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FXI a new target for antithrombotic therapy

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30'



Declaration of Conflict Of Interest

- I have no potential conflict of interest to report
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- I have the following potential conflict(s) of interest to report

Why we need new anticoagulant drugs (I)

Scenarios in which the available anticoagulants, VKAs and DOACs have not been investigated or have not performed satisfactorily

- patients with kidney failure requiring dialysis and transplantation are at high risk for cardiovascular events and major bleeding. In these patients DOACs are contraindicated and limited data are available using VKA.
- patients at high risk of bleeding as those with previous intracranial hemorrhages or other severe bleeding
- patients with acute coronary syndrome, requiring antiplatelet therapy
- Use of intravascular devices, and extracorporeal circuits
- pregnancy and breastfeeding

Why we need new anticoagulant drugs (II)

Warfarin performed better than DOACs in three clinical conditions:

- The thrombin-inhibitor dabigatran has not been effective in preventing thromboembolism in patients with mechanical prosthetic heart valves
- Rivaroxaban was associated with an excess number of composite outcomes comprising thromboembolic events, major bleeding and vascular death in high-risk APS patients
- Rivaroxaban led to a higher rate of a composite of cardiovascular events or death than VKA without a higher rate of bleeding in patients with rheumatic heart disease–associated atrial fibrillation.

Contact System as a Target for Safer Anticoagulants

- The contact system was so named because of its requirement for exogenous polyanion “surfaces” such as glass, silica, kaolin, or dextran sulfate for expression of activity.
- Naturally occurring polyanions serve as potent activators of the contact system. These polyanions include DNA and RNA released from dying or activated cells, neutrophil extracellular traps (NETs) extruded from activated neutrophils, polyphosphates released from the dense granules of activated platelets or from microorganisms, and misfolded proteins such as amyloid β -peptide.
- Because these activators are generated at the sites of cell or platelet activation, inflammation, or infection, they provide a link between coagulation and host defense mechanisms.

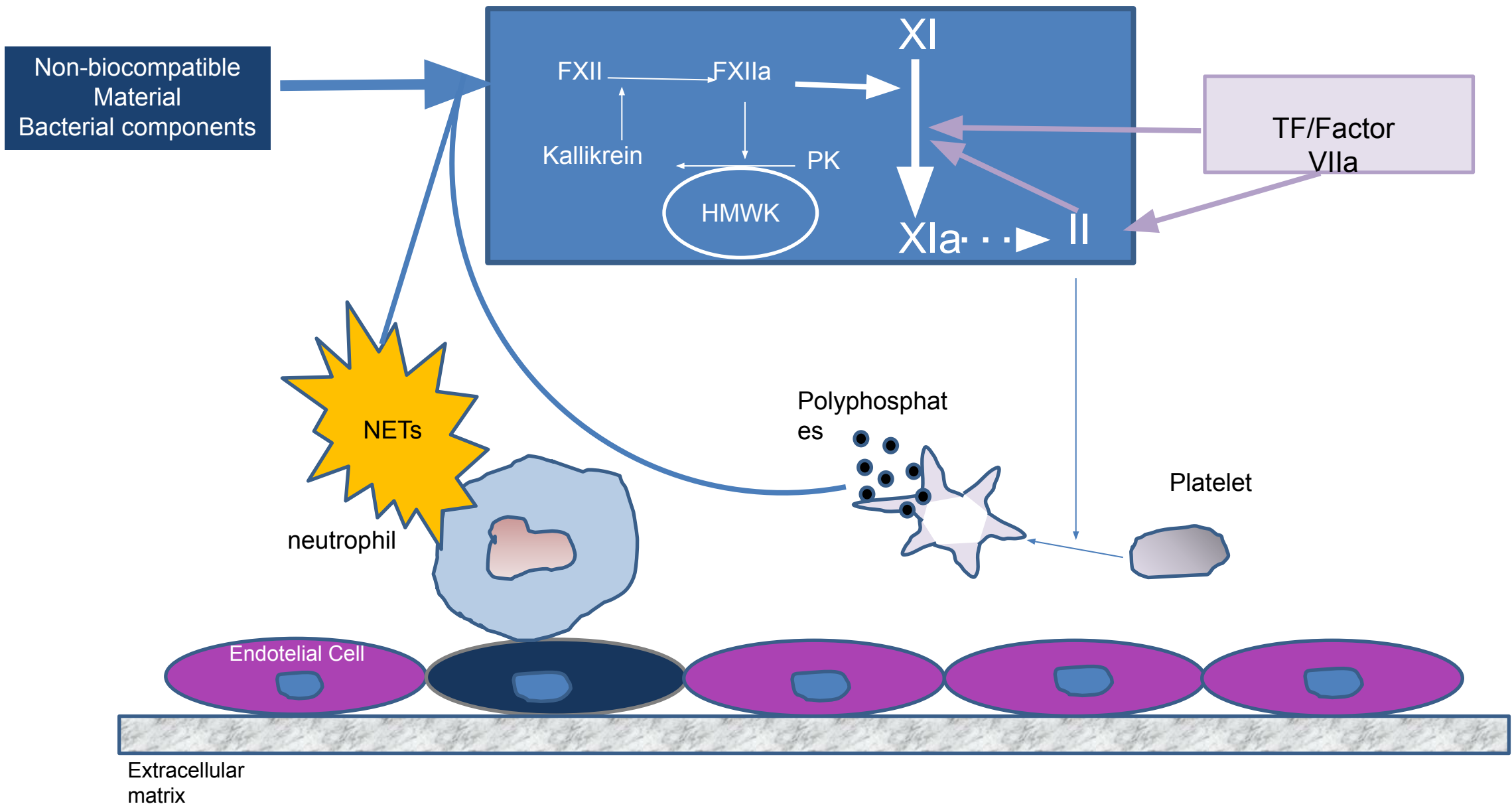


Figure 1

Results of Epidemiological studies on Factor XI

Demonstration of a correlation between FXI levels and the risk of thrombosis.

Patients with FXI deficiency are at lower risk for VTE and ischemic stroke than those with normal FXI levels, but not at increased risk of serious bleeding.

In contrast, patients with elevated FXI levels are at higher risk of thrombosis.

Furthermore, patients with congenital FXI deficiency, which is termed “hemophilia C,” have a mild bleeding diathesis and spontaneous bleeding is rare.

Therefore, there is epidemiologic evidence that the contact system is involved in thrombosis and may be less important for hemostasis.

Preis M et al. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. *Blood* 2017;129(09):1210–1215 12

Georgi B et al. Leveraging human genetics to estimate clinical risk reductions achievable by inhibiting factor XI. *Stroke* 2019;50(11):3004–3012 13

Yang DT et al. Elevated factor XI activity levels are associated with an increased odds ratio for cerebrovascular events. *Am J Clin Pathol* 2006;126(03):411–415

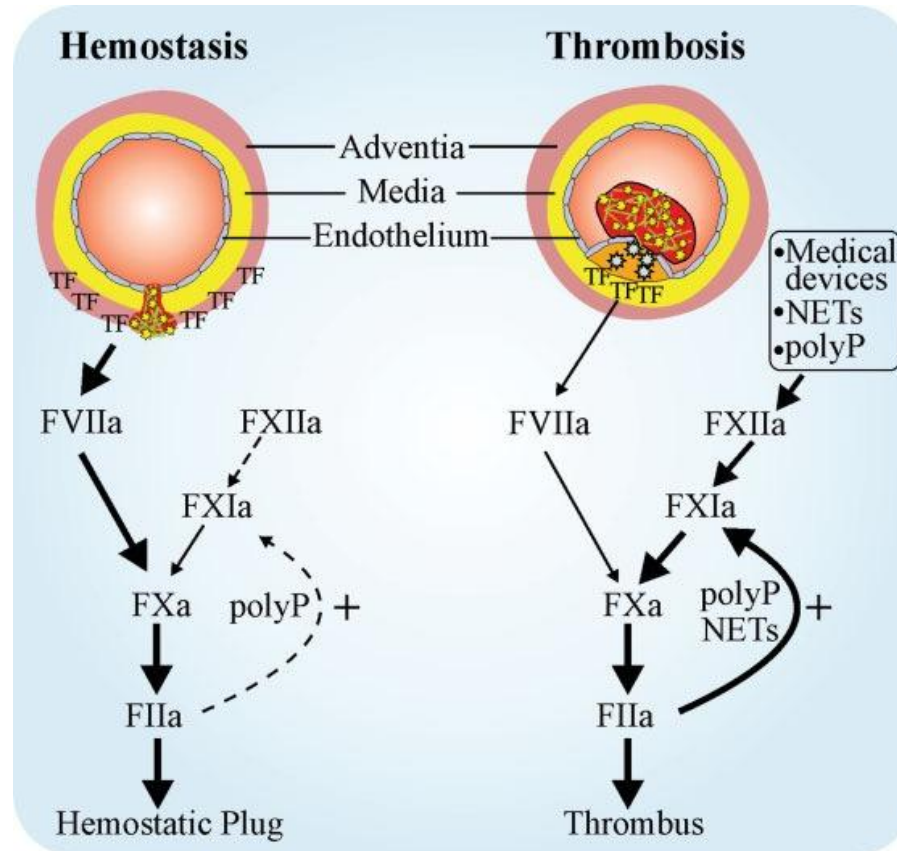
Meijers JC et al. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med* 2000;342(10):696–701

Duga S, Salomon O. Congenital factor XI deficiency: an update. *Semin Thromb Hemost* 2013;39(06):621–631

Separating Hemostasis from Thrombosis

Hemostasis is triggered when the hemostatic envelope of tissue factor in the adventitia of blood vessels is breached.

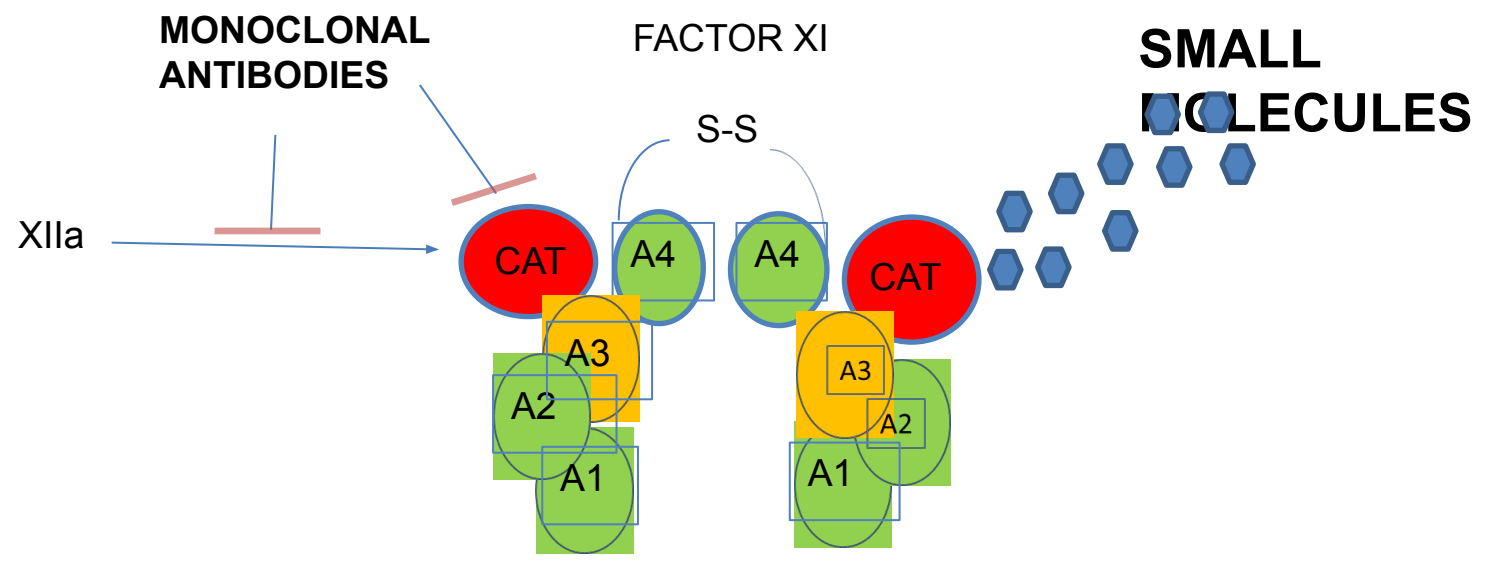
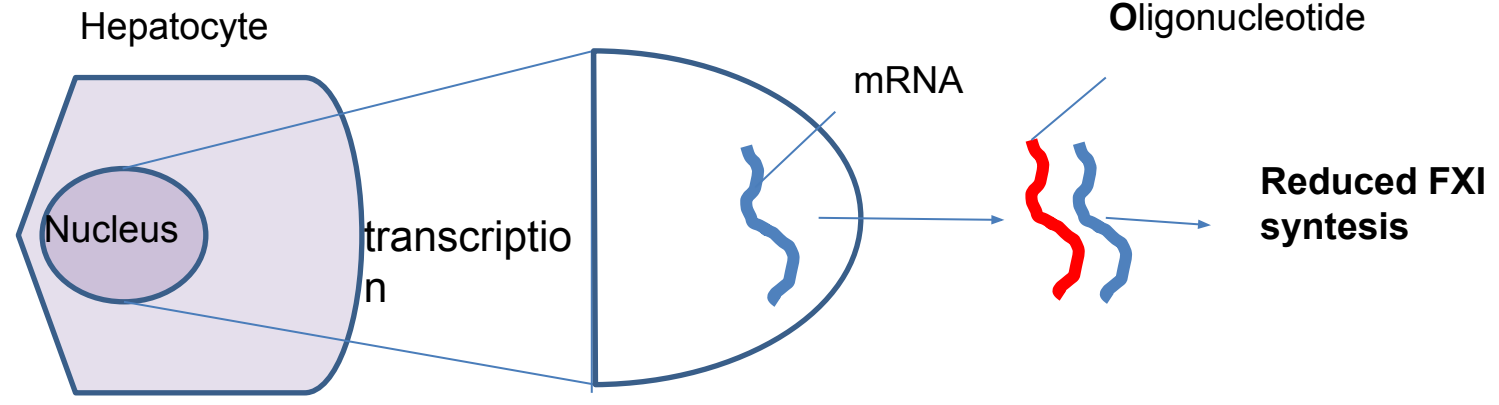
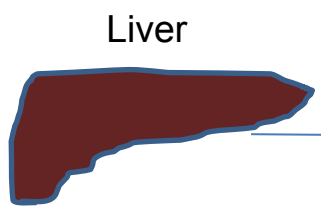
The explosive thrombin generation by TF makes it so that thrombin formation due to contact phase of coagulation is redundant.



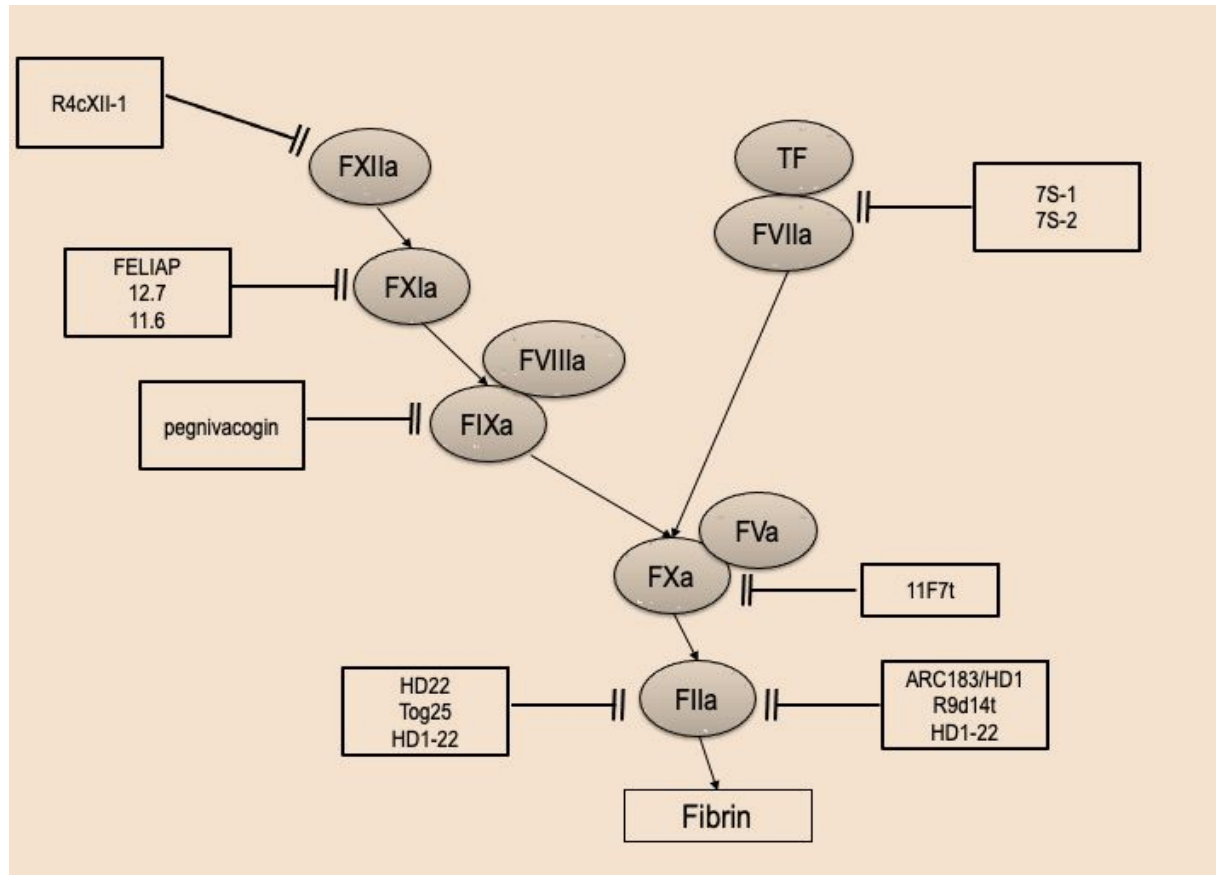
In contrast to hemostasis, thrombosis is usually initiated by low concentrations of tissue factor exposed at the sites of atherosclerotic plaque disruption or expressed on activated monocytes or microvesicles that are tethered to endothelial cells.

Thrombus growth and stabilization under these conditions depends on feedback activation of FXI by thrombin

ASO

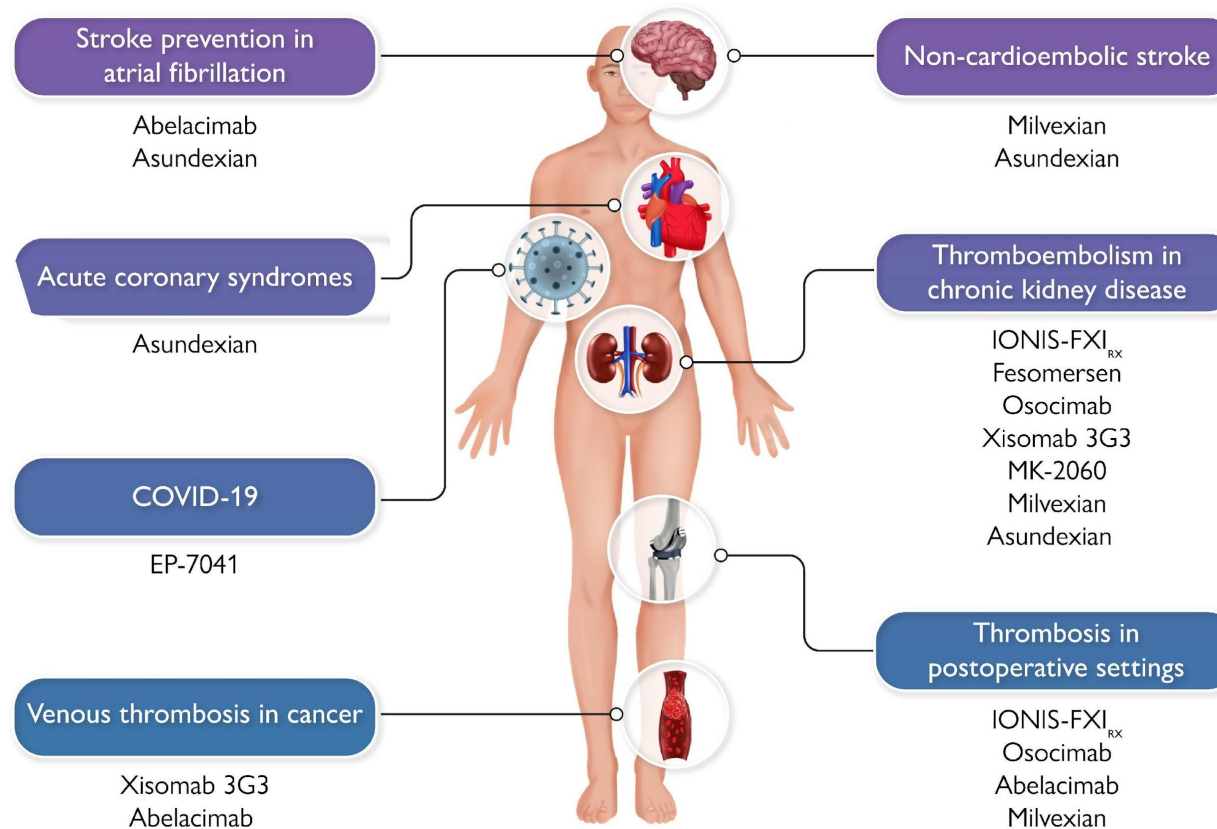


Aptamers*



*Short sequences of DNA, RNA or peptides that bind a specific target protein

Graphical Abstract Possible forthcoming therapeutic indications for FXI/XIa inhibitors.



Pharmacologic characteristics and properties of experimental anticoagulant drugs.

	Agents	Mechanism of action	Route of administration	Onset of action	Half-life	Renal excretion	CYP metabolism	Food and drug interactions
Antisense oligonucleotides	IONIS FXI-Rx, Fesomersen	block FXI biosynthesis	subcutaneous	slow (weeks)	long (weeks)	No	No	Not expected
Antibodies	Abelacimab Osocimsab Xisomab MK-2060 REGN9933 Garadacimab*	bind and inhibit FXI (* inhibits FXII)	subcutaneous or intravenous	hours to days	long (days to weeks)	No	No	Not expected
Small molecules	Milvexian Asundexian ONO-7684 SHR2285 EP-7041 BMS-962212	bind and inhibit FXI	intravenous or oral	rapid (minutes to hours)	short (hours)	Yes	Yes	Possible
Aptamers	FELIAP 11.16 12.7	bind and inhibit FXI	subcutaneous or intravenous	rapid (minutes to hours)	short (minutes to hours)	Yes (modifiable)	No	Not expected
Natural compounds	acaNAP10 Faxsiator Desmolaris Boophilin Ir-CPI**	bind and inhibit FXI (** inhibits FXI and FXII)	subcutaneous or intravenous	rapid (minutes)	short (hours)	Unknown	No	Unknown

Clinical trials with FXI inhibitors for stroke prevention in patients with atrial fibrillation.

Agent, dosage, registry number	Trial phase	Comparator	Number of patients	Age of patients	Follow-up	Results (efficacy)	Results (safety)	Comments
Abelacimab, 120 and 180 mg (3 monthly doses), NCT04213807	2a	placebo	18	18-85 years	170 days	abelacimab reduced FXI plasma levels and prolonged aPTT		limited ability to detect safety signals, due to study design
Asundexian, 20 and 50 mg once daily, NCT04218266	2	Apixaban, 5 mg twice daily	753	85% were ≥65 years; 46% were >75 years	12 weeks		lower rates of major or CRNM bleeding events with asundexian (pooled doses) vs apixaban	efficacy not tested
Abelacimab, two doses, NCT04755283	2	Rivaroxaban, dosing according to product label	1200	≥55 years	17 months	active study, not recruiting; primary outcomes: major or CRNM bleeding events		
Abelacimab, 150 mg once monthly, NCT 05712200	3	placebo	1900	≥65 years	up to 30 months	now recruiting; primary outcomes: ischemic stroke, systemic embolism, time to first occurrence of BARC type 3c/5 bleeding		
Asundexian, 50 mg once daily, NCT05643573	3	Apixaban, dosing according to product label	18000	≥18 years	9-34 months	now recruiting; primary outcomes: ischemic stroke, systemic embolism, ISTH major bleeding		
Milvexian	3	-	-	-	-	planned study; no details available at the time of this publication		

PACIFIC-AF trial of asundexian vs. apixaban in patients with atrial fibrillation

	Asundexian 20 mg (n = 249)	Asundexian 50 mg (n = 254)	Asundexian pooled (n = 503)	Apixaban (n = 250)
Cardiovascular death, myocardial infarction, ischemic stroke or systemic embolism	2	4	6	3
CRNM bleeding	3 *	1 **	4 ***	6
ISTH major bleeding	0	0	0	0
Drug related adverse events	118 (47%)	120 (47%)	238 (47%)	122 (49%)
Drug related serious adverse events	4 (2%)	0	4 (1%)	0

CRNM bleeding = clinically relevant non-major bleeding. ISTH = International Society on Thrombosis and Haemostasis.

* Incidence proportion 0.50 (0.14 – 1.68) vs apixaban

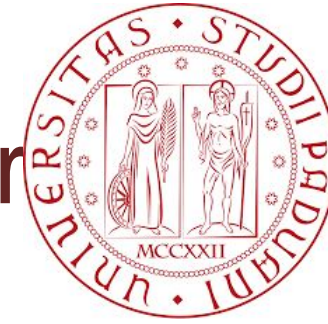
** Incidence proportion 0.16 (0.01 – 0.99) vs apixaban

*** Incidence proportion 0.33 (0.09 – 0.97) vs apixaban

Conclusions

- The introduction of DOACs has produced additional benefits with respect to the long-honored VKA, although limits and risks of anticoagulant therapy persist, among which hemorrhagic complications are of primary concern.
- These successes and related drawbacks justify the ongoing, intense search for new anticoagulant drugs, characterized by more favorable safety profiles.
- The possible advantage of new agents would be even more relevant in patients with a higher risk of bleeding, such as the elderly and those with advanced renal or liver disease.

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Established in 1222

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