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News at XI: moving beyond factor Xa inhibitors

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Abstract

Oral anticoagulants are a mainstay for the prevention and treatment of arterial and venous thrombosis. Direct oral anticoagulants (DOACs) have replaced vitamin K antagonists for many indications. Currently available DOACs include dabigatran, which inhibits thrombin, and apixaban, edoxaban, and rivaroxaban, which inhibit factor (F) Xa. A new class of DOACs is under development. These new DOACs, which include asundexian and milvexian, inhibit FXIa, which is positioned in the intrinsic pathway of coagulation. Anticoagulants that target FXIa have the potential to be safer than the current DOACs because there is emerging evidence that FXI is essential for thrombosis but mostly dispensable for hemostasis. In addition to the oral inhibitors of FXIa, parenteral inhibitors are also under development. These include fesomersen, an antisense oligonucleotide that reduces the hepatic synthesis of FXI; abelacimab, an antibody that binds to FXI and blocks its activation; and osocimab, an FXIa inhibitory antibody. Focusing on these new agents, this article describes the unmet needs in oral anticoagulation therapy, explains why FXI is a promising target for new oral anticoagulants, reviews phase 2 clinical data on new agents, describes ongoing phase 3 trials, and provides a perspective on the opportunities and challenges for FXI inhibitors.

KEYWORDS
anticoagulant, coagulation, factor XI, thromboembolism, thrombosis

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1 | INTRODUCTION

Oral anticoagulants are a cornerstone for the prevention and treatment of arterial and venous thrombosis. Currently available direct oral anticoagulants (DOACs), which came to the market in 2010, have taken over from vitamin K antagonists (VKAs) such as warfarin for many indications because they are at least as effective for stroke prevention in patients with atrial fibrillation (AF) and treatment of venous thromboembolism (VTE) and are associated with a lower risk of serious bleeding, particularly intracranial hemorrhage [1,2]. Furthermore, the currently available DOACs are more convenient to administer than VKAs because they can be given in fixed doses without the need for routine coagulation monitoring. With DOACs now firmly entrenched and with their uptake increasing with the introduction of generic versions, never have the hurdles in the development of new oral anticoagulants been higher.

Although VKAs and current DOACs target the distal end of the coagulation system, new anticoagulants targeting upstream factors in the contact pathway are under development. Thus, 2 oral factor (F) XIa inhibitors are under evaluation in phase 3 programs, and efforts to develop oral FXIIa inhibitors are continuing. In addition, parenteral FXI inhibitors that enable once-monthly dosing are also under evaluation in phase 2 or 3 programs for long-term indications. Focusing on these new agents, this article describes the unmet needs in oral anticoagulation therapy, explains why FXI is a particularly promising target for new anticoagulants, describes the pharmacologic properties of new oral and parenteral anticoagulants under development, reviews clinical data on new agents, and provides a perspective on the opportunities and challenges for this new class of anticoagulants.

2 | UNMET NEEDS IN ANTICOAGULATION THERAPY

The goal of anticoagulation therapy is to attenuate thrombosis with minimal disruption of hemostasis. Although currently available DOACs come closer to this goal than VKAs, bleeding is not eliminated. Thus, even with DOACs, the annual rate of major bleeding in patients with AF is 2% to 3%, whereas the annual rate of intracranial bleeding is 0.3% to 0.5% [1]. The fear of bleeding explains, at least in part, why one-third of patients with AF fail to receive anticoagulant prophylaxis and, among those administered anticoagulation therapy, why up to 50% are inappropriately treated with low doses of DOACs [3-5]. Therefore, there remains a need for safer anticoagulants.

The currently available DOACs have some limitations other than the potential for bleeding. For example, rivaroxaban and apixaban were less efficacious than VKAs in antiphospholipid syndrome [6], dabigatran and apixaban were less efficacious than warfarin in stroke prevention in patients with mechanical heart valves [7,8], and rivaroxaban was less efficacious than warfarin in preventing cardiovascular events or death in patients with AF associated with rheumatic heart disease [9]. Therefore, there is a need for more effective anticoagulants for certain patient populations, and FXI and FXII are potential targets for these new agents.

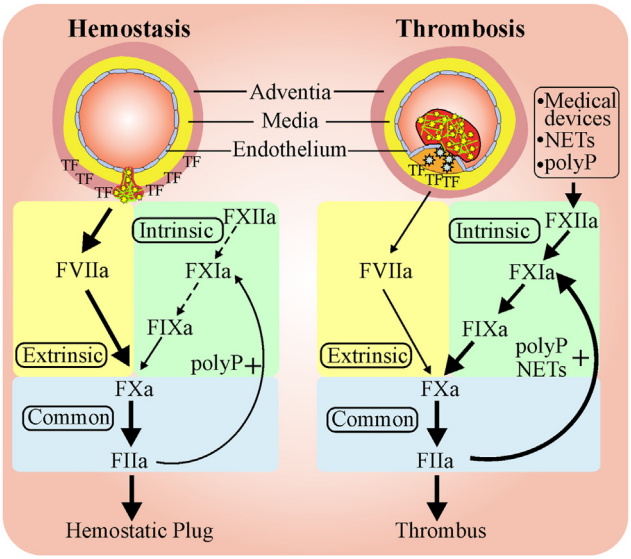

FIGURE Uncoupling hemostasis from thrombosis. Blood vessels are surrounded by a hemostatic envelope of tissue factor (TF) in the adventitia. Hemostasis is triggered when the adventitia is breached by vessel injury. The high concentrations of TF surrounding the vessel initiate explosive generation of thrombin via the extrinsic pathway (yellow), leading to the formation of a hemostatic plug that seals the leak. Factor (F) XII is dispensable for hemostasis, and feedback activation of FXI by thrombin is of minor importance for amplification of thrombin generation. Thrombosis is initiated by lower concentrations of TF exposed at the site of atherosclerotic plaque rupture or expressed by activated monocytes or microvesicles. The initial small amounts of thrombin produced in the common pathway (blue) feedback to activate FXI when stimulated by polyphosphate or neutrophil extracellular traps. These polyanions and blood-contacting medical devices can also bind to FXII and induce its autoactivation. FXIIa then activates FXI to trigger the generation of thrombin via the intrinsic pathway (green). *Source:* The figure was adapted from Fredenburgh JC, Weitz JI. Factor XI as a target for new anticoagulants. Hämostaseologie 2021;41:104–10. NETs, neutrophil extracellular traps.

3 | FXI AND FXII AS TARGETS

Currently available DOACs target FXa or thrombin, which are enzymes in the common pathway of coagulation that are essential for fibrin formation. Because they attenuate fibrin formation, DOACs are effective for the prevention and treatment of thrombosis. However, fibrin is a major component of physiologic hemostatic plugs and pathologic thrombi. Therefore, it is not surprising that the currently available DOACs are associated with risk of bleeding.

To circumvent inhibition of enzymes in the common pathway, upstream factors in the intrinsic pathway are being examined as new targets for anticoagulants. The focus on FXII and FXI stemmed from studies in animals that suggested that these factors are important in

thrombosis but are dispensable for hemostasis [10]. Consequently, by uncoupling thrombosis and hemostasis, inhibitors of FXII and FXI have the potential to be safer than currently available DOACs [11].

FXII or FXI inhibitors can uncouple thrombosis from hemostasis because although thrombin generation and fibrin formation are hallmarks of both processes, the pathways for thrombin generation and the sites of thrombus formation differ [11]. Thrombosis involves the formation of intravascular thrombi that block blood flow in arteries or veins. In contrast, hemostasis is a predominantly extravascular process that culminates in the formation of hemostatic plugs that stop the leakage of blood from damaged blood vessels (Figure).

Thrombosis is usually triggered by tissue factor (TF) exposed on disrupted atherosclerotic plaques or expressed on leukocytes or extracellular vesicles tethered to activated endothelial cells. TF binds to circulating FVII or FVIIa, and the TF:FVIIa complex activates FX to FXa, which then converts limited amounts of prothrombin into thrombin. This small amount of thrombin initiates fibrin formation and, along with FXa, provides positive feedback by activating the key cofactor proteins FV and FVIII. The TF:FVIIa complex also activates FIX, and the resultant FIXa, together with its cofactor FVIIIa, amplifies FXa and thrombin generation. However, once the thrombus expands beyond the site of injury, the TF:FVIIa complex can no longer sustain thrombus growth. Currently, it is believed that FXIa drives subsequent thrombus expansion.

FXI can be activated by FXIIa and thrombin [12,13]. Back activation of FXI by thrombin drives further thrombin generation and thrombus extension beyond the site of injury. FXI activation by FXIIa enhances this process. FXII is activated when the blood contacts medical devices such as central venous catheters, mechanical heart valves, or dialysis circuits [14]. FXII can also be activated by naturally occurring polyanions such as neutrophil extracellular traps, inorganic polyphosphate released from activated platelets, or DNA or RNA released from dead or dying cells [15]. The contribution of these polyanions to thrombosis in humans, however, is uncertain.

Although intravascular thrombus formation is a hallmark of thrombosis, hemostasis is a predominantly extravascular event that is initiated when TF in the hemostatic envelope surrounding blood vessels is exposed to blood by outside-inside damage to the vessel wall. The high concentration of TF in the adventitia surrounding blood vessels triggers explosive generation of thrombin. FXII activation is not part of this process, which explains why subjects with congenital FXII deficiency do not experience excessive bleeding. Likewise, FXI is mostly dispensable for hemostasis because feedback activation of FXI by thrombin is rarely needed to sustain the formation of hemostatic plugs. Consequently, spontaneous bleeding is rare in patients with congenital FXI deficiency and correlates poorly with FXI levels [16]. Furthermore, when bleeding occurs, it is usually mild, and bleeding after surgery is often localized to the oropharynx or urinary tract, where there is abundant fibrinolytic activity [17,18]. Spontaneous bleeds into muscles or joints and life-threatening intracranial or gastrointestinal bleeding, which are characteristics of hemophilia A or B, do not occur because of FXI deficiency. Therefore, although essential for thrombosis, FXI is mostly dispensable for hemostasis. The observations of absent-to-mild bleeding diatheses associated with deficiencies of FXII and FXI are central to the development of anticoagulants targeting these factors.

TABLE 1 Relative advantages and disadvantages of factor XII or factor XI as targets for new anticoagulants.

	FXII	FXI
Epidemiologic data	Weak	Strong
Risk of bleeding	None	Low
Level of evidence for role in thrombosis	Preclinical	Phase 2 and early phase 3
Potential for bypassing inhibition	Thrombin-mediated activation of factor XI could bypass factor XIIa inhibition	None
Potential for off-target effects	May modulate inflammation by inhibiting kinin generation	Unlikely

Source: The table was adapted from Fredenburgh JC, Weitz JI. Factor XI as a target for new anticoagulants. Hämostaseologie 2021;41:104–10.

4 | FXI OR FXII, WHICH IS THE BETTER TARGET?

The pros and cons of FXI and FXII as targets are listed in Table 1. FXII is a safer target than FXI because congenital FXII deficiency is not associated with bleeding, whereas FXI deficiency is associated with a mild bleeding diathesis. Nonetheless, most of the attention has been focused on FXI inhibition because of concerns about the contribution of FXII to thrombosis initiated by TF, weak epidemiologic data linking FXII with thrombosis, and potential for feedback activation of FXII by thrombin to bypass FXIIa inhibition. In contrast, regardless of whether thrombosis is driven by contact of blood with medical devices or naturally occurring polyphosphates or by TF, FXI plays a central part because of its activation by both FXIIa and thrombin. Furthermore, by its positioning at the nexus between coagulation and inflammation, FXI inhibition has the potential to be more effective than inhibition of FXa or thrombin for suppression of clotting in inflammatory disorders, such as antiphospholipid syndrome, or clotting induced by medical devices such as mechanical heart valves. Therefore, FXI appears to be a more important modulator of thrombosis than FXII.

Epidemiologic, Mendelian randomization, and genome-wide association studies have revealed links between FXI levels and thrombosis, whereas no such links exist for FXII [19–21]. In epidemiologic studies, congenital FXI deficiency was protective against VTE, ischemic stroke, and, at least in 1 study, myocardial infarction (MI) [22–24]. In contrast, FXII deficiency is not protective and may even be associated with an increased risk of VTE [25]. Although FXI was reported to be protective against heart failure in mice [26], there is no

TABLE 2 Pharmacologic features of factor XI-directed anticoagulants.

Feature	Antisense oligonucleotides	Antibodies	Small molecules
Delivery	Parenteral (SC)	Parenteral (IV or SC)	Oral
Onset of action	Delayed	Immediate (for IV)	Immediate
Offset of action	Delayed	Delayed	Rapid
Renal clearance	No	No	Yes
Hepatic metabolism	No	No	Yes
Reversal options	FFP or FXI concentrate	FVIIa or aPCC	FVIIa or aPCC

aPCC, activated prothrombin complex concentrate; FFP, fresh frozen plasma; FVIIa, activated factor VII; FXI, factor XI; IV, intravenous; SC, subcutaneous.
Source: The table was adapted from Fredenburgh JC, Gross PL, Weitz JI. Emerging anticoagulant strategies. Blood 2017;129:147–54.

evidence that subjects with congenital FXI deficiency are at increased risk for heart failure.

Mendelian randomization studies suggest that subjects with higher FXI levels are more prone to ischemic stroke and VTE than those with normal FXI levels, whereas those with lower FXI levels are at reduced risk [20]. Furthermore, the extent of elevation in FXI levels correlates with stroke risk in women taking oral contraceptives [27,28]. Although FXI levels correlate with the risk of thrombosis, there is a poor correlation with the risk of bleeding [29,30]. Therefore, because epidemiologic studies support the role of FXI in thrombosis and studies in animals demonstrate reduced thrombosis because of FXI deficiency or inhibition but no increase in bleeding, FXI has emerged as the preferred target for new anticoagulants.

5 | STRATEGIES TO INHIBIT FXI

Strategies to inhibit FXI include antisense oligonucleotides (ASOs) that reduce hepatic synthesis of FXI by binding to its messenger RNA and inducing its degradation; monoclonal antibodies that block FXI activation, FXIa activity, or both; and small molecules that block the active site of FXIa or induce allosteric modulation [31]. Each strategy not only differs in terms of the mechanism of action but also has unique pharmacologic characteristics that impact therapeutic indications (Table 2). Thus, ASOs and antibodies require parenteral administration, whereas small molecules are given orally. The onset and offset of the action of these agents also vary. For example, fesomersen, a second-generation ASO that is conjugated to an N-acetyl galactosamine ($GalNAc_3$) moiety to promote its uptake by hepatocytes, is more potent and has a more rapid onset of action than IONIS-FXI Rx, its unconjugated counterpart. Although IONIS-FXI Rx required twice-weekly subcutaneous injections to start and took 3 to 4 weeks to lower FXI levels to the therapeutic range [32], fesomersen is administered once monthly and lowers FXI levels to the therapeutic range within a week. In contrast, FXI-directed monoclonal antibodies have an immediate effect when administered intravenously and sustained effects when given subcutaneously on a once-monthly basis, whereas small-molecule FXIa inhibitors, which are given once- or twice-daily, achieve peak drug levels in 2 to 4 hours after oral administration.

Because of its slower onset of action, bridging therapy is needed if fesomersen is used for initial treatment of patients with or at high risk of thrombosis. In contrast, bridging therapy is unnecessary with oral FXIa inhibitors or FXI-directed monoclonal antibodies provided that the first dose is given intravenously. Oral FXIa inhibitors have half-lives of 8 to 17 hours, whereas fesomersen and monoclonal antibodies have half-lives of ≥30 days. These long half-lives could be problematic if there is life-threatening bleeding or urgent surgery is required. Periprocedural tranexamic acid may prevent or reduce bleeding in patients taking FXI inhibitors. If reversal is needed, plasma or FXI concentrate can replace FXI in patients treated with fesomersen, and bypassing agents such as recombinant FVIIa or activated prothrombin complex concentrate can overcome the anticoagulant effect of other agents [33]. With half-lives of <24 hours, reversal is less likely to be needed for oral FXIa inhibitors than for those with longer half-lives.

Like currently available DOACs, oral FXIa inhibitors are cleared, in part, by the kidneys and metabolized in the liver. Therefore, there is a potential for drug accumulation in patients with end-stage kidney disease, drug-drug interactions, and impaired metabolism in patients with severe liver disease. In contrast, these issues will not be observed with fesomersen or FXI-directed antibodies because they are not cleared by the kidneys or metabolized in the liver. Therefore, each strategy to inhibit FXI has its unique strengths and potential drawbacks.

6 | PHASE 2 CLINICAL TRIALS

Clinical evaluation of new anticoagulants usually starts in patients undergoing elective hip or knee replacement surgery because of their risk of postoperative deep-vein thrombosis, which can be efficiently detected using venography [31]. The first-generation antisense oligonucleotide IONIS-FXI Rx [34]; osocimab, a monoclonal antibody that inhibits FXIa [35]; abelacimab [36], an antibody that binds to FXI and prevents its activation by FXIIa or thrombin; and milvexian, an oral FXIa inhibitor [37] have been compared with enoxaparin in such patients in phase 2 proof-of-concept studies. Exploratory meta-analyses using postoperative VTE and clinically relevant bleeding (a

TABLE 3 Comparison of the pharmacologic properties of the oral factor Xa and factor XIa inhibitors.

Characteristic	Apixaban	Edoxaban	Rivaroxaban	Asundexian	Milvexian
Target	FXa	FXa	FXa	FXIa	FXIa
Molecular weight (Da)	460	548	436	593	626
Food effect	None	None	Enhances absorption	Minimal	Modest
Tmax (h)	1-2	1-2	2-3	2-4	2-4
Half-life (h)	12	5-11	7-11	14-17	8-14
Renal elimination (%)	27	50	33	14	18
Dose-proportional exposure	No	Yes	No	Yes	Yes
CYP3A4 interaction	Yes	No	Yes	No	Yes
Prolongation of PT	Yes	Yes	Yes	No	No
Prolongation of aPTT	Minimal	Minimal	Minimal	Yes	Yes

aPTT, activated partial thromboplastin time; CYP, cytochrome P450; FXa, activated factor X; FXIa, activated factor XI; PT, prothrombin time; Tmax, time to maximal concentration.

composite of major and clinically relevant nonmajor bleeding) for efficacy and safety analyses, respectively, reported a 40% to 50% reduction in VTE with FXI inhibition compared with that with enoxaparin and a 59% reduction in bleeding [38,39]. Once proof of concept was shown, attention shifted from thromboprophylaxis to indications with greater unmet needs.

In separate phase 2 studies (NCT04534114 and NCT04523220), fesomersen and osocimab were compared with a placebo in patients with end-stage kidney disease undergoing hemodialysis, a population at high risk for atherothrombotic complications and bleeding. Although the results have not been reported, both studies went to completion, and fesomersen was reported to be safe and well tolerated. In addition, in the ongoing double-blind phase 2 AZALEA TIMI-71 trial (NCT04755283), the efficacy and safety of once-monthly subcutaneous injections of abelacimab (90 or 150 mg) and rivaroxaban (20 mg once daily or 15 mg once daily for those with a creatinine clearance of <50 mL/min) are being compared in 1200 patients with AF. Although the results of this event-driven trial have not been reported, recruitment was completed in 2022, and follow-up is continuing without any safety concerns thus far. Therefore, phase 2 studies with parenteral FXI inhibitors support the concept that FXI inhibition is both effective and safe, thereby setting the stage for trials with oral FXI inhibitors.

The oral FXIa inhibitors in the most advanced stage of development are asundexian (BAY 2433334) [40] and milvexian (BMS-986177/JNJ-70033093) [41,42]. Both are small molecules that bind reversibly to the active site of FXIa and inhibit its activity. As illustrated in Table 3, asundexian and milvexian have many features in common with currently available oral FXa inhibitors. Asundexian and milvexian are rapidly absorbed after oral administration and have half-lives that permit once- or twice-daily oral dosing. The specificity of asundexian and milvexian for FXIa is highlighted by the fact that they prolong the activated partial thromboplastin time in a dose-dependent manner but have no effect on the prothrombin time. Asundexian and milvexian have both moved forward into phase 3 based on the results of the phase 2 trials, which are described below and summarized in Table 4.

6.1 | Asundexian

6.1.1 | Safety of the Oral Factor XIa Inhibitor Asundexian Compared with Apixaban in Patients with Atrial Fibrillation (PACIFIC-AF)

This randomized, double-blind, double-dummy, phase 2 trial enrolled 862 patients with AF who were aged ≥45 years and were at an increased risk of bleeding [43]. Participants were randomized to receive asundexian at doses of 20 or 50 mg once daily or apixaban at 5 mg twice daily, with dose reduction to 2.5 mg twice daily according to the usual criteria. The primary outcome of the trial was a composite of major or clinically relevant nonmajor bleeds based on the International Society on Thrombosis and Haemostasis criteria.

Of a total of 753 patients included in the final analysis, 249 and 254 received the 20- and 50-mg doses of asundexian, respectively, and 250 received apixaban. With the 20-mg asundexian dose, FXIa activity was inhibited by 90% and 81% at the peak and trough, respectively, whereas with the 50-mg dose, FXIa activity was inhibited by 94% and 92% at the peak and trough, respectively. There were no major bleeds with asundexian or apixaban. Clinically relevant nonmajor bleeds occurred in 3 patients in the 20-mg asundexian group, 1 patient in the 50-mg asundexian group, and 6 patients in the apixaban group, yielding incidence ratios of 0.50 for 20-mg asundexian (90% CI, 0.09-0.97), 0.16 for 50-mg asundexian (90% CI, 0.01-0.99), and 0.33 for both asundexian doses (90% CI, 0.09-0.97). Adverse events occurred in 47% of patients in each asundexian group and 49% of those in the apixaban group. The study was underpowered for efficacy; the efficacy outcome, a composite of ischemic stroke, systemic embolism, MI, or cardiovascular death occurred in 2, 4, and 3 patients in the 20-mg asundexian, 50-mg asundexian, and apixaban groups,

TABLE 4 Summary of phase 2 trials with asundexian and milvexian.

					Efficacy		Safety	
Trial	**N**	**Eligibility**	**Experimental**	**Control**	**Definition (composite)**	**Result**	**Definition (composite)**	**Result**
PACIFIC-AF	755	Age ≥ 45 y, AF, CHA_2DS_2-VASc score ≥ 2 if male or ≥3 if female, increased risk of bleeding	Asundexian at 20 or 50 mg once daily	Apixaban at 5 mg twice daily (2.5 mg twice daily if the criteria for dose reduction were met)	Ischemic stroke, systemic embolism, MI, or CV death	Asundexian at 20 mg once daily: 2 events, asundexian at 50 mg once daily: 4 events, vs apixaban: 3 events	ISTH major or clinically relevant nonmajor bleeding	Asundexian at 20 mg once daily: 1.2%, asundexian at 50 mg once daily: 0.4%, vs apixaban: 2.4%
PACIFIC-Stroke	1,808	Age ≥ 45 y, noncardioembolic ischemic stroke, to be treated with antiplatelet therapy, able to have MRI	Asundexian 10, 20, or 50 mg once daily	Placebo	Ischemic stroke or covert infarction detected using MRI	Asundexian at 10 mg once daily: 19%, asundexian at 20 mg once daily: 22%, asundexian at 50 mg once daily: 20%, vs placebo 19%	ISTH major or clinically relevant nonmajor bleeding	Asundexian at 10 mg once daily: 4%, asundexian at 20 mg once daily: 3%, asundexian at 50 mg once daily: 4%, vs placebo: 2%
PACIFIC-AMI	1,601	Within 5 d of acute MI	Asundexian at 10, 20 or 50 mg once daily	Placebo	CV death, MI, stroke, stent thrombosis	Asundexian at 10 mg once daily: 6.8%, asundexian at 20 mg once daily: 6.0%, asundexian at 50 mg once daily: 5.5%, vs placebo: 5.5%	BARC 2, 3, or 5 bleeding	Asundexian at 10 mg once daily: 7.6%, asundexian at 20 mg once daily: 8.1%, asundexian at 50 mg once daily: 10.5%, vs placebo: 9.0%
AXIOMATIC-SSP	2,366	Noncardioembolic ischemic stroke or TIA	Milvexian at 25 mg once daily or 25, 50, 100, or 200 mg twice daily	Placebo	Ischemic stroke or covert infarction detected using MRI	Milvexian at 25 mg once daily: 16.2%,milvexian at 25 mg twice daily: 18.5%, milvexian at 50 mg twice daily: 14.1%, milvexian at 100 mg twice daily: 14.8%, milvexian at 200 mg twice daily: 16.4%, placebo: 16.6%	BARC 3 or 5 bleeding	Milvexian at 25 mg once daily: 0.6%,milvexian at 25 mg twice daily: 0.6%, milvexian at 50 mg twice daily: 1.5%, milvexian at 100 mg twice daily: 1.6%, milvexian at 200 mg twice daily: 1.5%, vs placebo: 0.6%

AF, atrial fibrillation; AXIOMATIC-SSP, Antithrombotic Treatment with Factor XIa Inhibition to Optimize Management of Acute Thromboembolic Events for Secondary Stroke Prevention; BARC, Bleeding Academic Research Consortium; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female); CV, cardiovascular; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; MRI, magnetic resonance imaging; PACIFIC-AF, Safety of the Oral Factor XIa Inhibitor Asundexian Compared with Apixaban in Patients with Atrial Fibrillation; PACIFIC-AMI, Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following an Acute Heart Attack; PACIFIC-Stroke, Factor XIa Inhibition with Asundexian After Acute Non-cardioembolic Ischemic Stroke; TIA, transient ischemic attack.

Source: The table was adapted from Weitz JI, Eikelboom JW. What is the future of factor XI Iinhibitors? Circulation. 2022;146:1899-1902.

respectively. Therefore, at doses of 20 or 50 mg once daily, asundexian was associated with less bleeding compared with apixaban, but the trial was underpowered to determine the efficacy of these asundexian doses relative to that of apixaban.

6.1.2 | Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following an Acute Heart Attack (PACIFIC-AMI)

The goal of this double-blind, phase 2 trial was to assess the safety and efficacy of 3 doses of asundexian compared with those of a placebo in patients with acute MI who were treated with dual-antiplatelet therapy (DAPT) [44]. A total of 1601 patients were randomized in a 1:1:1:1 manner to receive 50 mg of asundexian once daily (n = 402), 20 mg of asundexian once daily (n = 401), 10 mg of asundexian oncedaily (n = 397), or placebo (n = 401). All patients were receiving aspirin (81 mg once daily) and a P_2Y_{12} inhibitor; ticagrelor or prasugrel was used by 80% of the patients. Over 99% of the patients underwent percutaneous coronary intervention for their index event, which was ST-elevation MI in 52% and non–ST-elevation MI in the remainder.

Asundexian inhibited FXIa in a dose-dependent manner, and there was >90% inhibition with the 50-mg asundexian dose. The primary safety outcome, Bleeding Academic Research Consortium 2, 3, or 5 bleeding at 6 months, occurred in 10.5%, 8.1%, and 7.6% of the patients in the 50-, 20-, and 10-mg asundexian groups, respectively, and 9.0% of those in the placebo group. Two patients in the 50-mg asundexian group and 1 in the placebo group had an intracerebral hemorrhage. The primary efficacy outcome, a composite of cardiovascular death, MI, stroke, and stent thrombosis, occurred in 5.5%, 6.0%, and 6.8% of patients in the 50-, 20-, and 10-mg asundexian groups, respectively, and 5.5% of those in the placebo group. Therefore, asundexian, in addition to DAPT, in patients undergoing percutaneous coronary intervention for MI did not significantly increase bleeding compared with the placebo. Recurrent ischemic events were infrequent, and there was no significant difference between the rates with asundexian and those with the placebo.

6.1.3 | Factor XIa Inhibition with Asundexian After Acute Non-cardioembolic Ischemic Stroke (PACIFIC-Stroke)

The trial was undertaken to assess the safety and efficacy of 3 once-daily doses of asundexian compared with those of a placebo in patients with noncardioembolic ischemic stroke who were enrolled within 48 hours from symptom onset [45]. A total of 1808 patients were randomized in a double-blind 1:1:1:1 manner to receive 50 mg of asundexian (n = 447), 20 mg of asundexian (n = 450), 10 mg of asundexian (n = 455), or a placebo (n = 456). These treatments were administered for 6 months.

The primary efficacy outcome, the composite of ischemic stroke or covert stroke on repeat brain imaging at 6 months, occurred in 20.1%, 22.0%, and 18.9% of patients in the 50-, 20-, and 10-mg asundexian treatment groups, respectively, and 19.1% of those given placebo. The principal safety outcome, a composite of major or clinically relevant nonmajor bleeding, occurred in 4.3%, 3.1%, and 4.3% of patients in the 50-, 20-, and 10-mg asundexian treatment groups, respectively, and 2.4% of those given placebo. In a post hoc analysis, recurrent ischemic stroke or transient ischemic attack (TIA) occurred in 5.4%, 6.2%, and 7.7% of patients in the 50-, 20-, and 10-mg asundexian treatment groups, respectively, and 8.3% of those given placebo. The hazard ratio for 50-mg asundexian versus that for placebo was 0.64 (95% CI, 0.41-0.98). Rates of hemorrhagic transformation in the 50-, 20-, and 10-mg asundexian groups were 1.4%, 1.1%, and 0.4%, respectively. There were no hemorrhagic transformations in the placebo group.

Therefore, asundexian was not associated with an increase in bleeding. Although asundexian did not reduce the composite of covert brain infarction or ischemic stroke compared with the placebo, there appeared to be a reduction in recurrent symptomatic ischemic stroke or TIA in the 50-mg asundexian group compared with placebo, particularly among patients with atherosclerosis.

6.2 | Milvexian

6.2.1 | Antithrombotic Treatment with Factor XIa Inhibition to Optimize Management of Acute Thromboembolic Events in Total Knee Replacement (AXIOMATIC TKR)

The goal of this proof-of-principle study was to demonstrate that milvexian has antithrombotic activity [37]. A total of 1242 patients undergoing knee arthroplasty were randomized to 1 of 7 postoperative regimens of oral milvexian (25, 50, 100, or 200 mg twice daily or 25, 50, or 200 mg once daily) or subcutaneous enoxaparin (40 mg once daily). The primary efficacy outcome was VTE, the composite of fatal or nonfatal pulmonary embolism and symptomatic or asymptomatic deep-vein thrombosis. With twice-daily milvexian dosing, VTE occurred in 27 of 129 patients (21%) taking 25 mg, 14 of 124 (11%) taking 50 mg, 12 of 134 (9%) taking 100 mg, and 10 of 131 (8%) taking 200 mg, while with once-daily milvexian dosing, VTE occurred in 7 of 28 patients (25%) taking 25 mg, 30 of 127 (24%) taking 50 mg, and 8 of 123 (7%) taking 200 mg. In those given enoxaparin, VTE occurred in 54 of 252 patients (21%). The dose-response relationship with twice-daily milvexian was significant (1-sided $p < .001$), and the 12% incidence of VTE with twice-daily milvexian was significantly lower than the prespecified benchmark of 30%. Consequently, the 2 prespecified criteria for efficacy were met. The incidence of bleeding of any severity was 4% with milvexian and enoxaparin. The incidence of clinically relevant bleeding, a composite of major and clinically relevant nonmajor bleeding, was 1% with milvexian and 2% with enoxaparin. Importantly, the incidence of clinically relevant bleeding was similar across the 16-fold range of milvexian doses. Serious adverse events were reported in 2% and 4% of patients in the milvexian and enoxaparin groups, respectively.

6.2.2 | Antithrombotic Treatment with Factor XIa Inhibition to Optimize Management of Acute Thromboembolic Events for Secondary Stroke Prevention (AXIOMATIC SSP)

The goal of this double-blind trial was to assess the safety and efficacy of 5 doses of milvexian compared with those of a placebo in patients with noncardioembolic ischemic stroke or TIA on the background of atherosclerotic disease who presented within 48 hours of symptom onset [46]. A total of 2295 patients were randomized in a 1:1:1:1:1:2 manner to receive 25 mg of milvexian once daily (n = 325), 25 mg of milvexian twice daily (n = 313), 50 mg of milvexian twice daily (n = 325), 100 mg of milvexian twice daily (n = 306), 200 mg of milvexian twice daily (n = 344), or a placebo (n = 682). All the patients received clopidogrel (75 mg once daily) and aspirin (100 mg once daily) for 21 days, followed by aspirin alone for 90 days.

The incidence of the primary efficacy outcome, the composite of symptomatic ischemic stroke and covert brain infarction on repeat brain imaging at 90 days, did not differ between milvexian and placebo. Symptomatic ischemic stroke or TIA occurred in 4.6%, 3.8%, 4.0%, 3.5%, and 7.7% of the patients in the 25-mg milvexian once-daily, 25-mg milvexian twice-daily, 50-mg milvexian twice-daily, 100-mg milvexian twice-daily, and 200-mg milvexian twice-daily groups, respectively, and 5.5% of those in the placebo group. Any Bleeding Academic Research Consortium bleeding occurred in 0.8%, 8.6%, 12.3%, 13.1%, and 10.2% of the patients in the 25-mg milvexian once-daily, 25-mg milvexian twice-daily, 50-mg milvexian twice-daily, 100-mg milvexian twice-daily, and 200-mg milvexian twice-daily groups, respectively, and 7.9% of those given placebo. There were no fatal bleeds, and symptomatic intracranial hemorrhage was rare. Therefore, milvexian was not associated with a reduction in the incidence of recurrent symptomatic ischemic stroke or covert brain infarction at 90 days compared with placebo, but post hoc analysis suggested that there was a reduction in recurrent symptomatic ischemic stroke. Milvexian was not associated with a significant increase in bleeding compared with the placebo.

7 | PHASE 3 CLINICAL TRIALS

Abelacimab, asundexian, and milvexian are currently under phase 3 evaluation. The ongoing trials with each of these agents are briefly described below and are summarized in Table 5.

7.1 | Abelacimab

Abelacimab is being compared with placebo in patients with AF deemed unsuitable for oral anticoagulants and with apixaban or dalteparin in patients with cancer-associated VTE.

7.1.1 | Study to evaLuate the effIcacy and Safety of abeLacimab in High-risk Patients With Atrial Fibrillation Who Have Been Deemed Unsuitable for Oral anticoagulation (LILAC-TIMI 76)

This is a multicenter, double-blind, placebo-controlled superiority trial that will randomize 1900 patients with AF who have been deemed unsuitable for oral anticoagulation to receive subcutaneous abelacimab (150 mg once monthly) or placebo (NCT05712200). Enrolled patients will have at least 1 risk factor for bleeding such as severe kidney disease, use of concomitant antiplatelet therapy, history of a critical site bleed, or risk for bleeding such as frailty, multiple falls, or chronic use of nonsteroidal anti-inflammatory drugs.

7.1.2 | A Study Comparing Abelacimab to Apixaban in the Treatment of Cancer-associated VTE (ASTER)

This is a randomized, open-label, blinded endpoint evaluation trial comparing abelacimab (150 mg intravenously, followed by 150 mg subcutaneously once monthly thereafter) with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily thereafter) in 1655 patients with cancer-associated VTE who are deemed eligible for apixaban therapy (NCT05171049).

7.1.3 | A study comparing abelacimab to dalteparin in the treatment of gastrointestinal/genitourinary cancer associated VTE (MAGNOLIA)

This is a randomized, open-label, blinded endpoint evaluation trial comparing abelacimab (in the same dosing regimen used in ASTER) with subcutaneous dalteparin (200 units/kg once daily for the first month, followed by 175 units/kg once daily thereafter) in 1020 patients with gastrointestinal/genitourinary cancer-associated VTE considered to be at a high risk of bleeding (NCT05171075). The treatments were administered for 6 months in both the ASTER and MAGNOLIA trials.

7.2 | Asundexian

In the Oral faCtor Eleven A iNhibitor asundexIan as novel antithrombotiC (OCEANIC) program, asundexian is being compared with apixaban in patients with AF and with a placebo in those with stroke.

7.2.1 | OCEANIC-AF

This is a multicenter, double-blind, double-dummy, randomized phase 3 trial that will compare the efficacy and safety of asundexian and

TABLE 5 Ongoing phase 3 clinical trials with factor XI inhibitors.

Drug	Trial name (NCT)	Indication	Comparator	N	Sponsor
Abelacimab	LILAC-TIMI 76 (NCT05712200)	patients with AF deemed unsuitable for oral anticoagulation	Placebo	1900	Anthos
	ASTER (NCT05171049)	Cancer-associated VTE	Apixaban	1655	
	MAGNOLIA (NCT05171075)	Gastrointestinal/genitourinary cancer-associated VTE	Dalteparin	1020	
Asundexian	OCEANIC-AF (NCT05643573)	AF	Apixaban	18000	Bayer
	OCEANIC STROKE (NCT05686070)	Secondary stroke prevention	Placebo	9300	
Milvexian	LIBREXIA-AF (NCT 05757869)	AF	Apixaban	15 500	BMS and Janssen
	LIBREXIA-Stroke (NCT05702034)	Secondary stroke prevention	Placebo	15 000	
	LIBREXIA-ACS (NCT05754957)	ACS	Placebo	16 000	

ACS, acute coronary syndrome; AF, atrial fibrillation; ASTER, A Study Comparing Abelacimab to Apixaban in the Treatment of Cancer-associated VTE; BMS, Bristol-Myers Squibb; LIBREXIA-AF, A Study of Milvexian Versus Apixaban in Participants With Atrial Fibrillation; LIBREXIA-ACS, A Study of Milvexian in Participants After a Recent Acute Coronary Syndrome; LIBREXIA-Stroke, A Study of Milvexian in Participants After an Acute Ischemic Stroke or High-Risk Transient Ischemic Attack; LILAC-TIMI 76, Study to evaLuate the effIcacy and Safety of abeLacimab in High-risk Patients With Atrial Fibrillation Who Have Been Deemed Unsuitable for Oral anticoagulation; MAGNOLIA, A study comparing abelacimab to dalteparin in the treatment of gastrointestinal/genitourinary cancer associated VTE; NCT, National Clinical Trial; OCEANIC, Oral faCtor Eleven A iNhibitor asundexIan as novel antithrombotiC; VTE, venous thromboembolism.

apixaban (5 mg twice daily or 2.5 mg twice daily for those with at least 2 of 3 dose reduction criteria) for the prevention of stroke or systemic embolism in 18 000 participants with AF (NCT05643573).

7.2.2 | OCEANIC STROKE

This is a multicenter, double-blind, randomized phase 3 trial that will compare asundexian with a placebo for the prevention of ischemic stroke in 9300 participants after acute noncardioembolic ischemic stroke or high-risk TIA against the background of systemic or cerebrovascular atherosclerosis. All participants will receive background DAPT or single-antiplatelet therapy (NCT05686070).

7.3 | Milvexian

In the LIBREXIA program, milvexian is being compared with apixaban in patients with AF and with a placebo in those with stroke and acute coronary syndrome (ACS).

7.3.1 | A Study of Milvexian Versus Apixaban in Participants With Atrial Fibrillation (LIBREXIA-AF)

This is a multicenter, double-blind, double-dummy, randomized phase 3 trial that will compare the efficacy and safety of milvexian with those of apixaban (5 mg twice daily or 2.5 mg twice daily for those with at least 2 of 3 dose reduction criteria) for the prevention of stroke or systemic embolism in 15 500 participants with AF (NCT05757869).

7.3.2 | A Study of Milvexian in Participants After an Acute Ischemic Stroke or High-Risk Transient Ischemic Attack (LIBREXIA-STROKE)

This is a multicenter, double-blind, randomized phase 3 trial that will compare milvexian with a placebo for the prevention of ischemic stroke in 15 000 participants after acute noncardioembolic ischemic stroke or high-risk TIA. All the participants will receive background DAPT or single-antiplatelet therapy (NCT05702034).

7.3.3 | A Study of Milvexian in Participants After a Recent Acute Coronary Syndrome (LIBREXIA-ACS)

This is a multicenter, double-blind, randomized phase 3 trial that will compare milvexian with a placebo in 16 000 participants within 7 days after ACS. All participants will receive background DAPT or single-antiplatelet therapy (NCT05754957).

8 | CONCLUSIONS AND FUTURE DIRECTIONS

The evidence from available phase 2 trials suggests that unlike the currently available DOACs, drugs that target FXI reduce thrombosis without a dose-dependent increase in bleeding, thereby raising the potential for a more favorable benefit-risk profile. Large phase 3 trials are needed to determine whether asundexian and milvexian can prevent stroke without increasing bleeding in AF. This is a high bar to achieve because numerous postmarketing studies have confirmed the efficacy and safety of DOACs for this indication, particularly apixaban [47,48].

Asundexian and milvexian may reduce recurrence in patients with noncardioembolic stroke, but choosing the right dose requires a balance between efficacy and safety. Capitalizing on the benefits of dual-pathway inhibition with aspirin and low-dose rivaroxaban seen in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46 [48,49] and Cardiovascular Outcomes for People Using Anticoagulation Strategies trials [47,50], the LIBREXIA-ACS trial will evaluate whether extended treatment with milvexian safely reduces recurrent ischemic events when started within 7 days after ACS and continued for several years.

Abelacimab, the first parenteral FXI inhibitor to undergo phase 3 evaluation, is being studied in patients with AF and cancer-associated VTE, trials that may identify a role for parenteral FXI inhibitors. The safety of abelacimab will be revealed in the LILAC trial, in which it is being compared with a placebo in patients with AF at a high risk of bleeding, and in the ASTER and MAGNOLIA trials, in which it is being compared with apixaban and dalteparin, respectively, in patients with cancer-associated VTE, a population at higher risk for bleeding than those without active cancer. Therefore, the future of FXI inhibitors appears bright, but the promise of uncoupling thrombosis from hemostasis requires confirmation in large phase 3 trials.

AUTHOR CONTRIBUTIONS

J.C.F. and J.I.W. wrote the manuscript.

DECLARATION OF COMPETING INTERESTS

J.C.F. has nothing to disclose. J.I.W. received honoraria from Alnylam, Anthos, Bayer AG, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Ionis, Janssen, Novartis, Pfizer, Regeneron, and Servier Pharmaceuticals and institutional grants from Bayer AG, Bristol-Myers Squibb, and Boehringer Ingelheim. J.I.W. holds the Canada Research Chair (Tier 1) in Thrombosis and the Heart and Stroke Foundation/JF Mustard Chair in Cardiovascular Research at McMaster University.

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REFERENCES

[1] Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–62.
[2] van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood*. 2014;124:1968–75.
[3] Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med*. 2010;123:638–45.e634.
[4] Park S, Je NK. Underutilization of anticoagulants in patients with nonvalvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants. *Int J Arrhythm*. 2022;23:1.
[5] Sanghai S, Wong C, Wang Z, Clive P, Tran W, Waring M, Goldberg R, Hayward R, Saczynski JS, McManus DD. Rates of potentially inappropriate dosing of direct-acting oral anticoagulants and associations with geriatric conditions among older patients with atrial fibrillation: the SAGE-AF study. *J Am Heart Assoc*. 2020;9:e014108.
[6] Wu X, Cao S, Yu B, He T. Comparing the efficacy and safety of direct oral anticoagulants versus vitamin K antagonists in patients with antiphospholipid syndrome: a systematic review and meta-analysis. *Blood Coagul Fibrinolysis*. 2022;33:389–401.
[7] Van de Werf F, Brueckmann M, Connolly SJ, Friedman J, Granger CB, Hartter S, Harper R, Kappetein AP, Lehr T, Mack MJ, Noack H, Eikelboom JW. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: the randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). *Am Heart J*. 2012;163:931–7.
[8] Artivion. Artivion follows recommendation to stop PROACT Xa clinical trial. https://investors.artivion.com/news-releases/news-release-details/artivion-follows-recommendation-stop-proact-xa-clinical-trial 2023. [accessed March 27, 2023].
[9] Connolly SJ, Karthikeyan G, Ntsekhe M, Haileamlak A, El Sayed A, El Ghamrawy A, Damasceno A, Avezum A, Dans AM, Gitura B, Hu D, Kamanzi ER, Maklady F, Fana G, Gonzalez-Hermosillo JA, Musuku J, Kazmi K, Zühlke L, Gondwe L, Ma C, et al. Rivaroxaban in rheumatic heart disease-associated atrial fibrillation. *N Engl J Med*. 2022;387:978–88.
[10] Müller F, Gailani D, Renne T. Factor XI and XII as antithrombotic targets. *Curr Opin Hematol*. 2011;18:349–55.
[11] Hsu C, Hutt E, Bloomfield DM, Gailani D, Weitz JI. Factor XI inhibition to uncouple thrombosis from hemostasis: JACC review topic of the week. *J Am Coll Cardiol*. 2021;78:625–31.
[12] Walsh PN. Roles of platelets and factor XI in the initiation of blood coagulation by thrombin. *Thromb Haemost*. 2001;86:75–82.
[13] Choi SH, Smith SA, Morrissey JH. Polyphosphate is a cofactor for the activation of factor XI by thrombin. *Blood*. 2011;118:6963–70.
[14] Jaffer IH, Fredenburgh JC, Hirsh J, Weitz JI. Medical device-induced thrombosis: what causes it and how can we prevent it? *J Thromb Haemost*. 2015;13:S72–81.
[15] Rangaswamy C, Englert H, Deppermann C, Renné T. Polyanions in coagulation and thrombosis: focus on polyphosphate and NETs. *Thromb Haemost*. 2020;121:1021–30.
[16] Duga S, Salomon O. Congenital factor XI deficiency: an update. *Sem Thromb Hemost*. 2013;39:621–31.
[17] Asakai R, Chung DW, Davie EW, Seligsohn U. Factor XI deficiency in Ashkenazi Jews in Israel. *N Engl J Med*. 1991;325:153–8.
[18] De Caterina R, Prisco D, Eikelboom JW. Factor XI inhibitors: cardiovascular perspectives. *Eur Heart J*. 2023;44:280–92.
[19] Key NS. Epidemiologic and clinical data linking factors XI and XII to thrombosis. *Hematology Am Soc Hematol Educ Program*. 2014;2014:66–70.
[20] Gill D, Georgakis MK, Laffan M, Sabater-Lleal M, Malik R, Tzoulaki I, Veltkamp R, Dehghan A. Genetically determined FXI (Factor XI) levels and risk of stroke. *Stroke*. 2018;49:2761–3.
[21] Yuan S, Burgess S, Laffan M, Mason AM, Dichgans M, Gill D, Larsson SC. Genetically proxied inhibition of coagulation factors and risk of cardiovascular disease: a Mendelian randomization study. *J Am Heart Assoc*. 2021;10:e019644.
[22] Preis M, Hirsch J, Kotler A, Zoabi A, Stein N, Rennert G, Saliba W. Factor XI deficiency is associated with decreased risk for cardiovascular and venous thromboembolism events. *Blood*. 2017;129:1210–5.

[23] Salomon O, Steinberg DM, Koren-Morag N, Tanne D, Seligsohn U. Reduced incidence of ischemic stroke in patients with severe factor XI deficiency. *Blood*. 2008;111:4113–7.
[24] Salomon O, Steinberg DM, Zucker M, Varon D, Zivelin A, Seligsohn U. Patients with severe factor XI deficiency have a reduced incidence of deep-vein thrombosis. *Thromb Haemost*. 2011;105:269–73.
[25] Endler G, Marsik C, Jilma B, Schickbauer T, Quehenberger P, Mannhalter C. Evidence of a U-shaped association between factor XII activity and overall survival. *J Thromb Haemost*. 2007;5:1143–8.
[26] Cao Y, Wang Y, Zhou Z, Pan C, Jiang L, Zhou Z, Meng Y, Charugundla S, Li T, Allayee H, Seldin MM, Lusis AJ. Liver-heart cross-talk mediated by coagulation factor XI protects against heart failure. *Science*. 2022;377:1399–406.
[27] Siegerink B, Govers-Riemslag JW, Rosendaal FR, ten Cate H, Algra A. Intrinsic coagulation activation and the risk of arterial thrombosis in young women: results from the Risk of Arterial Thrombosis in relation to Oral contraceptives (RATIO) case-control study. *Circulation*. 2010;122:1854–61.
[28] Suri MF, Yamagishi K, Aleksic N, Hannan PJ, Folsom AR. Novel hemostatic factor levels and risk of ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Cerebrovasc Dis*. 2010;29:497–502.
[29] Peyvandi F, Palla R, Menegatti M, Siboni SM, Halimeh S, Faeser B, Pergantou H, Platokouki H, Giangrande P, Peerlinck K, Celkan T, Ozdemir N, Bidlingmaier C, Ingerslev J, Giansily-Blaizot M, Schved JF, Gilmore R, Gadisseur A, Benedik-Dolničar M, Kitanovski L, et al. Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: results from the European Network of Rare Bleeding Disorders. *J Thromb Haemost*. 2012;10:615–21.
[30] Bolton-Maggs PH, Patterson DA, Wensley RT, Tuddenham EG. Definition of the bleeding tendency in factor XI-deficient kindreds–a clinical and laboratory study. *Thromb Haemost*. 1995;73:194–202.
[31] Greco A, Laudani C, Spagnolo M, Agnello F, Faro DC, Finocchiaro S, Legnazzi M, Mauro MS, Mazzone PM, Occhipinti G, Rochira C, Scalia L, Capodanno D. Pharmacology and clinical development of factor XI inhibitors. *Circulation*. 2023;147:897–913.
[32] Willmann S, Marostica E, Snelder N, Solms A, Jensen M, Lobmeyer M, Lensing AW, Bethune C, Morgan E, Yu RZ, Wang Y, Jung SW, Geary R, Bhanot S. PK/PD modeling of FXI antisense oligonucleotides to bridge the dose-FXI activity relation from healthy volunteers to end-stage renal disease patients. *CPT Pharmacometrics Syst Pharmacol*. 2021;10:890–901.
[33] van Es N, De Caterina R, Weitz JI. Reversal agents for current and forthcoming direct oral anticoagulants. *Eur Heart J*. 2023;44.
[34] Buller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, Segers A, Verhamme P, Weitz JI. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med*. 2015;372:232–40.
[35] Weitz JI, Bauersachs R, Becker B, Berkowitz SD, Freitas MC, Lassen MR, Metzig C, Raskob GE. Effect of osocimab in preventing venous thromboembolism among patients undergoing knee arthroplasty: the FOXTROT randomized clinical trial. *J Am Med Assoc*. 2020;323:130–9.
[36] Verhamme P, Yi BA, Segers A, Salter J, Bloomfield D, Büller HR, Raskob GE, Weitz JI. Abelacimab for prevention of venous thromboembolism. *N Engl J Med*. 2021;385:2161–72.
[37] Weitz JI, Strony J, Ageno W, Gailani D, Hylek EM, Lassen MR, Mahaffey KW, Notani RS, Roberts R, Segers A, Raskob GE. Milvexian for the prevention of venous thromboembolism. *N Engl J Med*. 2021;385:2161–72.
[38] Nopp S, Kraemmer D, Ay C. Factor XI inhibitors for prevention and treatment of venous thromboembolism: a review on the rationale and update on current evidence. *Front Cardiovasc Med*. 2022;9:903029.
[39] Galli M, Laborante R, Ortega-Paz L, Franchi F, Rollini F, D'Amario D, et al. Factor XI inhibitors in early clinical trials: a meta-analysis. *Thromb Haemost*. 2023. https://doi.org/10.1055/a-2043-0346
[40] Kubitza D, Heckmann M, Distler J, Koechel A, Schwers S, Kanefendt F. Pharmacokinetics, pharmacodynamics and safety of BAY 2433334, a novel activated factor XI inhibitor, in healthy volunteers: a randomized phase 1 multiple-dose study. *Br J Clin Pharmacol*. 2022;88:3447–62.
[41] Wong PC, Crain EJ, Bozarth JM, Wu Y, Dilger AK, Wexler RR, Ewing WR, Gordon D, Luettgen JM. Milvexian, an orally bioavailable, small-molecule, reversible, direct inhibitor of factor XIa: in vitro studies and in vivo evaluation in experimental thrombosis in rabbits. *J Thromb Haemost*. 2022;20:399–408.
[42] Perera V, Wang Z, Luettgen J, Li D, DeSouza M, Cerra M, Seiffert D. First-in-human study of milvexian, an oral, direct, small molecule factor XIa inhibitor. *Clin Transl Sci*. 2022;15:330–42.
[43] Piccini JP, Caso V, Connolly SJ, Fox KA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. *Lancet*. 2022;399:1383–90.
[44] Rao SV, Kirsch B, Bhatt DL, Budaj A, Coppolecchia R, Eikelboom J, James SK, Jones WS, Merkely B, Keller L, Hermanides RS, Campo G, Ferreiro JL, Shibasaki T, Mundl H, Alexander JH. A multicenter, phase 2, randomized, placebo-controlled, double-blind, parallel-group, dose-finding trial of the oral factor XIa inhibitor asundexian to prevent adverse cardiovascular outcomes after acute myocardial infarction. *Circulation*. 2022;146:1196–206.
[45] Shoamanesh A, Mundl H, Smith EE, Masjuan J, Milanov I, Hirano T, Agafina A, Campbell B, Caso V, Mas JL, Dong Q, Turcani P, Christensen H, Ferro JM, Veltkamp R, Mikulik R, De Marchis GM, Robinson T, Lemmens R, Stepien A, et al. Factor XIa inhibition with asundexian after acute non-cardioembolic ischaemic stroke (PACIFIC-Stroke): an international, randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet*. 2022;400:997–1007.
[46] Sharma M, Molina CA, Hankey GJ. Efficacy and safety of the FXIa inhibitor milvexian for secondary stroke prevention: final results of the AXIOMATIC-SSP dose-finding randomized trial. Paper presented at European Society of Cardiology Congress, Barcelona, Spain, August 28, 2022. https://www.acc.org/latest-in-cardiology/clinical-trials/2022/08/27/04/12/axiomatic-ssp. [accessed May 22, 2023].
[47] Hutto D, Siontis GC, Noseworthy PA, Siontis KC. On-treatment follow-up in real-world studies of direct oral anticoagulants in atrial fibrillation: association with treatment effects. *Int J Cardiol Heart Vasc*. 2022;40:101024.
[48] Menichelli D, Del Sole F, Di Rocco A, Farcomeni A, Vestri A, Violi F, Pignatelli P, Lip GY, Pastori D. Real-world safety and efficacy of direct oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of 605 771 patients. *Eur Heart J Cardiovasc Pharmacother*. 2021;7:f11–9.
[49] Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM. Atlas ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9–19.
[50] Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KR, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377:1319–30.