The atrial fibrillation conundrum in dialysis patients

An S. De Vriese, MD, PhD,[a] Rogier Caluwé, MD,[b] and Paolo Raggi, MD, PhD[c] *Brugge, Belgium; OLVZ Aalst, and Alberta, Canada*

Abstract The burden of atrial fibrillation (AF) and the risk of stroke are high in dialysis patients. The decision to use anticoagulation rests heavily on effective risk stratification. Because both the pathophysiology of the disease and the response to therapy differ in dialysis, data from the general population cannot be extrapolated. The effect of vitamin K antagonists (VKAs) on the risk of stroke in dialysis patients with AF has not been studied in randomized trials. The available observational data provide contradictory results, reflecting differences in the degree of residual confounding, quality of international normalized ratio control, and stroke characterization. Dialysis patients have a high baseline bleeding risk. It remains unclear to what extent VKAs affect the overall bleeding propensity, but they may significantly increase the risk of intracerebral hemorrhage. Vascular calcifications are extremely prevalent in dialysis patients and independently associated with an adverse outcome. Vitamin K antagonists inhibit the activity of key anticalcifying proteins and may thus compound the risk of vascular calcification progression in dialysis. In the absence of evidence-based guidelines for anticoagulation in dialysis patients with AF, we provide recommendations to assist clinicians in individualized risk stratification. We further propose that new oral anticoagulants may have a better benefit-risk profile in dialysis patients than VKA, provided appropriate dose reductions are made. New oral anticoagulant may yield more on-target anticoagulation, reduce the risk of intracerebral bleeding, and not interfere with vascular calcification biology. Clinical trials with new oral anticoagulant in dialysis patients are eagerly awaited, to reveal whether these assumptions can be confirmed. (Am Heart J 2016;174:111-119.)

Atrial fibrillation (AF) is very common in dialysis patients and its prevalence has risen substantially over the past few decades,[1] mainly reflecting the increasing age and comorbid conditions of the dialysis population. In accordance with recent guidelines,[2] a sizable proportion of these patients are treated with vitamin K antagonists (VKAs), with the intention to reduce the risk of stroke and systemic embolism. However, evidence is mounting that the benefit-risk ratio of VKA and patient risk stratification tools applicable to the general population may not be extrapolated to patients with end-stage renal disease (ESRD). Concerns about the use of VKA in dialysis patients have been mainly ventilated in the nephrology literature, although VKAs are preferentially prescribed by cardiologists. The present in-depth review intends to give a balanced account of the risks and benefits of VKA specifically in the dialysis population, highlighting 3 main aspects: protection against stroke, risk of major bleeding and in particular intracerebral hemorrhage, and progression of vascular calcifications.

Epidemiology and pathophysiology of AF in dialysis patients

A systematic review including 25 studies in patients with ESRD reported an average prevalence of 11.6% (range 5.4%-27%) and incidence of 2.7/100 patient-years (range 0.97-5.9/100 patient-years) of AF.[3] This wide scatter is undoubtedly related to the variability in age distribution and racial composition of the study population and to the AF identification strategies. Because two-thirds of AF in dialysis may be paroxysmal[3] and several studies only reported symptomatic episodes, the true incidence of AF in this population may be largely underestimated.

Age is one of the most important risk factors for development of AF, with an increase in odds of 25% per 5-year increments.[4] However, the occurrence of AF in dialysis patients markedly exceeds that in the general population for each age category,[4] in large part due to the high burden of comorbid conditions known to be associated with AF. For instance, patients 67 years or older when initiating dialysis had an incidence of AF of 14.8/100 patient-years,[1] as compared with 2.8/100

From the [a]Division of Nephrology and Infectious Diseases, AZ Sint-Jan Brugge, Brugge, Belgium, [b]Division of Nephrology, OLVZ Aalst, Belgium, and [c]Division of Cardiology and Department of Medicine, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada.

Submitted October 22, 2015; accepted January 16, 2016.

Reprint requests: An S. De Vriese, MD, PhD, Division of Nephrology and Infectious Diseases, AZ Sint-Jan Brugge, Ruddershove, 10, B-8000, Brugge, Belgium.
E-mail: an.devriese@azsintjan.be

0002-8703

http://dx.doi.org/10.1016/j.ahj.2016.01.010

patient-years in the general Medicare population in the same age range.[5] Blacks, Asians, Native Americans, and Hispanics are at substantially lower risk for incident AF compared with whites,[1] somewhat counterintuitively in view of the less favorable cardiovascular risk profiles of black and Hispanic patients, suggesting a role for genetic or epigenetic factors in the genesis of AF in dialysis.

Although chronic kidney disease (CKD) is a well-known risk factor for AF, incident AF is independently associated with a 67% higher rate of subsequent ESRD.[6] These observations highlight a bidirectional relationship between AF and CKD, fueled by inflammatory and profibrotic factors, neurohumoral activation, and altered hemodymamics. Finally, the hemodialysis procedure itself, with its periodic swings in fluid and electrolyte status, may be a risk factor for the onset of AF. Registration of the exact time of onset of AF, by continuous implantable cardioverter defibrillator monitoring, demonstrated that most episodes occurred during dialysis, especially toward the end of the procedure.[7] The occurrence of AF was associated with higher ultrafiltration rates and lower diastolic pressure after dialysis, suggesting a role of intravascular volume depletion.[7] In addition, dialysis induces a prolongation of the P-wave duration, a measure of intra-atrial conduction velocity, closely linked to the reduction of serum potassium concentration during the procedure.[8]

Epidemiology and pathophysiology of stroke in dialysis patients

Based on an overview of 20 studies in dialysis populations, the incidence of stroke can be estimated to be between 3.1 and 9.5/100 patient-years, and 71% to 87% of strokes can be characterized as ischemic.[9] Studies reporting on an exclusively Japanese population found a lower incidence, with a relatively higher proportion of hemorrhagic strokes.[9] The increased risk of stroke (up to 10 times higher than in the general population) obviously reflects the high burden of traditional stroke risk factors in the dialysis population, although emerging evidence reveals that CKD-specific risk factors, including mineral and bone disorders, chronic inflammation, and uremic toxins, may also play a role.[9] A particularly relevant question is whether in the dialysis population, AF poses a true risk of ischemic stroke and, as a consequence, whether (any form of) anticoagulation is warranted in these patients. It has been suggested that uremic platelet dysfunction and thrice-weekly systemic anticoagulation during dialysis protect against ischemic stroke in dialysis patients with AF. In addition, strokes are more likely to be hemorrhagic than in the general population. Although the association between stroke and AF appeared to be less apparent in some studies,[10] a meta-analysis of 13 studies reported an event rate of 5.2/100 patient-years in dialysis patients with AF vs 1.9/100 patient-years in those without AF.[3] Atrial fibrillation patients on renal replacement therapy not receiving VKA have a higher risk of stroke compared with AF patients without CKD, ranging from 5.5-fold in the low-risk to 1.6-fold in the high-risk CHA_2DS_2-VASc strata.[11] It would appear therefore that AF indeed causes ischemic stroke in dialysis patients, perhaps with a lower attributable risk than in the general population, which leads to the important question of risk stratification. Are the $CHADS_2$ and the CHA_2DS_2-VASc scores useful to stratify stroke risk in dialysis patients with AF and guide the decision to initiate anticoagulation? Although neither score has been formally validated in populations with CKD, both the $CHADS_2$[4,12] and the CHA_2DS_2-VASc score[13] were reported to adequately predict stroke risk in patients undergoing dialysis. However, a closer look at the data reveals a significant problem in applying these scores to ESRD patients. In a population of 10,999 Asian dialysis patients with AF perceived by physicians as being at low risk of stroke, less than 4% had a CHA_2DS_2-VASc score lower than 2.[13] Similarly, less than 10% of 12,284 US dialysis patients with newly diagnosed AF had a CHA_2DS_2-VASc score lower than 2.[14] In essence, the components of the CHA_2DS_2-VASc score (congestive heart failure, hypertension, advanced age, diabetes, previous stroke, vascular disease) are so prevalent in dialysis patients with AF, that most who would qualify for oral anticoagulation were the guidelines for the general population be extrapolated to ESRD. In our opinion, the current application of the CHA_2DS_2-VASc score does not adequately discriminate between dialysis patients deriving a net benefit and those suffering a net harm from anticoagulation. Perhaps the threshold for anticoagulation should be set higher than 2, the weight of certain components of the CHA_2DS_2-VASc score should be modified, and other more dialysis-specific factors should be taken into account.

Vitamin K antagonist and the risk of stroke in dialysis patients

In the general population with AF, VKAs are an extremely effective treatment, preventing nearly two-thirds of strokes with an acceptable risk of major bleeding.[15] In high-risk AF patients with stage 3 CKD, VKA have a similar efficacy for prevention of ischemic stroke with a low rate of major hemorrhage.[16] Such clear evidence derived from randomized controlled trials (RCTs) is absent in patients with ESRD. Observational studies[4,11,14,17–23] have yielded conflicting results (Table I) and generated clinical equipoise. A meta-analysis of 6 observational studies reported no benefit of VKA in ESRD,[24] but did not include a number of recent large studies.[11,14,18,22]

Observational studies inevitably suffer from confounding by indication. Patients at the highest risk for stroke receive anticoagulation; therefore, patients on VKA appear to have higher stroke rates. This was very nicely illustrated in the

Table I. Observational studies of VKA and the risk of stroke and/or death in patients undergoing renal replacement therapy

Study (reference)	Population	Outcome	HR (95% CI)
Benefit			
Olesen et al[17]	1074 hemodialysis, 212 peritoneal dialysis, 92 kidney transplant	Total stroke	0.44 (0.26-0.74)
Bonde et al[11]	1026 hemodialysis, 344 peritoneal dialysis, 25 kidney transplant with CHA_2DS_2-VASc score ≥2*	All cause mortality	0.85 (0.72-0.33)
Carrero et al[18]	478 post-MI with eGFR ≤15 mL/min	Composite of death, MI, ischemic stroke	0.57 (0.37-0.86)
Shen et al[14]	12,284 prevalent hemodialysis	Ischemic stroke	0.68 (0.47-0.99)
No benefit			
Wizemann et al[4]	1001 prevalent hemodialysis ≤65 y	Total stroke	1.29 (0.45-3.68)
	1137 prevalent hemodialysis 65-75 y	Total stroke	1.35 (0.69-2.63)
Winkelmayer et al[19]	2313 prevalent hemodialysis >65 y	Total stroke	1.08 (0.76-1.55)
		Ischemic stroke	0.92 (0.61-1.37)
		Hemorrhagic stroke	2.38 (1.15-4.96)
Wakasugi et al[20]	60 prevalent hemodialysis	Ischemic stroke	1.94 (0.63-5.93)
Shah et al[21]	1626 prevalent hemodialysis and peritoneal dialysis	Ischemic stroke	1.14 (0.78-1.67)
Genovesi et al[22]	290 prevalent hemodialysis	Ischemic stroke	0.12 (0.00-3.59)
Harm			
Chan et al[23]	1671 incident hemodialysis	Total stroke	1.93 (1.29-2.90)
		Ischemic stroke	1.81 (1.12-2.92)
		Hemorrhagic stroke	2.22 (1.01-4.91)
Wizemann et al[4]	1107 prevalent hemodialysis >75 y	Total stroke	2.17 (1.04-4.53)

A literature search was performed using the electronic databases PubMed, EMBASE, and the Cochrane Library Database to retrieve relevant articles from 1980 to September 2015. No language restrictions were applied. Keywords included were "atrial fibrillation"/"warfarin," "oral anticoagulation," "vitamin K antagonists," "thromboprophylaxis"/"dialysis," "hemodialysis," "end-stage renal disease," "chronic kidney disease"/"stroke." Guidelines from scientific committees and reference lists of identified studies were also reviewed for relevant publications.
Abbreviations: HR, hazard ratio; MI, myocardial infarction; eGFR, estimated glomerular filtration rate.
*A. Bonde, personal communication.

nondialysis CKD setting, where the 13% reduction in stroke reported by an observational trial[21] underestimated the 74% reduction observed in an RCT.[16] Even with sophisticated statistical methodology, unidentified and residual confounding remains, essentially because the simple prevalence of a risk factor (and not its severity, duration, and treatment) cannot capture the associated risk. Some studies included a small number of patients on peritoneal dialysis,[11,17,18,21] stage V CKD not yet on dialysis,[18] or kidney transplant recipients[11,17] besides most hemodialysis patients. Limited observational data suggest a benefit of VKA in peritoneal dialysis[25] and a neutral effect in transplant recipients.[26] It thus remains unclear if the heterogeneity of the CKD population included in various studies may have affected the outcome of the studies. Finally, absence of detailed stroke characterization and knowledge of the length of time the patient is in the therapeutic international normalized ratio (INR) range (TTR) further complicate the interpretation of the results. Intensity of anticoagulation is the most important predictor of VKA effectiveness and safety.[27] The cause of stroke could therefore have been inadequate as well as excessive anticoagulation in some of these studies. Indeed, a number of studies documented that dialysis patients on VKA experiencing a thromboembolic event had an INR less than 2.[20,22,28] Therefore, it may come as no surprise that studies reporting a benefit of VKA mainly have been performed in Scandinavian countries,[11,17,18] renowned for the quality of INR control.

Bleeding in dialysis patients

Impaired platelet function and routine trice-weekly administration of heparin significantly increase the bleeding risk in hemodialysis patients. Even in hemodialysis patients not taking antiplatelet agents or oral anticoagulants, the rate of bleeding requiring hospitalization is 4.9/100 patients-years.[12] None of the bleeding risk scores developed for the general population[29–31] (Table II) have been validated in dialysis patients. A review of the components of these risk scores reveals that most dialysis patients will fall in the high-risk categories, compromising the discriminative value in this specific population. However, history of gastrointestinal bleeding within the past 12 months was the strongest predictor of major future bleeding[12] and could therefore be used as a practical tool to stratify bleeding risk. Hemodialysis patients with a history of gastrointestinal bleeding had a very high rate of subsequent bleeding (nearly 20/100 patient-years) that substantially exceeded the stroke rate, even in those with a high estimated stroke risk.[12]

Bleeding complications with VKA in dialysis patients

In a large international cohort of hemodialysis patients, the use of oral anticoagulants was associated with a rate of bleeding requiring hospitalization of 7.8/100 patient-years,[12] to be compared with a rate of major bleeding of

Table II. Bleeding risk scores

Score acronym (reference)	Components	High risk
Modified Outpatient Bleeding Risk Index (mOBRI)[29]	Age >65 y (1), history of stroke (1), history of gastrointestinal bleeding (1), recent myocardial infarction (1), Hct <30% (1), Cr >1.5 mg/dL (1), diabetes (1)	Score ≥4
HEMORR$_2$HAGES[30]	Hepatic or renal disease (1), ethanol abuse (1), malignancy (1), age ≥75 y (1), reduced platelet count or function (1), rebleeding risk (2), hypertension (1), anemia (1), genetic factors (1), excessive fall risk (1), stroke (1)	Score ≥4
ATRIA Bleeding Risk Score[30]	Anemia (3), eGFR<30 mL/min (3), age ≥75 y (2), history of bleeding (1), hypertension (1)	Score ≥5
HAS-BLED Score[30]	Hypertension (1), abnormal renal (1) or liver (1) function, stroke (1), bleeding (1), labile INR (1), elderly—age >65 y (1), drugs (1) or alcohol (1)	Score ≥3
ORBIT Score[31]	Older age >74 y (1), reduced hemoglobin (2), bleeding history (2), insufficient kidney function (1), treatment with antiplatelets (1)	Score ≥4

approximately 2/100 patient-years in the general population using anticoagulants.[32] The existing literature consists exclusively of observational studies and is highly contradictory. Bleeding risk in hemodialysis patients on VKA as compared with those not on VKA has been reported to be significantly increased,[21,22] nonsignificantly increased,[17,33] or not increased.[14,18–20,23] However, VKA doubled the rate of hemorrhagic stroke (2.6 vs 1.1/100 patient-years),[19] which may be intrinsically related to its mode of action, as discussed below.

Maintaining a therapeutic INR in hemodialysis patients is challenging and requires close monitoring. Patients with severe CKD require lower doses of VKA, spend less time in the therapeutic range, and are at higher risk for excessive anticoagulation.[34] Several studies demonstrated that appropriate anticoagulation protects against bleeding complications[22,28] and, conversely, that major bleeding occurs during episodes of overanticoagulation.[23] Thrice-weekly administration of VKA to improve adherence resulted in higher TTR (57% vs 49%) and lower time with INR >4 (2.7% vs 4.3%).[35] Lowering the dose of heparin during dialysis, although not formally studied in this respect, may further minimize the risk of hemorrhagic complications.

Warfarin-related nephropathy is a form of acute kidney injury caused by widespread glomerular hemorrhage causing obstructive red blood cell cast formation during episodes of supratherapeutic INR, in particular in patients with preexisting CKD.[36] In a reanalysis of the RE-LY trial comparing VKA and dabigatran, the decline in renal function was more pronounced in the VKA arm.[37] In particular patients with poor INR control exhibited a faster decline in renal function.[37] Whether overanticoagulation may result in more rapid loss of residual renal function and contribute to adverse risk in hemodialysis patients on VKA has not been studied.

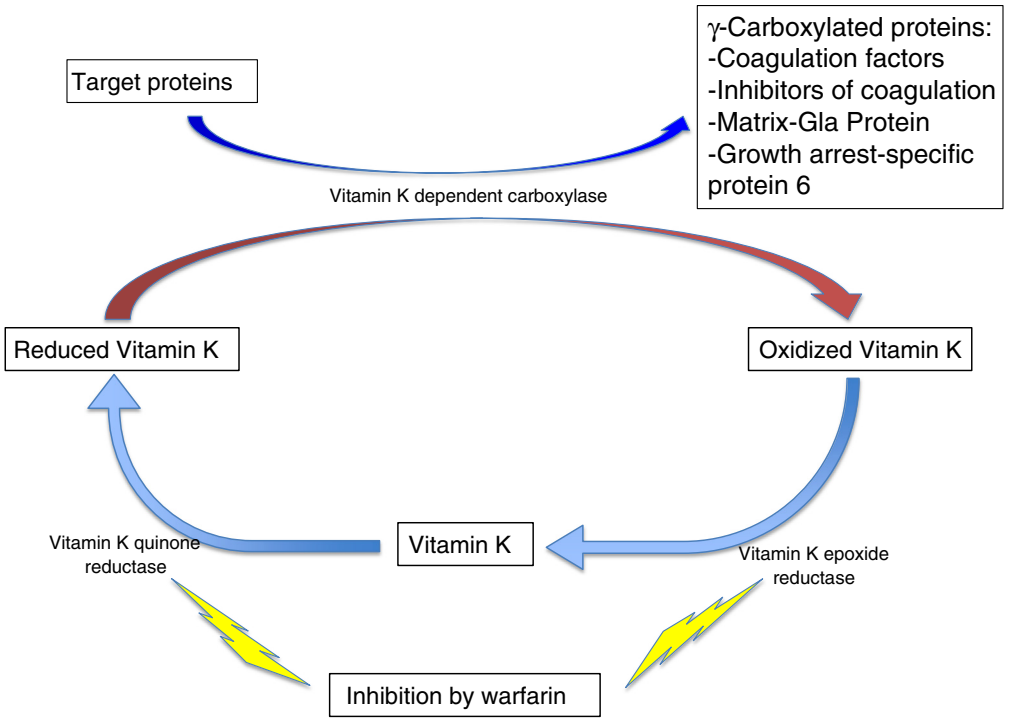
Vascular calcifications in dialysis patients

In patients with CKD and in particular in those on dialysis, vascular calcifications are highly prevalent, severe, and rapidly progressive. Accelerated calcification of intimal plaque, arterial media calcification,[38] and aortic and mitral valve calcification[39] are often present simultaneously. Both the extent and the rate of progression of vascular calcifications are potent predictors of all-cause and cardiovascular mortality in the dialysis population.[40] It has been argued that vascular calcifications are the end stage of vascular inflammation and thus merely a marker of arterial damage rather than causally related to adverse outcome.[41] However, patients with intimal calcification are at higher risk for myocardial infarction, stroke, peripheral vascular disease, and all-cause death. Medial calcification reduces arterial elasticity and contributes to left ventricular hypertrophy, diastolic dysfunction, and ultimately heart failure in dialysis patients. Because of the extensive interstitial fibrosis that accompanies left ventricular hypertrophy, dialysis patients may be at increased risk for arrhythmic death. Finally, valvular calcification, particularly calcific aortic stenosis, compounds the risk of left ventricular hypertrophy. Mitral valve annulus calcification is associated with restriction of leaflet opening, as well as increased transvalvular gradient and left atrium enlargement and may add to the risk of developing AF.[42] There is a growing consensus that vascular calcifications constitute a relevant treatment target[43] or, conversely, that therapies that promote vascular calcifications should be avoided.

Vascular calcifications and VKA use in dialysis patients

The anticoagulant effect of VKA hinges on the inhibition of 2 enzymes of the vitamin K cycle, resulting in endogenous vitamin K depletion (Figure). Vitamin K is vital for the γ-carboxylation of vitamin K–dependent proteins, including the coagulation factors (factor II, VII, IX, and X), the inhibitors of coagulation (proteins S and C), and a number of proteins responsible for inhibition of vascular calcification. The best known and most powerful inhibitor of calcification present in the arterial media is matrix-Gla protein (MGP). Growth arrest–specific protein 6 (Gas-6) is another vascular-protective vitamin K–dependent protein.[44] Vitamin K antagonist may accelerate the vascular

Figure



Inhibition of the vitamin K cycle by warfarin.

calcification process by impairing the activation of MGP and Gas-6, an undesirable side effect that is unfortunately intrinsic to the mechanism of action of these drugs. In addition, the transglutaminase-2/β-catenin axis has been identified as an MGP-independent mediator of VKA-induced vascular calcification.[45] Dialysis patients have subclinical vitamin K deficiency,[44] owing to poor dietary intake, exhaustion by high requirements in the procalcifying uremic environment, and possibly uremic inhibition of the vitamin K cycle.[46] The dialysis population may thus be particularly vulnerable to the procalcifying effects of VKA.

Although the theoretical concept of VKA-induced vascular calcification has been reinforced by convincing experimental animal data, conclusive clinical evidence is currently lacking.[44] Clinical studies, recently comprehensively reviewed,[44] reveal that patients on VKA have more pronounced coronary artery, aortic and mitral valve, and peripheral artery calcification. Unfortunately, all are either retrospective cohort studies or cross-sectional analyses, and thus suffer from the inevitable confounding by indication. One recent study, however, was able to minimize the bias imposed by the underlying cardiovascular disease that is to be expected in patients on long-term VKA.[47] The prevalence of breast arterial calcification detected on screening mammograms was 50% greater in women treated with VKA than in matched controls, although the prevalence was not increased in the mammograms performed prior to beginning therapy with VKA.[47] These results thus pointed at VKA rather than underlying patient characteristics as the potential mechanism responsible for the appearance and progression of vascular calcification. In a prospective evaluation of hemodialysis patients with similar aortic compliance at study initiation, treatment with VKA was independently associated with progression of aortic stiffness as an indirect marker of vascular calcification.[48]

Guidelines but no guidance

Given the lack of evidence from RCTs and the conflicting messages derived from observational studies, scientific societies[2,49–52] have not issued strong recommendations regarding anticoagulation management in dialysis patients with AF, despite the high risk of stroke in these patients (Table III). This uncertainty breeds inconsistent physician practice patterns. A survey of VKA prescribing practices of Canadian nephrologists revealed a remarkably high variability in response and physician uncertainty, especially for patients with a combined increased risk of stroke and bleeding.[53] The insecurity is also reflected in a particularly low rate of VKA use in ESRD compared with all other patient groups, despite higher risk scores in ESRD.[18] The ambiguity is further revealed in wide variations in VKA prescribing

Table III. Anticoagulation guidelines in ESRD patients with AF

Scientific society (reference)	Year	Guideline
K-DOQI[49]	2005	Antithrombotic therapy (warfarin and aspirin) should be considered, based on an assessment of the risk of embolism and of bleeding complications. Dialysis patients are at increased risk for bleeding and careful monitoring should accompany intervention.
KDIGO[50]	2011	Weighing the available evidence, the benefit of warfarin anticoagulation for primary prevention of stroke in CKD 5D patients is questionable.
European Society of Cardiology[51]	2012	AF patients with severe renal failure have not been adequately studied and their risk assessment is complex.
Canadian Society of Cardiology[52]	2014	There are no randomized trials data for nonvalvular AF patients who are dialysis dependent, and we therefore cannot recommend their routine anticoagulation.
American Heart Association/ American College of Cardiology/Heart Rhythm Society[2]	2014	For patients with nonvalvular AF with a CHA2DS2-VASc score of ≥2 and who have end-stage CKD (creatinine clearance <15 mL/min) or are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0-3.0) for oral anticoagulation. (*Level of Evidence: B*)

patterns for hemodialysis patients with AF across countries, ranging from 2% in Germany to 26% in the United States and 37% in Canada,[4] or within geographic regions, varying from 0% to 45% among Canadian facilities.[12]

New oral anticoagulants

The new oral anticoagulants (NOACs) inhibit thrombin (dabigatran) or activated factor X (rivaroxaban, apixaban, edoxaban, betrixaban). Dabigatran, rivaroxaban, apixaban, and edoxaban have been studied in large phase III trials in the setting of nonvalvular AF and were found to have an overall favorable risk-benefit profile vs VKA.[54] In patients with prosthetic heart valves, NOACs have generally not been studied and in a single study failed to prove of value.[55] Because of substantial renal clearance (dabigatran 80%, rivaroxaban 35%, apixaban 27%, edoxaban 50%), the key efficacy trials implemented dose adjustments in patients with mild to moderate CKD. Betrixaban has only minimal renal excretion, but has so far been evaluated in a small phase II trial only.[56] The relative efficacy and safety of the NOACs appears consistent across the range of renal function included in the individual trials,[57] provided dose recommendations are followed. As patients with a creatinine clearance <30 mL/min (<25 mL/min for apixaban) were systematically excluded from all available clinical trials, there are no data about the efficacy and safety of the NOACs in advanced CKD and in patients on dialysis. Nevertheless, the US Food and Drug Administration has extrapolated the efficacy and safety data and approved dabigatran and rivaroxaban for use in patients with a creatinine clearance of 15 to 30 mL/min and apixaban, even in patients with ESRD. Despite their formal contraindication in patients with a creatinine clearance <15 mL/min, dabigatran and rivaroxaban have been prescribed to, respectively, 3.1% and 2.8% of AF patients on dialysis.[58] In most cases, the reduced dose intended for patients with moderate CKD was used, and a substantial proportion of patients were given the full dose.[58] The finding of excess morbidity and mortality from bleeding with dabigatran and rivaroxaban compared with VKA is therefore not surprising[58] and epitomizes the discrepancies between RCTs, official recommendations, and "real-life" medicine.

Nevertheless, we contend that NOACs hold great promise for the dialysis population, on condition that appropriate dosing is implemented. Recently, a comprehensive pharmacokinetic analysis was performed for rivaroxaban, offering a dosing guideline specifically for the hemodialysis population.[59] Preliminary pharmacokinetic data in hemodialysis patients have also been reported for apixaban[60] and edoxaban.[61] For dabigatran, only pharmacokinetic modeling data are available.[62]

The NOACs may provide a substantially more favorable risk-benefit ratio than the VKA for hemodialysis patients for several reasons. First, anticoagulation may be more consistent and predictable, with less interaction with food and other drugs. In a population notorious for low TTR on VKA, more on-target anticoagulation with NOACs may translate in a better protection against stroke. Furthermore, NOACs may protect dialysis patients against hemorrhagic stroke. The high risk of intracranial hemorrhage seen with VKA has generally been attributed to impaired anticoagulation. However, NOACs pose a 50% lower risk of intracranial hemorrhage, consistent across studies.[54] Even when used in inappropriately high doses in dialysis patients, dabigatran and rivaroxaban were associated with a 4 times lower rate of hemorrhagic stroke than the VKA, despite an overall increased incidence of severe and fatal bleeding.[58] This surprising finding may be related to the inhibition of MGP by VKA. MGP knockout mice feature an abnormal angiogenesis and an increased risk of intracranial bleeding,[63] perhaps because they develop a more fragile microvasculature.

Finally, as NOACs do not interfere with vitamin K–dependent proteins, they are not expected to accelerate progression of vascular calcifications. Animal experiments even demonstrated beneficial effects of NOACs on the development of atherosclerosis.[64] The published efficacy NOAC trials were not designed to detect vascular calcification–related end points, but several trials comparing the effect of NOACs and VKA on progression of vascular calcification are currently ongoing.[65]

The lack of specific antidotes for NOACs is concerning, particularly in a frail and old population with a high baseline bleeding risk. Several agents that directly reverse the effects of NOACs are currently in different stages of development[66] and idarucizumab (Praxbind®, Boehringer Ingelheim), the first monoclonal antibody to reverse the effects of dabigatran,[67] was recently approved by the US Food and Drug Administration and the European Medicines Agency. Pending their broad availability for clinical use, reversal of the anticoagulant effect of anti-Xa antagonists (but not dabigatran) can be attempted with prothrombin complex concentrates that promote thrombin generation.[68]

Left atrial appendage closure

Percutaneous closure of the left atrial appendage is an alternative to oral anticoagulation for the prevention of stroke and systemic embolism in high-risk patients with AF. The clinical effectiveness and safety of this technique has been the subject of a series of clinical trials and registries, recently reviewed in a meta-analysis.[69] As compared with VKA, left atrial appendage closure was associated with similar rates of all-cause stroke, a higher rate of ischemic stroke, and a lower rate of hemorrhagic stroke and nonprocedural bleeding.[69] Unfortunately, patients with CKD were excluded from all published trials (D. Holmes, personal communication). The risk-benefit ratio of this technique in the dialysis population is therefore unknown.

Conclusion

Patients with CKD and in particular those on dialysis differ from the general population for their increased risk of both ischemic and bleeding events, and propensity to develop vascular calcification. These peculiarities profoundly alter the benefit-risk ratio of VKA and preclude the simple extrapolation of guidelines from the general population. In the absence of RCT that delineate effective risk stratification in dialysis patients with AF, clinicians are currently left with little but their common sense to decide whether or not to start or continue VKA in their patients.

Pending the development of a dialysis-specific stroke risk score that takes into account the actual determinants of stroke in this population, clinicians should know that AF remains important among the risk factors for stroke in dialysis patients, albeit less consistently than in the general population. Unfortunately, none of the available bleeding risk scores have a better predictive power than the simple assessment of history of gastrointestinal bleeding. In the absence of a dialysis-specific bleeding risk score, caution with VKA is warranted in frail, elderly patients, particularly when they have a history of major bleeding. When the decision to initiate VKA is made, the dose of heparin during dialysis should be minimized, and if the patient is already taking antiplatelet agents, their indication should be reevaluated. Finally, VKA should be avoided in patients with clinical evidence of vascular calcifications. Taken together, the threshold to initiate VKA in dialysis patients should probably be much higher than in the general population. New oral anticoagulants may have a more favorable risk-benefit ratio than VKA in dialysis patients, with the unassailable condition that appropriate dosing be implemented. So far, no clear dosing strategies are available for dialysis patients, except for rivaroxaban.[59] We look forward to a carefully designed clinical trial with NOACs in dialysis patients with AF,[65] providing data to support or dispute the assumption that they may have benefits in this population. Ideally, prospective validation in a large patient cohort of a (as yet to develop) dialysis-specific stroke and bleeding risk score should precede the conduction of such a trial.

No extramural funding was used to support this work.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

References

1. Goldstein BA, Arce CM, Hlatky MA, et al. Trends in the incidence of atrial fibrillation in older patients initiating dialysis in the United States. Circulation 2012;126(19):2293-301.
2. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64(21):e1-76.
3. Zimmerman D, Sood MM, Rigatto C, et al. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. Nephrol Dial Transplant 2012;27(10):3816-22.
4. Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int 2010;77(12):1098-106.
5. Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. Circ Cardiovasc Qual Outcomes 2012;5(1):85-93.
6. Bansal N, Fan D, Hsu CY, et al. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. Circulation 2013;127(5):569-74.

7. Buiten MS, de Bie MK, Rotmans JI, et al. The dialysis procedure as a trigger for atrial fibrillation: new insights in the development of atrial fibrillation in dialysis patients. Heart 2014;100(9):685-90.
8. Genovesi S, Vincenti A, Severi S. Insights into intradialytic atrial fibrillation onset mechanisms. Heart 2014;100(16):1302.
9. Herrington W, Haynes R, Staplin N, et al. Evidence for the prevention and treatment of stroke in dialysis patients. Semin Dial 2015;28(1): 35-47.
10. Findlay MD, Thomson PC, Fulton RL, et al. Risk factors of ischemic stroke and subsequent outcome in patients receiving hemodialysis. Stroke 2015;46(9):2477-81.
11. Bonde AN, Lip GY, Kamper AL, et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. J Am Coll Cardiol 2014;64(23):2471-82.
12. Sood MM, Larkina M, Thumma JR, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. Kidney Int 2013;84(3):600-8.
13. Chao TF, Liu CJ, Wang KL, et al. Incidence and prediction of ischemic stroke among atrial fibrillation patients with end-stage renal disease requiring dialysis. Heart Rhythm 2014;11(10):1752-9.
14. Shen JI, Montez-Rath ME, Lenihan CR, et al. Outcomes after warfarin initiation in a cohort of hemodialysis patients with newly diagnosed atrial fibrillation. Am J Kidney Dis 2015;66(4):677-88.
15. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857-67.
16. Hart RG, Pearce LA, Asinger RW, et al. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. Clin J Am Soc Nephrol 2011;6(11):2599-604.
17. Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 2012;367(7): 625-35.
18. Carrero JJ, Evans M, Szummer K, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. JAMA 2014;311(9):919-28.
19. Winkelmayer WC, Liu J, Setoguchi S, et al. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. Clin J Am Soc Nephrol 2011;6(11):2662-8.
20. Wakasugi M, Kazama JJ, Tokumoto A, et al. Association between warfarin use and incidence of ischemic stroke in Japanese hemodialysis patients with chronic sustained atrial fibrillation: a prospective cohort study. Clin Exp Nephrol 2014;18(4):662-9.
21. Shah M, Avgil Tsadok M, Jackevicius CA, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation 2014;129(11):1196-203.
22. Genovesi S, Rossi E, Gallieni M, et al. Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation. Nephrol Dial Transplant 2015;30(3):491-8.
23. Chan KE, Lazarus JM, Thadhani R, et al. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol 2009;20(10):2223-33.
24. Li J, Wang L, Hu J, et al. Warfarin use and the risks of stroke and bleeding in hemodialysis patients with atrial fibrillation: a systematic review and a meta-analysis. Nutr Metab Cardiovasc Dis 2015;25(8): 706-13.
25. Chan PH, Huang D, Yip PS, et al. Ischaemic stroke in patients with atrial fibrillation with chronic kidney disease undergoing peritoneal dialysis. Europace 2015. [pii: euv289. Epub ahead of print].
26. Lenihan CR, Montez-Rath ME, Shen JI, et al. Correlates and outcomes of warfarin initiation in kidney transplant recipients newly diagnosed with atrial fibrillation. Nephrol Dial Transplant 2015;30(2):321-9.
27. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349(11):1019-26.
28. Knoll F, Sturm G, Lamina C, et al. Coumarins and survival in incident dialysis patients. Nephrol Dial Transplant 2012;27(1):332-7.
29. Palareti G, Cosmi B. Bleeding with anticoagulation therapy—who is at risk, and how best to identify such patients. Thromb Haemost 2009;102(2):268-78.
30. Dzeshka MS, Lane DA, Lip GY. Stroke and bleeding risk in atrial fibrillation: navigating the alphabet soup of risk-score acronyms (CHADS2, CHA2 DS2 -VASc, R2 CHADS2, HAS-BLED, ATRIA, and more). Clin Cardiol 2014;37(10):634-44.
31. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. Eur Heart J 2015;36(46):3258-64.
32. Roskell NS, Samuel M, Noack H, et al. Major bleeding in patients with atrial fibrillation receiving vitamin K antagonists: a systematic review of randomized and observational studies. Europace 2013;15(6): 787-97.
33. Holden RM, Harman GJ, Wang M, et al. Major bleeding in hemodialysis patients. Clin J Am Soc Nephrol 2008;3(1):105-10.
34. Limdi NA, Beasley TM, Baird MF, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am Soc Nephrol 2009;20(4):912-21.
35. Sood MM, Rigatto C, Bueti J, et al. Thrice weekly warfarin administration in haemodialysis patients. Nephrol Dial Transplant 2009;24(10):3162-7.
36. Brodsky SV, Nadasdy T, Rovin BH, et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. Kidney Int 2011;80(2):181-9.
37. Böhm M, Ezekowitz MD, Connolly SJ, et al. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY trial. J Am Coll Cardiol 2015;65(23):2481-93.
38. Raggi P, Boulay A, Chasan-Taber S, et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol 2002;39(4):695-701.
39. Raggi P, Bellasi A, Gamboa C, et al. All-cause mortality in hemodialysis patients with heart valve calcification. Clin J Am Soc Nephrol 2011;6(8):1990-5.
40. Bellasi A, Raggi P. Vascular imaging in chronic kidney disease. Curr Opin Nephrol Hypertens 2012;21(4):382-8.
41. Zoccali C, London G. Con: vascular calcification is a surrogate marker, but not the cause of ongoing vascular disease, and it is not a treatment target in chronic kidney disease. Nephrol Dial Transplant 2015;30(3):352-7.
42. Movva R, Murthy K, Romero-Corral A, et al. Calcification of the mitral valve and annulus: systematic evaluation of effects on valve anatomy and function. J Am Soc Echocardiogr 2013;26(10):1135-42.
43. Bover J, Evenepoel P, Ureña-Torres P, et al. CKD-MBD Working Group of ERA-EDTA. Pro: cardiovascular calcifications are clinically relevant. Nephrol Dial Transplant 2015;30(3):345-51.
44. Chatrou ML, Winckers K, Hackeng TM, et al. Vascular calcification: the price to pay for anticoagulation therapy with vitamin K–antagonists. Blood Rev 2012;26(4):155-66.
45. Beazley KE, Deasey S, Lima F, et al. Transglutaminase 2-mediated activation of â-catenin signaling has a critical role in warfarin-induced vascular calcification. Arterioscler Thromb Vasc Biol 2012;32(1):123-30.
46. Kaesler N, Magdeleyns E, Herfs M, et al. Impaired vitamin K recycling in uremia is rescued by vitamin K supplementation. Kidney Int 2014;86(2):286-93.

47. Tantisattamo E, Han KH, O'Neill WC. Increased vascular calcification in patients receiving warfarin. Arterioscler Thromb Vasc Biol 2015;35(1):237-42.
48. Mac-Way F, Poulin A, Utescu MS, et al. The impact of warfarin on the rate of progression of aortic stiffness in hemodialysis patients: a longitudinal study. Nephrol Dial Transplant 2014;29(11):2113-20.
49. K/DOQI Workgroup,. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005;45(4 Suppl 3):S1-S153.
50. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80(6):572-86.
51. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33(21):2719-47.
52. Verma A, Cairns JA, Mitchell LB, et al. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol 2014;30(10):1114-30.
53. Juma S, Thomson BK, Lok CE, et al. Warfarin use in hemodialysis patients with atrial fibrillation: decisions based on uncertainty. BMC Nephrol 2013;14:174.
54. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383(9921):955-62.
55. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013;369(13):1206.
56. Connolly SJ, Eikelboom J, Dorian P, et al. Betrixaban compared with warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa). Eur Heart J 2013;34(20):1498-505.
57. Qamar A, Bhatt DL. Anticoagulation therapy: balancing the risks of stroke and bleeding in CKD. Nat Rev Nephrol 2015;11(4):200-2.
58. Chan KE, Edelman ER, Wenger JB, et al. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation 2015;131(11):972-9.
59. De Vriese AS, Caluwé R, Bailleul E, et al. Dose-finding study of rivaroxaban in hemodialysis patients. Am J Kidney Dis 2015;66(1):91-8.
60. Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol 2015, http://dx.doi.org/10.1002/jcph.628. [Epub ahead of print].
61. Parasrampuria DA, Marbury T, Matsushima N, et al. Pharmacokinetics, safety, and tolerability of edoxaban in end-stage renal disease subjects undergoing haemodialysis. Thromb Haemost 2015;113(4):719-27.
62. Liesenfeld KH, Clemens A, Kreuzer J, et al. Dabigatran treatment simulation in patients undergoing maintenance haemodialysis. Thromb Haemost 2015;115(3). [Epub ahead of print].
63. Yao Y, Yao J, Radparvar M, et al. Reducing Jagged 1 and 2 levels prevents cerebral arteriovenous malformations in matrix Gla protein deficiency. Proc Natl Acad Sci U S A 2013;110(47):19071-6.
64. Schurgers LJ, Spronk HM. Differential cellular effects of old and new oral anticoagulants: consequences to the genesis and progression of atherosclerosis. Thromb Haemost 2014;112(5):909-17.
65. Caluwé R, Pyfferoen L, De Boeck K, De Vriese AS. The effects of vitamin K supplementation and vitamin K antagonists on progression of vascular calcification: ongoing randomized controlled trials. *Clin Kidney* J 2016 [in press].
66. Sarich TC, Seltzer JH, Berkowitz SD, et al. Novel oral anticoagulants and reversal agents: considerations for clinical development. Am Heart J 2015;169(6):751-7.
67. Ansell JE. Universal, class-specific and drug-specific reversal agents for the new oral anticoagulants. J Thromb Thrombolysis 2016;41(2):248-52.
68. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011;124(14):1573-9.
69. Holmes Jr DR, Doshi SK, Kar S, et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis. J Am Coll Cardiol 2015;65(24):2614-23.