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ORIGINAL ARTICLE

Oral Anticoagulation for Atrial Fibrillation Thromboembolism Prophylaxis in the Chronic Kidney Disease Population: the State of the Art in 2019

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Abstract
Atrial fibrillation (AF) is the most common cardiac rhythm disturbance and is associated with increased risk of thromboembolism. Oral anticoagulants are effective at reducing rates of thromboembolism in patients with AF in the general population. Patients with AF and concurrent chronic kidney disease (CKD) have higher risk of thromboembolism and bleeding compared with patients with normal renal function. Among moderate CKD and end-stage renal disease (ESRD) patients on chronic dialysis, the use of oral anticoagulants is controversial. Use of warfarin, while beneficial in non-CKD patients, raises a number of concerns such as increased bleeding risk, labile anticoagulant effect, and calciphylaxis, especially in the ESRD population. The newer direct oral anticoagulant (DOAC) agents have demonstrated comparable efficacy and improved safety profiles compared with coumadin but are not as well studied in the CKD population. This review highlights the efficacy and safety of coumadin and the DOACs for thromboembolism prophylaxis in non-valvular AF patients with CKD.

Keywords Cardiovascular disease · Atrial fibrillation · Anticoagulant · Chronic kidney disease · End stage renal disease · Dialysis

Introduction

Atrial fibrillation (AF) is a common cardiac rhythm disturbance resulting from structural and/or electrophysiological alterations in impulse formation within atrial tissue. AF is associated with frequent hospitalizations, increased morbidity, and increased risk of systemic thromboembolism (TE)—including stroke. The importance of risk stratifying patients at risk for stroke/TE and the use of oral anticoagulants to reduce this risk are routine practices in managing AF [1].

Risk factors associated with developing AF include advanced age, hypertension, diabetes, ischemic heart disease, and chronic kidney disease (CKD). Prior studies have demonstrated that CKD is both an independent risk factor for developing AF and is associated with higher stroke risk compared with the non-CKD AF population [2, 3]. CKD presents an additional challenge when deciding on anticoagulation for stroke prevention. On the one hand, the CKD population has higher rates of stroke/TE compared with non-CKD patients, suggesting that anticoagulation may have a role in reducing TE risk. It has previously been proposed by Piccini et al. that kidney dysfunction (creatinine clearance (CrCl) < 60 mL/min) be incorporated into the widely used $CHADS_2$ and CHA_2DS_2VASc score as an independent predictor of stroke risk [4]. On the other hand, bleeding complications from warfarin use in CKD patients are also higher compared with non-warfarin users [5–7]. The net clinical benefit of anticoagulation in the treatment of AF within the CKD population is therefore an area of ongoing debate [7]. Randomized placebo-controlled trials of warfarin use in AF patients have historically made no mention of renal function or excluded severe CKD and ESRD populations [8–11].

Direct oral anticoagulants (DOACs) introduced in the last decade are now alternatives to warfarin for stroke/TE prevention. However, the large phase-3 clinical trials showing non-inferiority of these agents compared with warfarin largely excluded patients with severe CKD and end-stage renal disease

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on dialysis (ESRD). While the debate around the efficacy and safety of these agents in CKD and ESRD continues, smaller pharmacodynamic studies and retrospective observational studies have been used to justify their use in the absence of randomized clinical trials [7, 12].

This review will summarize the current literature on the benefit of warfarin and the individual DOACs for TE prevention in non-valvular AF for patients with mild-moderate CKD (i.e., CrCl 30–60 mL/min), severe CKD (i.e., CrCl < 30 mL/min), and ESRD populations.

Warfarin

Warfarin in Moderate CKD

Prior to the advent of DOACs, warfarin was the primary anticoagulant used for stroke and TE prophylaxis and prevention among AF patients. A large meta-analysis demonstrated stroke/TE reduction and mortality reduction of approximately 60% and 25%, respectively, in the general population [13].

Recent studies have illustrated that CKD is independently associated with higher stroke/TE risk [3]. Several studies have attempted to address the potential benefit of warfarin in AF patients with concurrent CKD. While some discrepancy exists, most studies suggest that warfarin is beneficial in mild-moderate CKD. In the Stroke Prevention in Atrial Fibrillation III trials, an analysis of stage 3 CKD patients (eGFR of 30–59 mL/min) showed that dose-adjusted warfarin conveyed a reduced risk of stroke/thromboembolism vs. aspirin plus low-dose warfarin. The magnitude of risk reduction was similar to that seen in non-CKD patients [14].

In a registry study from Denmark, Olesen et al. analyzed 132,372 AF patients, including 3587 (2.7%) with non-ESRD CKD and 901 (0.7%) with ESRD. Renal function by estimated glomerular filtration rate (eGFR) or CrCl was not specified within the non-end stage CKD population. The study showed a trend toward attenuated stroke risk with warfarin use among the population of AF with CHA_2DS_2-VASc ≥ 2 and non-ESRD CKD (HR, 0.84; CI, 0.69–1.01) [15]. Warfarin was also found to be superior to aspirin alone for TE prophylaxis. This benefit was balanced by a higher risk of bleeding (HR, 1.36; CI, 1.17–1.59) with warfarin [14].

In a separate Danish registry study, Bonde et al. analyzed 154,359 AF patients, including 11,128 (7.2%) with non-ESRD CKD and 1728 (1.1%) with ESRD. Similar to Olesen et al., warfarin use in the non-ESRD group was associated with a decreased composite outcome of fatal stroke/fatal bleeding (HR, 0.71; CI, 0.57–0.88), a lower risk of cardiovascular death (HR, 0.80; CI, 0.74–0.88), and reduced all-cause mortality (HR, 0.64; CI, 0.60–0.69) [3]. A separate study by the same group stratified 17,349 patients with AF by eGFR. Across all eGFR groups, warfarin use was associated with higher bleeding. For patients with eGFR ≥ 15 mL/min/1.73 m^2, warfarin was associated with lower stroke risk [16].

An analysis of the SWEDEHEART registry included 24,317 patients with AF after hospitalization for acute myocardial infarction (MI); 51.7% of these patients had moderate to severe CKD (eGFR ≤ 60 mL/min/1.73m^2). In the moderate CKD subset (eGFR 31–60 mL/min/1.73m^2), warfarin was associated with reduced risk of stroke (HR, 0.54; CI, 0.43–0.69) and reduced composite endpoint of all-cause mortality, recurrent myocardial infarction, and stroke (HR, 0.83; CI, 0.78–0.88) compared with no anticoagulation [2].

Analysis of the Loire Valley Atrial Fibrillation Project population included 5912 patients with AF and their corresponding eGFRs. In the 2641 patients with moderate CKD (eGFR 30–59 mL/min/1.73m^2), warfarin conveyed a reduction in the combined endpoint of stroke/TE/all-cause mortality (RR, 0.47; CI, 0.39–0.57). The risk reduction for ischemic stroke alone or stroke/TE was not statistically significant [17].

A propensity-matched population study of 7000 non-ESRD, CKD patients with AF in the UK showed higher rates of hemorrhage (HR, 2.42; CI, 1.44–4.05) and lower all-cause mortality (HR, 0.82; CI, 0.74–0.91) when taking anticoagulants, 72% of which were vitamin K antagonists. Contrary to other studies, the rate of ischemic stroke was higher in the anticoagulation group (HR, 2.60; CI, 2.00–3.38) [18].

A meta-analysis including several of the abovementioned observational studies by Dahal et al. included > 48,500 patients with > 11,600 warfarin users. This study showed an overall reduction in stroke/TE (HR, 0.70; CI, 0.54–0.89) and mortality (HR, 0.65; CI, 0.59–0.72) associated with warfarin use in patients with non-ESRD CKD [19]. Overall, the majority of studies appears to show that warfarin reduces the risk of stroke/TE, cardiovascular death, and all-cause mortality within the non-ESRD CKD population.

Warfarin in ESRD

Dialysis is independently associated with a higher risk of stroke/TE across all CHA_2DS_2-VASc scores [3], yet the net benefit of warfarin in patients with AF and ESRD remains unclear. While the prevalence of AF has been increasing in the older dialysis population, there is evidence that warfarin use has remained relatively low. This fact may reflect the lack of evidence demonstrating a clear benefit of warfarin in this population [20]. Some studies have demonstrated reduced stroke and mortality associated with warfarin use [3, 15], others have found either no benefit or increased rates of stroke, bleeding, and death [9, 21, 22].

Two large Danish registries studies have analyzed warfarin use in AF and CKD including 901 and 1728 ESRD patients, respectively. Olesen et al. showed a reduction in stroke/TE with warfarin alone compared with no anticoagulant (HR, 0.44; CI, 0.26–0.74). Unexpectedly, patients who received

warfarin combined with aspirin did not show a benefit for stroke/TE reduction (HR, 0.82; CI, 0.37–1.80). Bleeding was noted to be statistically higher in patients taking aspirin alone (HR, 1.63; CI, 1.18–2.26) but not elevated in patients taking warfarin alone (HR, 1.27; CI, 0.91–1.77) or combined warfarin and aspirin [15]. Contrarily, Bonde et al. showed no significant difference in cardiovascular death or all stroke/bleeding but noted a reduction in all-cause mortality (HR, 0.85; CI, 0.72–0.99) in patients with $CHA_2DS_2VASc \geq 2$ who received warfarin [3]. Carrero et al. found that warfarin was associated with reduced composite risk of death, MI, ischemic stroke (adjusted HR, 0.57; CI, 0.37–0.86) in the strata of eGFR ≤ 15 mL/min/1.73m^2 [2]. However, this particular study did not specify number/proportion of patients receiving chronic dialysis and warfarin use was not associated with a reduction in ischemic stroke alone. Shen et al. analyzed 12,284 dialysis patients with newly diagnosed AF, of which 1838 were initiated on warfarin. Compared with non-use, warfarin was associated with reduced mortality (HR, 0.84; CI, 0.73–0.97) [23].

In contrast to the above studies, which suggest some benefit of warfarin over no anticoagulation, a population-based retrospective cohort of Canadian patients with AF showed no benefit in ESRD patients. In this study comparing chronic dialysis to non-dialysis patients (renal function was not specified in the non-dialysis group), Shah et al. analyzed 204,210 patients, of whom 1626 had ESRD. The ESRD patients derived no benefit in terms of stroke risk from warfarin use (adjusted HR, 1.14; CI 0.78–1.67). A significant reduction in stroke, however, was found in non-ESRD patients using warfarin (HR, 0.87; CI, 0.85–0.90). In both groups, warfarin usage increased bleeding risk [24].

In a retrospective study of 41,425 ESRD patients receiving aspirin, clopidogrel, or warfarin, Chan et al. demonstrated an overall higher mortality with warfarin use (HR, 1.27; CI, 1.18–1.37) [9]. In a separate analysis of ESRD patients with concomitant AF, the same group showed double the rate of overall stroke with warfarin use compared with no anticoagulation (HR, 2.0; CI, 1.34–2.99). The risk of both ischemic stroke (HR, 1.81; CI, 1.12–2.92) and hemorrhagic stroke (HR, 2.22; CI, 1.01–4.91) was higher with warfarin use vs. patients not on the drug [22]. Use of aspirin and clopidogrel was not significantly associated with stroke rate.

Some studies have demonstrated that warfarin is associated with worse outcomes in ESRD patients. Wizeman et al. analyzed 17,513 ESRD patients from the Dialysis Outcomes and Practice Patterns Study, of whom 2188 patients also had AF. In the AF group, warfarin use was associated with increased risk of all stroke in patients > 75 years old (HR, 2.17; CI, 1.04–4.53) [21]. Unfortunately, the study did not detail the proportion of ischemic vs. hemorrhagic strokes.

In a propensity matched cohort of 5548 patients with AF and ESRD from Korea, Yoon et al. showed that warfarin conveyed an increased risk of hemorrhagic CVA (HR, 1.56; CI, 1.1–2.22) with no statistically significant difference in rates of ischemic stroke, GI bleeding, or peripheral vascular disease [25]. In the largest of several recent meta-analyses, Tan et al. included 20 observational studies and 56,146 patients with AF and ESRD. Warfarin was not associated with a significant reduction in ischemic stroke (HR, 0.80; CI, 0.58–1.11) or all cause stroke (HR, 0.92; CI, 0.74–1.16). There was however, a significant increase in all-cause bleeding (HR, 1.21; CI, 1.01–1.44) [26]. Two other large meta-analyses of AF and ESRD populations have drawn similar conclusions [19, 27].

A recent large meta-analysis performed by Randhawa et al. included 70,331 AF patients on dialysis across 19 studies, 25% of whom were taking warfarin. Their analysis showed a significantly higher risk of hemorrhagic stroke (HR, 1.49; CI,1.03–1.94), significantly higher risk of major bleeding (HR, 1.68; CI, 1.02–2.35) and no change in ischemic stroke risk or overall mortality [28].

While the overall benefit of warfarin in ESRD is debatable, there is general agreement that its narrow therapeutic index, labile anticoagulant effect, drug/food interactions, and susceptibility to genetic variance limit potential positive outcomes [29, 30]. Indeed, fluctuations in volume status leading to hepatic congestion and redistribution of body fluids are known to complicate warfarin management and may contribute its inconsistent benefit seen in this patient population [29].

The ability to maintain a narrow therapeutic window is notoriously difficulty in the CKD population. While warfarin metabolism is primarily directed by the CYP2C9 enzyme, kidney function is a significant determinant of warfarin clearance. Renal dysfunction frequently leads to a propensity for over-anticoagulation [31]. In patients with CKD, more severe kidney dysfunction is associated with higher bleeding rates upon initiating warfarin [32]. Disordered hemostasis and platelet function occur with advancing kidney disease and likely play a role in the higher incidence of bleeding seen with warfarin use in this population [32, 33].

Another special consideration is the increased incidence of calciphylaxis seen with warfarin use in the ESRD population [34]. Calciphylaxis, a process of systemic arterial calcification in vascular beds, frequently results in painful, nonhealing skin lesions and is associated with a 1-year mortality of 45–80% [35]. In a retrospective analysis of new ESRD patients, the strongest risk factor for development of calciphylaxis was warfarin use (OR, 3.22; CI, 2.11 to 4.65) [36]. A multicenter observational study by Di Lullo et al. demonstrated reduced cardiac valve calcium deposition and lower serum markers of inflammation in users of rivaroxaban as compared with warfarin [37]. Though the exact mechanism is unknown, these findings suggest vitamin K inhibition may accelerate the process of vascular calcification [37].

The uncertain benefit of warfarin for stroke prevention for patients with AF with ESRD is illustrated by differing recommendations by international societies. The ACC/AHA/HRS 2014 guidelines for stroke prevention in AF give a 2A recommendation for use of warfarin in ESRD, while the Canadian Cardiovascular Society guidelines and KDIGO recommend against routine use of warfarin in this population, citing lack of evidence for benefit [34]. The European Society of Cardiology (ESC) 2016 guidelines make no recommendations in this population, stating only that randomized trials are needed [38]. The recent ACC/AHA/HRS 2019 guideline focused update changed warfarin's recommendation to 2B [39].

Non-vitamin K Dependent Oral Anticoagulants

DOAC in Moderate CKD

Non-vitamin K-dependent target specific oral anticoagulants (DOACs) constitute a more convenient, more effective alternative to warfarin. DOACs have a more consistent therapeutic effect, no need for routine therapeutic monitoring, and no food-drug interactions [5]. The pivotal phase 3 trials for each DOAC have demonstrated non-inferiority (apixaban, rivaroxaban, edoxaban) [40–42] or superiority (dabigatran) [43] to warfarin for stroke/TE prevention in non-valvular AF patients. Apixaban and edoxaban have also demonstrated reduced bleeding risk compared with warfarin [7] (Table 1).

Unlike warfarin, which is less dependent upon renal function for drug clearance, all four DOACs are, to varying degrees, dependent on renal clearance; apixaban is the least dependent at 25%, and dabigatran is the most dependent at 80% [44]. Accordingly, summaries of product characteristics and dose adjustments for each DOAC in CKD are listed in Table 1 [6]. The Food and Drug Administration (FDA) and other major regulatory agencies have approved the use of DOACs according to their recommended dose adjustments in moderate CKD [45]. Each of the phase 3 DOAC trials included patients with moderate CKD while excluding those with severe CKD and ESRD on dialysis [40–43]. All trials defined CKD according to CrCl and generally excluded patients with CrCl < 25 mL/min (see Table 1).

Re-analysis was performed for each of the DOAC trials, comparing moderate CKD patients with those with normal renal function [46–49]. All trials showed a higher risk of bleeding and thromboembolism with worsening renal dysfunction; however, several key differences between the medications were noted. In RE-LY, dabigatran displayed significant lower rates of major bleeding compared with warfarin for eGFR ≥ 80 mL/min [46]. No difference was noted for patients with worse renal function. In ARISTOTLE, apixaban use demonstrated reduced rate of stroke, death, and major bleeding, regardless of renal function. For patients assigned apixaban, the greatest reduction in major bleeding compared with warfarin occurred in patients with eGFR ≤ 50 mL/min (HR, 0.48; CI, 0.37–0.64) [47]. In ENGAGE AF-TIMI 48, exploratory analyses in patients with a CrCl > 95 mL/min using edoxaban suggested lower relative efficacy compared with warfarin [49]. No significant interaction for efficacy or bleeding was noted for rivaroxaban across different renal functions in the ROCKET-AF study [49].

A recent meta-analysis of over 12,545 CKD patients within five randomized trials of DOACs demonstrated benefit of DOACs compared with warfarin. Strokes/TE events in patients taking DOACs, in comparison with warfarin, were numerically lower, though the difference was not statistically significant (RR, 0.82; CI, 0.66–1.02). Similarly, major bleeding events in comparison with warfarin also showed a trend toward reduction but did not meet statistical significance (RR, 0.80; CI, 0.62–1.03) [45].

Recent retrospective studies of non-dialysis patients with AF and moderate-severe CKD have demonstrated results in favor of DOACs. A comparison of rivaroxaban vs. warfarin in AF and CKD (eGFR 15–45 mL/min) patients concluded that it was safer than warfarin, with no bleeding in the rivaroxaban arm [50]. One small retrospective study of edoxaban use in AF, non-dialysis, severe CKD patients (eGFR 15–29 mL/min) demonstrated no major bleeding or thrombotic events observed during short duration of follow-up [51].

The currently available evidence suggests that DOACs in the CKD population are at least as effective as warfarin in reducing the risk of stroke/TE. The bleeding profiles appear similar as well (Table 1). Given their relative ease of use with reduced monitoring, minimal food-drug interaction, and consistent dosing, it is likely that DOACs will continue to be utilized more frequently than warfarin as first-line therapy for stroke prevention in patients with AF and moderate CKD. The ESC 2016 guidelines prefer DOACs in eligible patients over warfarin (class I, level of evidence A) but make no recommendations on DOAC use in CKD. The document does, however, cite a meta-analysis of the randomized trials concluding fewer strokes, systemic emboli, or major bleeding events for DOACs compared with warfarin [38]. The ACC/AHA/HRS 2014 guidelines give a class 2B, level of evidence C, recommendation for dose-adjusted NOAC use in non-ESRD CKD patients with AF and CHA_2DS_2-VASc ≥ 2 [1]; the 2019 ACC/AHA/HRS focused update makes a similar statement with slightly higher level of evidence (B-R) [39].

DOACs in ESRD on Hemodialysis

DOACs have not been well-studied in patients with AF on dialysis. All phase 3 DOAC trials excluded patients with CrCl < 25 mL/min, and there have been no adequate prospective studies documenting the safety and efficacy of these agents in

Table 1 Summary of DOACs in phase III trials and dosing recommendations for CKD based on International Regulatory Bodies for Non-valvular Atrial Fibrillation

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)
Number of patients	18,113	14,264	18,201	21,105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg or 30 mg once daily
Moderate CKD Definition (CrCl)	31–49 mL/min	25–50 mL/min	30–49 mL/min	30–50 mL/min
Dose adjustment for moderate CKD	75 mg twice daily	15 mg once daily	2.5 mg twice daily	30 mg once daily
Number of patients with moderate CKD	3554 (20%)	2950 (21%)	3017 (17%)	2740 (19.5%)
Exclusion criteria based on CrCl	< 30 mL/min	< 30 mL/min	Serum Cr > 2.5 mg/dL or CrCl <25 mL/min	< 30 mL/min
Primary efficacy outcome: stroke and SE vs. warfarin (HR, 95% CI)	150 mg: 0.56 (0.37–0.85) 110 mg: 0.85 (0.59–1.24)	0.84 (0.57–1.23)	0.79 (0.55–1.14)	0.87 (0.64–1.19)
Primary safety outcome: major bleeding (HR, 95% CI)	150 mg: 1.02 (0.79–1.30) 110 mg: 0.99 (0.77–1.28)	0.95 (0.72–1.26)	0.5 (0.38–0.66)	0.76 (0.58–0.98)

ESRD. Despite this, DOAC use in ESRD is becoming more commonplace in contemporary clinical practice [12]. In the case of dabigatran, the first record of its use in ESRD patients began as early as 45 days after US approval [12]. A recent analysis of Medicaid beneficiaries revealed increasing use of apixaban in the AF and ESRD population since its approval in 2013. In 2015, 26.6% of new anticoagulant prescriptions were for apixaban, with a concurrent decrease in warfarin use [52]. A few small clinical and pharmacodynamic studies have been performed to measure the effect of dialysis on DOAC levels. These studies used concentration-time curves to compare the exposure of DOACs at standard and reduced doses in ESRD patients to healthy volunteers [44].

Dabigatran is the only agent that is largely renally cleared and therefore reversible by dialysis. A single session eliminates 50–60% of dabigatran plasma concentrations according to a small pharmacologic study [53]. While the pharmacodynamic properties would seem to favor its use in ESRD, an observational study using the FMCNA database by Chan et al. showed a 1.5-fold higher risk of hospitalization/death in ESRD patients exposed to dabigatran vs. warfarin [12].

Rivaroxaban and edoxaban are poorly cleared by hemodialysis and accumulate quickly in ESRD patients [44]. Like dabigatran, rivaroxaban was also associated with higher hospitalization/death in ESRD patients when compared with warfarin in a retrospective analysis (HR, 1.38; CI, 1.03–1.83) [12]. The 2014 AHA/ACC/HRS guidelines do not recommend the use of dabigatran and rivaroxaban in ESRD patients (class III) [1]. The recent 2019 guideline focused update maintains a similar recommendation for dabigatran, rivaroxaban, and edoxaban, citing the lack of evidence of benefit vs. harm [39]. To our knowledge, no clinical studies have compared edoxaban with warfarin in the ESRD population.

A number of pharmacodynamic studies of apixaban suggest it is poorly dialyzable but accumulates at a reduced rate compared to its peers [44]. One observational study by Stanton et al. of low-dose apixaban in ESRD (73% of patients received apixaban for AF, the remaining for TE) suggested the bleeding rate was comparable to warfarin in ESRD patients [54]. Based on a single dose pharmacokinetic study, apixaban has been approved by the FDA for use in dialysis population. The reduced dose of 2.5 mg, twice daily achieved drug levels similar to those observed in patients with preserved kidney function [7].

A recent retrospective analysis of 25,523 Medicare beneficiaries with ESRD and AF on oral anticoagulants was published by Siontis et al. In total, 2351 patients were taking apixaban and the remainder was taking warfarin. Overall, there was no difference in risk of stroke/TE comparing apixaban with warfarin (HR, 0.88; CI, 0.69–1.12). The risk of major bleeding favored apixaban (HR, 0.72; CI, 0.59–0.87). Interestingly, matched cohort subgroup analysis by apixaban dosing suggested that standard 5 mg twice a day dosing was associated with statistically significantly lower risks of incident stroke/TE (HR, 0.64; CI, 0.42–0.97), major bleeding (HR, 0.71; CI, 0.53–0.95), and death (HR, 0.63; CI, 0.46–0.85) compared with warfarin. The lower 2.5 mg twice a day dosing was associated with a lower risk of major bleeding compared with warfarin (HR, 0.71; CI, 0.56–0.91), but no differences were noted for stroke/SE (HR, 1.11; CI, 0.82–1.50) or death (HR, 1.07; CI, 0.87–1.33) [52].

Of the four DOACs, rivaroxaban and apixaban have received FDA approval for use in ESRD based on pharmacodynamic studies [6, 55]. Despite a lack of prospective studies on safety and clinical efficacy, DOAC prescription in patients with ESRD appears to be on the rise in routine clinical practice [12]. Apixaban is associated with less bleeding than rivaroxaban and dabigatran and is emerging as the favored agent for treatment of AF in the ESRD population. The 2019 AHA/ACC/HRS guideline focused update includes the

use of apixaban or warfarin for thromboembolism prevention in AF and ESRD patients [39]. The recent FDA approval of DOAC antidotes—andexanet alfa (decoy proteins for apixaban and rivaroxaban) and idarucizumab (antibody fragment against dabigatran)—could potentially increase use of these agents [56]. Although it is clear that clinicians have already begun to embrace the role of these agents in dialysis patients, large-scale studies are still needed to demonstrate their efficacy and safety [29].

Conclusions

Oral anticoagulation for the prevention of stroke/TE and reduction in mortality in patients with AF and with moderate CKD appears to be beneficial, just as in the AF population with normal renal function. Multiple international guidelines have recommended either warfarin or a dose-reduced DOAC as standard therapy for these patients [34]. However, in severe CKD and ESRD patients on dialysis, the evidence is less clear. While the AHA/ACC/HRS guidelines recommend against DOACs and favor warfarin in this population, other society guidelines make no recommendations on any anticoagulation, including warfarin. It is clear that larger prospective clinical trials are needed to investigate the benefit and risks of oral anticoagulants in AF with moderate to severe CKD, including the ESRD population.

A number of clinical trials are currently underway to investigate oral anticoagulant use in ESRD. AXADIA (Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease) is an open-labeled, randomized, controlled, phase 3b trial that will compare the safety of apixaban versus the vitamin K antagonist phenprocoumon, a derivative of coumarin in AF with CKD-5D. RENAL-AF (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation) is a phase 4, open-labeled, randomized trial that will compare apixaban with warfarin in ESRD patients. AVKDIAL (Oral Anticoagulation in Hemodialysis Patients) is a phase 4 open-label randomized trial comparing the safety of oral anticoagulation with vitamin K antagonists versus no anticoagulation in 855 patients with AF with CKD-5D [34]. Data from these trials will better enable clinicians to assess net clinical benefit for individuals with AF and severe CKD and ESRD.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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