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Novel horizons in anticoagulation: the emerging role of factor XI inhibitors across different settings

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Abstract

Anticoagulants have long been fundamental in preventing and treating thromboembolic disorders, with a recent shift of focus towards direct oral anticoagulants, thanks to their ease of use, efficacy, and safety. Despite these advancements, bleeding complications remain a major concern with any anticoagulant, highlighting the need for safer drugs. Factor XI (FXI) inhibitors have emerged as promising agents in this regard, offering a novel approach by targeting upstream factors in the coagulation system. Phase 2 trials have shown encouraging outcomes, indicating a reduced bleeding risk compared to traditional anticoagulants, particularly in the context of cardiovascular disease management when combined with antiplatelet therapy. However, the variability in findings and limited efficacy data call for a cautious interpretation pending phase 3 trial insights. These trials are essential for validating the potential of FXI inhibitors to balance bleeding risk reduction and maintain anticoagulant efficacy.

This review explores the pharmacology, potential indications, clinical data, and future directions of FXI inhibitors, providing a perspective on their evolving role in anticoagulant therapy. It also provides a detailed analysis of data from published clinical trials on FXI inhibitors in various indications. Preliminary data from ongoing trials is also outlined. As the field moves forward, a cautiously optimistic outlook can be expected, focusing on comprehensive data from phase 3 trials to define the role of FXI inhibitors in various clinical scenarios.

Introduction

Anticoagulants are key in the prevention and treatment of arterial and venous thromboembolism (VTE). Historically, vitamin K antagonists (VKAs) like warfarin were the mainstay in anticoagulant therapy, prized for their effectiveness in a broad range of thromboembolic conditions. The emergence of direct oral anticoagulants (DOACs) since 2010 has marked a significant shift in this landscape. The DOACs have rapidly replaced VKAs for various indications after demonstrating at least comparable efficacy in stroke prevention in atrial fibrillation (AF) patients [**1,2**] and in the treatment of VTE, with enhanced safety [**3,4**]. In this aspect, a noteworthy advantage of DOACs is in the reduction of the risk of serious bleeding, especially intracranial hemorrhage (ICH), compared to VKAs. Additionally, DOACs offer the convenience of less drug-drug and food-drug interactions, and fixed-dose administration without the need for routine monitoring of the anticoagulant effect [**5**].

Despite the benefits presented by DOACs, thromboembolic diseases continue to pose substantial morbidity and mortality risks, and existing anticoagulants, by disrupting hemostasis, may result in bleeding complications that offset the benefits of antithrombotic treatment [**6**]. This underscores the ongoing need for effective anticoagulants with lower bleeding risks.

In response, research has shifted towards upstream factors in the coagulation system, focusing primarily on the contact pathway, where Factor XI (FXI) has emerged as a promising target. These new anticoagulants aim to address unmet clinical needs, offering potentially safer alternatives with minimal bleeding risks [**7,8**]. In the evolving landscape of anticoagulant therapy, patients requiring anticoagulation who are also at heightened risk for bleeding complications stand to gain considerably from the targeted action of FXI inhibitors.

The following review will explore the pharmacological properties of these new oral and parenteral anticoagulants, analyze clinical data on these agents, and provide a perspective on the opportunities and challenges faced by this emerging class of drugs.

Unmet clinical needs in antithrombotic treatment

The dilemma of bleeding risk and antithrombotic effect

The central challenge in anticoagulant therapy lies in achieving effective thrombosis prevention while minimizing the risk of bleeding. While DOACs have shown some improvement over VKAs in this regard, they have not eliminated bleeding risks entirely [**9**].

Anticoagulant treatment in AF patients at high-risk of bleeding

In a network meta-analysis of 23 randomized, controlled trials in AF patients, all DOACs significantly reduced the risk of ICH compared to warfarin (odds ratio range 0.31–0.46), with varying risks of major bleeding (MB) and gastrointestinal (GI) bleeding across different DOACs [**1**]. However, real-world data from European and Canadian studies involving 421,523 non-valvular AF patients showed no clear superiority of DOACs over VKAs in MB risks [**10**].

The risk-benefit profile becomes even more precarious in specific patient groups, where concerns about bleeding risk lead to many AF patients either not receiving or being underdosed with DOACs [**11,12**].

AF patients with coronary stent implantation or acute ischemic stroke (IS)

About 10% of patients receiving coronary stent implantation require anticoagulant treatment, predominantly due to coexisting AF. Combining antiplatelet therapy with anticoagulants further increases the bleeding risk associated with anticoagulant treatment, and these patients experience MB rates of 4% to 12% within the first year of triple therapy [**13,14**].

This dilemma is further exacerbated in patients with AF and acute IS, where the timing of initiation of anticoagulant treatment is critical to balance the risks of hemorrhagic transformation and recurrent IS. The optimal window for initiating anticoagulant treatment

for secondary stroke prevention is suggested to be 4 to 14 days post-stroke. Notably, large ischemic lesions, a high CHA2DS2-VASc score [CHADS, Congestive heart failure, Hypertension, Age 75 or more, Diabetes, Stroke; VASc, Vascular disease, Age 65–74, Sex category (female sex)], a high National Institutes of Health Stroke Scale score and the choice of antithrombotic treatment are all associated with a higher risk for both ischemic recurrence and bleeding [**15,16**].

Elderly patients and patients with comorbidities requiring anticoagulant treatment

Elderly patients, often burdened with comorbidities and polypharmacy, are at increased risk of both bleeding and thrombosis, confounding the risk-benefit of anticoagulation [**17,18**]. Patients with chronic conditions like liver cirrhosis and chronic kidney disease (CKD) also present unique challenges. Cirrhotic patients appear to have a rebalanced hemostasis with hypercoagulable elements [**19**], and are at risk of thrombotic complications, particularly splanchnic vein thrombosis [**20**]. Conversely, complications of portal hypertension like esophageal varices increase the risk of bleeding [**21**]. CKD, carries a risk of both bleeding and thromboembolic events due to platelet dysfunction. The thromboembolic risk is markedly increased in patients with concurrent AF and CKD, compared to those with either condition alone [**22**]. Cancer patients, particularly those with metastatic disease or primary GI and genitourinary malignancies, are at an increased risk of VTE recurrence as well as bleeding, making the management of anticoagulant therapy especially challenging [**23-25**]. These complexities underline the need for safer anticoagulants, preferably with minimal renal clearance and enhanced efficacy, with FXI inhibitors emerging as potential solutions.

Catheter-related thrombosis (CRT):

Currently, there is limited evidence guiding the optimal management of CRT, often resulting in treatment challenges in clinical practice. Central venous catheters (CVCs), widely used in cancer patients for chemotherapy delivery and obtaining blood samples, are associated with various complications, including CRT. While symptomatic CRT occurs in about 5% of cases, asymptomatic CRT is more prevalent, with incidences ranging from 14-18% [**26**]. In patients undergoing long-term total parenteral nutrition (TPN), the risk of CRT is a major concern, posing challenges in the maintenance of venous access and successful TPN. Despite various efforts to mitigate these thrombotic complications, including the use of heparinized solutions and heparin-bonded catheters, the lack of high-quality clinical trials and consensus limits effective intervention [**27**].

CRT of hemodialysis catheters can lead to dysfunction and potentially render vessels unusable for future access, resulting in significant limb morbidity. The best preventative approach involves minimizing CVCs use and ensuring meticulous care and vigilant monitoring when it is indispensable, to reduce the risk complications and preserve vascular access routes [**28,29**].

Orthopedic Surgery

In patients undergoing orthopedic surgery, especially total knee and hip arthroplasties, VTE prophylaxis is fundamental [**30**]. Conventional anticoagulants, which target factor Xa or thrombin, are efficacious but associated with a marked risk of bleeding [**31**]. This issue highlights the imperative for anticoagulation strategies that are both effective and safe. Against this backdrop, FXI inhibitors stand out as a promising avenue, potentially delivering effective thromboprophylaxis while minimizing bleeding risks, thus meeting the pressing demand for safer anticoagulants in patients undergoing arthroplasty procedures.

Patients with mechanical heart valves (MHVs) and external devices

In the management of valvular heart disease (VHD), particularly with MHVs, anticoagulation remains a pivotal yet challenging aspect. The standard treatment with warfarin presents considerable limitations, prompting the search for alternatives. However, the use of DOACs in patients with MHVs has encountered setbacks, as evidenced by the failure of dabigatran and apixaban in major clinical trials, while rivaroxaban showed promise in smaller studies. Meanwhile, VKAs continue to be the only approved oral anticoagulants for preventing valve thrombosis [**32-34**]. The situation is further complicated in settings involving external surfaces such as left ventricular assist devices (LVADs) or extracorporeal membrane oxygenation, where the safety profile and appropriate use of DOACs are yet to be clarified. In LVAD patients, the challenge lies in balancing the risk of pump thrombosis against bleeding complications due to coagulopathies such as an acquired von Willebrand syndrome [**35-37**]. Thus, there is a pressing need for randomized controlled trials to establish optimal antithrombotic regimens in these patients, particularly in the context of new valve designs and targeting different aspects of the coagulation cascade.

FXI as a therapeutic target in anticoagulation

The contact pathway of coagulation

The contact pathway of coagulation, comprising FXI, FXII, prekallikrein (PK), and high-molecular-weight kininogen (HK), participates in procoagulant and proinflammatory responses, thereby connecting inflammation and coagulation processes. Available data imply that this pathway is more contributory to pathological thrombosis and inflammation than to physiological hemostasis [**38-40**]. Contact activation occurs when negatively charged macromolecules, such as extracellular DNA, RNA from activated or dying cells, polyphosphates from activated platelets or microorganisms, or artificial surfaces, interact with plasma. This interaction leads to the downstream activation of both coagulation and inflammation. FXI functions as a serine protease responsible for thrombin generation through the activation of other coagulation factors. It acts as a bridge between tissue-factor mediated coagulation and the kallikrein-kinin system, primarily functioning in prolonged activation scenarios like VTE. Notably, FXI is less crucial for initiating clot formation, but appears to play a significant role in clot stabilization and expansion [**40**].

Elevated levels of FXI

Elevated levels of FXI have been linked to an increased risk of cardiovascular events in patients with type 2 diabetes mellitus, suggesting that FXI plays a critical role in thrombosis in these patients [**41**]. Similarly, circulating activated FXI has been identified as a predictor of arterial thromboembolic events in patients with stable coronary artery disease, further supporting the potential of FXI inhibitors as novel antithrombotic agents in these high-risk groups [**42**]. Additionally, a recent case–control study found that elevated FXI levels, especially when persistently high, significantly increase the risk of VTE [**43**]. This is further supported by a study that demonstrated the association of elevated FXI levels and activation

with acute VTE and recurrent events [**44**], highlighting the value of FXIa inhibition in the acute VTE setting. Although elevated FXI levels are associated with an increased risk of thrombotic events, the precise threshold beyond which FXI becomes a significant risk factor remains unclear.

FXI deficiency and its clinical implications

FXI deficiency is a rare disorder inherited in an autosomal recessive trait. Patients exhibit markedly prolonged activated partial thromboplastin times (aPTT), yet even individuals with extremely low FXI levels may remain asymptomatic, indicating a complex relationship between FXI levels and clinical manifestations. Bleeding in FXI-deficient patients typically occurs following trauma or surgery, particularly in tissues with high fibrinolytic activity, such as the oral cavity, nasal passages, and the urinary tract [**45,46**]. This pattern of bleeding underscores the role of FXI in clot stabilization rather than initiation, aligning with its involvement in the later stages of the coagulation cascade [**47**]. Treatment options for FXI deficiency include antifibrinolytics, fresh frozen plasma, plasma-derived FXI concentrates, and low-dose recombinant FVIIa. However, despite cautious usage, especially in the perioperative period, FXI concentrates were associated with a risk of thrombotic complications, as evidenced by rare instances of transient ischemic attack (TIA) and PE in treated patients [**48**].

Low FXI levels: available data

Evidence consistently points to a lower thrombotic risk among individuals with lower FXI levels. Patients with severe FXI deficiency exhibited a significantly reduced incidence of deep vein thrombosis compared to the general population, indicating a potential protective effect [**49**]. Similarly, a study suggested specific protection against IS [**50**]. Another cohort

study further supported these findings, showing a decreased incidence of both VTE and cardiovascular events in individuals with FXI deficiency [**51**]. A linear relationship between FXI activity levels and the risk of recurrent VTE has been observed, with patients exhibiting FXI activity below the 34th percentile experiencing significantly fewer recurrences [**52**], supporting the concept of FXI as a promising target for anticoagulation.

Differentiating thrombosis from hemostasis

The unique characteristics of FXI deficiency highlight the potential for targeting FXI in antithrombotic therapy, as patients often exhibit extended clotting times without a severe bleeding tendency and show a reduced risk of certain thrombotic events [**53**].

Thrombosis and hemostasis, while sharing enzymatic pathways, result in divergent physiological outcomes. Hemostasis, a natural response to vascular injury results in the formation of a localized hemostatic plug to halt bleeding. Thrombosis, typically pathologic, is characterized by the formation of intravascular thrombi that can interrupt blood flow and potentially lead to organ damage. Differentiating thrombosis from hemostasis is vital for the development of antithrombotic agents that prevent thrombosis without adversely affecting hemostasis, making the contact pathway a promising target for safer anticoagulants. Given its specific role in thrombosis without a significant impact on hemostasis, inhibition of upstream factors in this pathway can potentially decouple thrombosis from hemostasis, offering a promising strategy to reduce the risk of anticoagulant-related bleeding. This approach is particularly advantageous as it focuses on a singular pathway rather than affecting multiple coagulation factors or engaging with the tissue factor (TF)-FVIIa and common pathways (**Figure 1**). It potentially offers a safer alternative to currently available anticoagulants, which directly affect fibrin formation [**53-55**], however, while the contact pathway's involvement in pathological thrombosis presents a compelling target for intervention, the redundancy and

compensatory mechanisms within the coagulation system may pose challenges to the efficacy of targeting this pathway alone.

Preclinical studies

Preclinical studies in animal models have been instrumental in understanding the role of FXI in thrombosis. Notably, mice genetically modified to lack FXI showed protection against occlusive thrombosis in both venous and arterial systems, highlighting the role of FXI in thrombus formation [**56,57**]. Additionally, targeting FXI with monoclonal antibodies, antisense oligonucleotides, and specific small molecules has been shown to effectively prevent thrombosis in various mammalian models [**58-63**]. Pharmacological inhibition of FXI in low-density lipoprotein receptor-knockout mice reduced the extent of atherosclerotic lesions, suggesting that targeting FXI may even offer a safe and effective strategy to slow the progression of atherosclerosis [**64**].

These cumulative preclinical findings emphasize the efficacy and safety of FXI inhibition as a promising therapeutic approach to reduce thrombotic events while maintaining a favorable safety profile. Translating these findings into safe and effective clinical therapies requires careful navigation of the complex coagulation landscape in humans, where compensatory mechanisms and individual variability may influence therapeutic outcomes.

Available strategies to inhibit FXI

Pre-clinical studies have set the foundation for the development of a range of anticoagulants targeting FXI, demonstrating their ability to prevent venous and arterial thrombosis in various animal models. Subsequent early phase human studies have confirmed the safety profile of these agents [**65-72**].

A notable advantage of molecule-specific targeting is the substantial reduction in the risk of off-target adverse effects, however establishing non-inferior efficacy in thrombosis prevention compared to standard anticoagulants, while offering a potentially lower risk of bleeding, is essential for the advancement of FXI-targeting strategies in clinical trials [**8**].

Different strategies have emerged to inhibit FXI, including antisense oligonucleotides (ASOs) that reduce hepatic synthesis of FXI [**59-62,64,65,73-76**], monoclonal antibodies that inhibit FXI activation or its enzymatic activity [**66-69,77-82**], and small molecules designed to block the active site of FXI or induce its allosteric modulation [**63,70-72,83-91**]. These strategies not only differ in their mechanism of action but also possess unique pharmacological properties that shape their potential clinical applications.

The pharmacological attributes of these agents, including their pharmacodynamics, pharmacokinetics, and possible drug interactions, are presented in **Table 1**.

Additional approaches, such as parenteral small molecules targeting FXI's active site or exosites [**92-95**], DNA aptamers that selectively bind to and inhibit FXI [**96,97**] and natural inhibitors of FXIa derived from snakes [**98**], vampire bats [**99**], and ticks [**100**], have been explored in vitro and in animal models. These agents have not yet progressed into clinical studies and therefore fall outside the scope of this review.

<u>Antisense oligonucleotides</u>

FXI, primarily synthesized in the liver, presents an ideal target for ASOs therapy [**101**]. ASOs like IONIS FXI-Rx and fesomersen (formerly known as IONIS-FXI-LRx) specifically inhibit the biosynthesis of FXI by binding to its mRNA, leading to its degradation and reduce protein levels with a high degree of target selectivity [**59**]. ASOs have demonstrated effectiveness in various animal models [**59-62,64**] and in human studies [**65,73-76**]. They require parenteral administration by subcutaneous or intravenous injection, and have a slow onset of action; achieving therapeutic FXI levels typically takes 3 to 4 weeks, which limits their use in acute settings. ASOs have been investigated in phase 2 clinical trials as VTE prophylaxis in patients undergoing total knee arthroplasty (TKA) [**73**], and for the prevention of cardiovascular event in patients with ESRD [**74,76**].

Monoclonal antibodies targeting FXI

Monoclonal antibodies targeting FXI, such as abelacimab (MAA868), osocimab (BAY 1213790) and xisomab (AB023), have shown potential in selectively inhibiting FXI activation. Abelacimab acts by binding to the catalytic domain of FXI and locks it in an inactive conformation, thus preventing its activation by FXIIa or thrombin [**68**]. Osocimab binds adjacent to the active site of FXIa, preventing it from activating factor IX [**66**]. In contrast, xisomab functions as a backdoor inhibitor of FXIIa, reducing FXI activation by FXIIa as well as reciprocal activation of FXII by FXIa [**79**]. Monoclonal antibodies require parenteral administration and are characterized by a rapid onset of FXI inhibition and relatively long half-lives, which enable their use in both acute and chronic settings and could allow for less frequent dosing. However, this extended activity also underscores the need for effective reversal strategies in the event of bleeding complications. Antibodies have also been studied in phase 2 clinical trials as VTE prophylaxis in patients undergoing TKA [**77,78**], as

well as for the prevention of adverse cardiovascular outcomes in patients with ESRD [**81**], and are being investigated for stroke prevention in patients with AF.

Small molecules

Small molecule inhibitors of FXI, such as milvexian (BMS-986177/JNJ-70033093) and asundexian (BAY 2433334), directly inhibit FXI at its active site. They can be administered either orally or parenterally, and are designed for rapid FXI inhibition, making them suitable for both acute and chronic therapeutic settings, offering a more flexible and patient-friendly approach [**70,71**]. Unlike ASOs and antibodies, these small molecules have shorter half-lives, requiring once or twice daily dosing, similar to DOACs. Parenterally administered small molecules such as BMS-262084, BMS-654457 have been primarily studied in animal models [**93,94**]. Small molecule FXI inhibitors have been investigated for VTE prophylaxis in patients undergoing TKA [**84**], for secondary stroke prevention in patients with non-cardioembolic IS [**86,89**], for stroke prevention in patients with AF [**88**], and as antithrombotic treatment following acute MI [**90**].

Reversal strategies

The diversity of FXI inhibitor regimens, especially those of extended activity, underscores the need for a clear understanding of their bleeding risk implications, and as with current anticoagulants, establishing reversal protocols is essential. In cases of bleeding or need for urgent surgery, evidence indicates that, similar to the management in FXI deficiency, antifibrinolytics and, in some cases, recombinant factor VIIa (rFVIIa) can effectively address bleeding without the need for FXI replacement. This approach is expected to be applicable for those undergoing therapy with FXI inhibitors [**102**]. Currently, there is an active evaluation of fully human antibody Fab fragments, known for their remarkably high affinity

for FXIa inhibitors. This assessment is focused on determining their ability to counteract the anticoagulant effects of these inhibitors [**103**]. However, these strategies currently lack validation for FXI inhibitor reversal and need to be further assessed in randomized controlled trials. Any development of specific antidotes should take into account the varied mechanisms of action and unique pharmacokinetic properties of FXI inhibitors, ensuring targeted and effective reversal strategies, thereby optimizing safety and therapeutic outcomes.

FXI inhibitors in completed and ongoing clinical trials

The following sections will offer a comprehensive overview of the results already presented, along with insights into preliminary findings from ongoing phase 3 trials. Results of completed clinical trials are summarized in **Tables 2-4**. Ongoing clinical trials are outlined in **Table 5**.

VTE prevention in patients undergoing total knee arthroplasty (TKA)

In studies focused on the use of FXI inhibitors for VTE prophylaxis in patients undergoing TKS, significant findings demonstrate their potential efficacy and safety. In a randomized open-label study, IONIS-FXRx at doses of 200 mg and 300 mg lowered FXI activity, with the 200 mg dose showing a 4% lower risk and the 300 mg dose a 26% lower risk of thrombotic events compared to enoxaparin. However, differences in MB and clinically relevant non-major bleeding (CRNMB) were not statistically significant, with a risk difference of 6% for both doses [**73**].

The FOXTROT trial, comparing osocimab doses (0.3 mg/kg to 1.8 mg/kg) with enoxaparin or apixaban, found that higher osocimab doses (0.6, 1.2, and 1.8 mg/kg) were non-inferior to enoxaparin, with the 1.8 mg/kg dose superior in reducing VTE events. Bleeding occurred in up to 4.7% of osocimab patients versus 5.9% with enoxaparin and 2% with apixaban [**78**].

In the ANT-005 TKA trial, abelacimab at 30 mg, 75 mg, and 150 mg was compared with enoxaparin. VTE occurred in 13%, 5%, and 4% of the abelacimab groups, respectively, against 22% in the enoxaparin group, showing higher doses of abelacimab were more effective. Bleeding rates were low and comparable across all groups [**77**].

The AXIOMATIC-TKR trial found that higher doses of milvexian (50 mg, 100 mg, and 200 mg twice daily) significantly reduced VTE rates without major bleeding events, suggesting a favorable safety profile [**84**].

A meta-analysis combining data from these studies reported significant reductions in VTE and major or CRNMB events with FXI inhibitors. The odds ratio (OR) for reducing VTE events was 0.50 [95% CI 0.36-0.69], and for major or CRNMB events, it was 0.41 [95% CI 0.22-0.75], indicating a substantial improvement over LMWH [**104**]. While these studies collectively suggest a promising role for FXI inhibitors in reducing VTE risks post-TKA, variability in dosing regimens across trials underscores the need for standardized protocols and larger, multicenter phase 3 trials to confirm these findings and ensure generalizability. Further research, such as the ongoing REGN9933 study (NCT05618808), is expected to provide additional insights by August 2024; however, currently, there are no phase 3 trials investigating FXI inhibitors in this setting.

Prevention of stroke and systemic embolism in patients with AF

In the realm of FXI inhibitors for stroke prevention in AF patients, key studies present varied results. The phase 2 PACIFIC-AF trial showed that asundexian potentially reduces bleeding events compared to apixaban, with the incidence proportion ratios of 0.33 for pooled asundexian groups and 0.5 and 0.38 for the 20 mg and 50 mg doses, respectively [**88**]. However, the full scope of its efficacy and safety remains to be robustly analyzed.

The phase 2 AZALEA-TIMI 71 trial with abelacimab was stopped early due to significant reductions in major and CRNMB events, with hazard ratios (HR) of 0.33 and 0.23 for major and CRNMB, respectively, particularly noting a 93% reduction in major GI bleedings with the 150 mg dose. However, there was a slight, non-significant rise in IS and systemic embolism rates with abelacimab [**105**].

Contrastingly, the phase 3 OCEANIC-AF trial, comparing asundexian with apixaban, was halted prematurely due to concerns of inferior efficacy with asundexian [**106**]. The upcoming OCEANIC-AFINA trial will examine the efficacy of asundexian against placebo in older AF

patients unsuitable for DOACs [**107**]. The focus on older AF patients unsuitable for DOACs underscores the potential of FXI inhibitors to safely address anticoagulation needs in populations where traditional therapies pose significant risks. Additionally, ongoing phase 3 trials like LIBREXIA-AF (NCT05757869) and LILAC (NCT05712200) are assessing milvexian and abelacimab, respectively, for the prevention of IS and systemic embolism in AF patients.

Antithrombotic treatment in acute IS

In the evaluation of FXI inhibitors for preventing recurrent non-cardioembolic IS, recent trials have yielded nuanced findings. The phase 2 PACIFIC-Stroke trial compared asundexian with placebo in conjunction with standard antiplatelet therapy, finding no significant differences in primary efficacy outcomes, including symptomatic and covert brain infarction. Asundexian 50 mg showed a non-significant reduction in IS recurrence (HR 0.53, 90% CI 0.24-1.17) and no significant increase in major or CRNMB events (HR 1.57, 90% CI 0.91-2.71) [**89**].

Similarly, the AXIOMATIC-SSP trial assessed various doses of milvexian alongside dual antiplatelet therapy. Although fewer IS recurrences were noted with most milvexian doses (except the 200 mg daily dose) compared to placebo at 90 days, no dose showed significant efficacy in reducing the composite outcome of symptomatic IS or covert brain infarction. Risk of MB also did not significantly increase across different doses [**86**].

A meta-analysis of phase 2 trials found no significant reduction in IS occurrence compared to controls (RR 0.89, 95% CI: 0.67-1.17) and a non-significant increase in major and CRNMB events (RR 1.19, 95% CI: 0.65-2.16), though with considerable statistical heterogeneity [**108**]. Given the limited power of these phase 2 trials, ongoing phase 3 trials, OCEANIC-STROKE (NCT05686070) and LIBREXIA-STROKE (NCT05702034), are expected to

provide more definitive conclusions on the efficacy and safety of FXI inhibitors in this context.

Antithrombotic treatment in acute myocardial infarction (AMI)

In the context of FXI inhibition for treating patients with AMI the PACIFIC-AMI phase 2 trial stands out as a pivotal study. This trial investigated the combination of asundexian with dual antiplatelet therapy (aspirin and a P2Y12 inhibitor) in 1601 patients with recent AMI. The findings showed no significant differences in Bleeding Academic Research Consortium (BARC) types 2, 3, or 5 bleeding between pooled asundexian doses and placebo (HR 0.98, 90% CI 0.71-1.35). Additionally, the composite efficacy outcome of cardiovascular death, AMI, stroke, or stent thrombosis showed no notable difference when comparing pooled asundexian 20 and 50 mg doses with placebo (HR 1.05, 90% CI 0.69-1.61) [**90**]. The lack of significant differences in efficacy outcomes, raises questions about the benefit of adding a third drug to the treatment regimen, as it might not offer additional benefits over current antiplatelet and anticoagulant regimens for AMI patients.

The phase 2 LIBRXIA-ACS trial (NCT05754957) is ongoing, focusing on milvexian in a similar patient group. However, due to the modest outcomes in current studies and the lack of phase 3 trial data, the definitive role of FXI inhibitors in AMI treatment remains uncertain.

Patients with ESRD requiring hemodialysis

In phase 2 trials investigating FXI inhibitors in ESRD patients on hemodialysis, several studies have reported promising results. The IONIS-FXIRx study showed a reduction in FXI activity by up to 70.7%, with significant decreases in hemodialysis circuit thrombosis—28.9% for the 200 mg dose and 19.0% for the 300 mg dose, versus a 1.6% reduction in the placebo group. Major bleeding events were notably rare [**74**]. Similarly, the EMERALD trial

observed comparable rates of major and CRNMB events between IONIS-FXIRx doses and placebo, ranging from 3.8% to 6.0% versus 5.7% in the placebo group [**109**]. The RE-THINc ESRD trial reported similar rates of bleeding across all fesomersen doses and placebo [**110**]. A study of xisomab in this setting highlighted its potential role in reducing dialyzer clotting and influencing biomarkers like thrombin-antithrombin complexes and C-reactive protein levels [**81**]. In the CONVERT trial, osocimab showed non-significant reductions in major and CRNMB rates and incidence of dialysis circuit thrombosis compared to placebo, with hazard ratios of 0.66 and 0.71 for high and low doses, respectively [**111**]. The promising outcomes from these studies could herald a paradigm shift in the management of thrombotic complications for ESRD patients undergoing hemodialysis, potentially offering a safer anticoagulation strategy with FXI inhibitors that balances efficacy with a manageable bleeding risk profile. Yet, phase 3 trials are needed for conclusive evidence.

Cancer-associated thrombosis

Cancer-associated thrombosis represents a significant challenge in oncology, necessitating a delicate balance between anticoagulant efficacy and safety [**112**]. Two notable phase 3 trials, ASTER (NCT05171049) and MAGNOLIA (NCT05171075), are evaluating the effectiveness and safety of Abelacimab in various cancer types, with ASTER focusing on a broad range of malignancies and MAGNOLIA on GI malignancies, comparing abelacimab to dalteparin and apixaban, respectively. The role of abelacimab is supported by its observed reduction in GI bleeding in the AZALEA-TIMI 71 trial [**105**]. A phase 2 trial (NCT04465760) exploring xisomab in thrombosis prevention in cancer patients was terminated early due to manufacturing issues, with preliminary data from 9 patients showing one episode of CRT and no major or CRNMB events [**113**]. Given the high prevalence of thrombotic complications in oncology, especially with CVCs used for chemotherapy and nutrition, the ability of FXI

inhibitors to reduce thrombotic events while minimizing bleeding risks holds promise for enhancing patient care in various high-risk settings and could transform management strategies in oncology and related fields.

Conclusions and future directions

The diverse landscape of FXI inhibitors, from long-acting antisense oligonucleotides and monoclonal antibodies to the oral small molecule inhibitors, presents a range of dosing regimens and pharmaceutical properties that cater to different clinical needs. Initially heralded as a promising solution to separate bleeding risk from anticoagulation efficacy in preclinical studies, they have shown encouraging results in phase 2 trials. These trials collectively suggest a reduced bleeding risk compared to traditional anticoagulants, although results vary across different molecules and clinical scenarios. However, phase 2 trials are underpowered for efficacy, and confirmation from phase 3 trials is necessary. A number of meta-analyses have tried to provide some more robust results from currently available data, but the different dosages used in these dose-finding studies, as well as some heterogeneity in the definition of efficacy and bleeding outcome across studies, especially in cardiovascular settings, limit the validity of these studies, suggesting the need for more standardized approaches. The unexpected efficacy concerns leading to the premature termination of the OCEANIC-AF trial led to a greater caution and to some concerns about the ability of FXI inhibitors to reduce the risk of thrombosis in high risk patients, despite the potential for bleeding risk reduction. Yet, it is important to note that other phase 3 trials, including OCEANIC-STROKE that is assessing the same drug, have not been stopped for similar reasons. Furthermore, uncertainties persist regarding reversal strategies for bleeding episodes and potential off-target adverse effects. Ongoing phase 3 trials are essential in not only validating the potential of FXI inhibitors initially observed in phase 2 studies, but also in exploring these inhibitors' full potential across various dosages and administration strategies. In addition to the critical outcomes of phase 3 trials, future research directions could include investigating combination therapy approaches that might synergize with FXI inhibitors for enhanced efficacy or safety profiles. Novel drug formulations aimed at improving delivery,

reducing side effects, or tailoring dosing to patient-specific needs represent another promising area of investigation, potentially revolutionizing anticoagulant therapy. These upcoming results are expected to address the current unmet clinical needs and potentially open up new applications for FXI inhibitors in areas demanding high anticoagulant efficacy, such as mechanical heart valves and external devices. The path forward, while cautiously optimistic, calls for a nuanced understanding of each inhibitor's unique attributes to fully integrate them into the anticoagulation therapy paradigm.

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Table 1: Characteristics, mechanism of action and pharmacological properties of FXI and FXII inhibitors

	Developer	Mechanism of action	Route of administration	Onset of action	Half life	Administration frequency	Renal excretion	Metabolism by CYP	Potential for food and drug interactions	Tested indications
Antisense oligonucleotides (ASO):										
IONIS FXI-Rx (ISIS 416858) and Fesomersen	Ionis pharma	Degradation of FXI mRNA and inhibition of FXI biosynthesis	SC	Slow (3-12 weeks)	Long (mean elimination half-life 52 hours for IONIS FXI-Rx, Fesomersen ~30 days)	Once weekly to once monthly	No	No	No	VTE prophylaxis in TKA, ESRD
Antibodies										
Abelacimab (MAA868)	Anthos therapeutics	Binds to the catalytic domain of FXI and locks it in the inactive zymogen conformation, preventing its activation by FXII/thrombin	IV or SC	IV: Rapid (hours) SC: Slow (days)	Long (20-30 days), depending on route of administration	Once monthly	No	No	No	VTE prophylaxis in TKA, Stroke prevention in AF Cancer-associated VTE
Osocimab (BAY 1213790)	Bayer AG, Aronora	Binds next to the active site of FXIa, and inhibits the activation of factor IX	IV	Rapid (~2 hours)	Long (30 to 44 days)	Once monthly	No	No	No	TKA, ESRD
Xisomab (AB023)	Aronora	Inhibits FXIIa mediated activation of FXI but not FXI activation by thrombin	IV	Rapid (10-30 minutes)	Hours to days, half-life increases with high doses	Once monthly	No	No	No	ESRD, Prevention of catheter-related thrombosis in cancer patients receiving chemotherapy

Small molecules:										
Milvexian (BMS-986177/ JNJ-70033093)	Bristol-Myers Squibb (Janssen)	Active-site directed inhibitor of FXI	Oral	Rapid (minutes to hours) Saturable absorption with doses ≥ 300 mg	Short (terminal half-life 8.3 to 13.8 hours)	Once or twice daily	Yes, < 20%	Yes	Yes, CYP 3A4 inhibitors	VTE prophylaxis in TKA, Stroke prevention in AF, SSP, ACS
Asundexian (BAY 2433334)		Active-site directed inhibitor of FXI	Oral	Rapid (minutes to hours)	Short (terminal half-life 15.8 to 17.8 hours)	Once daily	Yes, < 15%	Yes	Yes, CYP 3A4 inhibitors, P-gp	Stroke prevention in AF, SSP, ACS

Abbreviations: ACS, acute coronary syndromes; AF, atrial fibrillation; CYP, cytochrome P450; ESRD, end-stage renal disease; FXI, factor XI; FXII, factor XII; IV intravenous; SC, subcutaneous; SSP; secondary stroke prevention; TKA, total knee arthroplasty; VTE venous thromboembolism

Table 2: Overview of FXI Inhibitors in Venous Thromboembolism Prevention Post-Total Knee Arthroplasty

	FXI-ASO (2015)	FOXTROT (2020)	ANT-005 TKA (2021)	AXIOMATIC TKA (2021)
Phase	Phase 2	Phase 2	Phase 2	Phase 2
Patients	300	813	412	1242
Population	VTE prevention after TKA	VTE prevention after TKA	VTE prevention after TKA	VTE prevention after TKA
Study drug	IONIS-FXIRx	Osocimab	Abelacimab	Milvexian
Comparator	Enoxaparin 40 mg once daily	Enoxaparin 40 mg once daily Apixaban 2.5 mg twice daily	Enoxaparin 40 mg once daily	Enoxaparin 40 mg once daily
Main efficacy outcome definition	Asymptomatic DVT, symptomatic VTE, fatal PE, or unexplained death for which PE could not be ruled out.	Asymptomatic DVT, objectively confirmed symptomatic DVT or PE, documented fatal PE, or unexplained death, for which PE could not be excluded.	Asymptomatic DVT, confirmed symptomatic DVT of the leg or nonfatal PE, fatal PE, or unexplained death for which PE could not be ruled out.	Asymptomatic, confirmed symptomatic VTE (symptomatic DVT of the leg or nonfatal PE), or death from any cause.
Main safety outcome definition	Major and clinically relevant nonmajor bleeding events.	Major or clinically relevant nonmajor bleeding.	Major or clinically relevant nonmajor bleeding	Major bleeding, clinically relevant nonmajor bleeding, and minimal bleeding.
Efficacy outcome rates	IONIS-FXIRx 200 mg: 27.0% IONIS-FXIRx 300 mg: 4.0% Enoxaparin: 30.0%	Osocimab 0.3 mg/kg: 23.7%a Osocimab 0.6 mg/kg: 15.7%a Osocimab 1.2 mg/kg: 6.5%a Osocimab 1.8 mg/kg: 17.9%a Enoxaparin: 26.3% Apixaban: 14.5%	Abelacimab 30 mg: 13.0% Abelacimab 75 mg: 5.0% Abelacimab 150 mg: 4.0% Enoxaparin: 22.0%	Milvexian 25 mg BID: 21.0% Milvexian 50 mg BID: 11.0% Milvexian 100 mg BID: 9.0% Milvexian 200 mg BID: 8.0% Milvexian 25 mg OD: 25.0% Milvexian 50 mg OD: 24.0% Milvexian 200 mg OD: 7.0% Enoxaparin: 21.0%
Safety outcome rates	IONIS-FXIRx 200 mg: 3.0% IONIS-FXIRx 300 mg: 3.0% Enoxaparin: 8.0%	Osocimab 0.3 mg/kg: 2.0%a Osocimab 0.6 mg/kg: 0.0%a Osocimab 1.2 mg/kg: 1.0%a Osocimab 1.8 mg/kg: 4.7%a Enoxaparin: 5.9% Apixaban: 2.0%	Abelacimab 30 mg: 2.0% Abelacimab 75 mg: 2.0% Abelacimab 150 mg: 0.0% Enoxaparin: 0.0%	All Milvexian doses: 4.0% Enoxaparin: 4.0%

BID, twice daily; DVT, deep vein thrombosis; OD, once daily; PE, pulmonary embolism; TKA, total knee arthroplasty; VTE: Venous thromboembolism.

a) Post-operative administration

Table 3: Overview of FXI Inhibitors in Various Cardiovascular Indications (Atrial fibrillation, Acute Myocardial Infarction and Stroke)

	PACIFIC-AF (2022)	**PACIFIC-AMI (2022)**	**PACIFIC-STROKE (2022)**	**AXIOMATIC-SSP (2023)**	**AZALEA TIMI 71 (2024)**
Phase	Phase 2	Phase 2	Phase 2	Phase 2	Phase 2
Patients	862	1601	1808	2366	1287
Population	Atrial fibrillation	Acute myocardial infarction	Stroke	Non-cardioembolic ischemic stroke and high-risk transient ischemic attack	Atrial fibrillation
Study drugs	Asundexian	Asundexian on top of usual antiplatelet therapy	Asundexian on top of usual antiplatelet therapy	Milvexian + ASA for 90 days and clopidogrel for 21 days	Abelacimab
Comparator	Apixaban 5 mg BID	Placebo on top of usual antiplatelet therapy	Placebo on top of usual antiplatelet therapy	Placebo + ASA for 90 days and clopidogrel for 21 days	Rivaroxaban 20 mg
Efficacy outcome	The composite of cardiovascular death, myocardial infarction, ischemic stroke, or systemic embolism.	The composite of cardiovascular death, recurrent MI, ischemic or hemorrhagic stroke or stent thrombosis.	The composite of symptomatic recurrent ischemic stroke and incident covert brain infarcts detected on follow-up MRI at or before 26 weeks after randomization.	The composite of incident ischemic stroke during the treatment period or new covert brain infarction detected by the comparison of 90-day and baseline MRIs.	The composite of, ischemic stroke, hemorrhagic stroke, or systemic embolism.
Main safety outcome	The composite of major bleeding and CRNMB (ISTH).	The composite of BARC type 2, 3, or 5 bleeding.	The composite of major bleeding and CRNMB (ISTH).	Occurrence of types 3 and 5 bleeding, according to the BARC classification system. Also analyzed with ISTH definition.	The composite of major bleeding and CRNMB (ISTH).
Efficacy outcome rates*	Asundexian 20 mg: 0.8% Asundexian 50 mg: 1.6% All doses of Asundexian: 1.2%	Asundexian 10 mg: 6.8% Asundexian 20 mg: 6.0% Asundexian 50 mg: 5.5% All doses of Asundexian: 6.1%	Asundexian 10 mg: 19% Asundexian 20 mg: 22% Asundexian 50 mg: 20% All doses of Asundexian: 20%	Milvexian 25 mg OD: 16.2% Milvexian 25 mg BID: 18.5% Milvexian 50 mg BID: 14.1% Milvexian 100 mg BID: 14.8% Milvexian 200 mg BID: 16.4%	Abelacimab 90 mg: 1.4b Abelacimab 150 mg: 1.1b
	Apixaban 5 mg: 1.2 %	**Placebo: 5.5%**	**Placebo: 19%**	**Placebo: 16.6%**	**Rivaroxaban 20 mg: 1.0b**
Main safety	Asundexian 20 mg: 1.2%	Asundexian 10 mg: 7.6%	Asundexian 10 mg: 4%	Milvexian 25 mg QD: 0.6%a	Abelacimab 90 mg: 1.9b

outcome rates*	Asundexian 50 mg: 0.4% All doses of Asundexian: 0.8 % **Apixaban 5 mg: 2.4%**	Asundexian 20 mg: 8.1% Asundexian 50 mg: 10.4% All doses of Asundexian: 8.7% **Placebo: 9.0%**	Asundexian 20 mg: 3% Asundexian 50 mg: 4% All doses of Asundexian: 4% **Placebo: 2.0%**	Milvexian 25 mg BID: 0.6%a Milvexian 50 mg BID: 1.5%a Milvexian 100 mg BID: 1.6%a Milvexian 200 mg BID: 1.5%a **Placebo: 0.6%**	Abelacimab 150 mg: 2.7b **Rivaroxaban 20 mg: 8.1b**

ASA, Aspirin; BARC, Bleeding Academic Research Consortium; BID, twice daily; CRNM, clinically relevant non-major bleeding; ISTH: International Society of Thrombosis and Hemostasis; MRI, magnetic resonance imaging; OD, once daily.

* Primary efficacy and safety outcome has been reported as rates of events in each group of treatment.

a) BARC classification system bleedings

b) Incidence rate per 100 people/year

Table 4: FXI Inhibitors in End-Stage Renal Disease Patients Undergoing Hemodialysis

	M. Walsh *et al.* (2021)	CU Lorentz *et al.* (2021)	EMERALD (2022)	RE-THINc ESRD (2023)	CONVERT (2023)
Phase	Phase 2	Phase 2	Phase 2	Phase 2	Phase 2
Patients	49	24	213	307	703
Population	ESRD on HD	ESRD on HD	ESRD on HD	ESRD on HD	ESRD on HD
Study drug	IONIS-FXI_{Rx}	Xisomab	IONIS-FXI_{Rx}	IONIS-FXI-L_{Rx}	Osocimab
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
HD Circuit thrombosis	IONIS-FXI_{Rx} 200 mg: -28.9%[c,d] IONIS-FXI_{Rx} 300 mg: -19.0%[d] Placebo: -0.2%[c,d]	Xisomab 0.25 mg/kg: 0%[c,e] Xisomab 0.5 mg/kg: -25%[c,e] Placebo: +4.5%[c,e]	NA	NA	Osocimab 210 mg LD + 105 mg/m: 27.2%[f] Osocimab 105 mg LD + 52.5 mg/m: 29.3%[f] Placebo: 41.3%[f]
Major bleeding and CRNMB (ISTH definition)	IONIS-FXI_{Rx} 200 mg: 0.0% IONIS-FXI_{Rx} 300 mg: 9.5%[a] Placebo: 7.7%	Xisomab 0.25 mg/kg: 0.0% Xisomab 0.5 mg/kg: 0.0% Placebo: 0.0%	IONIS-FXI_{Rx} 200 mg: 3.8% IONIS-FXI_{Rx} 250 mg: 5.6% IONIS-FXI_{Rx} 300 mg: 6.0% Placebo: 5.7%	IONIS-FXI-L_{Rx} 40 mg: 9.0 (2.5 to 18.9)[b] IONIS-FXI-L_{Rx} 80 mg: 9.1 (2.5 to 19.1)[b] IONIS-FXI-L_{Rx} 120 mg: 6.1 (1.1 to 14.5)[b] Placebo: 9.7 (2-7 to 20.4)[b]	Osocimab 210 mg LD + 105 mg/m: 4.9% Osocimab 105 mg LD + 52.5 mg/m: 6.9% Placebo: 7.8%

CRNM, clinically relevant non-major bleeding; ESRD, end stage renal disease; HD, hemodialysis; ISTH, International Society of Thrombosis and Hemostasis; LD, loading dose; NA, not available

a) Aggregated results from PK-cohort and randomized cohort

b) Reported as n/100 person-years (95% confidence intervals)

c) Reported using the percent of clotting score ≥3 (Category 3 events included clot formation on venous chamber and blood stripes affecting ≥5% of the fibers found at the surface of the dialyzer. Category 4 events included coagulated system (treatment cannot continue without new setup) and coagulated filter.

d) Subject difference in the percent of clotting scores ≥3 between weeks 6–13 and before week 6

e) Subject Difference in the percent of in High-grade dialyzer clotting (clotting score >3) between the week before and 3 days after treatment

f) Rates of clotting scores 2 or 3 (0, no clot; 1, trace of clot; 2, intermediate between 1 and 3; and 3, fully clotted system necessitating interruption of hemodialysis session)

Table 5: Ongoing clinical trials with FXI inhibitors

NCT	Trial name	Phase	Drugs	Patients	Population	Expected Conclusion
Total knee arthroplasty (TKA)						
NCT05618808	R9933-DVT-2230	Phase 2	REGN9933 vs. enoxaparin	373	TKA	29/05/2024
Cardiovascular indications						
NCT04755283	AZALEA	Phase 2	Abelacimab vs. rivaroxaban	1200	AF	01/01/2024
NCT05757869	LIBREXIA- AF	Phase 3	Milvexian vs. apixaban vs. placebo	15500	AF	05/05/2027
NCT05754957	LIBREXIA-ACS	Phase 3	(Milvexian vs. placebo) + DAPT	16000	AMI	19/10/2026
NCT05712200	LILAC	Phase 3	Abelacimab vs. placebo	1900	AF	01/03/2025
NCT05643573	OCEANIC-AF	Phase 3	Asundexian vs. apixaban	18000	AF	Interrupted
NA	OCEANIC-AFINA	Phase 3	Asundexian vs. placebo	NA	AF, with no AC alternatives	Planning
NCT05686070	OCEANIC STROKE	Phase 3	Asundexian vs. placebo	9300	Non-cardioembolic Stroke/TIA	10/10/2025
NCT05702034	LIBREXIASTROKE	Phase 3	Milvexian vs. placebo	15000	Non-cardioembolic Stroke/TIA	09/12/2026
Cancer-associated thrombosis (CAT)						
NCT05171049	ASTER	Phase 3	Abelacimab vs. apixaban	1655	CAT	01/10/2024
NCT05171075	MAGNOLIA	Phase 3	Abelacimab vs. dalteparin	1020	CAT (Gastrointestinal and genito-urinal tract malignancies)	01/01/2025

AC, anticoagulation; AF, atrial fibrillation; AMI, acute myocardial infarction; TIA, transient ischemic attack

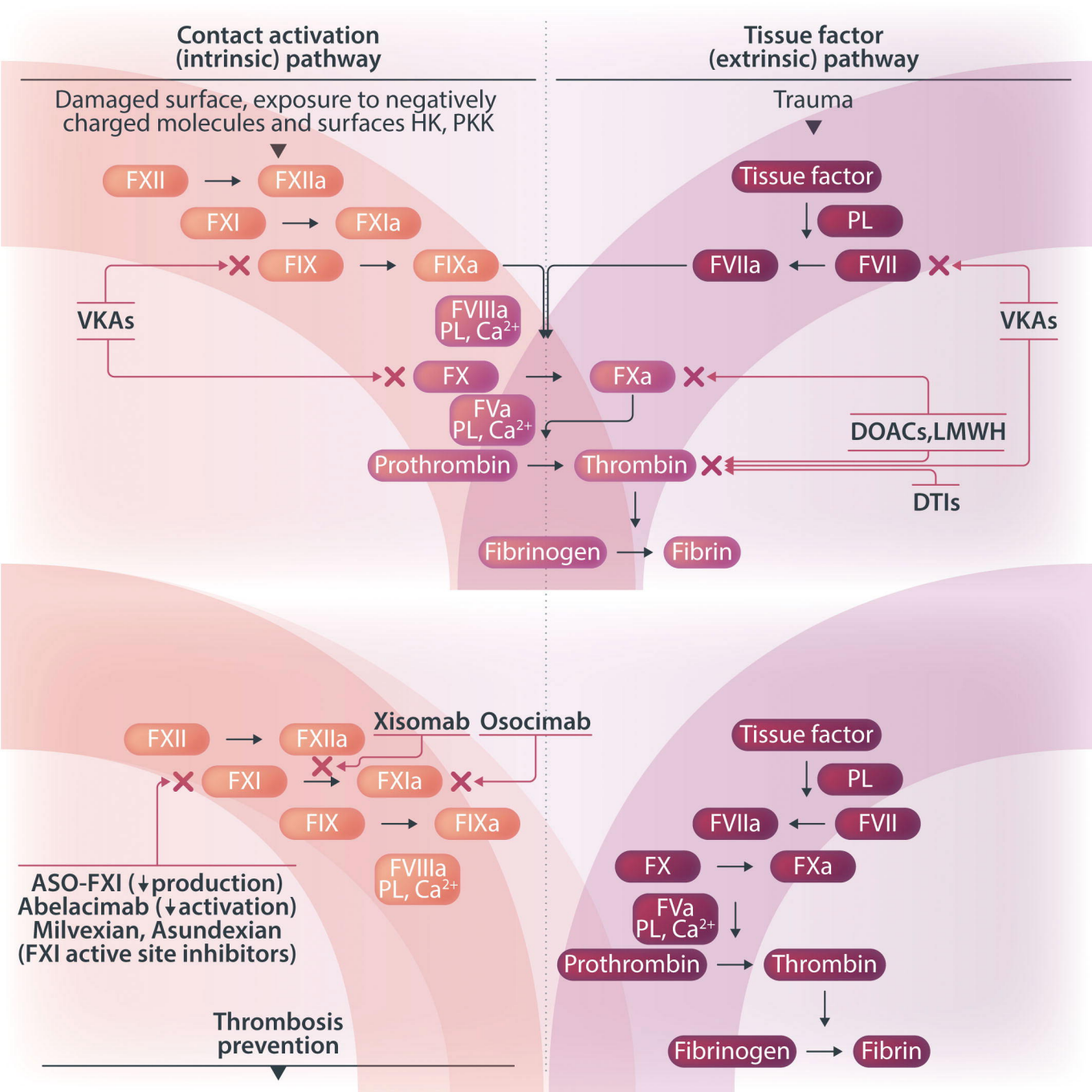
Figure Legend:

DOACs, direct oral anticoagulants; DTIs, direct thrombin inhibitors; F, factor; HK, high molecular weight kininogen; LMWH, low molecular weight heparin; PKK, prekallikrein; PL, phospholipids; VKAs, vitamin K antagonists

Differentiating thrombosis from hemostasis for safer anticoagulation

Differentiating thrombosis from hemostasis is vital for safer anticoagulation. Hemostasis stops bleeding through a local plug, while thrombosis can obstruct blood flow, risking organ damage.

The contact pathway, less involved in hemostasis but more in thrombosis, appears to offer a safer target for new anticoagulants. Inhibition of this pathway's is less likely to cause bleeding than drugs affecting multiple coagulation factors or the common pathways. Targeted agents include antisense oligonucleotides, monoclonal antibodies and small molecules, focusing on FXI to enhance safety profiles.


Contact activation (intrinsic) pathway
Damaged surface, exposure to negatively charged molecules and surfaces HK, PKK
FXII
FXIIa
FXI
FXIa
FIX
FIXa
VKAs
FVIIIa PL, Ca2+
FX
FXa
FVa PL, Ca2+
Prothrombin
Thrombin
Fibrinogen
Fibrin
Tissue factor (extrinsic) pathway
Trauma
Tissue factor
PL
FVIIa
FVII
VKAs
DOACs,LMWH
DTIs
Xisomab
Osocimab
ASO-FXI (↓production)
Abelacimab (↓activation)
Milvexian, Asundexian
(FXI active site inhibitors)
Thrombosis prevention