br J Clin Pharmacol*. 2013;75:476–87, <http://dx.doi.org/10.1111/j.1365-2125.2012.04369.x>.
112. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. *Circulation*. 2015;131:972–9, <http://dx.doi.org/10.1161/CIRCULATIONAHA.114.014113>.
113. Coleman CI, Kreutz R, Sood NA, Bunz TJ, Eriksson D, Meinecke AK, et al. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and severe kidney disease or undergoing hemodialysis. *Am J Med*. 2019;132:1078–83, <http://dx.doi.org/10.1016/j.amjmed.2019.04.013>.
114. De Vriese AS, Caluwé R, Van Der Meersch H, De Boeck K, De Bacquer D. Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter randomized controlled trial. *J Am Soc Nephrol*. 2021;32:1474–83, <http://dx.doi.org/10.1681/ASN.2020111566>.
115. Chan KE, Giugliano RP, Patel MR, Abramson S, Jardine M, Zhao S, et al. Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. *J Am Coll Cardiol*. 2016;67:2888–99, <http://dx.doi.org/10.1016/j.jacc.2016.02.082>.
116. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012;33:2821–30, <http://dx.doi.org/10.1093/eurheartj/ehs274>.
117. Schafer JH, Casey AL, Dupre KA, Staubes BA. Safety and efficacy of apixaban versus warfarin in patients with advanced chronic kidney disease. *Ann Pharmacother*. 2018;52:1078–84, <http://dx.doi.org/10.1177/1060028018781853>.

118. Nakase T, Moroi J, Ishikawa T. Anti-inflammatory, and antiplatelet effects of non-vitamin K antagonist oral anticoagulants in acute phase of ischemic stroke patients. *Clin Transl Med.* 2018;7:2, <http://dx.doi.org/10.1186/s40169-017-0179-9>.
119. Reed D, Palkimas S, Hockman R, Abraham S, Le T, Maitland H. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. *Res Pract Thromb Haemost.* 2018;2:291–8, <http://dx.doi.org/10.1002/rth2.12083>, eCollection 2018.
120. Siontis KC, Zhang X, Eckard A, Bhavne N, Schaubel DE, He K, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation.* 2018;138:1519–29, <http://dx.doi.org/10.1161/CIRCULATIONAHA.118.035418>.
121. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. *Clin J Am Soc Nephrol.* 2020;15:1146–54, <http://dx.doi.org/10.2215/CJN.11650919>.
122. De Vriese AS, Caluwé R, Baillieu E, De Bacquer D, Borrey D, Van Vlem B, et al. Dose finding of rivaroxaban in hemodialysis patients. *Am J Kidney Dis.* 2015;66:91–8, <http://dx.doi.org/10.1053/j.ajkd.2015.01.022>.
123. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. *J Am Soc Nephrol.* 2017;28:2241–8, <http://dx.doi.org/10.1681/ASN.2016090980>.
124. Clemens A, Noack H, Brueckmann M, Lip GY. Twice- or once-daily dosing of novel oral anticoagulants for stroke prevention: a fixed-effects meta-analysis with predefined heterogeneity quality criteria. *PLoS One.* 2014;9:e99276, <http://dx.doi.org/10.1371/journal.pone.0099276>, eCollection 2014.
125. Van den Bosch I, Bouillon T, Verhamme P, Vanassche T, Jacquemin M, Coemans M, et al. Apixaban in patients on haemodialysis: a single-dose pharmacokinetics study. *Nephrol Dial Transplant.* 2021;36:884–9, <http://dx.doi.org/10.1093/ndt/gfaa351>.
126. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med.* 2017;377:431–41, <http://dx.doi.org/10.1056/NEJMoa1707278>.
127. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. ANNEXA-4 Investigators. Report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med.* 2019;380:1326–35, <http://dx.doi.org/10.1056/NEJMoa1814051>.
128. Novak JE, Alamiri K, Yee J. Dabigatran reversal in a patient with end-stage liver disease and acute kidney injury. *Am J Kidney Dis.* 2018;71:137–41, <http://dx.doi.org/10.1053/j.ajkd.2017.03.025>.
129. Shroff GR, Stoecker R, Hart A. Non-vitamin K-dependent oral anticoagulants for nonvalvular atrial fibrillation in patients with CKD: pragmatic considerations for the clinician. *Am J Kidney Dis.* 2018;72:717–27, <http://dx.doi.org/10.1053/j.ajkd.2018.02.360>.
130. US Food and Drug Administration. ELIQUIS (apixaban) label. 2021. [accessed 28 Dec 2020] Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/202155s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf).
131. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2019;74:104–32, <http://dx.doi.org/10.1016/j.jacc.2019.01.011>.
132. Pokorney S, Kumbhani DJ, Bhatt DL. RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation - RENAL-AF [accessed 12 Dec 2020] Available from: <https://www.acc.org/latest-in-cardiology/clinical-trials/2019/11/15/17/29/renal-af>.
133. American College of Cardiology: RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation - RENAL-AF [accessed 24 Oct 2020]. Available from: <https://www.acc.org/latest-in-cardiology/clinical-trials/2019/11/15/17/29/renal-af>.
134. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation.* 2019;140:e125–51, <http://dx.doi.org/10.1161/CIR.0000000000000665>.
135. Kelly DM, Rothwell PM. Prevention and treatment of stroke in patients with chronic kidney disease: an overview of evidence and current guidelines. *Kidney Int.* 2020;97:266–78, <http://dx.doi.org/10.1016/j.kint.2019.09.024>.
136. Burlacu A, Genovesi S, Ortiz A, Combe C, Basile C, Schneditz D, et al. on behalf of the ERA-EDTA EUDIAL Working Group. Pros and cons of antithrombotic therapy in end-stage kidney disease: a 2019 update. *Nephrol Dial Transplant.* 2019;34:923–33, <http://dx.doi.org/10.1093/ndt/gfz040>.
137. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, et al. PRAGUE-17 Trial Investigators. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol.* 2020;75:3122–35, <http://dx.doi.org/10.1016/j.jacc.2020.04.067>.
138. Kefer J, Tzikas A, Freixa X, Shakir S, Gafoor S, Nielsen-Kudsk JE, et al. Impact of chronic kidney disease on left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation. *Int J Cardiol.* 2016;207:335–40, <http://dx.doi.org/10.1016/j.ijcard.2016.01.003>.
139. Zhang HF, Zhang QX, Zhang YY, Yang D, Xu Z, Jiao QB, et al. Efficacy and safety of left atrial appendage occlusion in atrial fibrillation patients with chronic kidney disease: a systematic review and meta-analysis. *Rev Cardiovasc Med.* 2020;21:443–51, <http://dx.doi.org/10.31083/j.rcm.2020.03.62>.
140. Genovesi S, Porcu L, Slaviero G, Casu G, Bertoli S, Sagone A, et al. Outcomes on safety and efficacy of left atrial appendage occlusion in end stage renal disease patients undergoing dialysis. *J Nephrol.* 2021;34:63–73, <http://dx.doi.org/10.1007/s40620-020-00774-5>.