A Review of FXIa Inhibition as a Novel Target for Anticoagulation

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Abstract

Limitations of vitamin K antagonists as chronic oral anticoagulant therapy have largely been supplanted by direct factor IIa and factor Xa inhibitor oral anticoagulants with similar efficacy but an overall better safety profile, lack of routine monitoring, and very limited drug–drug interactions compared with agents such as warfarin. However, an increased risk of bleeding remains even with these new-generation oral anticoagulants in fragile patient populations, in patients requiring dual or triple antithrombotic therapy, or high bleed risk surgeries. Epidemiologic data in patients with hereditary factor XI deficiency and preclinical studies support the notion that factor XIa inhibitors have the ability to be an effective but potentially safer alternative to existing anticoagulants, based on their ability to prevent thrombosis directly within the intrinsic pathway without affecting hemostatic mechanisms. As such, various types of factor XIa inhibitors have been studied in early phase clinical studies, including inhibitors of the biosynthesis of factor XIa with antisense oligonucleotides or direct inhibitors of factor XIa using small peptidomimetic molecules, monoclonal antibodies, aptamers, or natural inhibitors. In this review, we discuss how different types of factor XIa inhibitors work and present findings from recently published Phase II clinical trials across multiple indications, including stroke prevention in atrial fibrillation, dual pathway inhibition with concurrent antiplatelets post–myocardial infarction, and thromboprophylaxis of orthopaedic surgery patients. Finally, we refer to ongoing Phase III clinical trials of factor XIa inhibitors and their potential to provide definitive answers regarding their safety and efficacy in preventing thromboembolic events in specific patient groups.

Keywords
- factor XIa inhibitors
- direct oral anticoagulants
- thrombosis
- bleeding

Introduction

It has been more than a decade since small molecule direct oral anticoagulants (DOACs) targeting thrombin or factor Xa (FXa) have been introduced as novel oral anticoagulants to supplant vitamin K antagonists due to their lack of routine monitoring, minimal drug–drug and almost no drug–food interactions, and proven efficacy as well as overall improved safety profile across multiple indications. However, an accumulating body of evidence is assessing whether potentially further upstream inhibition of the coagulation cascade by targeting factor XI (FXI) or factor XII (FXII) has potential to uncouple mechanisms of thrombosis from hemostasis and thus provide an even safer approach to anticoagulation than the one that DOACs were based upon.[1] Although both FXI and FXII have been researched as potential targets in preclinical

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studies of novel anticoagulants, most clinical studies have assessed safety (and to a lesser extent efficacy) of FXIa inhibition.[1,2] This review will focus on the rationale assessing potential for FXIa inhibition as a novel mechanism for anticoagulation and results of early-to-mid phase clinical studies on the topic.

Rationale behind Factor XI Inhibitors

FXI is part of the intrinsic pathway of the coagulation cascade activated by FXII and is responsible for activating factor IX (FIX).[3] In contrast to coagulation factors such as FX leading to activation of the final common pathway to activate thrombin, FXIa plays a minor role in physiological hemostatic mechanisms activated after local vessel injury, where the release of tissue factor from the injured vessels activates the extrinsic pathway and mobilizes thrombin formation. Specific physiological conditions must be met for intrinsic pathway activation, including contact activation with negatively charged molecules like dextran sulfate and silica in vitro and in vivo release of negatively charged genomic material in the form of neutrophil-extracellular traps (NETs).[4] The main positive feedback mechanism for sustained FXIa activation is through its interaction with circulating thrombin during the amplification phase.[3] This effectively means that FXIa is mostly activated when thrombin is present for an extended duration, as is the case of thrombosis, compared with the quick resolution of hemostatic plugs in nonpathologic circumstances.[3] Based on these physiological coagulation mechanisms, inhibition of FXIa either by direct inhibition or inhibiting production of or dysfunctional FXIa would theoretically provide an antithrombotic effect without necessarily sacrificing its protective effects in hemostasis[5] (►Fig. 1). The available clinical data support this notion that FXIa inhibition may provide antithrombotic effects without bleed risk, as congenital FXI deficiency, a condition called hemophilia C,[6] is associated with a decreased incidence of cardiovascular events and especially venous thromboembolism (VTE) without an increase in intracerebral hemorrhage.[7–11] In addition, Ashkenazi Jews with severe FXIa deficiency have no evidence of serious or spontaneous bleeding.[11]

Mechanism of Action of Factor XIa Inhibitors and Preclinical Data

Mechanisms of inducing functional FXIa deficiency include inhibition of the biosynthesis of FXIa with antisense oligonucleotides (ASOs) or direct inhibition of FXIa using small peptidomimetic molecules, monoclonal antibodies, aptamers, or natural inhibitors (►Table 1). Preclinical studies with mouse models have yielded encouraging results

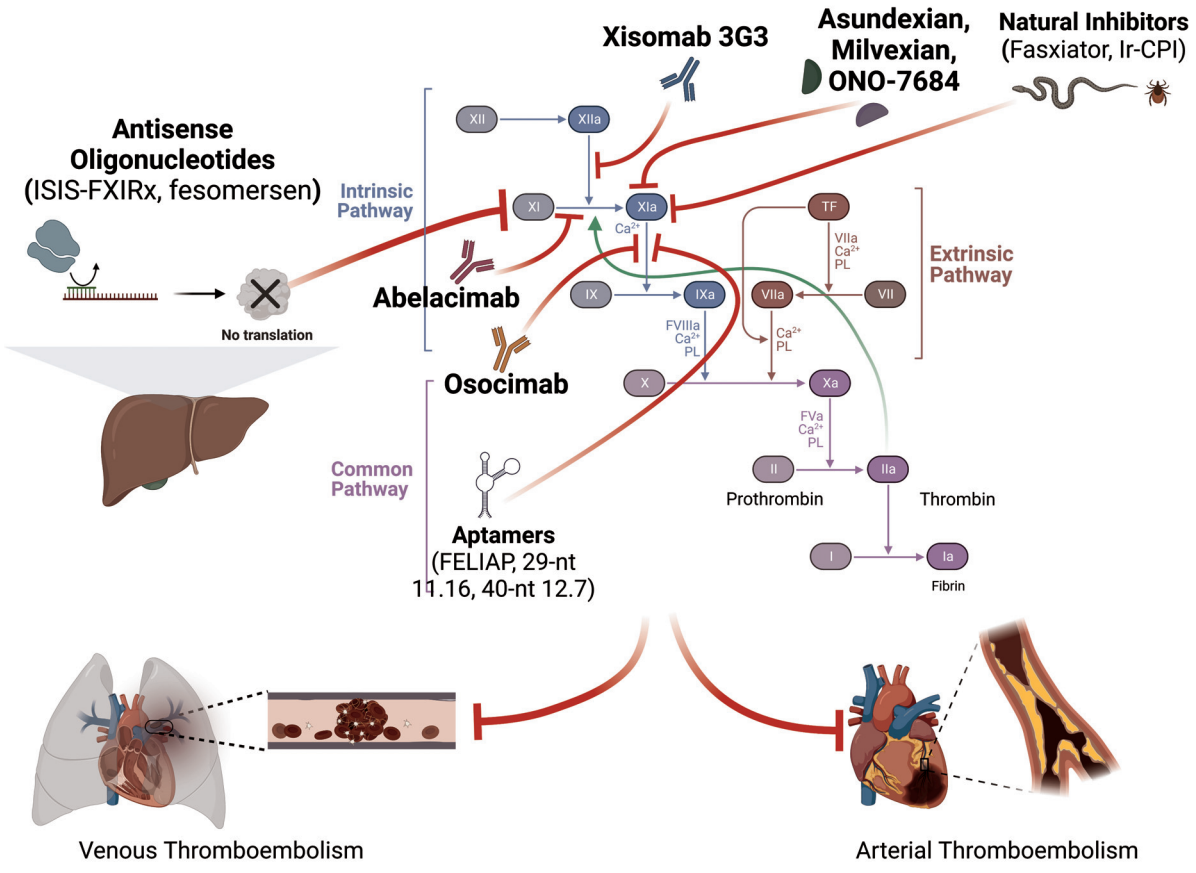

Fig. 1 Overview of factor XI/XIa inhibitors and their action site within the coagulation cascade. (Created with BioRender.com.) [rerif]

Table 1 Mechanism of action and pharmacokinetics of factor XIa inhibitors

	Small peptidomimetic molecules	*Antisense oligonucleotides*	*Monoclonal antibodies*	*Aptamers*	*Natural inhibitors*
Medication name	Asundexian, milvexian, ONO-7684	ISIS-FXIRx, fesomersen (IONIS-FXI-LRx/LICA)	Abelacimab, xisomab, osocimab, MK-2060	FELIAP, 29-nt 11.16, 40-nt 12.7	Fasxiator, Ir-CPI
Mechanism of action	Direct inhibition of FXIa	Inhibition of FXI biosynthesis	Direct inhibition of FXI/FXIa	Direct inhibition of FXIa	Direct inhibition of FXIa
Route of administration	IV or oral	SC	IV or SC	IV or SC	IV
Dosing	Daily	Weekly	Monthly	Daily	Daily
Onset of action	Minutes/Hours	Weeks	Hours	Minutes/Hours	Minutes
Offset of action	Minutes/Hours	Weeks	Weeks	Minutes/Hours	Hours
Renal excretion	Yes	No	No	No	Not enough information
Hepatic metabolism	CYP3A4	No	No	No	No

regarding the effects of FXIa inhibition in reducing thromboembolic events,[12] while studies in rabbit models show no difference in hepatic bleed times and blood loss with FXIa inhibition.[13] Although ASOs like IONIS FXI-LRx (ISIS 416858) provide "proof-of-concept" of improved adherence of long-term anticoagulation with a long half-life by inhibiting biosynthesis of FXIa, the clinical community has favored small molecule FXIa inhibitors like asundexian (BAY2433334) that have a "fast onset–fast offset" profile that can in theory be useful in patients on chronic anticoagulant therapy needing temporary interruption due to bleeding, need of critical care, or periprocedural situations.[14] The idea of long-term FXI inhibition could potentially be applied for similar indications as DOACs currently have for prevention of arterial or VTE, especially when perceived bleed risk causes providers to opt for inappropriate low-dose DOAC regimens. Oral FXI inhibitors could also be approved for novel long-term indications such as in the case of non-cardioembolic ischemic stroke prevention, where no anticoagulants are currently approved.

Results from Phase II Clinical Trials

Multiple Phase I and Phase II clinical trials have tested the safety profile of FXIa inhibitors as shown in ►Table 2. Most Phase II trials compared monoclonal antibodies or small molecules against the low-molecular-weight heparin (LMWH) enoxaparin or the direct oral FXa inhibitor apixaban, which is considered to have an excellent safety profile in low doses among the DOACs. A recent meta-analysis focusing on trials with patients undergoing total knee replacement showed that factor XIa inhibitors were associated with a significantly lower incidence of total VTE (14.5 vs. 23.6%; odds ratio [OR] = 0.50; 95% confidence interval [CI]: 0.36, 0.69; $p \leq 0.001$) in comparison to LMWH, with the incidence of composite major and clinically relevant non-major (CRNM) bleeding events being significantly lower (1.6 vs. 3.2%, OR = 0.41; 95% CI: 0.22, 0.75; $p = 0.003$).[15] A subsequent sensitivity analysis demonstrated that higher doses of factor XIa inhibitors when grouped together (namely, abelacimab: 75 and 150 mg; FXI-ASO: 300 mg; milvexian: 50 mg twice daily, 100 mg twice daily, 200 mg daily, and 200 mg twice daily and 1.8 mg/kg of osocimab of preoperative administration) are more efficacious in preventing symptomatic or asymptomatic VTE as a composite outcome compared with LMWH, without significantly increasing the occurrence of major and CRNM bleeding as a composite outcome. Another grouped analysis focusing only on lower doses of XIa inhibitors (abelacimab: 30 mg; FXI-ASO: 200 mg; milvexian: 25 mg once daily, 25 mg twice daily, and 50 mg once daily; 0.3 mg/kg of preoperative administration of osocimab; 0.3, 0.6, and 1.2 mg/kg postoperative administration of osocimab) showed significantly lower bleeding events, but without the effectiveness seen in higher doses.[15]

In 2022, the results from three major international, double-blinded Phase II trials with asundexian for patients with atrial fibrillation (AF), recent stroke, or recent

Table 2 Clinical trials with FXIa inhibitors

Medication name	Type of drug	Type of study	Study name/citations	Population	Intervention	Comparison	Primary/Key outcomes	Summary of key results and primary outcomes
ISIS-FXIRx	ASO	Phase I	Liu et al[21]	Healthy subjects aged 18–65 y	Single or multiple SC doses of 50/100/200/300 mg/kg	Placebo	Safety, pharmacokinetics	No bleeding events
Xisomab 3G3 (AB023)	Antibody	Phase I	Lorentz et al[22]	Healthy volunteers 18–48 y	Single dose IV	Placebo	Safety, pharmacokinetics	No bleeding events
ONO-7684	Small molecule	Phase I	Beale et al[23]	Healthy volunteers 18–55 y	Single/Multiple oral doses of 1/5/20/80/150/300 mg	Placebo	Safety, pharmacokinetics	No bleeding events
Asundexian (BAY2433334)	Small molecule	Phase I	Thomas et al[24]	Healthy volunteers 18–45 y	Single oral dose of 5/12.5/25/50/100/150	Placebo	Safety, pharmacokinetics	Favorable safety profile and dose-dependent inhibition of FXIa activity
Milvexian (BMS-986177) (JNJ70033093)	Small molecule	Phase I	Perera et al[25]	Healthy volunteers 18–45 y	Single oral doses of 4/20/60/200/300/500 mg or multiple oral doses of 5/20/70/200/500 mg	Placebo	Safety, pharmacokinetics	All bleeding events (2 in total) were mild in severity, not serious, and did not lead to discontinuation of treatment
Milvexian (BMS-986177) (JNJ70033093)	Small molecule	Open label	Perera et al[26]	Patients with mild hepatic impairment ($n = 9$), moderate hepatic impairment ($n = 8$), and normal hepatic function ($n = 9$)	Single-dose milvexian 60 mg	N/A	Safety, pharmacokinetics	No bleeding or clinically meaningful adverse events
Asundexian (BAY2433334)	Small molecule	Phase I	Kubitza et al[27]	Healthy volunteers 18–45 y	Single oral doses of 25/50/100 mg, 25 mg twice daily	Placebo	Safety, pharmacokinetics, interaction with midazolam (a CYP3A4 index substrate)	Favorable safety profile, no clinically relevant CYP3A4 induction or inhibition
Abelacimab (MAA868)	Antibody	Phase I	Yi et al[28]	ANT-003: healthy volunteers + obese patients (BMI $\geq 35\ kg/m^2$) aged 18–60 y ANT-004: patients with AF or flutter CHA_2DS_2-VASc of 0–1 (for men) or 1–2 (for women), aged 18–85 y	Abelacimab 30, 50, and 150 mg Obese patients: abelacimab 150 mg	Placebo	Safety, pharmacokinetics	No major or clinically relevant non-major bleeding events were reported; early stopping of the ANT-004 phase due to logistic issues caused by the COVID-19 pandemic
BAY 1831865	Antibody	Phase I	Nowotny et al[29]	Healthy volunteers 18–45 y	3.5 mg IV ($n = 8$), 7 mg IV ($n = 8$), 17 mg IV ($n = 8$), 35 mg IV ($n = 8$), 75 mg IV ($n = 8$), 150 mg IV ($n = 8$), 150 mg SC ($n = 8$)	Placebo IV ($n = 12$_ or SC ($n = 2$)	Safety, pharmacokinetics	No major or clinically relevant non-major bleeding events
IONIS FXI-LRx (ISIS 416858)	ASO	Phase II	Büller et al[30]	Patients undergoing total knee replacement	IONIS FXI-LRx 200 mg ($n = 134$) or 300 mg SC ($n = 71$)	Enoxaparin 40 mg ($n = 69$)	All DVT, symptomatic PE, fatal PE, death	Absolute risk difference of FXI-ASO vs. enoxaparin: total venous thromboembolism: −4% ($p = 0.59$) for 200 mg −26% ($p < 0.001$) for 300 mg Major or clinically relevant non-major bleeding: −6% ($p = 0.09$) for 200 mg −6% ($p = 0.16$) for 300 mg

(*Continued*)

Table 2 (*Continued*)

Medication name	Type of drug	Type of study	Study name/citations	Population	Intervention	Comparison	Primary/Key outcomes	Summary of key results and primary outcomes
Milvexian (BMS-986177) (JNJ70033093)	Small molecule	Phase II	Weitz et al[31] AXIOMATIC-TKR trial	Patients undergoing total knee replacement	Milvexian oral 25 mg ($n=129$), 50 mg ($n=124$), 100 mg ($n=134$), or 200 mg ($n=131$) twice daily or 25 mg ($n=28$), 50 mg ($n=127$), or 200 mg ($n=123$) once daily	Enoxaparin 40 mg SC ($n=252$)	VTE, bleeding (major, clinically relevant non-major and minimal), death	Relative risk vs. enoxaparin for VTE: 25 mg BID: 0.97 (0.65–1.45) 50 mg BID: 0.53 (0.31–0.90) 100 mg BID: 0.42 (0.23–0.76) 200 mg BID: 0.37 0.19–0.69) 25 mg QD: 1.00 (0.51–1.97) 50 mg QD: 1.15 (0.78–1.70) 200 mg QD: 0.30 (0.15–0.62) No statistically significant difference for bleeding events Any bleeding: 4% taking milvexian 4% taking enoxaparin Any major bleeding or clinically relevant non major: 1% taking milvexian 2% taking enoxaparin
Osocimab (BAY1213790)	Antibody	Phase II	Weitz et al[32] FOXTROT trial	Patients undergoing total knee replacement	Single IV osocimab postoperative doses of 0.3 mg/kg ($n=107$), 0.6 mg/kg ($n=65$), 1.2 mg/kg ($n=108$), or 1.8 mg/kg ($n=106$); preoperative doses of 0.3 mg/kg ($n=109$) or 1.8 mg/kg ($n=108$)	40 mg of subcutaneous enoxaparin once daily ($n=105$) or 2.5 mg of oral apixaban twice daily ($n=105$)	Composite endpoint of VTE events, major and clinically relevant non-major bleeding	Osocimab given postoperatively met criteria for noninferiority compared with enoxaparin at the 0.6-, 1.2-, and 1.8-mg/kg doses The preoperative dose of 1.8 mg/kg of osocimab met criteria for superiority (risk difference 15.1% [90% CI, 4.9–25.2%]; $p=0.007$) Major or non-major bleeding: Risk difference in favor of Osocimab for 0.6 and 1.2 mg doses [event rates: 5.9% (2.1–9.7) and 4.9% (0.8–9.1), respectively]
Abelacimab (MAA868)	Antibody	Phase II	Verhamme et al[33] ANT-005 TKA trial	Patients undergoing total knee replacement	Abelacimab 30 mg ($n=102$), 75 mg ($n=99$), 150 mg ($n=98$)	Enoxaparin 40 mg SC ($n=101$)	Composite endpoint of VTE events, death, major or clinically relevant non-major bleeding	Absolute risk difference vs. enoxaparin for VTE: −16.8% (−26.0 to −7.6) for 75 mg,

Table 2 (*Continued*)

Medication name	Type of drug	Type of study	Study name/citations	Population	Intervention	Comparison	Primary/Key outcomes	Summary of key results and primary outcomes
								−17.8% (−26.7 to −8.8) for 150 mg Major or clinically relevant non-major bleeding: 2% incidence in the 30-mg, 2% in the 75-mg No events in the other groups
Xisomab (AB023)	Antibody	Phase II	Lorentz et al[34]	ESRD patients undergoing heparin-free hemodialysis	Xisomab 0.25 mg/kg ($n=8$), 0.5 mg/kg ($n=8$)	Placebo ($n=8$)	Signs of clotting during dialysis, bleeding events at vascular access site	Favorable efficacy for Xisomab compared with placebo No clinically relevant bleeding event
Asundexian	Small Molecule	Phase II	Piccini et al, PACIFIC-AF[16]	Patients aged 45 y or older with AF, a CHA2DS2-VASc score of at least 2 if male or at least 3 if female, and increased bleeding risk	Asundexian 20 mg ($n=251$) or 50 mg ($n=254$) once daily	Apixaban 5 mg twice daily ($n=250$)	ISTH major or CRNM bleeding	ISTH major bleeding or CRNM bleeding: 1.20% for asundexian 20 mg 0.39% for asundexian 50 mg 2.40% for apixaban 5 mg BID No ISTH major bleeding reported No statistically significant difference for efficacy outcomes
Asundexian	Small molecule	Phase II	Rao et al, PACIFIC-AMI[17]	Patients aged 45 y or older with recent admission for acute MI)	Asundexian 10 mg ($n=395$), 20 mg ($n=397$) or 50 mg ($n=402$) once daily All received dual antiplatelet therapy (aspirin + P2Y12 inhibitor	Placebo ($n=399$) plus dual antiplatelet therapy	BARC type 2, 3, or 5 bleeding Cardiovascular death, recurrent MI, ischemic or hemorrhagic stroke, or stent thrombosis	BARC type 2, 3, or 5 bleeding events: 30 (7.59%) for 10 mg 32 (8.06%) for 20 mg 42 (10.45%) for 50 mg 36 (9.02%) for placebo No statistically significant difference for efficacy outcomes
Asundexian	Small molecule	Phase II	Shoamanesh et al[18] PACIFIC-STROKE	Patients aged 45 y or older with acute (within 48 hour) non-cardioembolic ischemic stroke	Asundexian 10 mg ($n=455$), 20 mg ($n=450$) or 50 mg ($n=447$) once daily	Placebo ($n=456$)	Ischemic stroke or covert infarcts ISTH major and CRNM bleeding	Ischemic stroke or covert infarcts 86 (19%) for 10 mg 99 (22%) for 20 mg 90 (20%) for 50 mg 87 (19%) for placebo ISTH-defined major and CRNM bleeding 19 (4%) for 10 mg 14 (3%) for 20 mg 19 (4%) for 50 mg 11 (2%) for placebo No statistically significant difference in any outcome

Abbreviations: AE, adverse effects; AF, atrial fibrillation; ASO, antisense oligonucleotide; BARC, Bleeding Academic Research Consortium; BID, twice daily; CI, confidence interval; CRNM, clinically relevant non-major; ESRD, end-stage renal disease; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; PE, pulmonary embolism; QD, once daily; VTE, venous thromboembolism.

myocardial infarction (MI) were made available to the public, all of which were powered mainly to detect safety outcomes in dose-ranging studies. In PACIFIC-AF, asundexian 20 or 50 mg once daily was compared against apixaban 5 mg twice daily in patients aged 45 years or older with AF and increased bleeding risk, with International Society on Thrombosis and Haemostasis (ISTH) major or CRNM bleeding being the primary endpoint.[16] The ratios of incidence proportions for the primary endpoint for asundexian once daily versus apixaban twice daily were 0.50 (90% CI: 0.14–1.68) for asundexian 20 mg and 0.16 (90% CI: 0.01–0.99) for asundexian 50 mg, compared with apixaban. Although the results are encouraging from a safety perspective, no statistically significant difference was seen in the exploratory analysis for the composite outcome of cardiovascular death, MI, ischemic stroke, or systemic embolism, with two events in the asundexian 20-mg arm (2/251, 0.80%), four events in the 50-mg arm (4/254, 1.57%), and three events in the apixaban arm (3/250, 1.2%).[16] PACIFIC-AMI recruited patients aged 45 years or older with recent admission for acute MI initiated on dual-antiplatelet therapy (aspirin + P2Y12 inhibitor), which were given either asundexian 10, 20, or 50 mg once daily in the intervention arm or placebo in the control arm.[17] The primary safety outcome was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding and the efficacy outcome was the composite of cardiovascular death, recurrent MI, ischemic or hemorrhagic stroke, or stent thrombosis. The results showed no significant difference in the primary safety outcome between patients on any dose of asundexian compared with placebo, whereas efficacy was paradoxically lower for the pooled 20 and 50 mg doses versus placebo (46 [5.73%] patients with CV death, MI, stroke, or stent thrombosis with asundexian vs. 22 [5.49%] with placebo) and borderline higher for the 50-mg dose (22 [5.47%] patients with asundexian vs. 22 [5.49%] with placebo). However, these results were not statistically significant and were attributed to the study's low power to detect meaningful differences regarding efficacy.[17] In PACIFIC-STROKE patients aged 45 years or older with acute non-cardioembolic ischemic stroke within 48 hours were placed on aspirin and either asundexian once daily or placebo.[18] From a safety point of view, there was no statistically significant difference in ISTH major or CRNM bleeding between the control arm and any dose of asundexian. However, no benefits of asundexian were seen in reducing recurrent ischemic strokes and MRI-detected brain infarcts versus placebo. In a post hoc analysis, treatment with asundexian 50 mg versus placebo reduced recurrent symptomatic ischemic stroke and transient ischemic attack (hazard ratios [HRs]: 0.18; 90% CI: 0.05–0.65) or recurrent symptomatic ischemic stroke or transient ischemic attack (HR: 0.64; 90% CI: 0.41–0.98).[18] The results of AXIOMATIC-SSP (ClinicalTrials.gov Identifier: NCT03766581), which investigates dose–response relationships of milvexian for secondary stroke prevention in participants with acute ischemic stroke treated with aspirin and clopidogrel,[19] were presented at the European Society of Cardiology congress (ESC) in August 2022. The primary efficacy endpoint was a composite of ischemic stroke during treatment or incident infarct on brain MRI at 90 days. The main safety endpoint was major bleeding, defined as BARC type 3 or 5 bleeding. The study showed that Milvexian numerically reduced the risk of clinical ischemic stroke (excluding covert brain infarction) in the intention-to-treat population at all doses except 200 mg twice daily with no difference in major bleeding, with doses from 25 to 100 mg twice daily demonstrating an approximately 30% relative risk reduction versus placebo, although there was no evident dose–response relationship.[20]

It is expected that by the end of 2022, additional Phase II trials will share their results and provide insight regarding the effectiveness of FXIa inhibitors. RE-THINC ESRD (NCT04534114) is a Phase II placebo-controlled study with a ligand-conjugated version of IONIS-FXIRx, named fesomersen, or IONIS-FXI-LRx, focusing on evaluating the risk of major and CRNM bleeding when administered to patients with ESRD on hemodialysis compared with placebo and was completed in May 2022.

Phase III Trials Outlook

The results of Phase II trials across multiple indications, including stroke prevention in AF, dual pathway inhibition with concurrent antiplatelets post-MI, and thromboprophylaxis of orthopaedic surgery patients, are encouraging from a lack of safety concerns such as major or CRNM bleeding, even in high doses, when compared with placebo, enoxaparin, or apixaban. Although these trials are underpowered to assess efficacy, meta-analyses suggest that FXIa inhibition may play a more pivotal role in reducing VTE when compared with LMWH, whereas no clear signal has emerged for a reduction of other cardiovascular events with "add-on" FXIa inhibition compared with apixaban or placebo in the setting of MI and embolic stroke of undetermined source (ESUS). Potential advantages of FXIa inhibition in high bleed risk populations include patients with cancer-associated thrombosis (CAT) or end-stage renal disease (ESRD). Two Phase III trials are currently ongoing including the MAGNOLIA trial (NCT05171075) where the FXIai monoclonal antibody abelacimab is compared with dalteparin in patients with gastrointestinal/genitourinary cancer and associated VTE, and the ASTER trial (NCT05171049) where abelacimab is compared with apixaban in patients with CAT. Since abelacimab is an antibody, it is administered parenterally and not depended on liver metabolism or renal clearance, thus avoiding common pharmacokinetic issues encountered with warfarin or oral direct FXa inhibitors in these patient groups. Additional Phase III trials are needed to give definitive answers regarding the effectiveness of FXIa inhibitors in patient groups of interest from previous Phase II trials, such as prevention of VTE in orthopaedic surgery patients and stroke prevention in AF patients, since DOACs have proven efficacy, good safety profile, and are soon expected to come off patent. Given the established dominance of DOACs for these indications, FXI inhibitors are more likely to address the clinical needs of specific subgroups at high risk of bleeding or requiring multimodal antithrombotic therapy, such as patients with ESRD on hemodialysis and patients on

medical devices such as central venous catheters and mechanical heart valves.

Conclusion

Factor XIa inhibitors have potential to be safer anticoagulants compared with existing agents due to their ability to target the intrinsic coagulation pathway without affecting hemostasis. Recent clinical trials have shown that FXIa inhibitors are potentially more effective than LMWH for VTE prevention in orthopaedic surgery and a safe (and potentially safer) alternative to DOACs for stroke prevention in AF, while no safety signal was seen for secondary prevention of cardiovascular events in patients on dual antithrombotic therapy. While post hoc analyses have indicated a potential effectiveness in decreasing arterial thromboembolic outcomes, larger Phase III trials are needed to provide evidence of efficacy before these medications become part of standard clinical care.

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Conflict of Interests

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