Canadian Journal of Cardiology 35 (2019) 1241–1255

Review

Anticoagulation in Patients With Advanced Chronic Kidney Disease: Walking the Fine Line Between Benefit and Harm

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ABSTRACT

Chronic kidney disease affects more than 3 million Canadians and is highly associated with cardiovascular diseases that require anticoagulation, such as atrial fibrillation and venous thromboembolism. Patients with chronic kidney disease are at a problematic crossroads; they are at high risk of thrombotic conditions requiring anticoagulation and bleeding complications due to anticoagulation. The limited high-quality clinical evidence to guide decision-making in this area further compounds the dilemma. In this review, we discuss the physiology and epidemiology of bleeding and thrombosis in patients with kidney disease. We specifically focus on patients with advanced kidney disease

RÉSUMÉ

L'insuffisance rénale chronique touche plus de trois millions de Canadiens et est fortement associée à des maladies cardiovasculaires nécessitant une anticoagulothérapie, dont la fibrillation auriculaire et la thromboembolie veineuse. Or, les patients atteints d'insuffisance rénale chronique se trouvent dans une situation doublement problématique : ils présentent à la fois un risque élevé d'affections thrombotiques nécessitant une anticoagulothérapie mais aussi de complications hémorragiques résultant de cette anticoagulothérapie. Le peu de données cliniques probantes de haute qualité susceptibles d'orienter la prise de décisions dans ce contexte complique le

Chronic kidney disease (CKD) is common among Canadians, afflicting more than 3 million adults.[1] The Kidney Disease: Improving Global Outcomes guidelines[2] define CKD as the presence of abnormal kidney function or structure for more than 3 months with implications for health. Abnormal kidney function consists of glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2, > 30 mg/g of albuminuria in 24 hours, urine sediment abnormalities, tubular disorders, structural abnormalities detected using histology or imaging or a history of kidney transplantation.[2] End stage kidney disease (ESKD) is the most severe form of CKD in which GFR is < 15 mL/min/1.73 m^2 and patients often require renal replacement therapy or transplantation.[2]

Primary care physicians and cardiologists are highly likely to be among the first to identify and manage early stages of CKD because nephrologists are usually involved with cases of more advanced CKD or specific types of kidney diseases (such as glomerulonephritis). This is on the basis of the strong inter-relationship between cardiac and kidney disease and the large body of evidence that has identified CKD as one of the biggest risk factors for cardiovascular (CV) disease (CVD). In fact, advanced CKD (GFR < 30 mL/min/1.73 m^2) is associated with a 22% risk of CVD.[3-5]

Aside from being a recognized risk factor for CVD, CKD is strongly associated with poor CVD outcomes. A study of > 1 million adults from California showed a graded increased risk of death, CV events, and hospitalization with a decreasing estimated GFR (eGFR).[6] The Framingham Heart Study showed an eGFR of 30-45 mL/min is associated with a higher relative risk (RR) of CVD (defined as coronary death, myocardial infarction, coronary insufficiency, angina pectoris, atherothrombotic stroke, intermittent claudication, or CV death) with a hazard ratio (HR) of 1.41 (95% confidence interval [CI], 1.05-1.91).[7] The **H**eart **O**utcomes and **P**revention **E**valuation (HOPE) study and pooled analysis of community-based studies consisting of **A**therosclerosis **R**isk **i**n **C**ommunities (ARIC), Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study showed a similar higher RR of CVD in patients with kidney disease.[8,9] The heightened CV risk is magnified in patients with ESKD because the risk of CVD is 10-20 times higher than that in the general population.[10]

Atrial fibrillation (AF) is the most common arrhythmia in the CKD and non-CKD population. A diagnosis of AF is noted in 13%-27% of patients with CKD and 13%-22% of patients with

Received for publication February 26, 2019. Accepted July 4, 2019.

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See page 1251 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.07.001
0828-282X/

(estimated glomerular filtration rate ≤ 30 mL/min) or who are receiving dialysis and focus on the nephrologist perspective regarding these issues. We summarize the existing evidence for anticoagulation use in the prevention of stroke with atrial fibrillation and provide practical clinical recommendations for considering anticoagulation use in this population. Last, we examine specific scenarios such as the use of a glomerular filtration rate estimating equation and dosing, the use of existing prediction tools for stroke and hemorrhage risk, current patterns of anticoagulation use (including during the dialysis procedure), and vascular calcification with vitamin K antagonist use in patients with chronic kidney disease.

dilemme. Dans le présent article, nous abordons la physiologie et l'épidémiologie de l'hémorragie et de la thrombose chez les patients atteints de néphropathie. Nous mettons tout particulièrement l'accent sur le cas des patients atteints d'insuffisance rénale avancée (débit de filtration glomérulaire estimé ≤ 30 ml/min/1,73 m^2) ou sous dialyse et envisageons la question du point de vue du néphrologue. Nous résumons les données probantes actuelles plaidant en faveur de l'anticoagulothérapie dans la prévention des accidents vasculaires cérébraux (AVC) en cas de fibrillation auriculaire et formulons des recommandations de pratique clinique touchant le recours aux anticoagulants au sein de cette population. Enfin, nous examinons des scénarios précis, comme l'utilisation d'une équation permettant d'estimer le débit de filtration glomérulaire et la détermination de la dose à administrer, l'utilisation des outils existants servant à prévoir le risque d'AVC et d'hémorragie, les modalités actuelles de l'anticoagulothérapie (notamment en cours de dialyse) et la calcification vasculaire associée à l'administration d'antivitamine K chez les patients atteints d'insuffisance rénale chronique.

ESKD.[11,12] From the ARIC study cohort of > 10,000 patients, the incidence of AF in patients with GFR < 30 mL/min/1.73 m^2 was 3 times higher than for those with normal GFR.[13] A potential under-recognized risk factor for AF is the presence of protein losses from the kidney, in the form of albuminuria. Elevations in albuminuria appear to be associated with a graded increase in the risk of AF.[13] A recent meta-analysis of the Jackson Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study showed a pooled HR of 1.04 (95% CI, 0.83-1.30), 1.47 (95% CI, 1.20-1.79), and 1.76 (95% CI, 1.18-2.62) for patients with urine albumin to creatinine ratio (ACR) for developing AF in patients with urine ACR of 15-29, 30-299, and ≥ 300 mg/g, respectively.[14]

Despite the high risks CKD patients face of CVD and thromboembolic conditions, the management of anticoagulation in patients with CKD is complex because they are paradoxically at an increased risk of bleeding and thrombosis. Therefore, the use of anticoagulation in such patients should be a collaborative decision process between nephrologists and cardiologists because a proper understanding of the hemostatic derangements that occur in advanced CKD are crucial to properly weighing the risks and benefits of anticoagulation.

In this review, we discuss the physiology and epidemiology of bleeding and thrombosis in patients with kidney disease. We summarize the evidence for anticoagulation use in the prevention of stroke with AF and examine special considerations for anticoagulation use in patients with kidney disease. We specifically focus on patients with advanced kidney disease (eGFR ≤ 30 mL/min) or who are receiving dialysis and focus on the nephrologist perspective regarding these issues.

Physiologic Abnormalities in Hemostasis and Thrombosis With Kidney Disease

Abnormalities leading to procoagulant state

Progressive declines in kidney function lead to a broad array in hemostatic biochemical disorders. These abnormalities are prominent in secondary hemostasis, including (but not limited to) elevations in fibrinogen, factor VII, factor VIII, factor XII, activated protein C complex, von Willebrand factor (vWF), homocysteine, and thrombin-antithrombin complex (see Fig. 1 for a summary of recognized hemostatic abnormalities).[15-20] These factors could be increased because of poor renal clearance and/or overproduction. For example, high fibrinogen levels are noted in CKD which is a proinflammatory state, noted by elevated levels of C-reactive protein and interleukin-6.[18,21] Collectively these alterations lead to a procoagulant state. Uremic conditions alter primary hemostasis by increasing platelet-surface presence of phosphatidylserine, inhibiting nitrogen oxide synthase, and increasing the expression of fibrinogen receptor (which binds first procaspase activating compound [PAC-1]) on the surface of platelets.[22,23] Furthermore, CKD affects tertiary hemostasis and activates the renin-angiotensin-aldosterone system with resultant increases in plasminogen activator inhibitor and less fibrinolysis.[24] Moreover, declining kidney function has been associated with increased levels of plasmin-antiplasmin complex which can further make thrombi resistant to degradation.[18,25,26]

Stasis of blood promotes thrombus formation in the heart and lower extremities. CKD patients with AF are at high risk of thrombus formation resulting in stroke and other embolic phenomena.[27,28] In the lower extremities, venous stasis and volume overload are associated with a high risk of deep vein thrombosis.[29] Fluid overload in CKD and hemodialysis is common with an estimated 2.7 L of excess fluid at the initiation of each dialysis session.[30,31] This typically prompts aggressive diuresis in CKD patients and large volume ultrafiltration in dialysis patients leading to hemoconcentration, in turn furthering hemostasis and thrombus formation.[32]

Direct endothelial injury by volume overload or vascular-related shear stress is a contributor to thrombus formation. Volume overload and hypertension are noted in > 50% of patients with CKD and > 80% of patients receiving dialysis.[33,34] CKD is also associated with atherosclerosis, arterial calcifications, and increased arterial wall stiffness leading to endothelial damage.[25,35] Specific to hemodialysis patients is the added insult from vascular access. With arteriovenous fistulas or prosthetic arteriovenous grafts, direct endothelial injury occurs during surgical creation and reinjury with continual use due to

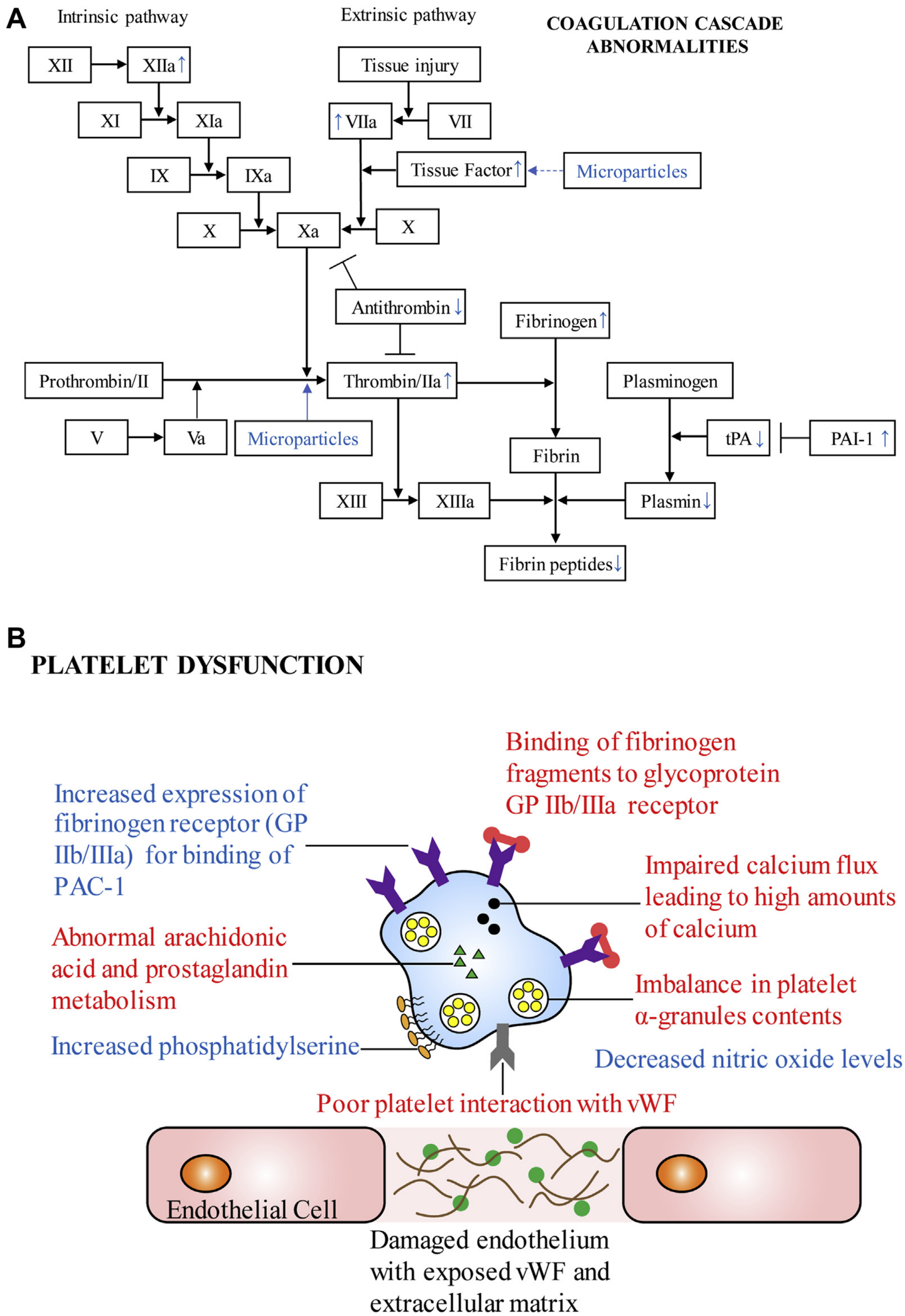

Figure 1. Physiology of increased thrombosis and bleeding risk in patients with kidney disease in (A) the coagulation pathway and (B) platelets. GP, glycoprotein; PAC-1, first procaspase activating compound; PAI, plasminogen activator inhibitor; tPA, tissue plasminogen activator; vWF, von Willebrand factor.

intimal hyperplasia.[36] This is reflected in the high rate of fistula thrombosis at 1 year; 40%-70% depending on the location of the fistula.[37] With central venous catheters used for dialysis, endothelial injury occurs at time of line insertion and again with the sliding motion of the catheter that occurs with head movement, respiration, and turbulent blood flow during dialysis. Overall, 42% of catheter malfunctions are directly related to catheter thrombosis.[38] In > 10% of the dialysis patients with a central venous catheter, ongoing severe endothelial injury results in chronic central vein stenosis.[39]

Abnormalities leading to increased bleeding

Platelet dysfunction contributes significantly to increasing bleeding risk in patients with kidney disease. Disorders in the balance of constituents within platelet α-granules (contain platelet factor 4, transforming growth factor-β1, platelet-derived growth factor, fibronectin, B-thromboglobulin, vWF, fibrinogen, and coagulation factors V and XIII) lead to reductions in overall platelet thrombus formation.[40] Poor platelet adhesion and aggregation have been associated with higher amounts of calcium, impaired calcium flux, abnormal arachidonic acid and prostaglandin metabolism, dysfunction of thromboxane A2 synthesis, and release and binding of fibrinogen fragments to platelet glycoprotein GP IIb/IIIa receptors.[41] Furthermore, uremic platelets have poor interactions with vWF, which can lead to increasing bleeding tendencies. This can be partially reversed by use of cryoprecipitate and/or desmopressin.[42,43] Patients with advanced CKD (eGFR < 30-40 mL/min) have erythropoietin-deficient anemia. It is suspected that anemia in and of itself increases bleeding tendencies because anemia correction with packed red blood cell transfusion(s) improves bleeding time (Fig. 1).[25,26,44]

The hemodialysis procedure corrects platelet dysfunction rapidly, reduces the risk of bleeding, and rapidly improves platelet function immediately post-procedure.[45,46] The normalization of platelet function is unfortunately transient because the reaccumulation of uremic by-products between dialysis treatments recreates the prohemorrhagic state. Further complicating the dialysis patient's hemostasis is the additional use of unfractionated heparin (UFH) or low molecular-weight heparin (LMWH) during dialysis in > 80% of the patients to prevent thrombosis of the dialyzer membrane. The use of anticoagulation during dialysis lasts more than 1.5 hours and more than 24 hours after dialysis in patients who receive UFH and LMWH, respectively.[47] These effects cumulatively result in dramatic swings in competing physiological states immediately before and after hemodialysis. Before dialysis, platelet function is impaired and anticoagulation effects are diminished. After dialysis, platelet function is normalized, plasma is hemoconcentrated (due to fluid removal), and anticoagulation is present. Hence, it is challenging to discern the extent to which a hemodialysis patient is in a prothrombotic or prohemorrhagic state at any given time.

In contrast, peritoneal dialysis is associated with a reduced risk of bleeding compared with hemodialysis because of efficient clearance of uremic toxins that occurs with enhanced removal of medium sized "middle" molecules daily without large swings between uremic and functional platelets.[48] Furthermore, platelet activation does not occur because peritoneal dialysis does not use an artificial membrane. Systemic heparin is not used with peritoneal dialysis and therefore does not confer any additional anticoagulation effects.[49] However, hypoalbuminemia from gradual loss of albumin through the peritoneal dialysate results in platelet hyperactivity and increased risk of bleeding.[50] Therefore, although bleeding risks are lower in peritoneal dialysis than in hemodialysis, they remain higher than that of the nondialysis population.[51,52]

The Epidemiology of Thrombosis With CKD

Venous and arterial thrombosis is highly prevalent in patients with CKD. Overall patients with kidney disease have a twofold overall higher RR of venous thromboembolism (VTE) compared with patients with normal kidney function and the risk differs according to CKD severity.[53] A population-level cohort study from Ontario, Canada reported the risk of VTE in 694,956 people according to eGFR and proteinuria status. In 15,180 VTE events, the VTE risk only increased marginally with eGFR declines alone (eGFR 15-29 mL/min: HR, 1.23; 95% CI, 1.00-1.50 vs eGFR > 90 mL/min: referent) but increased dramatically with an increase in albuminuria (ACR > 300 mg/g: HR, 1.61; 95% CI, 1.38-1.89 vs ACR < 30 mg/g: referent). This illustrated the underappreciated importance of elevations in albuminuria (measured according to the ACR) when determining the VTE risk in the CKD population.[54] Upon dialysis initiation, the VTE risk increases dramatically. A Canadian retrospective cohort study showed that close to 10% of dialysis patients were diagnosed with a VTE over 3 years compared with only 2% of the general population.[55] The elevated risk seems to return closer to that of the general population after kidney transplantation further strengthening the link between CKD/dialysis and VTE risk.[56]

Arterial thrombosis, specifically thromboembolism associated with AF, are common in patients with kidney disease. The risk of stroke in CKD, analogous to the risk of AF in CKD, increases in a graded manner with declines in eGFR and the worsening proteinuria. Go et al. reported an adjusted risk for stroke of 1.16 (95% CI, 0.95-1.40) and 1.39 (95% CI, 1.13-1.71) with an eGFR of 45-59 mL/min and < 45 mL/min in the **An**ticoagulation and **R**isk Factors **i**n **A**trial Fibrillation (ATRIA) cohort, respectively. Furthermore, the stroke risk in the presence of AF and proteinuria was HR, 1.54 (95% CI, 1.29-1.85) further illustrating the role of proteinuria as a risk factor or causative agent.[57] Comparable with VTE, the stroke risk rises dramatically with the start of dialysis. A US national study reported age-adjusted stroke rate ratios ranging between 4.3 and 10.1 depending on sex and race.[58] Another kidney-specific risk factor for stroke is the use of erythropoietin-stimulating agents for the correction of anemia. Higher hemoglobin targets (exceeding 130 g/L) increase the relative stroke risk (RR, 1.74) and other thromboembolic diseases risk (RR, 1.34).[59]

An assumption of these and other studies of stroke in AF is that the stroke events are related to thromboembolism; however, very little work has been done in distinguishing stroke types in patients with kidney disease.[60,61] Hypertension and diabetes mellitus are the 2 most common causes of CKD, are risk factors for the development of AF, and are associated with arteriosclerosis and lacunar infarcts.[62] Imaging studies of asymptomatic patients receiving hemodialysis have reported silent ischemic strokes in > 40% at 1 year with most being lacunar.[63] Because dialysis patients accrue silent stroke events even in the absence of AF, it becomes increasingly difficult to attribute the clear causality of stroke events in this population to a thromboembolism event.

The Epidemiology of Bleeding Risk With Kidney Disease

The 3-year cumulative incidence of hemorrhage (upper or lower gastrointestinal, intracerebral, subarachnoid, and other nontraumatic intracranial) increased more than 20-fold from

0.5% for patients with GFR > 90 mL/min/1.73 m^2 and ACR < 30 mg/g to 10.1% for patients with GFR < 15 mL/min/1.73 m^2 and ACR > 300 mg/g.[64] This risk was sustained after adjusting for anticoagulant and antiplatelet use.[64] Other factors that increase the risk of hemorrhage in patients with CKD include older age, diabetes, AF, stroke, anticoagulant use, and previous history of hemorrhage, all of which are prevalent in patients with kidney disease.[64] Use of nonsteroidal anti-inflammatory drugs are also a risk factor for bleeding in patients with ESKD.[65] Table 1 shows a summary of the risk of bleeding and all-cause mortality with warfarin use in patients with kidney disease.

With progression of CKD to ESKD, the risk of bleeding dramatically increases. Over 3 years, an alarming 1 in 7 dialysis patients in Canada will experience a hemorrhagic event requiring hospitalization.[66] Bleeding events were most common in the lower gastrointestinal tract at 8.9%, followed by upper gastrointestinal tract at 6.1%, intracerebral at 0.9%, and subarachnoid at 0.1%.[66] The risk of hemorrhage did not vary according to age and was similar between hemodialysis and peritoneal dialysis.

The risk of hemorrhage with anticoagulation (specifically vitamin K antagonists [VKAs]) among dialysis patients is exceedingly high. Approximately 30% of dialysis patients hospitalized with hemorrhage were prescribed warfarin within 120 days preceding their bleeding event.[66] A meta-analysis of warfarin use in patients with AF and ESKD showed an estimated pooled RR of bleeding at 1.35 (95% CI, 1.18-1.53; $P < 0.00001$).[67] This high risk is attributed to multiple factors including vitamin K deficiency (due to frequent antibiotic use, malnutrition), polypharmacy and drug interactions, and variable monitoring of the therapeutic targets within hemodialysis units.[68-70] As a result, only 21% of patients receiving dialysis achieved a time in the therapeutic range > 60%.[71] With anticoagulant use such was warfarin, hemorrhage might occur in the kidneys as well, specifically the glomerulus. This can lead to so-called warfarin-associated nephropathy or anticoagulant-related nephropathy, in which obstruction of tubules with red blood cells causes acute kidney injury and even kidney failure if bleeding is severe or anticoagulation is not discontinued.[72]

Information on the use of the newer direct oral anticoagulants (DOAC) agents and bleeding in patients with CKD is limited because they are not generally recommended for standard use in patients with low levels of kidney function. A recent systematic review of bleeding risk in AF patients with CKD showed bleeding risks with apixaban, dabigatran, and rivaroxaban comparable with that of warfarin.[73] However, among dialysis patients, bleeding and mortality-related bleeding rates were higher with dabigatran and rivaroxaban (dabigatran: RR, 1.76 [95% CI, 1.44-1.25]; rivaroxaban: RR, 1.45 [95% CI, 1.09-1.93]), dampening enthusiasm for their use.[73]

Evidence for the Use of Anticoagulation for Stroke Prevention in AF Patients With Advanced Kidney Disease

Summary of the evidence

To date, randomized controlled trials on the efficacy and safety of oral anticoagulants for stroke prevention in patients with AF excluded patients with advanced CKD (creatinine clearance [CrCl] < 25 mL/min) and dialysis patients (summarized in Tables 1-3).[74,75] As such, the evidence for the use of oral anticoagulation for stroke prevention in AF in patients with advanced CKD or who are receiving dialysis is derived from small observational studies or retrospective cohort studies. Despite advances in analytical techniques and statistical modelling methodology, inherent limitations in retrospective study designs leave much uncertainty regarding the true efficacy of anticoagulation for AF. Results from retrospective cohort studies to date are conflicting and when summarized in systematic reviews show no clear evidence of benefit. For example, a recent meta-analysis of observational studies comprising > 11,600 AF patients with ESKD, warfarin did not reduce the risk of AF-associated stroke (HR, 1.12; 95% CI, 0.69-1.82; $P = 0.65$) or death (HR, 0.96; 95% CI, 0.81-1.13; $P = 0.60$). Conversely, the signal for harm in the form of hemorrhage seems consistent and elevated (the risk of major bleeding HR, 1.30; 95% CI, 1.08-1.56; $P = 0.01$).[76] However, another meta-analysis of 14 observational studies did not show benefit or harm (stroke, bleeding, or mortality) with warfarin use in dialysis patients with AF.[77]

This uncertainty is illustrated in guideline recommendations regarding advanced CKD or dialysis. In general, the recommendations seem to clearly delineate situations when anticoagulation is safe and/or effective on the basis of trial evidence but differ in patients with advanced CKD or who are receiving dialysis (Table 3). The American Heart Association guidelines suggest using risk score criteria (**C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 Years, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, **A**ge 65 to 74 Years, **S**ex **C**ategory [CHA_2DS_2-VASc]) to identify patients with a CrCl < 15 mL/min for anticoagulation use in patients (with warfarin or apixaban) whereas the European Society of Cardiology and the Canadian Cardiovascular Society call for the need for trials and recommend no specific therapy. The American Heart Association recommendations seem to be influenced by the US Food and Drug Administration approval of the use of lower doses of DOACs (apixaban 2.5 mg twice daily, dabigatran 75 mg twice daily, edoxaban 30 mg daily, and rivaroxaban 15 mg daily) in patients with a CrCl of 15-30 mL/min on the basis of observational data.[78-83] Furthermore, the Food and Drug Administration approved apixaban 2.5 mg twice daily and rivaroxaban 15 mg daily in patients with CrCl < 15 mL/min and for patients receiving dialysis largely on the basis of pharmacokinetics studies.[81,84] A recent observational study showed that use of apixaban 5 mg twice daily has a lower risk of stroke and death compared with apixaban 2.5 mg daily and warfarin.[78] Because it was an observational study with high rates of anticoagulation discontinuation in the apixaban and warfarin groups, there are insufficient data to determine if apixaban 5 mg twice daily is beneficial over apixaban 2.5 mg twice daily in dialysis patients. Table 4 shows the various drugs, their metabolism, dialyzability, and dose adjustments on the basis of renal function.[84,85]

A practical, opinion-based and conservative approach to the management of anticoagulation for longstanding AF in patients with advanced kidney disease could be as follows:

(1) Forgo the use of current prediction scores because they have limited accuracy in the advanced CKD/dialysis

Table 1. Studies on warfarin use in patients with atrial fibrillation and kidney disease with their bleeding risk and stroke risk

Reference	Study design	Drugs compared (sample size)	Renal function	HR of all stroke (95% CI)	HR of major bleeding (95% CI)	HR of all-cause mortality (95% CI)
Banerjee et al.[129]	Prospective cohort study	Warfarin vs no warfarin	Serum Cr > 133 µmol/L in men and serum Cr > 115 µmol/L in women	0.79 (0.44-1.42)	0.96 (0.55-1.67)	0.77 (0.58-1.02)
Bonde et al.[130]	Retrospective cohort study	Warfarin (260) vs no warfarin (882)	Discharge from hospital with HD	Not reported	Not reported	CKD: 0.63 (0.59-0.67) HD: 0.85 (0.72-1.00)
Carrero et al.[131]	Prospective cohort study	Warfarin (66) vs no warfarin (412)	eGFR ≤ 15 mL/min	0.54 (0.42-0.69)	0.97 (0.78-1.21)	0.68 (0.61-0.76)
Chan et al.[132]	Retrospective cohort study	Warfarin (746) vs no warfarin (925)	HD	1.93 (1.29-2.89)	1.04 (0.73-1.46)	1.10 (0.94-1.29)
Chiu et al.[133]	Retrospective cohort study	Warfarin (31) vs no warfarin (73)	eGFR ≤ 60 mL/min	0.51 (0.10-2.55)	2.72 (0.38-19.30)	0.36 (0.16-0.81)
Findlay et al.[134]	Prospective cohort Study	Warfarin (118) vs no warfarin (175)	HD	1.024 (0.536-1.959)	Not reported	0.671 (0.505-0.891)
Friberg et al.[135]	Retrospective cohort study	Warfarin (3766) vs no warfarin (9669)	HD	0.78 (0.70-0.87)	1.10 (1.0-1.206)	0.75 (0.71-0.79)
Genovesi et al.[136]	Prospective cohort study	Warfarin (134) vs no warfarin (156)	HD	0.12 (0.00-14.41)	3.96 (1.15-13.64)	0.96 (0.59-1.56)
Lai et al.[137]	Retrospective cohort study	Warfarin (129) vs no warfarin (96)	HD and GFR < 15 mL/min	CKD: 0.71 (0.43-1.16) HD: 1.69 (0.72-3.97)	Not reported	Not reported
Olesen et al.[138]	Retrospective cohort study	Warfarin (178) vs no warfarin (723)	Discharged from hospital with HD	CKD: 0.85 (0.69-1.05) HD: 0.43 (0.26-0.71)	CKD: 1.36 (1.17-1.58) HD: 1.27 (1.01-1.60)	Not reported
Shah et al.[94]	Retrospective cohort study	Warfarin (756) vs no warfarin (870)	HD	1.14 (0.78-1.67)	1.44 (1.13-1.84)	Not reported
Shen et al.[139]	Retrospective cohort study	Warfarin (1838) vs no warfarin (10,446)	HD	0.83 (0.61-1.12)	Not reported	1.01 (0.92-1.11)
Tan et al.[140]	Retrospective cohort study	Warfarin (1651) vs no warfarin (4114)	HD and PD	Not reported	1.48 (1.32-1.66)	Not reported
Tanaka et al.[141]	Prospective cohort study	Warfarin (46) vs no warfarin (47)	HD	Not reported	Not reported	0.7117 (0.2475-2.0463)
Wakasugi et al.[142]	Prospective cohort study	Warfarin (28) vs no warfarin (32)	HD	3.36 (0.67-16.86)	0.85 (0.19-3.80)	1.00 (0.40-2.50)
Wang et al.[143]	Retrospective cohort study	Warfarin (59) vs no warfarin (82)	HD	1.01 (0.380-2.70)	3.26 (1.13-9.40)	0.825 (0.376-1.81)
Winkelmayer et al.[144]	Prospective cohort study	Warfarin (249) vs no warfarin (2064)	HD	0.92 (0.61-1.37)	1.11 (0.83-1.48)	1.06 (0.90-1.24)
Wizemann et al.[145]	Retrospective cohort study	Warfarin (509) vs no warfarin (2736)	HD	Age ≤ 65 years: 1.29 (0.45-3.68) Age 66-75 years: 1.35 (0.69-2.63) Age > 75 years: 2.17 (1.04-4.53)	Not reported	Not reported
Yodogawa et al.[146]	Retrospective cohort study	Warfarin (30) vs no warfarin (54)	HD	1.07 (0.20-5.74)	5.40 (0.59-49.66)	Not reported

CKD, chronic kidney disease; Cr, creatinine; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HD, hemodialysis; HR, hazard ratio; PD, peritoneal dialysis.

Table 2. Studies on direct oral anticoagulant use in patients with atrial fibrillation and kidney disease with their bleeding risk and stroke risk

Reference	Study design	Drugs compared (sample size)	Renal function	HR of stroke (95% CI)	HR of bleeding (95% CI)	HR of all-cause mortality (95% CI)
Eikelboom et al.[119]	RCT	Apixaban (857) vs aspirin (840)	eGFR 30-59 mL/min	0.32 (0.18-0.55)	Major bleeding: 1.2 (0.65-2.1)	0.86 (0.61-1.2)
Hohnloser et al.[120]	RCT	Apixaban (1365) vs warfarin (1382)	eGFR 25-50 mL/min	Cockcroft-Gault: 0.79 (0.55-1.14) CKD-EPI: 0.61 (0.39-0.94)	Major bleeding: Cockcroft-Gault: 0.50 (0.38-0.66) CKD-EPI: 0.48 (0.37-0.64)	Cockcroft-Gault: 0.86 (0.70-1.05) CKD-EPI: 0.78 (0.63-0.96)
Bohula et al.[121]	RCT	Edoxaban (1379) vs warfarin (1361)	CrCl 30-50 mL/min	0.87 (0.65-1.18)	Major bleeding: 0.76 (0.58-0.98)	0.82 (0.69-0.97)
Hijazi et al.[122]	RCT	Dabigatran 110 mg BID (1196) and dabigatran 150 mg BID (1232) vs warfarin (1126)	eGFR 30-50 mL/min	Dabigatran 110 mg BID Cockcroft-Gault: 0.85 (0.59-1.24) CKD-EPI: 0.78 (0.51-1.21) Dabigatran 150 mg BID Cockcroft-Gault: 0.56 (0.37-0.85) CKD-EPI: 0.55 (0.34-0.89)	Dabigatran 110 mg BID Major bleeding: Cockcroft-Gault: 0.99 (0.77-1.28) CKD-EPI: 1.02 (0.78-1.33) Dabigatran 150 mg BID Major bleeding: Cockcroft-Gault: 1.01 (0.79-1.30) CKD-EPI: 1.22 (0.95-1.58)	Dabigatran 110 mg BID Cockcroft-Gault: 1.16 (0.93-1.44) CKD-EPI: 0.97 (0.77-1.24) Dabigatran 150 mg BID Cockcroft-Gault: 1.00 (0.80-1.25) CKD-EPI: 1.03 (0.82-1.30)
Fox et al.[123]	RCT	Rivaroxaban (1474) vs warfarin (1476)	CrCl 30-49 mL/min	0.84 (0.57-1.23)	Major bleeding: 0.98 (0.84-1.14)	Not reported
Hori et al.[124]	RCT	Rivaroxaban (141) vs warfarin (141)	CrCl 30-49 mL/min	0.82 (0.25-2.69)	Major and minor bleeding: 1.22 (0.78-1.91)	Death from bleeding only: 1.04 (0.07-16.7)
Harel et al.[125]	Case-control study	Warfarin (2283 vs 5893) Dabigatran (52 vs 148) Rivaroxaban (10 vs 23) Cases: 2345 Controls: 6064	eGFR < 60 mL/min	N/A	Major bleeding Dabigatran: 0.98 (0.84-1.14) Rivaroxaban: 0.97 (0.44-2.11)	Not reported
Chan et al.[126]	Retrospective cohort study	Dabigatran (281) and rivaroxaban (244) vs warfarin (8064)	HD	Dabigatran: 1.71 (0.97-2.99) Rivaroxaban: 1.80 (0.89-3.64)	Major bleeding Dabigatran: 1.76 (1.44-2.15) Rivaroxaban: 1.45 (1.09-1.93) Minor bleeding Dabigatran: 1.10 (0.93-1.29) Rivaroxaban: 1.36 (1.12-1.64)	Not reported
Stanton et al.[127]	Retrospective cohort study	Apixaban (73) vs warfarin (73)	CrCl $\leq$ 25 mL/min and HD	No difference	Major bleeding: no difference	Not reported
Lee et al.[128]	Retrospective cohort study	Dabigatran/ rivaroxaban (59) vs warfarin (174)	eGFR < 60 mL/min	0.78 (0.21-3.00)	Major and minor bleeding: 0.18 (0.07-0.45)	Not reported
Siontis et al.[78]	Retrospective cohort study	Apixaban 5 mg BID (1034) vs apixaban 2.5 mg BID (1317) vs warfarin (23,172)	HD	Apixaban 5 mg BID: 0.64 (0.42-0.97) Apixaban 2.5 mg BID: 1.11 (0.82-1.50)	Apixaban 5 mg BID: 0.71 (0.53-0.95) Apixaban 2.5 mg BID: 0.71 (0.56-0.91)	Apixaban 5 mg BID: 0.63 (0.46-0.85) Apixaban 2.5 mg BID: 1.07 (0.87-1.33)
Sarratt et al.[82]	Retrospective cohort study	Apixaban (40) vs warfarin (120)	HD	Not reported	Not reported	Not reported

BID, twice per day; CKD-EPI, **C**hronic **K**idney **D**isease - **Epi**demiology Collaboration; CI, confidence interval; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HR, hazard ratio; N/A, not applicable; RCT, randomized controlled trial.

Table 3. Summary of guidelines about anticoagulation for stroke prevention in patients with nonvalvular AF and kidney disease

Canadian Cardiovascular Society	• NOAC is preferred over warfarin • Dose-reduced NOAC and warfarin (dose adjusted to target INR 2.0-3.0) can be used in patients with $CHADS_2 \geq 1$ and CrCl 30-49 mL/min[75]
American Heart Association	• Dabigatran 150 mg twice daily in patients with CrCl ≥ 30 mL/min • Rivaroxaban 20 mg od for patients with CrCl ≥ 50 mL/min • Apixaban 5 mg twice daily for patients with no more than 1 of the following characteristics: age ≥ 80 years, serum creatinine ≥ 1.5 mg/dL, or body weight ≤ 60 kg • Apixaban 2.5 mg twice daily for patients with at least 2 of the following: ≥ 80 years, body mass ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL74 • CHA2DS2-VASc score ≥ 2 in men or ≥ 3 in women and CrCl < 15 mL/min or receiving dialysis, reasonable to prescribe warfarin (INR 2.0-3.0) or apixaban • For moderate to severe CKD (serum creatinine ≥ 1.5 mg/dL [apixaban], CrCl 15-30 mL/min [dabigatran], CrCl ≤ 50 mL/min [rivaroxaban], or CrCl 15-50 mL/min [edoxaban]) with an elevated CHA2DS2-VASc score, reduced doses of direct thrombin or factor Xa inhibitors may be considered[114]
European Society of Cardiology	• Rivaroxaban 15 mg od if CrCl 30-49 mL/min • Apixaban 2.5 mg twice daily if Cr > 1.5 mg/dL, and age ≥ 80 years or weight ≤ 60 kg • Edoxaban 30 mg daily if CrCl < 50 mL/min • In dialysis patients: no consensus; controlled studies of anticoagulants (VKAs and NOAC) in AF patients receiving dialysis are needed[147]
Kidney Disease Improving Global Outcomes	• "Team-based, multidisciplinary active communication, particularly involving the nephrologist, cardiologist (or cardiac electrophysiologist), primary care physician, and when possible, clinical pharmacist, may be useful to evaluate the risk-benefit of any decision regarding choice of VKA or a DOAC"[84]
Asia Pacific Heart Rhythm Society	• For patients with eCrCl 30-49 mL/min, NOAC are preferred over VKA in stroke prevention in Asian individuals, because of a lower risk of ICH • Rivaroxaban 15 mg od dose is recommended when the Cockcroft-Gault CrCl is 30-49 mL/min • Apixaban 2.5 mg twice per day is used in patients with 2 or more of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL • Edoxaban, the 30-mg od dose is recommended in patients with any 1 of the following criteria: eGFR of 30-50 mL/min, a body weight ≤ 60 kg, or the concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors) • Low-dose NOAC (rivaroxaban 15 mg od, apixaban 2.5 mg twice per day, edoxaban 30 mg od) should be used with caution in patients with CrCl 15-30 mL/min) according to drug labels • Dabigatran should not be used in patients with CrCl < 30 mL/min • Until further RCTs to evaluate the net clinical benefit of OAC in dialysis patients with AF become available, the choice of long-term OAC should be highly individualized. We do not recommend the use of NOAC in patients with ESRD with an eCrCl < 15 mL/min or in patients receiving dialysis, until there are clinical data to confirm their safety and efficacy[148]

AF, atrial fibrillation; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); CKD, chronic kidney disease; CR, creatinine; CrCl, creatinine clearance; DOAC, direct oral anticoagulants; eCrCl, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ICH, intracranial hemorrhage; INR, international normalized ratio; NOAC, novel oral anticoagulants; OAC, oral anticoagulants; od, once daily; RCT, randomized controlled trial; VKA, vitamin K antagonist.

population.[86] If a patient had a previous stroke, lean toward anticoagulation, or a previous hemorrhage (within 1 year) lean toward no anticoagulation.

(2) For advanced CKD patients who are not receiving dialysis, lean toward anticoagulation with low-dose apixaban or warfarin.

(3) For dialysis patients, lean toward no anticoagulation and consider the patients' personal preference.

(4) If anticoagulation is being considered: (i) lean toward warfarin over DOACs if awaiting a kidney transplantation; (ii) ensure that reversal protocols or expertise for hemorrhage management is available with DOAC use; (iii)

Table 4. OACs metabolism and dosing based on eCrCl[84,85]

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Metabolism	Metabolized in liver, 25% excreted by kidney	80% Excreted by kidney	50% Excreted by kidney	66% Excreted by kidney	Metabolized by CYP2C9
Dialyzability	Low	High	None	None	None
eCrCl > 50 mL/min	5 mg twice daily	150 mg twice daily	60 mg once daily	20 mg once daily	Target INR 2-3
eCrCl 31-50 mL/min	5 mg twice daily	150 mg twice daily or 110 mg twice daily	30 mg once daily	15 mg once daily	Target INR 2-3
eCrCl 15-30 mL/min	Consider 2.5 mg twice daily	Unknown, consider 75 mg twice daily	Consider 30 mg once daily	Consider 15 mg once daily	Consider target INR 2-3
eCrCl < 15 mL/min (dialysis or no dialysis)	Unknown, possibly consider 2.5 mg twice daily	Not recommended	Not recommended	Unknown, possibly consider 15 mg once daily	No clear benefit or harm

CYP2C9, cytochrome P450 2C9; eCrCl, estimated creatinine clearance; INR, international normalized ratio; OAC, oral anticoagulant.

Table 5. Upcoming trials assessing safety of anticoagulation in CKD and ESKD

Trial name	Research question
Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) (AXADIA) NCT02933697	Assess safety of apixaban 2.5 mg twice daily vs VKA (target INR 2.0-3.0) in patients with nonvalvular AF and ESKD and receiving hemodialysis. Open-label, randomized controlled trial, phase IIIb[149]
Renal Hemodialysis Patients **Al**located-Apixaban versus Warfarin in Atrial Fibrillation (RENAL-AF) NCT02942407	Assess risk of bleeding in ESKD patients receiving hemodialysis who are treated with apixaban 5 mg twice daily or warfarin (target INR 2.0-3.0) for stroke prevention in AF. Prospective, randomized, open-label, blinded end point evaluation trial[150]
Oral Anticoagulation in Haemodialysis Patients (AVKDIAL) NCT02886962	Assess hemorrhagic and thrombotic risks of no anticoagulation with warfarin (target INR 2.0-3.0) in hemodialysis patients with AF. Open-label, prospective, randomized clinical trial[151]
Strategies for the Management of **A**trial **F**ibrillation in Pati**e**nts Receiving **H**emo**d**ialysis (SAFE-HD)	Assess feasibility and safety of VKA vs apixaban vs no anticoagulation among patients receiving hemodialysis with nonvalvular AF

AF, atrial fibrillation; CKD, chronic kidney disease; ESKD, end-stage kidney disease; INR, international normalized ratio; VKA, vitamin K antagonist.

calciphylaxis should be an absolute contraindication for warfarin; (iv) lean toward DOACs if a history of significant vascular calcification; (v) monitor the international normalized ratio judiciously with warfarin use; (vi) implement bleeding reduction strategies such as discontinuation of antiplatelet agents, minimize anticoagulation with the dialysis procedure, optimize dialysis treatment efficiency (maximize platelet function), treat vitamin K deficiencies, prescreen for occult gastrointestinal bleeding, and assess for prophylactic proton pump inhibitor use.

Ongoing trials of anticoagulation in the advanced kidney disease population are summarized in Table 5. Because the evidence remains uncertain and there is a strong propensity for harm with therapy, research in decision-making tools that incorporate kidney disease patient's values and preferences are a key area for future investigation.

Special considerations with the use of anticoagulation in patients with advanced kidney disease

Use of estimating equations for anticoagulation dosing. The GFR is commonly estimated using various estimated equations for practical use. The most common and widely used in Canada is the CKD-EPI formula with most jurisdictions having moved to automated eGFR reporting when outpatient serum creatinine laboratory values are ordered.[87,88] However most studies, including the more recent DOAC randomized trials, use the CrCl to estimate glomerular function and use the Cockcroft-Gault equation. This is a notable key detail because in extremes of age and weight, the 2 measures are highly discrepant. For example, a 60-year-old man who weighs 90 kg with a serum creatinine of 190 μmol/L will have a CrCl using Cockcroft-Gault of 30 mL/min and an eGFR of 19 mL/min. In this scenario, DOACs may be dose-reduced or discontinued altogether on the basis of the eGFR resulting in underdosing. Over-and underdosing with DOACs are associated with clinical adverse events. Yao et al. reported over- and underdosing of DOACs to be associated with an adjusted RR of 2.19 (95% CI, 1.07-4.46) of hemorrhage and 4.87 (95% CI, 1.30-18.26) for systemic embolism.[89] On the basis of these discrepancies, it is recommended that CrCl be used with DOAC dosing initiation and adjustments to mimic efficacy and safety determined in clinical trials.

The applicability of prediction scores in patients with kidney disease. Prediction tools for stroke or bleeding are the basis of clinical decision-making in the general population with AF. However the utility of such tools, even when including kidney-specific parameters, in patients with advanced CKD or who are receiving dialysis is less clear.[90] The currently existing portfolio of risk tools have poor discrimination (area under the receiver operator curve < 0.6 in most cases) when applied to patients with advanced CKD or who are receiving dialysis.[91] This is not surprising because current prediction tools were not derived in populations with advanced CKD or who were receiving dialysis, do not account for the high competing risk of death associated with kidney disease (50% at 5 years for dialysis), and incorporate limited kidney-specific risk factors such as chronic inflammation, anticoagulation with the dialysis procedure, disorders of mineral metabolism, and vascular calcification and anticoagulation use with the dialysis procedure. The scenario is similar for bleeding risk scores such as **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly (HAS-BLED), ATRIA, **H**epatic or Renal Disease, **E**thanol Abuse, **M**alignancy, **O**lder (Age > 75 Years), **R**educed Platelet Count or Function, **R**ebleeding Risk, **H**ypertension (Uncontrolled), **A**nemia, **G**enetic Factors, **E**xcessive Fall Risk, and **S**troke (HEMORR$_2$HAGES), and **O**utcomes **R**egistry for **B**etter **I**nformed **T**reatment of Atrial Fibrillation (ORBIT). A recent study in dialysis patients showed that all 4 risk scores had a poor discrimination (area under the receiver operator curve < 0.6) and significantly underestimated the bleeding risk.[92] So, with the poor applicability of current risk prediction tools, their utility in decision-making regarding the use of anticoagulation in this population is unclear.[27]

Patterns of anticoagulation use

These uncertainties are apparent when treatment patterns of anticoagulation use in AF patients with advanced CKD or who are receiving dialysis are examined. The **D**ialysis **O**utcomes and **P**ractice **P**atterns **S**tudy (DOPPS), an international dialysis registry used to examine practice patterns between countries and dialysis facilities, reported only 20% of Canadian dialysis patients with AF were being prescribed an oral anticoagulant and this was among the highest percentage of oral anticoagulation prescriptions compared with patients from Europe, United States of America, Japan, Australia, and New Zealand.[93] In addition to intercountry variation, there was significant within-country variation between facilities ranging from 0 to 45% of the dialysis patients were using an oral anticoagulant, mostly warfarin (85%).[93] More recent reports from Ontario/Quebec and the United States reported 46% and 24% of those with AF were prescribed warfarin.[94,95] DOAC use is increasing over time with recent reports from the United States showing 23.5% of CKD patients and 11.6% taking them regularly for stroke prevention.[96] Clinical uncertainty is further highlighted by a recent survey of Canadian nephrologists treating dialysis patients with nonvalvular AF, which revealed that warfarin was more likely to be recommended in patients with high stroke risk and low bleeding risk and less likely to be prescribed in patients with moderate stroke risk and high bleeding risk.[97]

Complications of VKA Use: Accelerated Vascular Calcification

Vitamin K deficiency is highly common in the advanced CKD and dialysis population due to low potassium-phosphate diets, malnutrition, and frequent antibiotic use.[98] This deficiency contributes to the inability to maintain anticoagulation with VKAs within the therapeutic range. Another key role of vitamin K is the inhibition and/or repair of vascular calcification (through activation of matrix Gla protein) and the use of VKAs are associated with accelerated vascular calcification. For example, in patients with CKD, 18 months of warfarin exposure was associated with an increased risk of aortic valve calcification (odds ratio, 3.77; 95% CI, 0.97-14.7; $P = 0.055$).[99] Because vascular calcification and vitamin K deficiency are so prevalent in the dialysis population, trials such as the **I**nhibiting the **P**rogression of **A**rterial **C**alcification With Vitamin **K** in **H**emo**d**ialysis Patients (iPACK-HD) are under way to examine if vitamin K supplementation in ESKD patients can attenuate the progression of vascular calcification.[100]

Vascular calcification at its most extreme and dangerous form is seen in a condition termed calcific uremic arteriolopathy, also known as calciphylaxis.[101] This can occur in patients with various stages of CKD, more commonly in patients who undergo peritoneal dialysis rather than hemodialysis and rarely in patients without any kidney disease.[102] In calciphylaxis, calcification of arterioles supplying adipose and skin tissues leads to subcutaneous painful calcific nodules. These lesions initially appear as violaceous skin plaques that can progress to ulcers with black eschars.[103] Pain and infection of these lesions contribute to significant morbidity with more than 70% of the patients requiring hospitalization.[104] This condition has poor survival, quoted at 45%-80% mortality at < 1 year.[103] Use of VKAs and reduced vitamin K levels are a major risk factor for calciphylaxis. The Evaluation of **Vit**amin **K** Supplementation for **C**alcific **U**remic **A**rteriolopathy (VitK-CUA) trial is ongoing to determine if vitamin K supplementation in chronic hemodialysis patients with calciphylaxis is safe, can increase levels of carboxylated matrix Gla protein and improve calciphylaxis pain and lesion size.[105] Half of calciphylaxis patients who are receiving dialysis and one-quarter of those with advanced CKD are associated with VKA use.[106,107] In this regard, a history of or current calcific uremic arteriolopathy should be considered an absolute contraindication for VKA use with careful consideration of VKA initiation in patients deemed at high risk (insulin-dependent diabetes mellitus, peritoneal dialysis use, disorders of mineral metabolism, concurrent corticosteroid or vitamin D use).[108]

Use of Anticoagulation During the Dialysis Procedure

Dialysis patients receive anticoagulants on a regular basis to prevent thrombosis that is promoted by contact of blood with the dialysis membranes. Approximately 81% of Canadian patients use heparin during dialysis for prevention of membrane thrombosis.[109] The use of LMWH was low at 3% in 2013; however, its use in recent years has been increasing.[93] Although the evidence for use of anticoagulants such as UFH or LMWH during dialysis are mostly observational, the National Kidney Foundation supports the use of heparin and LMWH during dialysis to increase urea clearance and dialysis adequacy.[110] Results are pending from the randomized controlled trial, Intermittent **Hemo**dialysis Anticoagulation With **Tin**zaparin Vs Unfractionated Heparin: A Pilot Multicentre Randomized Controlled Trial (HEMO-TIN), which was completed in Hamilton, Ontario to compare use of UFH with LMWH in dialysis patients.[111] For more than 60 years UFH has been used during hemodialysis to prevent thrombosis of the dialysis membranes. Despite this, because of lack of clinical trials, there is no standard dosing of heparin for dialysis. Although weight-based heparin dosing protocols exist, variability in patient's ability to eliminate heparin via the hepatic clearance affects the practical use of these protocols. Therefore, any dose adjustment is clinically on the basis of circuit thrombosis and signs of bleeding. On average, 2000-4000 IU of heparin is administered as a bolus at the start of dialysis followed by 500 to 2000 IU per hour infusion during dialysis. LMWH is as safe and efficacious as UFH for bleeding risks and prevention of circuit thrombosis. In fact, it is easier to dose according to weight. It might also have less risk of heparin-induced thrombocytopenia, triglyceridemia, and bone-related side effects compared with UFH, yet, UFH remains widely used in dialysis patients at present.[112] However, the use of LMWH during dialysis is increasing.[113]

Alternative Therapies: Left Atrial Appendage Closure

In the interim, for patients who have high bleeding risks and AF, an alternative option to reduce risk of stroke is AF ablation and left atrial appendage (LAA) occlusion. LAA occlusion can be done percutaneously using the Watchman device (Boston Scientific, Marlborough, MA) or during cardiac surgery. As per a recent update of the American Heart Association guidelines, percutaneous LAA occlusion using the Watchman device (Boston Scientific) is suggested for patients who are not candidates for receiving long-term oral anticoagulation therapy.[114] A registry study reported results of LAA closure in patients according to eGFR with 80 patients having an eGFR < 30 mL/min or are receiving dialysis.[115] A further Italian prospective cohort study reported only 3 complications in 50 dialysis patients who underwent LAA occlusion.[116] On the basis of a small number of complications (6 across 2 studies, all periprocedural), LAA occlusion appears to offer a potential safe alternative in advanced CKD. On the contrary, a systematic review and meta-analysis of 4 observational studies with more than 1000 patients showed that AF ablation has been shown to have high recurrence rates after single catheter ablation in patients with kidney disease (HR, 1.96; 95% CI, 1.35-2.85; $P = 0.0004$).[117] A Japanese study showed that multiple AF ablation procedures were successful in restoring sinus rhythm in dialysis patients.[118]

Conclusion

Patients with advanced CKD are at an increased risk of thrombosis and hemorrhage and this risk increases with worsening proteinuria and a progressive decline in GFR. For patients who are receiving dialysis, disorders of hemostasis and use of intravenous anticoagulation during dialysis further compound the risks of bleeding. Although oral anticoagulants have been proven beneficial in reducing thrombotic risks in the general population for indications such as VTEs and AF, their benefit in patients with advanced kidney disease and receiving dialysis is unclear. Unfortunately, available data show that they confer a high risk of major and minor bleeding, and life-threatening vascular calcification, and this varies on the basis of the type of oral anticoagulant. Therefore, at present, the important question of do dialysis patients need oral anticoagulation to prevent thrombosis remains unanswered. Because of the lack of large clinical trials to guide our decision-making, it is prudent to consider the recommendations from guidelines and weigh and discuss a given individuals' risks of bleeding and thrombosis with the patient. We have provided some principles to consider and guide therapeutic decision-making, but ultimately, the decision to anticoagulate and which anticoagulant to use needs to be a shared decision between the patient, their cardiologist, and their nephrologist. Randomized controlled trials comparing DOACs with warfarin and no anticoagulation are required to help physicians and patients decide whom to anticoagulate and with which anticoagulant.

Disclosures

M.M.S. has received a grant for Otsuka and speaker fees from Astrazeneca. The other authors have no conflicts of interest to disclose.

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