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REVIEW

Factor XI Inhibitors: A New Horizon in Anticoagulation Therapy

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ABSTRACT

Anticoagulation therapy has undergone significant evolution, marked by the emergence of direct oral anticoagulants with distinct advantages. Despite these advancements, challenges persist in managing residual thrombotic and bleeding risks, particularly among vulnerable populations. The pursuit of alternative drugs has honed in on factor XI/XIa inhibitors. This comprehensive review delves into several key aspects regarding this new target: (i) the role of factor XI in the coagulation cascade; (ii) the genetic evidence and pathophysiologic rationale supporting factor XI inhibition as a therapeutic target; (iii) an exploration of the various types of factor XI/XIa inhibitors currently under investigation; (iv) potential applications of these medications, spanning thromboprophylaxis after orthopedic surgery, stroke prevention in atrial fibrillation, secondary prevention after acute coronary syndrome, non-cardioembolic stroke, thromboprophylaxis after foreign material implantation, end-stage renal disease, and patients with cancer; and (v) an overview of ongoing studies, recent findings, and the future trajectory of research into these drugs.

Keywords: Anticoagulants; Factor XI; Hemorrhage; Venous thromboembolism; Atrial fibrillation; Stroke; Myocardial infarction; Chronic kidney failure; Review

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Key Summary Points

Current anticoagulants exhibit various limitations, including a notable risk of bleeding events and a scarcity of effective alternatives in critical areas like end-stage renal disease

Epidemiologic and genetic data imply that factor XI is a compelling therapeutic target since its deficiency is associated with significant reduction in cardiovascular events and its increase is associated with thrombosis

Factor XI/XIa inhibition is currently an intense area of study, with these drugs demonstrating a lower occurrence of clinically relevant bleeding events compared to existing options

However, the efficacy of these medications remains unproven, with the premature termination of the OCEANIC-AF study raising concerns about their effectiveness in preventing stroke or systemic embolism in atrial fibrillation

Ongoing phase III studies aim to determine the specific settings where these medications offer a beneficial benefit–risk ratio

INTRODUCTION

Over the past few decades, anticoagulation therapy has witnessed notable progress. Initially limited to options centered on heparin and vitamin K antagonists (VKA), the advent of direct oral anticoagulants (DOACs) has introduced significant benefits, including user-friendliness, convenience, fewer interactions with food or other medications, and a reduced need for frequent laboratory monitoring [1]. Alongside achieving positive outcomes in ischemic events, these medications have lowered the occurrence of major bleeding incidents, particularly intracranial hemorrhages, despite an associated heightened risk of gastrointestinal bleeding [2]. Consequently, DOACs have become the recommended choice for most thromboembolic diseases, with VKA remaining preferable only in specific scenarios such as mechanical valve prosthesis [3, 4], antiphospholipid syndrome [5], and significant rheumatic mitral stenosis [6].

Despite these advancements, current anticoagulation options face several limitations. Firstly, significant residual risks of thrombotic and hemorrhagic events persist. In the ROCKET-AF trial, which investigated the use of rivaroxaban in atrial fibrillation (AF), the annual occurrence of stroke or embolic events was 1.7%, while the annual occurrence of major or clinically relevant non-major bleeding events was 14.9% [7]. Secondly, concerns about bleeding risks in certain subgroups contribute to the underuse and underdosing of these medications, depriving a substantial portion of the population of the potential benefits of anticoagulation therapy. The elderly, in particular, pose a challenge due to their increased susceptibility to bleeding and falls, coupled with a high ischemic risk [8, 9]. Thirdly, most available anticoagulants are contraindicated in severe chronic kidney disease (CKD), not only because DOACs exhibit significant renal clearance but also because this population faces a considerably elevated bleeding risk, the frequency of bleeding events surpassing ischemic events by up to 10 times, thereby further diminishing potential advantages [10, 11]. Lastly, DOACs prove inefficient in preventing thrombosis associated with foreign material, primarily driven by the contact/intrinsic pathway of the coagulation cascade. A notable example is mechanical valve prosthesis, where anticoagulation remains mandatory to avert thrombotic complications. To date, VKAs remain the recommended antithrombotic treatment for this population, as the only two randomized controlled trials assessing DOAC use (RE-ALIGN; PROACT-Xa) demonstrated a higher risk of complications compared to VKAs [3, 4].

Considering these challenges, the imperative to explore alternative drugs to address existing gaps has become evident. Consequently, recent

attention has been directed towards the development of new anticoagulants that inhibit factor XI/XIa.

The purpose of this review is to offer an in-depth examination of the pathophysiology and rationale associated with each aspect of the investigation of factor XI/XIa inhibitors. Additionally, it aims to provide a detailed analysis of completed and ongoing phase II and III trials related to this topic. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

COAGULATION CASCADE AND FACTOR XI

The traditional in vitro model of the coagulation cascade historically partitions it into three pathways: the extrinsic or tissue-factor pathway, activated by exposure to tissue factor (TF) and the subsequent activation of factor VII; the intrinsic or contact pathway, initiated by blood exposure to inflamed or damaged tissue, or a foreign surface, comprising factors XII, XI, IX, and cofactor VIII; and the common pathway, resulting from the convergence of both other pathways, consisting of factors X, II, fibrinogen, and co-factor V.

Initially identified as part of the contact pathway, activation of factor XI occurs following contact of factor XII with negatively charged surfaces. However, an evolving comprehension of this system unveils intricate interconnections among these pathways, delineating the coagulation process into initiation, amplification, and propagation stages. Factor XI emerges as a pivotal participant in the amplification of the thrombus, activated by thrombin and influenced by various factors such as inorganic polyphosphates, DNA, and RNA [12, 13].

More recently, there has been speculation that the mechanisms underlying physiological hemostasis differ from those governing pathological thrombosis [2]. Physiological hemostasis represents the response initiated by blood vessel injury to halt bleeding with minimal disruption of normal blood flow within the vessel. Triggered by the exposure of TF and activation of factor VII, it results in the formation of a small amount of fibrin, sufficient to create an effective hemostatic thrombus [14]. Consequently, the contact pathway appears to have a limited role in this mechanism, potentially explaining the mild bleeding diathesis observed in patients with factor XI deficiency [15].

On the other hand, thrombosis is the pathologic process that compromises blood flow in the affected vessel, arising from the formation of a larger thrombus. This can be triggered by the exposure of TF in damaged endothelium; expressed on diseased endothelial cells or leukocytes; or, less frequently, by contact with foreign material via the intrinsic pathway [2, 14]. In this context, the capacity of the factor VIIa/TF complex to promote thrombus growth is limited. Instead, the intrinsic pathway and factor XI appear to play a central role in the amplification phase of coagulation, essential for the burst and growth of the thrombus. This emphasizes the dynamic and multifunctional nature of the activation pathways of coagulation instead of the classic static model, and suggests a more significant role of factor XI in thrombosis rather than in hemostasis, pinpointing it as a potential target to uncouple these mechanisms (see Fig. 1).

The interest in inhibiting factor XI/XIa is further supported by compelling bidirectional genetic evidence. Factor XI deficiency is linked to a low risk of atherothrombotic events and venous thromboembolism (VTE) without an increase in major bleeding [14, 16]. Conversely, elevated levels of factor XI are associated with thrombosis [17]. This is also supported by studies with factor XI knockout mice, which demonstrated resistance to both venous and arterial thrombosis, without an increase in spontaneous or induced bleeding compared with wild-type mice [17]. Additionally, proteomic studies identify factor XI as a key mediator of VTE risk in patients with cardiovascular risk factors such as obesity and smoking [18].

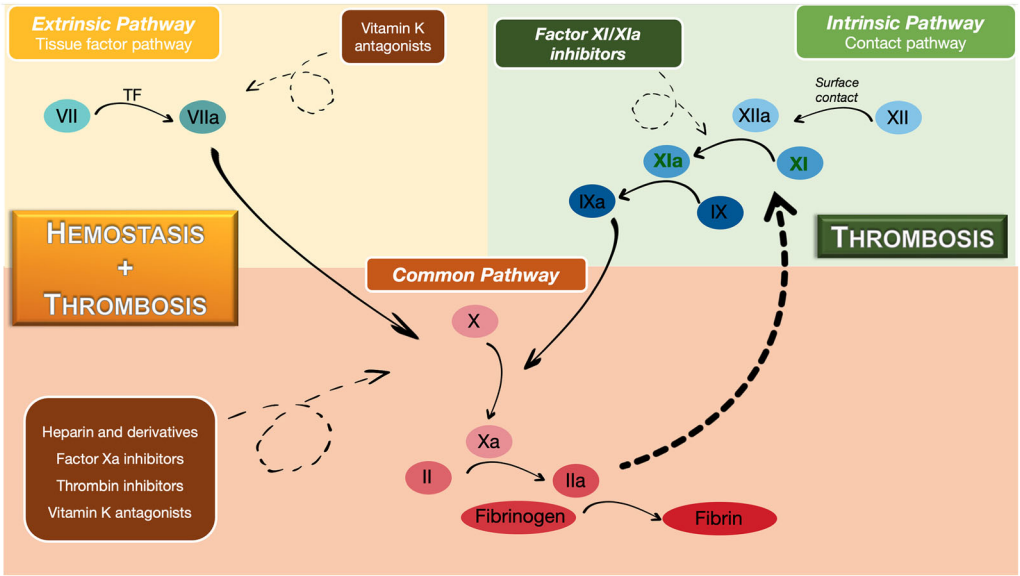

Fig. 1 Illustration depicting the processes of hemostasis and thrombosis, highlighting the specific sites targeted by existing anticoagulant medications

FACTOR XI INHIBITORS

A variety of factor XI/XIa inhibitors exhibit distinct pharmacodynamic and pharmacokinetic characteristics. Three primary types of molecules have completed phase II studies, namely antisense oligonucleotides (ASOs), monoclonal antibodies (mAbs), and synthetic small molecules. Table 1 summarizes the clinical characteristics of these inhibitors, while Table 2 enumerates the randomized clinical trials (RCT) in which factor XI/XIa inhibitors have been tested or are currently under investigation.

ASOs are RNA molecules that impede the translation of specific cellular mRNA chains, thereby regulating their degradation and hindering the biosynthesis of the corresponding protein [19]. Administered subcutaneously, their frequency ranges from once a week to once a month. With a slow onset of action, taking weeks to achieve full effect, they rely on the degradation of circulating factor for their efficacy [20]. Currently, IONIS-FXI$_{RX}$ and fesomersen are the two main ASOs under investigation.

MAbs directly bind to factor XI/XIa, inhibiting their activation/activity. These inhibitors offer a rapid onset of action, and their longer half-life extends over several weeks [19]. They are suitable for use in severe CKD since they are primarily metabolized by phagocytic cells and the reticuloendothelial system [14]. The three main mAbs currently under study are abelacimab, osocimab, and xisomab 3G3.

Finally, synthetic small molecules, characterized by low molecular weight, bind to factor XIa. Their superior oral bioavailability allows for oral administration, but their shorter half-life necessitates once or twice-daily dosing [21]. Asundexian and milvexian are the two main small molecules currently under investigation.

It is important to note that numerous other molecules are in early stages of development, primarily in dosage-finding and phase I studies. These include additional small molecules, monoclonal antibodies, aptamers, and natural peptides [14].

POTENTIAL AREAS OF INTEREST

Thromboprophylaxis in Major Orthopedic Surgery

The context of major orthopedic surgery holds particular significance in the investigation and

Table 1 Factor XI/XIa inhibitors with concluded/undergoing phase II clinical studies

Name of the drug	Type of agent	Mechanism of action	Administration frequency	Concluded studies	Comparator	Phase	Number of patients	Study population
Oral administration								
Asundexian	Small molecule	Inhibition of factor XIa	Once daily	PACIFIC-AF—NCT04218266	Apixaban	II	755	Atrial fibrillation
				PACIFIC-STROKE—NCT04304508	Placebo	II	1808	Non-cardioembolic stroke
				PACIFIC-AMI—NCT04304534	Placebo	II	1601	After acute myocardial infarction
Milvexian	Small molecule	Inhibition of factor XIa	Once/twice daily	AXIOMATIC-SSP—NCT03766581	Placebo	II	2295	Non-cardioembolic stroke
				AXIOMATIC-TKR—NCT03891524	Enoxaparin	II	1242	Major orthopedic surgery
				NCT03000673	Enoxaparin/unfractionated heparin	II	32	End-stage renal disease
SHR2285	Small molecule	Inhibition of factor XIa	Twice daily	NCT05203705	Enoxaparin	II	500	Major orthopedic surgery
Parenteral administration								

Table 1 continued

Name of the drug	Type of agent	Mechanism of action	Administration frequency	Concluded studies	Comparator	Phase	Number of patients	Study population
Abelacimab	Human monoclonal antibody	Binds to factor XI and prevents its activation by factor XIIa or thrombin	Once a month	ANT-004—NCT04213807	Placebo	II	28	Atrial fibrillation
				AZALEA-TIMI 71—NCT04755283	Rivaroxaban	II	1287	Atrial fibrillation
				ANT-005 TKA—EudraCT number: 2019–003756-37	Enoxaparin	II	412	Major orthopedic surgery
Fesomersen	Antisense oligonucleotide of factor XI	Bind to factor XI mRNA blocking translation	Once a month	RE-THINc ESRD—NCT04534114	Placebo	II	307	End-stage renal disease
IONIS-FXI_{RX}/FXI-ASO (ISIS 416858)	Antisense oligonucleotide of factor XI	Bind to factor XI mRNA blocking translation	Once a week	FXI-ASO TKA—NCT01713361	Enoxaparin	II	300	Major orthopedic surgery
				NCT02553889	Placebo	II	49	End-stage renal disease
				EMERALD—NCT03358030	Placebo	II	213	End-stage renal disease
Osocimab	Human monoclonal antibody	Inhibition of factor Xia, preventing activation of factor IX	Once a month	FOXTROT—NCT03276143	Apixaban/enoxaparin	II	813	Major orthopedic surgery
				CONVERT—NCT04523220	Placebo	II	704	End-stage renal disease

Table 1 continued

Name of the drug	Type of agent	Mechanism of action	Administration frequency	Concluded studies	Comparator	Phase	Number of patients	Study population
Xisomab 3G3	Recombinant humanized monoclonal antibody	Binds to factor XI preventing its activation	–	NCT03612856	Placebo	II	27	End-stage renal disease

application of anticoagulation therapy. From a pathophysiological perspective, the risk of thrombogenesis significantly escalates post-surgery. Factor XI, in particular, plays a crucial role driven by two primary factors. Firstly, the release of TF during surgery can generate thrombin, which factor XI may amplify. Secondly, the activation of factor XII by damaged cells and activated platelets may also contribute to this process [20]. Despite having various options to mitigate this risk, the use of currently available anticoagulants remains associated with an incidence of up to 30% in thrombotic events [22] and 5% in clinically relevant bleeding events [23]. Additionally, dosage-finding studies are frequently conducted in these patients to assess the antithrombotic effect of new anticoagulants, as routine venography allows for a substantial increase in the diagnosis of deep vein thrombosis, many of which are asymptomatic.

To date, four phase II trials have been published in the context of major orthopedic surgery (AXIOMATIC-TKR [24], FOXTROT [25], FXI-ASO TKA [26], and ANT-005 [27]), with one ongoing (NCT05203705). Various types of molecules have undergone testing, including antisense oligonucleotides (FXI-ASO), monoclonal antibodies (abelacimab and osocimab), and small molecules (milvexian). All these studies compared the new molecules with enoxaparin, except for FOXTROT, which also included an arm for apixaban. A meta-analysis of the four published studies revealed consistent results, showing a significant reduction in the incidence of VTE and clinically relevant bleeding events with factor XI inhibitors [28]. These findings underscore the potential benefits of these new drugs, paving the way for their investigation in other clinical scenarios.

Stroke and Systemic Embolism Prevention in Atrial Fibrillation

AF stands as the most common sustained arrhythmia and necessitates a primary focus on preventing thromboembolic events. The occurrence of these events is attributed to multiple factors. Firstly, the chaotic electrical activation

Table 2 Randomized clinical trials of factor XI/XIa inhibitor in comparison to placebo/alternative therapies, categorized on the basis of the study setting

Study	Active drug	Comparator	Phase of the study	Current stage
Atrial fibrillation				
LIBREXIA-AF—NCT05757869	Milvexian	Apixaban	III	Ongoing
PACIFIC-AF—NCT04218266	Asundexian	Apixaban	II	Finished
OCEANIC-AF—NCT05643573	Asundexian	Apixaban	III	Stopped
ANT-004—NCT04213807	Abelacimab	Placebo	II	Finished
AZALEA-TIMI 71—NCT04755283	Abelacimab	Rivaroxaban	II	Finished
LILAC-TIMI 76—NCT05712200	Abelacimab	Placebo	III	Ongoing
Non-cardioembolic stroke				
AXIOMATIC-SSP—NCT03766581	Milvexian	Placebo	II	Finished
LIBREXIA-STROKE—NCT05702034	Milvexian	Placebo	III	Ongoing
PACIFIC-STROKE—NCT04304508	Asundexian	Placebo	II	Finished
OCEANIC-STROKE—NCT05686070	Asundexian	Placebo	III	Ongoing
After myocardial infarction				
LIBREXIA-ACS—NCT05754957	Milvexian	Placebo	III	Ongoing
PACIFIC-AMI—NCT04304534	Asundexian	Placebo	II	Finished
Venous thromboembolism prevention in patients with cancer				
ASTER—NCT05171049	Abelacimab	Apixaban	III	Ongoing
MAGNOLIA—NCT05171075	Abelacimab	Dalteparin	III	Ongoing
Major orthopedic surgery				
AXIOMATIC-TKR—NCT03891524	Milvexian	Enoxaparin	II	Finished
FOXTROT—NCT03276143	Osocimab	Apixaban/enoxaparin	II	Finished
FXI-ASO TKA—NCT01713361	FXI-ASO (ISIS 416858)	Enoxaparin	II	Finished
ANT-005 TKA—EudraCT number: 2019-003756-37	Abelacimab	Enoxaparin	II	Finished
NCT05203705	SHR2285	Enoxaparin	II	Ongoing
Chronic kidney disease and end-stage renal disease				
NCT03000673	Milvexian	Unfractionated heparin/ enoxaparin	II	Finished
NCT03787368	Osocimab	Placebo	I	Finished
CONVERT—NCT04523220	Osocimab	Placebo	II	Finished

Table 2 continued

Study	Active drug	Comparator	Phase of the study	Current stage
NCT02553889	FXI-ASO (ISIS 416858)	Placebo	II	Finished
EMERALD—NCT03358030	FXI-ASO (ISIS 416858)	Placebo	II	Finished
RE-THINc ESRD—NCT04534114	Fesomersen	Placebo	II	Finished
NCT03612856	Xisomab 3G3	Placebo	II	Finished
MK-2060-004—NCT03873038	MK-2060	Placebo	I	Finished
MK-2060-007—NCT05027074	MK-2060	Placebo	II	Ongoing
MK-2060-011—NCT05656040	MK-2060	Placebo	I	Ongoing
MK-2060-012—NCT05769595	MK-2060	Placebo	I	Ongoing

of the atriums leads to blood stasis. Additionally, this arrhythmia is linked to other factors within Virchow's triad. Collectively, these factors contribute to a substantial increase in thromboembolic risk in individuals with AF [29]. Despite advancements in oral anticoagulation, treatment remains constrained by the occurrence of bleeding events, dissuading patients from using current options. Adherence to anticoagulant therapy is significantly affected even by minor bleeding events [30]. Additionally, there is a substantial risk of hemorrhagic transformation following a major stroke. Thus, the exploration of medications with lower bleeding risk becomes a compelling area of interest.

Factor XI inhibition emerges as a noteworthy research target for several reasons. Genetic deficiency of factor XI is linked to a lower risk of stroke [31], and the intrinsic pathway appears to contribute to the hypercoagulability state in these patients [29]. These findings, along with the pathophysiologic rationale, position factor XI as an appealing target for atrial fibrillation treatment.

So far, results from two phase II trials comparing factor XI inhibition with DOACs have been unveiled. In the initial trial, PACIFIC-AF (NCT04218266), involving 755 patients, asundexian showcased favorable tolerability and effectiveness in suppressing factor XIa activity, coupled with a notable reduction of over 50% in the incidence of bleeding events compared to apixaban. The second study, AZALEA-TIMI 71 (NCT04755283), although not yet published, has released its results. This trial, with 1287 participants, examined two doses of abelacimab (150 mg and 90 mg) versus rivaroxaban. Results revealed that the higher dose of abelacimab led to a remarkable 67% reduction in major or clinically relevant non-major bleeding and an impressive 93% reduction in major gastrointestinal bleeding compared to rivaroxaban. Both trials reported exceptionally low incidences of major bleeding events, with none in the PACIFIC-AF trial. It is essential to note that the published studies primarily focused on determining optimal dosage and safety, lacking the statistical power for a definitive assessment of efficacy outcomes. Nonetheless, these findings lay the groundwork and rationale for future, more extensive trials.

As of now, two phase III RCTs have enrolled patients in this setting: OCEANIC-AF (NCT05643573), which aimed to randomize 18,000 patients and compared asundexian

50 mg daily with apixaban; and LIBREXIA-AF (NCT05757869), aiming to enroll 15,500 patients and compare milvexian 100 mg twice daily with apixaban. Unexpectedly, the Independent Data Monitoring Committee of the OCEANIC-AF trial recently recommended its cessation due to the inferior efficacy of asundexian compared to apixaban for stroke prevention in AF, marking the first red flag on these drugs [32]. Complete data is yet to be published, and further analyses will be conducted to elucidate why asundexian did not yield the desired effect. However, it is important to highlight that the dosage chosen for this phase III study relied on a phase II study, which lacked sufficient statistical power to assess the efficacy of the new drug, as it observed only three stroke events in the active drug cohort. Furthermore, the lack of efficacy in preventing stroke in AF does not imply a drug or class effect, as observed with the lower dose of edoxaban in ENGAGE-AF trial [33].

Secondary Prevention After Acute Coronary Syndrome

Despite the development of potent antiplatelet therapies, the risk of recurrent acute coronary syndrome (ACS) remains substantial. Traditionally, the prevention of atherothrombotic events has relied heavily on antiplatelet therapies, given that arterial thrombosis primarily involves high shear stress and a thrombus composed predominantly of platelets. However, the COMPASS and ATLAS-ACS-2 trials challenged this paradigm by demonstrating that the combination of low-dose rivaroxaban with aspirin is associated with a reduced risk of ischemic outcomes [34, 35]. Nevertheless, the heightened risk of bleeding events resulting from its utilization significantly diminishes its overall net clinical benefit [34]. The ongoing search for safer and more effective alternatives has brought factor XI inhibition to the forefront as a potentially appealing target.

In animal models, factor XI inhibition has shown a significant reduction in thrombus growth rate, overall mass, and thrombo-occlusion in arterial thrombosis settings [36]. The benefits are attributed to the crosstalk between coagulation and platelets, with the common pathway (amplified by factor XI) playing a crucial role in platelet stimulation and thrombus formation [37]. Preclinical evidence also indicates various other benefits of targeting factor XI for preventing arterial thrombosis, including reduced infarct size, lower inflammation, endothelial dysfunction, and reactive oxygen species; diminished thrombus growth and inflammation; and slowed plaque progression and reduced macrophage infiltration in atherosclerotic plaque [37].

Epidemiological data further supports targeting factor XI. While not reaching statistical significance as a result of a low number of events, studies on individuals with factor XI deficiency suggest a potential negative association with cardiovascular events [38].

The PACIFIC-AMI study (NCT04304534) was the first phase II trial in this context, aiming to compare the safety of asundexian versus placebo in addition to double antiplatelet therapy in patients with recent ACS. The study found near-complete inhibition of factor XI without a significant increase in bleeding events [39]. To assess the efficacy of factor XI inhibition, the ongoing phase III clinical trial LIBREXIA-ACS (NCT05754957) is testing milvexian in patients within 7 days of an ACS. This trial aims to enroll 16,000 patients during a follow-up of up to 3 years and 6 months.

Secondary Prevention After Non-Cardioembolic Stroke

The concept of factor XI inhibition as a potential intervention in non-cardioembolic stroke aligns with the same pathophysiologic rationale observed in atherothrombosis. There is a potential advantage in reducing non-cardioembolic stroke, as evidenced by individuals with severe factor XI deficiency being significantly associated with a reduced incidence of ischemic stroke, up to nine times lower than expected [40]. This type of cardiovascular event holds particular significance due to its high recurrence rate, exceeding 6% in the year following a stroke [41]. Furthermore, despite

numerous studies investigating the effectiveness of anticoagulant therapy in this context, none have demonstrated efficacy in secondary prevention.

Currently, two phase II studies have been conducted to assess the safety of novel anticoagulants in patients who recently experienced non-cardioembolic stroke—AXIOMATIC SSP (NCT03766581) and PACIFIC-STROKE (NCT04304508). These trials evaluated the use of small molecule inhibitors of factor XIa (milvexian and asundexian, respectively) in addition to antiplatelet therapy (single or dual) and found no increased risk of bleeding events compared to placebo. While these studies were not designed to establish efficacy outcomes definitively, a post hoc analysis suggests the possibility that the higher dose of asundexian (50 mg daily) may be effective in secondary prevention of cerebrovascular events. Moreover, ongoing phase III studies aim to evaluate the efficacy of this strategy in reducing ischemic events: LIBREXIA-STROKE (NCT05702034), with a goal to enroll 15,000 patients, compares milvexian vs placebo in addition to single or dual antiplatelet therapy after acute ischemic stroke or high-risk transient ischemic attack; OCEANIC-STROKE (NCT05686070), aiming to enroll 9600 patients in a similar scenario.

Thromboprophylaxis After Foreign Material Implantation

Exposure of blood to foreign surfaces, especially in the context of medical devices, poses a significant risk of thrombosis. As a result, patients with mechanical valvular prostheses or those undergoing procedures like cardiopulmonary bypass, extracorporeal membrane oxygenation (ECMO), or dialysis require anticoagulation. The absence of an endothelial cell layer on these foreign surfaces leads to protein adsorption, resulting in a negatively charged surface. This, in turn, triggers the activation of contact factors (factor XII, prekallikrein, factor XI, factor XIIa, alpha-kallikrein, factor XIa), culminating in thrombus formation [42, 43]. Given this understanding, blockade of the contact pathway within the coagulation cascade emerges as a compelling target [19]. This is further substantiated by preclinical data, indicating that the reduction of factor XIa activity significantly delays catheter-induced thrombus formation [44] or thrombosis induced by thrombogenic thread [45].

Presently, only one phase II study is underway (NCT04465760), aiming to evaluate the role of xisomab 3G3 in preventing catheter-associated thrombosis in oncologic patients undergoing chemotherapy, comparing its efficacy to a placebo.

Special Populations: End-Stage Renal Disease

One of the primary unmet needs in this field pertains to achieving appropriate anticoagulation for patients with kidney failure undergoing dialysis. This population is recognized for its significantly elevated risk of ischemic events and bleeding tendencies. These challenges arise from dysfunction in both the coagulation system and platelet adhesion and aggregation [46]. Currently, there is limited evidence supporting the use of available oral anticoagulants in this context. The VALKYRIE trial, a small RCT, demonstrated that low-dose rivaroxaban (10 mg) was associated with a reduced risk of cardiovascular events and major bleeding complications compared to VKA [47]. However, no evidence of benefit over placebo has been established for these therapies.

The development of factor XI inhibitors holds particular promise for this patient subgroup, considering the prevalence of clinically relevant bleeding events in anticoagulated patients with kidney failure on dialysis, which may exceed 30% [11]. Moreover, many of the molecules under study exhibit minimal to no renal metabolization.

Several factor XI inhibitors have undergone phase II studies in this context, including milvexian, osocimab, FXI-ASO, fesomersen, xisomab 3G3, and MK-2060. Notably, published studies like the CONVERT trial (NCT04523220), EMERALD trial (NCT03358030), and RE-THINc ESRD (NCT04534114), which compared osocimab, FXI-ASO, and fesomersen to placebo,

indicated the efficacy of these medications in reducing factor XI activity without significantly increasing bleeding risk, meriting larger efficacy studies. Currently, there is one ongoing phase III trial that can include patients with end-stage renal disease (ESRD)—LILAC-TIMI 76 trial (NCT05712200). The use of abelacimab will be assessed in patients with AF who are deemed unsuitable for currently available anticoagulants, including high risk of bleeding due to severe CKD, history of bleeding from a critical area, concurrent use of antiplatelet medication, or other conditions that increase bleeding risk. This will allow the collection of safety/efficacy information in these patients at very high hemorrhagic/thrombotic risk.

Special Populations: Patients with Cancer

Patients with cancer present unique challenges in the use of anticoagulants, given their elevated risk of deep vein thrombosis, atrial fibrillation, and a heightened susceptibility to severe bleeding upon antithrombotic initiation [48]. The recently published CANVAS trial reported a 6.1% recurrence rate of VTE events at 6 months, with a concurrent 5.2% incidence of major bleeding events [49]. Given these considerations, it is not surprising that these patients have become a focal point for the investigation of new anticoagulants.

Currently, three phase 2 trials are ongoing in this specific population, all dedicated to VTE prevention. The ASTER trial (NCT05171049) is comparing abelacimab with apixaban. Abelacimab is also under investigation in the MAGNOLIA trial (NCT05171075), where it is being studied in patients with genitourinary or gastrointestinal cancer in comparison to dalteparin. Additionally, as mentioned earlier, xisomab 3G3 is undergoing assessment in patients with cancer receiving chemotherapy to prevent catheter-associated thrombosis (NCT04465760).

SUMMARY AND FUTURE DIRECTIONS

Inhibiting Factor XI/XIa has become a focal point of intense research. Current phase II data indicate that these inhibitors (a) provide safe prevention of VTE, significantly reducing clinically relevant bleeding events while maintaining efficacy comparable to prophylactic low molecular weight heparin (LMWH) doses; (b) reduce clinically relevant bleeding events in atrial fibrillation compared to DOACs; (c) do not increase bleeding risk significantly in non-cardioembolic stroke or ACS when added to antiplatelet therapy.

These findings suggest that these drugs hold the potential to enhance the benefit–risk ratio of anticoagulant therapy. However, despite demonstrating that factor XI/XIa inhibitors are safer than other current options, larger studies are necessary to confirm the efficacy of these new anticoagulants. Consequently, various phase III studies have recently commenced recruitment across diverse scenarios, as outlined in Table 3.

The future trajectory of these medications still holds many unanswered questions. The specific patient populations that might benefit from them remain unknown. To date, no large-scale RCT has demonstrated equivalent efficacy of these drugs compared to other existing options, irrespective of the usage context. While the use of asundexian 50 mg daily may be less effective than apixaban in the prevention of stroke for the general population with atrial fibrillation, it remains unclear whether different types of factor XI/Xia inhibitors are equivalent in efficacy. Moreover, different dosage regimens and distinct cohorts may still experience a favorable net clinical benefit compared to currently available DOACs. This includes the setting of patients with non-cardioembolic stroke or acute myocardial infarction, as well as other groups such as patients with AF and low ischemic risk or high bleeding risk. Furthermore, considering the pathophysiological rationale regarding the potential use of these drugs for preventing thrombus formation associated with foreign material (i.e., mechanical

Table 3 Ongoing phase III RCTs of factor XI/XIa inhibitor in comparison to placebo/alternative therapies

Study	Number of patients	Active drug	Dosage	Comparator	Dosage
Atrial fibrillation					
LIBREXIA-AF—NCT05757869	15,500	Milvexian	100 mg twice daily	Apixaban	2.5/5 mg twice a day
LILAC-TIMI 76—NCT05712200	1900	Abelacimab	150 mg s.c. once a month	Placebo	–
Non-cardioembolic stroke					
LIBREXIA-STROKE—NCT05702034	15,000	Milvexian	Once/twice daily	Placebo	–
OCEANIC-STROKE—NCT05686070	9300	Asundexian	Once a day	Placebo	–
After myocardial infarction					
LIBREXIA-ACS—NCT05754957	16,000	Milvexian	Once/twice daily	Placebo	–
VTE prevention in patients with cancer					
ASTER—NCT05171049	1655	Abelacimab	150 mg i.v. followed by monthly s.c. administration of the same dose	Apixaban	10 mg followed by 5 mg twice a day
MAGNOLIA—NCT05171075	1020	Abelacimab	150 mg i.v. followed by monthly s.c. administration of the same dose	Dalteparin	200 IU/kg/day followed by 150 IU/kg/day

prosthesis) this should also be a theme of focus, despite no phase III studies having been registered in clinicaltrials.gov as of the end of 2023. Other critical considerations for the future involve the advanced kidney disease population, where there is a scarcity of efficacious and safe medications for the prevention of ischemic events, and several phase III studies are currently underway.

CONCLUSION

Factor XI/Xia inhibitors appear to significantly decrease the occurrence of bleeding compared to alternative anticoagulation choices. These findings align with the plausible biological expectation that inhibition of factor XI/XIa plays a more crucial role in thrombosis than in hemostasis, potentially "uncoupling" these two events. Despite this encouraging phase II data, the premature termination of the OCEANIC-AF trial raises concerns and underscores the need for larger, well-designed phase III studies to confirm the potential benefits of factor XI/XIa inhibitors. Numerous large-scale studies are presently underway or in the planning stages to assess their role in diverse populations requiring antithrombotic therapy.

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Declarations

Conflicts of Interest. João Presume declares that he has no competing interests. Jorge Ferreira has received consulting and speaker fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis and Pfizer. Regina Ribeiras declares that he has no competing interests.

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