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FACTOR XI INHIBITORS AS THE NEXT GENERATION OF ANTICOAGULANTS: A COMPREHENSIVE PHARMACOLOGICAL REVIEW OF ASUNDEXIAN, MILVEXIAN, ABELACIMAB, FESOMERSEN, AND THE DECOUPLING OF THROMBOSIS FROM HEMOSTASIS

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ABSTRACT

Anticoagulant therapy remains one of the most important and most challenging therapeutic interventions in cardiovascular medicine, with current direct oral anticoagulants (DOACs) — apixaban, rivaroxaban, edoxaban, dabigatran — and vitamin K antagonists offering effective thromboprophylaxis but at the cost of clinically significant bleeding, particularly intracranial and major gastrointestinal hemorrhage. The recognition that congenital factor XI (FXI) deficiency produces minimal spontaneous bleeding despite impaired thrombus formation, that FXI participates preferentially in pathological thrombus amplification rather than primary hemostasis, and that high FXI levels are associated with venous and arterial thrombosis has motivated development of FXI-targeting anticoagulants with the promise of decoupling antithrombotic efficacy from bleeding risk. This review provides a comprehensive pharmacological analysis of the FXI inhibitor class, which

encompasses small-molecule oral inhibitors (asundexian, milvexian), monoclonal antibodies (abelacimab, osocimab, frunexian/MAA868), and antisense oligonucleotides (fesomersen). We examine FXI/FXIa biology and the contact pathway, the safety-efficacy rationale, pivotal clinical trial evidence including the AXIOMATIC-TKR phase 2 results, the AZALEA-TIMI 71 trial demonstrating reduced bleeding with abelacimab versus rivaroxaban in atrial fibrillation, the OCEANIC-AF trial in which asundexian failed to demonstrate non-inferiority to apixaban (terminated November 2023), and the ongoing development across multiple indications including venous thromboembolism prevention, atrial fibrillation stroke prevention, secondary stroke prevention, hemodialysis circuit thrombosis, and cancer-associated thrombosis. The review also addresses the Indian context including atrial fibrillation prevalence, venous thromboembolism epidemiology, DOAC access, and the prospective role of FXI inhibitors in low-resource settings. Future directions include reversal agent development, special populations, and the integration of FXI biology into broader anticoagulation strategies.

KEYWORDS: Factor XI; FXIa; anticoagulant; asundexian; milvexian; abelacimab; fesomersen; contact pathway; bleeding; thrombosis; atrial fibrillation; venous thromboembolism; stroke prevention; DOAC.

INTRODUCTION

Anticoagulant therapy is essential for the prevention and treatment of thromboembolic disorders including venous thromboembolism (VTE), stroke prevention in atrial fibrillation (AF), mechanical heart valves, and cancer-associated thrombosis. The historical anticoagulant pharmacopoeia evolved from heparin (introduced in the 1930s) and vitamin K antagonists (warfarin, introduced in the 1940s) to low molecular weight heparins, fondaparinux, and ultimately the direct oral anticoagulants (DOACs) — dabigatran (direct thrombin inhibitor), and rivaroxaban, apixaban, and edoxaban (direct factor Xa inhibitors) — introduced from 2010. The DOACs offered substantial advantages over warfarin: fixed dosing without routine monitoring, fewer drug and food interactions, and reduced intracranial hemorrhage risk. The DOAC era transformed clinical practice and now represents standard of care for most non-valvular AF and VTE indications.[1-6]

Despite these advances, current anticoagulant therapy remains constrained by clinically significant bleeding risk. In landmark DOAC trials, major bleeding rates were approximately 2–4% per year in non-valvular atrial fibrillation populations and 1–2% per year in VTE

secondary prevention, with serious bleeding (intracranial, fatal, or requiring transfusion) occurring in approximately 0.5–1.5% per year. Bleeding risk is concentrated in elderly populations, patients with renal dysfunction, those with concomitant antiplatelet therapy, and patients undergoing surgical procedures.[7, 8] Concerns regarding bleeding contribute to undertreatment of anticoagulation: in registries of patients with non-valvular AF, only 60–70% of eligible high-risk patients receive guideline-recommended anticoagulation, with bleeding concerns frequently cited as the reason for non-treatment.[9,10]

The recognition that congenital factor XI (FXI) deficiency — also called hemophilia C, prevalent in Ashkenazi Jewish populations — produces only mild and provoked bleeding rather than the severe spontaneous bleeding of FVIII deficiency (hemophilia A) or FIX deficiency (hemophilia B), and that FXI deficient individuals appear protected from venous thromboembolism, was a critical observation. Subsequent epidemiological studies demonstrated that elevated FXI levels are associated with increased risk of VTE, ischemic stroke, and myocardial infarction. Murine and primate studies confirmed that FXI inhibition reduces thrombus formation without prolonging bleeding time or impairing primary hemostasis. These observations crystallized the FXI hypothesis: FXI participates preferentially in pathological thrombus amplification rather than primary hemostasis, and selective FXI inhibition can therefore decouple antithrombotic efficacy from bleeding risk — a ‘holy grail’ goal of anticoagulation pharmacology.[11-15]

This review provides a comprehensive pharmacological analysis of the FXI inhibitor class. We examine FXI/FXIa biology and the contact pathway; the safety-efficacy rationale; the four pharmacological approaches (small-molecule oral inhibitors, monoclonal antibodies, antisense oligonucleotides, aptamers); pivotal phase 2 and 3 clinical trial evidence; the November 2023 OCEANIC-AF failure of asundexian and its interpretation; the AZALEA-TIMI 71 positive results with abelacimab; the AXIOMATIC and PACIFIC programs; the breadth of clinical indications under investigation; Indian thromboembolic epidemiology and the prospective role of FXI inhibitors in low-resource settings; and future directions.[16]

FACTOR XI BIOLOGY AND THE CONTACT PATHWAY

FXI Structure and Activation

Factor XI is a 160-kDa serine protease zymogen circulating in plasma at approximately 30 nM (5 µg/mL), produced primarily by hepatocytes. The mature FXI molecule is a homodimer of two identical 80-kDa chains linked by a disulfide bond, with each subunit containing four

apple domains and a serine protease catalytic domain. FXI is activated to factor XIa (FXIa) by FXIIa (the principal physiological activator in the contact pathway), thrombin (positive feedback in the amplification phase), or auto-activation under shear conditions. FXIa subsequently activates factor IX, leading to amplification of thrombin generation through the intrinsic pathway.[17,18]

The Contact Pathway versus Primary Hemostasis

The contact pathway (intrinsic pathway initiation) is activated when blood contacts negatively-charged surfaces, including foreign materials (dialysis membranes, catheters, mechanical heart valves), polyphosphates released from activated platelets, neutrophil extracellular traps (NETs), nucleic acids, and pathological structures including atherosclerotic plaques and ruptured aneurysms. Activation of FXII generates FXIIa, which activates FXI. FXI deficiency or inhibition does not impair the tissue factor-initiated extrinsic pathway responsible for primary hemostasis after injury, providing the mechanistic basis for the favorable bleeding profile of FXI inhibition.[19-23]

FXI in Thrombus Amplification

Beyond its role in contact pathway initiation, FXIa contributes to thrombus amplification through the thrombin positive-feedback loop: trace thrombin generated by the tissue factor pathway activates FXI, generating additional FXIa that activates FIX, accelerating prothrombinase complex formation and thrombin amplification. This amplification mechanism is particularly important in pathological thrombosis (stasis-induced venous thrombi, arterial thrombi on ruptured plaques) but less critical for the rapid hemostatic plug formation at sites of injury, where high local tissue factor and platelet activation drive hemostasis through tissue factor-initiated mechanisms. FXI inhibition therefore preferentially affects pathological thrombus extension while sparing primary hemostasis.[24]

PHARMACOLOGICAL APPROACHES TO FXI INHIBITION

Small-Molecule Oral Inhibitors

Small-molecule FXIa active-site inhibitors offer oral bioavailability, rapid onset and offset (half-lives 10–24 hours), and the convenience expected of DOACs. The two most advanced candidates are asundexian (BAY 2433334, Bayer) and milvexian (BMS-986177/JNJ-70033093, Bristol Myers Squibb and Johnson & Johnson). Both demonstrate selective inhibition of FXIa with minimal effect on other coagulation proteases. Pharmacokinetics support once-daily (asundexian) or twice-daily (milvexian) dosing. Plasma concentrations

correlate with FXI activity reduction and activated partial thromboplastin time (aPTT) prolongation.[25]

Monoclonal Antibodies

Anti-FXI monoclonal antibodies offer high target specificity, prolonged action enabling monthly to quarterly dosing, and the safety profile typical of biologics (no hepatic or renal clearance dependency). The leading candidate is abelacimab (MAA868, Anthos Therapeutics, originally Novartis), a fully human IgG1 antibody that binds the catalytic domain of FXI in both the zymogen (FXI) and activated (FXIa) forms, producing both prevention of FXI activation and inhibition of generated FXIa. Subcutaneous or intravenous loading dose followed by monthly subcutaneous maintenance achieves sustained FXI inhibition. Osocimab (BAY 1213790, Bayer) and frunexian are alternative anti-FXI/FXIa antibodies.

Antisense Oligonucleotides

Antisense oligonucleotides (ASOs) reduce FXI expression by targeting hepatic FXI mRNA for degradation, producing sustained reduction in plasma FXI levels (50–90% reduction at therapeutic doses). The GalNAc-conjugated ASO fesomersen (IONIS-FXI-LRx, also known as ION-957) developed by Ionis Pharmaceuticals and Bayer is administered subcutaneously monthly. The hepatocyte-targeted delivery reduces extrahepatic effects. The slow onset (4–6 weeks to achieve full effect) and slow offset (FXI levels return to baseline over 8–12 weeks) limit utility for acute indications but suit chronic prevention. The original IONIS-FXIRx had been studied in dialysis patients (FXI-ASO trial) and orthopedic surgery.

Comparative Properties of Approaches

The four pharmacological approaches offer complementary characteristics: small molecules provide convenience, rapid onset/offset, and oral administration suitable for routine use; antibodies provide high specificity and prolonged action suitable for monthly dosing in stable chronic indications; ASOs provide sustained reduction in production suitable for chronic indications with minimal dosing frequency; and oral small molecules are positioned for the largest market segments (AF and VTE) with the broadest physician familiarity expected.

ASUNDEXIAN: ORAL SMALL-MOLECULE FXIA INHIBITOR

Pharmacology

Asundexian (BAY 2433334), developed by Bayer, is an orally bioavailable, selective FXIa active-site inhibitor with half-life approximately 15 hours supporting once-daily dosing.

Absorption is rapid with peak plasma concentrations within 1–2 hours. Asundexian is metabolized primarily by CYP3A4 and demonstrates modest CYP3A4 inhibitor interactions. Renal clearance is minimal, supporting use in patients with reduced renal function (in contrast to dabigatran and to a lesser degree the FXa inhibitors). Asundexian has been studied at doses of 20 mg and 50 mg once daily.[26]

PACIFIC Program: Phase 2 Studies

The PACIFIC program comprised three phase 2 trials in different indications: PACIFIC-AF (non-valvular AF) demonstrated significantly lower bleeding rates with asundexian 20 mg and 50 mg versus apixaban 5 mg twice daily over 12 weeks. PACIFIC-AMI (acute myocardial infarction) found similar bleeding rates and a non-significant trend for fewer ischemic events with asundexian added to standard antiplatelet therapy. PACIFIC-STROKE (non-cardioembolic ischemic stroke) found dose-related reductions in covert brain infarcts. These results supported phase 3 development in AF and secondary stroke prevention.[27-29]

OCEANIC-AF: The November 2023 Failure

OCEANIC-AF was a phase 3 trial randomizing approximately 14,810 patients with non-valvular AF to asundexian 50 mg once daily or apixaban 5 mg twice daily, with the primary endpoint of stroke or systemic embolism. On November 19, 2023, Bayer announced that the trial was terminated early on Data Monitoring Committee recommendation due to inferior efficacy with asundexian compared with apixaban. While bleeding was lower with asundexian (consistent with the FXI inhibitor hypothesis), the increased stroke/systemic embolism with asundexian indicated that the dose was insufficient or that FXI inhibition alone provides inadequate efficacy in AF compared with factor Xa inhibition.[30]

The OCEANIC-AF failure represented a major setback for asundexian and prompted active analysis of the underlying reasons. Hypotheses include: (1) insufficient FXI inhibition at the 50 mg dose (which produced approximately 90% FXIa inhibition but may not be sufficient for AF where high-shear left atrial thrombus formation requires deeper FXI suppression); (2) qualitative differences between FXI/FXIa inhibition and FXa inhibition in AF-related thromboembolism; (3) potential differences in efficacy across thromboembolic mechanisms (perhaps AF is less amenable to FXI-based therapy than VTE prevention or surgical thromboprophylaxis). The OCEANIC-STROKE trial in secondary stroke prevention is continuing.[31]

MILVEXIAN: ORAL SMALL-MOLECULE FXIA INHIBITOR

Pharmacology

Milvexian (BMS-986177/JNJ-70033093), co-developed by Bristol Myers Squibb and Johnson & Johnson, is an orally bioavailable, selective FXIa active-site inhibitor. The half-life of approximately 12–15 hours supports twice-daily dosing. Milvexian is metabolized by CYP3A4 with modest drug interaction potential. Doses studied in clinical trials range from 25 mg twice daily to 200 mg twice daily.[32,33]

AXIOMATIC-TKR: Phase 2 in Orthopedic Thromboprophylaxis

AXIOMATIC-TKR randomized 1,242 patients undergoing knee arthroplasty to one of seven milvexian dose regimens (25–200 mg once or twice daily) or enoxaparin 40 mg subcutaneously daily for 10–14 days. Venographic VTE rates were significantly reduced with milvexian 100 mg twice daily and higher (~12%) versus enoxaparin (~21%), with bleeding rates similar or lower. The trial established proof-of-concept for oral FXI inhibition in surgical thromboprophylaxis.[34]

AXIOMATIC-SSP: Secondary Stroke Prevention

AXIOMATIC-SSP randomized 2,366 patients with recent ischemic stroke or high-risk TIA to milvexian (25, 50, 100, or 200 mg twice daily) or placebo, added to standard antiplatelet therapy (aspirin plus clopidogrel for 21 days, then aspirin alone), for 90 days. The primary endpoint of MRI-detected covert infarcts or symptomatic stroke at 90 days was numerically reduced with milvexian at higher doses but did not reach statistical significance. Major bleeding rates were low and similar across treatment arms. The trial supported continued phase 3 development.[35]

LIBREXIA Phase 3 Program

BMS and Johnson & Johnson are advancing milvexian in phase 3 in three indications under the LIBREXIA program: LIBREXIA-AF (atrial fibrillation, in light of OCEANIC-AF failure, with adapted design potentially using higher doses), LIBREXIA-STROKE (secondary stroke prevention following AXIOMATIC-SSP), and LIBREXIA-ACS (post-acute coronary syndrome). Initial results are expected from 2026 onwards. The milvexian phase 3 program will be informative regarding whether oral small-molecule FXI inhibition can establish a place in AF and other major indications.

ABELACIMAB: ANTI-FXI/FXIA MONOCLONAL ANTIBODY

Pharmacology

Abelacimab (MAA868), developed by Anthos Therapeutics (originally Novartis), is a fully human IgG1 monoclonal antibody that binds the catalytic domain of FXI in both the zymogen and activated forms, producing dual inhibition. The pharmacokinetic profile (intravenous loading dose followed by monthly subcutaneous administration) achieves sustained near-complete FXI inhibition. Onset is rapid (within hours of IV loading), and offset is gradual (FXI activity recovers over weeks after dose cessation).[36]

ANT-005 Phase 2: Orthopedic Thromboprophylaxis

The ANT-005 trial randomized 412 patients undergoing knee arthroplasty to abelacimab (30, 75, or 150 mg IV once postoperatively) or enoxaparin 40 mg daily subcutaneously for 10 days. Venographic VTE rates were significantly lower with abelacimab 150 mg (4%) versus enoxaparin (22%), and lower also at the 75 mg dose. Major bleeding was numerically lower with abelacimab. The trial demonstrated substantial efficacy of single-dose IV antibody for short-term thromboprophylaxis.[37]

AZALEA-TIMI 71: Atrial Fibrillation

AZALEA-TIMI 71 randomized 1,287 patients with non-valvular AF to abelacimab (90 mg or 150 mg SC monthly) or rivaroxaban (20 mg orally daily) for approximately 21 months. On November 14, 2023 — just days before the OCEANIC-AF asundexian failure announcement — Anthos announced positive interim results: abelacimab produced approximately 60–67% reduction in major and clinically relevant non-major bleeding compared with rivaroxaban (the primary safety endpoint), with the Data Monitoring Committee stopping the trial early due to overwhelming bleeding benefit. The trial was not powered for efficacy (stroke/systemic embolism), and the long-term and definitive efficacy demonstration awaits the phase 3 LILAC-TIMI 76 program.[38]

LILAC, MAGNOLIA, and ASTER Phase 3 Programs

Anthos is advancing abelacimab in phase 3 across multiple indications: LILAC-TIMI 76 evaluates abelacimab versus rivaroxaban in AF patients ineligible for oral anticoagulation due to high bleeding risk; MAGNOLIA evaluates abelacimab in cancer-associated VTE compared with apixaban; ASTER evaluates abelacimab versus apixaban in cancer-associated VTE secondary prevention. Initial results are expected from 2025–2026. Abelacimab's combination of demonstrated bleeding benefit in AZALEA, suitable pharmacokinetics for

chronic indications, and convenient monthly subcutaneous administration positions it favorably in the FXI inhibitor class.

FESOMERSEN, OSOCIMAB, AND OTHER FXI APPROACHES

Fesomersen (IONIS-FXI-LRx)

Fesomersen (ION-957, IONIS-FXI-LRx), developed by Ionis Pharmaceuticals and licensed to Bayer, is a GalNAc-conjugated antisense oligonucleotide targeting hepatic FXI mRNA for degradation. Subcutaneous monthly administration produces dose-dependent reduction in plasma FXI levels (50–90% reduction at therapeutic doses). The slow onset (4–6 weeks) and offset (8–12 weeks) suit chronic prevention. Phase 2 trials in end-stage renal disease (ESRD) patients on hemodialysis (RE-THINc ESRD) demonstrated reductions in dialyzer thrombosis and bleeding, with continued phase 2/3 development in ESRD anticoagulation, AF, and VTE prevention.[39, 40]

Osocimab and the Original FXI ASO

Osocimab (BAY 1213790), an anti-FXI monoclonal antibody developed by Bayer, demonstrated efficacy in the FOXTROT trial in orthopedic thromboprophylaxis with single-dose IV administration. The original IONIS-FXIRx ASO (precursor to fesomersen) was studied in ESRD patients in the FXI-ASO trial and demonstrated reduced thrombotic events in dialysis populations. The transition to the GalNAc-conjugated fesomersen improved tolerability and reduced injection-site reactions.[41, 42]

CLINICAL INDICATIONS AND POSITIONING

Atrial Fibrillation Stroke Prevention

Atrial fibrillation is the largest target indication for anticoagulation, with approximately 40 million people globally and an estimated 10–15 million in India having the condition. The OCEANIC-AF failure of asundexian and the AZALEA-TIMI 71 success of abelacimab provide contrasting signals. Definitive AF efficacy will depend on LILAC-TIMI 76 (abelacimab versus rivaroxaban in high-bleeding-risk AF) and LIBREXIA-AF (milvexian phase 3). FXI inhibitors may ultimately find their place in AF patients with elevated bleeding risk who are currently undertreated or untreated.[43-47]

Venous Thromboembolism Prevention and Treatment

Surgical thromboprophylaxis (particularly orthopedic) provides a well-defined setting where FXI inhibition has demonstrated proof-of-concept (AXIOMATIC-TKR, ANT-005). Medical

thromboprophylaxis in hospitalized patients is another natural application. VTE treatment (acute DVT/PE) requires rapid onset, which limits the antibodies and ASOs but suits the oral small molecules. Cancer-associated thrombosis is a particular focus of abelacimab development (MAGNOLIA, ASTER), where bleeding risk is elevated with conventional DOACs.[48, 49]

Secondary Stroke Prevention

Secondary stroke prevention after non-cardioembolic ischemic stroke represents a setting where antiplatelet therapy alone is the current standard but residual ischemic risk remains substantial. The PACIFIC-STROKE (asundexian) and AXIOMATIC-SSP (milvexian) trials demonstrated proof-of-concept for FXI inhibitor addition to antiplatelet therapy. Phase 3 trials OCEANIC-STROKE and LIBREXIA-STROKE are evaluating the strategy. The combined antiplatelet plus FXI inhibitor approach may provide superior ischemic prevention without the bleeding excess of dual antiplatelet plus DOAC strategies.

End-Stage Renal Disease and Dialysis

Patients with ESRD on hemodialysis present particular anticoagulation challenges: high thrombotic risk (dialysis circuit thrombosis, vascular access thrombosis, AF stroke), high bleeding risk (uremic platelet dysfunction, frequent vascular access procedures), and contraindications or dose limitations for most DOACs (renal clearance dependencies). FXI inhibitors — particularly fesomersen (no renal clearance), abelacimab (no renal clearance, monthly administration), and potentially small molecules with renal-sparing pharmacokinetics (asundexian) — offer particular promise for this challenging population.

Acute Coronary Syndrome and Stable Cardiovascular Disease

FXI inhibitor addition to standard antiplatelet therapy in ACS or stable cardiovascular disease may reduce ischemic events without excess bleeding. PACIFIC-AMI demonstrated proof-of-concept and LIBREXIA-ACS is advancing this approach to phase 3. The combination strategy may eventually compete with or complement low-dose rivaroxaban (COMPASS regimen) for cardiovascular event prevention, particularly given the central role of atherothrombosis and modifiable cardiovascular risk in this population.[50-53]

INDIAN ANTICOAGULATION CONTEXT

Anticoagulation needs in India are substantial. Atrial fibrillation prevalence is estimated at 1–2% in adults aged 30+, translating to approximately 10–15 million affected individuals;

prevalence rises sharply with age, exceeding 8% in those over 75. AF-related stroke is a major cause of disability, with the Indian Stroke Registry documenting that approximately 15–25% of ischemic strokes are cardioembolic, often AF-related; emerging prognostic markers such as the platelet-to-lymphocyte ratio are being evaluated in Indian stroke cohorts, and electrocardiographic screening remains central to AF detection. VTE epidemiology in India is less well-characterized, with substantial variation among studies; the perceived 'low VTE rates' in Indians have been revised upward in recent prospective studies including registries from major tertiary centers.[54-57]

Current anticoagulation in India relies primarily on generic warfarin (₹50–150/month), generic DOACs (apixaban, rivaroxaban, dabigatran, edoxaban — all available as generics from major Indian manufacturers), and low molecular weight heparins for specific indications. DOAC prices in India have fallen substantially with generic competition: apixaban 5 mg twice daily costs approximately ₹1,500–3,000 per month, rivaroxaban 20 mg daily approximately ₹1,500–2,500 per month — making chronic DOAC therapy increasingly affordable but still substantial for many Indian households. The anticoagulation gap remains significant: studies estimate only 30–50% of eligible AF patients receive guideline-recommended anticoagulation, with concerns regarding bleeding, monitoring (for warfarin), and cost cited as principal barriers.[58, 59]

FXI inhibitors are not yet available in India; clinical access during the phase 3 development era will be limited to clinical trial participation. The Indian Council of Medical Research (ICMR) and Indian cardiology and neurology societies will play important roles in trial participation, evidence evaluation, and ultimately pricing and access negotiations.[44] Indian pharmaceutical manufacturers will likely develop generic small-molecule FXI inhibitors after patent expiration, and biosimilar antibody development will follow established patterns. Pharmacology educators should integrate FXI biology, the contact pathway, and the FXI inhibitor approach into the curriculum in preparation for the eventual Indian clinical availability.

SUMMARY TABLES

Table 1: FXI/FXIa inhibitors — approaches and lead candidates.

Approach	Lead candidate(s)	Route	Half-life	Status
Oral small-molecule FXIa inhibitor	Asundexian (BAY 2433334)	Oral once daily	~15 hr	Phase 3 (OCEANIC-AF failed Nov 2023; OCEANIC-STROKE ongoing)
Oral small-molecule FXIa inhibitor	Milvexian (BMS-986177)	Oral twice daily	~12–15 hr	Phase 3 LIBREXIA program
Anti-FXI/FXIa monoclonal antibody	Abelacimab (MAA868)	IV load + SC monthly	~25–30 days	Phase 3 LILAC, MAGNOLIA, ASTER
Anti-FXI monoclonal antibody	Osocimab (BAY 1213790)	IV single dose	~30–45 days	Phase 2 (FOXTROT)
Antisense oligonucleotide (GalNAc)	Fesomersen (IONIS-FXI-LRx)	SC monthly	Weeks	Phase 2/3 (ESRD, RE-THINc ESRD)
Anti-FXI aptamer	Various (preclinical)	Various	—	Preclinical/early clinical

Table 2: Key phase 2 and phase 3 trial results.

Trial	Drug	Indication	N	Key result
AXIOMATIC-TKR	Milvexian	Knee arthroplasty VTE prophylaxis	1,242	12% VTE (100 mg BID) vs 21% enoxaparin
ANT-005	Abelacimab	Knee arthroplasty VTE prophylaxis	412	4% VTE (150 mg) vs 22% enoxaparin
FOXTROT	Osocimab	Knee arthroplasty VTE prophylaxis	813	12–20% VTE vs 26.3% enoxaparin
PACIFIC-AF	Asundexian	Atrial fibrillation	755	Bleeding lower than apixaban; 12-week phase 2
PACIFIC-AMI	Asundexian	Post-MI + DAPT	1,601	Similar bleeding, trend for fewer ischemic events
PACIFIC-STROKE	Asundexian	Non-cardioembolic stroke	1,808	Reduced covert infarcts (50 mg)
AXIOMATIC-SSP	Milvexian	Secondary stroke prevention + DAPT	2,366	Numerical reduction; not statistically significant
RE-THINc ESRD	Fesomersen	ESRD on HD	307	Reduced dialyzer thrombosis
AZALEA-TIMI 71	Abelacimab vs rivaroxaban	AF	1,287	60–67% reduction in major bleeding

				(stopped Nov 2023)
OCEANIC-AF	Asundexian 50 mg vs apixaban	AF	14,810	Inferior efficacy with asundexian (stopped Nov 2023)
OCEANIC-STROKE	Asundexian vs placebo	Secondary stroke prevention	Ongoing	Pending results
LILAC-TIMI 76	Abelacimab vs rivaroxaban	AF high-bleeding-risk	Ongoing	Phase 3
LIBREXIA-AF	Milvexian vs apixaban	AF	Ongoing	Phase 3
LIBREXIA-STROKE	Milvexian vs placebo + DAPT	Secondary stroke	Ongoing	Phase 3
LIBREXIA-ACS	Milvexian post-ACS	ACS	Ongoing	Phase 3
MAGNOLIA / ASTER	Abelacimab vs apixaban	Cancer-associated VTE	Ongoing	Phase 3

Table 3: Pharmacological comparison — FXI inhibitors versus DOACs and warfarin.

Property	**FXI inhibitors**	**DOACs (apixaban/rivaroxaban)**	**Warfarin**
Target	FXI/FXIa	FXa or thrombin (dabigatran)	Multiple vitamin K-dependent factors
Hemostasis impact	Minimal	Moderate	Substantial
Major bleeding (expected)	Lower	2–4%/year	3–5%/year
Intracranial hemorrhage	Anticipated very low	0.3–0.5%/year	0.7–1.0%/year
Monitoring	None required	None required	INR monitoring required
Renal clearance	Variable by agent	25–80% renal	Hepatic
Onset	Hours (orals)/days (Ab/ASO)	Hours	Days
Reversal	In development	Andexanet alfa, idarucizumab	Vitamin K, FFP, PCC
Drug interactions	Mostly CYP3A4	CYP3A4, P-gp	Multiple
Cost (estimated, India)	Future	Generic DOACs ₹1,500–3,000/month	₹50–150/month

Table 4: Clinical indications under investigation.

Indication	**Lead FXI inhibitor candidate(s)**	**Phase**	**Rationale**
Atrial fibrillation (stroke prevention)	Milvexian, abelacimab	Phase 3	Largest indication; need for bleeding-safer option
Secondary stroke prevention	Asundexian, milvexian	Phase 3	Add to antiplatelet; fill ischemic gap without bleeding

VTE prevention post-orthopedic surgery	Milvexian, abelacimab	Phase 2 proof-of-concept	Established setting
Cancer-associated VTE	Abelacimab (MAGNOLIA, ASTER)	Phase 3	High bleeding risk in oncology patients
ESRD on hemodialysis	Fesomersen, abelacimab	Phase 2/3	Both thrombotic and bleeding risk elevated
Post-ACS	Milvexian (LIBREXIA-ACS)	Phase 3	Reduce ischemic events without excess bleeding
Stable cardiovascular disease	Asundexian (PACIFIC-AMI extension)	Phase 2/3	Adjunct to antiplatelet

Table 5: Indian anticoagulation implementation considerations.

Element	Status (India)	Approximate cost (₹)	Notes
Generic warfarin	Widely available	50–150/month + INR monitoring	First-line in many settings
Apixaban (generic)	Widely available	1,500–3,000/month	Multiple Indian manufacturers
Rivaroxaban (generic)	Widely available	1,500–2,500/month	Multiple manufacturers
Dabigatran (generic)	Available	1,800–3,500/month	Renal clearance concerns
Edoxaban (generic)	Available	1,800–3,000/month	Less widely used
Enoxaparin LMWH	Widely available	200–400/dose	Acute/perioperative
Andexanet alfa (FXa reversal)	Limited availability	Very high	Tertiary centers only
Idarucizumab (dabigatran reversal)	Limited availability	High	Tertiary centers
FXI inhibitors (pipeline)	Not yet available	Future pricing TBD	Clinical trial access only
INR monitoring infrastructure	Variable	100–200/test	Limited in rural areas

FUTURE DIRECTIONS

Several developmental trajectories will shape the next phase of FXI inhibitor development and clinical integration. First, the ongoing phase 3 program — particularly LILAC-TIMI 76 (abelacimab in high-bleeding-risk AF) and the LIBREXIA program (milvexian in AF, secondary stroke, ACS) — will determine the place of FXI inhibitors in major clinical indications. The OCEANIC-AF failure highlighted that proof-of-concept does not guarantee

phase 3 success and that dose optimization, patient selection, and comparator choice critically affect outcomes.

Second, reversal agent development for FXI inhibitors is an active area. The reduced bleeding risk theoretically reduces the urgency of reversal, but specific reversal agents (anti-FXI antibody Fab fragments, FXI restoration via plasma or recombinant FXI) may be needed for major bleeding or urgent surgery; experience with andexanet alfa for factor Xa inhibitors and idarucizumab for dabigatran provides a template.[60, 61] Third, biomarker-guided patient selection — including aPTT prolongation, FXI activity, FXI antigen levels, and thrombin generation assays — may identify patients most likely to benefit from FXI inhibition and inform dose titration, building on laboratory-monitoring experience with the non-vitamin K oral anticoagulants.[62]

Fourth, novel indications include heparin-induced thrombocytopenia (where FXI inhibitors avoid the heparin-PF4 interaction), antiphospholipid syndrome, sepsis-associated coagulopathy, and prophylaxis in mechanical heart valves (where DOACs are contraindicated).[63, 64] Fifth, combination strategies with antiplatelet therapy, particularly in secondary stroke prevention and ACS, may produce superior ischemic prevention without the bleeding excess of dual antiplatelet plus DOAC strategies. Sixth, generic small-molecule FXI inhibitors after patent expiration will substantially reduce costs and expand global access, including in India and other low-resource settings.

CONCLUSION

Factor XI inhibitors represent a potentially transformative class of anticoagulants designed to decouple antithrombotic efficacy from bleeding risk, exploiting the foundational biological insight that FXI participates preferentially in pathological thrombus amplification rather than primary hemostasis. The class encompasses four pharmacological approaches: oral small-molecule active-site inhibitors (asundexian, milvexian), monoclonal antibodies (abelacimab, osocimab), antisense oligonucleotides (fesomersen), and emerging aptamers. The November 2023 dual announcements — AZALEA-TIMI 71 demonstrating 60–67% bleeding reduction with abelacimab versus rivaroxaban, and OCEANIC-AF failing to demonstrate non-inferiority of asundexian to apixaban — sharply illustrate both the potential and the challenges of the class.

The path to clinical integration will depend on the ongoing phase 3 trials including LILAC-TIMI 76, the LIBREXIA program, MAGNOLIA, ASTER, and OCEANIC-STROKE. The most likely initial clinical positioning will be in patients with elevated bleeding risk where current DOACs are underutilized — high-bleeding-risk AF, cancer-associated VTE, ESRD on hemodialysis, and elderly populations with multiple comorbidities. Secondary stroke prevention as an adjunct to antiplatelet therapy represents a major potential indication addressing substantial residual ischemic risk.

For Indian anticoagulation care, FXI inhibitors are not yet available but represent an important pipeline development. The Indian anticoagulation gap — with only 30–50% of eligible AF patients receiving guideline-recommended therapy due to bleeding concerns, monitoring requirements, and cost — could be substantially addressed by safer FXI inhibitors. Pharmacology educators should integrate FXI biology, the contact pathway, and the FXI inhibitor approach into the curriculum, illustrating the principle of mechanism-based decoupling of efficacy from adverse effects. The factor XI inhibitor era represents an instructive chapter in anticoagulation pharmacology and a window into the future of bleeding-conscious antithrombotic therapy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS

The first author conceived the review topic, conducted the literature search, drafted the manuscript, and prepared the tables. R. L. Manisha (corresponding author) supervised the work, critically reviewed and revised the manuscript, and finalized the scientific content. Muvvala Sudhakar provided institutional oversight, critically reviewed the manuscript, and approved the final version. All authors read and approved the final manuscript.

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