

Anticoagulation in advanced renal failure: do factor XI/XIa inhibitors represent the long-awaited shift?

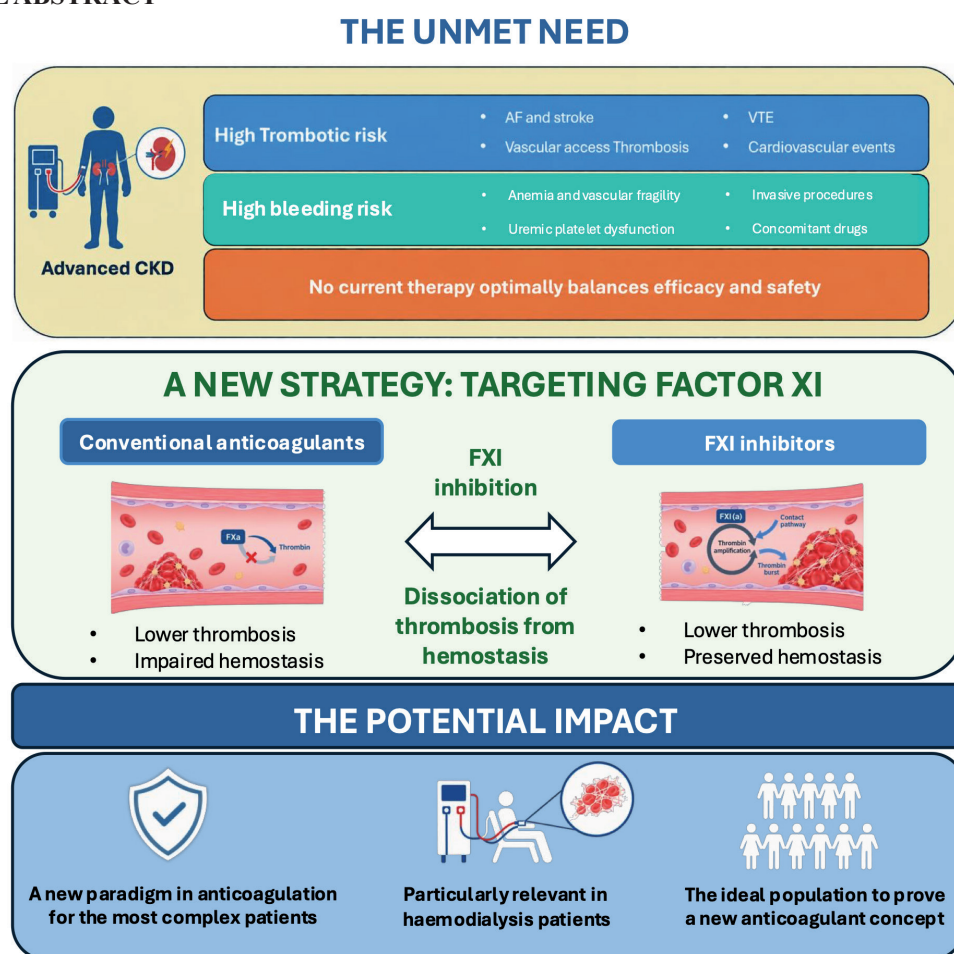
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ABSTRACT

Advanced chronic kidney disease (CKD), particularly stages G4-G5 and dialysis-dependent kidney failure, is one of the most challenging settings for anticoagulant therapy because thrombotic and bleeding risks coexist and often increase in parallel. Conventional anticoagulants, including vitamin K antagonists, direct oral anticoagulants and heparins, have important limitations in this population, owing to altered pharmacokinetics, limited evidence from randomized trials and an intrinsically unstable hemostatic balance. Inhibitors of factor XI (FXI) and activated factor XI (FXIa) have emerged as a novel strategy designed to attenuate thrombus amplification while preserving physiological hemostasis. Advanced CKD provides a particularly attractive clinical model in which to evaluate this concept, since it combines systemic thrombotic risk with uremic bleeding tendency and, in patients undergoing hemodialysis, repeated activation of the contact pathway by the extracorporeal circuit. This narrative review summarizes the hemostatic abnormalities of advanced CKD, discusses the limitations of currently available anticoagulants, reviews the biological rationale for FXI/FXIa inhibition and critically examines the available phase II clinical evidence in patients with advanced renal disease. Although early studies suggest a favorable safety profile and support the biological plausibility of this therapeutic approach, definitive evidence of clinical benefit is still lacking. Dedicated phase III trials will determine whether selective FXI inhibition can truly improve the net clinical benefit of anticoagulation in advanced CKD by dissociating the protection for pathological thrombosis from the impairment of physiological hemostasis.

GRAPHICAL ABSTRACT



Key words: chronic kidney disease; hemodialysis; factor XI; factor XIa; anticoagulation.

Introduction

Chronic kidney disease (CKD)—particularly in stages G4–G5 and in patients undergoing dialysis—is one of the most challenging settings for anticoagulant therapy. While conditions such as atrial fibrillation, venous thromboembolism, and—specifically—vascular access thrombosis are common in these patients, there is a concomitant bleeding risk that is markedly higher than that of the general population. Consequently, decisions regarding whether to initiate anticoagulation, which drug to use, and the duration of treatment must take into account an unstable hemostatic balance and clinical evidence that is less robust than that available for anticoagulant treatment in patients with preserved renal function.^{1–3}

Direct oral anticoagulants (DOACs) have profoundly modified the prevention and treatment of thromboembolic diseases; however, patients with severely reduced glomerular filtration rates

or those on dialysis have been excluded from, or underrepresented in, key registration trials. Consequently, clinical practice relies on small-scale randomized trials, pharmacokinetic analyses, registries, and observational studies, with recommendations that are not always consistent across various guidelines and regulatory documents. This persistent heterogeneity reflects the limited scientific evidence available regarding end-stage renal disease.^{1,2,4–7}

The development of inhibitors targeting factor XI (FXI) and/or activated factor XI (FXIa) introduces a rationale that differs from that of conventional anticoagulants. FXI contributes primarily to thrombus amplification and stabilization, whereas its role in physiological hemostasis appears relatively limited; consequently, inhibiting it could reduce thrombosis with a lesser impact on bleeding. Advanced CKD represents a particularly rigorous test of this hypothesis, as it combines a high thrombotic risk with a vulnerability to hemorrhage and, in the case of hemodialysis, repeated activation of the contact pathway by the extracorporeal circuit.^{8–10}

This narrative review analyzes the biological rationale and clinical evidence regarding FXI/FXIa inhibitors in advanced CKD, addressing a specific question: whether this population is the clinical model in which to convincingly demonstrate the possibility of dissociating the prevention of pathological thrombosis from the impairment of physiological hemostasis.

The hemostatic paradox of chronic kidney disease

Advanced CKD leads to complex remodeling of hemostasis, in which procoagulant and pro-hemorrhagic factors do not neutralize each other but coexist, potentially predominating alternately depending on clinical conditions, invasive procedures, and treatments. Both the risk of thrombosis and the risk of bleeding increase as renal function declines, reaching their peak in patients with end-stage renal disease. This paradox represents the primary obstacle to developing effective and safe antithrombotic strategies for these patients.^{3,4,11,12}

Regarding the thrombotic aspect, chronic inflammation and oxidative stress promote endothelial dysfunction and activation, elevated levels of von Willebrand factor and factor VIII, tissue factor expression, and increased thrombin generation. These processes are associated with reduced fibrinolytic activity, alterations in natural anticoagulant proteins, platelet activation, and the involvement of innate immune cells. The result is an immunothrombosis phenotype in which inflammation, endothelial damage, and coagulation reinforce one another.^{3,12} Furthermore, in hemodialysis patients, repeated contact of blood with membranes and other artificial surfaces can activate the contact system—including FXII, prekallikrein, and high-molecular-weight kininogen—which in turn interacts with the complement system, platelets, and leukocytes. FXII activation promotes FXI activation, thereby amplifying thrombin generation and contributing to coagulation activation within the circuit and to the thrombosis of vascular access. While the relative clinical significance of the individual components remains incompletely defined, the FXII–FXI system occupies a plausible position of convergence linking artificial surfaces, inflammation, and thrombosis.^{3,8–10}

At the same time, significant pro-hemorrhagic abnormalities coexist. Uremic toxins impair platelet adhesion, secretion, and

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aggregation, and alter the interaction between platelets, the endothelium, and the subendothelium. Anemia reduces platelet margination and the efficiency of primary hemostasis; vascular fragility and the presence of comorbidities, repeated procedures, vascular access issues, and the concomitant use of antiplatelet agents further increase the risk. Bleeding in CKD, therefore, does not stem from a single defect but rather from the combined effects of platelet dysfunction, vascular abnormalities, and acquired clinical factors.³

Advanced CKD cannot be defined simply as a state of hypercoagulability or a pro-hemorrhagic condition. Rather, it is a condition characterized by reduced hemostatic reserve, in which a therapy capable of selectively attenuating thrombotic amplification, without substantially interfering with the initial formation of the hemostatic clot, would be of particularly great clinical value.

The hemostatic paradox of advanced CKD is summarized in Figure 1.

For decades, vitamin K antagonists (VKAs) were the only option for oral anticoagulation in patients with advanced CKD. However, this population presents significant challenges: high variability in response, drug and dietary interactions, difficulty in maintaining an adequate time within the therapeutic range, and the frequent need to interrupt treatment for procedures. Furthermore, inhibiting vitamin K-dependent proteins involved in vascular protection can promote vascular calcification. Additionally,

the association with calciphylaxis, while rare, is of particular concern in patients with end-stage renal disease.^{1,3,4}

DOACs offer more predictable pharmacology than VKAs and, in the general atrial fibrillation population, a lower risk of intracranial hemorrhage. Although renal elimination varies among agents, the evidence in advanced CKD is increasingly supportive, particularly for apixaban. In non-dialysis CKD stages 4-5, a large US cohort found higher rates of major bleeding with warfarin (HR 1.85) and rivaroxaban (HR 1.69) than with apixaban, without significant differences in ischemic stroke.¹³ Similarly, a real-world cohort of patients with stage 4 CKD found no significant overall difference in major bleeding between DOACs and VKAs, while bleeding events were concentrated among patients receiving an inappropriate DOAC type or dose, emphasizing the importance of agent selection and guideline-concordant dosing.¹⁴ Randomized evidence in severe, non-dialysis CKD also supports this direction: analyses of ARISTOTLE and the individual-patient COMBINE-AF dataset indicate that standard-dose DOACs retain, and for some outcomes may increase, their relative benefit over warfarin as renal function declines, down to a CrCl of approximately 25 mL/min; inappropriate dose reduction did not reduce bleeding and was associated with higher risks of stroke/systemic embolism and death.^{15,16} In dialysis-dependent atrial fibrillation, RENAL-AF and AXADIA-AFNET 8 were individually underpowered, but

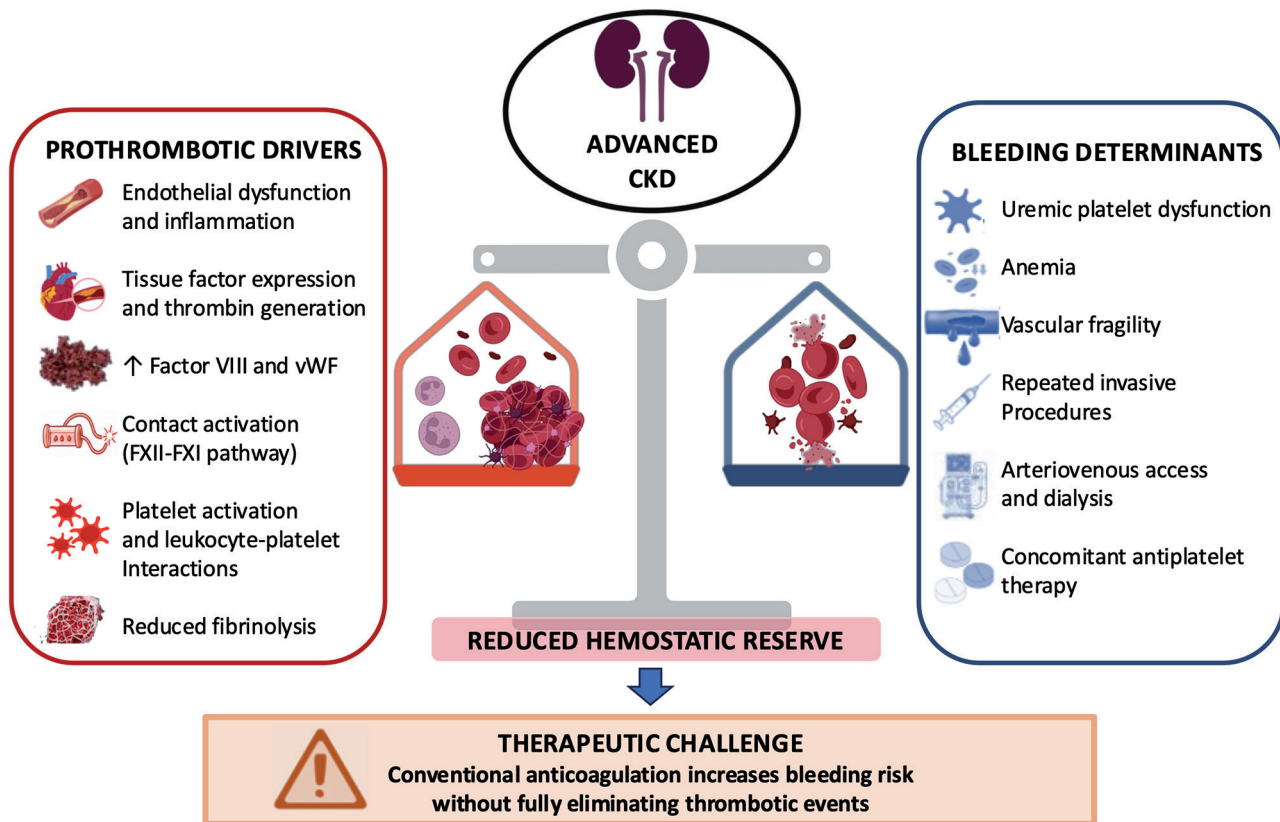


Figure 1. The hemostatic paradox of advanced chronic kidney disease.

more recent pooled randomized evidence provides a clearer safety signal. A meta-analysis of four RCTs (AXADIA-AFNET 8, RENAL-AF, Valkyrie, and SAFE-D; 486 patients) found that factor Xa inhibitors reduced major bleeding (RR 0.64, 95% CI 0.42–0.99) and intracranial bleeding (RR 0.40, 95% CI 0.17–0.96) compared with VKAs, with no significant difference in stroke or systemic embolism.¹⁷ These findings are consistent with broader meta-analytic evidence suggesting a favorable safety profile of DOACs compared with VKAs in CKD.^{18,19} Pharmacokinetic observations also support the relative suitability of apixaban in kidney failure: in a small prospective dialysis cohort receiving apixaban 2.5 mg twice daily, peak and trough levels generally remained within expected ranges without evidence of cumulative supratherapeutic exposure over three months.²⁰ Regulatory and guideline recommendations nevertheless differ by region and renal function. Reduced-dose factor Xa inhibitors are permitted in Europe for severe CKD (CrCl 15–29 mL/min), whereas US labeling also permits apixaban in patients with end-stage renal disease on dialysis; the latter recommendation is based largely on pharmacokinetic and pharmacodynamic data rather than definitive efficacy trials.^{2,15} Thus, declining renal function should be viewed as a reason for careful drug selection, correct dosing, and individualized assessment rather than as an intrinsic contraindication to DOAC therapy. In advanced CKD, and particularly in dialysis, apixaban now has a growing evidence base suggesting a more favorable safety profile than VKAs, although uncertainty regarding net clinical benefit and optimal patient selection remains.

Despite these increasingly reassuring data, an important question remains unresolved: in dialysis patients with atrial fibrillation, is anticoagulation itself always superior to non-anticoagulation in terms of net clinical benefit? Conventional scores for thromboembolic and bleeding risk were developed in different populations and show poor discrimination in a setting where age, comorbidities, anemia, inflammation, and mortality risk are very high. Consequently, prescribing DOACs in this context continues to require individual assessment, and recommendations remain cautious and, at times, divergent.^{1,2,4}

Unfractionated heparin and low-molecular-weight heparins retain an essential role in acute settings but do not solve the problem of chronic therapy. Unfractionated heparin requires parenteral administration and monitoring, while low-molecular-weight heparins can accumulate in cases of severely impaired renal function. Furthermore, all conventional anticoagulants act on key steps of thrombin generation or on the activity of thrombin itself, thereby creating an inevitable link between antithrombotic intensity and bleeding risk.^{1,3,4}

Thus, the limitation of conventional anticoagulation in CKD is not merely pharmacokinetic; it is primarily biological, as the available drugs interfere with factors that are essential for both thrombosis and hemostasis. This limitation makes a target located in the coagulation amplification phase, and less critical for the initial hemostatic response, particularly attractive.

The main characteristics, strengths and limitations of currently available anticoagulants in advanced CKD are summarized in Table 1.

Table 1. Anticoagulants in advanced chronic kidney disease: characteristics, limitations, and evidence.

Class	Renal clearance	Evidence in CKD G4–G5D	Points of strength	Main limitations	Present role
VKAs	Not dependent on renal clearance	Broad experience; RCT small and inconclusive in dialysis patients with atrial fibrillation	Can be used in end-stage renal disease, monitoring available	Variability, interactions, often low TTR; bleeding; calcification/calciophylaxis	Selected option, with individual assessment
Apixaban and other DOACs	Varies between molecules; apixaban has the lowest renal clearance among currently used DOACs (approximately 27%)	Registration trials largely excluded G5D; evidence now includes severe non-dialysis CKD cohorts, ARISTOTLE/COMBINE-AF analyses, and four dialysis RCTs with pooled safety data ^{13–16}	Predictable pharmacology; lower intracranial bleeding than VKAs; growing evidence favoring apixaban in advanced CKD	Dose and agent selection are critical; evidence remains less robust in G5D than in preserved renal function; regional regulatory differences persist	Reasonable option in CKD G4 with guideline-concordant dosing; apixaban may be considered in selected G5/dialysis patients according to local labeling/guidance and individual risk
Unfractionated heparin	Mainly non renal	Widely used in acute situations and during hemodialysis	Short half-life; titratable; reversible with protamine	Parenteral administration; monitoring; risk of thrombocytopenia (HIT)	Preferable when rapid titration is required
Low-molecular weight heparins	Predominant renal excretion	Data available, but accumulation possible in severe forms	Most predictable response; practicality	Anti-Xa adjustment/monitoring in selected cases; incomplete reversibility	Prudent and individualized use
FXI/FXIa inhibitors	Antibodies/antisense oligonucleotides not eliminated renally small molecules: 15–20% renal elimination	Phase II studies in hemodialysis; no definitive evidence of clinical efficacy	Favorable signs regarding bleeding	Long duration for some molecules; reversibility and peri-procedural management; efficacy yet to be demonstrated	Still under evaluation

CKD, chronic kidney disease; VKA, vitamin K antagonists; DOAC, direct oral anticoagulants.

Factor XI as a therapeutic target in advanced chronic kidney disease

Factor XI (FXI) is a zymogen that, once activated, supports thrombin generation via the activation of factor IX and reinforces the clot through feedback loops. Data from epidemiological studies on patients with congenital FXI deficiency and from experimental models indicate that reduced FXI activity is associated with a lower risk of thrombosis, whereas the bleeding phenotype is generally mild, heterogeneous, and most apparent in anatomical regions with high fibrinolytic activity.^{8-10,21-23} These observations have provided the rationale for attempting to pharmacologically dissociate thrombosis from hemostasis.

This concept does not imply that FXI is irrelevant to hemostasis, nor that its inhibition is devoid of risk. Bleeding may increase in the context of medical procedures, mucosal injury, antiplatelet therapy, or profound FXI suppression. The distinction

from conventional targets is quantitative and functional: FXI appears to contribute more to thrombus growth and persistence than to the initial formation of the hemostatic plug. Clinical efficacy will therefore depend on the indication, the intensity of inhibition, and the dominant mechanism of thrombosis in a given population.⁸⁻¹⁰

The biological rationale supporting FXI/FXIa inhibition in advanced CKD is illustrated in Figure 2.

In advanced CKD, the rationale for FXI inhibition is twofold. The first is general: to reduce the risk of bleeding in a population in which the net benefit of traditional anticoagulants is often uncertain. The second is specific: to attenuate thrombin amplification generated by contact activation during hemodialysis. This second component distinguishes CKD from many other indications because the pharmacological target coincides with a mechanism directly triggered by replacement therapy.^{3,8-10} The main pharmacological strategies targeting FXI/FXIa are summarized in Table 2.

Table 2. Factor XI inhibition strategies and potential benefits in advanced chronic kidney disease.

Class	Target	Administration	Renal clearance	Possible advantages in CKD
Antisense oligonucleotides	FXI liver synthesis	SC	Minimal	Stable exposure
Monoclonal antibodies	FXI/FXIa	IV or SC	Negligible	Long half-life
Small molecules	FXIa	Oral	Variable	Therapeutic simplicity

CKD, chronic kidney disease; FXI, factor XI; FXIa, activated factor XI; SC, subcutaneous; IV, intravenous.

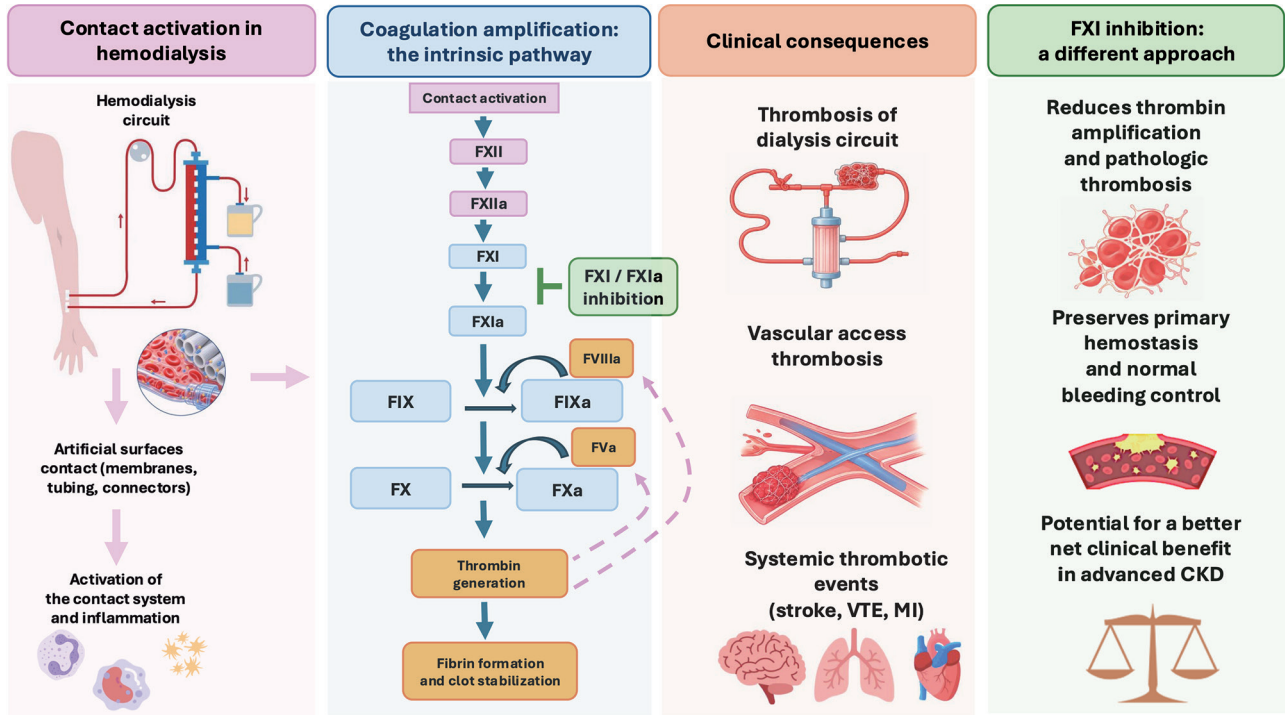


Figure 2. From contact activation to clinical events: the rationale for factor XI inhibition in chronic kidney disease.

The relationship between contact activation and clinical thrombosis, however, should not be oversimplified. Vascular access thrombosis also depends on stenosis, turbulence, endothelial trauma, graft or fistula characteristics, and systemic factors; blood coagulation in the circuit is influenced by flow, hemoconcentration, and membrane biocompatibility. FXI inhibition will therefore not replace the correction of mechanical factors nor intradialytic anticoagulation. Its value will have to be demonstrated on clinical endpoints, not only on biomarkers or circuit patency.^{3,24} It is precisely this complexity that makes CKD an important clinical model. A drug capable of reducing vascular access thrombosis and cardiovascular or thromboembolic events, without significantly increasing bleeding, would demonstrate the value of this strategy in a population where both risks are extreme. Conversely, a favorable bleeding profile in the absence of adequate efficacy would confirm that the biological dissociation between thrombosis and hemostasis does not automatically guarantee clinical benefit.

Clinical evidence for Factor XI/XIa inhibitors in chronic kidney disease

The interest in factor XI/XIa inhibitors for advanced CKD is supported by a biological rationale that is particularly compelling for this population, which faces the coexistence of increased thrombotic risk and high bleeding risk. However, available clinical data stem primarily from Phase II studies—involving antisense oligonucleotides, monoclonal antibodies, and small molecules, which were designed mainly to assess FXI level reduction and/or functional inhibition of the FXI/XIa pathway, pharmacodynamics, and safety, rather than the prevention of thrombotic events.²⁴

Evidence from other clinical indications provides an important context for interpreting the renal studies. Trials in orthopedic thromboprophylaxis and atrial fibrillation have investigated several FXI/FXIa inhibitors, with heterogeneous efficacy and bleeding findings; these results cannot be extrapolated directly to patients with advanced CKD.²⁵⁻³¹

Among the most significant trials, the initial study by Walsh *et al.*³² and the EMERALD study (results reported in the trial registry but not published in a peer-reviewed article),³³ as well as the RE-THINC study with fesomersen and the CONVERT study with osocimab,^{34,35} have provided important insights into FXI reduction and safety in hemodialysis patients.

Overall, four different agents have been evaluated, including two antisense oligonucleotides (IONIS-FXI Rx and fesomersen) and two monoclonal antibodies (xisomab 3G3 and osocimab), primarily assessing pharmacodynamic effects, dialysis circuit clotting,³⁶ and bleeding outcomes (Table 3). Collectively, these studies showed substantial, dose-dependent reductions in FXI activity or levels, with some evidence of reduced dialysis circuit clotting and no consistent increase in clinically relevant bleeding.

Other Phase II studies employing different FXI/XIa inhibition modalities have further helped define the pharmacodynam-

ics and tolerability of this therapeutic class. Nevertheless, as previously noted, these studies were not powered to provide conclusive evidence of efficacy regarding clinical thrombotic events, nor do they yet allow for a determination of the net benefit compared to conventional anticoagulation strategies. A recent systematic review of randomized trials involving FXI/XIa inhibitors confirmed the class favorable safety profile, showing no statistically significant increase in clinically relevant or major bleeding, but highlighted the lack of sufficient statistical power to evaluate clinical efficacy, mortality, or benefits in high-risk subgroups, such as patients with advanced CKD.²⁴

Overall, factor XI/XIa inhibitors represent a particularly promising therapeutic strategy for patients with advanced CKD; the ability to reduce thrombin formation without significantly interfering with primary hemostasis could offer a more favorable benefit-risk profile compared to conventional anticoagulants. However, Phase III trials conducted specifically in this population will be required to determine their actual clinical benefit and potential role in clinical practice. Future trials must be specifically designed for end-stage renal disease and be of sufficient size and duration to evaluate clinical thrombotic events, major and clinically relevant bleeding, mortality, and net clinical benefit. Furthermore, it will be necessary to distinguish between systemic end-points—such as stroke prevention in atrial fibrillation or the treatment of venous thromboembolism—and end-points directly related to dialysis, such as vascular access thrombosis and circuit clotting.

The choice of comparators will be crucial. A placebo-controlled comparison may be appropriate for preventing dialysis-related events or in patients lacking a well-established indication for systemic anticoagulation; conversely, for traditional indications, comparison with VKAs, DOACs, or heparins will be necessary, at the same time accounting for regulatory differences and the uncertainties that persist regarding CKD G5 and dialysis. Population heterogeneity presents a further challenge. Hemodialysis versus peritoneal dialysis, native fistulas versus grafts, prior bleeding, antiplatelet therapy, atrial fibrillation, venous thromboembolism, and varying levels of residual renal function all define distinct clinical phenotypes. Consequently, risk stratification must integrate thrombotic risk, bleeding risk, vascular access characteristics, dialysis modality, and the pharmacology of the single molecules.

The clinical development of FXI/FXIa inhibitors should also be interpreted in the context of improving conventional anticoagulation. In advanced non-dialysis CKD, growing evidence, particularly for appropriately dosed apixaban, suggests a more favorable bleeding profile than VKAs; pooled randomized evidence in dialysis also suggests a safety advantage for factor Xa inhibitors, although important uncertainties remain.¹³⁻²⁰ Therefore, future FXI/FXIa trials should demonstrate a clinically meaningful incremental benefit over contemporary, appropriately selected anticoagulant treatment, rather than over an outdated standard of care. Their potential added value may be particularly relevant to residual bleeding risk and dialysis-related thrombosis, but neither superiority nor clinical availability can currently be assumed.

Table 3. Phase II clinical evidence of FXI/XIa inhibition in patients with advanced chronic kidney disease undergoing hemodialysis.

Study	Sample size	Agent	Key end point	Safety end point	Intervention	Key findings	Safety outcome
Lorentz <i>et al.</i> , 2021 ³⁶	24	Xisomab 3G3 (AB023)	Dialysis circuit occlusive events requiring circuit exchange	Treatment-related AEs; bleeding; hemostasis at vascular access site	0.25 or 0.50 mg/kg IV before heparin-free HD; single dose, vs placebo	Occlusive events requiring circuit exchange decreased from 12.5% to 4.0% with 0.25 mg/kg and from 29.0% to 12.5% with 0.50 mg/kg; remained unchanged with placebo	No clinically relevant bleeding or impairment of hemostasis was reported
Walsh <i>et al.</i> , 2022 ³²	43	IONIS-FXIRx	Hemodialysis circuit clotting; FXI activity	Major and minor bleeding; AV-access bleeding	200 or 300 mg SC on days 1, 5, 8, 12, and 15, then weekly through day 78, vs placebo	FXI activity decreased by 56.0% and 70.7% with 200 and 300 mg, respectively; high-grade circuit clotting decreased during weeks 6–13 compared with the pre-treatment period	MB: 0% (200 mg), 6.7% (300 mg), 7.7% (placebo)
EMERALD ³³	210	IONIS-FXIRx	Exploratory dialysis-related thrombotic outcomes; FXI activity	MB/CRNMB	200, 250, or 300 mg SC once weekly, administered after dialysis, for up to 26 weeks, vs placebo	Dose-dependent reduction in FXI activity; not adequately powered assessment of clinical thrombotic efficacy	MB/CRNMB: 3.8% (200 mg), 5.6% (250 mg), 6.0% (300 mg), 5.7% placebo
RE-THINc ESRD ³⁴	307	Fesomersen (IONIS-FXI-LRx)	Major atherothrombotic events; HD circuit clotting; AV-access thrombosis	MB/CRNMB; post-dialysis AV-access bleeding	40, 80, or 120 mg SC every 4 weeks for up to 48 weeks, vs placebo	Major events occurred in 1 patient in each treatment group; lower predicted FXI levels were associated with reduced HD circuit clotting and AV-access thrombosis	MB/CRNMB: 6.5% (40 mg), 5.1% (80 mg), 3.9% (120 mg), 4.0% placebo
CONVERT ³⁵	686	Osocimab	Dialysis circuit clotting; AV-fistula/graft thrombosis; major vascular events; symptomatic VTE	MB/CRNMB	105 mg loading + 52.5 mg monthly (low dose) or 210 mg loading + 105 mg monthly (high dose), vs placebo	Moderate-to-complete circuit clotting occurred in 29.3% (low dose), 27.2% (high dose), and 41.3% (placebo); RR 0.71 and 0.66 vs placebo, respectively. AV-fistula/graft thrombosis: 1.7%, 2.7%, and 3.9%, respectively	CRNMB: 6.9% (low dose), 4.9% (high dose), 7.8% placebo; major bleeding: 1.3%, 0.9%, and 3.0%, respectively

AV, arteriovenous; AEs, adverse events; CRNMB, clinically relevant non-major bleeding; FXI, factor XI; HD, hemodialysis; MB, major bleeding; RR, relative risk; SC, subcutaneous; VTE, venous thromboembolism.

Conclusions

Anticoagulation in advanced CKD remains shaped by an unresolved paradox: thrombotic risk is high, yet treatments that reduce it can exacerbate an already pronounced bleeding vulnerability. VKAs, DOACs, and heparins have different limitations but share the characteristic of interfering with key components of hemostasis. FXI inhibition offers a different strategy, targeting the clot amplification phase and potentially providing greater selectivity for pathological thrombosis.^{1-3,8-10} Advanced CKD is a particularly suitable setting for testing this hypothesis. In the context of hemodialysis, the need for safer therapy is compounded by the repeated activation of the contact pathway caused by the extracorporeal circuit. Phase II studies demonstrate that FXI can be inhibited in dialysis patients without an apparent increase in bleeding, though it remains to be established whether this strategy reduces clinically relevant thrombotic events or improves survival.^{3,24,32-35} Importantly, FXI/FXIa inhibitors are being developed against a background of improving conventional anticoagulation options in advanced CKD: current evidence increasingly supports appropriately selected and dosed DOACs, particularly apixaban, over VKAs in many patients. Nevertheless, residual bleeding risk, uncertainty in dialysis-dependent patients, and dialysis-specific thrombotic mechanisms leave an unmet need that FXI/FXIa inhibition may potentially address.¹³⁻¹⁶

The contrasting results obtained with FXI/FXIa inhibitors in other indications call for caution. The reduction in bleeding observed with these drugs cannot be considered sufficient unless accompanied by at least adequate antithrombotic protection. A paradigm shift will therefore depend not only on confirming a pharmacological effect but also on demonstrating a net clinical benefit in large, dedicated trials designed around endpoints relevant to the renal population.²⁹⁻³¹

FXI/FXIa inhibitors represent one of the most compelling prospects for overcoming the traditional trade-off between efficacy and safety in anticoagulation. However, in advanced CKD, they remain a promise rather than a solution. For this reason, end-stage renal disease is not merely a potential indication; it is the clinical model in which the ability to dissociate pathological thrombosis from physiological hemostasis can be either demonstrated or definitively downplayed.

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