Frequently Asked Questions

Factor XI/XIa Inhibitors

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Frequently Asked Questions on Factor XI/XIa Inhibitors

Factor XI/XIa inhibitors are an emerging class of anticoagulants designed to “uncouple” thrombosis from hemostasis.[1-3] These agents aim to reduce pathologic (“bad”) clot formation while preserving hemostatic (“good”) clot formation to mitigate bleeding.

As these agents advance through late-phase trials, clinicians need a clear, mechanism-driven framework to understand where they may fit relative to existing anticoagulant and antiplatelet therapies.

This FAQ guide summarizes the current evidence, remaining uncertainties, and stewardship considerations relevant to clinical practice.

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1 Why are new antithrombotic strategies needed for secondary stroke prevention?

Ischemic stroke is a heterogeneous condition driven by multiple, overlapping mechanisms. Early classification systems such as TOAST (Trial of ORG 10172 in Acute Stroke Treatment) provided a foundation for categorizing stroke etiology,[4] such as cardioembolic, large artery atherosclerosis, small vessel "lacunar" disease, cryptogenic (unknown cause), and "other" (more rare etiologies), to inform secondary prevention strategies.

Later frameworks highlighted important limitations of TOAST including incomplete diagnostic evaluations and difficulty assigning causation when multiple potential mechanisms coexist.[5,6] Moreover, substantial heterogeneity in stroke subtype classification has been observed between institutions which can influence approaches to secondary prevention. For example, community hospitals report significantly higher rates of cryptogenic stroke than larger academic medical centers (83.6% vs. 33.1%, $p < 0.001$). Differences in diagnostic evaluation, access to specialized testing, and clinical expertise likely contribute to these discrepancies.[7]

More recent phenotyping approaches, culminating in the Ischemic Stroke Phenotyping System 2025 (ISPS25), emphasize identifying definite, probable, and possible mechanisms to better align secondary prevention strategies with underlying biology.[8]

Despite guideline-directed use of antithrombic therapy, residual ischemic risk persists among many stroke subtypes, while bleeding risk limits further intensification of existing therapies.[1] This imbalance underscores the need for new antithrombotic strategies that more precisely target thrombosis mechanisms and improve secondary stroke prevention without proportionally increasing bleeding risk.

Key point:
Stroke prevention is increasingly mechanism-specific; antithrombotic therapy must evolve accordingly.

2 What are Factor XI/XIa inhibitors, and how are they mechanistically designed to reduce bleeding?

Factor XI is part of the intrinsic coagulation pathway and primarily functions to amplify thrombin (FIIa) generation. When activated to Factor XIa, it enhances clot propagation through activation of Factor IX.[1-3]

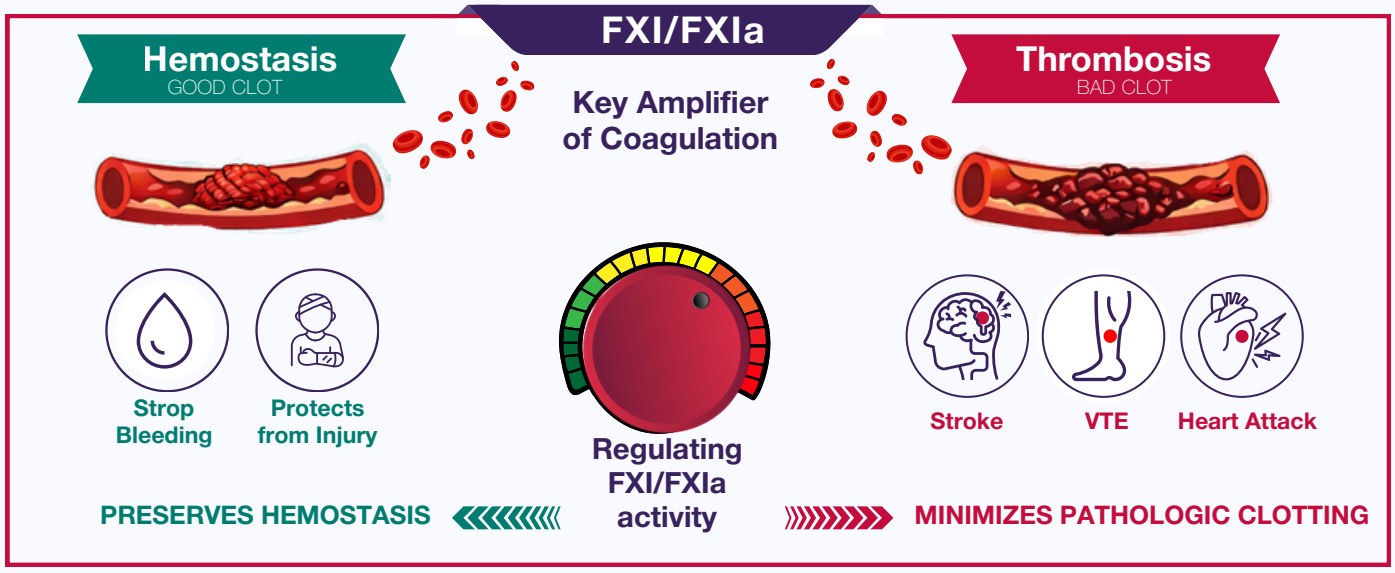
Epidemiologic and genetic studies show that individuals with congenital Factor XI deficiency (also known as hemophilia C) have:

- Reduced rates of venous thromboembolism and ischemic stroke[9-11]
- A relatively mild bleeding phenotype, typically mucocutaneous rather than spontaneous bleeding.[9,12]

In contrast, deficiencies of Factor VIII or Factor IX (hemophilia A and B), particularly if severe, are associated with spontaneous bleeding, including hemarthroses and life-threatening hemorrhage.[9]

These observations suggest that Factor XI plays a larger role in thrombus amplification than in baseline tissue factor-mediated hemostasis.[1-3, 9-12] Selective Factor XI/FXIa inhibition therefore aims to reduce pathologic thrombosis while largely preserving physiologic hemostasis (Figure 1).

Figure 1. Uncoupling Thrombosis from Hemostasis



Key point:

FXI contributes more to pathologic clot formation than to essential hemostasis, supporting the concept of "hemostasis-sparing" anticoagulation.

3 How do Factor XI/XIa inhibitors differ from existing antithrombotic therapies?

Traditional anticoagulants, including direct oral anticoagulants (DOACs) and warfarin, inhibit key components of the common coagulation pathway (e.g., Factor Xa or thrombin [FIIa]). Because these factors are essential for thrombin generation required for both physiologic hemostasis and pathologic thrombosis, their inhibition reduces thrombotic events but also increases bleeding risk.[1,2] This fundamental tradeoff reflects the central role of the common pathway in thrombin generation and normal clot formation.

Antiplatelet agents, by contrast, disrupt platelet adhesion, activation, and aggregation, processes that contribute to thrombus formation across multiple vascular beds.

Factor XI/XIa inhibitors occupy a distinct biologic position within the coagulation cascade. Rather than targeting the common pathway, these agents attenuate intrinsic pathway-mediated amplification of thrombin generation while preserving tissue factor–initiated coagulation through the extrinsic pathway, which is the primary driver of physiologic hemostasis. By avoiding inhibition of the central mediators of clot formation, FXI/XIa inhibition may reduce pathologic thrombosis while mitigating bleeding risk compared with traditional anticoagulant strategies.[1-3]

Table 1. Comparison of Antithrombotic Classes by Biologic Target and Effect

	Factor XI/XIa Inhibitors	DOACs/Warfarin	Antiplatelet Agents
Primary Target	Intrinsic pathway amplification	Common pathway (Factor Xa, IIa)	Platelet adherence, activation, aggregation
Effect on Hemostasis	Largely preserved	Directly impaired	Coagulation preserved
Bleeding Risk Profile	Hypothesized lower	Dose- and agent-dependent	Lower alone; higher in combination with other antithrombotics
Primary Development Focus	High bleeding-risk populations	Broad thrombotic indications	Arterial thrombosis

Key point:
FXI/XIa inhibitors occupy a biologically distinct position in the coagulation cascade.

4 What types of FXI/XIa inhibitors are in development?

FXI/XIa inhibitors are being developed across several pharmacologic platforms, including antisense oligonucleotides, monoclonal antibodies, and small-molecule inhibitors, each with distinct pharmacologic and operational implications.[2,3,13]

Table 2. FXI/XIa Inhibitor Platforms[2,3]

Pharmacologic Modality	Example Agents	Target	Route	Half-Life	Dosing Frequency	Considerations
Antisense Oligonucleotides	Fesomersen	FXI synthesis	SQ	10-20 days	Monthly	• Gradual onset as hepatic FXI production declines • Prolonged offset due to reduced protein synthesis • Convenient infrequent dosing but limited flexibility around procedures
Monoclonal Antibodies	Abelacimab, Osocimab	FXI or FXIa	IV/SQ	20-44 days	Monthly–Quarterly	• Immediate FXI/XIa inhibition with long half-life • Sustained anticoagulant effect with infrequent dosing • Prolonged anticoagulant activity if bleeding or urgent/emergent surgery occurs
Small Molecules	Asundexian, Milvexian	FXIa	Oral	~12-20 hours	QD/BID	• Oral administration with relatively rapid onset and offset • Shorter half-life may allow greater flexibility if bleeding or urgent/emergent surgery occurs

The pharmacologic modality of FXI/XIa inhibitor influences onset and offset of anticoagulant effect, reversibility, and periprocedural management considerations. Agents that reduce FXI synthesis produce gradual declines in circulating FXI levels, whereas direct inhibitors of FXI/XIa produce more immediate anticoagulant effects. Differences in half-life and route of administration also influence dosing frequency, clinical workflow, and management of interruptions around invasive procedures. Readers are referred to recent comprehensive reviews for additional details.[1-3]

Key point:

The pharmacologic modality of FXI/XIa inhibitors influences onset and offset of anticoagulant effect, dosing frequency, periprocedural management and other practical considerations for clinical workflow.[2,3]

5 What do FXI/XIa inhibitor clinical trials show so far?

Clinical development has evaluated FXI/FXIa inhibition across atrial fibrillation, cancer-associated thrombosis, acute coronary syndromes, and non-cardioembolic ischemic stroke populations.[2,3,14-17]

Table 3. Selected Late-Phase Trial Landscape[2,3,14-17]

Agent	Trial name	Population	Intervention	Comparator	Status	Key Signal
Asundexian	OCEANIC-AF	Atrial Fibrillation	Asundexian	Apixaban	Phase III Stopped Early	↑ Thrombosis ↓ Bleeding Did not meet noninferiority vs apixaban
Asundexian	OCEANIC-STROKE	Non-cardioembolic ischemic stroke/ high-risk TIA	Asundexian + SAPT/DAPT	SAPT/DAPT	Phase III Completed	↓ Thrombosis ↔ Bleeding Reduced recurrent ischemic stroke; no significant increase in major bleeding
Milvexian	LIBREXIA-AF	Atrial Fibrillation	Milvexian	Apixaban	Phase III Ongoing	? Thrombosis ? Bleeding Stroke prevention and bleeding outcomes under investigation
Milvexian	LIBREXIA-ACS	Post–myocardial infarction	Milvexian + SAPT/DAPT	SAPT/DAPT	Phase III Stopped Early (Futility)	? Thrombosis ? Bleeding No superiority vs placebo
Milvexian	LIBREXIA-STROKE	Non-cardioembolic ischemic stroke/ high-risk TIA	Milvexian + SAPT/DAPT	SAPT/DAPT	Phase III Ongoing	? Thrombosis ? Bleeding Recurrent stroke and bleeding outcomes under investigation
Abelacimab	ASTER	Cancer-Associated VTE	Abelacimab	Apixaban	Phase III Ongoing	? Thrombosis ? Bleeding Recurrent VTE and bleeding outcomes under investigation
Abelacimab	MAGNOLIA	Cancer-Associated VTE with GI/GU Cancer	Abelacimab	Dalteparin	Phase III Ongoing	? Thrombosis ? Bleeding Bleeding and efficacy outcomes under investigation
Abelacimab	AZALEA TIMI 71	Atrial Fibrillation	Abelacimab	Rivaroxaban	Phase IIb Completed	? Thrombosis ↓ Bleeding Stopped early for improved safety; not powered for efficacy

SAPT: Standard Antiplatelet Therapy
DAPT: Dual Antiplatelet Therapy
LMWH: Low Molecular Weight Heparin
TIA: Transient Ischemic Attack
GI: Gastrointestinal
GU: Genitourinary

While several development programs to date have explored FXI/XIa inhibition across diverse thrombotic conditions, clinical signals have varied by indication and comparator. For example, OCEANIC-AF did not achieve noninferiority over apixaban in patients with atrial fibrillation. In contrast, OCEANIC-STROKE demonstrated superiority versus placebo in patients with non-cardioembolic ischemic stroke or high-risk TIA receiving standard-of-care single or dual antiplatelet therapy. In this population, asundexian 50 mg orally once daily reduced recurrent ischemic stroke (HR 0.74; 95% CI, 0.65–0.84; $p<0.001$) without an increase in ISTH major bleeding (HR 1.10; 95% CI, 0.85–1.44).[16]

Overall, across development programs, reductions in bleeding have generally been more consistent than demonstrations of superior efficacy compared with established therapies.

Key point:

Across clinical trials to date, FXI/XIa inhibition has shown the most consistent signal for reduced bleeding, while superiority for thrombotic efficacy has varied by indication and comparator.

6 Where might Factor XI/XIa inhibitors fit into clinical practice, and in which patients?

If ongoing Phase 3 trials confirm favorable safety and efficacy, Factor XI/XIa inhibitors are most likely to be positioned as an alternative for patients in whom residual thrombotic risk persists despite guideline-directed therapy or where bleeding risk limits intensification of current regimens.

In non-cardioembolic secondary stroke prevention, current trials evaluate Factor XIa inhibitors as adjunctive therapy added to SAPT or DAPT.[16,17] They are not currently positioned to replace DOACs in atrial fibrillation or VKAs in mechanical heart valves.[3]

Beyond stroke, these agents are being studied in clinical settings characterized by competing thrombotic and bleeding hazards.[3,14]

Table 4: Potential Clinical Positioning of Factor XI/XIa Inhibitors[3,14-17]

Clinical Scenario	Current Standard Approach	Potential Role of FXI/XIa Inhibition*
Non-cardioembolic ischemic stroke	SAPT or short-course DAPT[3]	Add-on therapy under investigation to reduce recurrent stroke[16,17]
Large artery atherosclerosis (high-grade stenosis)	DAPT (time-limited)[3]	Potential extended protection with attention to bleeding risk
Atrial fibrillation	DOAC preferred[3]	Not currently positioned to replace DOAC; role dependent on outcomes
Cancer-associated thrombosis	DOAC preferred[3]	Possible bleeding-reduction signal; evidence evolving[14]
Device/contact pathway thrombosis	Standard anticoagulation	Strong biologic rationale; clinical data emerging[15]

*Potential roles are investigational and based on emerging Phase 2/3 trial data. FXI/XIa inhibitors are not currently approved for these indications, and their clinical positioning will depend on results of ongoing studies and future guideline recommendations.

Key point:

Early clinical signals suggest FXI/XIa inhibitors may have their greatest near-term role as adjunctive therapy in selected non-cardioembolic stroke populations, with additional investigations exploring potential applications in other high-risk thrombotic conditions.[3,16,17]

7 What safety, operational, and evidence gaps remain?

Important uncertainties remain as FXI/XIa inhibitors continue to advance through late-phase development and early clinical use. Key considerations include:

- Reversal strategies and emergency management
- Periprocedural interruption and reinitiation protocols
- Management of prolonged anticoagulant effects with some agent
- Potential drug–drug interactions
- Transitions-of-care coordination across inpatient and outpatient settings
- Long-term real-world safety and effectiveness
- Financial implications for patients and health systems

These uncertainties highlight the importance of thoughtful implementation planning and structured antithrombotic stewardship to support safe and appropriate adoption as evidence continues to evolve.

Key point:
Important safety, operational, and evidence gaps remain; structured stewardship and careful implementation planning are essential as FXI/XIa inhibitors enter clinical practice.

8 Why is structured antithrombotic stewardship essential, and what should institutions consider before adopting Factor XI/XIa Inhibitors?

Anticoagulants are among the highest-risk medication classes in clinical practice.[18] The introduction of a new mechanistic class spanning multiple pharmacologic modalities, routes of administration, and pharmacokinetic profiles increases the potential for inappropriate prescribing and management, care fragmentation, and suboptimal patient outcomes.[18,19] Pre-implementation planning is therefore essential to ensure safe, effective, and equitable adoption.

The Anticoagulation Forum Core Elements of Anticoagulation Stewardship provide a practical framework for institutions to guide implementation, oversight, and ongoing quality improvement when introducing new antithrombotic therapies.[19,20]

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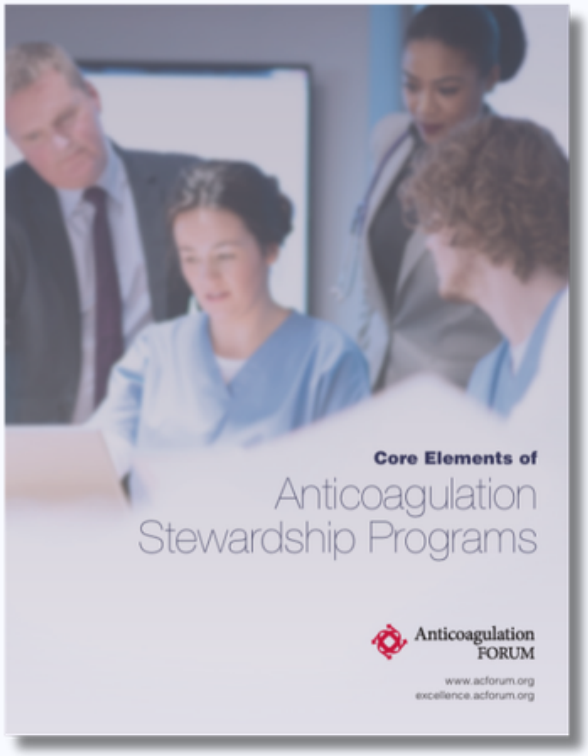

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Key point:
Structured antithrombotic stewardship is essential to ensure safe, appropriate, and coordinated use of FXI/XIa inhibitors.

Table 5 summarizes key antithrombotic stewardship considerations relevant to the adoption of FXI/XIa inhibitors.

Table 5. Antithrombotic Stewardship Considerations for Factor XI/XIa Inhibitor Adoption[19,20]

Core Element	Example Stewardship Considerations*
Secure administrative leadership commitment	• Recognize FX/FXIa inhibitors as high-alert agents requiring structured oversight • Support formulary review and phased adoption with protected time and resources • Allocate protected time and resources for FXI/FXIa protocol development, education, and safety monitoring
Establish professional accountability and expertise	• Define clinical ownership for FXI/XIa inhibitor prescribing and stewardship oversight • Develop institutional expertise in FXI/XIa pharmacology, emerging clinical trial data, and bleeding management • Designate expert consultation pathways for complex cases
Engage multidisciplinary support	• Align stakeholders on formulary role, indications, and target populations • Coordinate across inpatient, outpatient, and procedural settings • Integrate stewardship teams into stroke, thrombosis, and cardiovascular care pathways
Perform data collection, tracking, and analysis	• Capture FXI/XIa inhibitor use within the EHR using discrete data fields • Monitor utilization patterns, patient selection, and clinical outcomes • Track bleeding events, thrombotic outcomes, and periprocedural management to inform quality improvement initiatives
Implement systematic care	• Develop standardized protocols for patient selection, initiation, dose selection, and interruption • Establish institutional guidance for periprocedural management and bleeding response • Embed clinical decision support within the EHR to guide appropriate use
Facilitate transitions of care	• Ensure medication reconciliation and continuity across inpatient and outpatient settings • Address access, coverage, and affordability considerations • Define follow-up pathways to reassess therapy, safety, and adherence
Advance education, comprehension, and competency	• Provide targeted clinician education on FXI/XIa mechanisms, trial evidence, and clinical positioning • Educate patients on expected benefits, bleeding risks, and when to seek medical care using teachback methods • Maintain ongoing competency assessment as evidence and indications evolve

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