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Invited Review

Pathophysiology of Atrial Fibrillation and Chronic Kidney Disease

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Unstructured abstract

Atrial fibrillation (AF) and chronic kidney disease (CKD) are closely related conditions with shared risk factors. The growing prevalence of both AF and CKD indicates that more patients will suffer from concurrent conditions. There are various complex interlinking mechanisms with important implications for the management of these patients. Furthermore, there is uncertainty regarding the use of oral anticoagulation in AF and CKD that is reflected by a lack of consensus between international guidelines. Therefore, the importance of understanding the implications of co-existing AF and CKD should not be underestimated. In this review, we discuss the pathophysiology and association between AF and CKD, including the underlying mechanisms, risk of thromboembolic and bleeding complications, influence on stroke management, and evidence surrounding the use of oral anticoagulation for stroke prevention.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with an estimated global prevalence of 33.5 million in 2010 [1]. The condition is associated with serious complications such as stroke and heart failure that results in significant morbidity and mortality [1–5]. Furthermore, with a trend of increasing incidence and prevalence, the condition poses a significant healthcare economic burden [6,7]. It is projected that as many as 17.9 million people will be affected in Europe by 2060 [8].

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function lasting more than three months with implications on health [9]. A meta-analysis of 100 studies involving close to 7 million patients reported an estimated global CKD prevalence of 13.4% [10]. It is widely accepted that glomerular filtration rate (GFR) is the best overall index of kidney function that is readily accessible in clinical practice. Various equations exist to estimate GFR such as Modification of Diet in Renal Disease (MDRD) Study [11], Cockcroft-Gault [12], and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [13,14]. Normal ranges of GFR in young healthy adults may be up to 120-130 mL/min/1.73m^2 though this declines with age. In addition to low levels of estimated glomerular filtration rate (eGFR), other markers of kidney damage include albuminuria. Overall, the severity of CKD is classified by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines into five main stages (**Table 1**). Patients at the most severe end of the spectrum with end-stage renal disease (ESRD) may require renal replacement therapy (RRT), often in the form of haemodialysis (HD) or peritoneal dialysis (PD), or kidney transplantation.

Atrial fibrillation and CKD are closely linked conditions that share commonality in terms of risk factors such as hypertension, diabetes mellitus and coronary artery

disease [15–17]. The growing prevalence of both AF and CKD indicates that more patients will suffer from concurrent conditions. Therefore, the importance of understanding the implications of co-existing AF and CKD should not be underestimated.

In this review, we discuss the pathophysiology and association between AF and CKD, including the underlying mechanisms, risk of thromboembolic and bleeding complications, influence on stroke management, and evidence surrounding the use of oral anticoagulation (OAC) for stroke prevention.

Relationship between AF and CKD

Atrial fibrillation and CKD have a bidirectional relationship such that the presence of CKD increases the risk of incident AF while the presence of AF associates with the development and progression of CKD [18–21]. A previous meta-analysis of 25 studies found that patients with ESRD on RRT appeared to have an increased risk of incident AF compared to the general population [22]. Further studies have expanded on this finding by demonstrating that the risk of AF is increased in a dose-response fashion among patients with moderate CKD [23,24], and potentially even in those with only mild CKD [25].

The incidence of AF has been associated with a significant increase in the development of CKD [26]. In patients with a prior diagnosis of CKD, AF may contribute to deteriorating renal function leading to ESRD requiring RRT [19,27]. A detailed description of studies evaluating the bidirectional relationship of AF and CKD is provided in **Table 2**.

There is an important limitation of the aforementioned studies involving patients with AF and CKD. In general, patients with CKD tend to be older with multiple

comorbidities. Therefore, to investigate the effects of CKD on incident AF, these studies performed their analyses using multivariable adjustments to account for potential confounders. However, this method may have resulted in overfitting of models as some risk factors such as hypertension, acute coronary syndrome and heart failure are established consequences of CKD. Moreover, the studies employed different measures of kidney function which have been shown to have varying degrees of accuracy [28,29]. Thirdly, given that the rates of previously undiagnosed AF are increasing with more intensive cardiac monitoring [30,31], there is a possibility that many studies investigating the association between AF and outcomes in CKD could be biased towards the null hypothesis (as the control groups may have included significant number of patients with undiagnosed AF). All these factors may provide an explanation for the attenuated effects between AF and CKD that has been observed in some studies [32,33].

Of note, there are suggestions that treatment of AF with catheter ablation may lead to a significant improvement in renal function compared to medical therapy alone [34–36]. Furthermore, the authors found that this benefit was only realised in patients who were able to maintain sinus rhythm, and not in those who had AF recurrences post-ablation.

The prevalence of AF in CKD is about two- to three-fold higher than the estimated 2-4% in the general population [37,38]. In the prospective CRIC (Chronic Renal Insufficiency Cohort) study, the prevalence of AF in CKD patients was 18% [39]. In addition, an eGFR <45 mL/min/1.73m^2 was associated with a greater prevalence of AF, although this was accounted for by other risk factors. A limitation of the CRIC study was that it relied on self-reporting of AF which could have led to misclassification bias. Given the dose-response relationship between incident AF and

CKD, it may be expected that AF is more prevalent among patients with worsening CKD. Indeed, a population-based cohort study of 26,917 participants found that AF was present in 1.0%, 2.8%, 2.7% and 4.2% of patients without CKD, and stage 1 to 2, stage 3, and stage 4-5 CKD, respectively [40]. Zimmerman *et al.* reported that as many as 11.6% of patients with ESRD had a diagnosis of AF [22]. On the contrary, up to half of the patients with AF may be affected by CKD [41,42].

Underlying mechanisms

There are several mechanisms connecting AF and CKD. For example, elevated levels of inflammatory markers have been reported in the early stages of CKD which becomes more significant as the disease progresses [43]. In turn, the effects of inflammation have been shown to contribute to the development and persistence of AF [44]. Furthermore, the role of inflammation as a common mechanism between AF and CKD is supported by the fact that medications with anti-inflammatory properties such as glucocorticoids and statins may offer some protection against AF and preserve kidney function [45,46].

Activation of the renin-angiotensin-aldosterone system (RAAS) is another important link between AF and CKD. The RAAS is a major factor in the pathogenesis and progression of CKD through various processes including increased production of reactive oxygen species; upregulation of cytokines, cell adhesion molecules and profibrotic growth factors; induction of transforming growth factor β1 (TGF-β1) expression; increased synthesis of extracellular matrix proteins; stimulation of plasminogen activator inhibitor-1 production; and macrophage activation and infiltration [47–49]. It may also contribute to the development of AF by promoting atrial pressure overload and fibrosis [50]. The precise mechanism involved in the development of atrial fibrosis remains ill-defined. However, it does appear that the

atria are more susceptible to fibrosis than the ventricles with involvement of three interrelated pathways - RAAS, TGF-β1 and oxidative stress [51]. Transgenic mouse models with overexpression of cardiac angiotensin-converting enzyme (ACE) developed AF with significant atrial (but not ventricular) enlargement and fibrosis [52]. Similar to animal models, Goette *et al.* found that an ACE-dependent increase in activated Erk1/Erk2 may contribute to the development of atrial fibrosis in patients with AF [53]. Further support for the role of RAAS in the pathogenesis of AF may be derived from clinical and animal studies which have shown that the use of ACE inhibitors reduced the incidence of AF and levels of atrial fibrosis [54–57].

The RAAS may also induce the activation of TGF-β1/Smads pathway which contributes to the production of reactive oxygen species and oxidative stress [58]. In a transgenic mouse model with overexpression of a constitutively active form of TGF-β1, there was selective atrial fibrosis that resulted in an increase in conduction heterogeneity and AF vulnerability [59,60]. Moreover, reducing the expression of TGF-β1 with pirfenidone has been shown to reduce the extent of lung [61], liver [62], renal [63] and cardiac fibrosis [64]. A study of 5/6 nephrectomy rats, that have been widely used to represent the pathogenesis of CKD in humans, by Fukunaga *et al.* successfully demonstrated the role of oxidative stress mediated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the generation of left atrial fibrosis and enhanced AF vulnerability [65]. Additionally, the authors found that treatment with a potent antioxidant agent, sodium zinc dihydrolipoylhistidinate, was effective at reducing the inducibility of AF. Therefore, inhibition of RAAS activation may have an important role in reducing both the progression of CKD and the incidence of AF [66,67].

Calcium-handling abnormalities are critical elements in the pathogenesis of AF with central roles in atrial ectopic activity, re-entry and remodelling [68]. A recent animal study demonstrated that accumulation of uraemic toxin indoxyl sulfate, as seen in CKD, caused a larger calcium leak in the pulmonary veins [69], which are known to have a significant role in triggering AF [70]. Chen *et al.* found that this resulted in important electrical changes including more pulmonary vein delayed afterdepolarisations, reduced spontaneous activation of the sinoatrial node, shortening of left atrial action potential duration and increased AF inducibility [69]. A separate study in rabbits found that CKD, induced by neomycin and cefazolin, led to significant abnormalities in calcium homeostasis within the pulmonary veins such as larger calcium transient amplitudes, sarcoplasmic reticulum calcium contents and sodium/calcium exchanger currents but smaller L-type calcium current densities through the activation of protein kinase A and reactive oxygen species [71]. Moreover, changes in calcium (and phosphate) metabolism in CKD predispose to valvular heart disease often manifested as mitral annular or aortic valve calcification [72]. These structural changes may further contribute to the development of AF via pressure overload.

In addition to indoxyl sulfate, other uraemic toxins (indole-3 acetic acid, *p*-cresol and *p*-cresyl sulfate) that accumulate in CKD have also been implicated in pathways of oxidative stress, inflammation and neurohormonal activation that lead to cardiovascular fibrosis and oxidative injury [73]. The effects of reduced cardiac output coupled with the risk of renal microthrombi secondary to AF may also cause a progressive decline in renal function over time [74,75]. Moreover, certain medications used in multimorbid patients with AF are nephrotoxic (*e.g.* non-steroidal anti-inflammatory drugs). Finally, the development of AF in CKD may be driven by

upregulation of the sympathetic system and an increased risk of cardiovascular diseases [76,77].

Prothrombotic state

Atrial fibrillation and CKD are both characterised by a prothrombotic state through their effects on the individual components of Virchow's triad [78,79]. The prothrombotic state in AF has been widely established [80]. In terms of the latter, worsening CKD in patients with AF has been shown to promote stasis of blood in the left atrium, as identified by the presence of dense spontaneous echo contrast and reduced flow velocity [81,82]. Several studies have also demonstrated that CKD results in impaired endothelial function that is responsible for regulating clot formation under physiological conditions [83–87]. Furthermore, platelet activation occurs in early-stage CKD and is inversely related to renal function [43,88]. Lastly, the presence of CKD is directly responsible for increased procoagulant and inflammatory biomarkers [43,89,90].

Given its prothrombotic effects, it is unsurprising that CKD results in an increased risk of occlusive vascular events including stroke. A meta-analysis of 21 prospective studies found that an eGFR <60 mL/min/1.73m^2 was independently associated with a significant increase in stroke risk with a possible dose-response relationship [91]. Furthermore, the authors reported that this elevated risk persisted across a variety of subgroups. In this meta-analysis, the presence of albuminuria was not linked to an increased stroke risk [91]. However, the finding was based on only three studies. In contrast, two separate meta-analyses have demonstrated that albuminuria per se was independently associated with greater stroke risk [92,93].

Having defined the elevated thromboembolic risk in AF and CKD, it is important to recognise that not all such complications are equal. In this regard, the effects of CKD

in AF may extend beyond its influences on the incidence rate of thromboembolism. Studies have shown that among patients with an acute stroke, those with lower levels of renal function had worse outcomes for mortality and functional status [94]. Additionally, there was a greater risk of haemorrhagic transformation post-stroke in patients with CKD [95].

Bleeding risk in CKD

Bleeding and thrombosis are often viewed as two ends of the same spectrum which has perpetuated the common misconception that a change in either factor causes an opposite effect on the other. In fact, there are situations where these phenomena may be mutually exclusive and occur in tandem with one another. This is exemplified in patients with CKD who suffer from a higher thromboembolism risk *and* a paradoxical rise in bleeding events. In a large retrospective cohort study of 516,197 patients, it was found that there was a 9% increase in haemorrhagic risk for each 10-mL/min/1.73m^2 reduction in eGFR, after adjustment for other risk factors [96].

Interestingly, Wasse *et al.* found that the rate of upper gastro-intestinal haemorrhage in CKD was not associated with conventional risk factors such as age, gender, diabetes mellitus, hypoalbuminaemia, nourishment status, treatment modality, and aspirin, non-steroidal anti-inflammatory drug or anti-coagulant use [97]. Furthermore, these bleeding complications led to greater mortality rates in these patients[98], highlighting the importance of preventing such incidents. In a Japanese study, the stroke rate among patients on HD was five to ten times higher than the general population with a preponderance of haemorrhagic events [99].

There are a number of pathophysiological basis for the increased risk of bleeding in CKD. Severe CKD has been associated with haemostatic defects including platelet dysfunction [100,101]. This may occur secondary to competitive binding of fibrinogen

fragments to glycoprotein IIb/IIIa receptor [102], reduced production of thromboxane A2 [103], decreased binding of von Willebrand factor and fibrinogen to stimulated platelets [104], and biochemical abnormalities in platelet adenosine diphosphate and serotonin content [105]. In addition, there may be changes to the levels of prostacyclin and nitric oxide which may contribute to dysfunction haemostasis [106]. The risk of anticoagulation-related bleeding events is beyond the scope of this article.

Thromboembolic risk and management

It is apparent that thromboembolic risk is significantly increased with co-existent AF and CKD compared to either condition alone. However, the magnitude of this increase remains debatable.

An earlier study by Vazquez *et al.* found that new-onset AF in CKD patients on RRT was linked with a dramatic increase of 9.8-fold in stroke risk [107]. In contrast, an observational study of 17,518 randomly sampled HD patients demonstrated that AF was associated with a 1.8-fold greater risk of stroke [108]. The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study found that the presence of proteinuria increased the risk of thromboembolism by 1.5-fold, after adjustment for stroke risk factors and other confounders [109]. Furthermore, there was a graded, increased risk of stroke associated with progressively lower levels of eGFR. A Danish registry study of 132,372 patients reported that CKD and ESRD requiring RRT were related to an elevated risk of stroke or systemic embolism by 1.5-fold and 1.8-fold, respectively [110].

Overall, the presence of both AF and CKD causes a significant rise in the risk of thromboembolism and all-cause mortality, coupled with a paradoxical rise in bleeding events[22,111]. Therefore, management of such patients presents a challenging scenario for physicians, especially in relation to the use of OAC. Typically, the use

of such medications have been established to be effective in stroke prevention among patients with AF, hence great efforts to improve OAC prescription and uptake, as well as adherence and persistence with therapy[112,113]. As patients with AF and CKD suffer from changes in drug pharmacokinetics and an increased risk of bleeding, the net benefit of anticoagulation among these patients are yet to be proven. For these similar reasons, the non-vitamin K oral antagonists (NOACs) are often postulated to be more advantageous than VKA given their stable pharmacokinetics, rapid onset of action, shorter half-life and reduced drug-to-drug interactions [114]. Nonetheless, their reliance on renal excretion (ranging from 27- 80%, depending on the choice of NOAC) may have significant implications in their overall efficacy and safety.

The randomised controlled trials from which we derive much of our evidence have systematically excluded patients with severe CKD [115–118]. As a result, there are currently no published randomised trials assessing the role of OAC in patients with ESRD. Furthermore, patients with moderate-to-severe CKD were under-represented in the landmark trials of NOACs, as shown in **Figure 1**. With this limitation in mind, a meta-analysis of patients with a creatinine clearance ≤50 mL/min from these randomised controlled trials found that full/single dose NOACs were associated with a significant reduction in the odds of stroke or systemic embolism, and major bleeding compared to warfarin [114]. On the contrary, the authors found that there was a trend towards a reduced incidence of stroke when comparing warfarin to low-dose NOACs.

A retrospective matched-cohort study of AF patients with ESRD found that the use of apixaban was not associated with a significant difference in the risk of stroke or systemic embolism compared to warfarin (despite a reduction in major bleeding) [119]. This finding was consistent with an earlier meta-analysis of five observational

studies in patients with stage 4-5 CKD or dialysis-dependent ESRD where the use of apixaban was indicated by AF in the majority of patients (87%) [120]. Moreover, similar results are reported with rivaroxaban [121].

The uncertainty regarding the use of OAC in AF and CKD is reflected by a lack of consensus between international guidelines (**Figure 2**). The KDIGO 2012 guidelines suggest that a lower dose of warfarin with close monitoring is permitted among patients with an eGFR <30 mL/min/1.73m^2 [9]. However, in a more recently published conference report, the group acknowledges that there was insufficient high-quality evidence to recommend OAC for stroke prevention in AF patients on RRT [122]. It was suggested that an alternative of apixaban 2.5mg bid may be considered while awaiting more clinical efficacy and safety data.

The Canadian Cardiovascular Society (CCS) 2014 guidelines suggest that warfarin may be considered in patients with an eGFR between 15-30 mL/min and who are not on RRT, but do not recommend anticoagulation in ESRD patients on RRT [123]. In contrast, the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines do not restrict the use of vitamin K antagonist (VKA) or apixaban by renal function or RRT, while permitting other NOACs to be prescribed down to a creatinine clearance (CrCl) of 15 mL/min [124,125]. The European Society of Cardiology (ESC) 2016 guidelines suggest that anticoagulation may be safely used in AF patients with a CrCl >15 mL/min but do not provide clear recommendations for patients with ESRD [126]. Furthermore, the ESC recommends that regular monitoring of renal function should be undertaken to allow dose adaptation of NOACs.

The CHEST 2018 guidelines from the American College of Chest Physicians recommend that in severe non-dialysis CKD (Stage IV, CrCl 15-30 mL/min), VKAs

and selected NOACs (rivaroxaban 15 mg QD, apixaban 2.5 mg bid, edoxaban 30 mg QD and [in USA only] dabigatran 75 mg bid) may be used with caution, based on pharmacokinetic data [127]. In ESRD (CrCl <15 mL/min or dialysis-dependent), individualised decision-making is appropriate, using well-managed VKA with time-in-therapeutic range (TTR) >65-70% (ungraded consensus-based statement), and while NOACs should generally not be used, the guideline noted that apixaban 5 mg bid is approved in USA for use in AF patients receiving hemodialysis[127].

What's the evidence base for stroke prevention using VKAs?

VKA in dialysis-dependent ESRD

Much of the observational data on the use of OAC in AF patients with severe CKD have traditionally been focused on VKA. Given their relatively shorter duration of use, there is a paucity of data on NOACs in this population. As a result, much of our present understanding on the role of OAC in stroke prevention among patients with AF and CKD stems from observational-type studies evaluating the use of VKA in this cohort.

Warfarin, the most widely used VKA, has an oral bioavailability of 95% with a renal clearance of 8% (excreted unchanged) and mean half-life of 40 hours. Importantly, it is not dialysed [128].

In order to evaluate the role of VKA in stroke prevention among patients with AF and dialysis-dependent ESRD, we performed a semi-systematic review of all published clinical studies on this topic. A comprehensive search was undertaken using the PubMed database, and this was supplemented by scanning reference lists from included studies and other systematic reviews. Search terms included: atrial

fibrillation, end-stage renal disease, dialysis, vitamin K antagonist, warfarin and stroke. Only studies which compared the effects of VKA vs no VKA for stroke prevention in AF patients with dialysis-dependent ESRD were included. Relevant studies were initially identified by screening titles and abstracts. Subsequently, a detailed review of each study was undertaken to generate a list of 23 included studies (**Table 3**).

A majority (n=17, 74%) of the observational studies were retrospective in nature with varying cohort sizes, ranging from 61 to 9,974 patients. The use of VKA was between 6 to 54.8% across the studies. There were conflicting results on the effects of VKA on stroke prevention in AF and dialysis-dependent ESRD. The use of VKA was associated with no difference in outcomes in 16 studies [95–110], better outcomes in five studies [110,145–148] and worse outcomes in two studies [108,149]. The study by Wizemann *et al.* reported no difference in terms of stroke risk with the use of VKA in AF patients on HD who were under 75 years old but an increased risk of stroke when used in patients above this age [108]. Overall, the current evidence on VKA do not support its use for stroke prevention in AF patients with dialysis-dependent ESRD.

There were several limitations of the included studies. First, they were subject to the inherent shortcomings of observational study designs and should therefore be interpreted with caution. Second, many studies did not differentiate the study outcomes for aetiology such as ischaemic (atherosclerotic or thromboembolic) and haemorrhagic strokes [108,110,129,131,132,139,142,149]. Therefore, it was difficult to determine whether VKA had a differential effect on the various stroke subtypes. From the remaining 15 studies that reported on the risk of ischaemic stroke, four found beneficial effects with the use of VKA [145–148], while 11 had neutral outcomes [130,133–

[138,140,141,143,144]. The risk of haemorrhagic stroke was increased by 1.4- to 2.4-fold with VKA therapy [135,137].

Third, many studies demonstrated poor quality of anticoagulation control as reflected by a low TTR and sub-therapeutic mean international normalised ratio (INR) in AF patients with dialysis-dependent ESRD who were treated with VKA [131–133,141,148]. This is unsurprising given previous reports of poor anticoagulation control in CKD [150,151], which deteriorated with worsening severity of renal failure [152].

In previous studies of predominantly non-dialysis-dependent CKD patients, a low TTR has been directly linked to increased complication rates of stroke, bleeding and mortality [150,151]. The study by Lai *et al.* found that 43% of the total thromboembolic strokes that occurred in the VKA group, happened while patients had an INR of less than two [145]. Similarly, Genovesi *et al*. reported that two-thirds of those with thromboembolic events in the VKA group had sub-therapeutic INR [143]. In addition, Kai *et al.* showed that all-cause mortality was lowest in the VKA subgroup with the highest TTR [148].

Fourth, most studies analysed the results using information on VKA collected at baseline ('intention-to-treat' principle) with no assessment for subsequent modifications to anticoagulation treatment. However, patients who were initiated on VKA may have subsequently discontinued their therapy while those who were VKA naïve may have been commenced on anticoagulation at a later date. For example, Shen *et al.* reported that the rate of warfarin discontinuation was 70% within one year [146]. Therefore, many studies were likely subject to misclassification bias which may have had significant impact on the results. From the six studies that employed either a time-varying exposure to treatment or as-treated analyses, stroke risk

associated with the use of VKA was no different in four studies [134,137,139,146], lower in one study [110], and higher in one study [149].

Fifth, few studies referred to AF as an encompassing term to include atrial flutter and true AF [133,146,148]. Despite some overlap in the management of both conditions, their underlying mechanism is very different. Therefore, their combined analyses may have introduced a confounding effect. Two studies which included patients with atrial flutter reported that the use of warfarin was associated with lower stroke risk [133,148]. Sixth, as expected, the mortality rates among AF patients with dialysis-dependent ESRD were extremely high. The mean survival of this cohort was 1.8 years with mortality rates up to 40% at two years and 77% at five years [130,143,144]. A significant proportion of the cause of death were unrelated to cardiovascular events. As a result, death was a competing factor for stroke events among these patients.

There are several potential explanations for the observed lack of efficacy of VKA for stroke prevention in AF patients with dialysis-dependent ESRD. The effects of uraemia on platelet dysfunction, as discussed above, may provide some protection against thrombus formation. Moreover, these patients receive routine administrations of heparin during HD sessions which may further reduce their stroke risk. Impaired drug metabolism and pharmacokinetics secondary to renal failure may also influence the effects of medications and contribute to unwanted interactions. Haemodialysis itself is known to disrupt the therapeutic levels of VKA by promoting the binding of free fractions of warfarin to serum albumin [153].

In addition, warfarin has been linked to accelerated vascular calcification, possibly through inhibition of vitamin K-dependent factors such as matrix Gla protein [154–156]. Matrix Gla protein is a secreted protein that is widely distribution in the bone, cartilage, heart and kidney, and has a high affinity to calcium ions. In mice models,

gene deletion of matrix Gla protein resulted in enhanced bone morphogenetic protein signalling that stimulates the endothelium to contribute osteoprogenitor cells to vascular calcification [157]. Genetic variation and differential gamma-carboxylation at the glutamate residues is thought to be responsible for the varying phenotypes and patient susceptibility [158]. Overall, calciphylaxis is a rare disorder and is most often related to ESRD with an incidence of 0.4 to 3.9 per 1,000 patients on dialysis [159]. In three separate reports, about half of the dialysis patients who were diagnosed with calciphylaxis were on warfarin [160–162]. The condition is characterised by endothelial injury, medial calcification, arteriolar narrowing and thrombosis of dermal- hypodermal arterioles, generally in subcutaneous adipose tissue. Prognosis is poor with a 1- year mortality rate of up to 45%. Thus, this may negate any beneficial anticoagulant effects of warfarin.

Given that some of proposed factors applies mainly to HD, it is important to consider whether the mode of RRT per se may be implicated for the observed lack of efficacy of VKA for stroke prevention. Ten of the studies in our semi-systematic review included AF patients on PD. Nevertheless, in the majority of studies, these patients formed a small percentage of the total cohort and the results were not analysed according to the mode of dialysis. Only two studies evaluated the effects of VKA in a PD-specific population with AF. Interestingly, these demonstrated opposing findings. The study by Chan *et al.* found that VKA use in AF patients with PD was associated with a significant reduction in stroke risk [147]. In contrast, Phan *et al.* showed a trend towards increased stroke risk with VKA (p = 0.07) [133]. The main difference between these studies were the inclusion of patients with a greater number of comorbidities and higher thromboembolic risk by Phan *et al.* [133]. As such, it may be postulated that any positive effects of VKA (if it existed) would have been more

readily detected in this study. Overall, there is insufficient evidence to conclude whether the effects of VKA differs by the mode of RRT in ESRD patients with AF.

In light of the current ambiguity, there is a strong need for future research on the role of anticoagulation in ESRD. There are currently two ongoing trials with such an aim in mind (AVKDIAL trial, ClinicalTrials.gov NCT02886962; AXADIA trial, ClinicalTrials.gov NCT02933697). Both are in the recruitment phase and results will be unavailable for several years yet. In the meantime, the recently completed RENAL-AF trial (ClinicalTrials.gov NCT02942407) may soon be published.

VKA in non-dialysis-dependent CKD

The lack of benefits with OAC in AF patients may extend beyond those with the most severe form of CKD. Indeed, an observational study based on primary care records in the United Kingdom found that the use of OAC (predominantly VKA) in AF patients with an eGFR <50 mL/min/1.73m^2 was associated with a greater risk of ischaemic stroke compared to patients not receiving OAC [163]. Therefore, the presence of CKD may have important implications for the use of OAC for stroke prevention in AF. Interestingly, in the same study, the authors found that patients treated with OAC had lower all-cause mortality [163].

In order to evaluate the role of VKA in stroke prevention among patients with AF and non-dialysis-dependent CKD, we performed a semi-systematic review of all published clinical studies on this topic. The methods used were similar to that described above. Search terms included: atrial fibrillation, chronic kidney disease, vitamin K antagonist, warfarin and stroke. Only studies which compared the effects of VKA vs no VKA for stroke prevention in AF patients with non-dialysis dependent CKD were included. The final review comprised of eight studies (**Table 4**). A study

by Carrero *et al.* was excluded as it focused primarily on the use of warfarin in post-MI patients with AF [164].

All the eight studies were observational and retrospective in nature. The cohort sizes ranged from 306 to 14,827 patients. Estimated GFR was calculated using the CKD-EPI equation in four studies [163,165–167], and MDRD equation in two studies [139,145]. The method used to determine eGFR in the remaining two studies were not reported [110,168]. Overall, treatment with VKA was associated with no difference in stroke risk in one study [110], lower stroke risk in five studies [139,145,166–168] and higher stroke risk in two studies [163,165]. Although the study by Keskar *et al.* initially found that the use of warfarin did not alter the risk of ischaemic stroke or transient ischaemic attack (TIA) in AF patients with an eGFR <45 mL/min/1.73m^2, application of a time-varying model for exposure to anticoagulation revealed that VKA instead led to an unintended higher stroke risk [165].

The two studies that reported on stroke risk according to eGFR categories had conflicting results for patients with mild CKD (eGFR ≥60 mL/min/1.73m^2). Jun *et al.* found that the use of VKA in AF patients with mild CKD did not modify the stroke or TIA risk [166], while Bonde *et al.* found that VKA decreased the risk of stroke, TIA or thromboembolism in such patients [167]. However, the latter study relied solely on eGFR for the diagnosis of CKD while the study by Jun *et al.* utilised the presence of albuminuria, in accord with the KDIGO criteria for CKD [9]. This may provide some explanation for the differences observed. As discussed previously, the presence of albuminuria has been shown to be independently associated with a higher stroke risk [92]. Furthermore, serum albumin is known to have important interactions with warfarin [169]. Interestingly, Jun *et al.* found that the use of VKA in AF patients with an eGFR <30 mL/min/1.73m^2 was related to a lower stroke risk [166],

while Bonde *et al.* reported that VKA led to better outcomes only in AF patients with severe CKD (eGFR 15-29 mL/min/1.73m^2) but not in those with non-dialysis-dependent ESRD (eGFR <15 mL/min/1.73m^2) [167].

A separate study by Bonde *et al.* showed that warfarin was only effective in terms of stroke risk reduction among AF patients with non-dialysis-dependent CKD who had a CHA_2DS_2-VASc score ≥2 [139]. A limitation of the study was the lack of analyses based on stroke subtypes. Therefore, it may be possible that the use of VKA in low-risk patients was successful in minimising the rates of ischaemic stroke but that this minor benefit was nullified by an increase in haemorrhagic stroke. Overall, the beneficial effects of VKA for stroke prevention in AF patients may be attenuated by the presence of CKD, with the potential for harm in certain situations (**Central Illustration**).

Conclusion

AF and CKD are closely related with many common risk factors. There are various complex interlinking mechanisms with important implications for the management of patients with co-existing AF and CKD, requiring a holistic or integrated approach to management in these high risk multimorbid patients[170]. Appropriate cardiovascular (and stroke) risk stratification and optimised management of comorbidities are essential to improve clinical outcomes, given some debates over of the value of VKA for stroke prevention.

Contributorship statement

WYD performed the literature search, interpreted the data and drafted the manuscript. DG, CFW and GYHL provided critical revisions. All authors approve the final version of the manuscript for publication.

Disclosures

WYD: None declared.

DG: Speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Biosense Webster and Boston Scientific. Proctor for Abbott. Research Grants from Medtronic, Biosense Webster and Boston Scientific.

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Tables

Table 1. Stages of chronic kidney disease

Stage	GFR (mL/min/1.73 m^2)	Description
1	≥90	Kidney damage with normal or high function
2	60-89	Kidney damage with mildly decreased function
3a	45-59	Mild to moderately decreased kidney function
3b	30-44	Moderately to severely decreased kidney function
4	15-29	Severely decreased kidney function
5	<15	Kidney failure or ESRD

ESRD, end-stage renal disease; GFR, glomerular filtration rate.

Adapted from KDIGO 2012 [9]

Table 2. Bidirectional relationship between AF and CKD

Study, year	Population	n	Groups	Follow-up (years)	Finding(s)
Guo, 2019 [18]	Chinese adults	88,312	CKD vs non-CKD	NA	Increased prevalence of AF by 4-fold in CKD; dose-response relation between incident AF and worsening CKD
Carrero, 2018 [20]	eGFR <60 without AF	116,184	eGFR 45-60 vs eGFR 30-44 vs eGFR <30	3.9	Dose-response relation between incident AF and worsening eGFR; eGFR <30 was associated with a 1.6-fold increased risk of incident AF (reference eGFR 45-60)
Marcos, 2017 [32]	Population-based cohort, enriched by those with albuminuria	8,265	Creatinine, eGFR, cystatin C and urine albumin excretion as continuous variables	9.8	No association between incidence of AF and markers of renal function (creatinine, eGFR and cystatin C); dose-response relation between incident AF and urine albumin excretion
Laukkanen, 2016 [23]	Population-based cohort	1,840	eGFR ≥90 vs eGFR 60-89 vs eGFR 15-59; macroalbuminuria vs no albuminuria	3.7	eGFR 15-59 was associated with a 2.7-fold increased risk of incident AF (reference eGFR ≥90); higher incidence of AF with macroalbuminuria
Alonso, 2011 [25]	Population-based cohort	10,328	eGFR ≥90 vs eGFR 60-80 vs eGFR 30-59 vs eGFR 15-29; macroalbuminuria vs microalbuminuria vs no albuminuria	10.1	Dose-response relation between incident AF and worsening eGFR; risk of incident AF increased even with mild renal dysfunction; eGFR 15-29 was associated with 3.2-fold increased risk of incident AF (reference eGFR ≥90); higher incidence of AF with albuminuria
Deo, 2010 [33]	Ambulatory elderly patients	4,663	Cystatin C quartiles; eGFR ≥60 vs eGFR <60	7.4	No association between incidence or prevalence of AF and eGFR; two highest quartiles of cystatin C levels were each associated with a 1.5-fold increased risk of

					incident AF (reference Quartile 1); no association between prevalence of AF and cystatin C levels
Iguchi, 2008 [24]	Population-based cohort	41,417	eGFR tertiles	NA	Higher prevalence of AF with decreasing eGFR tertiles; OR 1.91 (95% CI of 1.54 - 2.38) in the lowest tertile compared to the highest tertile
Bansal, 2016 [27]	CKD without AF and ESRD	3,091	Incident AF vs no incident AF	5.9	Incident AF in CKD was associated with a 3.2-fold increased risk of developing ESRD requiring RRT or kidney transplant
Bansal, 2013 [19]	eGFR <60 without AF and ESRD	206,229	Incident AF vs no incident AF; eGFR 45-59 vs eGFR 30-44 vs eGFR 15-29 vs eGFR <15; dipstick albuminuria	5.1	Incident AF in CKD was associated with a 1.7-fold increased risk of developing ESRD requiring RRT or kidney transplant; dose-response relation between incident AF and both worsening eGFR and albuminuria
Watanabe, 2009 [26]	Population-based cohort	235,818	Incident AF vs no incident AF; eGFR ≥60 vs eGFR 30-59 vs eGFR <30	5.9	Incident AF was associated with a 3-fold increased risk developing CKD; higher incidence of AF with worsening eGFR

AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RRT, renal replacement therapy.

Table 3. Effects of VKA on stroke risk in AF and dialysis-dependent ESRD

Study, year (ref)	Dialysis type	Prospective or retrospective	n (% VKA)	Outcome measure(s)	Finding(s) for VKA vs no VKA (95% CI and *p* values where provided)
Tan, 2019 [134]	Any dialysis	Retrospective	5,765 (29%)	Any stroke Ischaemic stroke	HR 0.91 (0.75 - 1.10) HR 0.87 (0.70 - 1.09)
Phan, 2019 [133]	PD	Retrospective	476 (24%)	Ischaemic stroke	HR 2.30 (0.94 - 5.40, *p* = 0.07)
Yoon, 2017 [135]	HD	Retrospective	9,974 (29%)	Ischaemic stroke Haemorrhagic stroke	HR 1.06 (0.90 - 1.26, *p* = 0.47) HR 1.44 (1.09 - 1.91, *p* = 0.01)
Kai, 2017 [148]	HD	Retrospective	4,286 (23%)	Ischaemic stroke	HR 0.76 (0.69 - 0.84)
Tanaka, 2016 [136]	Any dialysis	Prospective	93 (49%)	Ischaemic stroke rate	VKA: 4.3% No VKA: 4.3% (*p* = 0.982)
Yamashita, 2016 [132]	Any dialysis	Prospective	92 (38%)	Any stroke or SE	HR 0.26 (0.01 - 1.52)
Yodogawa, 2016 [131]	HD	Retrospective	84 (36%)	Any stroke	HR 1.07 (0.20 - 5.74)
Wang, 2016 [130]	Any dialysis	Retrospective	141 (42%)	Ischaemic stroke rate	VKA: 8.5% No VKA: 12.2% (*p* = 0.59)
Chan, 2016 [147]	PD	Prospective	271 (25%)	Ischaemic stroke	HR 0.19 (0.06 - 0.65, *p* = 0.01)
Garg, 2016 [144]	HD	Retrospective	302 (39%)	Ischaemic stroke	HR 0.93 (0.49 - 1.82, *p* = 0.88)
Genovesi, 2015 [143]	HD	Prospective	290 (46%)	Ischaemic stroke or TE	HR 0.12 (0 - 3.59, *p* = 0.20)
Findlay, 2015 [142]	HD	Retrospective	293 (40%)	Any stroke rate	VKA: 14.4% No VKA: 11.4% (*p* = 0.45)
Shen, 2015 [146]	HD	Retrospective	12,284 (15%)	Any stroke Ischaemic stroke	HR 0.83 (0.61 - 1.12) HR 0.68 (0.47 - 0.99)
Wakasugi, 2014 [141]	HD	Prospective	60 (47%)	Ischaemic stroke	HR 3.36 (0.94 - 11.23)
Shah, 2014 [140]	Any dialysis	Retrospective	1,626 (46%)	Ischaemic stroke, TIA or retinal infarct	HR 1.14 (0.78 - 1.67)
Bonde, 2014 [139]	Any	Retrospective	1,728 (NA)	Any stroke or TE rate/100 PYs	VKA: 4.8 (3.2 - 6.4)

	dialysis or prior kidney transplant			(CHA_2DS_2-VASc score ≥2) Any stroke or TE rate/100 PYs (CHA_2DS_2-VASc score of 1)	No VKA: 7.3 (6.2 - 8.5) VKA: 3.3 (0.8 - 5.7) No VKA: 2.8 (1.6 - 4.1)
Chen, 2014 [138]	Any dialysis or prior kidney transplant	Retrospective	4,899 (6%)	Ischaemic stroke or TIA (VKA vs no anti-thrombotics) Ischaemic stroke or TIA (VKA vs no antiplatelets)	HR 0.77 (p = NS) HR 0.82 (p = NS)
Olesen, 2012 [110]	Any dialysis or prior kidney transplant	Retrospective	901 (25%)	Any stroke or systemic TE (VKA vs no VKA) Any stroke or systemic TE (VKA with aspirin vs neither)	HR 0.44 (0.26 - 0.74, p = 0.002) HR 0.82 (0.37 - 1.80, p = 0.62)
Winkelmayer, 2011 [137]	HD	Retrospective	1,185 (20%)	Ischaemic stroke Haemorrhagic stroke	HR 0.92 (0.61 - 1.37) HR 2.38 (1.15 - 4.96)
Wizemann, 2010 [108]	HD	Prospective	3,245 (16%)	Any stroke (according to age categories)	≤65 years: HR 1.29 (0.45 - 3.68) 66 - 75 years: HR 1.35 (0.69 - 2.63) ≥75 years: HR 2.17 (1.04 - 4.53)
Lai, 2009 [145]	HD	Retrospective	93 (55%)	TE stroke rate	VKA: 10% No VKA: 38% (p < 0.005)
Chan, 2009 [149]	Incident HD	Retrospective	1,671 (45%)	Any stroke rate/100 PYs Any stroke	VKA: 7.1 (5.7 - 8.7) No VKA: 2.9 (2.0 - 4.4) HR 1.74 (1.11 - 2.72)
Wiesholzer, 2001 [129]	HD	Retrospective	61 (22%)	Any stroke rate/100 PYs	VKA: 4.46 (-1.54 - 10.46) No VKA: 1.00 (-0.95 - 2.95)

AF, atrial fibrillation; CI, confidence interval; ESRD, end-stage renal disease; HD, haemodialysis; HR, hazard ratio; NA, not available; NS, not significant; PD, peritoneal dialysis; PYs, patient-years; SE, systemic embolism; TE, thromboembolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Table 4. Effects of VKA on stroke risk in AF and non-dialysis-dependent CKD

Study, year (ref)	Study population	Prospective or retrospective	n (% VKA)	Outcome measure(s)	Finding(s) for VKA vs no VKA (95% CI and *p* values where provided)
Kumar, 2018 [163]	eGFR <50	Retrospective	4,868 (50%)	Ischaemic stroke or TIA	HR 2.60 (2.00 - 3.38)
Jun, 2017 [166]	Any eGFR	Retrospective	7,750 (50%)	Ischaemic stroke or TIA (according to eGFR categories)	eGFR ≥60: HR 1.20 (0.68 - 2.12) eGFR 45 - 59: HR 0.69 (0.50 - 0.96) eGFR 30 - 44: HR 0.57 (0.37 - 0.88) eGFR <30: HR 0.44 (0.22 - 0.91)
Keskar, 2017 [165]	eGFR <45	Retrospective	2,834 (50%)*	Ischaemic stroke or TIA	HR 1.59 (1.34 - 1.90)
Bonde, 2016 [167]	Any eGFR	Retrospective	14,827 (44%)	Ischaemic stroke, TIA or TE (according to eGFR categories)	eGFR 60 - 89: HR 0.57 (0.51 - 0.64) eGFR 30 - 59: HR 0.0.48 (0.44 - 0.54) eGFR 15 - 29: HR 0.60 (0.45 - 0.80) eGFR <15: HR 1.18 (0.58 - 2.40)
Friberg, 2015 [168]	Any eGFR	Retrospective	13,435 (28%)	Ischaemic stroke rate/100 P-Y	VKA: 2.7 (2.3 - 3.1) No VKA: 4.6 (4.2 - 4.9)
Bonde, 2014 [139]	Any eGFR	Retrospective	11,128 (NA)	Any stroke or TE rate/100 PYs (CHA_2DS_2-VASc score ≥2) Any stroke or TE rate/100 PYs (CHA_2DS_2-VASc score of 1) Any stroke or TE rate/100 PYs (CHA_2DS_2-VASc score of 0)	VKA: 5.8 (5.1 - 6.4) No VKA: 7.2 (6.7 - 7.7) VKA: 1.8 (0.7 - 2.8) No VKA: 1.5 (0.9 - 2.2) VKA: 1.3 (0 - 3.7) No VKA: 2.1 (0.9 - 3.4)
Olesen, 2012 [110]	Any eGFR	Retrospective	3,587 (25)	Any stroke or systemic TE (VKA vs no VKA) Any stroke or systemic TE (VKA with aspirin vs neither)	HR 0.84 (0.69 - 1.01, *p* = 0.07) HR 0.76 (0.56 - 1.03, *p* = 0.08)
Lai, 2009 [145]	eGFR <60	Retrospective	306 (59%)	TE stroke rate (eGFR <15) TE stroke rate	VKA: 11% No VKA: 33% (*p* = NA) VKA: 5%

	(eGFR 15 - 29)	No VKA: 21% ($p < 0.05$)
	TE stroke rate	VKA: 10%
	(eGFR 30 - 59)	No VKA: 20% ($p < 0.05$)

AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NA, not available; PYs, patient-years; TE, thromboembolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

* Few (<5%) on low-molecular weight heparin or non-vitamin K oral antagonist

Figure Legends

Figure 1. Distribution of renal function in landmark trials of non-vitamin K oral antagonists

Figure 2. Comparison of international guidelines on anticoagulation in atrial fibrillation and chronic kidney disease. (ACC/AHA/HRS, American College of Cardiology/American Heart Association/Heart Rhythm Society; AF, atrial fibrillation; ASA, acetylsalicylic acid; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ESRD, end-stage renal disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes)

Central Illustration. Pathophysiology of atrial fibrillation and chronic kidney disease with the effects on thromboembolic complications and management. (AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; CRP, C-reactive protein; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IL-6, interleukin-6; RAAS, renin-angiotensin-aldosterone system; TNF-α, tumour necrosis factor alpha; VHD, valvular heart disease.

Figure 1

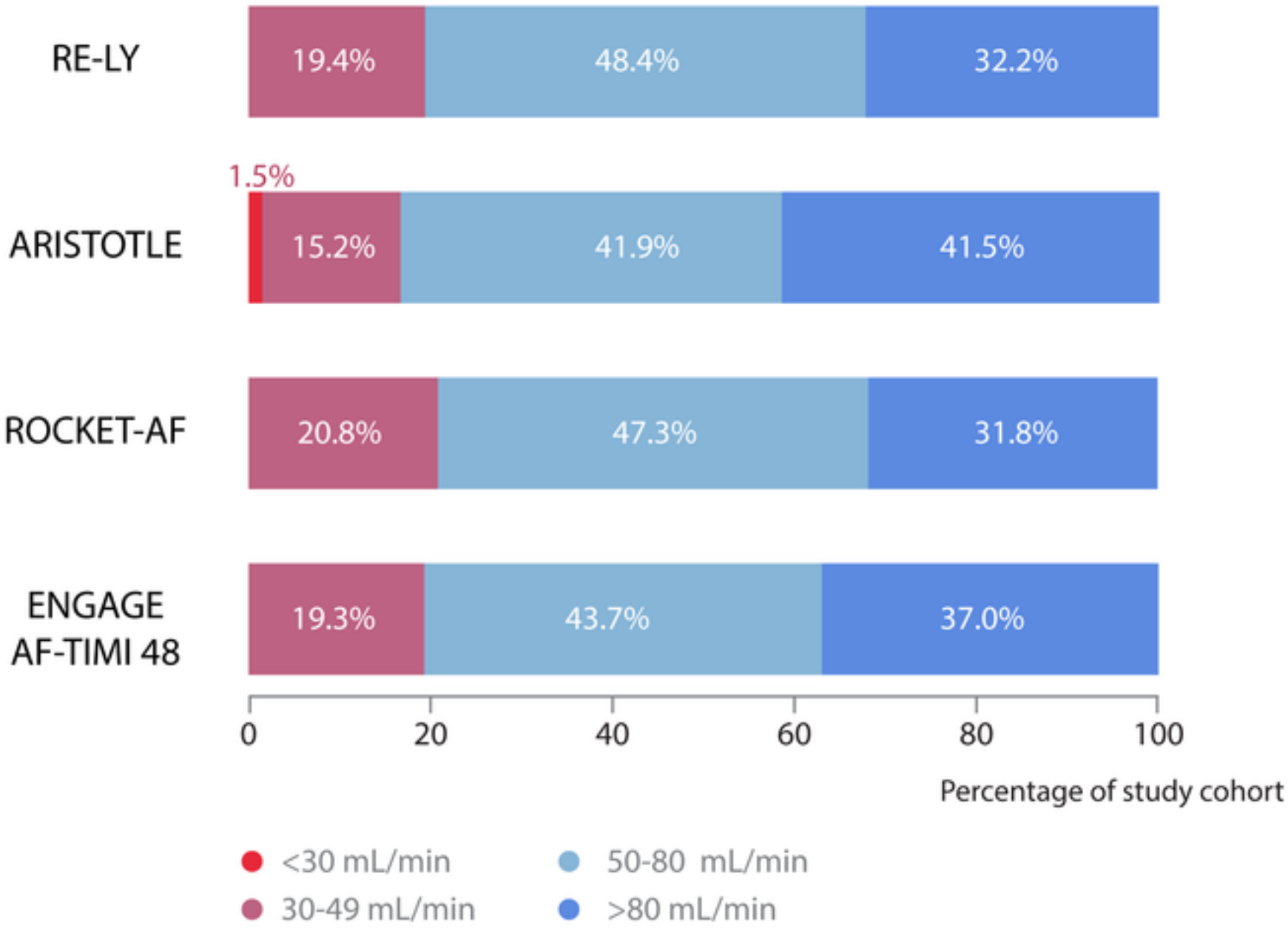

Figure 2

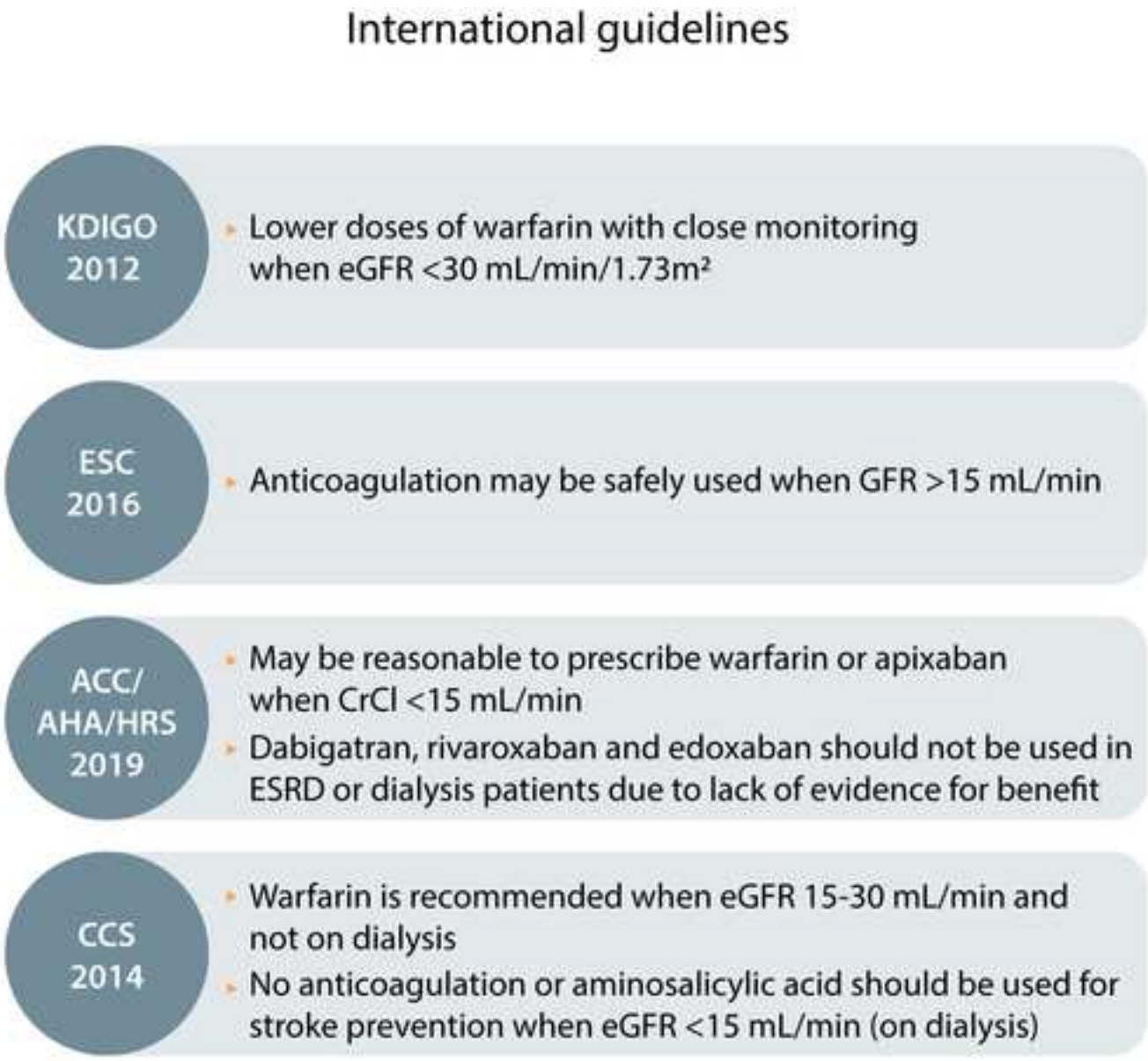

Figure 3