https://doi.org/10.31925/farmacia.2025.2.1 **REVIEW**

FACTOR XI, THE TARGET OF NEW CLASSES OF ANTICOAGULANTS – REALITY AND PERSPECTIVES

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Abstract

Factor XI is an important element in the classical intrinsic coagulation pathway and has a nuanced role in cellular coagulation. Its involvement in thrombogenesis is major, while it plays a minor role in haemostasis. Clinical trials in Haemophilia C have shown reduced venous/arterial thrombotic events and minimal to moderate bleeding. These data have led to the development of pharmacological FXI inhibitors, which either reduce the synthesis or the activity of FXI. Unlike classical anticoagulants - heparins, vitamin K antagonists, new direct oral anticoagulants - FXI inhibitors have the effect of decoupling haemostasis from thrombosis, thereby presenting a lower risk of bleeding. Multiple Phase II clinical studies using FXI inhibitors have shown antithrombotic (anticoagulant) efficacy similar to classical anticoagulants, but with a lower risk of bleeding. Overall, results are somewhat different in preventing stroke in atrial fibrillation, venous thromboembolism in orthopaedic interventions or cancer, and complications of end-stage renal disease with haemodialysis. There are several ongoing phase II and III clinical trials investigating the role of FXI inhibitors. These drugs are not thought to replace treatment with classical anticoagulants, but they appear to be an alternative in several specific pathological situations.

Rezumat

Factorul XI este un element important al căii clasice intrinseci a coagulării si are un rol nuanțat în coagularea celulară. Implicarea sa în trombogeneză este majoră, în timp ce în hemostază prezintă un rol minor. Studiile clinice investigând Hemofilia C au arătat o reducere a evenimentelor trombotice venoase/arteriale și și prezența sângerărilor minime - moderate. Aceste date au condus la dezvoltarea unor inhibitori farmacologici ai FXI, care, fie reduc sinteza, fie activitatea FXI. Spre deosebire de anticoagulantele clasice - heparine, antagoniști ai vitaminei K, sau noile anticoagulante orale directe - inhibitorii FXI au un efect de decuplare a hemostazei de tromboză, prezentând astfel un risc hemoragic mai mic. Mai multe studii clinice de fază II investigând inhibitorii FXI au evidențiat o eficacitate antitrombotică (anticoagulantă) similară cu cea a anticoagulantelor clasice, dar cu un risc mai scăzut de sângerare. În general, rezultatele sunt oarecum diferite atunci când ne referim la prevenirea accidentului vascular cerebral în fibrilația atrială, a trombembolismului venos în intervențiile ortopedice sau in cancer și a complicațiilor bolii renale în stadiu terminal cu hemodializă. Sunt în desfășurare mai multe studii clinice de fază II și III investigând rolul inhibitorilor FXI. Se crede că inhibitorii FXI(a) nu înlocuiesc tratamentul cu anticoagulantele clasice, dar par a reprezenta o alternativă în unele situații patologice specifice.

Keywords: factor XI inhibitors, FXI inhibitors, thrombosis, asundexian

Introduction

Thrombosis in the venous and arterial systems is a pathological process that represents a primary pathological concern due to its locations and effects. For over 70 years, pharmacological agents with anticoagulant effects have been targeting the prevention and treatment of thrombotic processes. The first generation of anticoagulant agents, heparin and vitamin K antagonists (VKAs), have proven effective in preventing and treating thrombosis. However, due to the nonspecific inhibition of multiple coagulation factors, VKAS come with an inherent risk of bleeding. Additionally, VKAs require repeated biological monitoring to assess efficacy. The new direct oral anticoagulants (DOACs) specifically target Factor X and thrombin, and they have demonstrated antithrombotic efficacy at least equal to VKAs but with a significantly lower risk of bleeding. However, long-term use of DOACs carries a "residual" risk of bleeding, which varies among different products and is estimated to be approximately 3 - 4% *per* year [1].

Basic data on the structure and function of FXI in the coagulation process and its effects on decoupling thrombosis from haemostasis and stabilising the

formed thrombus have led to research on FXI as a target for anticoagulation. Rosenthal's discovery of congenital FXI deficiency (Haemophilia C or Rosenthal Syndrome) [2] and observational studies of both the reduction of venous/arterial thrombosis risk in FXI deficiency and the increased thromboembolic risk induced by elevated levels of FXIa activity intensified research for the discovery of new pharmacological agents, *i.e.*, the FXI inhibitors [2-4].

It was anticipated that FXI inhibitors might have antithrombotic effects equal to DOACs, but with a better safety profile, by reducing the "residual" bleeding risk of DOACs. FXI inhibitors are currently being investigated in Phase II and III trials targeting multiple pathological conditions for the prevention and treatment of thrombosis with minimal risk of bleeding.

Factor XI, Haemostasis, and Thrombosis

Coagulation is a complex process, involving multiple coagulation factors and cellular surfaces, by which blood forms clots. It is an important part of haemostasis (stopping bleeding caused by damage to a blood vessel). At the site of injury to the vascular wall, a platelet plug is initially formed (due to the processes of adhesion, activation and aggregation of platelets), which is further strengthened by the deposition and polymerisation of fibrin [5, 6, 7]. The canonical coagulation occurs through the intrinsic and extrinsic pathways. Blood thrombus formation is currently believed to occur in three stages of cellular coagulation: initiation, amplification, and propagation (consolidation) [8-10].

Factor XI is synthesised predominantly in the liver and represents the zymogen of FXIa [11]. Its role was initially defined in the classical intrinsic pathway of the clotting cascade. In contrast to its position in the downstream stage of the cell-based coagulation model, it is now accepted that FXI has a major role in thrombosis and a minor role in physiological haemostasis [12].

Tissue factor (TF), a cell surface glycoprotein in subendothelial tissue, is expressed by TF-bearing cells and released at the site of vascular injury, which is responsible for initiating the clotting cascade. TF can activate and form a complex with FVII, which then activates FX to Xa (directly or indirectly, following FIX activation). FXa activates FV to FVa and forms the prothrombinase complex, which converts prothrombin (FII) to thrombin (FIIa). FIIa converts fibrinogen to fibrin (initially soluble, later becoming insoluble). A small amount of thrombin is produced in the initiation phase of haemostasis, leading to the formation of a small amount of fibrin and the generation of an unstable haemostatic plug. In the amplification and consolidation (propagation) phases, the amount of thrombin formed in the earlier step activates other recruited platelets, FV, FVIII and FXI through positive feedback loops, generating a thrombin burst and a stable, consolidated clot [10, 13, 14].

Unlike haemostasis, in which the haemostatic clot forms at and near the injury of the vessel wall to seal the leak, stop bleeding, and produce minimal interruption of blood flow, thrombosis compromises blood flow, partially or completely obstructing the blood vessel and even leading to organ damage. Thrombosis generally results from the interaction of coagulation factors, endothelial injury, and hemodynamic changes in blood vessels [8, 15]. In thrombosis, coagulation is initiated mainly by forming the TF/VIIa complex. Less commonly, coagulation is triggered by activation of the contact pathway, following contact between the plasma and negatively charged macromolecules (polyanions, *e.g.*, in the extracorporeal circulation), leading to FXII activation [8, 14].

As previously mentioned, FXI represents a key factor in thrombosis, appearing to be more important than physiological haemostasis. Thrombus growth in the vascular lumen beyond the source of TF requires amplification of coagulation, and this can be achieved through intense feedback loops whereby thrombin activates important coagulation factors, *i.e.* FV, FVIII, and FXI [8, 16]. In thrombosis, thrombin is likely the main activator of FXI [8]. Under certain circumstances (*e.g.*, when blood is exposed to artificial surfaces), FXIIa may be the major activator of FXI. Once activated to FXIa, coagulation is consolidated by activating FIX. Through this pathway, an additional amount of FIXa is generated, much higher than that produced following the formation of the TF/FVIIa complex. Meanwhile, the thrombin burst activates more neighbouring platelets, closing the pathogenic circuit of thrombus formation [8, 16]. A secondary role of FXI is to attenuate fibrinolysis. High concentrations of thrombin at the level of the thrombus, induced by the feedback loop through which thrombin amplifies FXI activity, lead to the activation of thrombin-activatable fibrinolysis inhibitor (TAFI), a plasma zymogen that protects the fibrin clot against lysis [17].

Oral anticoagulants (OACs) -VKAs, DOACs - used in the prevention and treatment of thrombotic events, inhibit multiple coagulation factors and, through their effects, do not distinguish between the physiological process of haemostasis and the process of thrombosis [18, 19]. The lack of specificity of OACs is responsible for the increase in haemorrhagic complications. FXIa inhibitors have the effect of uncoupling haemostasis from thrombosis, making them attractive targets for haemostasis-sparing therapies, with better safety profiles than current OACs [20-22]. FXI inhibitors are agents that reduce FXI level and FXIa activity, a situation also encountered in congenital

FXI deficiency (Haemophilia C). In Haemophilia C, spontaneous mucosal bleeding is not as severe as in Haemophilia A or B, and thrombotic processes in the venous and arterial systems are greatly reduced [8].

Anti-FXI Agents

To date, several types of FXI inhibitory agents have been developed: antisense oligonucleotides (ASOs), monoclonal antibodies, and small synthetic molecules. These pharmacological agents either block the synthesis of FXI at the hepatic level, inhibit circulating FXI, or prevent its activation to FXIa. Factor XI has become a new target for antithrombotic treatment [20]. ASOs act at the hepatic level through binding to mRNA and blocking the synthesis of FXI. ASOs are administered subcutaneously, have a long half-life ($t_{½}$), and require 3 - 4 weeks to reach a significant level of FXI inhibition [16]. Among the ASOs products, IONIS-FXI is being tested in Phase II studies to prevent venous thromboembolism (VTE) in orthopaedic knee arthroplasty surgeries, with significant results [23]. Currently, the antithrombotic effects of a new product, fesomersen, which also reduces hepatic synthesis of FXI, are being investigated [24].

Monoclonal antibodies are administered intravenously. They bind directly to the catalytic domain (active site) of FXI and/or FXIa, rapidly reducing FXI level and/or FXIa activity, in correlation with plasma antibody levels [25]. They have a $t_{½}$ of several weeks and are given in single or repeated doses. The metabolism and excretion of monoclonal antibodies do not involve the liver and kidneys, and the decrease in their activity depends on phagocytic cells and the reticuloendothelial system [19]. The main products used in multiple clinical studies are abelacimab, osocimab, and xisomab.

Small synthetic molecules are low-molecular-weight compounds administered orally in various daily doses. Pharmacokinetically, they reversibly bind to FXIa, blocking its activity. They have a relatively short $t_{½}$ (12 - 17 hours) and relatively rapid effects, reducing thrombotic processes but also the risk of bleeding [19]. The drugs widely used in multiple Phase II clinical studies are milvexian and asundexian.

In animal experimental research, there are two new types of FXI inhibitors: natural peptides that rapidly inhibit FXI activity and aptamers that inhibit either FXI or its activation to FXIa [1]. Table I summarises the pharmacological characteristics of the main FXI(a) inhibitors [19, 26-31].

Table I

Pharmacological characteristics of FXIa inhibitors

	Asundexian	**Milvexian**	**Abelacimab**	**Xisomab 3G3**	**Osocimab**	**Ionis - FXI Rx**	**Fesomersen**
Class of FXI(a) inhibitory drug	Small synthetic molecules	Small synthetic molecules	Monoclonal antibodies	Monoclonal antibodies	Monoclonal antibodies	ASOs	ASOs
Route of drug administration	p.o	p.o	s.c. / i.v.	i.v.	s.c. / i.v	s.c.	s.c.
Mechanism of action	Binds to FXIa and inhibits it	Binds to FXIa and inhibits it	Binds to FXI and FXIa, and inhibits them	Binds to FXI and inhibits its activation by FXIIa	Binds to FXIa and inhibits it	Blocks the mRNA of FXI translation	Blocks the mRNA of FXI translation
Administration frequency	q.d.	q.d. / b.i.d.	Single dose/q.mos.	Single dose	Single dose/q.mos.	q.wk.	q.mos.
Onset of action	Rapid	Rapid	Rapid	Rapid	Rapid	Slow	Slow
Offset of action	Rapid	Rapid	Slow	Slow	Slow	Slow	Slow
$t_{½}$	14.2 -17.4h	8.3 - 13.8h	20 - 30days	1.3 - 121.5h	30 - 44days	14 days	14 - 20 days
T - $(FXI_i)_{max}$	1h (p.o. sol.) 2-4h (tablets)	3 - 4 h	1h	U/A	1h	36 days	36 days
Drug interaction	-	Activators/ Inhibitors of CYP3A4	-	-	-	-	-
Reversible FXI administration	-	-	-	-	-	Yes	Yes
Drug clearance	Hepatic (Renal < 15%)	Hepatic (Renal < 20%)	Phagocytic cells & RES	Phagocytic cells & RES	RES	Hepatic (Renal ≃ 25%)	Hepatic (Renal ≃ 25%)

Abbreviations: ASOs - antisense oligonucleotides; p.o. - per os; s.c. - subcutaneously; i.v. - intravenously; q.d. - once a day; b.i.d. - twice daily; q.mos. - monthly; q.wk. - weekly; $t_{½}$ - the terminal half-life; sol - solution; T - $(FXI_i)_{max}$ - time to FXI maximal inhibition; CYP3A4 - Cytochrome P450 3A4; RES - proteolysis by reticuloendothelial system.

FXI Inhibitors in Clinical Studies

To date, the results of more than 10 clinical studies using FXI inhibitors have been reported, targeting the following domains: 1) knee arthroplasty; 2) end-stage renal disease (ESRD) and dialysis; 3) atrial fibrillation (AF); 4) non-cardioembolic ischemic stroke; 5) post-acute myocardial infarction; 6) cancer. Other studies are ongoing. The efficacy and safety results of FXI inhibitors in Phase II (III) trials are briefly presented in this review, with examples provided.

Knee arthroplasty

In knee arthroplasty, FXI inhibitors have been used for VTE prophylaxis, considering the high postoperative risk. The results of four Phase II clinical studies have been published, showing the effect of FXI inhibitory agents from different classes (IONIS-FXI, osocimab, abelacimab, milvexian), when compared to enoxaparin or apixaban. The studies focused on efficacy (in reducing VTE) and safety/risk balance for haemorrhagic events. For example, in the AXIOMATIC study, 1241 knee arthroplasty patients were administered 200 and 300 mg/day of oral milvexian and compared with those receiving enoxaparin treatment. VTE was lower with 100 mg/day of enoxaparin but significantly lower with 200 mg/day (7% and 21%, respectively). The incidence of bleeding was 4% for both agents. Activated partial thromboplastin time (aPTT) values increased proportionally with milvexian dose (with the inhibition of FXI activity**)** [32].

A meta-analysis of phase II clinical studies using FXI inhibitors in knee arthroplasty reported beneficial effects in terms of efficacy and safety. Treatment with multiple doses of FXI inhibitors compared to 40 mg of enoxaparin was associated with a reduced risk of VTE. Moreover, the number of clinically relevant haemorrhagic events was also reduced in patients treated with FXI(a) inhibitors compared with enoxaparin [33].

ESRD

Patients with severe renal insufficiency (Class IV ESRD) undergoing haemodialysis are at increased risk of thromboembolic and haemorrhagic events. The risk is multifactorial, combining the adverse effects of haemodialysis (enhanced contact phase of coagulation), inflammation (due to renal dysfunction), platelet dysfunction, and administered medications (recombinant erythropoietin) [34]. The use of certain types of anticoagulants - heparin, DOACs, and VKAs can increase the haemorrhagic risk due to the lack of separation between haemostasis and thrombosis. DOACs, due to their effects on renal clearance, lead to product accumulation and increased haemorrhagic risk. AVKs are difficult to control therapeutically and are not used in haemodialysis. Commonly used unfractionated heparin has a short T ½ and a manageable haemorrhagic risk, but can induce thrombocytopenia with difficult-to-control bleeding. In this context, FXI inhibitors could represent an alternative worth considering.

Walsh *et al*. monitored the evolution of haemodialysis patients who received two doses of IONIS-FXI (200 and 300 mg), before or after dialysis. The average level of FXI activity decreased after 12 weeks of treatment by 56% and 70.7%, respectively, compared to 3.9% in the placebo group. Major bleeding occurred in 0% (at 200 mg), 6.7% (at 300 mg), and 7.7% in the placebo group [35]. The study results suggest that ASOs and monoclonal antibodies can be used as alternatives in ESRD patients.

A systematic review of the safety and efficacy of FXI(a) inhibitors has been recently published, including a meta-analysis of four phase II studies and encompassing 1270 ESRD patients on haemodialysis. The risk of bleeding in patients treated with FXI(a) inhibitors was not significantly increased compared to placebo, clinically relevant bleeding, or clinically relevant non-major bleeding. For prevention of thromboembolic events and all-cause mortality, suggesting that these end points need to be evaluated in sufficiently powered, randomised controlled phase III trials [36].

Atrial fibrillation

Atrial fibrillation is the most common cardiac tachyarrhythmia affecting more than 30% of the elderly. It is the most common cause of cardioembolic stroke (15-20% of all strokes) and is associated with cognitive impairment up to dementia. In addition, through its haemodynamic effects, it potentiates or worsens heart failure. Currently, FX (rivaroxaban, apixaban, edoxaban) and FII (dabigatran) inhibitors are the standard of anticoagulant treatment in AF: they decrease thromboembolic risk and cerebral bleeding, when compared to VKAs. DOCAs limits, in the prolonged treatment of AF, are related to a "residual" risk of approximately 3-4% *per* year of clinically relevant significant and non-major bleeding [37].

Two FXI inhibitors - asundexian and abelacimab - have been studied in the prevention of stroke in AF, as an alternative to DOACs. The PACIFIC-AF study followed 753 patients with AF receiving two oral doses (50 mg and 20 mg) of asundexian *versus* apixaban. After 4 weeks of treatment, FXI activity was significantly decreased (between 81% and 91%) relative to baseline. The incidence of major or clinically relevant non-major bleeding for asundexian was 0.50 for a dose of 20 mg asundexian, 0.16 for a dose of 50 mg asundexian, and 0.33 for pooled asundexian versus apixaban [38]. The PACIFIC-AF study is the first study to show reduced bleeding with an XI inhibitor compared with apixaban (DOAC). The study did not analyse the efficacy of asundexian as an antithrombotic agent, being limited to the safety aspects of the treatment [19].

The results of the phase II AZALEA-TIMI 71 study were recently published in January 2025. The study tracked the safety and efficacy of 2 doses of abelacimab (150 mg and 90 mg) compared with rivaroxaban (20 mg/day) in patients with AF and moderate-to-high risk for stroke. Both doses of abelacimab were superior compared with rivaroxaban in reducing bleeding events in patients with AF and a high CHA_2DS_2-VAS_c score [39]. The results of the AZALEA trial were debated in academia, and the trial was discontinued by the monitoring committee due to the "unusual" - "excessive" reduction in bleeding. The incidence rate of clinically relevant non-major or major bleeding was 3.2 events *per* 100 person-years at a dose of 150 mg abelacimab, and 2.6 events *per* 100 person-years at a dose of 90 mg abelacimab, *versus* 8.4 events *per* 100 person-years following rivaroxaban administration [39-41].

On the other hand, the phase III OCEANIC-AF trial, investigating the effectiveness and safety of asudexian in the prevention of stroke or systemic embolism in patients with AF and at risk for stroke, was stopped prematurely by the manufacturing company in November 2023, due to inferior efficacy when compared to apixaban: 1.3% of patients receiving asundexian developed stroke or systemic embolism, compared to 0.4% of patients assigned to receive apixaban. However, there were fewer major bleeding events in patients receiving asundexian (0.2%) than in patients receiving apixaban (0.7%) [42-44]. A systematic review and meta-analysis in press, including the randomised controlled trials (with 16852 patients in total) testing the safety of oral FXI(a) inhibitors *versus* DOACs in AF revealed a lower risk of significant bleeding, and a lower risk of the composite of major and clinically relevant non-major bleeding [45]. Overall, studies with FXI inhibitors in AF have reported a significant reduction in bleeding risk with prolonged treatment, compared to apixaban and rivaroxaban. The results are more than promising.

Non-cardioembolic stroke

Non-cardioembolic (large vessel and small vessel) stroke is a significant cause of morbidity and mortality, especially in the elderly. It has a high 1-year recurrence rate (approximately 6%) and haemorrhagic risk when anticoagulants or dual antiplatelet therapy are given [19]. Prevention of ischemic stroke and reduction of bleeding risk were assessed in two phase II trials with XI inhibitors, one testing asundexian (PACIFIC-STROKE), and the other testing milvexian (AXIOMATIC-SSP). The PACIFIC-STROKE study investigated the efficacy and safety of asundexian (10, 20, 50 mg/day) added to dual antiplatelet therapy in the prevention of recurrent non-cardioembolic stroke. At 26 weeks, there was no difference between the asundexian group *versus* placebo for recurrent stroke and haemorrhagic infarction (approximately 19%). Major bleeding, including haemorrhagic transformation of cerebral infarction, or clinically relevant bleeding was 2% in the placebo group, and 3-4% in the asundexian group [46]. The results of treatment with asundexian and milvexian in the treatment of patients with non-cardioembolic stroke appear modest or negative. The risk of bleeding was not increased when combined with dual therapy (aspirin, clopidogrel**)** [29, 46, 47].

Post-acute myocardial infarction

Dual antiplatelet therapy or monotherapy after acute myocardial infarction (AMI), treated with thrombolysis or percutaneous coronary intervention (PCI), does not provide maximal protection against the recurrence of atherothrombotic events (angina pectoris, acute coronary syndrome - ACS, stent thrombosis). The combination of rivaroxaban (low dose) and antiplatelet therapy has been shown to be effective in patients with angina pectoris and ACS, but with an increased risk of bleeding. The search for a different type of antithrombotic drug has become necessary in the presence of recurrences of atherothrombotic events at various locations, including AMI. In the PACIFIC-AMI study, the efficacy of asundexian at escalating doses (10 mg, 20 mg, or 50 mg), in patients with AMI and PCI on dual antiplatelet therapy, was investigated compared with placebo. At steady-state, asundexian was associated with reduced FXI level (between 65% and 90%). The efficacy of asundexian on cerebrovascular death, myocardial infarction, and stent thrombosis was roughly similar to placebo - 6.8% (for 10 mg asundexian), 6% (for 20 mg asundexian), and 5.5% (for 50 mg asundexian), versus 5.5% (placebo). At a follow-up of approximately 1 year, clinically relevant major or non-major bleeding did not differ for the doses investigated - pooled asundexian compared to placebo. The investigators suggested that the 50 mg/day dose of asundexian be tested in the post-IMA study [48].

Cancer

The use of central venous catheters in cancer patients predisposes to the occurrence of thromboembolic events, and, unfortunately, there are no effective prophylactic strategies that are currently applied [49]. In a phase II prospective study, the safety and efficacy of a FXI monoclonal antibody - Xisomab (Gruticibart) to prevent the catheter-associated thrombosis has been assessed. Following a single dose administration (2 mg/kg, i.v., *via* venous catheter), follow-up surveillance ultrasound at day 14 revealed thrombosis occurrence only in 12.5% of patients receiving Gruticibart, compared to 40% of patients in the matched comparator group ($p < 0.001$). No notable adverse effects or bleeding-related events were noted in the intervention group. The author suggested that targeting FXI could be a safe

intervention to prevent catheter-related thrombosis [49]. Two phase III trials (ASTER and MAGNOLIA) are ongoing, testing the effectiveness of another FXI monoclonal antibody, abelacimab, in the prevention of cancer-related thrombosis compared to apixaban or dalteparin, respectively. VTE recurrence at 6 months is evaluated in a randomised study of 1655 patients with non-skin cancer and 1020 patients with gastrointestinal or genitourinary cancer, respectively [19, 30].

FXI inhibitors – Realities and perspectives

The results of clinical trials using FXI inhibitors in various cardiovascular conditions require broader comment. The primary objective of most studies has been to reduce the risk of bleeding with anticoagulants, and less to reduce the risk of thrombosis. A meta-analysis included results from 8 randomised clinical trials and 9616 patients. In particular, the safety of using FXI(a) inhibitors, compared to enoxaparin, DOACs (apixaban, rivaroxaban), or placebo, was investigated. Treatment with FXI(a) inhibitors resulted in a reduction in any bleeding and reduced trial-defined efficacy outcome at high-dose regimens, when compared with enoxaparin. FXI(a) inhibitors were associated only with a trend toward reduced any-bleeding, and no difference in trial-defined efficacy outcome, when compared with DOACs. The author suggested increased safety and efficacy of FXI inhibitors compared with enoxaparin, and modest increased safety compared to DOACs [50]. A year later (2024), a systematic review analysing data from 8 phase II clinical trials related to antithrombotic therapy with FXI(a) inhibitors revealed an acceptable efficacy and safety profile when compared to the currently available antithrombotic therapies, and a more favourable benefit-risk ratio in terms of VTE prophylaxis in patients undergoing total knee arthroplasty (the overall thrombotic complication rate decreased by 50%, while the bleeding rate decreased by 60%, when compared to enoxaparin). When addressing other scenarios (patients with stroke, AF, and myocardial infarction), the results were noted as modest, requiring more data from ongoing phase III trials to define the most appropriate doses for these drugs and their indications [51]. Table II summarises most clinical trials that are completed or ongoing (phase II and III) with various types of FXI(a) inhibitors [19, 29, 47].

Table II

Major clinical trials of FXI inhibitors

Study	Used agent	Clinical settings
AXIOMATIC - TKR (NCT03891524; Phase II)	milvexian *vs*. enoxaparin for VTE prevention in pts. undergoing TKA surgery	**TKA**
FOXTROT (NCT03276143; Phase II)	osocimab *vs*. enoxaparin for VTE prevention in pts. undergoing TKA surgery	
ANT-005 TKA (2019-003756-37; Phase II)	abelacimab *vs*. enoxaparin for VTE prevention in pts. undergoing TKA surgery	
FXI-ASO TKA (NCT01713361; Phase II)	IONIS-FXI$_{Rx}$ *vs*. enoxaparin for VTE prevention in pts. undergoing TKA surgery	
CONVERT (NCT04523220; Phase II)	osocimab *vs*. placebo in ESRD pts. requiring regular haemodialysis	**ESRD**
NCT03612856 - Phase II	xisomab 3G3 *vs*. placebo in ESRD pts. on chronic haemodialysis	
NCT02553889 - Phase II	IONIS-FXI$_{Rx}$ *vs*. placebo in ESRD pts. on haemodialysis	
EMERALD (NCT03358030; Phase II)	IONIS-FXI$_{Rx}$ *vs*. placebo in ESRD pts. on haemodialysis	
RE-THINc ESRD (NCT04534114; Phase II)	fesomersen *vs*. placebo in ESRD pts. on haemodialysis	
PACIFIC-AF (NCT04218266; Phase II)	asundexian *vs*. apixaban in pts. with AF	**AF**
OCEANIC-AF (NCT05643573; Phase III)	asundexian *vs*. apixaban in pts. with AF at risk for stroke	
LIBREXIA-AF (NCT05757869; Phase III)	milvexian *vs*. apixaban in pts. with AF	
LILAC-TIMI 76 (NCT05712200; Phase III)	abelacimab *vs*. placebo in high-risk pts. with AF who have been deemed unsuitable for OACs	
AZALEA - TIMI 71 (NCT04755283; Phase II)	abelacimab *vs*. rivaroxaban in pts. with AF	
PACIFIC-STROKE (NCT04304508; Phase II)	asundexian *vs*. placebo in pts. following an ANCIS	**IS**
OCEANIC-STROKE (NCT05686070; Phase III)	asundexian *vs*. placebo for the prevention of IS in pts. after an ANCIS, or high-risk TIA	

Study	Used agent	Clinical settings
AXIOMATIC-SSP (NCT03766581; Phase II)	milvexian *vs*. placebo for the prevention of a stroke in pts. receiving aspirin and clopidogrel	
LIBREXIA-STROKE (NCT05702034; Phase III)	milvexian *vs*. placebo for stroke prevention in pts. after an AIS or high-risk TIA	
PACIFIC-AMI (NCT04304534; Phase II)	asundexian *vs*. placebo in pts. following an AMI	**AMI**
LIBREXIA-ACS (NCT05754957; Phase III)	milvexian *vs*. placebo in pts. after a recent ACS	
NCT04465760 - Phase II	xisomab 3G3 *vs*. control for the prophylaxis of catheter-associated thrombosis in pts. with cancer receiving chemotherapy	**Cancer**
ASTER (NCT05171049; Phase III)	abelacimab *vs*. apixaban for the prophylaxis of VTE recurrence in pts. with cancer-associated VTE	
MAGNOLIA (NCT05171075; Phase III)	abelacimab *vs* dalteparin for the prophylaxis of VTE recurrence and bleeding in pts. with GI/GU cancer associated VTE	

Abbreviations: TKA - total knee arthroplasty; ESRD - end-stage renal disease; AF - atrial fibrillation; IS - ischemic stroke; AMI - acute myocardial infarction; VTE - venous thromboembolism; pts - patients; OACs - oral anticoagulants; ANCIS - acute non-cardioembolic ischemic stroke; TIA - transient ischemic attack; AIS - acute ischemic stroke; ACS - acute coronary syndrome; GI/GU - gastrointestinal/genitourinary

Other third-generation anticoagulants include FXII(a) and FXIII(a) inhibitors. They represent a promising alternative in preventing thrombus formation with a safety profile regarding bleeding. Various factor XII(a) inhibitors have been tested in animal models, such as synthetic peptides [52, 53], recombinant proteins [54, 55], anti-FXII/FXIIa antibody [56, 57], or anti-FXII ASOs [58, 59]. Similarly, various FXIII(a) inhibitors have been developed and tested *in vitro* and preclinical studies, such as natural compounds [60, 61], nitric oxide donors [62], alkylamines [63-65], synthetic Michael acceptor-containing inhibitors [66, 67], or polypeptides [68]. However, while FXI(a) inhibitors have been extensively studied (seven phase III clinical trials are ongoing and one completed), further clinical trials with higher statistical power are needed for FXII(a) and FXIII(a) inhibitors to verify in humans the beneficial outcomes highlighted by animal studies. As a general remark, FXI(a) inhibitors do not replace the "classic" anticoagulant treatments - VKAs, DOACs, and heparins - which have multiple studies proving efficacy and safety.

FXI/XIa inhibitors have advantages over DOACs in stroke prevention, including fewer drug interactions, less bleeding, and lower renal elimination [31, 69]. On the other hand, current limitations of FXI inhibitors relate to the inadequacy of antidotes, cost, and general underutilisation of these drugs [30, 31]. Currently, there are prospects for continuing phase II studies and identifying new conditions for testing FXI(a) inhibitors. The need for better anticoagulants with improved efficacy and safety can be grouped into two categories of patients [24, 33, 47]: *i*) patients in whom the effects of DOACs have been tested, with minimal or negative results, *e.g.* mechanical valvular prostheses, intracardiac assist devices, long-term central venous catheters, extracorporeal circuits, conditions in which thrombotic events are attributed to activation of the contact coagulation pathway. This category also includes testing FXI inhibitors in ESRD patients on hemodialysis, for which four studies are ongoing; *ii*) patients at increased risk of bleeding or patients in whom the treatment results with DOACs or heparins have not demonstrated significant efficacy. This category includes people with a (repeated) history of bleeding (digestive, intracranial), elderly or frail people, and patients who need triple therapy (anticoagulants and antiplatelet therapy in patients with antiphospholipid syndrome). This category also includes people with cancer and with high risk of thrombosis, or established thrombosis, and who present hypercoagulability syndrome due to biological factors related to the type of cancer, antineoplastic medication and so on. Two new clinical trials are ongoing for cancer-associated thrombosis, with monoclonal antibodies versus apixaban or dalteparin.

Conclusions

FXI(a) inhibitors have the effect of uncoupling haemostasis from thrombosis, making them attractive targets for haemostasis-sparing therapies with better safety profiles than traditional anticoagulant agents. Evidence derived from phase II studies shows that FXI(a) inhibitors exert a thromboprophylactic effect in a dose-dependent manner, without a parallel increase in bleeding. FXI(a) inhibitors manifest a superior benefit-to-risk ratio regarding VTE prevention than low-molecular-weight heparin in patients undergoing orthopaedic surgery. FXI(a) inhibitors did not increase the risk of bleeding compared with placebo in ESRD patients on haemodialysis, and appear to reduce clinically significant bleeding compared with DOACs in patients with AF. The addition of FXI(a) inhibitors to antiplatelet therapy in patients with non-cardioembolic stroke, or ACS, did not significantly

increase the risk of bleeding. No significant benefit of FXI inhibitors was found in terms of the primary efficacy outcome in patients with AMI or non-cardioembolic ischaemic stroke. The first phase III trial evaluating thrombotic end points (OCEANIC-AF) provided negative results.

Overall, the results of phase II clinical trials with FXI inhibitors are promising in VTE prophylaxis in knee arthroplasty, AF and ESRD patients, and almost negative in non-cardioembolic stroke and post-AMI. Large-scale, well-designed phase III trials are currently underway to assess the safety and efficacy of FXI(a) inhibitors in various clinical settings. In light of the results of current clinical trials, FXI(a) inhibitors are emerging as a prospective group of anticoagulants for use in many medical and surgical specialties where thrombosis is the major pathologic event.

Conflict of interest

The authors declare no conflict of interest.

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