Chapter 4

Anticoagulation for Atrial Fibrillation in Patients with End-Stage Kidney Disease

Quoc Tran, Bassim Jebeili, Kamal Sud and Bhadran Bose

Additional information is available at the end of the chapter

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Abstract

Atrial fibrillation (AF) is common in patients with kidney disease, with prevalence several times greater than in the general population. Anticoagulation agents are used to prevent thromboembolic events as a consequence of AF. Several randomized trials have established the efficacy of antithrombotic drugs for preventing stroke in patients with AF, with both antiplatelet agents and oral anticoagulants showing benefit. End-stage kidney disease (ESKD) patients have known platelet defects/dysfunction and also receive heparin during their dialysis treatment, which contributes to their overall coagulopathy. Warfarin being vitamin-K antagonist can augment calciphylaxis in patients with ESKD. Taken together, formal anticoagulation use in patients with ESKD may confer additional risk that is not appreciated in patients without kidney disease. In particular, patients on new oral anticoagulants show excess morbidity and mortality from bleeding when compared to warfarin.

Keywords: anticoagulation, warfarin, end-stage kidney disease, hemodialysis, atrial fibrillation, new oral anticoagulation

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia that can lead to thrombus formation in the atria and atrial appendages. It also causes reduction in cardiac output and affected individuals are at increased risk of mortality. The prevalence of AF in patients with end-stage kidney disease (ESKD) is higher than in general population.

Patients with AF are managed with antiarrhythmic agents to control their heart rate and with anticoagulant agents to prevent thromboembolic events. The benefits of anticoagulation in patients with AF (without kidney disease) are well established; however, the benefits and safety of anticoagulation in patients with AF and ESKD are still not clear.

In this chapter, we discuss the prevalence of AF in ESKD and management of AF in these patients focusing on anticoagulation including the direct oral anticoagulants (DOACs).

2. Epidemiology

The 2010 Global Burden of Disease (GBD) study estimated that the prevalence of AF approximated at 33.5 million individuals worldwide [1]. In particular, AF is believed to affect between 2.2 and 5.0 million Americans, 4.5 million Europeans and is estimated to affect 1.4% of Australians [1, 2]. The prevalence of AF is expected to increase globally over the next decade [3]. The prevalence of AF increases with age, occurring in approximately 1% of the population under 60 years of age and 15% of the population over 80 years of age. Furthermore, the age-adjusted prevalence of AF is higher for men than women [1, 4]. In terms of complications of AF, ischemic stroke is the most common cause of cerebrovascular incident with 75% of these strokes directly linked to AF [3]. In addition, proportion of strokes from embolic sources increases with age, and greater than 35% of strokes in patients over 80 years of age are cardiac in origin, predominantly due to AF [3], making AF the commonest cause of stroke in this patients older than 80 years [1, 3, 4].

The health burden of renal disease is high for patients as well as for health services globally. The 2010 GBD study found that chronic kidney disease (CKD), which previously ranked 27th in the list of causes of total number of global deaths in 1990, ranked 18th in 2010 [1, 5]. The incidence and prevalence of ESKD vary significantly across different countries. The incidence of ESKD is increasing, with reports indicating doubling in the number of patients being treated for ESKD in Europe, the Americas, and Australia, with diabetes and hypertension being the most common causes in developed and many developing countries; however, glomerulonephritis and "undetermined causes" were more common in Asia and sub-Saharan Africa [5].

Cardiovascular disease and its sequelae occur more frequently in patients with CKD, compared to the general population, and it is often more severe [6]. Patients with impaired renal function (estimated glomerular filtration rate (eGFR) ≤80 mL/min) are deemed to be at higher risk for all cardiovascular events. Current literature examining the prevalence of AF in hemodialysis (HD) patients varies widely, describing a range from 7 to 27% [4]. Furthermore, paroxysmal AF was present in 3.5%, persistent AF in 9.6% of patients and permanent AF in 13.9% of patients [4]. In a large cohort study conducted by Cheng-Huang et al., the prevalence of AF in patients receiving peritoneal dialysis and HD was examined [7]. The incidence rate ratios for AF were 2.07 and 1.78 in HD and PD groups, respectively. Additionally, after adjusting for age, gender and comorbidities, the hazard ratios for the AF risk were 1.46 and 1.32 in HD and PD groups, respectively.

In particular, in a study reported by Hohnloser et al., the risk of stroke in patients with CKD increased with decreasing eGFRs, the annual stroke rate was 1.05% in patients with an eGFR of >80 mL/min, 1.46% in patients with an eGFR of 50–80 mL/min and 2.39% in patients with an eGFR of ≤50 mL/min [8].

3. Goals of therapy for AF

The mechanisms initiating and maintaining AF may be multifactorial in individual patients, including electrophysiological and structural abnormalities. The primary goals of therapy for AF are to control symptomatic effects of the disease and to prevent any disease-related complications such as thromboembolism and tachycardia-induced cardiomyopathy [9]. The management of AF therefore revolves around strategies for rate control, rhythm control and prevention of thromboembolic strokes. In relation to the former two strategies, multiple international guidelines, including the American College of Cardiology (ACC), the American Heart Association (AHA), European Society of Cardiology (ESC) and the Heart Rhythm Society (HRS) recommend that patients with no structural heart disease should be initiated with dofetilide, dronedarone, flecainide, propafenone, or sotalol, as these agents are found to have the lowest level of cardiac toxicity [9]. If first line therapy is contraindicated or shown to be ineffective, second-line therapy is considered and includes either amiodarone or catheter-directed ablation [9]. Interestingly, amiodarone is considered as first line therapy in patients with substantial left ventricular (LV) hypertrophy as these patients are seen to be at increased proarrhythmic risk with most other first line antiarrhythmic drugs.

The prevention of thromboembolism including stroke prevention has been widely proven with the use of anticoagulants such as warfarin and DOACs. Stroke is seen to be the most common clinical thromboembolic event in patients with AF, with AF attributing to 36% of all strokes in individuals aged 80–89 years [10]. Furthermore, stroke occurring in patients who have AF tend to have a higher degree of severity as compared to those without AF [11]. Clinical markers predicting increased risk of stroke in patients with AF include previous history of transient ischemic attacks (TIA) or prior strokes, coronary artery disease, mitral stenosis, left ventricular dysfunction, heart failure (HF), hypertension, diabetes mellitus, female gender and age more than 75 years [9].

Thrombus formation within the left atrial appendage occurs secondary to reduced blood flow velocities due to the loss of organized mechanical contraction in this anatomical area [12, 13]. Along with reduced flow velocity, other factors have also been attributed to the enhanced thrombogenicity in patients with AF. This includes reduced nitric oxide (NO) production in the left atrial endocardium, increased levels of the prothrombotic protein plasminogen activator inhibitor 1 (PAI-1), as well as elevated levels of β-thromboglobulin and platelet factor 4, von Willebrand factor (vWF), soluble thrombomodulin and fibrinogen [14].

4. Evaluation of embolic risk

All individuals who have AF are not at equally high risk for thromboembolic events, and several predisposing clinical factors can identify those patients at relatively higher or lower risk. Risk stratification for embolic events assumes added importance, since the individual's risk of embolic events needs to be carefully balanced against the risk of bleeding which is associated with anticoagulation. In patients without CKD, AF in association with any form of valvular heart disease (VHD) is considered for anticoagulation commencement as the stroke risk in this population subset is high [3, 15, 16]. Patients with nonvalvular heart disease (NVHD),

however, do not necessarily require anticoagulation, and the decision to anticoagulate for stroke prevention depends on their individual risk of stroke [15–17].

There are several risk scores that can be used to evaluate stroke and bleeding risk in the NVHD sub-group including the HAS-BLED score, the $CHADS_2$ and CHA_2DS_2-VASc score and the ATRIA stroke risk score [18–21]. The $CHADS_2$ stroke risk scoring system was developed based on the analysis of 1773 patients in the National Registry for Atrial Fibrillation and in 2006 and was used in the ACC/AHA/ESC guidelines to tailor therapy for stroke prevention in AF [15]. The scoring system includes points for congestive heart failure, hypertension, age, diabetes and stroke [15, 20]. Previous stroke or TIA is the strongest predictor of stroke and equates for two points, whereas the other risk factors carry one point each. The final score measures the adjusted stroke rate per 100 patient-years [15, 18, 20]. The CHA_2DS_2-VASc score is an updated version of the $CHADS_2$ score as not all patients with a $CHADS_2$ score of 0 were found to be at low risk and was also noted that other risk factors that had been identified were not encompassed by this tool [18, 20, 22]. With the improvement to the CHA_2DS_2-VASc score, the 2012 ESC guidelines and 2014 ACC/AHA/HRS guidelines changed their recommendations to support the use of CHA2DS2-VASc score over the $CHADS_2$ scoring system [18, 20, 22]. In addition to the $CHADS_2$, the CHA_2DS_2-VASc acknowledges that stroke risk in patients with AF is related to age as a continuous variable, the higher risk of stroke in women, and incorporates risk associated with vascular disease, prior MI, complex aortic plaque, and peripheral arterial disease [18, 20, 22]. The CHA_2DS_2-VASc score states that antithrombotic therapy may be omitted for a score of 0, either oral anticoagulants, aspirin, or no antithrombotic therapy can be considered for a score of 1, and oral anticoagulation is recommended for patients with a prior stroke, TIA, or a score of 2 or more [3, 9, 15, 16, 18, 20, 22–26]. Although $CHADS_2$ and CHA_2DS_2-VASc scores were useful tools in the past in assisting to quantify risk of stroke in patients with NVAF, recent studies have shown that the CHA_2DS_2-VASc score is only able to correctly predict strokes in approximately 68% of cases [3, 18, 22]. The HAS-BLED scoring system was developed in 2010 as a result of the Euro Heart Survey and aims to assess the 1-year risk of major bleeding in patients with AF [18, 21]. The scoring system includes points for hypertension (Systolic >160 mmHg), abnormal renal function, liver function, stroke in past, bleeding, labile international normalized ratio (INR), age ≥65, consuming drugs and consuming alcohol [19, 21]. The scoring system is based on a maximum of nine points with each risk factor worth one point each [18, 21]. A score of 3 or more indicating an increased 1-year bleed risk on anticoagulation is sufficient to justify caution or more regular review [19–21].

While there are other more contemporary risk assessment scoring systems available, such as the ABC (age, biomarkers, clinical history) stroke risk score as devised from Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARIS-TOTLE) study, their applicability is somewhat limited, as several key risk factors included are not routinely measured, and have also yet to be widely validated in population studies [27].

Information on how to best predict stroke risk in the ESKD population is limited and precludes the ability to identify patients at high risk for stroke. No stroke risk prediction scores have been specifically developed for patients with ESRD with AF. Existing thromboembolic and bleeding risk prediction scores show good standardization of stroke risk in the general population, but performs poorly in the ESKD population. McAlister et al. conducted a retrospective large cohort study comparing the effectiveness of current thromboembolic and

bleeding risk prediction scores in patient with NVAF and CKD [28]. The seven risk prediction models examined included $CHADS_2$, $CHA2DS_2$-VASc, $R_2CHADS2$, ATRIA stroke, HAS-BLED, $HEMORR_2HAGES$ and ATRIA bleed. The study showed that the thromboembolic risk scores did not perform differently from each other, where the negative predictive value was not seen to be significantly different from each other. In terms of bleeding risk score, $HEMORR_2HAGES$ was the observed to be the most accurate with the highest c-statistic of 0.66 [28]. Furthermore, the study also showed that each of the seven risk prediction scores performed significantly better for patients with normal kidney function than in patients with CKD with performance significantly worsened as severity of kidney disease increased [28]. Therefore, the study suggests that current thromboembolic and bleeding risk prediction scores are inadequate for use in patients with CKD.

There is no difference in the indications for anticoagulation therapy between paroxysmal, persistent, or permanent AF. Clinical risk assessment tools such as the CHA_2DS_2-VASc score do not fully account for thromboembolic risk, and stroke can occur even after a sinus rhythm is restored by either pharmacological or electrical cardioversion.

5. Anticoagulation therapy in atrial fibrillation

As stipulated previously, no stroke risk prediction scores have been specifically developed for patients with CKD and AF. It has been shown, however, that patients with CKD and nonvalvular AF have a heightened stroke risk regardless of CHADS2DS2-VASc score, where 80% of patients having scores of ≥2 [29]. Current ACC/AHA/ESC guidelines advise that for a $CHADS_2$ score of ≥2 for either men or women, formal anticoagulation is recommended for patients [3, 9, 15, 16, 20, 22–26, 30]. Those with a $CHADS_2$ score of 1, formal anticoagulation or aspirin alone should be considered in conjunction with patient specific comorbidities [3, 9, 15, 16, 20, 22–26]. Finally, the guidelines state for patients with a $CHADS_2$ score of 0, no anticoagulation, neither formal nor antiplatelets, is recommended [3, 9, 15, 16, 20, 22–26]. In comparison with the American guidelines, the European guidelines recommend that males with a CHA_2DS_2-VASc score of ≥2 then anticoagulation should be used for stroke prevention, whereas those with a score of 1 should only be considered for anticoagulation, depending also on patient comorbidities and other risk factors [15, 20, 22–24]. Furthermore, for females, as female gender has been shown to be a weak risk factor for stroke in AF, guidelines advise that a CHA_2DS_2-VASc score of ≥3, then anticoagulation is recommended; however if the score is 2, then anticoagulation be considered [15, 20, 22–24]. If the CHA2DS2-VASc score is 0 in men and women or is 1 in women, neither formal anticoagulation nor antiplatelet therapy is advised or required [15, 20, 22–24].

5.1. Antiplatelets

There are few studies available that directly compare antiplatelet therapy, either single or dual agent, directly with formal anticoagulation. In a study conducted by Connely et al., it was investigated whether the addition of clopidogrel to aspirin in patients would reduce the risk of vascular events in patients with atrial fibrillation [11]. The primary end points examined included stroke, myocardial infarction, noncentral nervous system systemic embolism

and death from vascular causes. The study showed that in patients with AF where vitamin-K antagonists were deemed unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events, in particular stroke, by 28%; however, the combination increased the risk of major hemorrhage from 1.3 to 2.0% per year [10, 11].

The Stroke Prevention in Atrial Fibrillation (SPAF) II study was the only major study to show a positive outcome for use of aspirin in AF for stroke prevention [31]. The study showed that patients treated with aspirin had a statistically significant reduction of 42% in stroke rate over the placebo group [31]. In the more recent Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin-K Antagonist Treatment (AVERROES) study, 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin-K antagonist therapy was unsuitable were assessed and divided into groups whom received apixaban or aspirin [10]. The primary outcome assessed in the study was the occurrence of stroke or systemic embolism. The study was halted at 18 months as a significant benefit from apixaban over aspirin was observed with a 55% risk reduction in ischemic stroke [10]. Furthermore, it was also found that bleeding was comparable between aspirin and apixaban, 44 major bleeding events (a rate of 1.4% per year) among patients taking apixaban and 39 (1.2% per year) among those taking aspirin (hazard ratio with apixaban, 1.13; 95% CI, 0.74–1.75; P = 0.57) [10].

Olesen et al. examined aspirin's use for stroke prevention in patients with AF and CKD. The retrospective cohort study found that aspirin was associated with an increased risk of stroke or systemic thromboembolism among patients who had any form of renal disease, (hazard ratio, 1.17; 95% CI, 1.01–1.35; P = 0.04) [9]. Furthermore, the risk of stroke or systemic thromboembolism in association with CKD was of the same magnitude when adjusted for all baseline characteristics [9].

Aspirin, however, is still frequently used to reduce stroke risk in many patients with high CHA2DS2-VASc scores who would benefit from anticoagulation.

5.2. Vitamin-K antagonist

Vitamin-K antagonist, for example, warfarin, was first used as an anticoagulant in the 1960s when it was validated through multiple randomized, controlled clinical trials comparing it versus placebo or no therapy, that it had superior efficacy in reducing strokes in patients with NVAF [31, 32]. Warfarin's effectiveness was confirmed in the pivotal 1992 Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) trial [33]. This trial definitively proved that warfarin reduced stroke rates in patients with NVAF by approximately 70% and mortality by approximately 30% [33]. Furthermore, when investigated with regard to intention to treat, it was found that there was a 68% risk reduction in stroke for patients taking warfarin when compared to the control groups who were not anticoagulated [34, 35].

Although warfarin is extremely effective in reducing stroke and mortality, it is an incredibly difficult drug to use in clinical practice. Warfarin has a slow onset and offset of action and has multiple drug and food interactions. Warfarin requires constant monitoring to ensure the INR remains within the therapeutic range of 2–3. Studies have shown that an INR <2 carries

an increased risk of stroke, whereas an INR of >3 confers an increased risk of bleeding [31, 32, 36, 37]. From an Australian perspective, the difficulties of warfarin's clinical usage were seen in multicenter trials showing the time in therapeutic range (TTR) is near 70% at best, but more often found to be around 50–60% [38]. Interestingly there seems to be an increased risk of bleeding and intracranial hemorrhage (ICH) with warfarin in Asian populations, even in patients with an INR within the therapeutic range. This has seen some major centers in Asia adopt a lower therapeutic range of 1.5–2 [31, 32].

Formal anticoagulation using Warfarin has been shown to significantly reduce the incidence of stroke in CKD patients with AF. The Stroke Prevention in Atrial Fibrillation [SPAF-III] Study analyzed 516 AF participants with CKD and showed that warfarin was able to reduce ischemic stroke or systemic embolism by 76% (95% CI 42–90, $P < 0.001$) [39]. In a population-based retrospective cohort study conducted by Mitesh et al., it was found that CKD patients requiring dialysis with AF, warfarin use, in comparison with no-warfarin use, did not reduce the risk for stroke however it was associated with a 44% higher risk for having a bleeding event, whereas warfarin use in nondialysis patients with AF was associated with a 13% lower risk for stroke with a 19% higher risk for bleeding event [32, 40]. Bleeding in this study was grouped and defined as intracerebral bleeding, gastrointestinal bleeding, intraocular bleeding, hematuria, and unspecified location of bleeding. This data should not be surprising though as it is well known that HD patients have both platelet and coagulation abnormalities and also have associated comorbidities such as uncontrolled hypertension and diabetes mellitus, all of which contribute to an increase in the risk for stroke and bleeding [32, 41]. Furthermore, HD patients usually also receive heparin during dialysis, which also adds to their increased risk for bleeding. Warfarin use in HD patients, through the inhibition of matrix Gla protein and Gas-6, thus causing calciphylaxis, can accelerate vascular calcification, which may also increase the risk for ischemic stroke [32, 42, 43]. This is further supported by a 134,410 patient retrospective study cohort by Chen et al. who compared ESRD patients requiring renal replacement therapy with AF receiving either monotherapy with antiplatelets or Warfarin with a control group who were not using either of the medications [44]. They showed that the incidence of ischemic stroke or TIAs was no different between the intervention group and the control group [44]. Furthermore, the results stayed unchanged after propensity match and also showed no beneficial effect of antiplatelet or warfarin therapy in any subgroups, such as age and gender [44].

5.3. Direct oral anticoagulation drugs

Currently available oral direct acting anticoagulants are the direct thrombin inhibitor dabigatran, and the factor Xa inhibitors rivaroxaban and apixaban. Their clinical use in the normal population is favored due to their rapid onset and offset of action. Direct oral anticoagulations (DOACs) achieve full anticoagulation within 2 h of dosing, and are mostly excreted within 24 h of taking the last dose. In addition to their appeal, none of the DOACs require routine monitoring to evaluate their extent of anticoagulation performance. There has been minimal evidence in investigating DOACs for stroke prophylaxis in ESKD patients with AF. All major trials, comparing DOACs to warfarin for AF and stroke prophylaxis, excluded patients with a calculated creatinine clearance rate of <25 or 30 mL/min [45, 46].

The RE-LY study was the first open label study to compare dabigatran, a direct thrombin inhibitor, to warfarin in patients with one or more risk factors for stroke [45]. The study concluded that a higher dose (110 and 150 twice daily) of dabigatran was superior to warfarin in reducing stroke and systemic embolism. The study also revealed the effect of creatinine clearance and renal function on dabigatran's action and pharmacokinetics. Dabigatran is highly dependent on renal excretion with 80% being excreted unchanged in the urine. A 20% of patients in the RE-LY study had a CrCl of 30–50 mL/min (Patients with CrCl<30 were excluded). These patients had a higher risk of major bleeding compared to patients with a CrCl of >80 mL/min [46]. The RE-LY study also saw that warfarin-assigned patients with an eCrCl of 30–49 mL/min had a significant rate of major hemorrhage at 5.4% per year compared to other participants at 3.2% per year [45]. Large-scale trials for dabigatran use in CKD patients are not available, and although dabigatran is partially removed by dialysis, it remains not recommended for anticoagulation during HD [47].

The Rivaroxaban—once daily, oral, direct factor Xa inhibition compared with vitamin-K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial—examined rivaroxaban versus warfarin in patients with two or more risk factors for a stroke. The study showed that rivaroxaban had similar efficacy to warfarin in reducing stroke and embolism but a significant reduction in ICH. The study was also able to show a statistically significant trend toward a decrease in all-cause mortality, as with other DOACs [48]. Patients with CrCl <30 mL/min were excluded from the trial, whereas patients with moderate renal insufficiency (CrCl of 30–50 mL/min) were included but given an adjusted dose of 15 mg daily based on data showing 25–30% higher residual serum concentration of rivaroxaban in these patients compared to patients with normal renal clearance [49, 50]. The ROCKET AF study was unable to demonstrate noninferiority or superiority of rivaroxaban in patients with moderate renal insufficiency in comparison with warfarin therapy. The rates of stroke and systemic embolism were higher in patients with moderate renal impairment compared to patients with better renal function [47]. The ROCKET AF trial also examined the primary outcome of major hemorrhage in comparison with warfarin and was shown to occur in 3.2% of patients per year for those with an eCrCl of >50 mL/min as compared to 4.7% per year in those with an eCrCl of 30–49 mL/min [48]. There are no major trials for rivaroxaban therapy in patients with a creatinine clearance of <30 mL/min or on dialysis. Rivaroxaban has been shown to be able to be completely and immediately reversed with 50 U/kg prothrombin complex concentrate on patients with normal renal function [51].

Apixaban's effectiveness was examined in the ARISTOTLE trial, which was similar to the other DOAC trials, included patients with one or more risk factors for stroke. The trial revealed that apixaban was superior to warfarin in stroke reduction and systemic embolism [52]. Major and clinically relevant nonmajor bleeding was also found to be significantly less with apixaban when compared to warfarin with ICH being also significantly reduced [3, 52]. Of the three DOACs available, only apixaban has proven to be statistically significant for reduction in total mortality when compared with warfarin, regardless of renal function.

The ARISTOTLE trial involved examining the efficacy of a apixaban in patients with creatinine of 133–221 μmol/L (1.5–2.5 mg/dL) and lower or creatinine clearance of >25 mL/min [45], and noted that the incidence of major bleeding events with apixaban was inversely related to renal functions [8]. Patients with moderate to severe renal insufficiency (creatinine 133–221 μmol/L or CrCl of <25 mL/min) were given 2.5 mg doses twice daily while patients with normal

renal function were given 5 mg twice daily. Bleeding episodes were higher in patients with moderate/severe renal failure when compared to the normal renal function group, however remained lower with apixaban compared to patients with renal impairment on warfarin. In terms of observing patients on warfarin, the ARISTOTLE trial showed that major hemorrhage was at least twice as likely among patients with an eCrCl of 25–50 mL/min compared with others [52]. The ARISTOTLE trial therefore eludes to apixaban being safe for oral anticoagulation in AF patients with creatinine clearance of >25 mL/min, with dose adjustment as decided by the treating physician.

Again, there are no major trials investigating the effectiveness of apixaban on ESKD patients with stroke risks. Further research in this area is awaited. Apixaban like rivaroxaban is not dialyzable and therefore albeit the small renal excretion of 27 and 36%, respectively, they may build up in patients with ESKD [53]. Therefore, it is always advisable to continue monitoring patients with moderate to severe (CrCl 30–80 mL/min) for worsening renal function and possibility of toxicity.

6. Conclusions

In conclusion, patients with ESKD have higher prevalence of AF. In the absence of DOACs that can be used in patients with ESRD, vitamin-K antagonists still remain the gold standard for systemic anticoagulation in this group of patients. Anticoagulation with vitamin-K antagonist in patients with ESKD is challenging due to the adverse events such as increased risk of bleeding and augmentation of risk of calciphylaxis.

The risks of administering vitamin-K antagonists in patients with ESRD should be carefully weighed against benefits of these agents in preventing embolic episodes. Since newer DOACs may have a better benefit-risk profile in dialysis patients than vitamin-K antagonists, provided appropriate dose reductions are made, this strategy may yield more on-target anticoagulation, reduce the risk of intracerebral bleeding, and not interfere with vascular calcification biology. Clinical trials with direct oral anticoagulant in dialysis patients are eagerly awaited. In addition, development of a DOAC that has nonrenal mode of excretion and can be safely given in patients on dialysis may also result in lower rates of bleeding complications, thereby shifting the risk-benefit balance toward systemic anticoagulation with this group of agents in the future.

Author details

Quoc Tran[1], Bassim Jebeili[1], Kamal Sud[2,3] and Bhadran Bose[2,3]*

*Address all correspondence to: bhadran.bose@health.nsw.gov.au

1 Department of Vascular Surgery, Nepean Hospital, Kingswood, NSW, Australia

2 Department of Renal Medicine, Nepean Hospital, Kingswood, NSW, Australia

3 Nepean Clinical School, The University of Sydney, Sydney, NSW, Australia

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