

Factor XI inhibitors: can the efficacy and safety of VKAs and DOACs be improved?

Inhibidores del factor XI: ¿se puede mejorar la eficacia y seguridad de AVK y ACOD?

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Abstract

Current available anticoagulants, represented by vitamin K antagonists (AVKs) and direct oral anticoagulants (ACODs), have demonstrated their efficacy in the prevention and treatment of venous and arterial thrombosis, but they are associated with an increase of bleeding complications. Inhibition of factor XI has emerged as a promising strategy to mitigate bleeding while preserving antithrombotic efficacy, because factor XI inhibition uncouples thrombosis from hemostasis. A variety of novel drugs, including antisense oligonucleotides, monoclonal antibodies and small molecules, have demonstrated both efficacy and safety in phase II trials, with phase III studies ongoing, which are covered in the current review.

Keywords: Factor XI inhibitors. Venous thrombosis. Arterial thrombosis. Acute myocardial infarction. Cancer and thrombosis.

Resumen

Los anticoagulantes orales de uso clínico, representados por los antivitaminas K (AVK) y los anticoagulantes orales de acción directa (ACOD), han demostrado su eficacia en la prevención y tratamiento de numerosos problemas trombóticos arteriales y venosos, pero su empleo se asocia con un aumento de complicaciones hemorrágicas. La inhibición del factor XI emerge como una estrategia prometedora en el tratamiento de esos procesos, pero con una menor incidencia de hemorragias, por la menor contribución de este factor en la hemostasia en relación con su importante papel en la trombosis. Ello ha favorecido el desarrollo clínico de diversos grupos de inhibidores del factor XI, tales como oligonucleótidos antisentido, anticuerpos monoclonales y pequeñas moléculas. Estos agentes han demostrado marcada eficacia y seguridad en estudios en fase II, y se están completando estudios en fase III en la prevención y tratamiento de trombosis venosas y arteriales, motivo de la presente revisión.

Palabras clave: Inhibidores factor XI. Trombosis venosa. Trombosis arterial. Infarto agudo de miocardio. Cáncer y trombosis.

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Introduction

Arterial and venous thrombosis, responsible for clinical conditions such as acute myocardial infarction, ischemic stroke, and venous thromboembolism (VTE), is a significant cause of morbidity and mortality. Therefore, anticoagulant therapy, primarily based on the use of heparins, vitamin K antagonists (VKAs), or direct oral anticoagulants (DOACs), is highly effective in the prevention and treatment of thrombosis. However, these therapies are not without bleeding complications, some of which, such as intracranial hemorrhage, can be potentially fatal^{1,2}. Heparin and VKAs act on various coagulation factors, while DOACs target specific factors, resulting in a lower but still clinically significant bleeding risk (Fig. 1)^{1,2}.

Factor XI, a precursor of the contact system in the coagulation cascade, plays a minor role in hemostasis but significantly contributes to the propagation of thrombosis³. Various experimental and clinical evidence supports this: individuals with congenital factor XI deficiency experience fewer bleeding complications and a reduced thrombotic risk, epidemiological studies indicate an elevated risk of venous thrombosis in individuals with high factor XI levels, and inhibition of this factor reduces thrombosis in animal models without increasing bleeding⁴⁻⁷.

Factor XI is a serine protease primarily synthesized in the liver, which is converted into active factor XI (FXIa) by the action of factor XII or thrombin. During hemostasis, coagulation activation depends on the tissue factor (TF) pathway, which forms a complex with factor VII to generate thrombin and form fibrin, without the need for FXIa. However, during thrombosis, FXIa significantly contributes to thrombus growth^{3,8,9}.

In summary, FXIa plays an important role in pathological thrombosis, particularly during the amplification phase, promoting the generation of significant amounts of thrombin that contribute to intravascular thrombus growth. This paper reviews recent studies on the use of factor XI inhibitors in thrombotic pathologies and various clinical scenarios.

Pharmacological features of factor XI inhibitors

Several agents targeting FXI or FXIa have been developed, including antisense oligonucleotides, monoclonal antibodies, small molecule inhibitors, and aptamers¹⁰⁻¹³. Table 1 illustrates the pharmacological characteristics of the compounds with the most clinical development¹⁴.

Antisense oligonucleotides

Composed of 12 to 30 base pairs, they specifically bind to mRNA, modulating the degradation of factor XI and inhibiting its synthesis in the liver. Their effect is slow and occurs several weeks after administration, with a half-life of 2 weeks, allowing for monthly administration. The preparations under clinical investigation are fesomersen and IONIS-FXIRx.

Monoclonal antibodies

They exert their neutralizing effect by blocking either the activation of factor XI or the activity of FXIa. The preparations under clinical investigation are osocimab, abelacimab, and sixomab, administered parenterally with a half-life of 30 up to 44 days. As they are not metabolized or excreted by the liver and kidneys, they are of particular interest in patients with renal insufficiency.

Small molecules

They block the active site of factor XI, show good oral bioavailability, and have a rapid onset of action. They undergo hepatic metabolism and renal excretion, with a half-life of 14 to 24 hours. The preparations under clinical investigation are asundexian and milvexian.

Aptamers

These are single-stranded oligonucleotides that directly inhibit factor XI or FXIa. They have a rapid onset and cessation of action, low immunogenicity, and no renal elimination. They have a short half-life and are administered subcutaneously or intravenously. The most developed preclinical preparation is the factor eleven inhibitor aptamer (FELIAP).

Clinical trials with factor XI inhibitors

Venous thromboembolism

The main studies in VTE have been conducted in patients undergoing major orthopedic surgery¹⁵⁻¹⁸ (Table 2).

- Antisense oligonucleotides: the most important study used IONIS-FXIRx, initiated at different subcutaneous doses 36 days before surgery and continued until 3 days postoperatively. The rate of VTE, determined by bilateral venography, was 27% at 200 mg, 4% at 300 mg, and 20% with enoxaparin (comparator

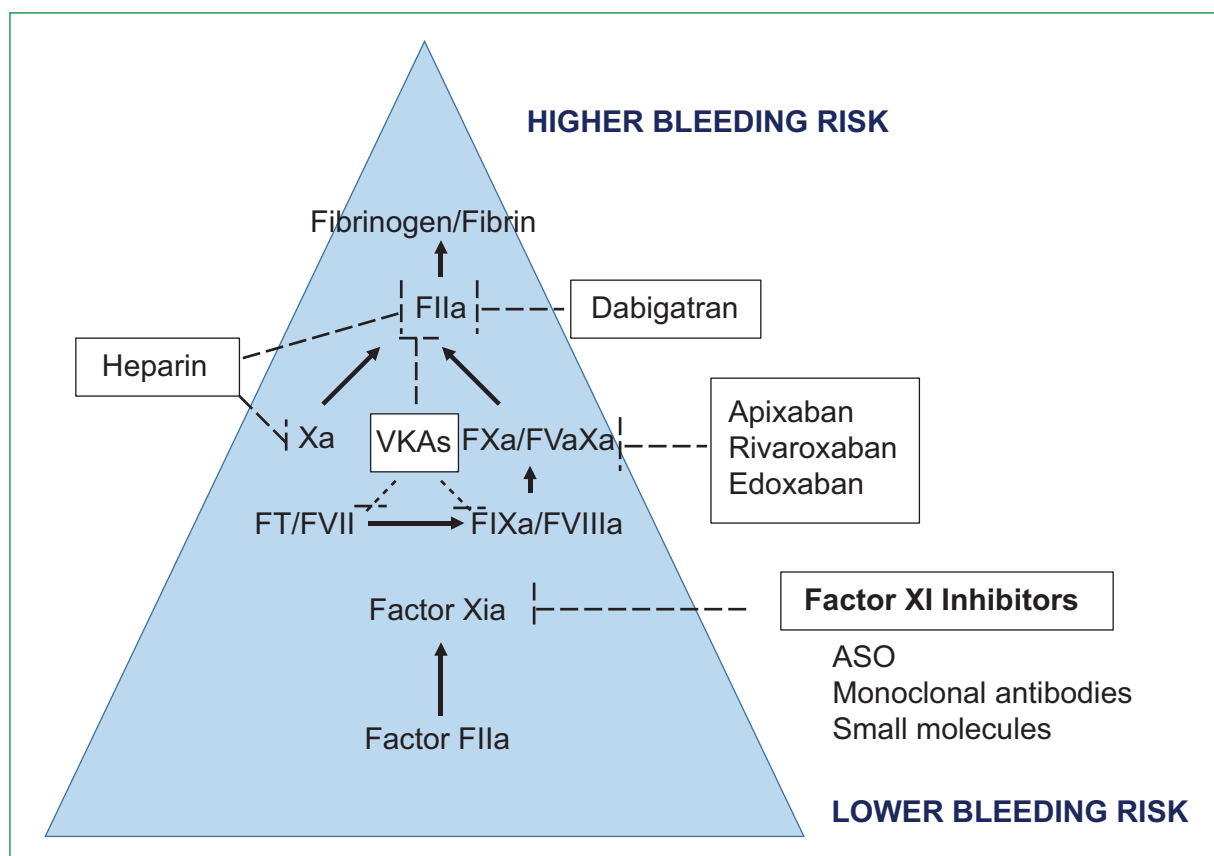


Figura 1. Threshold of bleeding complications associated with different anticoagulants. ASO: antisense oligonucleotide; TF: tissue factor.

Table 1. Pharmacology of FXI inhibitors in clinical use (phase 2 and 3 studies)

Drug	ASO	Monoclonal antibodies	Small molecules
Agents	Fesomersen, IONIS/FXIRS	Abelacimab, Xisomab, Osocimab	Asundexian, milvexian
Mechanism	mRNA degradation	Direct FXI, FXIa, or FXIIa inhibition	Direct FXIa inhibition
Administration route	SC	IV or SC	Oral
Dosing	Weekly	Monthly	Daily
Onset of action	Weeks	Hours	Minutes/Hours
Half-life	2 weeks	30-44 days	14-24 hours
Drug interactions	None	None	Cytochrome P450 (milvexian)
Renal excretion	Minimal	No	No
Hepatic metabolism	Minimal	No	No

Ac.: antibodies; ASO: antisense oligonucleotide; IV: intravenous; SC: subcutaneous.

- group). The rate of bleeding was 3% in the IONIS group vs. 8% with enoxaparin¹⁵.
- Monoclonal antibodies: the FOXTROT study compared escalated doses of osocimab with enoxaparin and

apixaban. Although high doses of osocimab were not inferior to enoxaparin in preventing VTE, none were superior to apixaban¹⁶. Bleeding complications were 5% with osocimab, 6% with enoxaparin, and 2% with

Table 2. Randomized trials for venous thromboembolism prevention in major orthopedic surgery

	FXI-ASO TKA ¹⁵	FOXTROT ¹⁶	ANT005 ¹⁷	AXIOMATIC-TKR ¹⁸
Patients	300	813	412	1,242
Drug	IONIS-FXIRX	Osocimab	Abelacimab	Milvexian
Dosage	200 or 300 mg SC on days 36, 35, 33, 31, 28, 21, 14, 7 pre-op & 6 hrs, 3 days post-op	0.3 or 1.8 mg/kg pre-op	0.3, 0.6, 1.2, or 1.8 mg/kg IV post-op	30, 75, 150 mg IV 4-8 hrs post-op; 25, 50, 100, or 200 mg PO twice daily; 50 or 200 mg/day PO
Control	Enoxaparin 40 mg SC	Enoxaparin 40 mg SC vs. Apixaban 2.5 mg twice daily	Enoxaparin 40 mg SC	Enoxaparin 40 mg SC
Follow-up	8-12 days post-op	10-13 days post-op	8-12 days post-op	10-14 days post-op
Rate of thrombosis	27% (200 mg), 4% (300 mg), 30% (control)	29.9%, 0.3 mg pre-op 11.3%, 1.8 mg pre-op 23.7%, 0.3 mg post-op 15.7%, 0.6 mg post-op 16.5%, 1.2 mg post-op 17.9%, 1.8 mg post-op 26.3%, enoxaparin 14.5%, apixaban	VTE 13% (30 mg) 5% (75 mg) 4% (150 mg) 22% (enoxaparin)	VTE 21%, 25 mg twice daily 11%, 50 mg twice daily 9%, 100 mg twice daily 8%, 200 mg twice daily 25%, 25 mg/day 24%, 50 mg/day 7%, 200 mg/day 21%, enoxaparin
Rate of bleeding	3% (IONIS), 8% (enoxaparin)	MH/CRNMH: 4.7% (osocimab), 5.9% (enoxaparin), 2% (apixaban)	MH/CRNMH: 2%, 2%, and 0% (abelacimab 30, 75, 150 mg), 0% (enoxaparin)	4% (milvexian and enoxaparin)

MH: major hemorrhage; CRNMH: clinically relevant non-major hemorrhage; HR: hazard ratio; IV: intravenous; VTE: venous thromboembolism; PO: oral administration; SC: subcutaneous.

apixaban. Another small study used abelacimab, demonstrating superiority over enoxaparin¹⁷.

- Small molecules: the AXIOMATIC-TKR study examined different doses of milvexian vs enoxaparin, observing a significant reduction in thrombotic events (12% vs. 30%), with a similar rate of bleeding complications¹⁸.

One meta-analysis comparing factor XI inhibitors with low molecular weight heparin in VTE prevention, including 4 randomized clinical trials, found a reduction in thrombotic events (OR: 0.50; 95%CI, 0.36-0.69) and a significant reduction in bleeding complications (OR, 0.41; 95%CI, 0.22-0.75)¹⁹.

Arterial thrombosis

The main studies in arterial thrombosis have focused on the prevention of ischemic stroke in patients with non-valvular atrial fibrillation (AF) (Table 3), non-cardioembolic stroke (Table 4), and acute myocardial infarction:

- Monoclonal antibodies: The phase II AZALEA-TIMI71 trial was terminated early after demonstrating a reduction in major and clinically relevant

non-major bleeding with 2 monthly subcutaneous doses of abelacimab vs rivaroxaban in AF patients. A phase III study with a 150 mg dose is currently underway (American Heart Association communication 2023).

- Small molecules: The PACIFIC-AF trial compared 2 oral doses of asundexian with apixaban in AF patients, observing a significant reduction in bleeding complications (50% with the lower dose and 84% with the higher dose)²⁰. The OCEANIC-AF phase III study compared asundexian 50 mg/day with apixaban and demonstrated the non-inferiority of asundexian for ischemic stroke prevention, with an incidence of 1.3% vs. 0.4% with apixaban and a lower rate of bleeding complications (0.2% vs. 0.7%)²¹. An ongoing study, LIBREXIA-AF, compares another small molecule, milvexian, with apixaban in stroke prevention in AF patients²².

In the ischemic stroke setting, the PACIFIC-STROKE study used 3 different doses of asundexian or placebo administered 36 hours after stroke. The highest dose (50 mg) showed a non-statistically significant benefit, with no differences in bleeding complications²³.

Table 3. Phase II and III randomized clinical trials in atrial fibrillation

Variable	PACIFIC-AF ²⁰	OCEANIC-AF ²¹
Patients	755	14,830
Drug	Asundexian	Asundexian
Dosage	20 mg or 50 mg/day PO	50 mg/day PO
Control	Apixaban 5 mg twice daily PO	Apixaban 5 mg twice daily PO
Follow-up	12 weeks	155 days
Thromboembolic rate	0.8% asundexian 20 mg 1.6% asundexian 50 mg 1.2% apixaban	1.3% asundexian 0.4% apixaban HR 3.79
Rate of bleeding (MH/CRNMH Ratios vs. Apixaban)	0.50 asundexian 20 mg 0.16 asundexian 50 mg 0.33 pooled asundexian	HM 0.2% asundexian 0.7% apixaban HR 0.32

MH: major hemorrhage; CRNMH: clinically relevant non-major hemorrhage; HR: hazard ratio; SC: subcutaneous administration; PO: oral administration.

Table 4. Phase II randomized clinical trials in non-cardioembolic stroke

Variable	PACIFIC-STROKE	AXIOMATIC-SSP
Patients	1,808	2,366
Drug	Asundexian	Milvexian
Dosage	10, 20, 50 mg/day PO	25 mg/day 25, 50, 100, 200 mg twice daily PO
Control	Placebo	Placebo
Follow-up	26 weeks	90 days
Rate of thrombosis	19% asundexian 10 mg 22% asundexian 20 mg 20% asundexian 50 mg 19% placebo	16.7% milvexian 25 mg vs. 16.8% placebo No dose-response relationship observed for milvexian
Rate of bleeding	MH/CRNMH 4% asundexian 10 mg 3% asundexian 20 mg 4% asundexian 50 mg	MH/CRNMH 1% milvexian 25 mg/day 1% milvexian 25 mg twice daily 2% milvexian 50 mg twice daily 2% milvexian 100 mg twice daily 1% milvexian 200 mg twice daily 1% placebo

MH: major hemorrhage; CRNMH: clinically relevant non-major hemorrhage; PO: oral administration.

A subsequent study showed that asundexian reduced the composite outcome of stroke and transient ischemic attack. The AXIOMATIC-SSP study evaluated 5 doses of milvexian vs placebo in patients with recent stroke who were also on dual antiplatelet therapy. While no differences were observed in the primary outcome of new stroke or infarction detected by brain MRI, a secondary analysis found lower rates of ischemic stroke with milvexian²⁴.

In acute myocardial infarction setting, the PACIFIC-AMI study investigated escalating doses of asundexian in patients undergoing coronary intervention, 80% of whom received dual antiplatelet therapy. At the 1-year follow-up, no differences were observed in the primary endpoint of major or clinically relevant non-major bleeding with asundexian vs. placebo²⁵. Future studies will evaluate the effect of asundexian 50 mg/day in these patients.

Cancer and thrombosis

Two ongoing phase III studies, ASTER (NCT0517049), evaluating abelacimab with apixaban administered for 6 months, and MAGNOLIA (NCT05171075), evaluating abelacimab vs. dalteparin in cancer-related thrombosis, will determine if this strategy is beneficial vs other anti-coagulant measures used in these patients.

Renal insufficiency and hemodialysis

Patients with renal disease on hemodialysis have a high risk of thromboembolic and bleeding complications, posing a significant challenge for anticoagulant use. The fact that the hemodialysis circuit stimulates coagulation activation via the contact system makes inhibitors of this phase particularly interesting in this clinical setting.

- Antisense oligonucleotides: different monthly doses of fesomersen were used in phase II in hemodialysis patients, with no significant increase in bleeding risk²⁶.
- Small molecules: the COVERT trial compared osocimab with placebo, observing no increase in bleeding complications but a reduction in the incidence of clots in the dialysis circuit²⁷.

Conclusions

The “ideal” anticoagulant for the prevention and treatment of thrombosis would be one with high efficacy and

no bleeding complications. From a hemostasis perspective, factor XI inhibition represents a promising target. Several agents, including antisense oligonucleotides, monoclonal antibodies, and small molecules, have shown efficacy and safety in phase II studies in patients with thrombosis. Ongoing phase III studies will need to demonstrate their superiority over conventional anticoagulants.

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None.

Conflicts of interest

None.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data and does not require ethical approval. The SAGER guidelines do not apply.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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