Anticoagulation in patients with kidney failure on dialysis: factor XI as a therapeutic target

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Chronic kidney disease is present in almost 10% of the world population and is associated with excess mortality and morbidity. Reduced glomerular filtration rate and the presence and extent of proteinuria, key domains of chronic kidney disease, have both been shown to be strong and independent risk factors for cardiovascular disease. Patients with kidney failure requiring dialysis are at highest risk for cardiovascular events (e.g., stroke or myocardial infarction), and of developing chronic cardiovascular conditions, such as heart failure. Despite the high burden of cardiovascular disease, there is a paucity of evidence supporting therapies to reduce this risk. Although long-term anticoagulant treatment has the potential to prevent thromboembolism in persons with kidney failure on dialysis, this possibility remains understudied. The limited data available on anticoagulation in patients with kidney failure has focused on vitamin K antagonists or direct oral anticoagulants that inhibit thrombin or factor (F) Xa. The risk of bleeding is a major concern with these agents. However, FXI is emerging as a potential safer target for new anticoagulants because FXI plays a greater part in thrombosis than in hemostasis. In this article, we (i) explain the rationale for considering anticoagulation therapy in patients with kidney failure to reduce atherothrombotic events, (ii) highlight the limitations of current anticoagulants in this patient population, (iii) explain the potential benefits of FXI inhibitors, and (iv) summarize ongoing studies investigating FXI inhibition in patients with kidney failure on dialysis.

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Chronic kidney disease (CKD), as indicated by a reduced glomerular filtration rate or persistent proteinuria, is a direct cause of global morbidity and mortality.[1] The Global Burden of Disease study estimated the worldwide prevalence of CKD to be 9.1% in 2017.[2] Although the global mortality attributable to noncommunicable diseases, such as cardiovascular disease, cancer, and chronic obstructive pulmonary disease, has declined by 30%, 15%, and 41%, respectively, the age-standardized mortality of CKD has remained unchanged between 1990 and 2017.[2] Therefore, there is a continuing urgent need for improvements in CKD management.[2,3]

The burden extends beyond CKD itself, as CKD is also associated with an array of comorbid conditions. In particular, reduced glomerular filtration rate and presence and extent of proteinuria, both key domains of CKD, have been shown to be strong and independent risk factors for cardiovascular disease.[1] Indeed, patients with the most progressive form of CKD, those with end-stage kidney disease, also known as kidney failure[4] requiring dialysis, are at highest risk for cardiovascular events, including myocardial infarction, stroke, and other thromboembolic events, such as deep vein thrombosis and pulmonary embolism. These patients often have evidence of systemic atherosclerosis that can lead to heart failure, abdominal aortic aneurysms, and peripheral artery disease (PAD).[1] However, despite the high burden of cardiovascular disease, there is a paucity of evidence supporting therapies to reduce this risk in patients with kidney failure requiring dialysis. Most cardiovascular outcome trials (randomized or observational) have excluded patients with advanced kidney disease.[3] Indeed, the few trials that did specifically test cardiovascular interventions in this population were inconclusive.

Anticoagulation therapy has the potential to reduce atherothrombotic events and venous thromboembolism (VTE) in patients with kidney failure on dialysis. However, such therapy has been understudied in this patient population because of concerns about the risk of bleeding. Although anticoagulants reduce the risk of thromboembolic events in patients with early-to-moderate-stage CKD,[5] their use in patients with kidney failure requiring dialysis is complicated by the fact that several oral anticoagulants are cleared by the kidneys. Despite

a particularly high unmet need for treatment among patients with kidney failure undergoing dialysis, studies investigating the effectiveness of anticoagulants have therefore typically excluded patients with kidney failure requiring dialysis.[6–9] Moreover, trials of oral anticoagulation in patients with kidney failure on dialysis who have atrial fibrillation have been attempted, but problems with patient recruitment have precluded their planned completion targets.

Most of the evidence on long-term anticoagulation in individuals with kidney failure undergoing dialysis has focused on treatment with vitamin K antagonists[10] or direct oral anticoagulants (DOACs) that inhibit thrombin or factor Xa. However, other targets in the coagulation cascade have recently attracted interest for potential intervention. In particular, factor XI (FXI) plays a key role in thrombosis but appears to be less important for hemostasis; targeting it may, therefore, be particularly attractive in patients undergoing hemodialysis, a population who are particularly prone to bleeding.[11]

Phase 2 trials assessing the efficacy and safety of FXI and FXIa inhibitors for the prevention of cardiovascular events in patients with kidney failure undergoing hemodialysis have started enrolling worldwide. This review explains the rationale for such studies by defining the unmet need and describing the burden of disease, with a focus on the contribution of atherothrombotic events to morbidity and mortality. It also highlights the limitations of currently available anticoagulants in patients with kidney failure and the potential advantages of the emerging class of FXI/FXIa inhibitors, and briefly describes ongoing studies investigating FXI inhibition in patients with kidney failure.

Burden of kidney failure and its comorbidity with cardiovascular disease

From 1990 to 2017, the global incidence of kidney failure treated by dialysis increased by 43.1%.[12] Globally, 2.62 million people received kidney replacement therapy in 2010; 78% of them underwent dialysis, and 22% lived with a kidney transplant.[13] In the United States alone, the reported prevalence of kidney failure requiring dialysis or kidney transplant in the second quarter of 2020 was 802,759.[14]

Cardiovascular disease is common in patients with kidney failure. Numerous studies indicate a link between declining kidney function and increased mortality, cardiovascular events, and hospitalizations[15]; adjusted mortality in people with kidney failure requiring dialysis was reported as 164 per 1000 patient-years in the United States in 2016.[14] Almost half the deaths of people with kidney failure are attributed to cardiovascular disease.[14,16] The risk of cardiovascular events increases with worsening kidney function, with patients starting hemodialysis being particularly likely to experience them.[15,17] In addition, compared with the general population, individuals with kidney failure undergoing dialysis in the United States have a 2.1- to 2.3-fold higher risk of pulmonary embolism, depending on the absence or presence of comorbidities.[18] Moreover, the presence of VTE in patients undergoing dialysis is associated with an increased risk of bleeding and all-cause mortality compared with that seen in patients on dialysis without VTE.[19] The likelihood of stroke also increases as the glomerular filtration rate declines,[20] with risks several fold higher in patients with kidney failure than in the general population.[21,22] In long-term hemodialysis patients, around 44% of overall mortality is due to cardiac disease, with about 22% of these cardiovascular deaths attributed to myocardial infarction.[23] Furthermore, there are indications of an early hazard of myocardial infarction related to dialysis initiation. A database review study in the United States reported that 29% of the myocardial infarctions occurred within 1 year and 52% occurred within 2 years of dialysis initiation. In kidney transplant patients, 15% of the myocardial infarctions occurred within the first year after transplantation, and 29% occurred within 2 years.[23] Another cardiovascular comorbidity for patients with CKD with significant consequence is PAD. In the general population, the prevalence of PAD increases with age, from 3% to 5% between the ages of 45 and 49 years, to up to 15% to 18% in individuals aged ≥85 years.[24] Among patients on hemodialysis, the prevalence of PAD is much higher: a prevalence of 24% in those aged 61 years has previously been reported.[25] A retrospective analysis revealed that patients with both CKD and PAD had a mortality of 45%, whereas mortality rates in patients with CKD alone, PAD alone, and neither condition were 28%, 26%, and 18%, respectively.[26] Patients with kidney failure are greatly affected by PAD and have particularly high rates of amputations. In 2014, the rate of lower extremity amputation in US dialysis patients was 2.66 per 100 person-years, and the 1-year mortality following amputation was 42.6%.[27]

Pathophysiology of cardiovascular events in kidney failure

Several reviews explain the pathophysiology of cardiovascular events in kidney failure[28–32]; as such, a summary is provided here for context.

There is evidence of a strong bidirectional relationship between CKD and cardiovascular disease. In the context of the kidney, mechanisms associated with the development of cardiovascular disease include traditional (e.g., age, sex, and family history), nontraditional (e.g., oxidative stress and fibrosis), and CKD (uremia)–related factors, such as disturbances of bone-mineral metabolism, accelerated cardiovascular and valvular calcification, endothelial dysfunction, and uremic cardiomyopathy.[28] In the context of the heart, disturbed hemodynamics and the activation of neurohormonal and inflammatory mediators are associated with the development and progression of CKD.[28]

Individuals with CKD, including those with kidney failure, usually have multiple risk factors for cardiovascular disease, many of which result in myocardial and blood vessel remodeling. Modifiable risk factors include hypertension, dyslipidemia, diabetes, albuminuria, estimated glomerular filtration rate, obesity, and smoking; potentially modifiable factors include toxic metabolites, inflammation, oxidative

stress, endothelial dysfunction, hyperuricemia, anemia, and malnutrition, whereas nonmodifiable risk factors include age, sex, and family history (Figure 1).[33–35] During the later stages of CKD, there is an increased risk of bleeding even in the absence of coagulation-modifying therapies. This reflects a dysfunction of the coagulation system (Figure 2).[36] Reduced platelet adhesion and aggregation, reflecting alterations in prostaglandin metabolism and thromboxane A_2 release, are common findings,[37] coupled with a reduction in platelet–vessel wall interactions.[36] CKD-related anemia can exacerbate the impaired platelet–vessel wall interaction due to decreased adenosine diphosphate release and increased production of prostaglandin I_2, an inhibitor of platelet aggregation. Therapeutics used in patients with kidney failure may further increase the risk of bleeding: β-lactam antibiotics can interfere with adenosine diphosphate receptors, and aspirin and other nonsteroidal anti-inflammatory drugs are known to affect platelet function via the cyclooxgengase pathway.[38]

The high risk of thromboembolic complication in patients undergoing hemodialysis may reflect, at least in part, the impact of extracorporeal devices, such as the dialysis membrane, on their coagulation system as well as other risk factors, such as arrhythmias and temporary interruptions of the extracorporeal circuit occurring during dialysis, in addition to uremic factors, and the presence of inflammation. Indeed, most patients undergoing dialysis are considered to have a hypercoagulable state, as evidenced by high levels of von Willebrand factor, fibrinogen, and D-dimer.[39]

Patients with CKD are also at higher risk of intracranial hemorrhage: patients with an estimated glomerular filtration rate <45 ml/min per 1.73 m^2 have a 4-fold higher risk of mortality compared with patients with no kidney impairment (estimated glomerular filtration rate >60 ml/min per 1.73 m^2).[40] In patients on dialysis, intracranial hemorrhage is associated with the highest mortality risk of all stroke subtypes, and is likely exacerbated by uremic platelet dysfunction and the use of heparin or other anticoagulants during dialysis.[41]

The use of long-term anticoagulation therapy in patients with kidney failure is low, likely because of the associated risk of bleeding,[42] but also due to the uncertainty as to the extent to which the cardiovascular events are atherothrombotic in origin. The approval of newer, target-specific oral anticoagulants for the prevention of cardiovascular events, such as stroke and pulmonary embolism, including the 2 factor Xa inhibitors, rivaroxaban and apixaban, is welcome, yet there are limited data in this population of interest, because individuals with kidney failure undergoing dialysis were

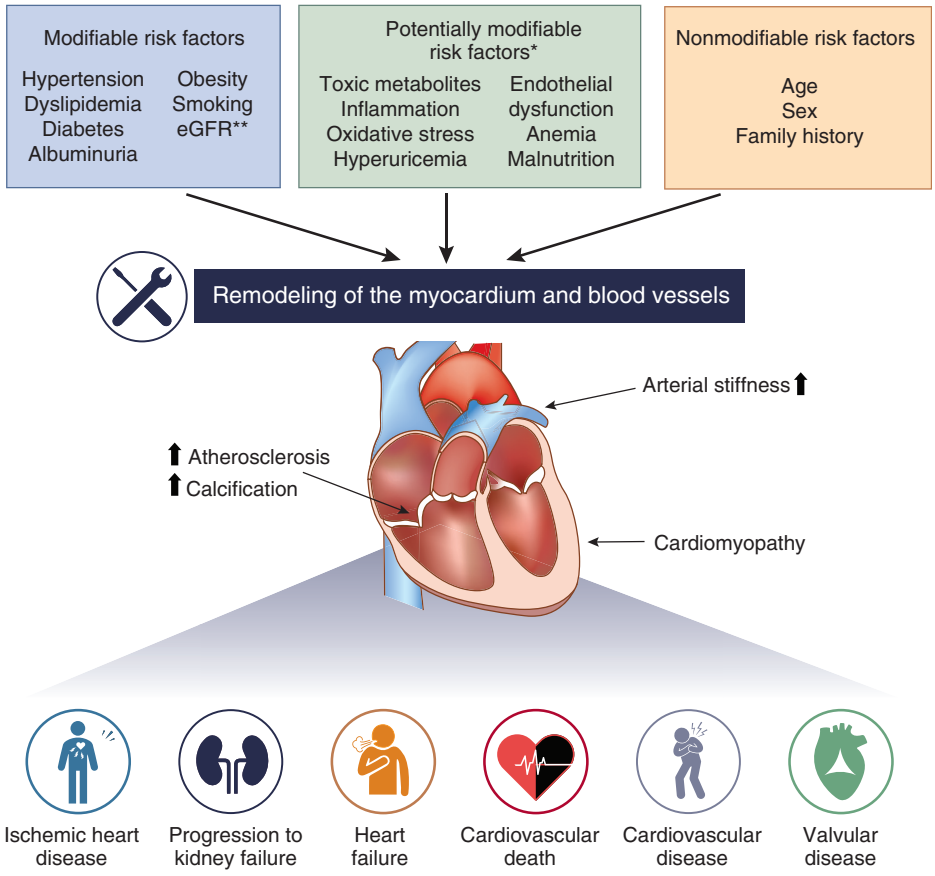

Figure 1 | Multiple risk factors in the pathophysiology of cardiovascular events in chronic kidney disease. *A potentially modifiable factor is one that is not fixed, but no intervention has been identified to (i) modify that factor and (ii) reduce cardiovascular risk. **Estimated glomerular filtration rate (eGFR) decrease with renin-angiotensin system blocker or sodium/glucose cotransporter-2 inhibitor is beneficial.

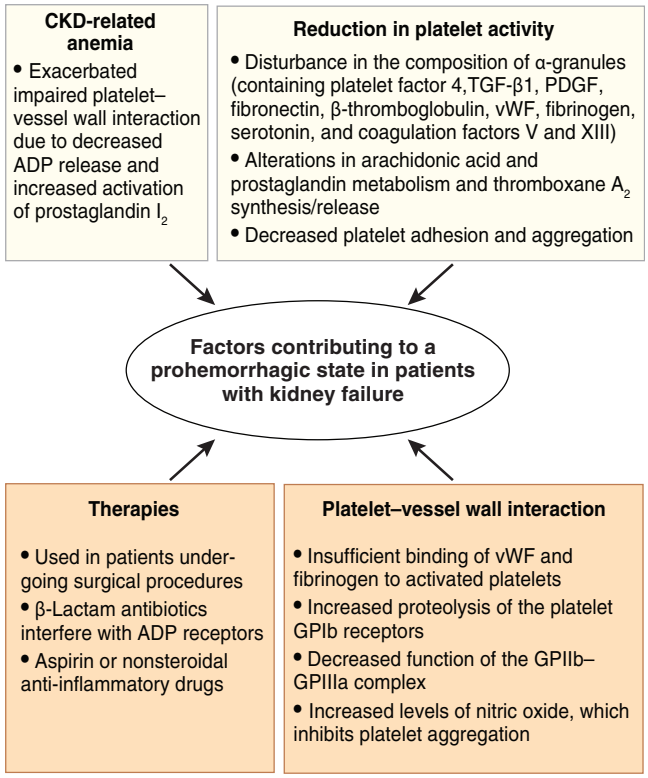

Figure 2 | Factors contributing to a prohemorrhagic state in patients with kidney failure. ADP, adenosine diphosphate; CKD, chronic kidney disease; GPIb, platelet glycoprotein Ib; GPIIb, platelet glycoprotein IIb; GPIIIa, platelet glycoprotein IIIa; PDGF, platelet-derived growth factor; TGF-β1, transforming growth factor beta 1; vWF, von Willebrand factor.

excluded from the pivotal trials. Despite this, dose recommendations for the use of these agents in dialysis were subsequently introduced on the basis of scant evidence.[43–45] These therapies are being used in patients with kidney failure with atrial fibrillation, where there is a known risk of stroke, but are not routinely used in patients with kidney failure without atrial fibrillation.

Thrombosis prevention using anticoagulants in patients with kidney failure: the ongoing debate

In patients with kidney failure, the rationale for considering anticoagulant therapy over no treatment or the use of acetylsalicylic acid has been reported in patients with atrial fibrillation, because much of the existing, although limited, literature on long-term anticoagulation has focused on this population owing to the elevated stroke risk.[46] The potential of anticoagulants to prevent major adverse cardiovascular events in patients with kidney failure without atrial fibrillation is even less well supported. However, there are important reasons why anticoagulation should be considered more broadly to prevent adverse cardiovascular outcomes other than ischemic stroke, and several sources of evidence from the general population further support this.

The benefits and risks of antithrombotic therapy (both antiplatelet and anticoagulant) must be carefully evaluated in patients at high risk of bleeding.[47] Results of observational studies in patients with kidney failure on dialysis suggest that the harms of vitamin K antagonists, such as warfarin, outweigh their potential benefits.[16] A systematic review[48] of trials with patients with nonvalvular atrial fibrillation who do not have advanced kidney disease concluded that DOACs have a more favorable safety profile than vitamin K antagonists, but bleeding remains a potential risk because they are eliminated, at least in part, by the kidneys, and moderate-to-severe kidney disease increases the likelihood of bleeding.[49,50] In the Valkyrie study, encompassing 132 patients on hemodialysis with atrial fibrillation, treatment with a reduced dose of rivaroxaban significantly decreased the composite outcome of fatal and nonfatal cardiovascular events and major bleeding complications compared with vitamin K antagonist.[51] Most evidence of the benefit-risk balance of DOAC therapy in patients with kidney failure comes from observational studies rather than randomized controlled trials,[22,46] owing largely to the fact that DOACs are not specifically approved for use in patients with kidney failure.

A retrospective cohort study of older patients with newly diagnosed atrial fibrillation undergoing maintenance hemodialysis found that treatment with warfarin compared with nonuse of warfarin was associated with a 32% reduction in the rate of ischemic stroke but found no effect on cardiovascular or all-cause mortality.[52] In a subsequent analysis using a similar design, initiation of apixaban therapy did not reduce the risk of ischemic stroke or myocardial infarction compared with no anticoagulation treatment.[53] Apixaban therapy was, however, associated with a higher incidence, even with reduced apixaban dosage, of fatal or intracranial bleeding compared with no anticoagulant use.[53]

Although these 2 observational studies compared an oral anticoagulant with no anticoagulant use, a different retrospective cohort study of patients with kidney failure and atrial fibrillation undergoing dialysis compared new users of warfarin versus apixaban. This study found that treatment with apixaban was associated with a lower rate of major bleeding compared with warfarin and resulted in reductions in the risk of thromboembolism and mortality.[54]

Few randomized trials have investigated oral anticoagulation in patients undergoing hemodialysis. The RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (NCT02942407) trial sought to enroll 760 patients with atrial fibrillation undergoing maintenance hemodialysis to receive warfarin or apixaban (5 mg twice daily with label-compliant dose adjustment) to evaluate noninferiority in terms of major and clinically relevant bleeding events.[55] Unfortunately, enrollment was slower than expected, and the study was terminated after recruitment of 154 patients. Consequently, the study was underpowered for its intended noninferiority comparison. Nonetheless, the results from the trial suggest that apixaban was associated with similar rates of bleeding and stroke compared with warfarin in the studied population. Of value was the inclusion of 69 (45%) patients who were of African American descent,

making the trial unique in terms of its significant minority cohort.[56] Detailed pharmacokinetic and pharmacodynamic data were obtained from participants in the apixaban group, and these data may provide new insights. Enrollment difficulties have also been reported for a similar phase 3 study in Germany (ClinicalTrials.gov identifier: NCT02933697) with a planned apixaban dose of 2.5 mg.[57] Both of these studies had active arm comparisons. We are aware of a study aspiring to evaluate the overall benefits and risks of vitamin K antagonists in patients with atrial fibrillation and kidney failure undergoing dialysis (ClinicalTrials.gov identifier: NCT02886962); to date (April 2021), recruitment of participants into this study has started.[58] The lack of evidence of the effectiveness of oral anticoagulation in this particularly high-risk population highlights an unmet need for more studies of anticoagulants that can be used effectively and safely in people with CKD.[59]

Rationale for studying FXI inhibitors in patients undergoing hemodialysis

FXI inhibition is a potential therapeutic avenue currently under investigation that may be particularly attractive in populations at high background bleeding risk, such as those with kidney failure on dialysis. FXI is part of the intrinsic (contact-activated) pathway of coagulation (Figure 3).[60] FXI is believed to be essential for thrombus growth and stabilization,[61] and can be activated by factor XIIa or by thrombin[48] via the positive feedback amplification loop.[50]

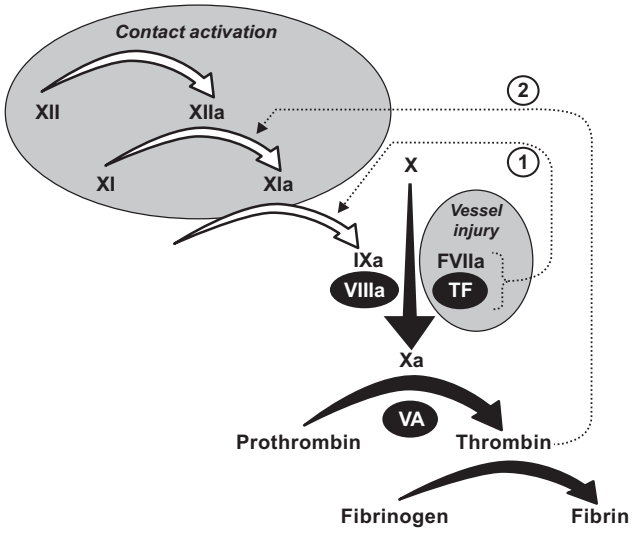

Figure 3 | Overview of factor XIa in the coagulation cascade. Roman numerals indicate unactivated coagulation factors; activated factors are shown with a lowercase *a*. White arrows indicate reactions of the intrinsic coagulation pathway. The dotted lines (*1*) and (*2*) indicate reactions that are not part of the classic coagulation model. The VIIa/tissue factor (TF) complex of the extrinsic pathway is activated by tissue trauma. Reproduced with permission from Gailani D, Renné T. Intrinsic pathway of coagulation and arterial thrombosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, volume 27, issue 12, pages 2507–2513,[60] https://www.ahajournals.org/doi/10.1161/ATVBAHA.107.155952, American Heart Association. Copyright © 2007 The Authors.

Congenital FXI deficiency is rare in the general population (around 1 in 1,000,000), with a higher prevalence of around 1 in 450 in the Ashkenazi Jewish community.[62] It is associated with a relatively mild bleeding diathesis that is not clearly correlated with plasma levels of FXI.[63] Spontaneous bleeding into muscles, joints, or the brain does not occur, which distinguishes FXI deficiency from deficiencies of factor VIII or factor IX, hemophilia A and B, respectively. Patients with FXI deficiency rarely have spontaneous bleeding, but can experience bleeding events after trauma or surgery, particularly in tissues with high fibrinolytic activity, such as the oral cavity, nose, and urinary tract.[52,61] Consequently, treatments that target the inhibition of FXI are hypothesized to have the potential to reduce the risk of thrombosis, due to its essential role in feedback amplification in thrombus stabilization and growth, with little impact on hemostasis,[61] which is believed to be predominantly mediated by the extrinsic pathway of coagulation.[64]

A population-based historical cohort study of adults in Israel with known FXI status showed that FXI deficiency was associated with a decreased incidence of cardiovascular events (stroke, transient ischemic attack, and myocardial infarction) and VTE.[65] Using data from participants in the UK Biobank and 2 other large-scale genome-wide association studies, another analysis found that in individuals with 22% lower FXI levels, which resulted from genetic predispositions compared with individuals without genetic predisposition, there was a reduced risk of venous thrombosis and ischemic stroke without an increase in major bleeding events.[66]

Several approaches to FXI and FXIa inhibition are under investigation (Table 1). The FXI and FXIa inhibitors most advanced in clinical testing include the antisense oligonucleotide BAY 2976217 (IONIS FXI-LRx), the monoclonal antibodies osocimab, xisomab 3G3 (AB023), and abelacimab, and the small molecules BAY 2433334 and BMS-986177. Although small-molecule inhibitors are thought to have low clearance by the kidneys (8%–20%), antisense oligonucleotides and monoclonal antibodies are not cleared by the kidneys and therefore offer an additional benefit in patients with kidney failure undergoing hemodialysis.[67] Dialysis will not remove monoclonal antibodies or antisense oligonucleotides, and we are unaware of any studies that determine whether dialysis removes specific small-molecule inhibitors; however, the fact that they are highly protein bound would unlikely make them dialyzable.

Targeting the FXI zymogen with an antisense oligonucleotide (IONIS-FXI Rx) resulted in dose-dependent reductions in arterial and venous thrombosis with no increase in bleeding time in mouse models.[68] A similar approach in a rabbit model of catheter thrombosis resulted in prolongation of the time to catheter occlusion compared with control.[69] Furthermore, administration of IONIS-FXI Rx resulted in a sustained antithrombotic effect without an increase in bleeding in a baboon model of thrombosis and hemostasis.[70] IONIS-FXI Rx was investigated in an open-label, parallel-group, phase 2 trial in patients undergoing elective unilateral total knee arthroplasty.[71] Patients received IONIS-FXI Rx, 200

Table 1 | Overview of FXI and FXIa inhibitors in clinical development

Name	Type	Clearance by kidneys[67]	Stage of clinical development
BMS-986177 (milvexian)	Small-molecule inhibitor of FXIa	8%–20% clearance by kidneys	Phase 2
BAY 2433334 (asundexian)	Small-molecule inhibitor of FXIa		Phase 2
AB023/xisomab 3G3	Monoclonal antibody to FXI	Does not depend on kidney function	Phase 2
Osocimab	Monoclonal antibody to FXIa		Phase 2
Abelacimab	Monoclonal antibody to FXI/FXIa		Phase 2
IONIS-FXI Rx	FXI antisense oligonucleotide	Does not depend on kidney function	Phase 2
BAY 2976217 (FXI-LICA)	FXI antisense oligonucleotide		Phase 2

F, factor.

or 300 mg enoxaparin (a low-molecular-weight heparin), over a 35-day period before surgery, to ensure full anticoagulant activity. IONIS-FXI Rx, 300 mg, was superior to enoxaparin in reducing the incidence of total VTE events (the 200-mg dose was noninferior to enoxaparin). Both doses of IONIS-FXI Rx were associated with numerically fewer bleeding events than enoxaparin.[71]

BAY 2976217 (also known as FXI-LICA and IONIS-FXI-L Rx) is a ligand-conjugated version of IONIS-FXI Rx.[72] The safety, tolerability, pharmacokinetics, and pharmacodynamics of BAY 2976217 have been investigated in a double-blind, placebo-controlled, phase 1 trial in healthy volunteers.[73]

The anti-FXIa antibody osocimab (BAY 1213790) demonstrated antithrombotic effects without significantly increasing the bleeding time in a rabbit model of arterial thrombosis.[74] Osocimab was investigated in a randomized, open-label, phase 2 trial (Factor XIa Inhibition for the Prevention of Venous Thromboembolism in Patients Undergoing Total Knee Arthroplasty [FOXTROT]) in patients undergoing elective unilateral knee arthroplasty.[75] Osocimab (0.6, 1.2, or 1.8 mg/kg) administered postoperatively was noninferior to enoxaparin, whereas osocimab, 1.8 mg/kg, administered preoperatively was superior to enoxaparin for prevention of postoperative VTE.[75] In a similar open-label trial, administration of a single postoperative infusion of the dual FXI/FXIa monoclonal antibody, abelacimab, reduced VTE during the 30 days after total knee arthroplasty to 5% (75-mg dose) and 4% (150-mg dose) compared with 22% in patients randomized to receiving 40 mg enoxaparin administered s.c. daily.[76] Abelacimab, 30 mg, was noninferior to enoxaparin (VTE in 13%).[76]

FXI inhibitors have the potential to improve safety outcomes compared with other oral anticoagulants. For example, in the FOXTROT study, postoperative osocimab reduced major or clinically relevant nonmajor bleeding to 0% to 3% of patients compared with 6% of those randomized to enoxaparin.[75] In another phase 2 study, clinically relevant bleeding occurred in 3% of patients who received IONIS-FXI Rx compared with 8% of those who received enoxaparin.[71] Moreover, although dose adjustment can be made to reduce clotting, FXI inhibitors may be safer than heparin for the prevention of clotting in extracorporeal circuits,[49] such as in hemodialysis. Evidence from studies in patients with mechanical heart valves showed that targeting thrombin with dabigatran failed versus warfarin.[77] Furthermore, *in vitro*, FXI depletion abolished mechanical valve–induced thrombin generation.[78]

Indeed, a phase 2 multicenter study conducted in patients with kidney failure undergoing hemodialysis demonstrated that IONIS-FXI Rx reduced visual clotting on the dialysis membrane, compared with standard heparin use, and this warrants further clinical evaluation in this patient population.[79] Thus, an opportunity exists to evaluate these novel FXI inhibitory agents in individuals with kidney failure undergoing dialysis, not only for stroke prevention in atrial fibrillation but also more broadly for the prevention of adverse cardiovascular events in this population of patients at high risk of such outcomes.

Ongoing trials of FXI inhibitors in kidney failure

Several ongoing or recently completed trials are investigating FXI inhibitors in patients with kidney failure (Table 2). It is of note that atrial fibrillation is not listed in the inclusion or exclusion criteria of any of these trials; inclusion of patients both with and without atrial fibrillation will hopefully provide direct evidence of the efficacy and safety of this therapeutic approach.

Two trials are assessing antisense oligonucleotides in patients with kidney failure. A randomized, double-blind, placebo-controlled, phase 2 trial of IONIS-FXI Rx in patients with kidney failure undergoing hemodialysis, investigating the safety, pharmacokinetics, and pharmacodynamics of s.c. doses (EMERALD; ClinicalTrials.com identifier: NCT03358030), has recently been completed and results are pending.[80] A randomized, double-blind, parallel-group, placebo-controlled, phase 2 trial of BAY 2976217 (RE-THINC; ClinicalTrials.com identifier: NCT04534114) has begun recruiting patients with kidney failure undergoing dialysis.[81]

Two ongoing trials involve the monoclonal antibody osocimab. A randomized, observer-blind, parallel-group, placebo-controlled, phase 1 pilot study of a single dose of i.v. osocimab in patients with kidney failure undergoing hemodialysis (ClinicalTrials.com identifier: NCT03787368) aims to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of the drug.[82] A randomized, double-blind, parallel-group, placebo-controlled, phase 2 trial (CONVERT; ClinicalTrials.com identifier: NCT04523220) is investigating the safety and tolerability of monthly s.c. administrations of low-dose (52.5-mg) and high-dose (105-mg)

Table 2 | Prospective randomized trials of FXI inhibitors for blood clot prevention in patients with kidney failure

	EMERALD (NCT03358030)	RE-THINC (NCT04534114)	CONVERT (NCT04523220)
Study design	Phase 2, randomized, double-blind, placebo-controlled study of the safety, PK, and PD of multiple doses of IONIS-FXI Rx	Phase 2, randomized, double-blind, placebo-controlled study of the safety, PK, and PD of multiple doses of BAY 2976217	Phase 2, randomized, double-blind, parallel-group study of monthly low- and high-dose osocimab
Treatment	S.c. IONIS-FXI Rx, 200, 250, or 300 mg, or matching placebo administered 2 h after dialysis, once weekly for up to 26 wk	S.c. 40, 80, or 120 mg BAY 2976217 or matching placebo	S.c. osocimab loading dose followed by monthly maintenance dose or matching placebo, for up to 6 mo • Low dose: 105 mg loading, 52.5 mg maintenance • High dose: 210 mg loading, 105 mg maintenance
Inclusion criteria	Adults aged 18–85 yr with ESKD maintained on outpatient hemodialysis at a health care center for >3 mo from screening undergoing hemodialysis ≥3 times/wk for a minimum of 9 h/wk of prescribed treatment time and plan to continue this throughout the study	Adults aged ≥18 yr with ESKD on hemodialysis for ≥3 mo, undergoing dialysis for ≥9 h/wk	Adults aged ≥18 yr with ESKD on hemodialysis for ≥3 mo, undergoing dialysis for ≥9 h/wk, body weight of ≥50 kg
Primary outcomes	TEAEs (safety and tolerability)	Major bleeding and clinically relevant nonmajor bleeding	Composite of major and clinically relevant nonmajor bleeding events, as assessed by blinded Central Independent Adjudication Committee; composite of moderate/severe AEs and SAEs
Secondary outcomes	Other safety measures, PK, PD	TEAEs, trough drug concentrations, FXI antigen levels	Activated aPTT and FXIa activity trough levels
Enrollment	Spanish, multicenter, 213 participants	Global, 288 participants expected	Global, 600 participants expected
Actual or expected completion	July 2019 (actual)	September 2022 (estimated)	November 2022 (estimated)

AE, adverse event; aPTT, activated partial thromboplastin time; ESKD, end-stage kidney disease; F, factor; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
EMERALD is available at https://clinicaltrials.gov/ct2/show/NCT03358030; RE-THINC is available at https://clinicaltrials.gov/ct2/show/NCT04534114; and CONVERT is available at https://clinicaltrials.gov/ct2/show/NCT04523220.

osocimab in patients with kidney failure undergoing regular hemodialysis. The co–primary outcome measures are (i) a composite of major and clinically relevant nonmajor bleeding events and (ii) a composite of moderate, severe, and serious adverse events.[83]

The humanized anti-FXI antibody AB023/xisomab 3G3 binds FXI and blocks its activation by factor XIIa but not by thrombin. A phase 2 placebo-controlled study in patients with kidney failure of a single dose administered at the beginning of heparin-free hemodialysis showed that anticoagulation with AB023 was well tolerated and reduced clot formation within the hemodialysis circuit; however, only 16 of the 24 patients in the trial received AB023, so further investigation is required to confirm these findings (ClinicalTrials.com identifier: NCT03612856).[84,85]

Conclusion and future directions

Patients undergoing hemodialysis are at high risk of experiencing thromboembolic complications.[39] There is currently a lack of evidence from randomized trials to inform the use of DOACs in patients with kidney failure, particularly for these patients without atrial fibrillation; however, real-world evidence has shown an increase in bleeding events.[53] It is hypothesized that FXI inhibition will reduce the risk of thrombosis, including arterial thromboembolism, while having a minimal effect on hemostasis.[71,75] This makes FXI inhibition a particularly attractive proposition in settings where DOAC use is contraindicated owing to increased bleeding risk, such as patients with kidney failure without atrial fibrillation. To address this hypothesis, randomized trials are under way, including those with the FXI inhibitors IONIS-FXI Rx (EMERALD), BAY 2976217 (RE-THINC), and osocimab (CONVERT) in patients with kidney failure to determine the feasibility of targeting FXI in this patient population, and to strengthen the quality and quantity of efficacy and safety outcome data.[80–82] In conclusion, FXI inhibitors have the potential to safely limit thromboembolic complications, thereby reducing morbidity and mortality from cardiovascular events.

DISCLOSURE

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All authors contributed to formulating the concept underlying this article, the identification and interpretation of appropriate data sources, drafting of the article, and approval of the final version for submission.

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