Reshaping Anticoagulation: Factor XI Inhibition in Thrombosis Management

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Abstract

Factor XI is critical in thrombosis but almost dispensable for haemostasis. By specifically targeting factor XI, factor XI inhibitors have the potential to protect patients against thrombosis without increasing the risk of serious bleeding. Multiple strategies to inhibit factor XI have been developed with different pharmacokinetic characteristics, advantages and disadvantages. Phase 2 trials have affirmed the improved safety profile of factor XI inhibitors and have established their efficacy in preventing venous thromboembolism after major orthopaedic surgery. However, their efficacy in other clinical indications, such as atrial fibrillation, end-stage renal disease, treatment of venous thromboembolism and secondary prevention after acute myocardial infarction and ischemic stroke, remains to be elucidated. Several phase 3 trials are currently underway. This review explains the rationale for factor XI inhibition as anticoagulant strategy and provides an overview of the various factor XI inhibitors and the ongoing clinical trials in different clinical indications.

Keywords
► factor XI inhibition
► factor XI inhibitors
► thrombosis
► bleeding
► FXI

Zusammenfassung

Faktor XI spielt eine entscheidende Rolle bei der Thrombose, ist jedoch für die Hämostase nahezu entbehrlich. Die gezielte Beeinflussung von Faktor XI könnte daher dazu beitragen, Thrombose von der Hämostase zu trennen. Diese Übersichtsarbeit erläutert die zugrunde liegenden Mechanismen von Thrombose und Hämostase und erläutert die Begründung für die Verwendung von Faktor-XI-Inhibitoren auf der Grundlage der Pathophysiologie sowie epidemiologischer und präklinischer Daten. Darüber hinaus werden die vielfältigen Ansätze zur Faktor-XI-Inhibition beschrieben. Schließlich bietet der Artikel einen umfassenden Überblick über die bestehenden klinischen Belege für Faktor-XI-Inhibitoren in verschiedenen klinischen Kontexten und stellt eine Übersicht über laufende Studien bereit.

Schlüsselwörter
► Faktor-XI-Inhibition
► Faktor-XI-Inhibitoren
► FXI
► Thrombose
► Blutung

Introduction

The coagulation system plays a pivotal role in our survival, as it ensures haemostasis. However, dysfunction of this complex cascade poses a significant risk and can lead to thrombotic and bleeding disorders. Thrombosis underlies conditions such as venous thromboembolism (VTE), ischemic stroke and myocardial infarction, which are leading causes of morbidity and mortality worldwide.[1] Anticoagulant therapy can reduce the burden of thrombosis but exposes the patient to an increased and potentially fatal risk of bleeding. Over the past decade, direct oral anticoagulants (DOACs) have replaced vitamin K antagonists (VKAs) for most indications for anticoagulation due to their similar or even better efficacy and fewer bleeding

events, particularly less intracranial haemorrhages.[2–4] Additional advantages in favour of DOACs include their fixed-dose administration, faster onset and offset, fewer interactions with food and drugs and no need for routine laboratory monitoring.

Nevertheless, despite their improved safety profile, DOACs still carry a notable risk of bleeding, with an annual major bleeding risk in patients with atrial fibrillation (AF) ranging from 2 to 4% and a case-fatality rate for major bleeding of ∼8%.[4–8] The fear of bleeding leads to undertreatment because of reluctance to start anticoagulant therapy or inappropriate underdosing. Therefore, the need for safer anticoagulants persists.
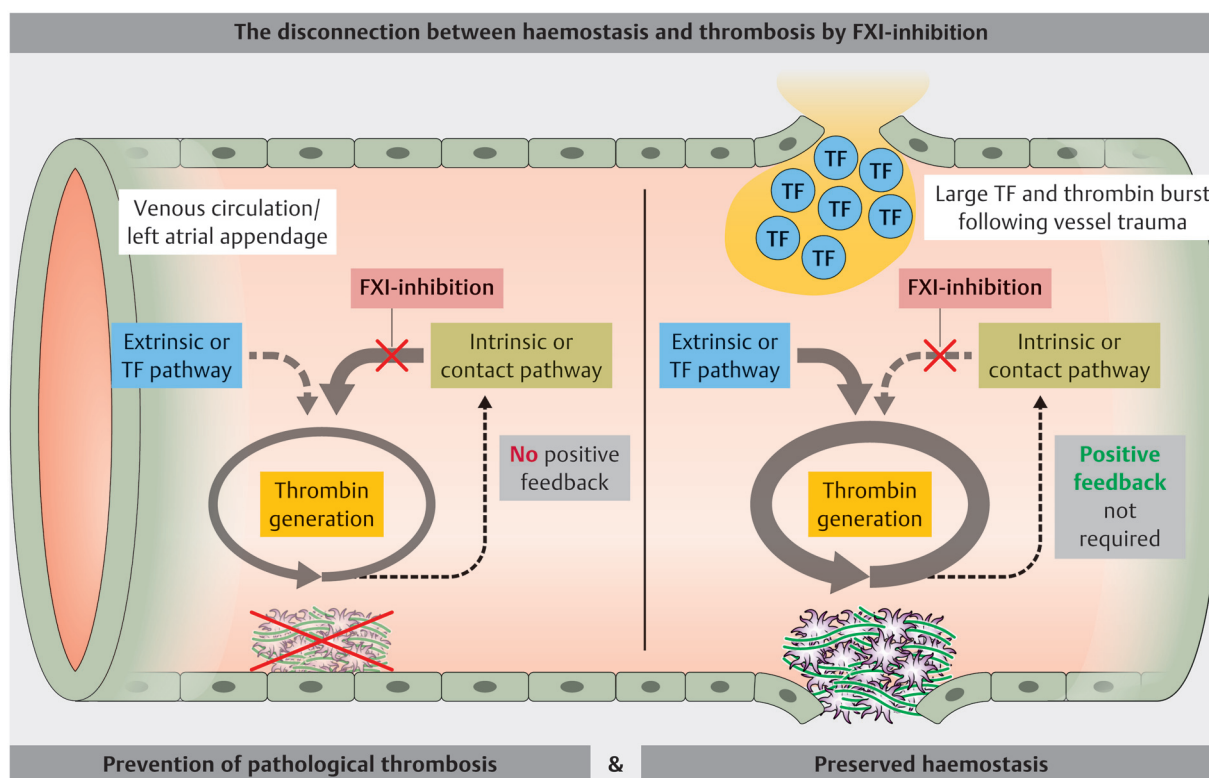
Targeting Factor XI to Uncouple Thrombosis and Haemostasis

Factor XI in Thrombosis and Haemostasis

Thrombosis and haemostasis were traditionally viewed as separate outcomes from a single process, as they share many coagulation proteins. Consequently, bleeding has been considered an unwanted, yet inevitable side-effect of antithrombotic drugs. However, in recent years, there has been a growing understanding that the mechanisms behind thrombosis and haemostasis are somewhat different and that targeting factor XI (FXI) could be able to differentiate the thrombosis from the haemostasis pathway (►Fig. 1).

Haemostasis is a physiologic process that protects against ongoing bleeding from damaged blood vessels by the formation of an appropriate extravascular haemostatic plug to seal the defect within the vessel wall. The initiation of haemostasis relies on the exposure of subendothelial tissue factor at the site of blood vessel injury, leading to the formation of the extrinsic tenase complex comprising FVIIa and tissue factor (extrinsic coagulation pathway). Subsequently, this complex activates FX into FXa, which converts a limited amount of prothrombin into thrombin, the key coagulation enzyme. The extrinsic tenase complex also activates FIX, ensuring further activation of FX. As the thrombus grows and seals the site of injury, the extrinsic tenase complex becomes unable to sustain thrombin generation, thus preventing further propagation beyond the damaged area. However, thrombin-mediated activation of FIX and FXI amplifies this cascade and contributes to the consolidation of the physiological blood clots.

Thrombosis is a pathological condition where the inappropriate formation of intraluminal thrombi partially or completely blocks blood flow in arteries and veins, leading to organ damage. Unlike in haemostasis, the amplification of the coagulation cascade via FXI is essential for venous and arterial thromboembolism. The continued growth and spread of thrombi beyond the injury site depend on the activation of FXI. This activation can occur through two

Fig. 1 Targeting factor XI (FXI) to uncouple thrombosis and haemostasis. Haemostasis is initiated when large amounts of subendothelial tissue factor (TF) become exposed at damaged blood vessels. Thrombin generation primarily relies on the activation of the extrinsic coagulation cascade via TF and FVIIa. Amplification of thrombin generation by thrombin-mediated activation of FXI is not required for haemostasis, but only contributes to the consolidation of physiological blood clots. However, the amplification of thrombin generation by FXIa is crucial for thrombosis. FXI is either activated backward by thrombin resulting from exposure of low concentrations of TF on diseased endothelium, or by FXIIa after contact with foreign surfaces. Thus, FXI inhibitors can attenuate thrombosis with minimal to no impact on haemostasis.

distinct pathways. Usually, FXI is activated backward by thrombin generated via the extrinsic coagulation pathway. FXI can also be activated by FXIIa after contact with foreign surfaces, such as in haemodialysis, mechanical valves, or extracorporeal membrane oxygenation (intrinsic coagulation pathway).

Preclinical Evidence for Factor XI Inhibition

The role of FXI in thrombosis and the subsequent interest in using it as a target for anticoagulation emerged primarily from epidemiological studies that identified a correlation between FXI levels and the risk of thrombosis. Around the turn of the century, Meijers et al were the first to document a substantial increase in FXI levels in patients with VTE compared with those without VTE.[9] Subsequent research has further reported elevated FXI levels in individuals with both VTE and stroke.[10,11] Conversely, observational studies have reported a reduced occurrence of VTE and stroke in individuals with FXI deficiency.[12–15] Moreover, individuals with severe congenital FXI deficiency, known as haemophilia C, infrequently experience spontaneous bleeding. Bleeding episodes are typically triggered by trauma and primarily affect tissues characterized by elevated fibrinolytic activity, such as the nasopharynx and the urinary tract.[16] These data support that FXI is a key player in thrombosis, but almost dispensable in haemostasis.

Beyond epidemiological data, further support for the development of FXI inhibitors stemmed from animal research. In a mouse model involving ferric chloride-induced carotid artery thrombosis, FXI knockout mice showed complete protection against carotid occlusion.[17] Nonetheless, FXI-deficient and wild-type mice displayed comparable bleeding times in a tail bleeding time assay.[17] Subsequent research in primates demonstrated the antithrombotic effect of various modes of FXI inhibition without an increased risk of bleeding, which prompted further clinical research.[18,19]

Modes of Factor XI Inhibition

Several drugs have been developed to target FXI, each with its specific mode of action, pharmacological characteristics, advantages and disadvantages (►Table 1).

Natural Inhibitors

There exist several natural inhibitors of FXIa. The Ixodes Ricinus contact pathway inhibitor (Ir-CPI) is isolated from the salivary glands of the tick *Ixodes ricinus* and is a natural inhibitor of FXIIa and FXIa. Preclinical animal studies have demonstrated the promising antithrombotic potential of Ir-CPI.[20,21] Fasxiator, derived from the venom of the banded krait snake, serves as a natural inhibitor of FXI. In a murine

Table 1 Overview of different FXI inhibitors

	Monoclonal antibodies	Antisense oligonucleotides	Small molecules	Aptamers
Mechanism of action	Block FXI activation or FXIa activity	Degrade FXI mRNA and reduce FXI biosynthesis	Block FXIa activity	Block FXI activation or FXIa activity
Administration	IV or SC	SC	IV or PO	IV or SC
Onset	Hours	Weeks	Minutes to hours	Minutes to hours
Offset	Weeks	Weeks	Minutes to hours	Minutes to hours
Renal clearance	No	No	Yes	No
Hepatic metabolism	No	No	Yes	No
Examples	Abelacimab, xisomab, osocimab, MK-2060	IONIS-FXI$_{Rx}$ and FXI-LICA	Asundexian and milvexian	FELIAP, 12.7, 11.16
Clinical consequences	+ ↑ Compliance due to infrequent dosing + No need for bridging + Usage in ESRD + ↓ Risk for drug interactions − Slow reversal if bleeding or surgery	+ ↑ Compliance due to infrequent dosing + Usage in ESRD + ↓ Risk for drug interactions − Slow reversal if bleeding or surgery − Need for bridging	+ PO availability + No need for bridging + Fast reversal if bleeding or surgery − ↓ Compliance due to daily dosing − Dose adjustments or no use in ESRD − ↑ Risk for drug interactions	+ No need for bridging + Fast reversal if bleeding or surgery + Usage in ESRD + ↓ Risk for drug interactions − ↓ Compliance due to daily dosing

Abbreviations: ESRD, end-stage renal disease; FXI, factor XI; IV, intravenous; SC, subcutaneous; PO, per os.

model of induced carotid artery thrombosis, fasxiator significantly extended the occlusion time of the carotid artery.[22]

Monoclonal Antibodies

Similar to other areas in medicine, monoclonal antibodies targeting various coagulation factors have also been developed as anticoagulants.[23,24] The antibodies targeting FXI exert a neutralizing effect: they either block FXI activation or FXIa activity. Several drugs are under development and have already been tested in phase 2 clinical trials, including abelacimab (MAA868), xisomab (AB023) and osocimab (BAY 1213790).[25–27] Like all monoclonal antibodies, they require parenteral administration. Monoclonal antibodies offer a rapid onset of action, particularly when administered intravenously, but their effects wane more gradually due to an extended half-life, which allows less frequent administration. The slow offset of action may raise concerns if these long-acting drugs would increase life-threatening bleeding. Nonetheless, current and ongoing clinical trials have yielded no such evidence yet.[25–27] It is noteworthy that monoclonal antibodies do not depend on hepatic or renal function for their metabolism and excretion, which holds promise for patients with end-stage renal disease (ESRD) or patients susceptible to drug interactions. Instead, their degradation depends on phagocytic cells and the reticuloendothelial system.

Antisense Oligonucleotides and Silencing RNA

Antisense oligonucleotides (ASOs) and small interfering RNA (siRNA) interfere with the translation of FXI in the liver. ASOs are short, single-stranded oligonucleotides that specifically attach to complementary FXI messenger RNA (mRNA) within the liver. This binding triggers the degradation of FXI mRNA, subsequently leading to a decrease in FXI synthesis by the liver. Examples currently under investigation encompass IONIS-FXI$_{Rx}$ (BAY 2306001) and FXI-LICA (fesomersen or BAY 2976217).[28,29] In contrast to monoclonal antibodies, their onset is gradual, reflecting their influence on FXI biosynthesis. Their offset is slow owing to a long half-life. Like monoclonal antibodies, ASOs require parenteral administration and do not rely on hepatic metabolism and renal excretion. An additional benefit is their lower drug design cost compared with monoclonal antibodies.

Small Molecules

Small molecules are chemical compounds designed to target the active domains of human proteins, thereby inhibiting their functions. Similar to the small molecule thrombin inhibitors (dabigatran) and FXa inhibitors (apixaban, edoxaban and rivaroxaban), small molecules that block the active site of FXIa have also been developed. Currently, the two best-studied small molecules in humans are asundexian (BAY 2433334) and milvexian (BMS-986177).[30,31] These compounds exhibit good oral bioavailability, enabling oral delivery instead of parenteral administration. Their pharmacological profile resembles that of thrombin and FXa inhibitors, featuring a rapid onset and offset of action. This necessitates daily administration, yet facilitates ease of in-terruption in cases of bleeding or perioperative settings. Unlike monoclonal antibodies and ASOs, small molecules undergo hepatic CYP3A4 metabolism and are excreted by the kidneys requiring evaluation for drug interactions and dose adjustments in patients with impaired kidney function. Compared with oligonucleotides and antibody-based drugs, small molecules tend to be more stable and less costly to produce.

Aptamers

Aptamers are single-stranded oligonucleotides (DNA or RNA) that bind to target proteins or nucleic acids with high affinity and selectivity. While aptamers targeting FXI and/or FXIa have been developed (FELIAP, 12.7 and 11.16), no human studies have been conducted thus far.[32,33] They necessitate daily administration, either subcutaneously or intravenously, due to their rapid onset and offset of action. Importantly, they do not undergo hepatic metabolism and renal excretion.

Current Evidence for Factor XI Inhibition

Presently, the safety and efficacy of FXI inhibitors are being evaluated in six distinct clinical areas: prevention of VTE after major orthopaedic surgery, ESRD, AF, non-cardioembolic stroke, acute myocardial infarction and cancer-associated VTE. To date, only a limited number of phase 2 studies have been published, while phase 3 trials are underway (►Table 2). This article provides an overview of the existing evidence of FXI inhibition within these clinical contexts.

Total Knee Arthroplasty

A proof-of-concept study with a novel anticoagulant is typically conducted in patients undergoing elective total knee arthroplasty (TKA). This approach is highly efficient for evaluating the safety and efficacy of anticoagulants, primarily due to the high risk of VTE following orthopaedic surgery and the possibility for objective evaluation of (sub-)clinical lower extremity deep vein thrombosis using venography. Currently, four phase 2 randomized trials employing various modes of FXI inhibition have been completed.

Current Evidence

In the FXI-ASO TKA trial of 2015, two subcutaneous doses of the ASO IONIS-FXI$_{Rx}$ (200 and 300 mg, initiated 36 days before surgery) were compared with 40 mg of enoxaparin in 300 patients.[34] Both doses of IONIS-FXI$_{Rx}$ effectively lowered FXI levels and demonstrated non-inferiority to enoxaparin in thromboprophylaxis. Notably, the highest dose (300 mg) exhibited superiority in preventing VTE, as detected with mandatory venogram post-operatively (4% with 300 mg IONIS-FXI$_{Rx}$ vs. 30% with enoxaparin, $p < 0.001$). There was a non-significant trend for less bleeding in the IONIS-FXI$_{Rx}$ group (3% with both doses vs. 8% with enoxaparin).

In the FOXTROT trial, which included 800 TKA patients, various pre- and postoperative doses of the monoclonal antibody osocimab (administered as a single intravenous dose) were compared against enoxaparin and apixaban.[26] The three highest postoperative doses of osocimab (0.6, 1.2

Table 2 Overview of phase 2 and 3 clinical trials with FXI inhibitors

Trial	Sample, n	Intervention	Control	Primary endpoints	Follow-up
Prevention of VTE—TKA					
Phase 2: completed					
- FXI-ASO TKA[34]	300	IONIS-FXI$_{Rx}$	Enoxaparin	(sub-)clinical VTE	8–12 d post-TKA
- FOXTROT[26]	813	Osocimab	Enoxaparin	(sub-)clinical VTE	10–13 d post-TKA
- ANT-005 TKA[25]	412	Abelacimab	Enoxaparin	(sub-)clinical VTE	8–12 d post-TKA
- AXIOMATIC-TKR[31]	1,242	Milvexian	Enoxaparin	(sub-)clinical VTE	10–14 d post-TKA
AF					
Phase 2: completed					
- PACIFIC-AF[30]	755	Asundexian	Apixaban	Major or CRNM bleeding	12 wk
- AZALEA-TIMI 71[39]	1,287	Abelacimab	Rivaroxaban	Major or CRNM bleeding	21 mo
Phase 3: ongoing					
- LILAC-TIMI 76[40]	1,900	Abelacimab	Placebo	Ischemic stroke or SE; major bleeding	30 mo
- OCEANIC-AF[41]	18,000	Asundexian	Apixaban	Stroke, SE; major bleeding	34 mo
- LIBREXIA-AF[42]	15,500	Milvexian	Apixaban	Stroke, SE	48 mo
ESRD					
Phase 2: completed					
- Lorentz et al[27]	24	Xisomab 3G3	Placebo	AE (incl. bleeding)	21 d
- Walsh et al[28]	43	IONIS-FXI$_{Rx}$	Placebo	AE (incl. bleeding)	23 wk
- EMERALD[45]	213	IONIS-FXI$_{Rx}$	Placebo	Major or CRNM bleeding	9 mo
- RE-THINc-ESRD[29]	307	Fesomersen	Placebo	Major or CRNM bleeding	6 mo
- CONVERT[46]	704	Osocimab	Placebo	Major, CRNM bleeding; AE	6 mo
Phase 2: ongoing					
- MK-2060-007[47]	489	MK-2060	Placebo	AV graft thrombosis	34 mo
Non-cardioembolic stroke					
Phase 2: completed					
- PACIFIC-STROKE[49]	1,808	Asundexian	Placebo	Ischemic stroke or covert infarcts	6 mo
- AXIOMATIC-SSP[50]	2,366	Milvexian	Placebo	Ischemic stroke or covert infarcts	3 mo
Phase 3: ongoing					
- OCEANIC-STROKE[51]	9,300	Asundexian	Placebo	Ischemic stroke; major bleeding	31 mo
- LIBREXIA-STROKE[52]	15,000	Milvexian	Placebo	Ischemic stroke	41 mo
ACS					
Phase 2: completed					
- PACIFIC-AMI[56]	1,601	Asundexian	Placebo	Major or CRNM bleeding; MACE	12 mo
Phase 3: ongoing					
- LIBREXIA-ACS[57]	16,000	Milvexian	Placebo	MACE	42 mo
Treatment of VTE—cancer					
Phase 3: ongoing					
- ASTER[58]	1,655	Abelacimab	Apixaban	VTE recurrence	6 mo
- MAGNOLIA[59]	1,020	Abelacimab	Dalteparin	VTE recurrence	6 mo

Abbreviations: ACS, acute coronary syndrome; AE, adverse events; AF, atrial fibrillation; AV, arteriovenous; CRNM, clinically relevant non-major; ESRD, end-stage renal disease; MACE, major adverse cardiovascular events; TKA, total knee arthroplasty; SE, systemic embolism; VTE, venous thromboembolism.

and 1.8 mg/kg) were non-inferior to enoxaparin in preventing (sub-)clinical VTE, and the highest pre-operative dose (1.8 mg/kg) demonstrated superiority. There were no significant differences for VTE prevention between the osocimab and apixaban group. Major or clinically relevant non-major bleeding occurred in 4.7% of those receiving

osocimab, 5.9% receiving enoxaparin and 2% receiving apixaban.

In the ANT-005 TKA trial involving 400 patients, various postoperative doses (30, 75, 150 mg) of the monoclonal antibody abelacimab (administered as a single intravenous dose) were compared with enoxaparin.[25] All doses of abelacimab were effective in preventing VTE after TKA, and the two highest doses were superior to enoxaparin (5% VTE with 75 mg abelacimab and 4% VTE with 150 mg abelacimab vs. 22% VTE with enoxaparin, $p < 0.001$). No significant differences in bleeding events were observed.

In the AXIOMATIC-TKR trial, seven different regimens of the oral small molecule milvexian were compared with enoxaparin.[31] All milvexian regimens effectively prevented VTE, and a significant dose–response relationship was observed with twice-daily milvexian. The incidence of bleeding events was similar between the milvexian group (4%) and the enoxaparin group (4%).

Two meta-analyses of the four randomized controlled trials validate the previously mentioned outcomes: FXI inhibitors demonstrate a significant reduction in both VTE (with odds ratios ranging from 0.50 to 0.59) and bleeding incidents (with an odds ratio of 0.41) in comparison to low-molecular-weight heparin following TKA.[35,36] No phase 3 trials are currently undertaken within the field of VTE prevention.

Atrial Fibrillation

AF is the most prevalent cardiac arrhythmia and contributes significantly to global morbidity and mortality. The lifetime risk of developing AF among men and women aged 40 and older is estimated at 1 in 4.[37] While anticoagulants protect against the inherent risk of stroke and thromboembolism in AF, it is essential to acknowledge that this risk is not reduced to zero. Real-world data from over 30,000 AF patients under DOAC treatment reveal a consistent 1-year risk of stroke and thromboembolism ranging from 1.7 to 2.8%.[38] Furthermore, anticoagulation therapy is still associated with a substantial risk of bleeding, with an annual major bleeding risk ranging from 2 to 4%, and an (anticipated) risk of bleeding is the most important reason for not treating patients with anticoagulants.[5–8] Consequently, clinical studies evaluating the efficacy and safety of FXI inhibition in the context of AF are of clinical importance.

Current Evidence

The PACIFIC-AF trial is the first completed randomized trial exploring FXI inhibitors in AF.[30] This dose-finding study included 750 AF patients at increased bleeding risk. Participants were randomly assigned to one of three regimens: either asundexian 20 or 50 mg once daily, or apixaban 5 mg twice daily. Both doses of asundexian effectively inhibit FXIa activity. Additionally, therapy with asundexian resulted in lower bleeding events compared with apixaban, with a ratio of incidence proportion of 0.33 (90% confidence interval [CI]: 0.09–0.97) for pooled asundexian versus apixaban. However, the CIs were wide and the number of bleeding events was limited (four in the asundexian group and six in the apixaban group).

The second phase 2 study is the AZALEA-TIMI 71 trial.[39] Here, two subcutaneous doses of abelacimab (90 or 150 mg once monthly) were compared with rivaroxaban (20 mg once daily) in 1,200 patients at moderate-to-high stroke risk. The primary endpoint was the incidence of major and clinically relevant non-major bleeding over an average 17-month follow-up. The study was halted prematurely by the data monitoring committee after a significant reduction in major and clinically relevant non-major bleeding was observed in both abelacimab groups compared with the rivaroxaban group (incidence rate 2.7% for abelacimab 150 mg, 1.9% for abelacimab 90 mg and 8.1% for rivaroxaban, $p < 0.001$ for both doses of abelacimab vs. placebo). Gastrointestinal bleeding, the predominant bleeding with DOACs, was nearly eradicated with abelacimab with an incidence rate of 0.1% in both abelacimab groups compared with 2.1% in the rivaroxaban group ($p < 0.05$). There were no significant differences in stroke or systemic embolism; however, the overall incidence rate was low (1.1% for abelacimab 150 mg, 1.4% for abelacimab 90 mg and 1.0% for rivaroxaban).

Both completed phase 2 trials were not designed to look at the efficacy of FXI inhibitors. Despite the strong and growing suggestion of improved safety, the efficacy of FXI inhibition in the context of AF remains uncertain. Further clinical studies are imperative to address this crucial question and to determine the place of FXI inhibitors in patients with AF.

Ongoing Trials

Multiple phase 3 trials are ongoing to elucidate the role for FXI inhibitors in patients with AF. The LILAC-TIMI 76 trial (NCT05712200) is evaluating the efficacy and safety of abelacimab (150 mg once monthly) versus placebo in AF patients over 65 years who are deemed unsuitable for anticoagulation.[40] In the OCEANIC-AF trial (NCT05643573) and the LIBREXIA-AF trial (NCT05757869), asundexian and milvexian, respectively, are being compared with apixaban for the prevention of stroke and systemic embolism in AF.[41,42]

End-Stage Renal Disease

From all large-scale randomized trials comparing DOACs with VKAs, it has become evident that patients with chronic kidney disease face increased risks of both thrombotic and bleeding complications.[43,44] The elevated thrombotic risk results from the combination of a hypercoagulable state (increased prothrombotic blood constituents and increased blood platelet activity), deranged haemodynamics (chronic RAAS activation and altered vessel wall contractility) and vessel wall injury (arteriosclerosis and vascular remodelling). Several factors also contribute to the increased bleeding risk: decreased drug clearance, dysfunctional blood platelets from accumulation of uremic toxins and exposure to invasive procedures such as haemodialysis. Yet, many patients with chronic kidney disease require anticoagulation, such as those with AF or undergoing haemodialysis. Currently, there is little evidence supporting DOACs in ESRD. Alternative anticoagulants like (low-molecular weight) heparin and VKAs have their own limitations, including heparin-induced thrombocytopenia, hypertriglyceridemia and osteoporosis, and VKA-related calcification and nephropathy.

By tackling thrombotic complications with minimal impact on bleeding, FXI inhibitors are particularly promising for patients with ESRD.

Current Evidence

Two small phase 2 studies have been reported, examining FXI inhibitors in haemodialysis-dependent ESRD patients. In a first small phase 2 trial ($n = 24$), two doses of the monoclonal antibody xisomab 3G3 (0.25 mg/kg or 0.5 mg/kg) reduced clot formation within the dialyzer while preserving normal haemostasis.[27] Similarly, another small phase 2 study ($n = 43$) evaluated two doses of the ASO IONIS-FXI$_{Rx}$ (200 or 300 mg) against placebo. IONIS-FXI$_{Rx}$ significantly reduced FXI activity with similar major bleeding events across the groups (0 with 200 mg IONIS-FXI$_{Rx}$, 1 with 300 mg IONIS-FXI$_{Rx}$ and 1 with placebo).[28]

Several other phase 2 randomized clinical trials have been completed in ESRD, of which only preliminary results are available at this time. The EMERALD trial (NCT03358030) examined IONIS-FXI$_{Rx}$'s safety, pharmacokinetics and pharmacodynamics in more than 200 patients requiring haemodialysis.[45] Preliminary results reveal incidence of major and clinically relevant non-major bleeding of 3.8, 5.6, 6.0 and 5.6% in the IONIS-FXI$_{Rx}$ 200-, 250- and 300-mg group and the placebo group, respectively. Likewise, fesomersen was investigated in the RE-THINc-ESRD trial (NCT04534114) involving more than 300 patients.[29] The incidence of major or clinically relevant non-major bleeding at 10 months was 4.0% with placebo, 6.5% with fesomersen 40 mg, 5.1% with fesomersen 80 mg and 3.9% with fesomersen 120 mg. Lastly, in the CONVERT trial (NCT04523220), the safety of two doses of the monoclonal antibody osocimab was evaluated.[46] Clinically, relevant bleeding occurred in 6.9% of the low-dose osocimab group (loading dose of 105 mg followed by monthly doses of 52.5 mg), 4.9% in the high-dose osocimab group (loading dose of 210 mg followed by monthly doses of 105 mg) and 7.8% in the placebo arm.

Overall, the preliminary data suggest that bleeding rates with ASOs and monoclonal antibodies are comparable to placebo-treated patients, with a tendency toward a lower incidence of dialysis circuit clotting in the intervention group. Nevertheless, more extensive and comprehensive clinical trials are necessary to draw a definitive conclusion about their efficacy.

Ongoing Trials

The MK-2060-007 trial (NCT05027074) is investigating the efficacy of the monoclonal antibody MK-2060 in preventing arteriovenous graft thrombosis compared with placebo in patients with ESRD receiving haemodialysis.[47]

Non-cardioembolic Stroke

Non-cardioembolic ischemic stroke, which includes stroke resulting from large artery atherosclerosis, small vessel disease, or of undetermined cause (cryptogenic), accounts for around 75% of all stroke cases.[48] With the current strategies for secondary prevention after non-cardioembolic stroke, the risk of recurrence is high, with a 10-year cumulative incidence ranging from 11% to as high as 21%.[48] Given this suboptimal prevention, elevated FXI activity in stroke patients and the potential for a reduced risk of haemorrhagic transformation, FXI inhibitors are also explored in this context.[10]

Current Evidence

Two double-blind, randomized phase 2 trials have already been completed. In the PACIFIC-STROKE trial, a study involving 1,800 patients who experienced an acute non-cardioembolic stroke (within 48 hours of onset), different dosages of asundexian (10, 20, or 50 mg once daily) were compared with placebo in addition to standard antiplatelet therapy.[49] Over a 6-month follow-up, the incidence of covert, MRI-detected brain infarction and recurrent ischemic stroke did not show significant differences between the groups. This outcome was largely driven by the lack of reduction in incident covert brain infarctions, which constituted 75% of the primary outcome events. However, in a post hoc analysis, the highest dose of asundexian (50 mg) demonstrated a significant reduction in the composite of recurrent transient ischemic attack or recurrent symptomatic stroke. Additionally, asundexian did not increase the risk of bleeding. Likewise, the AXIOMATIC-SSP trial examined five doses of milvexian compared with placebo in patients with recent stroke on dual antiplatelet therapy.[50] Similar to the findings in the PACIFIC-STROKE trial, milvexian did not decrease the incidence of symptomatic ischemic stroke and covert brain infarction at 90 days. However, a post hoc analysis indicated a potential trend toward reduced symptomatic ischemic stroke in the intention-to-treat population for all doses of milvexian except for the 200-mg twice-daily regimen. Milvexian did not elevate the bleeding risk compared with placebo.

These studies offer further support for the safety of a FXI inhibition strategy, with comparable bleeding rates as placebo on top of a background treatment of antiplatelet therapy. Nevertheless, the efficacy of FXI inhibition in secondary prevention following non-cardioembolic stroke remains uncertain. It may be prudent for future studies to concentrate solely on assessing the impact on symptomatic stroke recurrence, as the genuine clinical significance of covert MRI-detected brain infarctions is still not fully understood.

Ongoing Trials

Two major phase 3 randomized trials are actively recruiting patients to provide additional insights into the efficacy and safety of asundexian (OCEANIC-STROKE, NCT05686070) and milvexian (LIBREXIA-STROKE, NCT05702034) for secondary prevention after an acute non-cardioembolic stroke or high-risk transient ischemic attack.[51,52] In both trials, the oral FXI inhibitor is compared with placebo in addition to standard antiplatelet therapy. The OCEANIC-STROKE trial aims to enrol 9,300 patients with an intended follow-up of 31 months. In the LIBREXIA-STROKE trial, the objective is to follow up 15,000 patients during 41 months. The primary efficacy outcome for both trials is the time to first occurrence of ischemic stroke.

Acute Myocardial Infarction

Despite the growing attention and advancements in primary and secondary prevention of cardiovascular disease, ischemic heart disease remains the leading global cause of death.[1] Even with optimal treatment following the initial acute myocardial infarction, there continues to be a significant risk for recurrent myocardial infarction, with a 7-year cumulative incidence of ~15%.[53] Major randomized controlled trials have already shown that a more intensive antithrombotic therapy, involving the addition of rivaroxaban to single or dual antiplatelet therapy, leads to improved cardiovascular outcomes in both patients with stable atherosclerotic vascular disease or a recent acute coronary syndrome.[54,55] However, this improved efficacy comes at the cost of an increased risk of major bleeding.

Current Evidence

As of now, only the PACIFIC-AMI trial has explored FXI inhibition in this specific area.[56] In this trial, patients who recently suffered a myocardial infarction (within 5 days) and were already on dual antiplatelet therapy were randomly divided into two groups. One group received various daily doses of oral asundexian (10, 20, or 50 mg), while the other received placebo for 6 to 12 months. Adding asundexian to dual antiplatelet therapy resulted in a dose-dependent inhibition of FXIa activity without an increase in the risk of bleeding (OR: 0.98, 90% CI: 0.71–1.35 for pooled asundexian vs. placebo). Overall, the rate of ischemic events was low and similar across groups. Although these results hold potential, further phase 3 trials are needed.

Ongoing Trials

Currently, there is one phase 3 program investigating the role of FXI inhibitors in the secondary prevention after an acute myocardial infarction. The LIBREXIA-ACS trial will randomize 16,000 patients within 7 days after an acute coronary syndrome and compare the efficacy and safety of milvexian to placebo in addition to standard-of-care single or dual antiplatelet therapy.[57] The intended follow-up duration extends to 42 months. The primary endpoint is the time to first occurrence of major adverse cardiovascular events.

Treatment of Venous Thromboembolism

Currently, the treatment of VTE with FXI inhibition is evaluated only in cancer patients, a well-known risk factor for VTE. While no phase 2 trials involving FXI inhibitors have been completed in the treatment of VTE, two phase 3 trials are currently underway to assess the efficacy and safety of abelacimab (150 mg once monthly) in patients with active cancer and confirmed VTE. The ASTER trial (NCT05171049, $n = 1,655$) involves a comparison between abelacimab (150 mg, once monthly) and apixaban (10 mg followed by 5 mg, twice daily) for the management of VTE and the prevention of recurrence in patients with non-skin cancer.[58] The MAGNOLIA trial (NCT05171075, $n = 1,020$) evaluates abelacimab (150 mg, once monthly) against dalteparin in patients with gastrointestinal or genitourinary cancers, which are typically associated with a higher risk of bleeding when treated with DOACs.[59]

Further Considerations and Conclusion

Monitoring

All different FXI inhibitors impact on the activated partial thromboplastin time (aPTT) without affecting the prothrombin time (PT), underscoring their specificity for the intrinsic coagulation pathway. Nonetheless, there is no apparent correlation between the extent of aPTT prolongation and the intensity of the anticoagulant effect. Therefore, relying on aPTT to monitor the anticoagulant effect is not a viable approach. The measurement of FXI levels can be useful to monitor the effects of ASOs and siRNA. Anti-FXIa assays could be developed to monitor the small molecules and antibodies, similar to the anti-FXa assays currently used for DOACs targeting FXa.

Management of Bleeding with Factor XI Inhibitors

While epidemiological data and phase 2 trials suggest that reducing FXI activity has a limited effect on haemostasis, some patients under FXI inhibitors will still experience abnormal bleeding or necessitate urgent surgery. At present, there are no available antidotes to reverse the effect of FXI inhibitors. Based on their experience in managing bleeding in FXI-deficient patients, Salomon and Gailani proposed a strategy for dealing with acute bleeding under FXI inhibitors.[60] In cases of non–life-threatening bleeding, local measures and antifibrinolytic agents, such as tranexamic acid, are considered sufficient. For severe or life-threatening bleeding, they recommend the administration of recombinant FVIIa alongside antifibrinolytic agents to enhance haemostasis via mechanisms independent of FXI.

Conclusion

Never before has a class of anticoagulant drugs shown such positive results in the prevention of VTE following major orthopaedic surgery. Historically, successful phase 2 trials in the prevention of VTE were always followed by successful programs in AF and treatment of VTE. Phase 2 studies show a more favorable safety profile of FXI inhibitors compared with current anticoagulants. However, at this time, it remains unclear whether the efficacy of FXI inhibitors will extend beyond the domain of VTE prevention and whether they will be effective in preventing arterial thrombosis. Phase 3 trials with asundexian, milvexian and abelacimab are underway to address these questions in the area of AF, secondary prevention after non-cardioembolic ischemic stroke and treatment of cancer-associated VTE.

Authors' Contribution

A.V. reviewed the literature, wrote the manuscript, designed the tables and made adjustments according to the suggestions of the co-authors. C.V.E. designed the figure. P.V. supervised this paper. M.M.E., T.V, C.V.E. and P.V. critically reviewed the manuscript.

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