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Review Article

Anticoagulation for Atrial Fibrillation in End-stage Kidney Disease

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia in the general population and it has been found to have a higher prevalence in end-stage kidney disease (ESKD). It is associated with a higher risk of stroke and mortality compared to those without AF. Patients with ESKD have generally been excluded from randomized controlled trials (RCTs) evaluating the efficacy of anticoagulation in reduction of stroke risk. Current observational evidence for anticoagulation for AF in the ESKD population has yielded conflicting results, but in aggregate favours a lack of benefit in stroke risk reduction with an increase in bleeding risk. There are also reports that warfarin use in ESKD patients on dialysis is associated with greater International Normalised Ratio (INR) variability and increased risk of vascular calcification and calciphylaxis (uraemic calcific arteriolopathy). RCTs are required to assess the net clinical benefit of anticoagulation in this group.

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the general population, and the incidence is appreciably higher in patients with end-stage kidney disease (ESKD). A meta-analysis of twenty-five studies found the prevalence of AF in ESKD patients to be 11.6% and overall incidence to be 2.7/100 patient years (1). The prevalence appears to be increasing over time, with one analysis from the United States Renal Data System (USRDS) showing a three-fold increase in prevalence from 1992 to 2006 (2). This may reflect the increasing age and comorbidity burden in the dialysis population. The risks of mortality and stroke are significantly increased in ESKD patients with AF (26.9 and 5.2 per 100 patient-years, respectively) compared to those without (13.4 and 1.9 per 100 patient-years) (1). In the general population, systemic anticoagulation is typically indicated for reduction of stroke risk (3), but the benefit-to-risk ratio is uncertain in the ESKD population given the

lack of randomized controlled trial (RCT) evidence. In this review, we will discuss the observational data pertaining to the effect of warfarin on stroke and bleeding risk in ESKD patients and the need for a high quality RCT to address this controversial issue.

Risk of AF in CKD

The prevalence of AF in the general population is approximately 1%, although it appears to increase markedly with advancing age to a prevalence of 9-18% in individuals aged 80 years or older (4, 5). Patients with ESKD on dialysis are reported to have a prevalence of AF from 7-27% (6-9). Many of the risk factors for AF in the general population are also common in the dialysis population, including obesity, hypertension and heart failure (10). The inverse relationship between AF and renal function has been demonstrated in several population-based studies (11, 12). The Atherosclerosis Risk in Communities (ARIC) study found hazard ratios of 1.3, 1.6 and 3.2 in patients with cystatin C-based estimated glomerular filtration rate (eGFR) values of 60-89, 30-59 and 15-29mL/min, respectively, compared to the reference population (eGFR ≥90mL/min) (11). The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study similarly reported age-, race- and sex-adjusted odds ratios for prevalent AF to be 2.67, 1.68 and 3.52 for those with stage 1 to 2, stage 3 and stage 4 to 5 chronic kidney disease (CKD), respectively (12).

Stroke risk in AF in the dialysis population

CKD has been shown to be a risk factor for stroke in several studies. Holzmann et al. performed a very large longitudinal study of 539287 patients with 12 years of follow-up, and found an increase in ischaemic stroke risk with worsening CKD (HR 1.09, 95% CI 1.04-1.14 for stage 2 CKD; HR 1.24, 95% CI 1.10-1.39 for stage 3 CKD and HR 2.27, 95% CI 1.63-2.27 for stage 4 CKD) (13). In a USRDS report, the annual stroke incidences in matched non-CKD, CKD and HD patients were 2.6%, 9.6% and 15.1%, respectively (14).

In the general population, the absolute risk of stroke can be estimated with the CHADS2 score, or more recently the CHA2DS2-VASc score (15). The CHA2DS2-VASc score can be calculated by assigning points for Congestive heart failure (1 point); Hypertension (1 point); Age ≥75 years (2 points); Diabetes mellitus (1 point); prior Stroke, transient ischaemic attack or thromboembolism (2 points), Vascular disease (1 point), Age 65-74 years (1 point) and Sex category (female 1 point).

In the absence of a specific tool validated to assess stroke risk in the dialysis population, several studies have suggested a correlation between higher CHADS2 score and stroke risk in this group (8, 16-18). Olesen et al. found the unadjusted incidence of stroke to be 1.99, 2.35 and 3.55 events per 100 person-years in dialysis patients with CHADS2 scores of 0, 1 and 2, respectively (16). Of note, the stroke risk in every category of CHADS2 score was higher than a comparison group of non-dialysis patients with AF, suggesting the CHADS2 score may underestimate stroke risk in dialysis patients.

Warfarin in dialysis patients

Warfarin (Wisconsin Alumni Research Foundation coumARIN) is a vitamin K antagonist that inhibits vitamin K epoxide reductase, interfering with the production of vitamin K-dependent coagulation factors II, VII, IX and X, protein C and protein S (19). There is reasonable evidence that warfarin may accelerate vascular calcification in dialysis patients, potentially via antagonism of the vitamin K-dependent matrix G1a protein (MGP), a potent inhibitor of vascular calcification. Mice that lack MGP were found to die within two months of birth due to severe arterial calcification leading to vessel rupture (20). In humans, a loss-of-function mutation in the gene encoding MGP (Keutel syndrome) leads to widespread large vessel vascular calcification and abnormal cartilage calcification (21).

The effect of warfarin on MGP and vascular calcification has been demonstrated in a mouse model, where administration of warfarin was found to induce arterial medial calcification, associated with a reduction in

MGP mRNA expression, which could be reversed with vitamin K treatment (22). McCabe et al. (23) similarly reported increased vascular calcification in rats with CKD on warfarin, which was also blunted by vitamin K. In a retrospective study of 108 haemodialysis (HD) patients, an association was found between duration of warfarin exposure and degree of aortic valve calcification after adjustment for dialysis vintage, calcium and calcitriol intake (24). Furthermore, a recent Japanese study found an 11-fold risk in HD patients on warfarin for calciphylaxis (uraemic calcific arteriolopathy), an uncommon complication of ESKD characterised by skin ulceration and necrosis with small vessel medial calcification and intimal proliferation (25).

The time in therapeutic range (TTR) of the international normalised ratio (INR) is an important predictor of warfarin efficacy and safety in the general population (26). A systematic review of 47 studies reporting INR control found approximately 60% of INR measurements to be within the therapeutic range (27). Patients on HD tend to have lower warfarin dose requirements and greater INR variability (28). To further add to this unpredictability, anticoagulation catheter-locking solutions may interfere with INR measurement when samples are collected from the catheter directly (29). Two studies have attempted to reduce INR variability with daily low-dose vitamin K supplementation (30) and thrice-weekly post-HD warfarin dosing (31). Both interventions were associated with modest improvements in TTR but their effects on bleeding risk remained unclear.

Uncertainty of warfarin net benefit

Warfarin and, to a lesser extent, antiplatelet agents have been found to reduce the stroke risk in patients with AF. A 2007 meta-analysis of 29 trials including 28044 patients found relative reductions in stroke risk of 64% with warfarin and 22% with antiplatelet agents (3). The 2014 ACC/AHA (American College of Cardiology/American Heart Association) guideline for management of patients with atrial fibrillation recommends oral anticoagulation if the CHA2DS2-VASc score is two or greater (32). The guideline extends this recommendation to patients with ESKD on haemodialysis. However, there have been no RCTs (RCTs) investigating the benefit of anticoagulation for stroke risk in the ESKD population, who have largely been excluded from the trials in the general population. Consequently, the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (33, 34) caution that, given the lack of RCTs, the risk-to-benefit ratio of routine anticoagulation for primary or secondary prevention of stroke remains uncertain. More recently, the International Society for Peritoneal Dialysis (ISPD) Cardiovascular Guidelines suggest "individualization of warfarin prescription for prevention of stroke in peritoneal dialysis patients with atrial fibrillation in view of an increased risk of bleeding and uncertain effects on cerebrovascular outcomes. (2D)" (35, 36).

Clinical equipoise exists among nephrologists regarding the benefit-to-risk ratio of anticoagulation for stroke risk reduction in the dialysis population. A survey of 56 Canadian nephrologists found agreement in the majority (72%) that there was a state of uncertainty regarding this clinical question (37). Each nephrologist was presented six clinical scenarios and given a choice as to whether they were likely to start warfarin, unlikely to start warfarin or were uncertain. The level of uncertainty increased when a patient was on haemodialysis and when risk factors for bleeding were present, including a history of gastrointestinal bleeding or a risk for falls.

Stroke and bleeding risk with warfarin

In the absence of a RCT addressing the net benefit of warfarin for AF in ESKD patients, the best available data so far remains observational in nature. Chan et al. performed a retrospective cohort analysis of 1671 incident HD patients with atrial fibrillation followed up for a mean of 1.6 years (38). The use of warfarin was associated with an increased risk of stroke (hazard ratio [HR] 1.93, 95% CI 1.29-2.90) after Cox regression analysis, and propensity matching did not significantly affect the findings of the analysis. There was a four-fold increase in mortality from stroke (p=0.009) and increase in hospitalisation from stroke (HR 1.89, 95% CI 1.16-3.09), but no significant difference in rates of

hospitalisation for bleeding (HR 1.04, 95% CI 0.73-1.46). The classification of haemorrhagic stroke as a stroke outcome in this study may have partially accounted for the reported increase in stroke risk.

Wizemann et al. sampled 2188 patients with AF out of 17513 HD patients from the international Dialysis Outcomes and Practice Patterns Study (DOPPS) (8). They found a significant association between warfarin and increased stroke risk in patients aged over 75 years, with reported hazard ratios of 1.29 (95% CI 0.45-3.68), 1.35 (95% CI 0.69-2.63) and 2.17 (95% CI 1.04-4.53) in the patient groups aged <65, 66-75 and >75 respectively. Patients with a CHADS2 score of 3 or greater on warfarin were also found to have higher stroke risk, although this finding was explained by the age component of the score rather than the other variables. Bleeding risk data were not provided in this study.

Phelan et al. compared stroke and bleeding risks in 141 HD patients on warfarin, 704 HD patients not on warfarin and 3266 non-dialysis patients on warfarin (28). In the patients with AF, the HD warfarin group had a higher risk of ischaemic stroke than the non-dialysis warfarin group (2.2 vs 0.4 events per 100 person-years, p=0.024). The incidence of major haemorrhage per 100 patient-years was significantly greater in the HD warfarin group (10.8) compared to 2.1 in the non-HD warfarin group (p<0.001), but similar to the HD non-warfarin group (8.0, p=0.593).

In contrast, Winkelmayer et al. evaluated outcomes in HD patients with incident AF rather than pre-existing AF by use of an inception cohort of older patients aged 66 years or older at the time of dialysis commencement (39). They identified 2313 patients with new AF who survived at least 30 days from discharge, and compared 237 patients started on warfarin within 30 days of discharge with 948 propensity-matched patients not on warfarin. There was no significant difference in ischaemic stroke risk (HR 0.92, 95% CI 0.61-1.37) but the risk of haemorrhagic stroke was doubled in the warfarin group (HR 2.38, 95% CI 1.15-4.96). The use of an inception cohort and new-user design may have reduced bias related to variations in risk with disease duration or medication (40), which may have accounted for the difference in reported ischaemic stroke risk compared to the previous three studies. The risk of mortality and gastrointestinal bleeding was similar between the two groups. The unexpected lack of association between warfarin and increased gastrointestinal bleeding risk may have been explained by the wide use of gastroprotective medication in the cohort, with 70% of patients being on a proton-pump inhibitor or histamine-2 antagonist.

Olesen et al. searched Danish national registries to identify 901 patients requiring renal replacement therapy (RRT) discharged from hospital with a diagnosis of nonvalvular atrial fibrillation between 1997 and 2008 (16). Warfarin use was associated with a lower risk of stroke or systemic thromboembolism (HR 0.44, 95% CI 0.26-0.74, p=0.002), but was not associated with bleeding risk (HR 1.27, 95% CI 0.91-1.77, p=0.15). The finding of reduced stroke risk may have been explained by the inclusion in the study group of peritoneal dialysis (PD) patients and kidney transplant recipients, who may have had different risk-to-benefit profiles on warfarin compared to HD patients. Alternatively, the results may have been confounded by indication.

Wakasugi et al. performed a prospective multicenter cohort study of 60 Japanese HD patients with chronic sustained AF (18). They found no difference in the incidence of new ischaemic stroke between 28 warfarin users and 32 non-warfarin users (HR 3.36, 95% CI 0.94-11.23) after adjustment for CHADS2 score. There was also no difference in major bleeding risk (HR 0.85, 95% CI 0.19-3.64) or all-cause mortality (HR 1.00, 95% CI 0.40-2.52). Although the sample size was limited, this study provides further evidence towards the lack of benefit of warfarin for stroke risk in HD patients with AF.

Shah et al. conducted a population based retrospective cohort study of 1626 Canadian dialysis (HD and PD) patients aged 65 years or older admitted to hospital with a diagnosis of AF (17). After adjustment for potential confounders, warfarin was not

associated with risk of stroke (HR 1.14, 95% CI 0.78-1.67) but was associated with higher bleeding risk (HR 1.44, 95% CI 1.13-1.85). Although this study had a large sample size, a major limitation was the inclusion criterion used to identify dialysis patients, defined as patients who had undergone three or more haemodialysis or peritoneal dialysis procedures in the prior year, which may have included a significant number of patients with acute kidney injury. Furthermore, patients were assigned to the warfarin group if they filled a prescription for warfarin in the first 30 days after discharge, and the duration of warfarin use was not captured.

A meta-analysis by Li et al. (41) of six observational cohort studies (8, 16-18, 38, 39) provides the highest level of evidence so far until a RCT can be implemented. For the assessment of stroke risk, a total of 9816 participants from the six studies were included with 2466 of these patients on warfarin. No significant association was observed between warfarin use and the risk of stroke (HR 1.23, 95% CI 0.80-1.87, p=0.347), although the validity of this result is questionable in view of the statistically significant, high-level trial heterogeneity that was identified (I2=79.2%, p=0.000). A subgroup analysis of the four trials that included only HD patients found an increase in stroke risk with warfarin use (HR 1.57, 95% CI 1.09-2.25, p=0.015). For the assessment of bleeding risk, a total of 6571 patients in five studies were included with 1957 of these patients on warfarin. The fixed-effects model was used due to the absence of significant heterogeneity (I2=20.4%, p=0.285) and found that warfarin significantly increased bleeding risk (HR=1.20, 95% CI 1.03-1.39, p=0.019).

Although the accumulating evidence suggests an absence of benefit for stroke risk for ESKD patients on warfarin and perhaps even an increased stroke risk in HD patients, several limitations exist. Due to the observational nature of the data, indication bias with residual confounding cannot be excluded. Patients on warfarin were likely to have a higher risk of stroke, as assessed by their clinician, and this may not have been fully adjusted for by covariates. The use of registry data may have led to ascertainment bias, whereby more severe stroke or bleeding events were preferentially recorded. Previous warfarin use was not ubiquitously recorded and patients who had previously ceased warfarin therapy due to a bleeding event may have been included in the non-warfarin group. Finally, there was significant heterogeneity in stroke risk among the six studies included in the meta-analysis, which may be accounted for by differences in study design, study population and covariate adjustment.

Use of newer anticoagulants

The novel oral anticoagulants include the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors, apixaban and rivaroxaban. Several recent large RCTs have shown these agents to be non-inferior to warfarin for stroke risk reduction in patients with AF (42-44). The use of these drugs in ESKD patients appears to be steadily rising, with one recent study by Chan et al. reporting 5.9% of anticoagulated HD patients on dabigatran or rivaroxaban (45). Despite this, there are significant concerns with the use of the novel anticoagulants in ESKD. Firstly, patients with moderate to severe CKD have generally been excluded from these trials, so there are no data to support the efficacy of these agents in this population. Secondly, there are no effective options for anticoagulation reversal in the setting of major bleeding or requirement for an urgent surgery, except for dabigatran, for which idarucizumab has been found to rapidly and effectively reverse the anticoagulant effect (46). Finally, these drugs are invariably excreted renally to some extent, which can lead to accumulation in patients with CKD. The study by Chan et al. found a higher risk of hospitalization or death from bleeding with dabigatran (HR 1.48, 95% CI 1.21-1.81) or rivaroxaban (HR 1.38, 95% CI 1.03-1.83) compared to warfarin in anticoagulated HD patients (45).

Dabigatran is primarily renally excreted, with 80-85% of the drug excreted unchanged in the urine. The half-life of the drug increases from 9 hours with normal renal function to 25-30 hours in patients with creatinine clearance <30mL/min (47). It is dialysable, with 50-60% of the drug removed after a 4 hours of haemodialysis (48). Rivaroxaban undergoes 33% renal

excretion via proximal tubule secretion, but is not dialysable due to 92-95% protein binding (49).

Apixaban is 27% excreted as unchanged drug in the urine and 14% of the drug is removed via dialysis (50). A single dose pharmacokinetic study of apixaban compared eight HD patients with eight controls with normal renal function and found a 36% increase in area under the curve (AUC) (51). Following this study, FDA labeling for the product changed from "no data to inform the use of patients with creatinine clearance <15mL/min or on dialysis" to a recommended dose in ESKD of 5mg twice daily or 2.5mg twice daily if the patient is aged over 80 years or body weight is less than 60kg (50). However, the pharmacokinetics of cumulative drug dosing remains to be evaluated, and there are currently no data on bleeding risk or efficacy in this population.

Need for a RCT

Given the uncertainty that exists regarding the benefit-to-risk ratio of anticoagulation for AF in ESKD patients, a high-quality RCT is required to answer this clinical question. Previous observational studies have yielded conflicting results and in aggregate have shown no reduction in stroke risk but an increase in bleeding risk. Although there is clear evidence for the benefit of warfarin for stroke risk reduction in the general population (3) and evidence that this benefit extends to stage 3 CKD (52), it cannot reasonably be extrapolated to the ESKD group. As an example highlighting this point, another intervention commonly used in the CKD population, HMG-CoA reductase inhibitor (statin) therapy for cardiovascular risk reduction, was found to significantly reduce risk of death and major cardiovascular events in patients with CKD not requiring dialysis (53), but this benefit did not extend to patients on dialysis (54).

Several challenges arise in designing and implementing a RCT on warfarin use in HD. Firstly, it may be considered unethical to randomise patients to the use of warfarin if previous observational data have shown a clear increase in bleeding risk without a significant benefit in stroke risk. However, there remains a degree of uncertainty as to the net benefit, and a rigorous RCT would provide a higher level of evidence to answer this question than the previous observational studies (55). Secondly, nephrologists and patients may have strong preferences for or against anticoagulation that may limit recruitment, although in a Canadian survey of nephrologists, the majority indicated that they would be willing to enroll their patients in such a trial (37). Finally, funding is unlikely to come from the pharmaceutical industry as generic warfarin is cheap and bioequivalent to brand-name warfarin (56), so it would likely need to be sourced publicly. An alternative would be a randomised placebo-controlled trial of one of the newer oral anticoagulants.

In conclusion, patients with ESKD have generally been excluded from RCTs of anticoagulation for AF, although the risks of AF and stroke have been found to be higher in this population. Several considerations arise when prescribing warfarin in ESKD patients, including greater INR variability and increased risk of vascular calcification and calciphylaxis. Numerous observational studies have failed to identify an association between warfarin use and risk of stroke, but have identified a clear association with heightened bleeding risk. There is a need for a RCT to answer this clinical question, although several financial and ethical barriers need to be overcome to implement such a trial.

Conflict of Interest

David Johnson has received consultancy fees, research funds, travel sponsorships and speaker's honoraria from Fresenius Medical Care and Baxter Healthcare. Gavin Lee declares no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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