New Kids on the Block: Factor XI Inhibitors, the New Novel Oral Anticoagulant Agents

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Objectives

- Review the coagulation cascade and the pharmacology of the Factor XI inhibitors
- Explain current literature and trials examining the efficacy of Factor XI inhibitors
- Describe the current place in anticoagulant management for Factor XI inhibitors

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Financial Disclosures

- Nothing to disclose

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Baseline Knowledge Check

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Coagulation Basics

Objective #1: Review the coagulation cascade and the pharmacology of the Factor XI inhibitors

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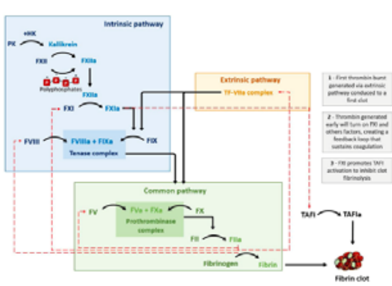

Bentounes NK, et al. J Med Vasc. 2023;48(2):69-80.

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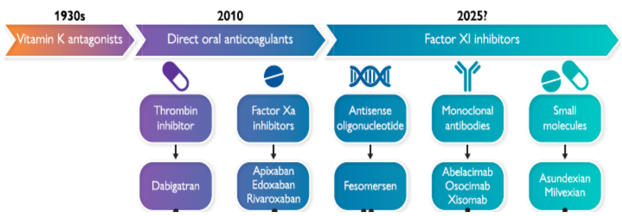

van Es N. Eur Heart J. 2023;44(20):1795-1806.

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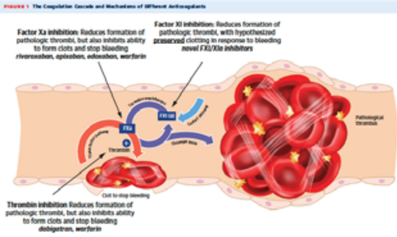
FIGURE 1 The Coagulation Cascade and Mechanisms of Different Anticoagulants



Direct oral anticoagulants and warfarin all act on the common pathway, inhibiting both hemostasis and pathologic thrombus formation. By inhibiting FXI, it may be possible to reduce the risk of thrombi while preserving the functionality of the clotting cascade in response to bleeding.

Harrington J, et al. J Am Coll Cardiol. 2023;81(8):771-779

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The New Kids – Factor XI Inhibitors

Objective #2: Explain current literature and trials examining the efficacy of Factor XI inhibitors

Objective #3: Describe the current place in anticoagulant management for Factor XI inhibitors

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Factor XI – Filling an Unmet Need

- Unmet need → need for anticoagulation without increased risk of bleeding
  - Direct oral anticoagulants (DOACs) provided alternative to vitamin K antagonists (VKAs), however, not without limitations
- What is Factor XI?
  - Coagulation protein associated with decreased risk of thrombosis and low bleeding tendency
  - Factor XI Deficiency → hemophilia C
    - Prolongs activated partial thromboplastin time (aPTT)

De Caterina R, Prisco D, Eikelboom JW. Eur Heart J. 2023;44(4):280-292.

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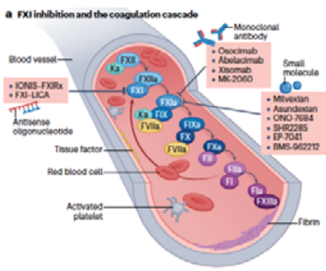

Gigante B, Ten Cate H. Nat Rev Cardiol. 2023;20(8):511-512.

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Pharmacological and Pharmacokinetic Data of FXI/XIa Inhibitors

Drug	IONIS-FXI_{Rx}	Fesomersen	Osocimab	Abelcimab	Xisomab 3G3	Milvexian	Asundexian
Type	Antisense oligonucleotide of FXI	Antisense oligonucleotide of FXI	Monoclonal antibody to FXIa	Monoclonal antibody to FXI/FXIa	Monoclonal antibody to FXI	Small molecule inhibitor of FXIa	Small molecule inhibitor of FXIa
APTT	↑	↑	↑	↑	↑	↑	↑
PT	No effect	No data	No effect	No effect	No effect	No effect	No effect
TT	No data	No data	No data	No effect	No data	No data	No data
Platelets	No effect	No data	No effect	No data	No data	No effect	No data
Mechanism of Action	Inhibits FXI messenger RNA	Inhibits FXI messenger RNA	Binds and inhibits FXIa	Binds and inhibits FXI and FXIa	Binds FXI and blocks activation by FXIIa	Binds and inhibits FXIa	Binds and inhibits FXIa
Administration	SQ (weekly)	SQ (weekly)	IV, SQ (monthly)	SQ (monthly)	IV (monthly)	Oral	Oral
Half-life	20 days	1-122 hours	30-44 days	25-30 days	20-28 days	11-18 hours	16-18 hours
Activity	Slow and long-acting	Slow and long-acting	Fast and long-acting	Fast and long-acting	Fast and long-acting	Fast and short-acting	Fast and short-acting
Renal excretion	No	No	No	No	No	20% renal elimination	15% renal elimination
CYP metabolism	No	No	No	No	No	CYP 3A4	CYP 3A4
Drug-drug interactions	Low risk	Low risk	Low risk	Low risk	Low risk	Limited	Midazolam

Adapted from: Bentounes NK, Melicine S, Martin AC, Smadja DM, Gendron N. J Med Vasc. 2023;48(2):69-80.

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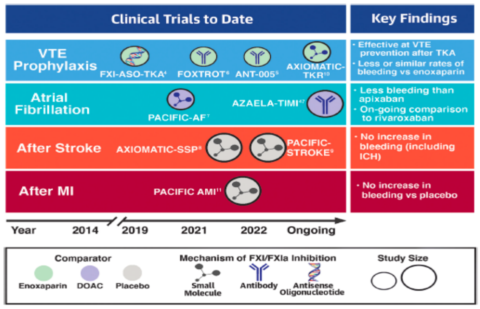
Factor XI Inhibitors – Clinical Trials



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Looking Ahead – Trials in Progress

Trial	Name	Sponsor	Intervention	Primary Objective	Phase	Estimated Completion Date
NCT05618808	A Phase 2, Multicenter, Randomized, Open-Label, Active-Control Study of REGN9933, a Factor XI Monoclonal Antibody, for Prevention of Venous Thromboembolism After Elective, Unilateral, Total Knee Arthroplasty	Regeneron Pharmaceuticals	Drug: REGN9933 Drug: Enoxaparin Drug: Apixaban	Evaluate the efficacy of REGN9933 for the prevention of venous thromboembolism (VTE) after unilateral total knee arthroplasty (TKA), compared to enoxaparin.	Phase 2	2024-08-10
NCT05027074	A Randomized Parallel-group, Placebo-controlled, Double-blind, Event-driven, Multi-center Phase 2 Clinical Outcome Trial of Prevention of Arteriovenous Graft Thrombosis and Safety of MK-2060 in Patients With End Stage Renal Disease Receiving Hemodialysis	Merck Sharp & Dohme LLC	Drug: MK-2060 Drug: Placebo	Evaluate the efficacy and safety of two different doses of MK-2060 (a monoclonal antibody against Factor XI) in end stage renal disease (ESRD) participants receiving hemodialysis via an arteriovenous graft (AVG). Data from this study will be used to aid dose selection of MK-2060 in future studies.	Phase 2	2024-07-10

https://clinicaltrials.gov/search?term=Factor%20XI%20inhibitor&aggFilters=status:act%20rec. Accessed February 25, 2024

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Key Takeaways

- Factor XI is a coagulation protein associated with decreased risk of thrombosis and low bleeding tendency
- Factor XI/XIa inhibitors are hypothesized to prevent the formation of pathological clots while decreasing the risk of bleeding
- Several trials have demonstrated the efficacy of the Factor XI/XIa inhibitors in various conditions requiring the use of anticoagulants

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Knowledge Check

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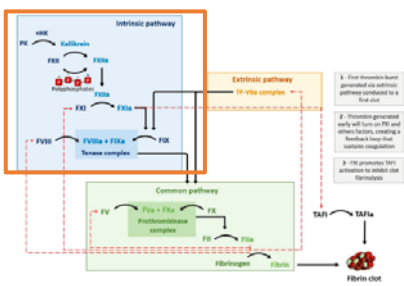

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