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REVIEW ARTICLES

Factor XI and coagulation. Factor XI inhibitors – antithrombotic perspectives

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Abstract. Factor XI is a zymogen with an important role in the coagulation cascade. It is activated by FXII, thrombin and/or it can be autoactivated. It has a prothrombotic effect after being activated by thrombin, but also through its antifibrinolytic action, stabilizing the formed clot.

Hereditary deficiency of FXI causes haemophilia C – a disease manifested by an usually provoked, small to moderate mucosal bleeding. People with severe FXI deficiency have a low risk of thrombotic events. Conversely, increased FXI values have been found to be associated with increased risk of venous thromboembolism and ischemic stroke.

Lowering serum FXI levels has become a treatment target for the prevention of thrombotic events. New pharmacological agents – FXI inhibitors – have been investigated in phase II clinical trials, with promising results in terms of efficacy and safety in the prevention of thrombotic events. FXI inhibitors are emerging as new anticoagulant agents with broad indication prospects beyond direct oral anticoagulants and vitamin K antagonists.

Keywords: factor XI deficiency, factor XI Inhibitors, haemostasis, thrombosis, new class of anticoagulants, Haemophilia C.

What is new? What is important?

Factor XI has a limited role in haemostasis, but a major role in thrombosis.
It is mainly involved in the thrombus consolidation phase, after its activation by thrombin.
Factor XI deficiency is frequently asymptomatic. It may be associated with a low risk of 'haemophilia' bleeding.
High level of factor XI activity is associated with an increased risk of venous thromboembolism and stroke.
Reducing the level of factor XI has become a therapeutic target. FXI inhibitors in phase II of clinical trials have shown an important and attractive potential antithrombotic effect.

Coagulation and the 'coagulation cascade' consist of a complex of coagulation factors and cell surfaces that normally ensure blood homeostasis or, under special conditions, haemostasis and thrombosis.

The clotting process proceeds in 3 interconnected steps: initiation, amplification and propagation [1]. The place occupied by Factor XI or FXIa in these three stages of coagulation and its involvement in pathology and therapeutics represents a chapter of major multidisciplinary interest.

STRUCTURE AND FUNCTION OF FXI

Factor XI is a zymogen (the inactive form of FXIa enzyme). It circulates in plasma at a concentration of about 30 μM and as a noncovalent complex with the high molecular weight kininogen (HMWK) glycoprotein. The importance of the FXI-HMWK interaction is incompletely elucidated, but it is thought to facilitate the binding of FXIa to the surface of blood platelets and endothelial cells [2].

Structurally, FXI is a dimer consisting of two identical subunits connected by a disulfide bond [2]. The site of FXI formation is mainly the liver, similar to other clotting factors, but also in other cell types, such as Langerhans cells, megakaryocytes, or renal tubular cells [3].

The role of FXI is classically defined in the intrinsic coagulation pathway (Figure 1). It is now generally accepted that FXIa, upon its activation from FXI, has a major role in thrombosis and a minor role in haemostasis [1, 4].

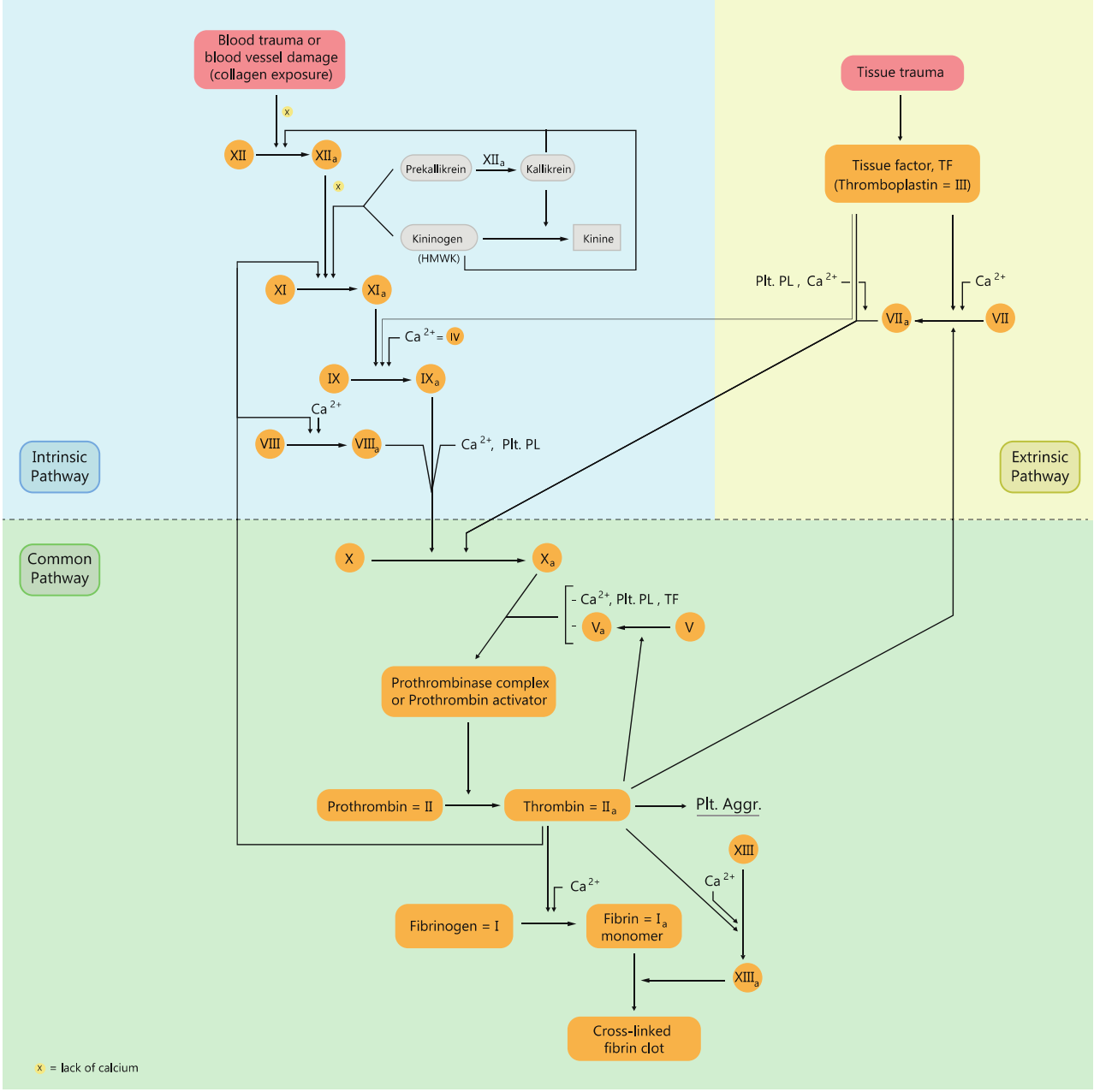


Figure 1. Schematic representation of the classical model of extrinsic and intrinsic coagulation pathways.
Abbreviations: HMWK – high molecular weight kininogen; Plt. PL – platelet phospholipids; TF – tissue factor; Plt. Aggr – platelet aggregation.

FXI is converted to its active form - FXIa by thrombin, FXIIa or by autoactivation in the presence of polymers.

Haemostasis and thrombosis involve several common coagulation factors (e.g. FX, FV, FII) but are uncoupled processes. FXIa has a major role in thrombogenesis, in the amplification and propagation (consolidation) phases.

Haemostasis is a physiological process in response to injury to the vascular wall and tends to stop bleeding. The haemostatic process is initiated when circulating FVII and FVIIa bind to tissue factor (TF) expressed by the TF - bearing cells at the site of vascular injury.

The FVIIa / TF complex activates FX to FXa, which in turn converts a small amount of prothrombin to thrombin. The limited amount of thrombin at the initiation phase of haemostasis is sufficient to trigger the insult response (generating an unstable clot). The FVIIa / TF complex, in addition to activating FX to FXa, also converts FIX to FIXa, which together with FVIIIa maintains thrombin generation for a longer period of time (amplification process), ultimately leading to the formation of a stable clot (Figure 2).

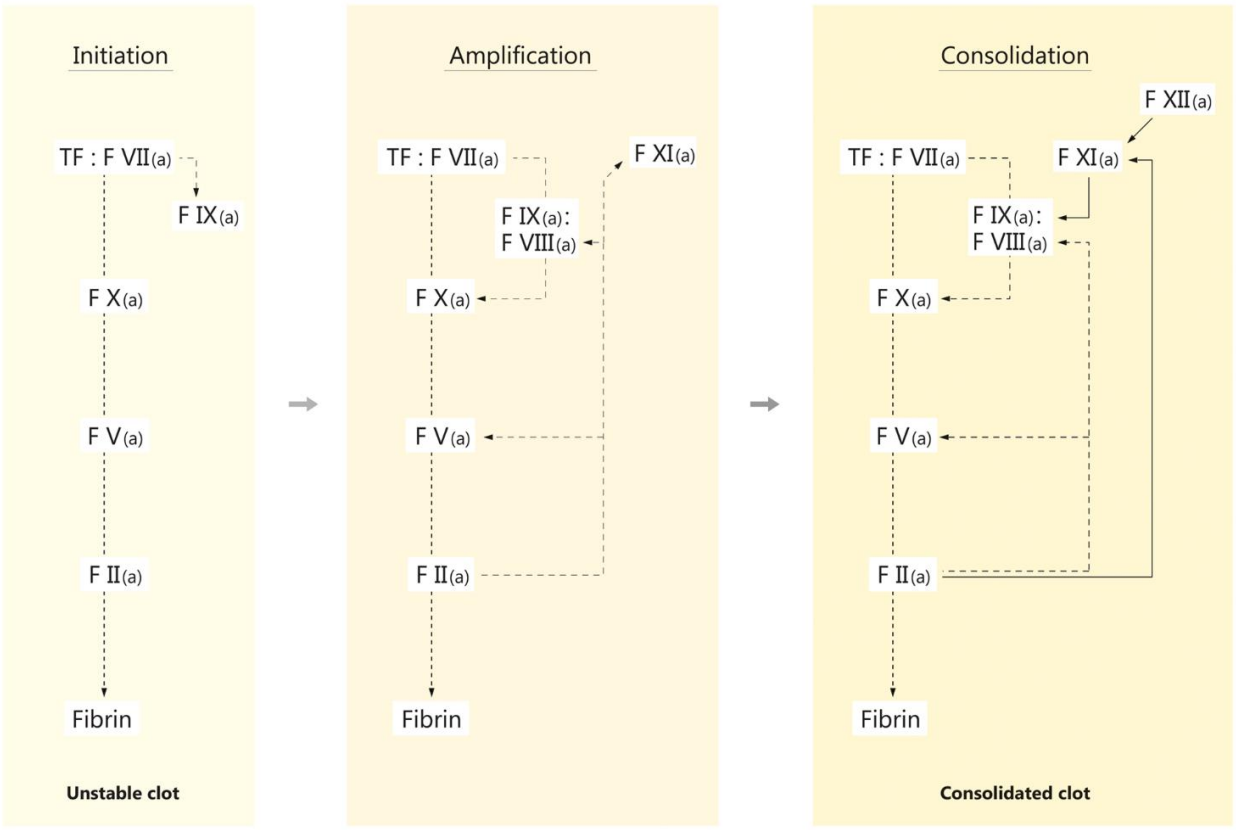


Figure 2. Schematic representation of the clotting process, from the initial phase to thrombus amplification and consolidation. The three phases are successive and contain common and specific coagulation factors, as follows: 1. *Initiation phase:* FVIIa/tissue factor (TF) complex located on the surface of TF-bearing cells activates FX to FXa, leading to the generation of a limited amount of thrombin and fibrin; the FVIIa/TF complex also converts FIX to FIXa, which can then move to the surface of nearby platelets. 2. *Amplification phase:* The small amount of thrombin generated in the earlier phase migrates to the platelet surface and amplifies the procoagulant signal by activating platelets, FV, FVIII, and FXI. 3. *Consolidation (propagation) phase:* In this final stage FXIa activates FIX and assembles with FIXa in the tenase complex, which results in FX activation and generation of the prothrombinase complex. A burst of thrombin is produced that activates other neighboring recruited platelets, leading to the final clot formation. In thrombosis, thrombin has the most important role of activating FXI, but FXII can also activate FXI. FXII can be activated by neutrophil extracellular traps (NETs), inorganic phosphate polymers (PPs), or artificial surfaces (central venous catheters, cardiopulmonary bypass, intracardiac devices, hemodialysis).

Tissue factor is a protein structure present in vascular subendothelial tissue or adventitia, and is expressed under conditions of vascular injury (physical, atheroma plaque rupture) or upon inflammatory stimuli e.g., Tumor Necrosis Factor alpha (TNFα). TF has a high affinity for FVII or FVIIa, and once the FVIIa / TF complex is formed, it initiates the process of clot formation by activating FX and subsequent coagulation factors.

Tissue factor, a key element in the initiation of haemostasis and thrombosis, can be inhibited by an inhibitory protease – Tissue Factor Pathway Inhibitor (TFPI) present in plasma and synthesised by the vascular endothelium. The TF / TFPI complex contributes to the control of haemostasis in the endothelium of the vascular wall [3].

In contrast to minimal involvement in haemostasis, FXI and FXIa play a major role in thrombosis.

Vascular thrombosis is the pathological process in which a thrombus formed in the vascular lumen reduces or stops blood flow.

In most cases thrombus formation is initiated by the FVIIa / TF complex to ensure haemostasis. When FVIIa / TF ability to develop a proper intraluminal thrombus is reduced, FXI becomes the main element driving thrombus growth and stabilization [1].

The development of the thrombotic process through the intrinsic coagulation pathway depends on the activation of FXI. Actually, this process is triggered by thrombin (FIIa) in a retroactive

feedback loop, by FXIIa (the ancient contact phase), or FXI can be auto-activated. FXI activation by FXIIa is less common and occurs mainly when blood flow is exposed to artificial surfaces (such as cardiopulmonary bypass, central venous catheters, and intracardiac devices) or to short polyphosphate chains.

Activated factor XI activates in turn FIX to its active form FIXa, which participates together with its cofactor VIIIa (FVIIIa) in the formation of the intrinsic tenase complex. Factor IXa is potentiated by FVIIIa, the latter being activated by thrombin in a feedback loop. Further, the intrinsic tenase complex activates FX to FXa, which is a central element in the coagulation cascade especially in the thrombosis process. Factor Xa activity is potentiated by its cofactor Va (FVa), the latter being activated by thrombin in a feedback loop. Factor Xa and FVa form the prothrombinase complex, through which the enzymatic chain of coagulation leads to the formation of thrombin (FIIa) in a thrombin burst. Thrombin then converts fibrinogen into soluble fibrin, which at a later stage becomes insoluble, forming a network of highly resistant fibrils that will lead to the formation of a stable thrombus (Figure 1).

The consolidation phase subsequently occurs through an intense amplification process: thrombin additionally amplifies the activation of FXIa (and also cofactors VIII and V in a retrograde feedback loop) and closes the circuit of the pathogenic coagulation cascade in the thrombosis process.

In summary, FXIa has a procoagulant role, amplifies the coagulation cascade and additionally generates thrombin (leading to a thrombin burst) after clot initiation [4].

Activated factor XI has also a secondary role in reducing fibrinolysis. Thrombin formed in excess at the thrombus level, when it reaches a critical level, activates an inhibitor – Thrombin Activatable Fibrinolysis Inhibitor – TAFI. Activated TAFI protects the fibrin plug from fibrinolysis, stabilizes the clot by increasing resistance to fibrinolysis [5].

Factor XI, like other clotting factors, interacts with receptors and cofactors on the platelet surface. Glycoprotein Ib is the main receptor for FXIa. FXI interaction with platelets prevents FXI inhibition by the protease nexin-II, which is abundant in α-granules and secreted upon platelet activation [6].

Platelets participate in haemostasis through 3 major processes: activation, adhesion and aggregation. Blood platelets are essential for primary haemostasis (unstable clot), whereas FXI is not essential for haemostasis but promotes thrombosis.

The significance of the FXI – platelet interaction is not yet fully understood.

FXI DEFICIENCY (FUNCTIONAL DEFICIENCY) AND HAEMOPHILIA C

Basic data on the structure and function of FXI in the clotting process have directed clinical research toward the relationship between plasma levels of FXI and the process of thrombogenesis. FXI deficiency and its consequences have become a major topic in haematology.

Rosenthal *et al.* described in 1953 FXI deficiency in 4 generations of many families who had bleedings caused by dental procedures or surgery [4]. The congenital FXI deficiency described in these primary observations is now known as Haemophilia C or Rosenthal syndrome.

Haemophilia C is an inherited disease caused by a deficiency of FXI activity. It results most commonly from a mutation in gene 117, i.e. the F111 (type II) gene variant [7]. Currently, approximately 200 mutations of the FXI gene have been identified as being involved in congenital FXI deficiency [4]. Haemophilia C is currently considered a 'rare disease', distinct from classical Haemophilia and it affects both men and women.

Haemophilia C is manifested by minimal to moderate mucosal bleeding (e.g. during dental extractions or tonsillectomy, and suspected by prolonged menses, or intra/post-partum bleeding). Surgical procedures with non-operative related bleeding frequently diagnose FXI deficiency, after the plasma level of FXI is assessed. The higher tendency of mucosal (oral, urogenital) bleeding would be explained by an increased fibrinolytic activity at this level [2, 3].

Bleeding is generally induced by trauma (most frequently) or surgical act, and unlike Haemophilia A, is not intra-articular (haemarthrosis) or muscular (haematoma). Spontaneous bleeding may occur especially at severely low FXI values (< 20%).

Haemophilia C is more often asymptomatic than symptomatic and may be discovered incidentally during coagulation assessment, when elevated values of activated partial thromboplastin time (aPTT or APTT) are found while other coagulation parameters are normal [8].

FXI deficiency is estimated by measuring the level of FXI activity compared to values considered normal. Deficiency is severe at values < 20% (< 20 U/dl), or partial at values between

20% and 60% [6]. FXI deficiency in haemophilia C is more common in heterozygotes. They have a level of FXI activity between 20% and 60%, which does not exclude the risk of bleeding. Individuals with Haemophilia C are rarely homozygous, the heterozygosity being predominant [7, 9].

Generally, there is a poor correlation between low levels of FXI activity and the risk of bleeding (negative correlation) [4, 8].

Congenital FXI deficiency – haemophilia C – is a rare disease. The FXI gene is located on the G chromosome. Hereditary transmission of FXI deficiency is autosomal recessive. The population with homozygosity is much smaller than that with heterozygosity in epidemiological studies [9].

The prevalence of FXI deficiency in the general population is very low: 1 case per 1 million people. In descendants of the Ashkenazi population, congenital FXI deficiency occurs in 1 from 450 individuals or in approximately 10% of individuals evaluated in epidemiological studies [7, 10, 11]. In Western European countries, the prevalence is much higher – 5 per 1 million individuals. Prevalence appears to be remarkably higher in England and the Basque region of Spain [9].

Diagnosis of haemophilia C, as a prototype of FXI deficiency, but also of other conditions with low FXI levels, is ensured by laboratory exploration of the main global indicators of anticoagulation [12].

Generally, the diagnosis of FXI deficiency (and Haemophilia C) is based on the clinical picture expressed mainly as a haemorrhagic syndrome (in fact, most often a provoked one) with elevated aPTT values, or on the incidental finding of elevated aPTT values, without affecting other coagulation tests.

Typically, aPTT values are elevated when the level of FXI activity is very low (< 20%). Partial FXI deficiency (20%–60%) may be accompanied by normal aPTT values, although it may be associated with significant bleeding [3].

Low FXI values are not only seen in Haemophilia C, but also in the situation of multiple clotting factors consumption (e.g. disseminated intravascular coagulation), or in cases of severely reduced clotting factors production (e.g. severe liver failure).

A special condition of FXI deficiency is the development of FXI inhibitors [13]. These are autoantibodies that occur in some autoimmune diseases, particularly Systemic Lupus Erythematosus, but also in various types of cancers, including haematological cancers. Exposure to FXI concentrate administration for severe or critical bleeding, may develop up to 30% inhibitory autoantibodies in patients homozygous for the type II gene variant [14].

The presence of FXI inhibitors is rarely accompanied by spontaneous bleeding, but may manifest as bleeding in trauma or surgery.

Since the 2000s, data have been published not only on FXI deficiency (and haemophilia C) but also on the prothrombotic action of high FXI levels. Thus, a study published in 2000 that assessed 417 individuals for plasma FXI values reported a direct-response relationship between FXI levels and the risk of venous thromboembolism (VTE). Also, values of Factor XI more than 90% doubled the risk of VTE (RR 2.2) in 10% of evaluated patients [15]. At the same time, an increased risk of cerebrovascular events (ischemic stroke) was reported at high FXI values [16].

From the same period, large population studies began in Israel (where the Ashkenazi population is more numerous) regarding the prevalence of FXI in the population and cardiovascular risk. Study participants were from the Israeli Health Care System.

A cohort study tracked the incidence of ischemic stroke in patients with severe FXI deficiency (< 15 U/ dl, or < 15%) compared to the general population. Out of 9509 participants, 115 had severe FXI deficiency (approx. 8%). After adjustment for the 4 risk factors for ischemic stroke (hypertension, atrial fibrillation, diabetes mellitus, dyslipidemia), the incidence of ischemic Stroke was lower (1:115) in patients with severe FXI deficiency compared to the evaluated individuals (19:115) [11]. The same highly competent group of researchers compared the incidence of deep vein thrombosis (DVT) in 219 individuals with severe FXI deficiency versus a control group (2094). No cases of VTE were reported in the severe FXI-deficient group compared to the study population [17].

In a similar topic, a cohort study (10193 patients) tested for FXI activity (considered normal > 50%, mild deficiency for 30%–50%, and moderately severe for < 30%), analyzing the incidence of cardiovascular events (stroke, transient ischemic stroke, myocardial infarction) and VTE in relation to FXI levels. FXI values were "normal" at 28.5%, slightly decreased at 6.8%, and moderately-severe decreased at 5.3%. When comparing to individuals with normal FXI activity, the adjusted hazard ratio (HR) for cardiovascular events was 0.52 (CI 0.31–0.87) and 0.57 (CI 0.35–0.93) for mild,

or moderate-severe FXI deficiency, respectively. Incidence of VTE was lower for individuals with FXI activity < 50% compared to those presenting a normal activity (HR = 0.26, CI 0.08–0.84) [10].

A very recent cohort study of over 10000 people confirmed data coming from previous studies describing the cardiovascular risk, or the bleeding risk in relation to FXI deficiency [18].

STUDIES WITH AGENTS THAT REDUCE THE THROMBOGENIC RISK OF FXI

The results of clinical and epidemiological research – partly cited above – have confirmed the direct relationship between low FXI values and reduced cardiovascular risk, especially for thrombotic events. The reduction of thrombotic events at venous or arterial level suggested the potential anticoagulant effects of FXI inhibitors, with minimal bleeding risk compared to "classical" anticoagulants. Factor XI has become a target for the development of FXI or FXIa inhibitor-type anticoagulant agents [19, 20].

Initial and ongoing clinical trials using FXI inhibitors have varied themes, with the pivotal element being the thrombotic process. The fields of study refer to: 1) VTE prophylaxis; 2) Atrial fibrillation (AF) and stroke; 3) Secondary prophylaxis in non-cardioembolic ischemic stroke; 4) Acute coronary syndrome [22, 23].

To date, new types of pharmacological agents (FXI inhibitors) have been developed to reduce the level of FXI activity, by targeting the site of FXI formation or activation. They correspond to many classes:

– Antisense oligonucleotide (ASOs), that reduce hepatic synthesis of FXI;

– Monoclonal antibodies, which block FXI and FXIa activity;

– Synthetic small molecules, that reduce FXI synthesis.

Several published clinical trials demonstrate the effectiveness and safety of FXI inhibitors.

1. **Antisense therapy** used in haematology refers to base-pair hybridisation, whereby a highly specific **ASOs** binds to the complementary mRNA target. Cleavage of the mRNA leads to the corresponding reduction of the target protein. In the case of FXI, ASOs acts on the liver mRNA and blocks FXI synthesis [13].

ASOs given subcutaneous require 3–4 weeks to decrease FXI and reach therapeutic levels. They also have a prolonged half-life, allowing administration every 3–4 weeks to achieve significant FXI inhibition.

The effectiveness and safety of a 2nd generation oligonucleotide antisense (FXI-ASOs) were assessed in 300 knee arthroplasty patients at doses of 200 or 300 mg, compared to enoxaparin. The incidence of VTE (by venographic assessment) was 27% (200 mg dose), 4% (300 mg dose) and 30% in patients receiving enoxaparin. The 300 mg therapeutic regimen was superior to enoxaparin thromboprophylaxis ($p < 0.001$). The incidence of relevant non-major bleeding was 3% on FXI-ASOs administration, compared to 8% with enoxaparin [8]. Coagulation evaluation showed an increase in aPTT and a lack of effect on prothrombin time or on other coagulation factors, such as FVIII, XII, IX, suggesting a high product specificity and safety (decreased risk of bleeding in VTE prophylaxis) [21].

The antithrombotic effects of a novel antisense oligonucleotide - fosemersen, which reduces FXI synthesis, are currently being investigated.

2. **Monoclonal antibodies** bind to the catalytic domain (active site) of FXI and block its activity or activation, thereby preventing the generation of thrombin [22]. Administered i.v. they reduce FXI and FXIa levels in about one hour, in correlation with the plasma antibody concentration levels. The half-life is long (20–30 days), and there is no specific antidote in case of major bleeding. Metabolization of monoclonal antibodies does not involve the kidney and liver; elimination occurs via the reticuloendothelial system and phagocytic cells [23].

Abelacimab has been tested in the prevention of postoperative VTE and the bleeding risk has been assessed [19].

In an international clinical trial, 412 knee arthroplasty patients received in a single administration three types of Abelacimab antibodies doses postoperatively (30 mg, 75 mg, 150 mg), being compared with those who received enoxaparin. VTE was identified in 13% of patients at the 30 mg dose, 5% at 75 mg and 4% at 150 mg, compared to 22% of patients receiving enoxaparin. Single dose administration of Abelacimab 75 mg, or 150 mg was clearly superior to enoxaparin in the postoperative prevention of VTE. Clinically relevant bleeding was reported in 2% of patients after Abelacimab, and in none after enoxaparin [24]. Cost-effectiveness ratio limits the use of monoclonal antibodies, compared with other agents targeting the decrease of FXI activation or activity.

Good effectiveness and safety results in the use of Abelacimab in VTE prophylaxis led to a large study assessing patients with AF. The AZALEA Timi 71 study investigated the effectiveness and safety of using Abelacimab in 1287 patients with AF and moderate-to-high risk of stroke. The mean follow-up period was 21 months. There was a significant (unprecedented) reduction in major bleeding after Abelacimab compared with direct oral anticoagulants (rivaroxaban).

The AZALEA Timi 71 study provides evidence of a reduction in bleeding when using Abelacimab versus direct oral anticoagulants (DOACs), that is the standard of care with oral anticoagulants in patients with AF. Abelacimab appears to cancel out the residual bleeding risk of 2–3% per year when DOACs are used (European Congress of Cardiology - 2023).

3. Several **synthetic small molecules**, including Milvexian and Asundexian, have been investigated for their antithrombotic effect in VTE prophylaxis, or in AF and non-cardiogenic ischemic stroke.

Unlike ASOs or Monoclonal antibodies that are used parenterally, Milvexian has been tested orally in VTE prophylaxis. Milvexian is a small synthetic molecule that is rapidly absorbed when administered orally, and selectively inhibits FXI at the site of venous thrombus formation.

It has been used in an international phase 2 clinical trial as an antithrombotic agent after knee arthroplasty, versus enoxaparin [25]. A total of 1241 patients were randomized, and VTE and bleeding incidence were evaluated using various Milvexian doses. The incidence of VTE was significantly lower when Milvexian was used (at a dose of 100 mg/day or more) than when enoxaparin was used (7% at 200 mg/day vs 21% at enoxaparin). The incidence of bleeding was 4% for both agents used. APTT values increased above normal in a dose-dependent manner with Milvexian.

Asundexian is a small molecule and a potent inhibitor of FXIa. It is administered orally once daily and reduces FXIa activity by 80–90%, indicating substantial target inhibition during treatments.

It has been tested in 3 international randomised clinical trials in patients with AF (PACIFIC-AF), non-cardioembolic ischaemic stroke (PACIFIC-Stroke), and in patients with acute myocardial infarction (PACIFIC-AMI). The basis for this research was provided by previous studies showing that patients with ischemic stroke had increased FXI levels, and patients with inherited FXI deficiency had a lower risk of stroke.

In the PACIFIC-AF trial, 255 patients with AF and CHA_2DS_2-VASc score > 1 were randomised and monitored for major or non-major bleeding at two doses of Asundexian (20 mg or 50 mg) versus Apixaban. Asundexian produced an inhibition of FXIa activity between 92% and 94%. Asundexian treatment had a lower bleeding rate (4 events) versus Apixaban (6 events). Tolerance was similar for the 2 agents used, but 1 out of 20 patients discontinued treatment due to adverse reactions [26].

The PACIFIC-Stroke trial, an international randomized trial (1808 participants), aimed to assess the efficacy and safety of Asundexian administered in varying doses (20–50 mg/day) added to antiplatelet therapy versus placebo in the prevention of recurrent non-cardioembolic stroke [27]. The mean time from the index stroke was 36 hours. Participants received antiplatelet therapy for a mean duration of 70 days and underwent magnetic resonance imaging (MRI) evaluations for brain infarction or recurrent symptomatic ischemic stroke. At 26 weeks of progression, efficacy was seen in 19% of the placebo group versus 19% in the Asundexian group (no difference). Safety of therapy (major bleeding or clinically relevant non-major bleeding) was observed in 2% of the placebo group, versus 3–4% in the Asundexian group (at 20 or 50 mg/day) [27].

The PACIFIC-AMI study monitored 1605 patients with recent myocardial infarction treated with Asundexian and adjunctive antiplatelet medication (dual or monotherapy) versus placebo. The active treatment group achieved > 90% inhibition of FXIa activity, with no significant increase in bleeding risk and a low rate of ischemic events [28].

A meta-analysis of 8 randomized clinical trials including 9216 patients compared the bleeding risk and safety outcomes of FXI inhibitors versus anticoagulants (enoxaparin, DOACs) or placebo. Treatment with FXI inhibitors was associated with a reduction in overall bleeding (RR 0.49, Ci 95%), but not major bleeding, when compared with enoxaparin. Treatment with FXI inhibitors was also associated with reduced overall bleeding (RR 0.66, Ci 95%), but no change in major bleeding, when compared with DOACs [29].

In addition to the major clinical trials mentioned above, and for which partial results have been reported (phase II), other large trials with broader themes are in development (Table 1). Additional data are sought on the efficacy and safety of FXI agents as anticoagulant agents, particularly in terms of reducing significant bleeding compared with current anticoagulants (including DOACs).

Table 1

Ongoing studies with FXI inhibitors

Trial Name	*Agent used, objectives*
OCEANIC AF	Asundexian versus Apixaban in the prevention of stroke and end-stage renal disease in patients with atrial fibrillation and risk of stroke
OCEANIC-STROKE	Asundexian in the secondary prevention of non-cardioembolic ischemic stroke in patients with stroke in history
LIBREXIA AF	Milvexian versus Apixaban in patients with atrial fibrillation
LIBREXIA STROKE	Milvexian in addition to antiplatelet therapy (mono or dual) in secondary prevention after acute ischemic stroke or intracerebral hemorrhage
LIBREXIA ASC	Milvexian versus placebo after acute coronary syndrome
ASTER	Abelacimab subcutaneously versus Apixaban in patients with evolving cancer-associated thrombosis
MAGNOLIA	Abelacimab versus Dalteparin in patients with gastrointestinal/ urinary neoplasms and thrombosis
LILAC TIMI 76	Abelacimab versus placebo in patients with atrial fibrillation who cannot receive anticoagulants (e.g. severe chronic kidney disease, antiplatelet therapy, frailty)

The phase III OCEANIC-AF trial aimed to investigate the efficacy and safety of Asudexian in the prevention of stroke in patients with atrial fibrillation and risk factors, compared to Apixaban. Recently, on November 19, 2023, the manufacturing company (Bayer) decided to stop the study, the interim data showing inferior efficacy compared to the control group (Apixaban). Data analysis from the OCEANIC-AF study has not yet been published.

Asudexian is being studied in the OCEANIC program, including also the ongoing OCEANIC-STROKE and OCEANIC-AMI trials.

In summary, the results of phase II clinical trials using FXI inhibitors have provided partial evidence of antithrombotic effectiveness and, additionally, reduced bleeding compared to current anticoagulants (DOACs). The studies focused in particular on: stroke prevention in AF, secondary prevention of non-cardioembolic stroke, and VTE prophylaxis in surgery.

There are also ongoing studies regarding VTE prophylaxis in cancer patients – cancer associated thrombosis (CAT), FXI inhibitors being very attractive in this field. There are many pathophysiological data regarding the importance of FXI in the development of CAT [31].

Currently, pharmacological inhibitors of FXI do not replace "classical" anticoagulants (DOAC, antivitamin K), which have firm evidence of effectiveness and safety for a broad spectrum of indications.

Looking ahead, there are other clinical conditions in which FXI inhibitors can be tested in therapy, such as: mechanical valvular prostheses; intracardiac ventricular assist devices; central venous catheter (prolonged duration); antiphospholipid syndrome with thrombosis; patients requiring anticoagulation and dual antiplatelet medication; elderly, frail patients, at risk of "falling" and requiring anticoagulant treatment for AF or stroke.

In practice FXI inhibitors could be used for patients with a firm indication for anticoagulation and for whom DOACs cannot be used for various individual or medication reasons [13].

In conclusion, the interim data on factor XI inhibitors from phase II trials brought partial, incomplete evidence regarding the antithrombotic effectiveness and safety profile compared to direct oral anticoagulants (DOACs). The results regarding the efficacy of Asudexian in atrial fibrillation (PACIFIC-AF and OCEANIC-AF) require further consideration and new research [32]. However, multiple trials assessing other types of pharmacological FXI inhibitors (antisense oligonucleotides, monoclonal antibodies, and new synthetic small molecules) are currently underway and could provide more data on the possible antithrombotic role of these preparations.

Factor XI is a zymogen with an important role in the coagulation cascade. It is activated by FXII, thrombin and/or it can be autoactivated. It has a prothrombotic effect after being activated by thrombin, but also through its antifibrinolytic action, stabilizing the formed clot.

Hereditary deficiency of FXI causes haemophilia C – a disease manifested by an

usually provoked, small to moderate mucosal bleeding. People with severe FXI deficiency have a low risk of thrombotic events. Conversely, increased FXI values have been found to be associated with increased risk of venous thromboembolism and ischemic stroke.

Lowering serum FXI levels has become a treatment target for the prevention of thrombotic events. New pharmacological agents – FXI inhibitors – have been investigated in phase II clinical trials, with promising results in terms of efficacy and safety in the prevention of thrombotic events. FXI inhibitors are emerging as new anticoagulant agents with broad indication prospects beyond direct oral anticoagulants and vitamin K antagonists.

Factorul XI este un zimogen cu rol important în cascada coagulării. Este activat de FXII, trombină, sau poate fi autoactivat. Are efect protrombotic după ce a fost activat de trombină, dar și prin acțiunea sa antifibrinolitică, stabilizând cheagul format.

Deficitul ereditar de FXI determină hemofilie C – o boală manifestată printr-o sângerare a mucoasei, de obicei provocată, mică până la moderată. Persoanele cu deficit sever de FXI au un risc scăzut de evenimente trombotice. În schimb, valorile crescute ale FXI s-au dovedit a fi asociate cu un risc crescut de trombembolism venos și accident vascular cerebral ischemic.

Scăderea nivelurilor serice de FXI a devenit o țintă de tratament pentru prevenirea evenimentelor trombotice. Noi agenți farmacologici – inhibitorii FXI – au fost investigați în studiile clinice de fază II, cu rezultate promițătoare în ceea ce privește eficacitatea și siguranța în prevenirea evenimentelor trombotice. Inhibitorii FXI apar ca noi agenți anticoagulanți cu perspective largi de indicație, dincolo de anticoagulantele orale directe și antagoniștii vitaminei K.

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Declaration of interest: The authors declare that there are not conflicts of interest.

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Received 18th September 2023