ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΘΕΡΑΠΕΥΤΙΚΗ ΚΛΙΝΙΚΗ ΝΟΣ. ΑΛΕΞΑΝΔΡΑ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΚΛΙΝΙΚΕΣ ΜΕΛΕΤΕΣ: ΣΧΕΔΙΑΣΜΟΣ ΚΑΙ ΕΚΤΕΛΕΣΗ»

MSc: "Clinical Trials: Design and Conduct"

Διευθυντής
Ευάγγελος Τέρπος, Καθηγητής Ιατρικής Σχολής ΕΚΠΑ

Τίτλος ΜΔΕ: «Ο ρόλος των αναστολέων του παράγοντα XI στην πρόληψη θρομβοεμβολικών επεισοδίων»

«The role of factor XI inhibitors in the prevention of thromboembolic events»

Όνομα: Δέσποινα-Ραφαηλία Μπενέτου

Αρ. μητρώου: 7450492200030

Επάγγελμα: Ιατρός

Επιβλέπων καθηγητής ΜΔΕ: Μπριασούλης Αλέξανδρος, Επίκουρος Καθηγητής Θεραπευτικής Καρδιολογίας, Ιατρική Σχολή Ε.Κ.Π.Α.

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<u>Τα Μέλη της Εξεταστικής Επιτροπής</u>

Επιβλέπων: Μπριασούλης Αλέξανδρος, Επίκουρος Καθηγητής Ιατρική Σχολής Ε.Κ.Π.Α.

Γαβριατοπούλου Μαρία, Αναπληρώτρια Καθηγήτρια Ιατρικής Σχολής Ε.Κ.Π.Α.

Τέρπος Ευάγγελος, Καθηγητής Αιματολογίας, Ιατρική Σχολή Ε.Κ.Π.Α.

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ΠΡΟΛΟΓΟΣ - ΕΥΧΑΡΙΣΤΙΕΣ

Η παρούσα Μεταπτυχιακή Διπλωματική Εργασία (ΜΔΕ) πραγματοποιήθηκε σε συνεργασία με τον Επίκουρο Καθηγητή κ. Αλέξανδρο Μπριασούλη, τον οποίο και ευχαριστώ για τα σχόλια και την καθοδήγηση κατά τη συγγραφή της. Επιπλέον, θα ήθελα να ευχαριστήσω τον Καθηγητή κ. Ευάγγελο Τέρπο για την ευκαιρία να συμμετάσχω στο συγκεκριμένο Πρόγραμμα Μεταπτυχιακών Σπουδών, καθώς και την κα Μαρία Γαβριατοπούλου που συμμετείχε στην εξεταστική επιτροπή της συγκεκριμένης ΜΔΕ. Τέλος, θα ήθελα να ευχαριστήσω θερμά την οικογένεια μου, το σύζυγό μου, και κυρίως τη μητέρα μου, που φρόντιζε τις δύο μου κόρες, Μαρία και Ηλιάνα, όσο εγώ συνέγραφα την παρούσα εργασία.

ΠΙΝΑΚΑΣ ΠΕΡΙΕΧΟΜΕΝΩΝ ΚΑΙ ΕΥΡΕΤΗΡΙΟ ΠΙΝΑΚΩΝ ΚΑΙ ΣΧΗΜΑΤΩΝ

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Περίληψη

Τόσο η αρτηριακή όσο και η φλεβική θρόμβωση αποτελούν μείζονες αιτίες θνησιμότητας, επηρεάζοντας ένα μεγάλο κομμάτι του πληθυσμού. Η κύρια θεραπεία, τόσο για την πρόληψη όσο και για την αντιμετώπιση της θρομβοεμβολικής νόσου, βασίζεται στη χρήση αντιπηκτικών παραγόντων, όπως τα νεότερα από του στόματος αντιπηκτικά, η χαμηλού μοριακού βάρους ηπαρίνη ή οι ανταγωνιστές της βιταμίνης Κ. Λόγω του μη-αμελητέου ποσοστού αιμορραγικών επιπλοκών που αυτά φέρουν, η κλινική έρευνα έχει στραφεί στην ανάπτυξη νεότερων παραγόντων που στοχεύουν τον παράγοντα πήξης XI, με την προοπτική να αποτρέπουν την παθολογική θρόμβωση, χωρίς να επηρεάζουν σημαντικά τη φυσιολογική διαδικασία της αιμόστασης. Η έρευνα σχετικά με τους αναστολείς του παράγοντα XI ανέδειξε υποσχόμενα αποτελέσματα, όσον αφορά την ασφάλεια των παραγόντων αυτών, ενώ η αποτελεσματικότητά τους έναντι των κλασσικών αντιπηκτικών φαρμάκων, δεν έχει αξιολογηθεί επαρκώς. Η παρούσα ανασκόπηση στοχεύει στην περιγραφή των διαφορετικών τύπων αναστολέων του παράγοντα XI, που βρίσκονται υπό κλινική αξιολόγηση, υπογραμμίζοντας τα αποτελέσματα των μελετών φάσης 2 καθώς και στην αναφορά εν εξελίξει μελετών και πιθανών εφαρμογών των αναστολέων του παράγοντα XI στην κλινική πράξη.

Λέξεις-Κλειδιά: Αρτηριακή Θρόμβωση, Θρομβοεμβολική Νόσος, Κολπική Μαρμαρυγή, Αντιπηκτικά, Αντιθρομβωτική αγωγή, Αναστολείς Παράγοντα XI

Abstract

Both arterial and venous thromboembolic events are a major cause of mortality, affecting a significant part of the population. The mainstay therapy, for prevention and treatment of thromboembolic disease, is currently based on anticoagulant agents, such as direct oral anticoagulants (DOACs), low molecular weight heparin (LMWH) or vitamin-K antagonists (VKA). Due to their non-negligible rates of bleeding, clinical research has focused on the development of newer agents targeting coagulation factor XI, with a view to prevent pathologic thrombosis, with little or no impact on physiologic hemostasis. Research on factor XI inhibitors has shown promising results, especially regarding safety, whereas their efficacy, compared to contemporary anticoagulant agents, has yet to be evaluated. This review aims to describe the characteristics of different types of factor XI inhibitors, currently under clinical evaluation, highlighting phase 2 clinical trials' results as well as discussing ongoing trials and potential indications of factor XI inhibitors in clinical practice.

Keywords: Arterial thrombosis, Thromboembolism, Atrial fibrillation, Anticoagulants, Antithrombotic agents, Factor XI inhibitors

LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
ANT-005 TKA	A Multicenter, Randomized, Open-Label, Blinded Endpoint Evaluation, Active- Controlled, Dose-Ranging Study to Compare the Efficacy and Safety of i.v. MAA868 and s.c. Enoxaparin in Adult Patients Under- going Elective Unilateral Total Knee Arthroplasty
ASCAT	Artificial Contact Surfaces Associated Thrombosis
ASO	Antisense Oligonucleotide
ASTER	A Multicenter, Randomized, Open-label, Blinded Endpoint Evaluation, Phase 3 Study Comparing the Effect of Abelacimab Relative to Apixaban on Venous Thromboembolism (VTE) Recurrence and Bleeding in Patients With Cancer Associated VTE
AXIOMATIC-SSP	Antithrombotic Treatment With Factor XIa Inhibition to Optimize Management of Acute Thromboembolic Events for Secondary Stroke Prevention
AXIOMATIC-TKR	Antithrombotic Treatment with Factor XIa Inhibition to Optimize Management of Acute Thromboembolic Events in Total Knee Replacement
AZALEA-TIMI 71	Safety and Tolerability of Abelacimab (MAA868) vs. Rivaroxaban in Patients With Atrial Fibrillation
BARC	Bleeding Academic Research Consortium

CI	Confidence interval
CNS	Central nervous system
CONVERT	Study to Investigate the Safety of a Drug Called Osocimab at Low and High Doses in Adult Patients With Kidney Failure Requiring Regular Hemodialysis
CRNM	Clinically-relevant non major
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation
ESRD	End-stage renal disease
FELIAP	Factor ELeven Inhibitory APtamer
FIX	Factor IX
FOXTROT	Factor XIa Inhibition for the Prevention of Venous Thromboembolism in Patients Undergoing Total Knee Arthroplasty
FX	Factor X
FXI-ASO TKA	Factor XI-ASO Total Knee Arthroplasty
HR	Hazard ratio
IR	Incidence rates
LIBREXIA-ACS	A Phase 3, Randomized, Double-blind, Placebo-controlled, Event-driven Study to Demonstrate the Efficacy and Safety of Milvexian, an Oral Factor XIa Inhibitor, After a Recent Acute Coronary Syndrome

LIBREXIA-AF	A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel Group, Active-Controlled Study to Evaluate the Efficacy and Safety of Milvexian, an Oral Factor XIa Inhibitor, Versus Apixaban in Participants With Atrial Fibrillation
LIBREXIA-STROKE	A Phase 3, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Demonstrate the Efficacy and Safety of Milvexian, an Oral Factor XIa Inhibitor, for Stroke Prevention After an Acute Ischemic Stroke or High-Risk Transient Ischemic Attack
LILAC-TIMI 76	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to evaLuate the effIcacy and Safety of abeLacimab in High-risk Patients With Atrial Fibrillation Who Have Been Deemed Unsuitable for Oral anticoagulation
LMWH	Low molecular weight heparin
MACE	Major Adverse Cardiovascular Event
MAGNOLIA	A Multicenter, Randomized, Open-label, Blinded Endpoint Evaluation, Phase 3 Study Comparing the Effect of Abelacimab vs. Dalteparin on Venous Thromboembolism (VTE) Recurrence and Bleeding in Patients With GI/GU Associated VTE
MI	Myocardial infarction
OCEANIC-STROKE	A Multicenter, International, Randomized, Placebo Controlled, Double-blind, Parallel Group and Event Driven Phase 3 Study of the Oral FXIa Inhibitor Asundexian (BAY 2433334) for the Prevention of Ischemic Stroke in Male and Female Participants Aged 18 Years and Older After an Acute Non-cardioembolic Ischemic Stroke or High-risk TIA
PACIFIC-AF	Study to Gather Information About the Proper Dosing of the Oral FXIa Inhibitor BAY 2433334 and to Compare the Safety of the

	Study Drug to Apixaban, a Non-Vitamin K Oral Anticoagulant (NOAC) in Patients With Irregular Heartbeat (Atrial Fibrillation) That Can Lead to Heart-Related Complications
PACIFIC-AMI	Study to Gather Information About the Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following an Acute Heart Attack
PACIFIC-STROKE	Study to Gather Information About Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following a Recent Noncardio-embolic Ischemic Stroke Which Occurs When a Blood Clot Has Formed Somewhere in the Human Body (But Not in the Heart) Travelled to the Brain
PE	Pulmonary embolism
RCT	Randomized clinical trial
RE-THINC ESRD	Factor XI LICA to Reduce Events Such as Heart Attack and Stroke in Patients Whose Kidneys Are No Longer Able to Work as They Should and Require Treatment to Filter Wastes From the Blood: Focus Is on the Safety of BAY2976217 and the Way the Body Absorbs, Distributes and Removes the Study Drug
TIA	Transient ischemic attack
TKA	Total knee arthroplasty
VKA	Vitamin K antagonist

1. INTRODUCTION

Thromboembolic events are an important cause of morbidity and mortality, accounting for nearly 1 in 4 deaths worldwide. They are divided into arterial thrombotic events, such as myocardial infarction (MI) and ischemic cerebrovascular accident, and venous thromboembolic events, such as deep vein thrombosis (DVT) and pulmonary embolism (PE). Global incidence rates (IR) for ischemic heart disease and ischemic cerebrovascular accident, reach 1518 and 139 per 100000, respectively, whereas, for venous thromboembolism (VTE), IR ranges between 115-269 per 100000. [1] Atrial fibrillation (AF), affecting nearly 3% of population, is the most commonly encountered arrythmia and is a major predisposing factor to thrombus formation or embolism. [2]

The management of patients under prothrombotic states, such as those with AF, patients with a medical history of ischemic heart disease or cerebrovascular accident, end-stage renal disease (ESRD) or even post-surgical thromboprophylaxis, relies mainly on anticoagulant therapy. Most currently prescribed anticoagulants inhibit factor X and/or thrombin, directly or indirectly. The above coagulation factors have a major role not only in the pathogenesis of thrombotic events but also in the process of physiological hemostasis; therefore, their administration coincides with an increased bleeding risk. [3] In everyday clinical practice, traditional drugs, such as low molecular weight heparin (LMWH), fondaparinux or vitamin K antagonists (VKAs) have been largely replaced by direct oral anticoagulants (DOACs) like dabigatran, apixaban, rivaroxaban and edoxaban. [4]

Although associated with fewer bleeding events, especially intracranial, major bleeding rates in patients receiving DOACs are not negligible, reaching almost 2-3% of patients with AF under DOACs; out of which, 0.3-0.5% represent intracranial bleedings. [5] Furthermore, the administration of DOACs is not recommended in high bleeding risk clinical scenarios, like patients with gastrointestinal or genitourinary cancer, in specific patient situations such as pregnancy, breastfeeding, ESRD, mechanical valves or patients with anti-phospholipid syndrome. [6-10] Additionally, there are clinical scenarios where DOACs have been proven of inferior efficacy compared to VKA, or cases where there are not sufficient evidence to recommend the use of DOACs, such as patients with left ventricular assist devices or extracorporeal membrane oxygenation (ECMO). [11] Therefore, there is an unmet need of an anticoagulant drug, with improved safety profile, that will prevent pathological thrombotic events with a minimal impact on the physiological process of hemostasis (thrombosis-

hemostasis uncoupling). With a view to minimize bleeding complications, recently, research has focused on factor XI as a potential therapeutic target. [4]

In our narrative review, we will discuss factor XI's role in both thrombosis and hemostasis, the types of factor XI inhibitors, current clinical data regarding the efficacy and safety of treatments targeting factor XI, as well as highlight ongoing clinical trials, and discuss potential future implications.

2. METHODS

Relevant information and clinical evidence discussed in our narrative review were retrieved through online, electronic databases of medical research literature, such as PubMed database (Medline) and Google scholar, with search dates up to May 25, 2024, as well as hand searches of relevant references ("snowball" procedure). Our search algorithm included a combination of MeSH terms: (factor XI OR anti-XI OR factor XIa OR anti-XIa OR "factor XI inhibitors") AND (thromb* OR bleed*). Results were filtered by language (English) as well as publication date (last 10 years).

3. MAIN BODY

3.1 Factor XI's role in coagulation

Coagulation factor XI, a blood coagulation zymogen, is a component of the contact activation (intrinsic) coagulation pathway. The active form of factor XI (Factor XIa) is produced as factors in the cascade upstream are enzymatically cleaved and activated. Factor XIa, in turn, activates factor IX (FIX), which activates factor X (FX). On the other hand, the tissue factor (extrinsic) pathway is initiated by the exposure of blood components to tissue factor and activated factor VII complex, inducing the activation of FX, as well. Activated FX is the initiator of the common coagulation pathway that ultimately leads to thrombin generation and formation of fibrin (**Figure 1**). As an amplification mechanism, thrombin also activates factor XI, via a feedback activation loop. This mechanism is thought to play a more important in the process of thrombosis rather than physiological hemostasis. [12]

First data regarding the role of factor XI derived from observational studies of individuals with factor XI deficiency. Patients with genetic deficiency of factor XI (often called hemophilia C) were shown to have lower risk for cardiovasular and venous thromboembolic events. In detail, compared to patients with normal activity, those with factor XI deficiency had almost 50% decreased risk for cardiovascular events [Hazard Ratio (HR) = 0.52; 95% Confidence Interval (CI) = 0.31 - 0.87 for mild deficiency patients, and HR = 0.57; 95% CI = 0.35 - 0.93 for moderate-severe deficiency patients) as well as nearly 75% lower risk for VTE (HR = 0.26; 95% CI = 0.08 - 0.84). [13] On the other hand, patients with high levels of factor XI seem to have higher risk for DVT, with a dose-response relation of factor XI levels and risk of thromboembolic events. [14]

Additionally, genetic studies in knock-out mice pointed out that factor XI deficiency was associated with decreased rates of vena cava thrombosis with minimal effects in physiological hemostasis, since bleeding time of factor XI-deficient mice remained unchanged in comparison with wild-type mice. [15]

3.2 Types of factor XI inhibitors and clinical studies

The promising role of factor XI in thrombosis prevention, alongside with potential sparing of physiological hemostasis, have led to an increased research of pharmacologic strategies targeting factor XI's synthesis, activation and/or action (**Figure 2**). Main types of factor XI inhibitors, currently under clinical development, include monoclonal antibodies, small molecules, antisense oligonucleotides (ASOs) and aptamers. Apart from differences in way of action, these strategies have varying onset, duration of effect as well as route of administration; monoclonal antibodies, ASOs and aptamers are to be administered parenteraly, whereas small molecules can be given either orally or parenteraly. [16-18] A summary of different types of factor XI inhibitors under development, along with some of their pharmacological features, is presented in **Table 1**.

3.2.1 Antibodies

Humanized monoclonal immunoglobulin G (IgG) antibodies, which inhibit factor XI activation or factor XI action, have been shown to reduce thrombus growth and prolong activated partial thromboplastin time (aPTT). They can be administered either subcutaneously or intravenously and their half-life period is relatively long, allowing for monthly administration. [19]

Abelacimab

Abelacimab (a.k.a. MAA868) is a human monoclonal antibody capable to inhibit both factor XI and factor XIa, via binding to their catalytic domains with high affinity and locking them into an inactive, zymogen-like conformation. Additionaly, it binds to its target with high speicificity, since no inhibitory effect on other coagulation factors was observed. [3, 16, 17]

The pharmacokinetics and pharmacodynamics properties of abelacimab were investigated in healthy individuals as well as AF patients, in ANT-003 phase 1 study and ANT-004 phase 2a, multiple ascending dose study, respectively. Results showed that either intravenous or once-a-month subcutaneous administration of abelacimab was safe and well-tolerated in both patient groups. Additionally, abelacimab was shown to suppress factor XI levels, with the suppresion of free factor XI sustaining throughout the monthly administration interval; thus, it may be given as monthly infusions or even as a single infusion in the post-operative setting.[20]

The ANT-005 TKA study was a parallel-group, open-label, randomized phase 2 trial comparing three dosage schemes of abelacimab (30 mg, 75 mg, 150 mg) administered post-operatively to enoxaparin 40 mg once daily in more than 400 patients who underwent total knee arthroplasty (TKA). Baseline characteristics were similar, with a median age of 67 years (68 for abelacimab 150 mg group), median duration of surgery of 1.3 hours and median in-hospital stay of 10 days. The primary efficacy endpoint was adjudicated VTE, while safety endpoint included major or clinically relevant non-major (CRNM) bleeding up to 1 month post-TKA. VTE was diagnosed in 22% of patients receiving enoxaparin, while only in 13%, 5% and 4% of patients receiving abelacimab 30 mg, 75 mg or 150 mg, respectively. All three

abelacimab regimens were proven non-inferior while the two latter regimens of 75 mg and 150 mg were proven superior to enoxaparin regarding prevention of VTE (Risk Difference = −16.8 percentage points; 95% CI = −26.0 to −7.6, P < 0.001 for 75 mg; Risk Difference = −17.8 percentage points; 95% CI = −26.7 to −8.8, P < 0.001 for 150 mg). As long as bleedings are concerned, clinically relevant bleeding was observed in 2% of patients in the 30 mg and 2% of patients in the 75 mg group, while in none of the patients in the 150 mg abelacimab group or the enoxaparin group. Serious adverse events (AE) were noted in 1%, 3%, and 1% of the patients in the 30 mg, 75 mg, and 150 mg abelacimab groups, respectively, while no serious AE were noted in the enoxaparin group.[21]

The largest study on factor XI inhibitors to date, AZALEA-TIMI 71 was a phase 2b, open-label, active-controlled, multicenter randomized trial, comparing abelacimab (90 mg and 150 mg) to rivaroxaban in AF patients with moderate-to-high risk of stroke. More than 1,200 patients were enrolled, with a median follow-up duration of 1.8 years, covering more than 2,000 patient-years. Regarding patient characteristics, median age was 74 years, median CHA_2DS_2 -VASc score was 5, whereas 15% of patients had history of ischemic stroke and 7% had a prior bleeding event. Initial topline analysis showed that abelacimab 90 mg given once monthly (subcutaneously) achieved 97% inhibition of factor XI, whereas 150 mg achieved 99% inhibition. Regarding the primary safety outcome of major or CRNM bleeding, abelacimab 90 mg was associated with 77% reduced risk of bleeding (HR = 0.23; 95% CI = 0.13 – 0.42, P < 0.001), and abelacimab 150 mg with 67% lower risk (HR = 0.33; 95% CI = 0.19-0.55, P < 0.001), compared to rivaroxaban 20 mg once daily. Especially, concerning major gastrointestinal (GI) bleedings, abelacimab reduced bleedings by 93% at both doses (HR = 0.07; 95% CI = 0.01-0.51, P = 0.009 for 90 mg and HR = 0.07; 95% CI = 0.01-0.50, P = 0.008 for 150 mg). With no significant differences in efficacy exploratory endpoints, net clinical outcome (including ischemic stroke, embolism, clinically relevant bleedings and all-cause death) was greatly reduced with abelacimab, compared to rivaroxaban (HR = 0.49; 95% CI = 0.34 – 0.73, P < 0.001 for 90 mg and HR = 0.49; 95% CI = 0.33 – 0.71, P < 0.001 for 150 mg). Regarding safety, no statistically significant differences were observed between the 2 drugs, in terms of any or serious AE or drug discontinuation. The aforementioned initial results led to a premature discontinuation of the trial, following the recommendation of the independent Data Monitoring Commitee in September 2023, since an “overwhelming reduction” in bleeding rates was evident with abelacimab. Evaluation of abelacimab, with a view to confirm such promising results, will continue with LILAC-TIMI 76, a phase 3 double-

blind, randomized trial, assessing the safety and efficacy of abelacimab (150 mg) compared to placebo in AF patients unsuitable for currently available anticoagulation therapies. [22, 23]

Additionally, two more phase 3 trials on abelacimab are ongoing, concerning oncologic patients. ASTER trial aims to examine recurrence of VTE as well as major or CRNM bleeding, comparing abelacimab with apixaban, whereas MAGNOLIA trial focuses on patients with gastrointestinal or genitourinary cancer and aims to compare abelacimab with dalteparin. [24]

Ocosimab

Osocimab (BAY 1213790) is a fully human monoclonal antibody which specifically targets the active site of factor XIa and inactives it; thereby, preventing thrombotic cascade and clot formation.

CONVERT trial was a phase 2b, randomized, placebo-controlled, double-blind study with a view to assess the safety of Osocimab in ESRD patients undergoing hemodialysis. More than 700 patients, with a median age of 61 years, were recruited and randomized to receive lower (105 mg loading dose and maintenance with 52.5 mg once-a-month) or higher (210 mg loading dose and maintenance with 105 mg once-a-month) dosage regimen of osocimab or placebo. The co-primary outcomes included a composite of major and CRNM bleeding as well as a composite of moderate, severe or serious AE rate. Bleeding rates were 6.9%, 4.9% for patients on lower- and higher-dose osocimab groups, respectively, compared to 7.8% for patients receiving placebo treatment group (HR = 0.90; 95% CI = 0.46 – 1.77, P = 0.760 for lower-dose osocimab vs placebo and HR = 0.62; 95% CI = 0.29 – 1.31, P = 0.206 for higher-dose osocimab versus placebo for treatment-emergent primary outcome). Concerning AE, 51% and 47% of patients under lower-dose ocosimab and higher-dose osocimab experienced an event, respectively, in comparison with 43% of patients in the placebo group; suggesting that osocimab is of low bleeding risk and is well-tolerated in patients with kidney failure on regular hemodialysis. As regards exploratory outcomes, major adverse vascular events were observed in 1.3% of patients under lower-dose, 2.7% of patients under higher-dose osocimab and 3.0% of patients under placebo; in those with history of atherosclerosis, vascular events occurred in 2.4% of patients under osocimab versus 7.3% of patients under placebo. Finally, the risk of clotting of dialysis circuit was significantly reduced in osocimab group, with relative risk (RR)

of 0.71 (95% CI = 0.54 – 0.93, P = 0.0085) for lower-dose osocimab versus placebo and RR of 0.66 (95% CI = 0.49 – 0.87, P = 0.0021) for higher-dose osocimab versus placebo. [25]

Osocimab was also investigated in FOXTROT study, a phase 2, non-inferiority, randomized, open-label, but observed-blinded (for the different experimental drug doses) trial that aimed to investigate the safety and efficacy of osocimab in VTE prevention in patients undergoing primary TKA, compared to enoxaparin and apixaban (non-inferiority design). More than 800 patients underwent randomization during October 2017 – April 2018, with 600 (73.8%) comprising the population of the per-protocol analysis. Baseline demographic and clinical characteristics were similar between patient groups, with mean age around 66 years. Osocimab was administered in different dosing schemes, either pre-operatively or post-operatively. The primary efficacy endpoint was the rate of VTE (asymptomatic or symptomatic), whereas the primary safety endpoint was the rate of clinically significant bleeding (major or CRNM bleedings) from randomization to 10-13 days post-surgery. Regarding efficacy, in the per-protocol analysis, post-operative osocimab was proven non-inferior to enoxaparin with risk differences of 10.6% (1-sided 95% CI = -.1,2% to ∞), 9.9% (1-sided 95% CI = -0.9% to ∞) and 8.4% (1-sided 95% CI = -2.6 to ∞) for the 0.6 mg/kg, 1.2 mg/kg and 1.8 mg/kg group, respectively; whereas, osocimab 0.3mg/kg did not meet non-inferiority criteria (risk difference = –2.6% (1-sided 95% CI = –8.9% to ∞). Additionally, pre-operative osocimab at 1.8 mg/kg dose seemed to be superior to enoxaparin (risk difference = 15.1%; 2-sided 90% CI = 4.9% - 25.2%, P = 0.007). As long as safety is concerned, clinically significant bleeding rates in patients receiving osocimab ranged from 0% to 4.7% (patients in 1.8 mg/kg pre-operative osocimab group), while, bleeding occurred in 5.9% of patients in enoxaparin group and 2% of patients in apixaban group. Interestingly, the highest dose scheme (1.8mg/kg) resulted in higher bleeding incidence when administered pre-operatively compared with post-operatively, a trend that was not observed in the low dose of 0.3 mg/kg. Of note, all clinically significant bleeding events concerned bleedings associated with the surgical site, while no intracranial bleeding was observed. Regarding secondary outcomes, the incidence of serious AE ranged from 1.5% to 5.6% (mean = 3.1%) for osocimab, whereas rates for enoxaparin and apixaban reached 5.9% and 1%, respectively. In summary, post-operative dosage schemes of 0.6 mg/kg, 1.2 mg/kg and 1.8 mg/kg were non-inferior to enoxaparin while pre-operative dosage scheme of 1.8 mg/kg osocimab was superior to enoxaparin regarding VTE prevention at 10-13 days post-TKA. [26]

Xisomab 3G3

Xisomab 3G3 (aka AB023 or Gruticibart) is a recombinant antibody targeting factor XI, inhibiting its activation by activated factor XII, but not by thrombin. Lorentz et al., assessed the safety and efficacy of AB023 in ESRD patients on hemodialysis in a phase 2, placebo-controlled, double-blind, randomized trial. A total of 24 patients had a single administration of AB023 (0.25 mg/kg or 0.5 mg/kg) or placebo injected into the hemodialysis circuit at the start of heparin-free hemodialysis session. AB023 was proved safe and well tolerated in this high-risk subset of patients since nor drug-related AE neither clinically relevant bleedings were noted. AB023 administration prolonged aPTT (about 2-fold), with dose of 0.5 mg/kg resulting in a prolongation that remained for up to 9 days. Furthermore, administration of AB023 reduced clotting within the hemodialysis circuit with the rate of occlusion, requiring circuit exchange, dropping by 68% and 50% in the 0.25 mg/kg and 0.5 mg/kg dosing subgroups, respectively. [27]

Gruticibart was also evaluated in oncologic patients following central venous catheter placement. A total of 22 patients were administered a single dose of the experimental drug (dosage of 2 mg/kg) and had a follow-up ultrasound at 14 days post-infusion. The rate of catheter thrombosis reached 12.5%, compared to 40% in the control study - an internal, parallel-non interventional study that was used as a comparator. Additionaly, gruticibart significantly prolonged aPTT in all patients on day 14 compared with baseline values ($P < 0.001$), while its administration was proven safe and well-toleated; no infusion reactions, significant AE or bleedings were noted. [28]

Similarly, another trial of Xisomab 3G3 focused on the prevention of catheter-associated thrombosis on oncologic patients (NCT04465760), but was terminated due to insufficient accrual rate.

Some additional antibodies are under early stages of clinical research, such as MK-2060, with an ongoing, phase 2, placebo-controlled trial evaluating its safety and efficacy in ESRD patients receiving hemodialysis (NCT05027074), as well as REGN9933, currently in phase 1, pharmacokinetic and pharmacodynamic study in healthy participants (NCT05102136). [17]

3.2.2 Small molecules

Small molecules are selective, reversible agents that directly inhibit factor XIa. With low molecular weight, they are able to easily diffuse across cell membranes and bind to factor XIa active site, inhibiting its action. Due to their characteristics, their onset and offset of action is fast, and thus, they can be administered, orally, once or twice a day. [19]

Asundexian

Asundexian, also known as BAY 2433334, is the molecule in the most advanced stage of clinical development. It was studied in more than 4000 patients, enrolled in the PACIFIC program, which included 3 different phase 2 trials, focused on the safety and efficacy of asundexian. The first trial of the program, PACIFIC-AMI, was a dose-finding, double-blind, placebo-controlled, randomized clinical trial in 1,601 patients who had, recently, suffered an acute MI and were under dual antiplatelet therapy (DAPT). Patients were randomized to receive asundexian (10 mg, 20 mg or 50 mg) on top of DAPT, or placebo and were followed for 6-12 months. Key exclusion criteria included hemodynamic instability at the time of randomization, bleeding predisposition or active bleeding, severe renal disease, or planned administrastion of full-dose anticoagulation. The prespecified primary safety endpoint was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding while efficacy endpoint was the composite of MI, stroke, stent thrombosis, or cardiovascular death). Regarding patient demographic characteristics, median age was 68 years and 77% were male, whereas, regarding type of MI, almost half (51%) had ST-elevation MI and nearly everyone (99%) had percutaneous coronary intervention prior to randomization. Concerning background antiplatelet therapy along with aspirin, most patients received ticagrelor (53%), with 27% and 20% receiving prasugrel and clopidogrel, respectively. Asundexian achieved a dose-related inhibition, with doses of 10, 20 and 50 mg reaching more than 70%, 80% and 90% inhibition of baseline factor XIa activity, respectively. As long as safety is concerned, there was a numerical increase of bleeding rates as doses of asundexian increased, although rates with 10 mg or 20 mg were lower than placebo (7.6% and 8.1% vs 9%, respectively). No significant differences were noted in pooled asundexian groups vs placebo, regarding primary safety

outcome, i.e. rates of BARC bleeding type 2, 3, or 5 (HR = 0.98; 90% CI = 0.71 - 1.35). Interestingly, rates of any bleeding tended to be numerically lower with asundexian than with placebo (17.7% - 20.4% vs 21.3%, HR = 0.90; 90% CI = 0.73 - 1.11). There were 2 events of intracranial hemorrhage (1 patient under asundexian 50 mg and 1 under placebo), while no fatal (BARC type 5) bleeding events were noted. As long as efficacy is concerned, there was a numerically lower rate of the composite efficacy endpoint with increasing doses of asundexian; nevertheless, event rates were not lower than placebo in none of the asundexian group. Compared to placebo, pooled asundexian 20 mg and 50 mg groups, did not achieve a statistically significant decrease in thrombotic events (HR, = 1.05; 90% CI = 0.69 - 1.61), neither highest dose of 50 mg alone versus placebo (HR = 1.01; 90% CI = 0.61 - 1.66). Of note, there was a numerically higher decrease of thrombotic events with asundexian in patients with ST-elevation MI (STEMI), rather than non-ST-elevation MI (NSTEMI), as well as, in patients receiving potent $P2Y_{12}$ inhibitors, rather than clopidogrel. Regarding study drug-related AE, rates were comparable between groups, with no clinically or statistically significant differences, ranging from 16.2% to 21.4%.[29]

PACIFIC-STROKE was a phase 2b, placebo-controlled, double-blind randomized trial, that focused on efficacy and safety of asundexian in prevention of recurrent stroke. More than 1,800 patients with acute non-cardioembolic ischemic stroke were enrolled and randomized to receive asundexian (10 mg, 20 mg or 50 mg) or placebo, on top of usual antiplatelet therapy (single or dual). Participants had a mean age of 67 years, the majority (66%) were male, mean National Institutes of Health Stroke Scale (NIHSS) score at randomization was 2.8 and 43% were on DAPT for a mean duration of 70.1 days post-randomization. Follow-up extended over a period of 26 - 52 weeks. Primary efficacy endpoint concerned the composite of symptomatic ischemic stroke and incident covert infarcts [detected by magnetic resonance imaging (MRI)] at or before 6 months post-randomization, whereas, primary safety outcome concerned International Society on Thrombosis and Haemostasis (ISTH) major or CRNM bleeding. Primary efficacy endpoint was observed in 19% of patients in the placebo group versus 19%, 22% and 20% in asundexian 10 mg, 20 mg and 50 mg group, respectively; no significant differences were noted among asundexian groups and placebo and no significant dose-response association was observed (E-max model *t* statistic = –0,68, P = 0.80), attributable in part to the absence of reduction in incident covert infarcts. However, in post-hoc exploratory outcomes' analysis, asundexian was shown to result in lower rates of recurrent symptomatic ischemic stroke and transient ischemic attack (TIA) compared to placebo, particularly at the dose of 50 mg (HR = 0.64; 90% CI = 0.41 – 0.98). Of interest, among patients with any extra-/intracranial

atherosclerosis, protective effects of asundexian 50 mg were even greater (HR = 0.39; 90% CI = 0.18 – 0.85). Nevertheless, these results should be interpreted cautiously, taking into account the post-hoc nature of the analysis, in an otherwise neutral trial, regarding primary efficacy endpoint results. As long as safety is concerned, no dose-response association and no significant increase in clinically significant bleeding rates were observed between pooled asundexian and placebo groups (HR = 1.57; 90% CI = 0.91 – 2.71); there were also no significant differences in total bleedings rates as well as secondary hemorragic transformation of stroke.[30]

The third study of the PACIFIC program was PACIFIC-AF, which focused on patients with AF at increased risk for ischemic cerebrovascular accident. Regarding trial design, it was a randomized, double-blind, active-comparator phase 2 trial, aiming to evaluate asundexian compared to apixaban; apart from quantification of factor XIa inhibition, study's primary safety endpoint concerned ISTH major and CRNM bleeding, while, exploratory efficacy endpoint was the composite of stroke, systemic embolism, cardiovascular death and MI. A total of 755 AF patients, ≥ 45 years old, were enrolled and randomized to receive asundexian (20 mg or 50 mg) once a day, or apixaban 5 mg twice a day. Participants had a mean age of 73.7 years, mean CHA_2DS_2-VASc score of 3.9 and 59% were male. Follow-up extended over a period of 12 weeks. Asundexian administration resulted in a dose-dependent inhibition of factor XIa, reaching 90% and 94% inhibition at peak concentrations of 20 mg and 50 mg, respectively. Rates of any AE were similar among treatment arms (47% in asundexian groups and 49% in apixaban group), whereas, concerning safety endpoint, patients receiving asundexian had decreased bleeding rates, compared to those receiving apixaban (HR = 0.16; 90% CI = 0.01 – 0.99 for asundexian 50 mg vs apixaban and HR = 0.33; 90% CI = 0.09 – 0.97 for asundexian pooled vs apixaban). Of note, no ISTH major bleeding was observed in any treatment group. As regards all bleeding events, asundexian was associated with lower rates, as well, compared with apixaban (HR = 0.42; 90% CI = 0.26 – 0.67 for pooled asundexian, HR = 0.46; 90% CI = 0.23 – 0.83 for asundexian 20 mg and HR = 0.38; 90% CI = 0.16 – 0.68 for asundexian 50 mg). Lastly, concerning exploratory thrombotic composite endpoint, events were scarce, hindering comparisons between treatment groups. [31]

In a pooled analysis of the 3 aforementioned PACIFIC trials, regarding bleeding outcomes, asundexian was shown to have lower major or CRNM bleeding rates compared to apixaban in AF patients, highlighting its potentially improved safety, whereas the rates of

bleedings were similar compared to placebo in MI or stroke patients, already receiving antiplatelet therapy. [32]

Following results from phase 2 trials of the PACIFIC program, a phase 3 development program for asundexian was announced. OCEANIC clinical trial program includes three large, multinational phase 3 studies, planned to enroll up to 30000 patients; OCEANIC-Stroke (NCT05686070), OCEANIC-AFINA and OCEANIC-AF (NCT05643573). However, the latter, aiming to compare asundexian to apixaban in AF patients at risk for stroke, was terminated early, as per the Independent Data Monitoring Committee (IDMC) recommendation, since an inferior efficacy of asundexian versus the control group was evident. OCEANIC-STROKE, still in the recruiting stage, aims to assess the safety and efficacy of asundexian, on top of antiplatelet therapy, for ischemic stroke prevention in patients after a TIA or acute non-cardioembolic ischemic stroke, whereas OCEANIC-AFINA, not yet initiated, aims to focus on AF patients at increased risk for stroke or embolism, unsuitable for oral anticoagulant treatment; however, in the light of OCEANIC-AF preliminary results, OCEANIC-AFINA trial is under re-evaluation. [33]

Milvexian

Milvexian is another small molecule which can be administered pes os and acts via directly inhibiting activated factor XI. It was evaluated, initially, in AXIOMATIC-TKR study, which focused on patients undergoing TKA. In this phase 2, active-comparator trial, more than 1,200 TKA patients were randomized to receive milvexian post-operatively (25 mg, 50 mg, 100 mg or 200 mg twice a day or 25 mg, 50 mg, or 200 mg once a day) or enoxaparin 40 mg once a day for 10 to 14 days after surgery. Primary efficacy endpoint included asypmptomatic or symptomatic VTE and death from any cause, whereas, main safety endpoint concerned all bleeding events (major, CRNM and minor bleedings). Patients' baseline characteristics were similar in the different treatment groups and follow-up period extended over 30 days for all patients. As for efficacy, asundexian exhibited a notable dose-response relationship, with 21%, 11%, 9% and 8% of patients under 25 mg, 50 mg, 100 mg and 200 mg milvexian, respectively, having a thromboembolic event ($P < 0.001$). The rate of VTE with milvexian administered twice-a-day (12%) was significantly reduced compared to the prespecified benchmark of 30%, with one-sided P-value < 0.001. Bleeding events were observed in 4% of patients receiving

milvexian and 4% of patients receiving enoxaparin. Most bleeding events concerned minor bleedings and involved the surgical site, while clinically significant bleeding events were observed in 1% and 2%, respectively. No major bleeding events were recorded in the milvexian group. As long as AE are concerned, they were reported in 39% of patients under milvexian and 38% of patients under enoxaparin, with serious events being noted in 2% and 4%, respectively. [34]

Milvexian was also tested in patients who had suffered an ischemic cerebrovascular accident or a TIA, in AXIOMATIC-SSP study, a phase 2, randomized, double-blind, placebo-controlled trial, which enrolled 2,366 participants. Patients were randomized to milvexian (25 mg once-a-day, 25 mg, 50 mg, 100 mg, or 200 mg twice-a-day) or placebo for 90 days, on the background of antiplatelet therapy (DAPT with aspirin and clopidogrel for the first 3 weeks and only aspirin for the remaining period). Primary efficacy outcome consisted of ischemic stroke or, MRI-detected, incident covert brain infarct, at 90 days; similarly to PACIFIC-STROKE trial, though with a shorter time-frame of patient evaluation. Main safety outcome included major bleeding events at 90 days. Participants had a median age of 71 years, with 35% aged ≥75 years, and the majority (64%) were male. Milvexian did not seem to reduce symptomatic ischemic strokes or covert infarcts, on top of DAPT, and no significant dose-response relationship was noted among the dosage schemes of milvexian with estimated percentages reaching 16.8% (90.2% CI = 14.5 – 19.1) for placebo group, 16.7% (90.2% CI = 14.8 – 18.6) for 25 mg milvexian once-a-day, 16.6% (90.2% CI = 14.8 – 18.3) for milvexian 25 mg twice-a-day, 15.6% (90.2% CI = 13.9 – 17.5) for milvexian 50 mg twice-a-day, 15.4% (90.2% CI = 13.4 – 17.6) for milvexian 100 mg twice-a-day and 15.3% (90.2% CI – 12.8 – 19.7) for milvexian 200 mg twice-a-day. Of interest, in a prespecified secondary analysis, milvexian resulted in a lower rate of symptomatic ischemic stroke compared to placebo at all doses except the high dose of 200 mg twice-a-day. Regarding safety, modified BARC type 3 or 5 bleedings were observed in 1%, 1%, 1%, 2%, 2% and 1% of patients taking placebo, milvexian 25 mg once-a-day, 25 mg twice-a-day, 50 mg twice-a-day, 100 mg twice-a-day and 200 mg twice-a-day, respectively; no significant dose-response was noted. No fatal bleeding events were reported, however milvexian doses of ≥50 mg twice-a-day were associated with a numerically higher rate of BARC type 3 bleedings, mainly in gastrointestinal system. Lastly, concerning AE, rates were similar between milvexian groups and placebo; however, patients in milvexian 200 mg twice-a-day arm reported more AE in the renal and urinary system organ class (14% versus 4% for placebo and 3% for milvexian 25 mg, 50 mg and 100 mg). [35]

3.2.3 Antisense Oligonucleotides (ASOs)

Antisense Oligonucleotides (ASOs) are short sequences of nucleotides that bind to specific domains of mRNA, regulating the expression of specific genes. Thus, anti-factor XI ASOs target factor XI mRNA in the liver, leading to its catalytic degradation and resulting in inhibition of factor XI synthesis in the liver. [36] Advantages of ASOs include high target specificity, predictable pharmacokinetic, high compliance without frequent doses and minimal food or drug interactions. However, their development is hindered by the complex drug design process, in order to increase stability and activity of ASOs, as well as, their slow onset and offset of action. They are administered subcutaneously and need up to a month in order to reduce levels of factor X; their increased half-life period permits a once-a-month dosing. [16]

IONIS-FXI_{Rx}/FXI-ASO, was the first ASO investigated in an open-label, phase 2 clinical trial. In FXI-ASO TKA trial, a total of 300 patients undergoing TKA were randomized to receive FXI-ASO (one of two doses; 200 or 300 mg) or enoxaparin 40 mg once-a-day. As per the primary efficacy outcome, incidence of VTE, results showed that FXI-ASO at the dose of 200 mg was non-inferior (27% vs 30%, P = 0.57) while 300 mg FXI-ASO was superior to enoxaparin (4% vs 30%, P < 0.001). Apart from reduction in VTE rates, interestingly, FXI-ASO was, additionaly, associated with a numerically lower incidence of major or CRNM bleedings (3% with FXI-ASO vs 8% with enoxaparin, P = 0.09 for 200 mg and 0.16 for 300mg). [37] IONIS-FXI_{Rx} was also tested, in a phase 2 clinical trial of 49 ESRD patients on hemodialysis. In the first stage of the trial, 6 patients received IONIS-$FXI_{Rx,}$ prior and following hemodialysis, while in the next stage, 43 patients were randomized to receive the experimental drug (at doses of 200 mg or 300 mg) or placebo for 3 months. The study was not powered to assess efficacy or safety, but focused on pharmacokinetic and pharmacodynamic drug properties as well as drug AE. Administration of IONIS-FXI_{Rx}, was associated with reduction of factor XI activity (56.0% and 70.7% in 200 mg and 300 mg group, respectively, vs 3.9% in the placebo arm) while no treatment-related serious AE were noted. Although minor bleeding rates were numerically higher in the experimental drug group, major bleeding events were observed in none of the patients receiving 200 mg (0.0%), 1 patient receiving 300 mg (6.7%), and 1 patient under placebo treatment (7.7%). [38]

Another study evaluating IONIS-FXI_{Rx} in patients with ESRD (NCT03358030) has been completed, but results' announcement awaits. [38]

Additionaly, fesomersen (formerly known as IONIS-FXI-L_{Rx}), the ligand-conjugated version of IONIS-FXI_{Rx} was investigated in RE-THINC ESRD study, a randomized, placebo-controlled phase 2b trial, including 307 ESRD patients. While final data are yet to be published, Ionis, recently, announced positive topline results; fesomersen met its primary endpoint of no increase in major and CRNM bleeding, as compared to placebo, while its administration on a monthly basis (at dosage schemes of 40 mg, 80 mg and 120 mg and up to nearly a year of drug administration) was proven safe and well-tolerated by participants. Furthermore, fesomersen was shown to significantly reduce factor XI activity levels. [39]

3.2.4 Aptamers

Aptamers are short sequences of single-stranded nucleic acids with high specifity and low immunogenicity, acting as potent antagonist of their target protein. They have a fast onset of action and are administered parenterally. [40] Aptamers targeting factor XI, are still under early stages of development, with no clinical studies to human reported yet. [41, 42] In preclinical research, FELIAP, a DNA aptamer targeting factor XIa, achieved a competitive inhibition of factor XIa-mediated FIX activation, inhibiting plasma clotting and generation of thrombin; however, with low potency. Additionaly, aptamers 12.17 and 11.6, were shown to non-competetively inhibit factor XIa activity, while aptamer 12.7 led to significant prolongation of aPTT clotting time in human plasma.[41]

Although they have low cost of production and allow the development of universal as well as specific antidotes, [43], it seems that their potential is outmached by that of more direct inhibitors, such as small molecules and antibodies; therefore, research interest has declined.[44]

3.2.5 Other inhibitors under development

Apart from the aforementioned factor XI inhibitors, there are numerous compounds at early stages of development. BAY-1831865 is a humanized monoclonal antibody that inhibits binding and, thus, activation of FIX as well as factor XIIa-mediated activation of factor XI via

a mechanism of steric hindrance. It was shown to be well-tolerated in healthy individuals and led to a significant dose-dependent aPTT prolongation. [45] ONO-7648 is a small molecule, administered per os, which inhibits activated factor XI. It was well tolerated in a first-in-human, multiple dose study in healthy individuals with a low rate of treatment-emergent AE. It was shown to increase aPTT, with a mean maximum inhibition of 92% versus baseline. [46] Two additional small molecules, SHR-2285 and BMS-962212 are also under evaluation with results from early phase 1 studies showing favorable safety, pharmacokinetic and pharmacodynamic properties. [47, 48] EP-7041, another direct inhibitor of activated factor XI, is currently under evaluation as antithrombotic therapy during extracorporeal membrane oxygenation (ECMO). [49] Lastly, several natural peptides, like Fasxiator, acaNAP10, Desmolaris and Boophilin, derived from snakes, nematodes, bats and ticks, respectively, are under clinical development. [50-53]

3.3 Meta-analyses of clinical trials

In the systematic review and meta-analysis, by Presume et al., factor XI inhibitors were associated with a reduction in VTE rates as well as bleeding events, compared to LMWH (enoxaparin), in patients undergoing TKA. In detail, their review included 4 RCTs, with a total of 2,269 patients. Efficacy outcome included (asymptomatic and symptomatic) VTE, whereas safety included clinically relevant bleedings, AE and blood transfusion necessities. Compared with enoxaparin, factor XI inhibitors, namely, IONIS-FXIRx/FXI-ASO, abelacimab, osocimab and milvexian, were associated with a lower rate of VTE (14.5% versus 23.6%; OR = 0.50; 95% CI = 0.36 – 0.69, P < 0.001); however, symptomatic VTE rates were not significantly different in subgroup analysis (0.7% versus 0.8%; OR = 0.78; 95% CI = 0.24 – 2.57, P = 0.680). Concerning safety, factor XI inhibitors were shown to reduce major or CRNM bleedings by almost 60%, compared to enoxaparin (OR = 0.41; 95% CI = 0.22 – 0.75, P = 0.003). Of note, no statistically significant differences were identified in blood transfusion necessities or rate of AE. [54] Acknowledged limitations of the aforementioned review include the limited number of included trials and their open-label design, the low incidence of clinically relevant, and mostly major, bleedings as well as the inclusion and evaluation of different factor XI inhibitors, with various ways of action, administration routes and dosages.

Similarly, an exploratory meta-analysis of phase 2 studies was published by Nopp et al., focusing on patients undergoing TKA. Compared with enoxaparin, factor XI inhibitors,

were shown to have a 41% reduced risk of VTE (Risk Ratio = 0.59; 95% CI = 0.37 – 0.94, P = 0.038], whereas, bleeding risk was also reduced, with 59% reduction in clinically relevant bleeding events (Risk Ratio = 0.41; 95% CI = 0.19 – 0.92, P = 0.039). However, the aforementioned studies on TKA patients have some limitations; patients at high bleeding risk were excluded and recorded thrombotic events were mostly asymptomatic DVT, an entity with less clinical significance than other thrombotic complications. [55]

In light of the aforementioned results, Galli et al. recently published a systematic review and meta-analysis of early clinical trials of factor XI inhibitors, including 8 phase 2 RCTs, with 9,216 patients. Mean follow-up period extended over 142 (range 42 – 368) days, whereas the molecules tested in the included trials were IONIS-FXIRx/FXI-ASO, abelacimab, osocimab, milvexian and asundexian; compared either with placebo or other anticoagulants (such as enoxaparin or DOACs). When compared with LMWH, factor XI inhibitors achieved a 51% reduction of total bleedings (RR = 0.49; 95% CI = 0.31 – 0.77); however, there was not a statistically significant reduction in major bleeding events (RR = 0.96; 95% CI = 0.41 – 2.28). On the other hand, as long as efficacy is concerned, factor XI inhibitors achieved a 38% reduction in efficacy endpoints, compared with LMWH (RR = 0.62; 95% CI = 0.49 – 0.79), with high doses showing superior efficacy versus lower doses (P for interaction < 0.001). A trend toward lower bleeding risk was evident with factor XI inhibitors, in comparison with DOACs, without, however, reaching statistical significance (RR = 0.66,; 95% CI = 0.31 – 1.38). There were also no significant differences in major bleeding events (RR = 1.03; 95% CI = 0.22 – 4.78) as well as in trial-defined efficacy outcomes (RR = 1.23; 95% CI = 0.88 – 1.70). Lastly, compared with placebo, in patients under background antiplatelet therapy, factor XI inhibitors were shown to increase total bleedings by 25% (RR = 1.25; 95% CI = 1.08 – 1.43), though they did not significantly increase major bleedings (RR = 1.21; 95% CI = 0.75 – 1.93). Concerning efficacy, there was not a statistical significant difference between placebo and factor XI inhibitors (RR = 1.02; 95% CI = 0.92 – 1.13). In summary, factor XI inhibitors were shown to be safer and more effective than LMWH, whereas their superiority against DOACs is still under question. On the other hand, when added on top of antiplatelet therapy, factor XI inhibitors seem to increase bleeding events without being more effective than placebo. [56]

4. CONCLUSION

Factor XI inhibition seems a promising strategy for patients in need for anticoagulant therapy, and especially those with high bleeding tendency or prior bleeding history, since they have been proven safer than LMWH as regards to total bleeding risk. However, the efficacy of factor XI inhibitors, in comparison with "traditional" anticoagulant drugs, is still under evaluation. Randomized, phase 2 trials' results showed superiority against enoxaparin in regards to post-surgery thromboprophylaxis but did not manage to prove superiority against DOACs or placebo when added on top of antiplatelet treatment in AF, MI or stroke patients; of note, phase 2 trials were designed and powered to evaluate mostly safety and not efficacy of factor XI inhibitors. Potential indications for factor XI inhibitors cover a wide spectrum of clinical scenarios. In detail, long-acting agents, such as ASOs or antibodies, could be used for primary or secondary thromboprophylaxis in patients after orthopedic surgeries or patients in prothrombotic situations, such as oncologic patients. Agents with no renal clearance could be used for ESRD patients, while AF patients at high bleeding risk, usually unsuitable for DOACs, could be benefited from a factor XI-directed treatment strategy. Additionaly, patients with artificial surfaces in contact with their blood, such as patients with medical devices or extracorporeal circuits, may be another patient population in which factor XI inhibitors could be used; specifically, for the prevention or treatment of "Artificial Contact Surfaces Associated Thrombosis" (ASCAT). [57] Lastly, factor XI inhibitors could play a significant therapeutic role in clinical cases where DOACs are not efficacious or have not been evaluated, such as patients with rheumatic valve disease, mechanical valves, or antiphopsholipid syndrome. [19] Therefore, there is a need for more, multicenter, large-scale, phase 3 trials, in order to establish the safety and efficacy of factor XI inhibitors, probably focusing on specific patient sub-populations, with complicated comorbidities or high bleeding tendencies.

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TABLES & FIGURES

Table 1. Pharmacologic features of Factor XI inhibitors

Type of Inhibitor	Antibodies	Small molecules	ASOs	Aptamers
Way of action	Inhibition of FXI activation and/or FXIa activity	Inhibition of FXI active site or heparin allosteric site on FXIa	Inhibition of hepatic synthesis of FXI	Inhibition of FXI/FXIa activity
Route of administration	Parenteral (IV or SC)	Parenteral (IV) or per os	Parenteral (SC)	Parenteral (IV or SC)
Onset of action	Rapid (IV)	Rapid	Slow	Rapid
Offset of action	Slow	Rapid	Slow	Rapid
Renal clearance	No	Yes	No	No
Hepatic metabolism	No	Yes	No	No
Half-life	Long	Short	Long	Short

ASOs indicate antisense-oligonucleotides; FXI, Factor XI; FXIa, activated factor XI; IV, intravenous; SC, subcutaneous

Table 2. Ongoing phase 3 clinical trials with factor XI inhibitors

Drug	Study name	Study Population	Endpoints	Comparator	N
Abelacimab	LILAC-TIMI 76 (NCT05712200)	AF patients, unsuitable for oral anticoagulation	-Ischemic stroke or systemic embolism -BARC type 3c or 5 bleeding	Placebo	1900
	ASTER (NCT05171049)	Cancer patients	-VTE recurrence -ISTH major or CRNM bleeding -Net clinical benefit	Apixaban	1655
	MAGNOLIA (NCT05171075)	GI/GU cancer patients	-VTE recurrence	Dalteparin	1020

			-Major or CRNM bleeding -Net clinical benefit		
Asundexian	OCEANIC-STROKE (NCT05686070)	Non-cardioembolic ischemic stroke or high-risk TIA patients	-Ischemic stroke -ISTH major bleeding	Placebo	9300
Milvexian	LIBREXIA-AF (NCT05757869)	AF patients	-stroke and non-CNS systemic embolism	Apixaban	15500
	LIBREXIA-STROKE (NCT05702034)	Non-cardioembolic ischemic stroke or high-risk TIA patients	-Ischemic stroke	Placebo	15000

	LIBREXIA-ACS (NCT0754957)	ACS patients	-MACE	Placebo	16000

ACS indicates acute coronary syndrome; AF, atrial fibrillation; ASTER, A Multicenter, Randomized, Open-label, Blinded Endpoint Evaluation, Phase 3 Study Comparing the Effect of Abelacimab Relative to Apixaban on Venous Thromboembolism (VTE) Recurrence and Bleeding in Patients With Cancer Associated VTE; CRNM, clinically relevant non major; BARC, Bleeding Academic Research Consortium; CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; ISTH, International Society on Thrombosis and Haemostasis; LIBREXIA-ACS, A Phase 3, Randomized, Double-blind, Placebo-controlled, Event-driven Study to Demonstrate the Efficacy and Safety of Milvexian, an Oral Factor XIa Inhibitor, After a Recent Acute Coronary Syndrome LIBREXIA-AF, A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel Group, Active-Controlled Study to Evaluate the Efficacy and Safety of Milvexian, an Oral Factor XIa Inhibitor, Versus Apixaban in Participants With Atrial Fibrillation; LIBREXIA-STROKE, A Phase 3, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Demonstrate the Efficacy and Safety of Milvexian, an Oral Factor XIa Inhibitor, for Stroke Prevention After an Acute Ischemic Stroke or High-Risk Transient Ischemic Attack; LILAC-TIMI 76, A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to evaLuate the effIcacy and Safety of abeLacimab in High-risk Patients With Atrial Fibrillation Who Have Been Deemed Unsuitable for Oral antiCoagulation; MACE, Major Adverse Cardiovascular Event; MAGNOLIA, A Multicenter, Randomized, Open-label, Blinded Endpoint Evaluation, Phase 3 Study Comparing the Effect of Abelacimab vs. Dalteparin on Venous Thromboembolism (VTE) Recurrence and Bleeding in Patients With GI/GU Associated VTE; OCEANIC-STROKE, A Multicenter, International, Randomized, Placebo Controlled, Double-blind,

Parallel Group and Event Driven Phase 3 Study of the Oral FXIa Inhibitor Asundexian (BAY 2433334) for the Prevention of Ischemic Stroke in Male and Female Participants Aged 18 Years and Older After an Acute Non-cardioembolic Ischemic Stroke or High-risk TIA; TIA, transient ischemic attack; VTE, venous thromboembolism

Figure 1. Simplified diagram of coagulation cascade

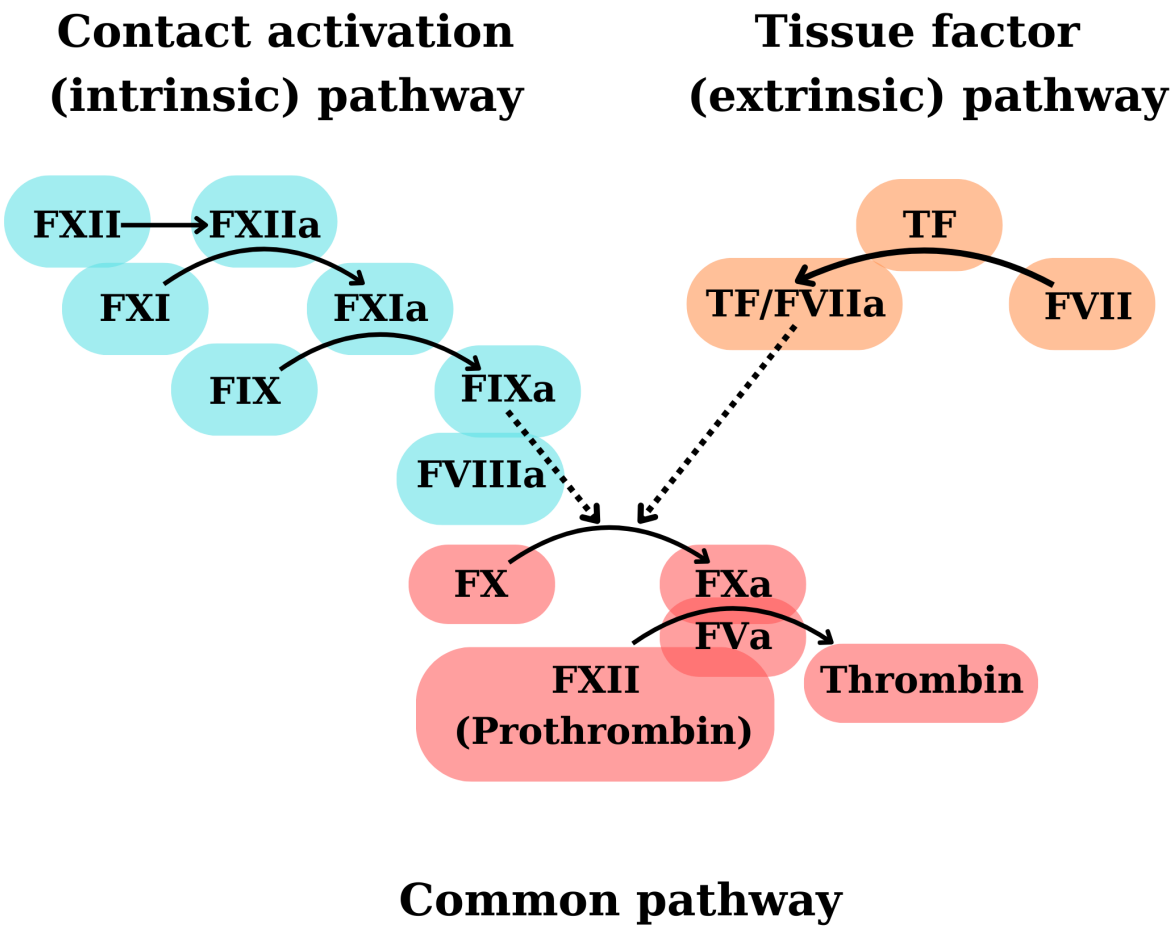

Figure 2. Sites of action of different factor XI/XIa inhibitors

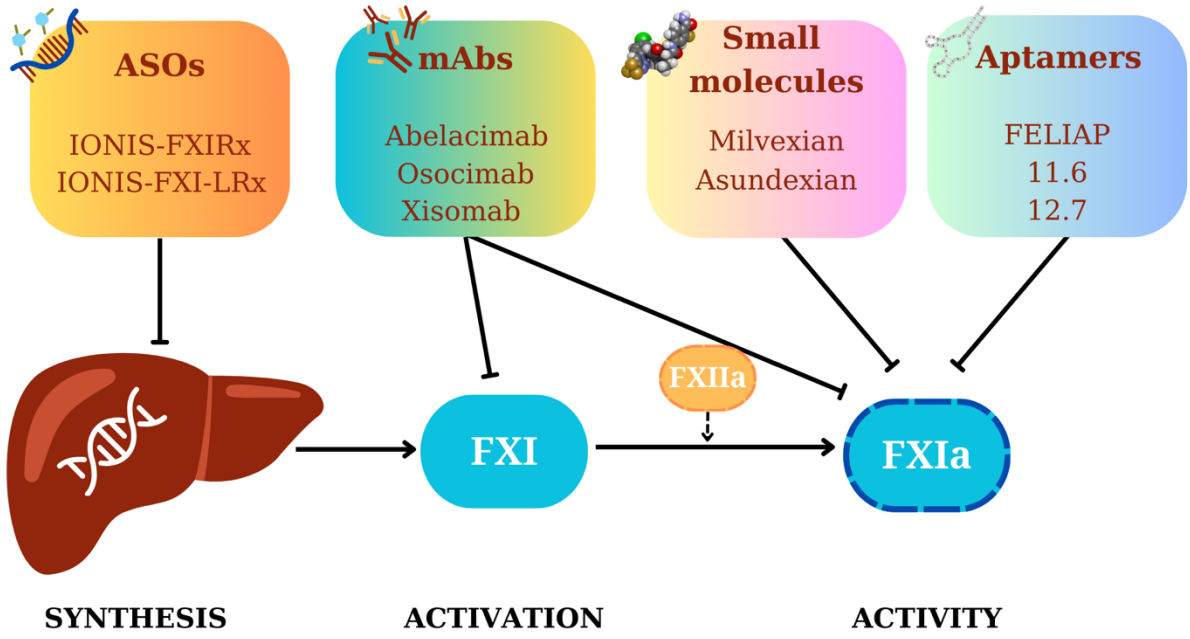

Figure 3. Potential indications for factor XI/XIa inhibitors, currently under evaluation