Unmet Needs in Atrial Fibrillation (AF) and the Promise of Factor XI as a New Therapeutic Target

An unrestricted educational grant was provided by Anthos Therapeutics.

Anticoagulation and State of the Art: Dr. Christian Ruff Commentary

- “Providing warfarin anticoagulant therapy to patients with atrial fibrillation reduces the risk of stroke and systemic embolism by as much as 64% but significantly increases the risk of serious bleeding.”[1]
- “Direct oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban) are as effective in reducing stroke risk, far safer with respect to intracranial hemorrhage, and do not require routine laboratory monitoring but significant bleeding still occurs.”[2]
- “In the future, Factor XI inhibitors, in both oral and injectable formulations, hold the promise of preventing stroke and systemic embolism while substantially reducing the risk of bleeding.”[3]

1. Hart RG, et al. *Ann Intern Med*. 2007;146(12):857-867. 2. Ruff CT, et al. *Lancet*. 2014;383(9921):955-962. 3. De Caterina R, et al. *Eur Heart J*. 2023;44(4):280-292.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Vasculearn Network

Medical Advisory Board

- Tara Lech, PharmD
- Aviva Schwartz, MA
- Behnood Bikdeli, MD, MS
- Heather Johnson, MD
- Margo Minissian, PhD, ACNP
- JoMarie Monzon, FNP-BC, MSN
- Scott Woller, MD
- LaVon Woodard
  (Patient Advocate)

Executive Board

- Christian Ruff, MD, MPH
- John Fanikos, RPh, MBA
- Joelle Hochman, RRT
- Jelena Spyropoulos, PhD
- Nathan T. Connell, MD, MPH
- Kathryn Mikkelsen, MBA
- Courtney Anderson

Content Review

- Jean Connors, MD
- Christian Ruff, MD, MPH
- Charles Pollack, MD
- Alex C. Spyropoulos, MD
- Ruth Morrison, RN
- Aviva Schwartz, MA
- John Fanikos, RPh, MBA

Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Objectives

- Review burden of atrial fibrillation (AF) and challenges of medical management
- Understand physician perspectives on underuse of anticoagulants in AF
- Describe patient perspectives on underuse of anticoagulants in AF
- Review pharmacokinetic and pharmacodynamic challenges for current anticoagulants
- Introduce Factor XI Inhibitors: A new frontier in anticoagulation

AF is common, underestimated, and a substantial cause of serious strokes

In the US, AF will be diagnosed in
12 million people
by 2030[1–3]
16 million people
by 20503,4

- AF increases the risk of stroke **5-fold**1,4,5
  1 in 7 of all strokes are caused by AF[1]
- AF-associated strokes are more likely to cause **disability or death**1,4,5

Globally, the risk of developing AF is
1 in 4
for people over 45[4]

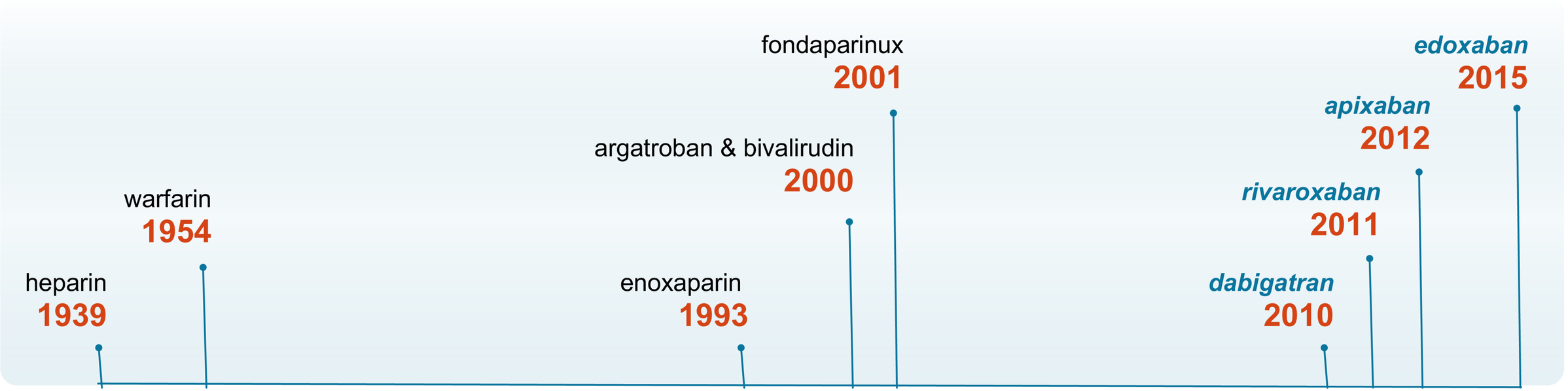
True prevalence of AF may be underestimated, because it is **often undiagnosed** until a stroke occurs1,4

1. About atrial fibrillation. Centers for Disease Control and Prevention. Accessed March 5, 2025. https://www.cdc.gov/heart-disease/about/atrial-fibrillation.html.
2. Colilla S, et al. *Am J Cardiol*. 2013;112(8):1142-1147. 3. Miyasaka Y, et al. *Circulation*. 2006;114(2):119-125. 4. Linz D, et al. *Lancet Reg Health Eur*. 2024;37:100786.
5. Piccini JP, Fonarow GC. *JAMA Cardiol*. 2016;1(1):63-64.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Thrombotic conditions like AF require safe and effective anticoagulation

- **1 in 4 deaths** worldwide are caused by thromboembolic disorders[1]
- Heparin and VKAs were the only available anticoagulants for **60-70 years**[1–4]
- Since 2010, DOACs have become the **treatment of choice** for most patients[1]



DOACs, direct-acting oral anticoagulants; VKAs, vitamin K antagonists.

1. Hsu C, et al. *J Am Coll Cardiol*. 2021;78(6):625-631. 2. Heestermans M, et al. *Cells*. 2022;11(20):3214. 3. Franchini M, et al. *Blood Transfus*. 2016;14(2):175-184.
4. Food & Drug Administration. www.accessdata.fda.gov.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Despite the importance of stroke prevention in AF, DOACs remain underutilized in this population[1]

40% to 60% of high-risk patients are not prescribed oral anticoagulants[2–6]

20% to 40% of patients taking DOACs receive inappropriately low doses[6–10]

A substantial number of preventable strokes likely occur every year[1]

DOACs, direct-acting oral anticoagulants.

1. Piccini JP, Fonarow GC. *JAMA Cardiol*. 2016;1(1):63-64. 2. Hsu JC, et al. *JAMA Cardiol*. 2016;1(1):55-62. 3. Ko D, et al. *JAMA Network Open*. 2022;5(11):e2242964.
4. Sussman M, et al. *Curr Med Res Opin*. 2021;38(1):7-18. 5. Willey V, et al. *BMJ Open*. 2018;8(6):e020676. 6. Weitz JI, Fredenburgh JC. *Front Med (Lausanne)*. 2017;4:19.
7. Arbel R, et al. *Am J Med*. 2019;132(7):847-855.e3. 8. Sanghai S, et al. *J Am Heart Assoc*. 2020;9(6):e014108. 9. Steinberg BA, et al. *J Am Heart Assoc*. 2018;7(4):e007633.
10. Yao X, et al. *J Am Coll Cardiol*. 2017;69(23):2779-2790.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Reasons for underuse of anticoagulation in AF are complex and intersect with one another

	Physician perspective	Patient perspective
BLEEDING:	**Risk of serious bleeding** (including patient-specific factors such as age and fall risk)	Fear of serious bleeding QoL impact of bleeding/bruising
POLYPHARMACY:	Renal status and metabolic clearance Drug-drug interaction	Pill burden Frequent dosing
RESULTING IN:	Underprescribing & underdosing	Poor adherence & persistence

Cannon CP, et al. *JAMA Netw Open*. 2023;6(4):e239638.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

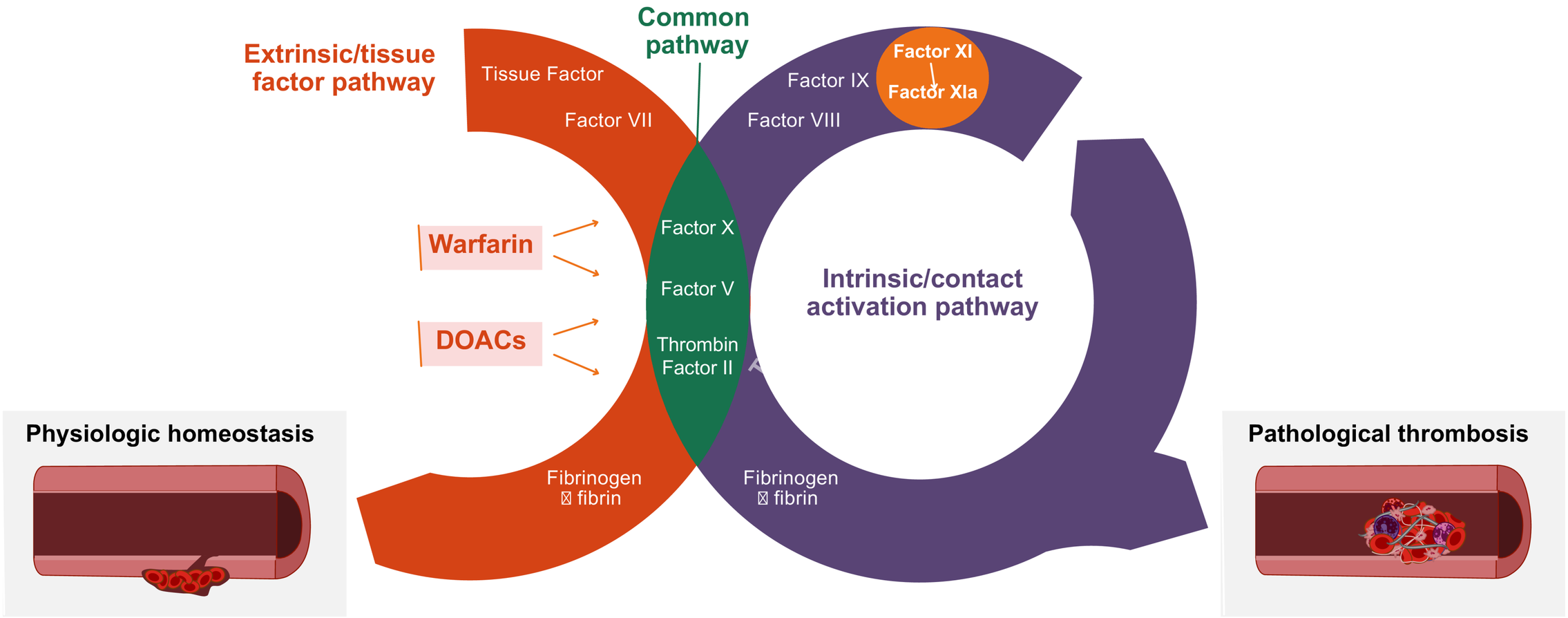
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Physician perspectives on underuse of anticoagulants in AF

- Risk of bleeding
- Polypharmacy and drug-drug interactions

An unrestricted educational grant was provided by Anthos Therapeutics.
Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Understanding Factor XI and Thrombosis



Patel SM, Ruff CT. *Curr Cardiol Rep*. 2024;26(9):911-917. Hsu C, et al. *J Am Coll Cardiol*. 2021;78(6):625-631.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

DOACs have an improved bleeding profile compared with VKAs, but risk of bleeding remains a concern

Events in meta-analysis of DOAC trials[1]	Risk reduction (DOAC vs VKA)
Ischemic stroke	↓ 8%
Hemorrhagic stroke	↓ 51%
All-cause mortality	↓ 10%
Major bleeding	
Overall	↓ 14%
Gastrointestinal bleeding	↑ **25%**

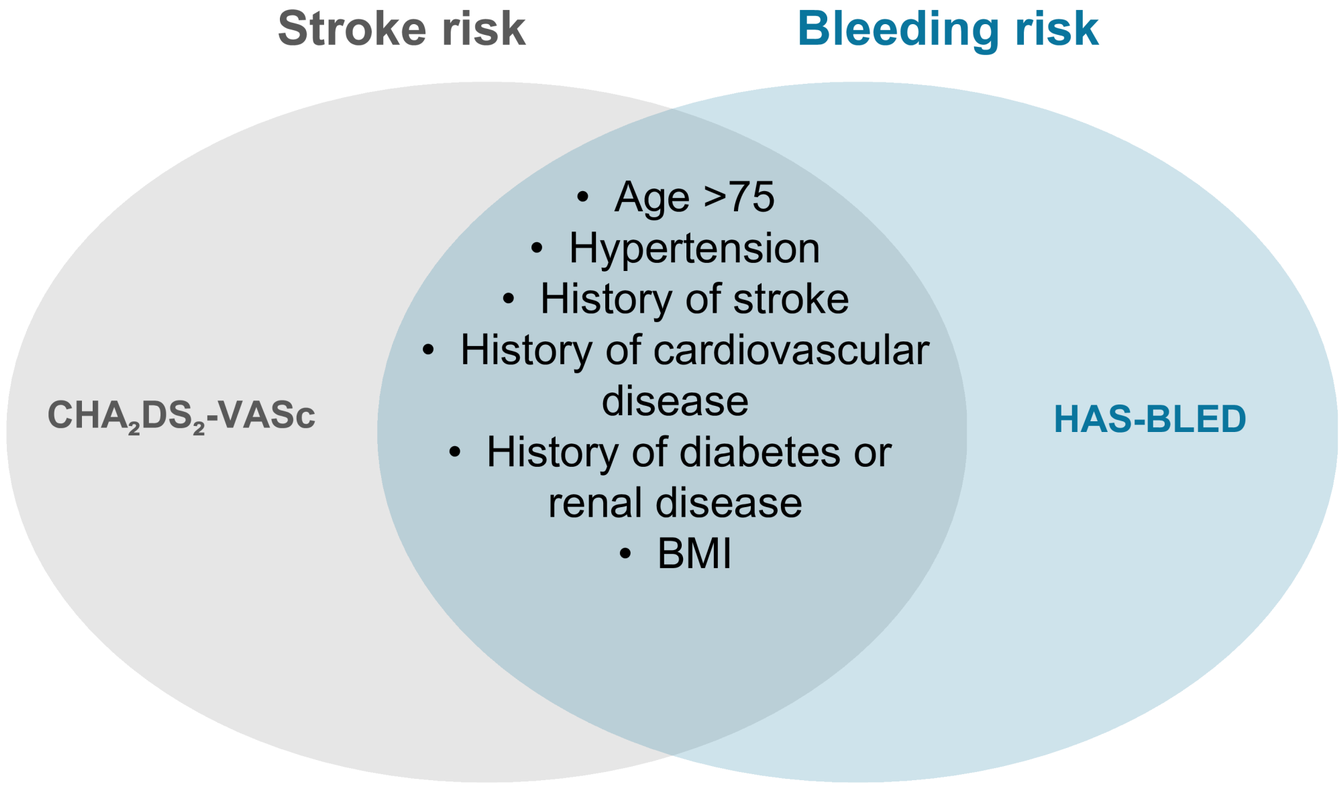
- Despite the improvement in bleeding profile over warfarin, DOACs remain associated with a **2-5% annual major bleeding rate** in clinical trials1,2
- Major bleeding → **8X higher risk of mortality**[3]
- Importantly, real-world studies suggest DOAC clinical trials significantly **underestimate bleeding risk**[4]

An increased risk of **GI bleeding** is consistent with DOAC activation in the gut5,6

1. Ruff CT, et al. *Lancet.* 2014;282:955-962. 2. Fredenburgh JC, Weitz JI. *J Thromb Haemost*. 2023;21(7):1692-1702. 3. Bassand JP, et al. *Blood Adv*. 2021;5(4):1081-1091.
4. Buderi R, et al. *Res Pract Thromb Haemost*. 2021;5(suppl 2):50. 5. Martin AC, et al. *Am J Cardiovasc Drugs*. 2023;23(4):407-418. 6. Ido T, et al. *Am Heart J Plus:* 2022;22:100203.

The decision to treat with anticoagulation in AF is a delicate balance between stroke risk and bleeding risk

Because of the substantial overlap in factors contributing to stroke risk and bleeding risk, guidelines **do NOT recommend withholding DOAC** based on bleeding risk alone[1–3]

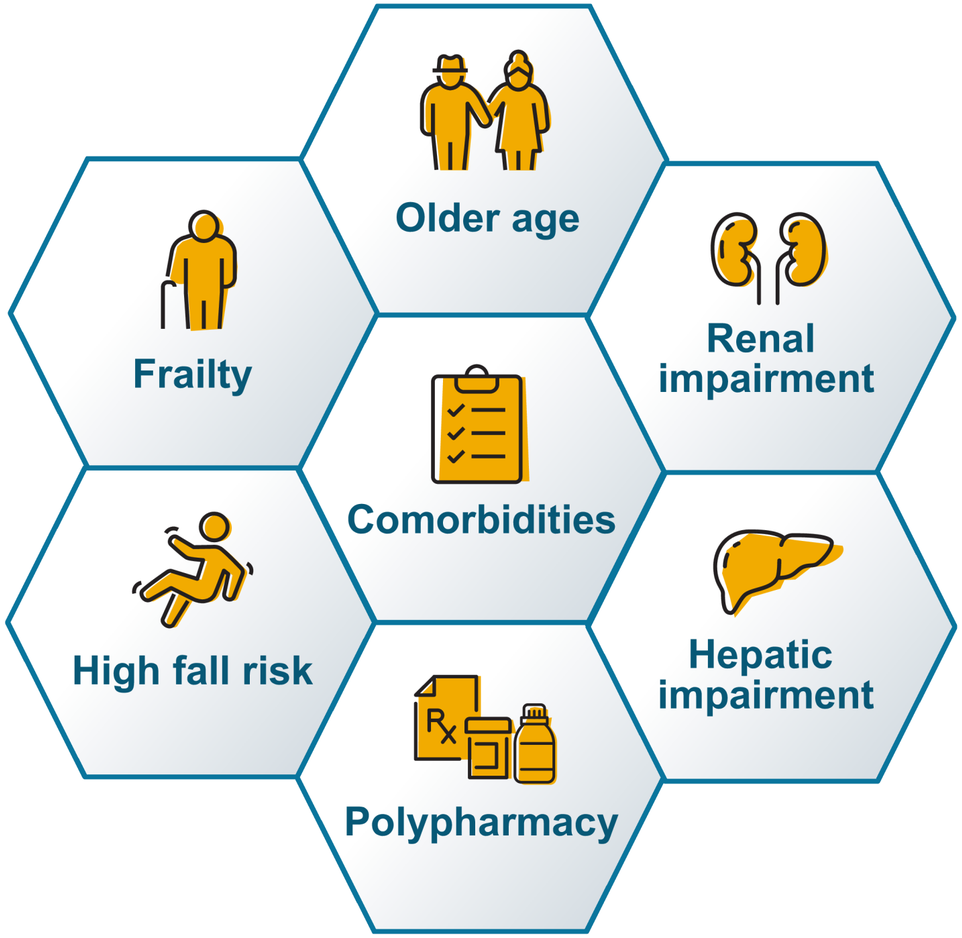


BMI, body mass index; DOAC, direct-acting oral anticoagulant.

1. Joglar JA, et al. *J Am Coll Cardiol*. 2024;83(1):109-279. 2. Hindricks G, et al. *Eur Heart J*. 2021;42(5):373-498. 3. Kodani E, Akao M. *Eur Heart J Suppl*. 2020;22(suppl O):O1-O13.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Patients with AF are medically complex, further complicating the evaluation of bleeding risk[1–4]



DOACs may be **contraindicated** and/or require **dose modification** in many patients[1–3]

DOACs, direct-acting oral anticoagulants.

1. Joglar JA, et al. *J Am Coll Cardiol*. 2024;83(1):109-279. 2. Hindricks G, et al. *Eur Heart J*. 2021;42(5):373-498. 3. Kodani E, Akao M. *Eur Heart J Suppl*. 2020;22(suppl O):O1-O13.
4. Shantsila E, et al. *Lancet Reg Health Eur*. 2024;37:100784.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

The medical complexity of patients with AF also puts them at higher risk of drug-drug interactions (DDIs)

Among patients with AF:[1]

- **63%** take **≥5** prescription medicines per day
- **21%** take **>9** prescription medicines per day

- DOACs are associated with DDIs that can result in **bleeding and/or thrombosis**[2]
- In the SAGE-AF registry (patients ≥65y), **25%** of patients taking DOACs were coprescribed medication with potential interaction[3]

DDIs, drug-drug interactions; DOACs, direct-acting oral anticoagulants.

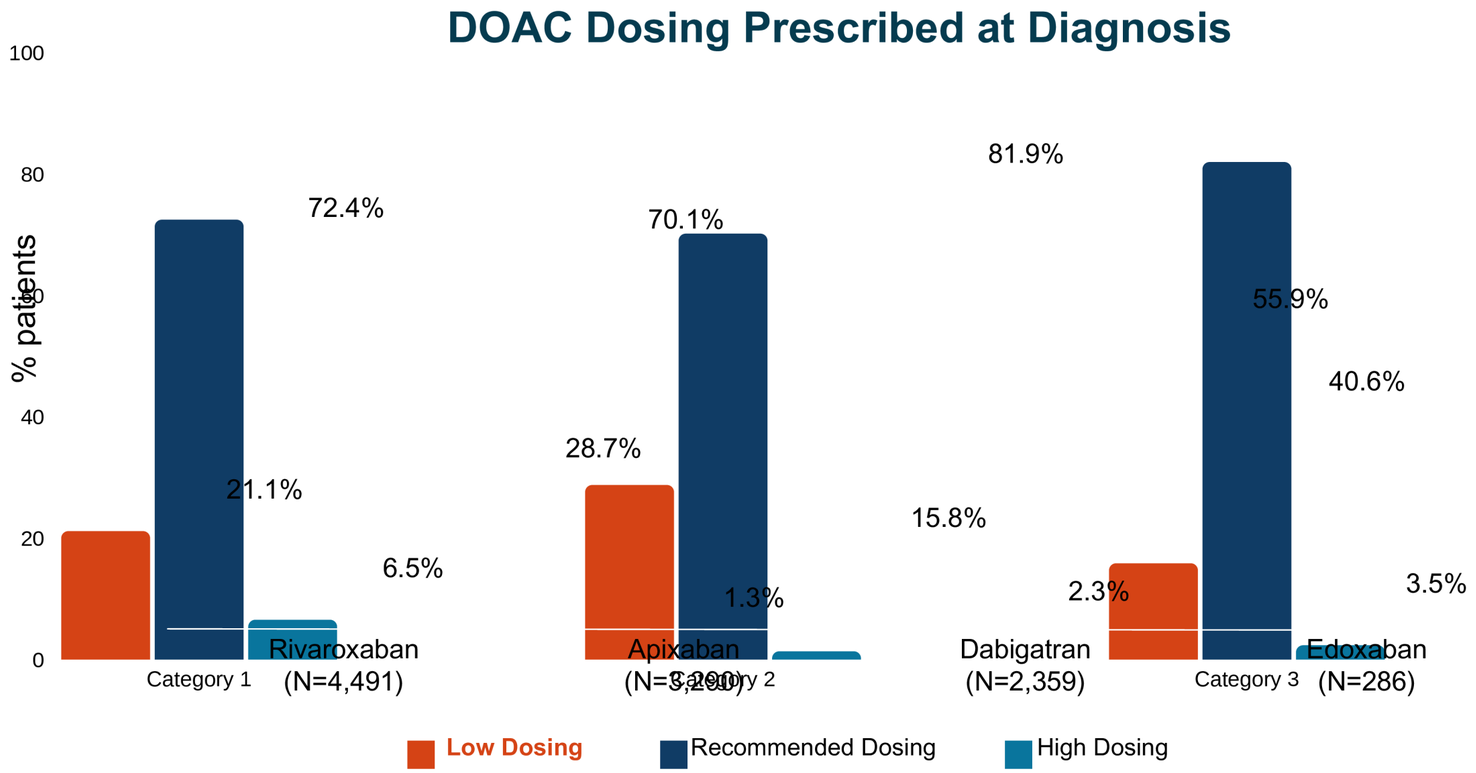
1. Gallagher C, et al. *Open Heart*. 2020;7(1):e001257. 2. Li A, et al. *Thromb Res*. 2020;194:240-245. 3. Sanghai S, et al. *J Am Heart Assoc*. 2020;9(6):e014108.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Physicians may reduce DOAC dose for safety reasons, but this can be inappropriate according to guidelines and indication

In the GARFIELD-AF Registry:[1]

23% of all patients taking DOACs were underdosed



Across AF studies, **underdosing** is associated with significantly worse CV outcomes and **no decrease in bleeding risk**[1–3]

CV, cardiovascular; DOAC, direct-acting oral anticoagulant.

1. Camm AJ, et al. *J Am Coll Cardiol*. 2020;76(12):1425-1436. 2. Steinberg BA, et al. *J Am Heart Assoc*. 2018;7(4):e007633. 3. Yao RJR, et al. *J Am Heart Assoc*. 2023;12(6):e026605.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Summary: Physician perspectives on underuse of anticoagulants in AF

- Current anticoagulants are associated with a substantial bleeding risk
- The weighing of stroke risk vs bleeding risk in patients with AF is a difficult balance
- Metabolic issues and concomitant medications add further complexity because of the increased potential for drug-drug interaction (DDI)
- Physicians will sometimes reduce dose to address safety concerns, but this is often done in a manner that is inconsistent with guidelines

> As a result, patients with AF are often **untreated** or **undertreated** with anticoagulation, leaving them **at risk for thromboembolic events**

Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

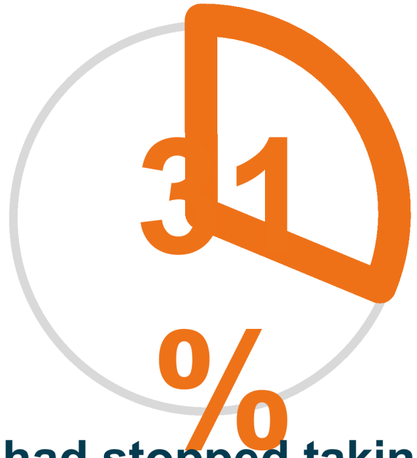
Patient perspectives on underuse of anticoagulants in AF

- Impact of major and patient-relevant bleeding
- Pill burden

An unrestricted educational grant was provided by Anthos Therapeutics.
Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Adherence to oral anticoagulants is generally low in AF populations

In a meta-analysis of real-world observational studies of patients with AF taking DOACs:



had stopped taking their anticoagulant at 1 year

showed poor adherence

Patients missed a DOAC dose **once every 4 days**

Poor adherence was associated with a **39% greater risk** of thromboembolic events

DOACs, direct-acting oral anticoagulants.

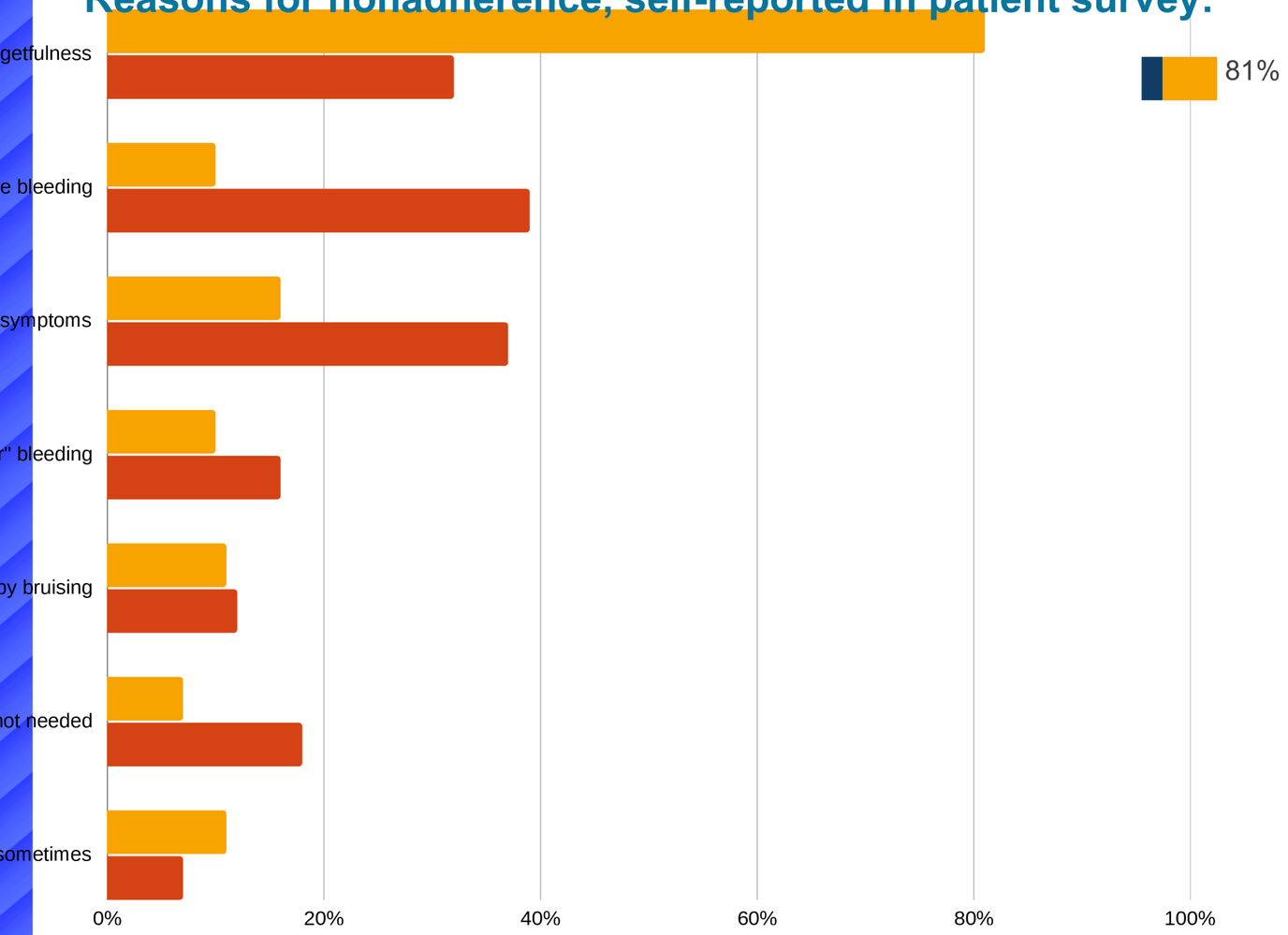
Ozaki AF, et al. *Circ Cardiovasc Qual Outcomes*. 2020;13(3):e005969.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Reasons for poor adherence in AF often relate to forgetfulness, fear of bleeding, and perception that the medication is not needed

Reasons for nonadherence, self-reported in patient survey:



These survey findings suggest:

- Patients have difficulty keeping up with daily oral medication
- Patients fear bleeding, while also underestimating the risk of thrombosis if undertreated

Tarn DM, et al. *JACC Adv*. 2023;2(1):100175.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

A global survey by patient advocacy groups established that patient concerns around bleeding go beyond major events

59%

of patients reported experiencing a bleeding problem since starting an anticoagulant

Of those patients reporting bleeding:

86%

experienced both bleeding and bruising

47%

acknowledged bleeding may have an emotional impact

Anxiety, embarrassment, depression

54%

adjusted their lifestyle to avoid bleeding

Avoid hobbies, travel, and household tasks

Wear clothing to cover bruises

Types of bleeding events:

Easy bruising of the skin	80%
Bleeding from cuts and other small injuries	44%
Heavy periods	21%
Nosebleeds	20%
Bleeding gums	27%
Bleeding hemorrhoids (piles)	18%
Blood in the white of your eyes	8%

% of patients experiencing specific events: sometimes, quite often, or very often

StopAfib.org
For patients by patients

National Blood Clot Alliance
Stop The Clot®

Bloomfield D, et al. Presented at: 2023 ISTH Congress; June 24-28, 2023; Montreal, Canada. Oral presentation OC 21.4.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Importantly, the survey found that almost a third of patients who experienced bleeding considered stopping their anticoagulant

29% of patients who experienced bleeding **considered stopping** or changing the dose of their anticoagulant

Many patients stopped taking their anticoagulant medication **without notifying their physician**

Bloomfield D, et al. Presented at: 2023 ISTH Congress; June 24-28, 2023; Montreal, Canada. Oral presentation OC 21.4.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Summary: Patient perspectives on underuse of anticoagulation in AF

Patients regularly skip doses of anticoagulant (intentionally and unintentionally)

- Don’t understand the importance of stroke prevention in AF
- Fear the risk of major bleeding
- Worry about the impact of any bleeding on quality of life
- Struggle to keep up with numerous prescriptions and frequent pill-taking

Importantly, patients commonly **skip doses** without telling their physician

Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Pharmacokinetic and Pharmacodynamic Challenges for Current Anticoagulants

An unrestricted educational grant was provided by Anthos Therapeutics.
Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

DOACs have a short half-life and must be dosed frequently

	Direct Thrombin Inhibitor	Xa Inhibitors		
	Dabigatran	Edoxaban	Rivaroxaban	Apixaban
Target	Thrombin (Factor IIa)	Factor Xa		
Prodrug	Yes	No	No	No
Oral bioavailability	3-7%	62%	80-100%*	50%
Renal clearance of absorbed active drug	~80%	~50%	~35%	~27%
Elimination half-life, hours	12-14	10-14	5-9 (young) 11-13 (elderly)	12
Dosing for AF indication	BID	Once daily	Once daily*	BID
Drug interactions	Inhibitors and inducers of P-gp	Inhibitors and inducers of P-gp	Inhibitors and inducers of CYP3A4 and P-gp	Inhibitors and inducers of CYP3A4 and P-gp

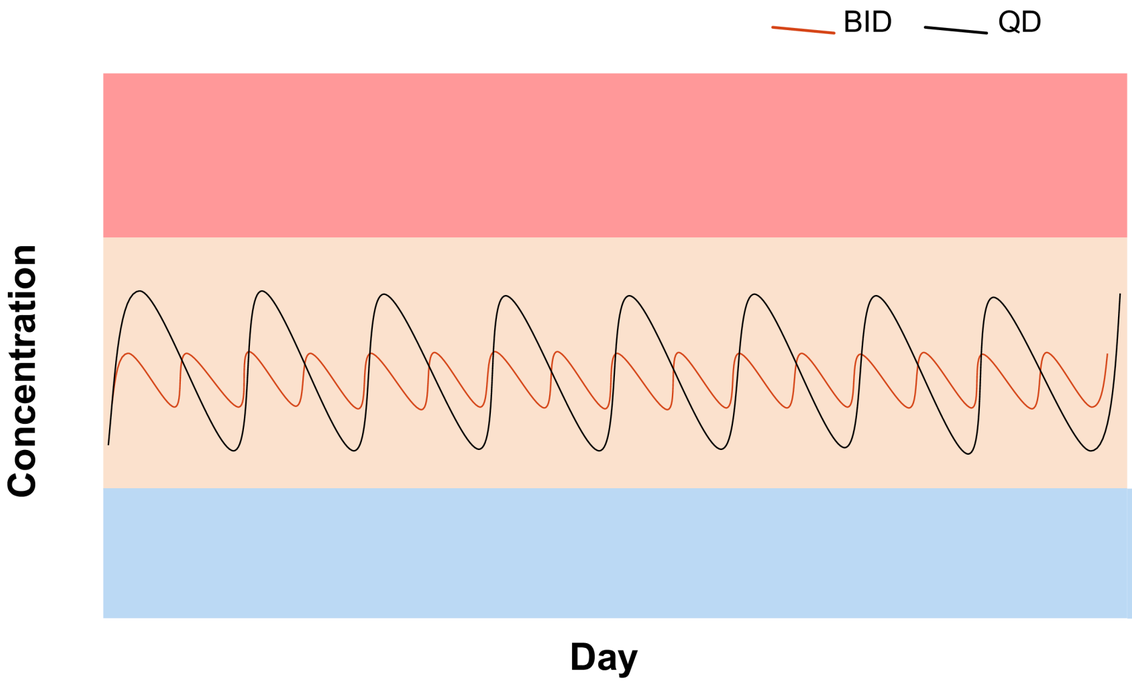
*with food

BID, twice daily; CYP3A4, cytochrome P450 3A4; P-gp, P-glycoprotein.

Roberti R, et al. *Front Pharmacol*. 2021;12:684638. Steffel J, et al. *Eur Heart J*. 2018;39(16):1330-1393.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Short half-life for DOACs equates to a narrow therapeutic index and challenges attaining optimal drug levels



High bleeding risk

Therapeutic index = range of concentration at which a drug is effective and nontoxic

High thrombotic risk

Half-lives of DOACs range from 5-14 hrs; **drug levels may be very low by the time a second dose is taken**[1–4]

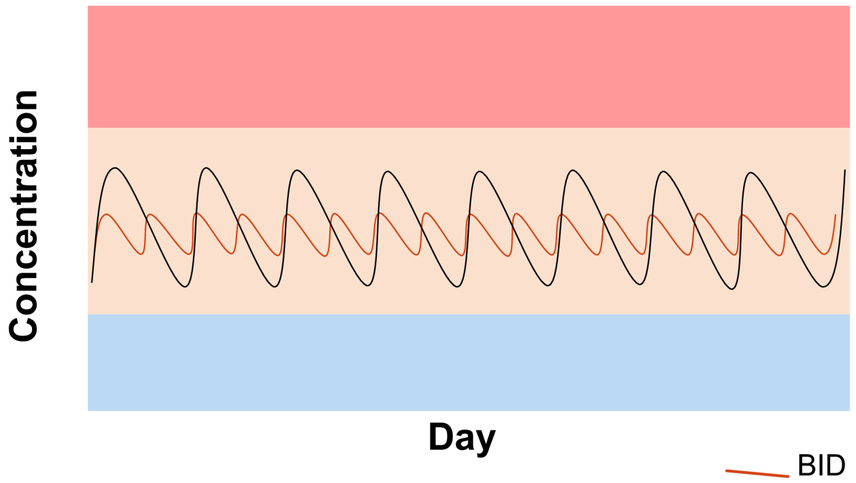
BID, twice daily; DOACs, direct-acting oral anticoagulants; QD, daily.

1. Ido T, et al. *Am Heart J Plus*. 2022;22:100203. 2. Roberti R, et al. *Front Pharmacol*. 2021;12:684638. 3. Gosselin RC, et al. *Thromb Haemost*. 2018;118(3):437-450.
4. Testa S, et al. *J Thromb Haemost*. 2018;16(5):842-848.

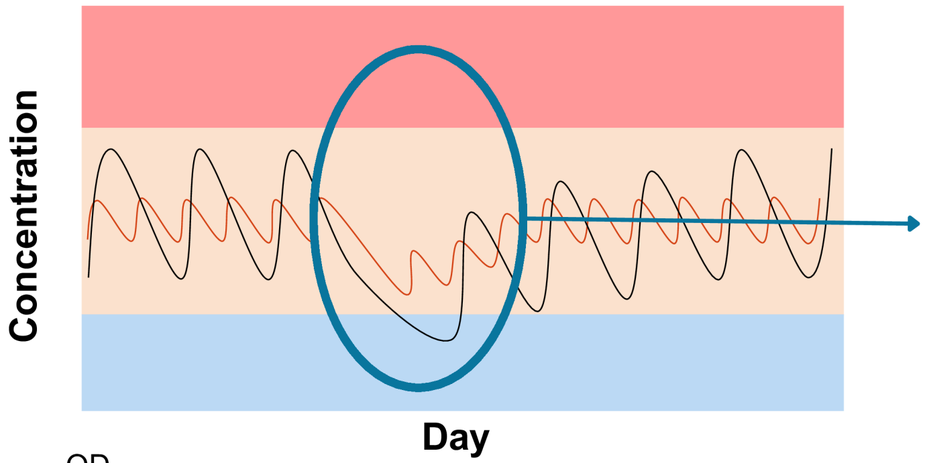
Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Underdosing and skipped doses of DOACs are widespread in the AF population, increasing the likelihood of PK variations

PK of QD and BID DOACs[1]



Consequences of a missed dose[1]



1 missed dose is expected to drop DOAC concentration into the low protection zone1,2

This is especially true for DOACs dosed QD

Patients miss a DOAC dose **once every 4 days**[2]

BID, twice-daily; DOACs, direct-acting oral anticoagulants; PK, pharmacokinetic; QD, daily.

1. Ido T, et al. *Am Heart J Plus*. 2022;22:100203. 2. Ozaki AF, et al. *Circ Cardiovasc Qual Outcomes*. 2020;13(3):e005969.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

VKAs (eg, warfarin) are the preferred choice in many patients but can be even more challenging for maintaining therapeutic range

Therapeutic window for VKAs is extremely narrow and difficult to maintain[1–3]

- VKA dose response is heavily influenced by multiple patient factors[1–3]
  - DDI, dietary vitamin K, hepatic function, gut flora, alcohol use, and overall compliance
- Real-world evidence suggests that most patients taking VKAs have a **time in therapeutic range <50%**[1–3]
- Less time spent in therapeutic range is associated with **poorer cardiovascular outcomes**[4]

VKA therapeutic monitoring is burdensome and not readily acceptable to patients[1]

- Monitoring algorithms are **complicated, iterative, and lifelong**[1–3]
- Self-monitoring is only successful in patients with high level of compliance and physical/cognitive capabilities[1–3]
- Nonadherence to monitoring is associated with a **50% increase in risk** of thromboembolism[5]

DDI, drug-drug interaction; VKAs, vitamin K antagonists.

1. De Caterina R, et al. *Thromb Haemost*. 2013;110(6):1087-107. 2. Joglar JA, et al. *J Am Coll Cardiol*. 2024;83(1):109-279. 3. Camm AJ, et al. *Eur Heart J*. 2010;31(19):2369-2429. 4. Bonde AN, et al. *J Am Coll Cardiol*. 2018;72(12):1357-1365. 5. Witt DM, et al. *Thromb Res*. 2013;132(2):e124-e130.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Patients taking VKAs spend substantial time below the therapeutic levels required for protection from thrombosis

FANTASIIA Registry

Spain, n=1,484 patients with AF receiving VKA, n=472 patients with AF receiving a DOAC

55% of Warfarin-treated patients exhibited poor quality of anticoagulation control

Risk of cardiac events was significantly increased in patients with poor quality of warfarin control

Warfarin Management and Outcomes

	<65% TTR *poor control*	≥65% TTR	*P*
Total mortality	**21%**	14%	0.05
CV mortality	**14%**	5%	0.001
MACE	**17%**	10%	0.03

- **The risk of adverse cardiovascular outcomes and death was higher in diabetic patients, particularly in those with worse quality of anticoagulation control**

CV, cardiovascular; DOAC, direct-acting oral anticoagulant; MACE, major adverse CV event; TTR, time in therapeutic range; VKAs, vitamin K antagonists.

García-Fernández A, et al. *Ann Med*. 2020;52(6):300-309.

Summary: Complex PK properties of VKAs and DOACs make effective and consistent protection from thrombosis difficult to attain

PK properties of VKAs/DOACs	Factors influencing exposure to VKAs/DOACs
Narrow therapeutic range	Impaired renal/ hepatic function
Substantial time spent outside of therapeutic range	Underprescribing and underdosing
	Low adherence

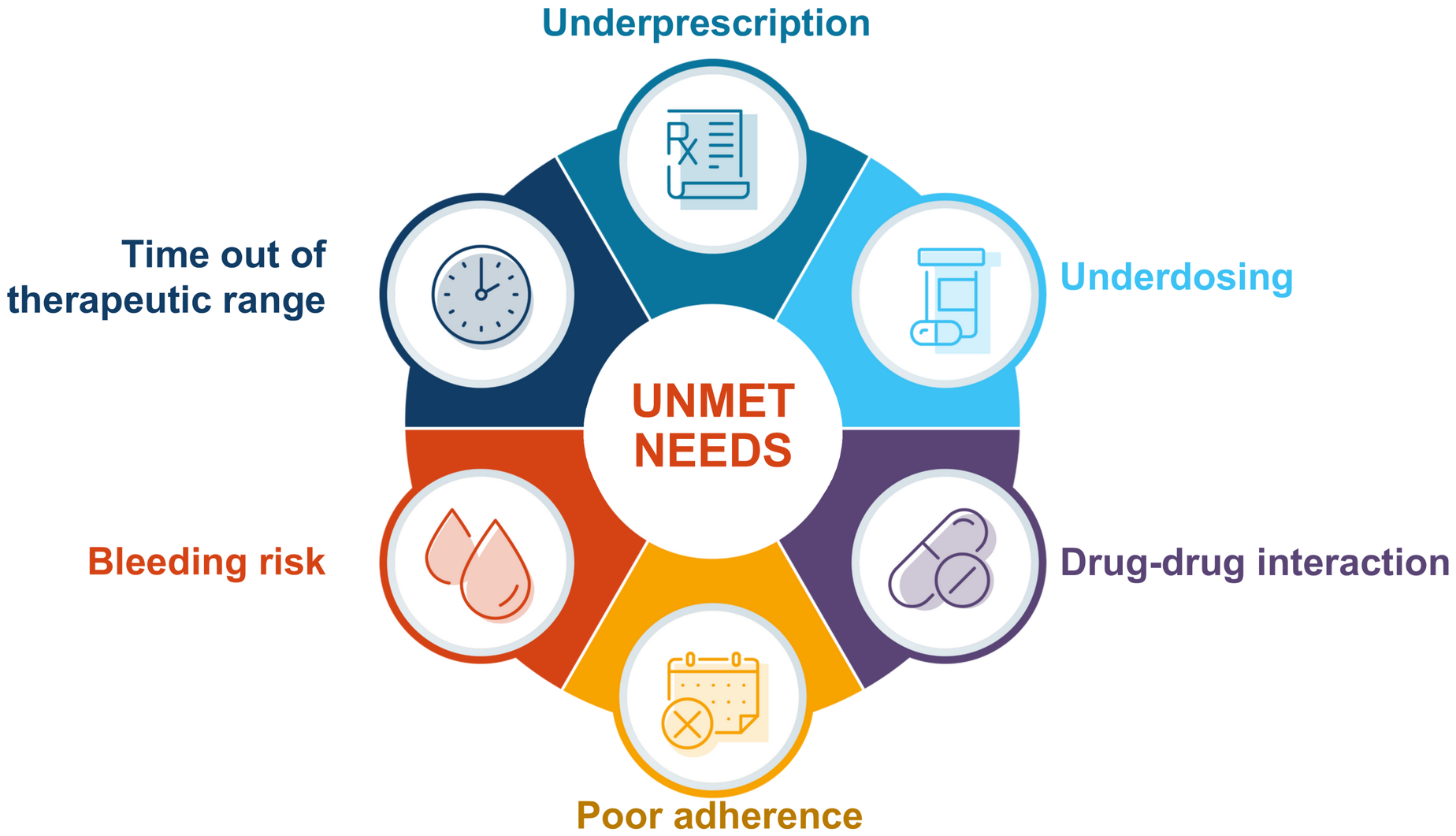
Lack of **safe, consistent protection** from thrombosis

Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Factor XI Inhibitors:
A New Frontier in Anticoagulation

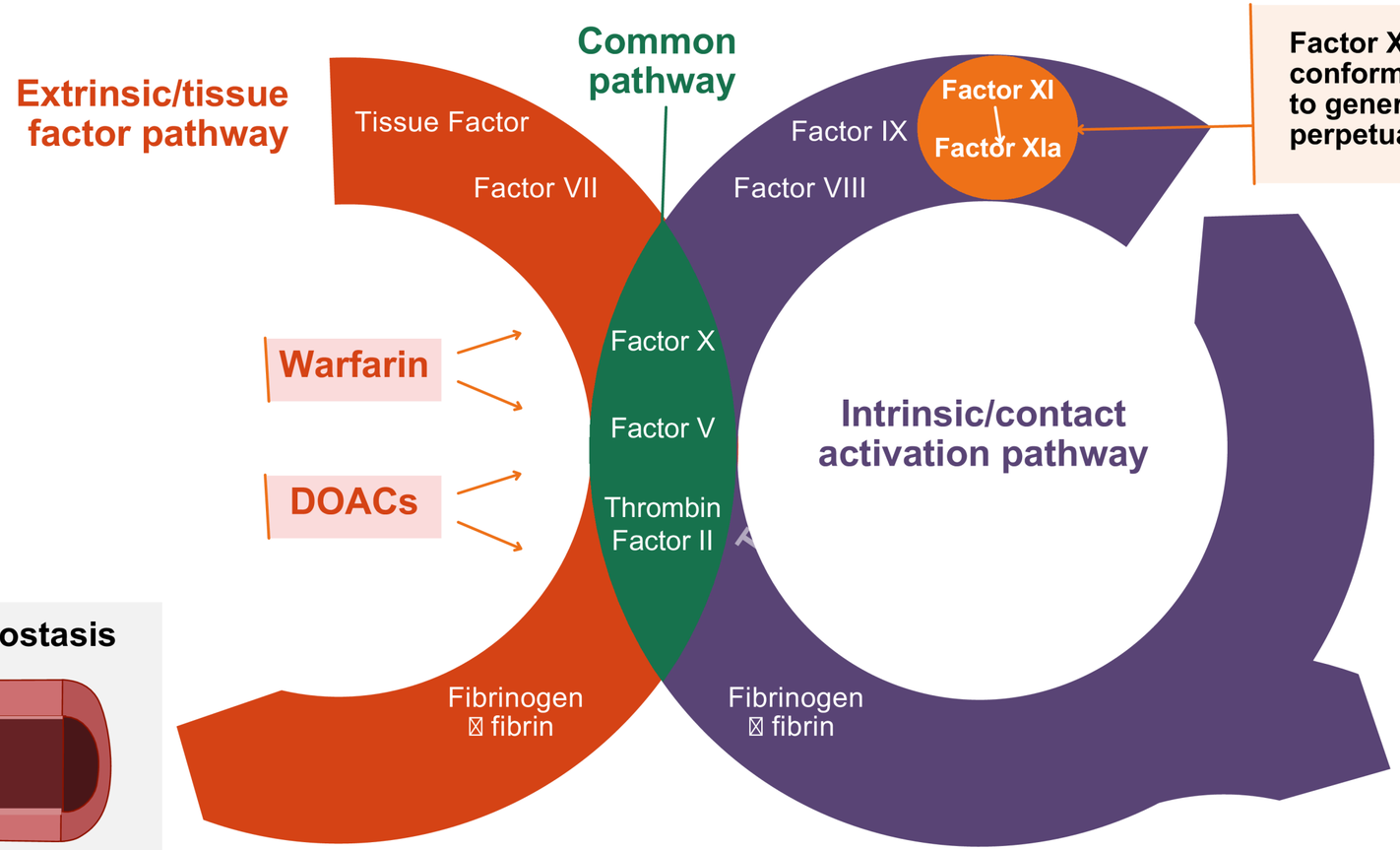
An unrestricted educational grant was provided by Anthos Therapeutics.
Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Call to Action
Unmet Needs in Anticoagulation



Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

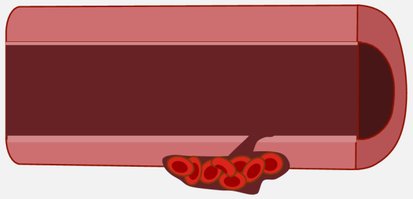
DOAC and VKA targets overlap hemostatic and thrombotic pathways; Factor XI (FXI) inhibitors are thought to be hemostasis-sparing



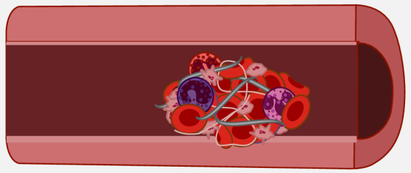
Factor XIIa or thrombin induces conformational changes in FXI to generate active FXIa and perpetuate the pathway

Factor XI inhibitors inhibit pathological thrombosis by preventing the formation and/or the activity of FXIa (active subunit of FXI)

Physiologic homeostasis



Pathological thrombosis



Hsu C, et al. *J Am Coll Cardiol*. 2021;78(6):625-631. Patel SM, Ruff CT. *Curr Cardiol Rep*. 2024;26(9):911-917.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Human and animal studies provide evidence supporting FXI as a target

Human Genetic Deficiency[1]

Patients with severe inherited FXI deficiency

- Are at reduced risk of thrombosis
- Rarely experience spontaneous bleeding

Genetic Epidemiology2,3

Risk of thrombosis in the general population is

- 2-fold higher in those with higher FXI levels
- 40% to 90% lower in those with reduced FXI levels

Animal Studies[4]

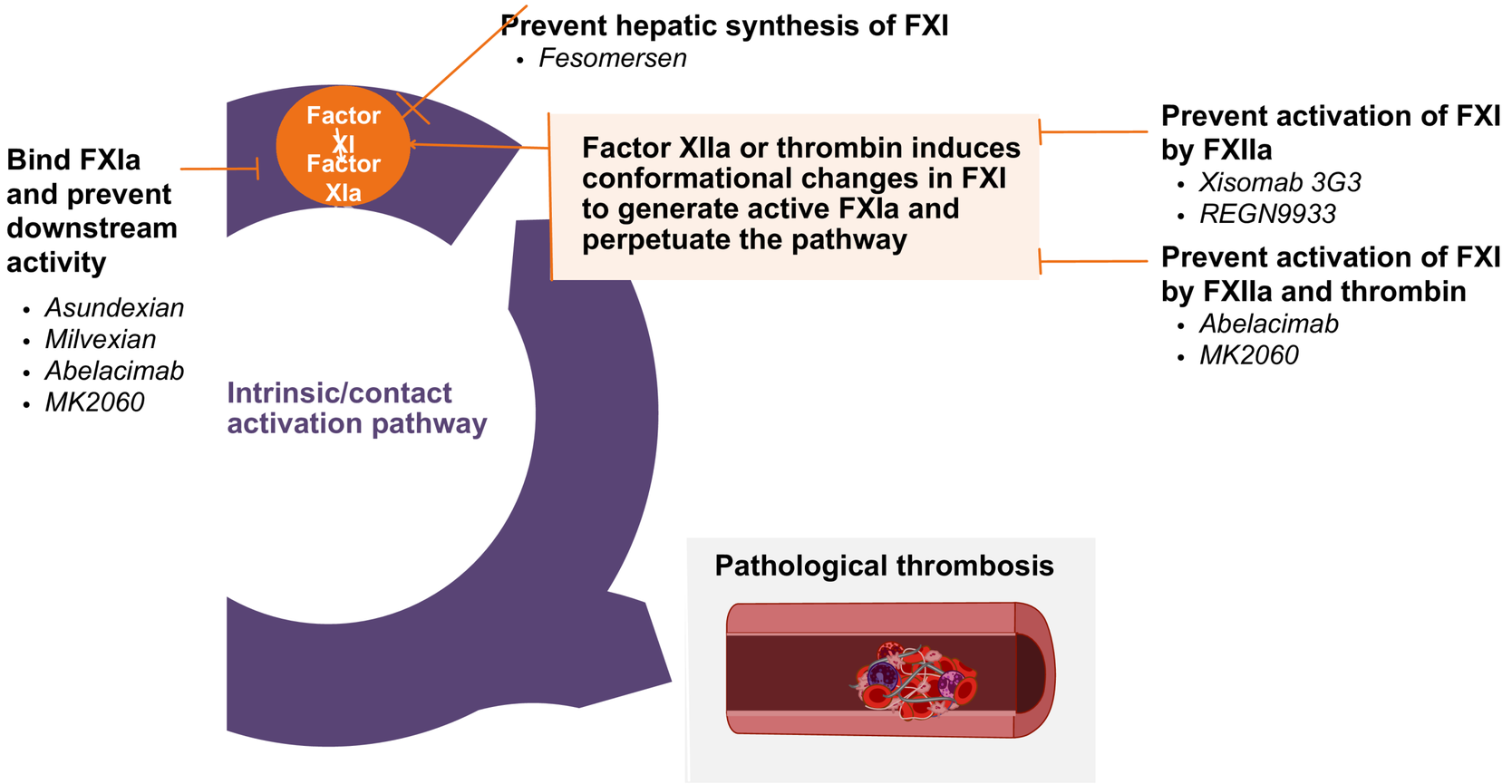
FXI inhibition in mouse, rabbit, monkey, and baboon models

- Attenuates thrombosis
- No increase in bleeding

1. Georgi B, et al. *Stroke*. 2019;50(11):3004-3012. 2. Meijers J, et al. *N Engl J Med*. 2000;9;342(10):696-701. 3. Preis M, et al. *Blood*. 2017;129(9):1210-1215.
4. Gailani D, Gruber A. *Arterioscler Thromb Vasc Biol*. 2016;36(7):1316-1322.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Strategies for targeting FXI/FXI vary among the investigational candidates



Patel SM, Ruff CT. *Curr Cardiol Rep*. 2024;26(9):911-917. Barnes GD. *J Thromb Haemost*. Published online December 14, 2024. doi:10.1016/j.jtha.2024.12.003.
Marin E, et al. Presented at: THSNA 2024; April 4-6, 2024; Chicago, IL. Abstract 231.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

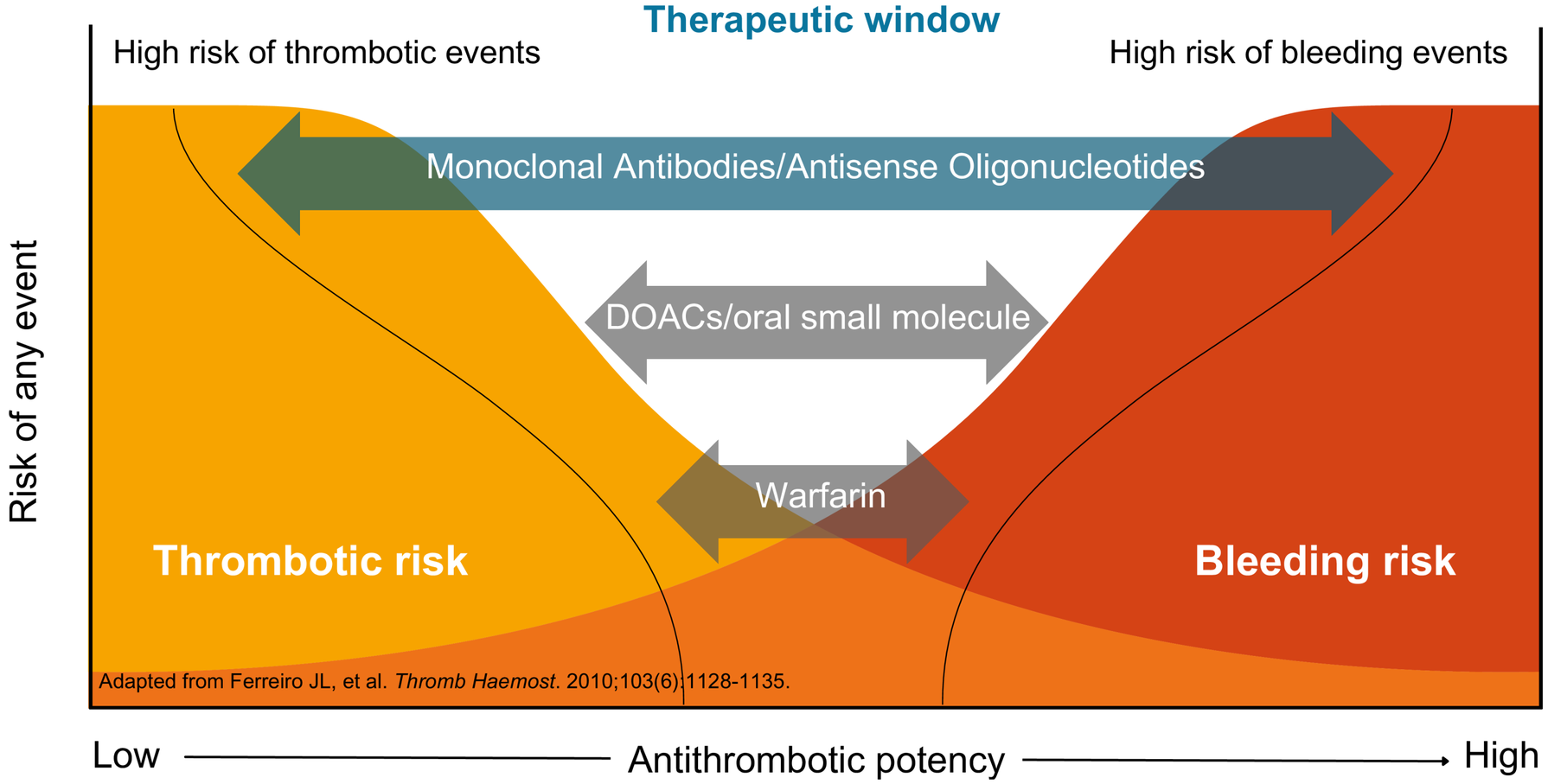
Factor XI inhibitors under investigation have multiple important distinctions in mechanism, metabolism, and dosing[1–3]

	Abelacimab	Osocimab*	Fesomersen	Asundexian	Milvexian	REGN9933, REGN7508	Xisomab 3G3	MK-2060	Conventional DOAC[4]
Agent	Monoclonal antibody (fully human)	Monoclonal antibody (fully human)	Antisense oligonucleotide	Small molecule	Small molecule	Monoclonal antibody	Monoclonal antibody	Monoclonal antibody	Small molecule
Mode of action	Inhibits conversion of FXI to FXIa	Inhibits FXIa	Decreases FXI synthesis	Inhibits FXIa	Inhibits FXIa	Inhibits FXI activation by FXIIa	Inhibits FXI activation by FXIIa	Inhibits FXI	Inhibits FXa or thrombin
Administration	SC or IV	SC or IV	SC	Oral	Oral	IV	IV	IV	Oral
Frequency of dosing	Once monthly	Once monthly	Weekly to Monthly	Once daily	Twice daily	Single dose	Single dose	Single, multiple doses	Once or twice daily
Onset of action	Rapid	Rapid	Slow	Rapid	Rapid	Rapid	Rapid	Not reported	Rapid
Offset of action	Slow	Slow	Slow	Rapid	Rapid	Slow	Variable	Not reported	Rapid
Renal clearance	No	No	No	Some	Some	No	No	Not reported	Yes
Drug-drug interactions	No	No	No	Possible	Possible	-	-	-	Yes
CYP3A4 Interaction	No	No	No	Yes	Yes	No	No	Not reported	Yes

*Osocimab not currently under further development.
IV, intravenous; SC, subcutaneous.
1. Goodman SG, et al. *Crit Pathw Cardiol*. 2024;23(2):47-57. 2. Occhipinti G, et al. *Eur Heart J Cardiovasc Pharmacother*. 2024;10(3):245-258. 3. Information compiled by Dr. Fanikos.
4. Roberti R, et al. *Front Pharmacol*. 2021:12:684638.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Several of the FXI/FXIa options being studied have prolonged half-lives for improved stability of therapeutic windows[1–3]

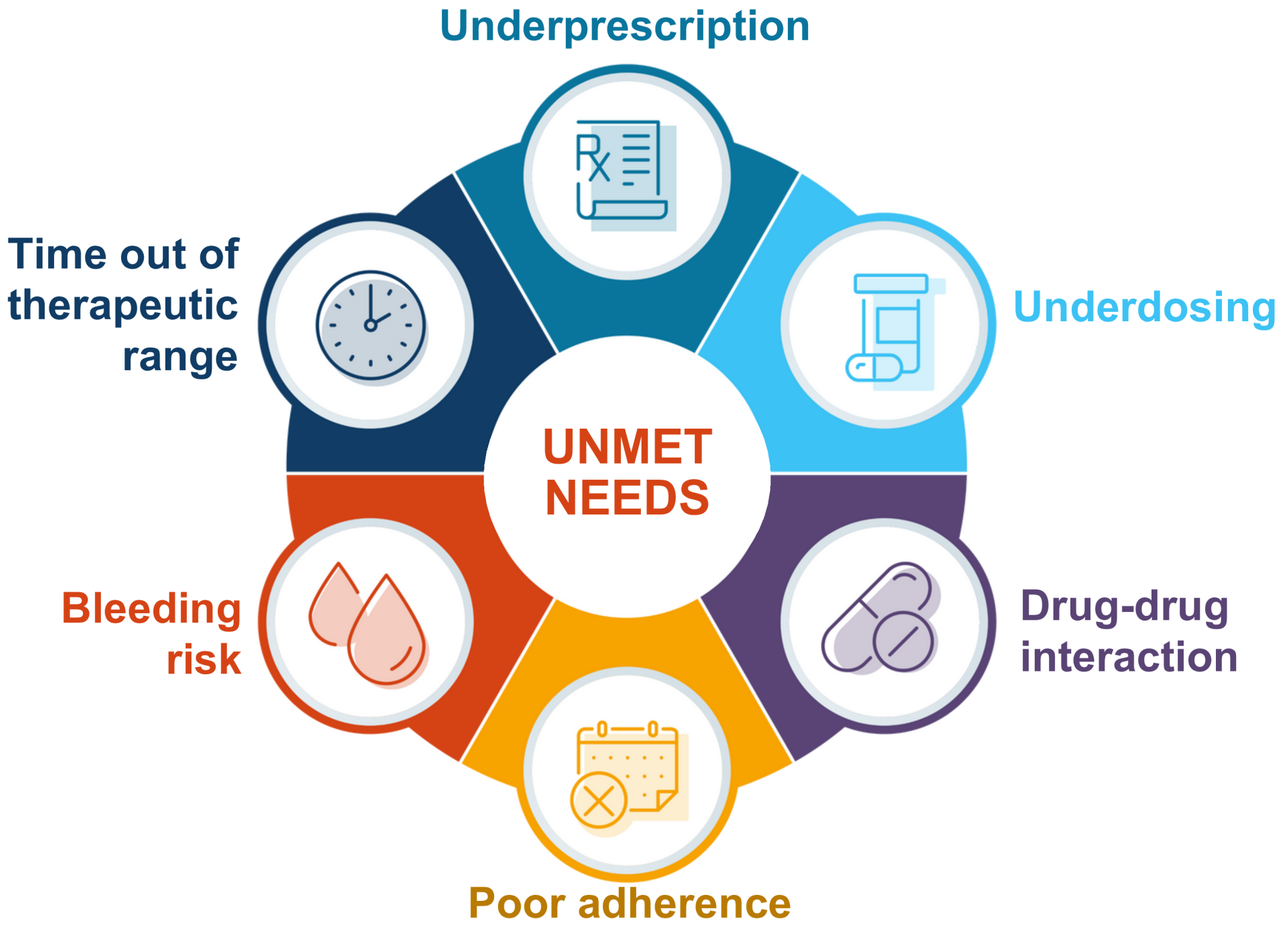


1. Greco A, et al. *Circulation*. 2023;147(11):897-913. 2. Roberti R, et al. *Front Pharmacol*. 2021:12:684638. 3. Joglar JA, et al. *J Am Coll Cardiol*. 2024;83(1):109-279.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Features of FXI inhibitors may help address important unmet patient needs in anticoagulation



Less risk of bleeding
including for those who are older, frail, and/or at risk of falls

And for parenterally administered antibodies:

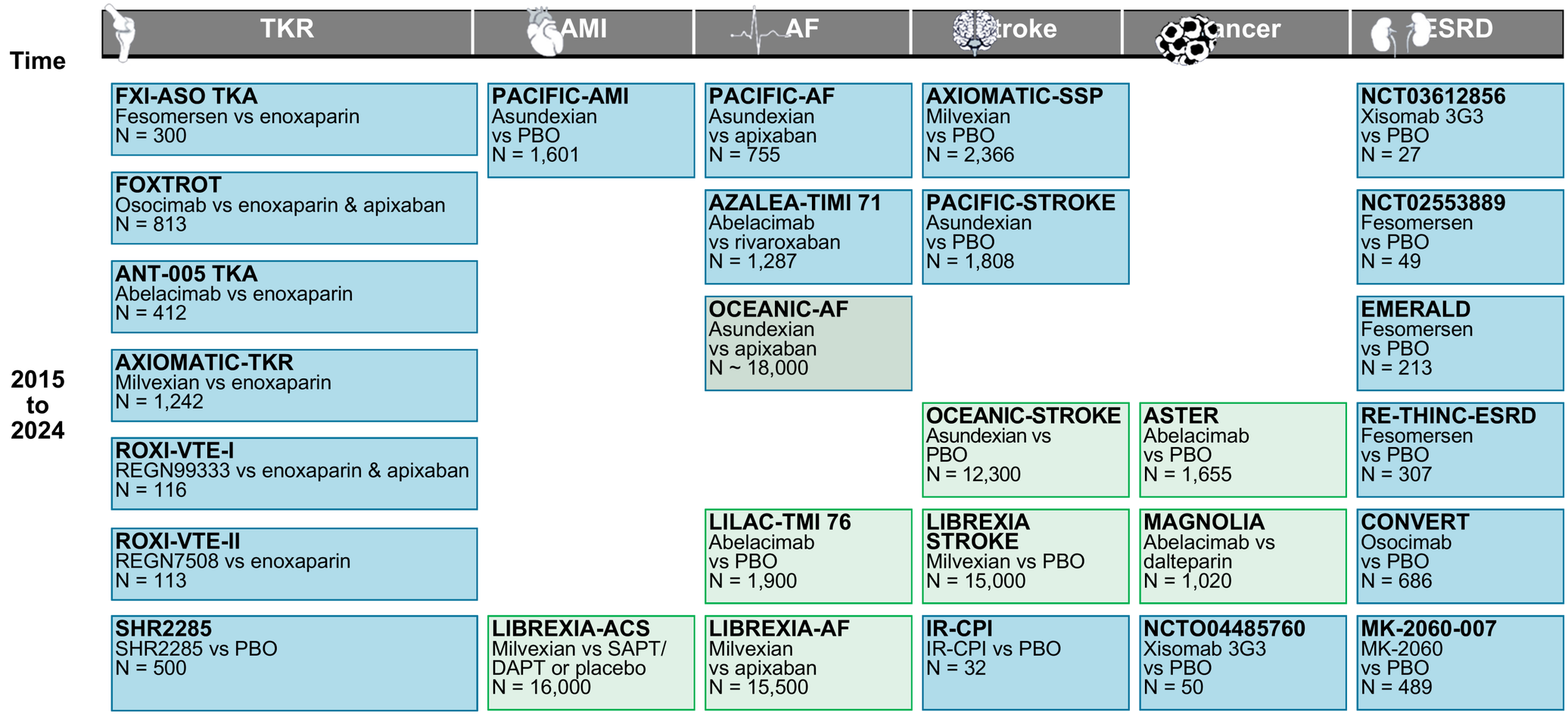
Less risk of DDIs
with no liver/renal implications or need to dose adjust

Less frequent dosing
may improve adherence and compliance

Stable drug levels
for consistent thrombotic protection with no frequent monitoring

Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

FXI candidates are being evaluated in a variety of prothrombotic conditions



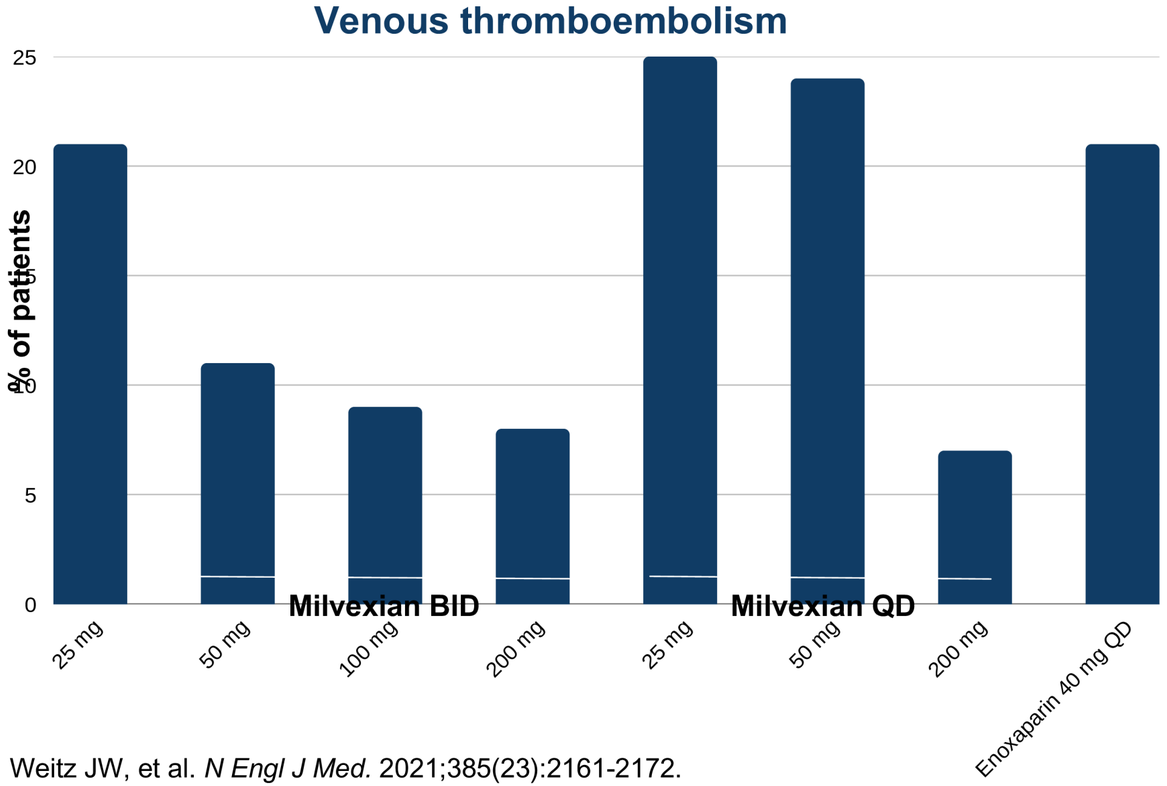
TKR, total knee replacement; VTE, venous thromboembolism.

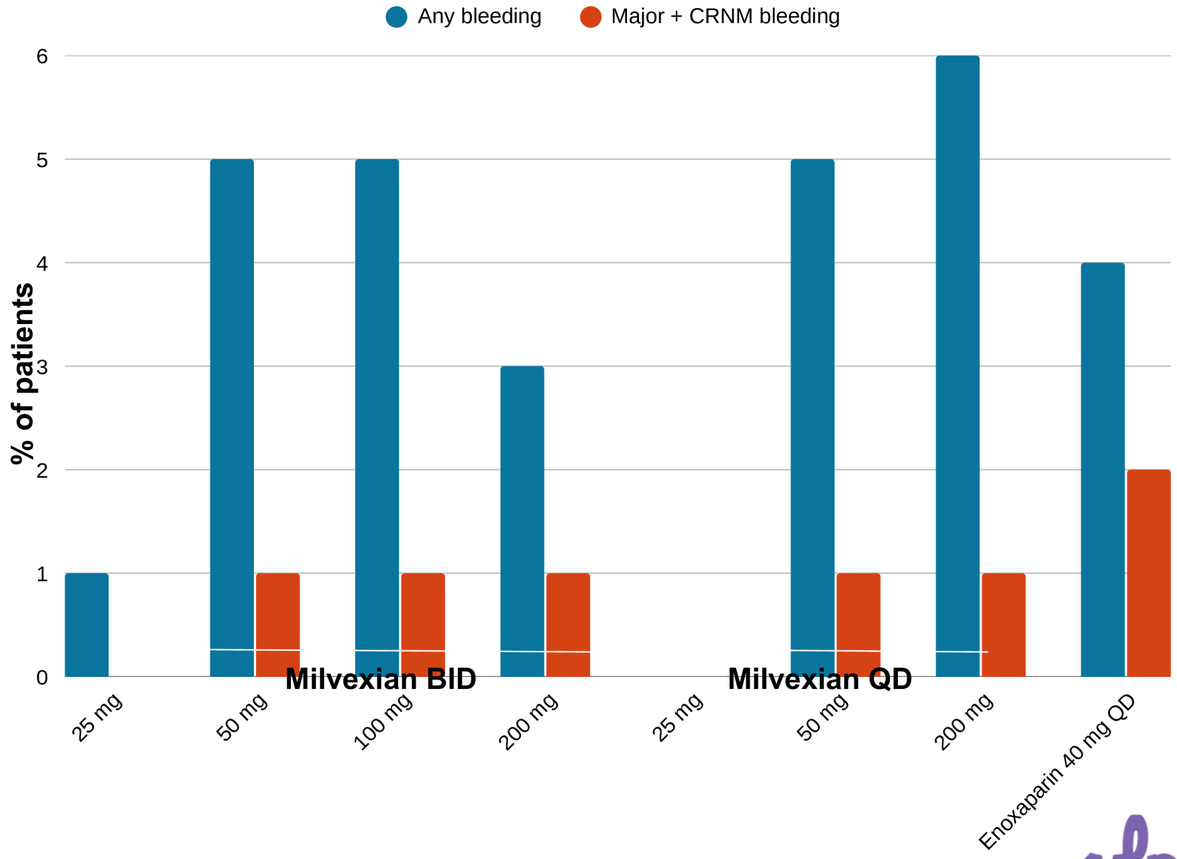
Adapted from Occhipinti G, et al. *Eur Heart J Cardiovasc Pharmacother*. 2024;10(3):245-258. Updated December 19, 2024.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Phase 2 studies: AXIOMATIC-TKR (milvexian vs enoxaparin)

- N=1242 patients undergoing total knee arthroplasty
- Postoperative milvexian was effective for VTE prevention, without increased bleeding



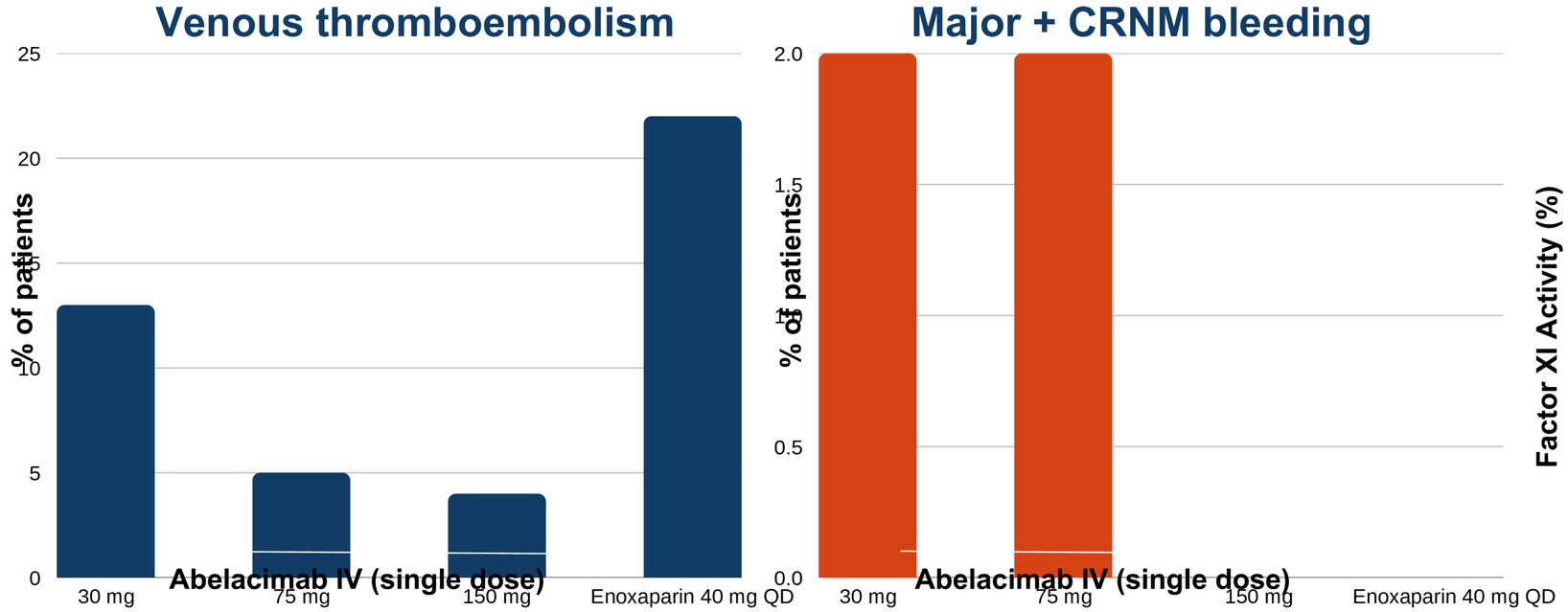


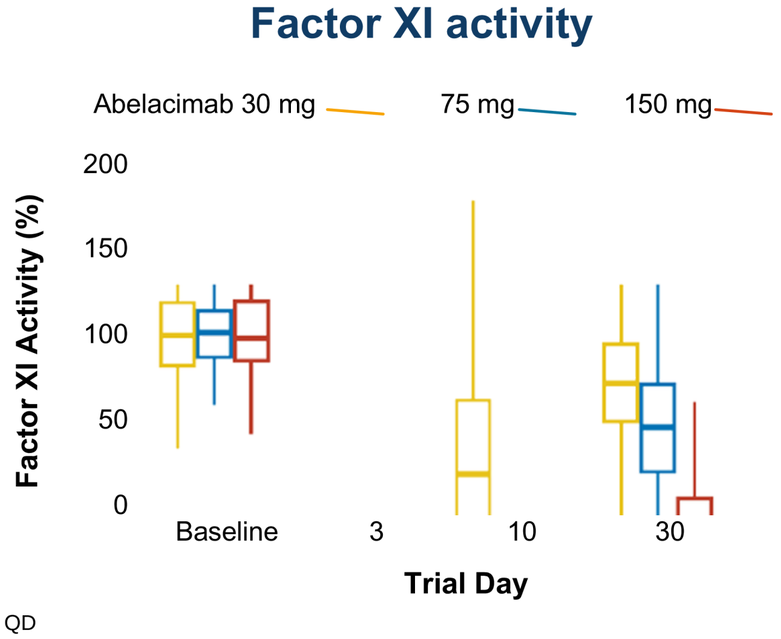
Weitz JW, et al. *N Engl J Med.* 2021;385(23):2161-2172.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Phase 2 studies: ANT-005 TKA (abelacimab vs enoxaparin)

- N=412 patients undergoing total knee arthroplasty
- Postoperative abelacimab was effective for VTE prevention, without increased bleeding
- Abelacimab 150 mg also demonstrated substantial shutdown of FXI activity





Verhamme P, et al. *N Engl J Med*. 2021;385(7):609-617.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Phase 2 studies: ROXI-VTE-I, ROXI-VTE II (REGN7508, REGN9933 vs enoxaparin, apixaban)

- Patients undergoing unilateral total knee arthroplasty
- All treatments given 12-24 hours postoperatively were effective for VTE prevention
- There was no major bleeding (including surgical site bleeding) or clinically relevant non-major bleeding in any arm; the only treatment-related adverse event in any arm was 1 case of minimal bleeding (contusion) reported in the enoxaparin arm of ROXI-VTE-I

	REGN7508	REGN9933	Enoxaparin	Apixaban	Historical Controls
Patients with asymptomatic and symptomatic VTE	7% (8/113)	17% (20/116)	21% (36/175)	12% (14/113)	48% (43/89)
Difference in VTE incidence (95% confidence interval)	REGN7508 vs apixaban: -5% (-13% to 2%)^				

* Superiority met.
^ Non-inferiority met with a margin of 9%.

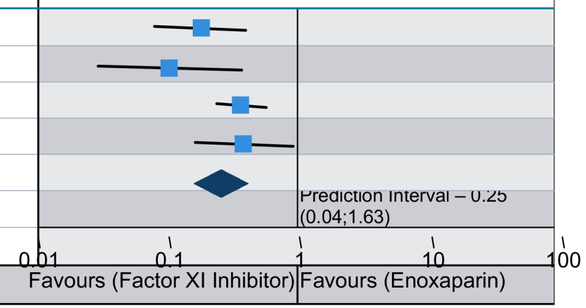
Regeneron to advance two factor XI antibodies into a broad phase 3 program following positive phase 2 proof-of-concept results. News release. Regeneron Pharmaceuticals Inc; December 19, 2024. Accessed March 5, 2025. https://investor.regeneron.com/news-releases/news-release-details/regeneron-advance-two-factor-xi-antibodies-broad-phase-3-program

Factor XI inhibitors vs LMWH for VTE prevention in major orthopedic surgery—Meta-analysis

- Meta-analysis of evidence up to 2022 on FXI inhibitors for thromboprophylaxis in major orthopedic surgery
- 4 RCTs included, with 2269 patients,
  372 VTE events, and 50 major or CRNM bleeding events
- Efficacy: FXI inhibitors were associated with a significant reduction in the incidence of VTE events (OR, 0.50; 95% confidence interval [CI: 0.36, 0.69])
- Safety: FXI inhibitors significantly reduced major or CRNM bleeding events (OR, 0.41; 95% CI [0.22, 0.75])

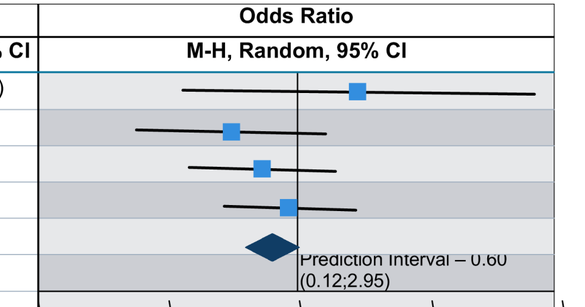
Incidence of Venous Thromboembolism

	Factor XI Inhibitor		Enoxaparin			Odds Ratio	Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Abelacimab ≥75 mg	9	197	22	101	23.5%	0.17 (0.08, 0.39)	
IONIS-FXIRx 300 mg	3	71	22	71	12.9%	0.10 (0.03, 0.35)	
Milvexian ≥100 mg/day	44	512	54	252	41.4%	0.34 (0.22, 0.53)	
Osocimab 1.8 mg/kg pre-op	9	80	20	77	22.1%	0.36 (0.15, 0.85)	
Total (95% CI)		**860**		**501**	**100.0%**	**0.25 (0.15, 0.42)**	
Total events	65		118				
Heterogeneity: Tau²= 0.12; Chi² = 5.29, df = 3 (P = 0.15); I² = 43%							
Test for overall effect: Z = 5.27 (P < 0.00001)							



Incidence of Major or CRNM Bleeding

	Factor XI Inhibitor		Enoxaparin			Odds Ratio	Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Abelacimab ≥75 mg	2	197	0	101	5.6%	2.60 (0.12, 54.58)	
IONIS-FXIRx 300 mg	2	77	6	72	19.6%	0.29 (0.06, 1.50)	
Milvexian ≥100 mg/day	5	592	5	296	33.6%	0.50 (0.14, 1.73)	
Osocimab 1.8 mg/kg pre-op	6	107	7	102	41.21%	0.81 (0.26, 2.49)	
Total (95% CI)		**973**		**571**	**100.0%**	**0.60 (0.29, 1.24)**	
Total events	15		18				
Heterogeneity: Tau²= 0.00; Chi² = 1.98, df = 3 (P = 0.58); I² = 0%							
Test for overall effect: Z = 1.38 (P = 0.17)							



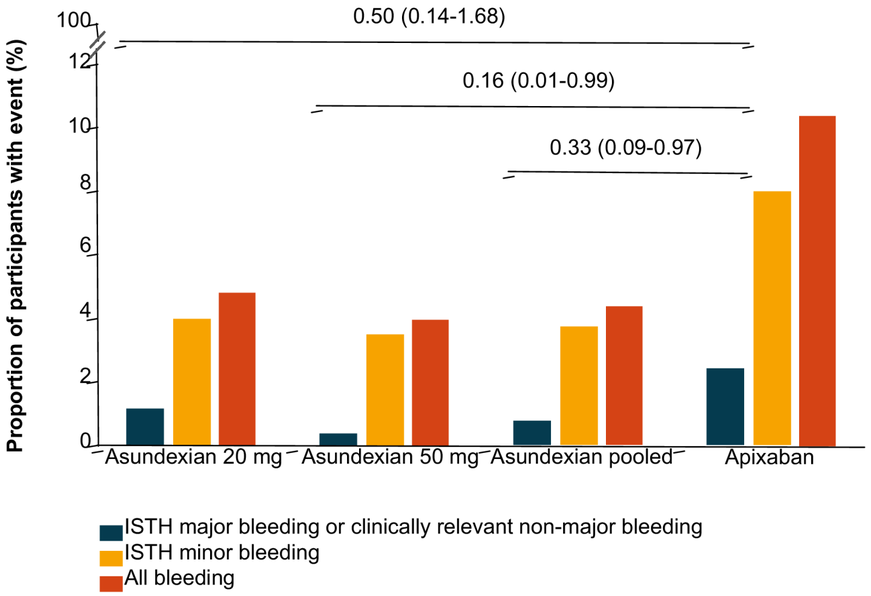
Adapted from Presume J, et al. *J Thromb Haemost*. 2022;20(12):2930-2938.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

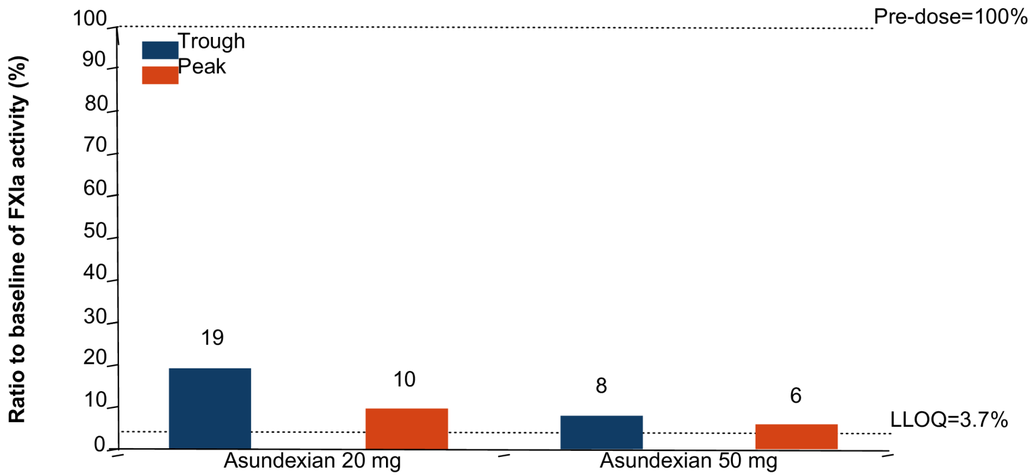
Phase 2 studies: PACIFIC-AF (asundexian vs apixaban)

- N=755 patients with AF
- Asundexian treatment resulted in lower rates of bleeding compared with apixaban
- Asundexian 50 mg QD yielded >90% inhibition of FXI (according to a unique, proprietary assay)

Major + CRNM bleeding



Factor XI activity



n	224	222	228	228
Analysis value (95% CI)	14.82 (12.65-16.99)	7.42 (6.33-8.51)	6.59 (5.15-8.02)	4.32 (3.60-5.05)
Mean ratio to baseline (95% CI)	0.19 (0.16-0.22)	0.10 (0.08-0.12)	0.08 (0.07-0.10)	0.06 (0.05-0.07)

Piccini JP, et al. *Lancet*. 2022;399(10333):1383-1390.

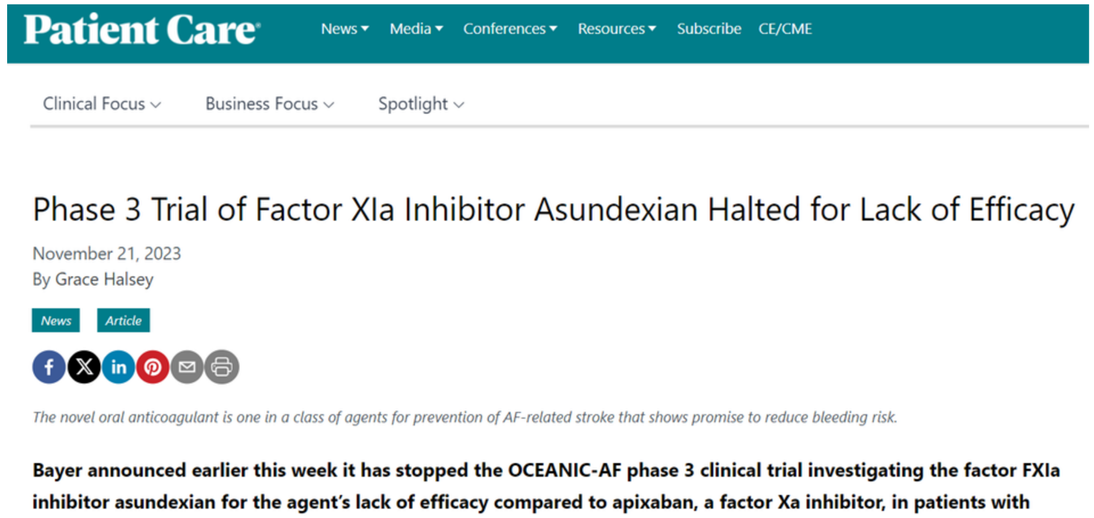
Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Phase 3 data in AF presented in 2023 raised questions about the differences among FXI/FXIa inhibitors

September 2023: AZALEA-TIMI 71 trial halted

IDMC members unanimously recommended the termination of AZALEA because of the **substantially greater than anticipated reduction in major and clinically relevant non-major bleeds** in the abelacimab arms compared with rivaroxaban

https://www.tctmd.com/news/overwhelming-reduction-bleeding-abelacimab-vs-rivaroxaban-af



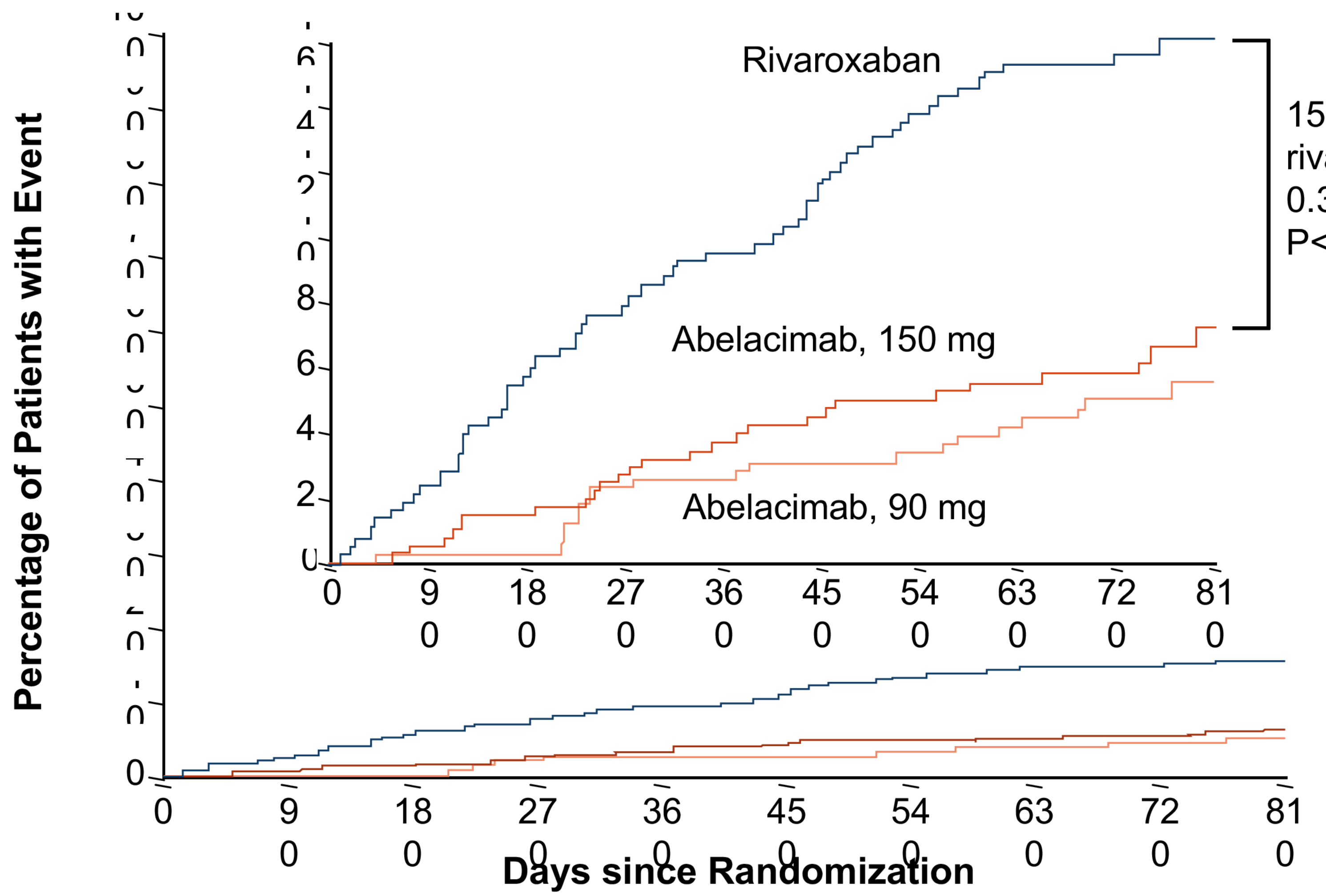
November 2023: OCEANIC-AF trial halted

Stopped early due to **inferior efficacy in prevention of stroke and systemic embolism** for asundexian vs apixaban; however, asundexian also demonstrated a substantial reduction in the amount of bleeding compared to apixaban

https://www.patientcareonline.com/view/phase-3-trial-of-factor-xia-inhibitor-asundexian-halted-for-lack-of-efficacy

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

AZALEA-TIMI 71: Both doses of abelacimab significantly reduced bleeding compared with rivaroxaban



150 mg Abelacimab vs. rivaroxaban (hazard ratio, 0.38; 95% CI, 0.24-0.60; P<0.001)

90 mg Abelacimab vs. rivaroxaban (hazard ratio, 0.31; 95% CI, 0.19-0.51; P<0.001)

No. at Risk										
Rivaroxaban	42	41	39	37	36	35	33	32	31	12
Abelacimab, 150 mg	42	41	40	38	37	36	35	34	32	11
Abelacimab, 90 mg	42	41	39	37	37	35	34	33	30	17
	5	3	8	8	2	7	9	8	8	7

Abelacimab 150 mg vs rivaroxaban:

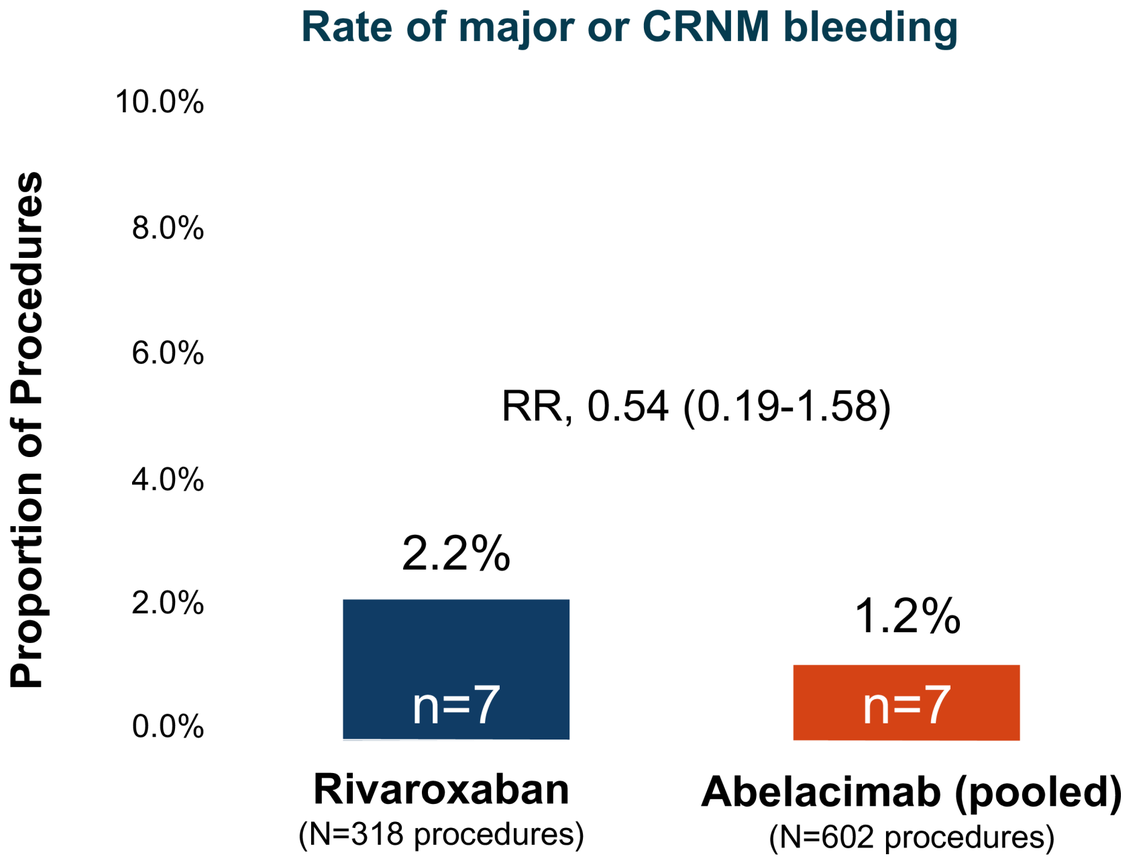
- 99% inhibition of FXI/FXIa
- 62% □ major or clinically relevant non-major bleeding
- 67% □ major bleeding
- 89% □ major GI bleeding

Trial was stopped prematurely due to “overwhelming reduction” in bleeding

Open-label extension was made available

Ruff CT, et al. *N Engl J Med.* 2025;392(4):361-371.
Anthos AZALEA Press Release. September 18, 2023.

AZALEA-TIMI 71: Data were also collected in the periprocedural subpopulation



- n=336 (56%) of all procedures in abelacimab patients were performed **within 30 days of last dose**, yielding a bleeding rate of 0.9% (n=3)
- In contrast, DOACs and warfarin were stopped prior to surgical procedures

These periprocedural findings suggested that FXI inhibitors may not need to be stopped for surgery

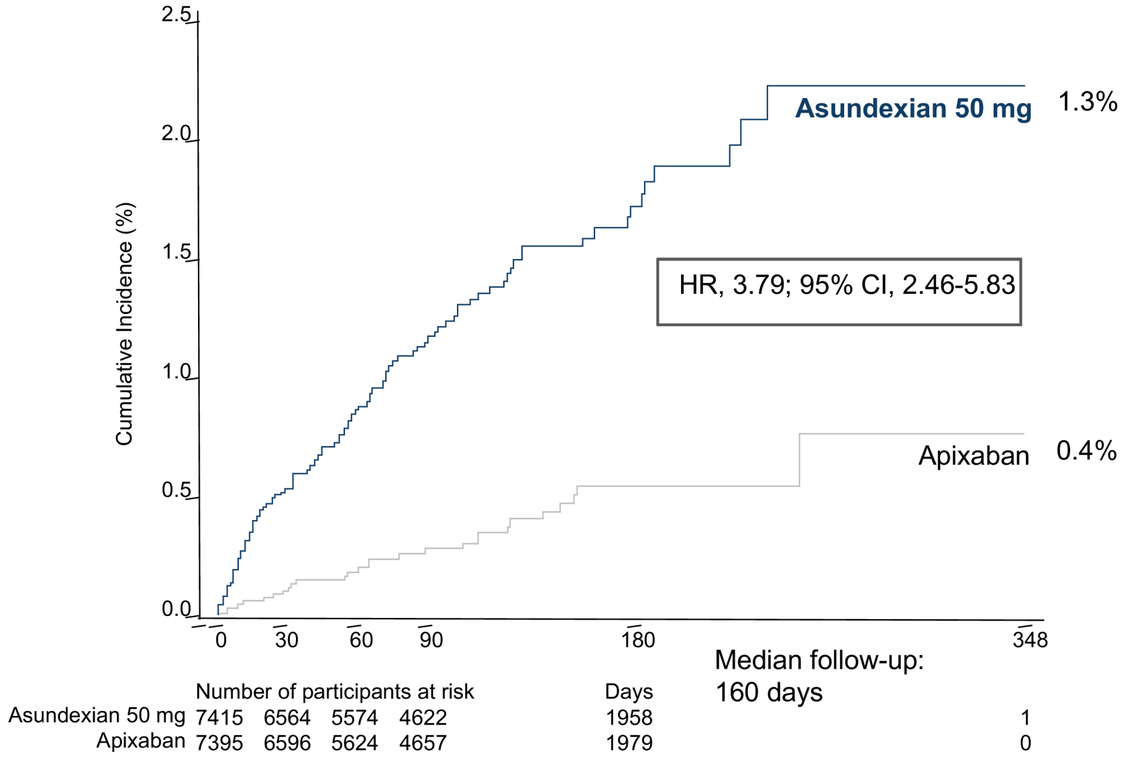
Patel SM, et al. Presented at: ESC Congress 2024; August 30-September 2, 2024; London, UK.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

OCEANIC-AF: Asundexian showed improvements in bleeding rates compared with control (apixaban) but a marked increase in stroke

Cumulative Event Rate for the Primary Efficacy Endpoint



Safety Events

	Asundexian 50 mg (n=7373)	Apixaban (n=7364)	Total (n=14,737)	csHR (95% CI)
ISTH major bleeding	17 (0.2%)	53 (0.7%)	70 (0.5%)	0.32 (0.18-0.55)
ISTH major and CRNM bleeding	83 (1.1%)	188 (2.6%)	271 (1.8%)	0.44 (0.34-0.57)
ISTH CRNM bleeding	67 (0.9%)	140 (1.9%)	207 (1.4%)	0.48 (0.36-0.64)
Hemorrhagic stroke	1 (<0.1%)	6 (0.1%)	7 (<0.1%)	0.17 (0.02-1.42)
Symptomatic intracranial hemorrhage	3 (<0.1%)	18 (0.2%)	21 (0.1%)	0.16 (0.05-0.55)
Fatal bleeding	0 (0%)	4 (0.1%)	4 (<0.1%)	Not calculated
ISTH minor bleeding	187 (2.5%)	317 (4.3%)	504 (3.4%)	0.59 (0.49-0.70)
Stroke, SE, or ISTH major bleeding (net clinical benefit endpoint)	120 (1.6%)	75 (1.0%)	195 (1.3%)	1.61 (1.21-2.15)

CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; SE, systemic embolism.

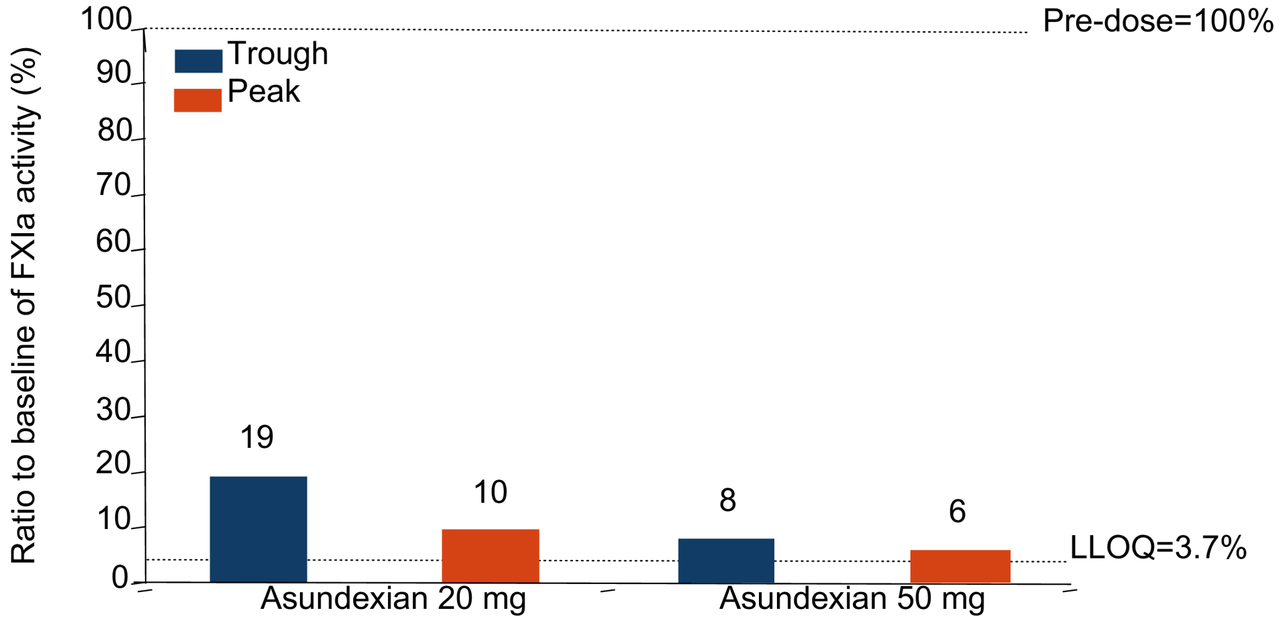
Piccini JP, et al. *N Engl J Med*. 2025;392(1):23-32.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

OCEANIC-AF failure: Exploring the possibility of incomplete inhibition of FXI/FXIa signaling

- No Phase 2 TKA trial for asundexian was performed to establish efficacious dose1,2
- Inhibition assays suggest **6-8% residual FXIa activity** for asundexian 50 mg[1–3]
  - Inhibition of FXIa activity for asundexian was also measured using a unique, proprietary, unpublished assay[1]

FXIa Activity – Inhibition Data[3]



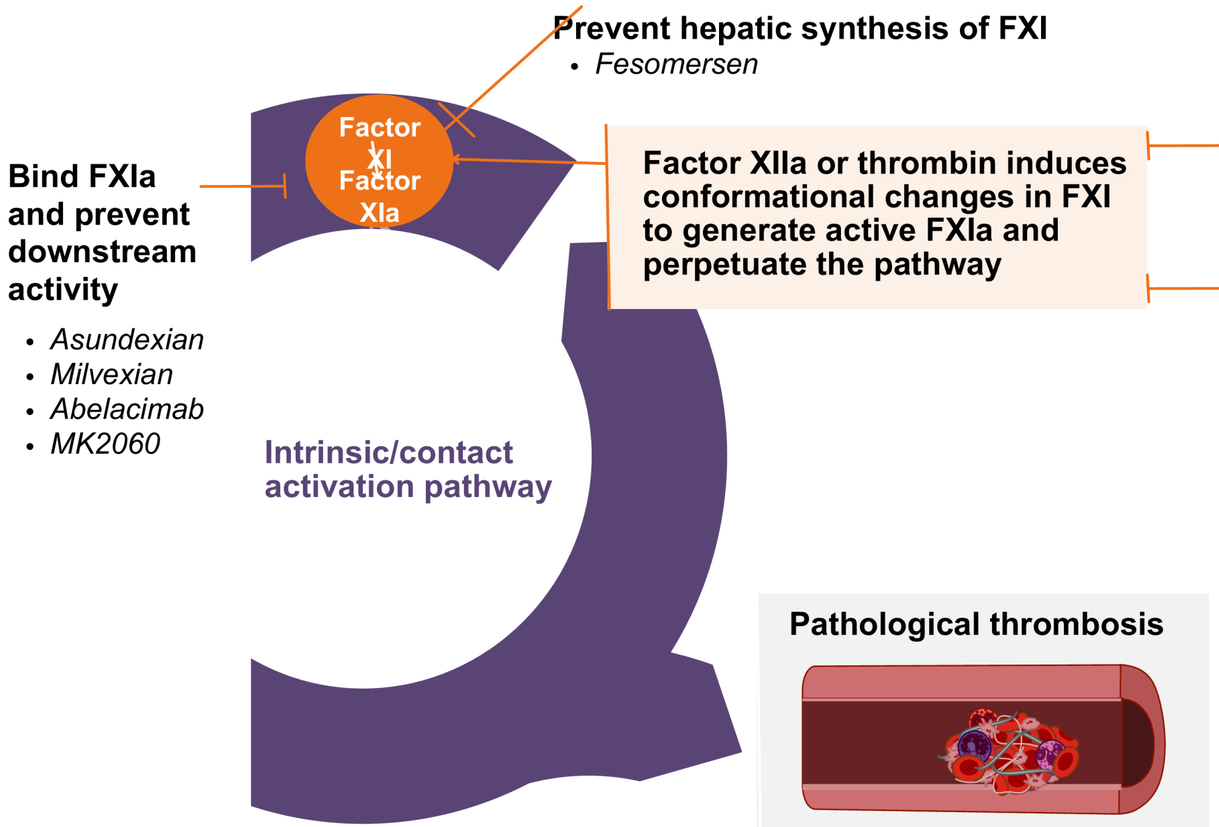
	Asundexian 20 mg		Asundexian 50 mg	
n	224	222	228	228
Analysis value (95% CI)	14.82 (12.65-16.99)	7.42 (6.33-8.51)	6.59 (5.15-8.02)	4.32 (3.60-5.05)
Mean ratio to baseline (95% CI)	0.19 (0.16-0.22)	0.10 (0.08-0.12)	0.08 (0.07-0.10)	0.06 (0.05-0.07)

TKA, total knee arthroplasty.

1. Gibson CM. *J Am Coll Cardiol*. Published online November 26, 2024. doi:10.1016/j.jacc.2024.10.105. 2. Piccini JP, et al. *N Engl J Med*. 2025;392(1):23-32.
3. Piccini JP, et al. *Lancet*. 2022;399(10333):1383-1390.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Strategies for targeting FXI/FXI vary among the investigational candidates



More complete upstream suppression of the thrombotic pathway, preventing the generation of active FXI, may be necessary for thromboembolic protection in AF

Patel SM, Ruff CT. *Curr Cardiol Rep*. 2024;26(9):911-917. Barnes GD. *J Thromb Haemost*. Published online December 14, 2024. doi: 10.1016/j.jtha.2024.12.003. Marin E, et al. Presented at: THSNA 2024; April 4-6, 2024; Chicago, IL. Abstract 231. Piccini JP, et al. *N Engl J Med*. 2025;392(1):23-32.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Ongoing Phase 3 clinical trials will provide more information on the efficacy and safety of FXI inhibitors

Drug	Trial name (NCT)	Indication	Comparator	N	Sponsor
Abelacimab	LILAC-TIMI 76 (NCT05712200)	Patients with AF deemed unsuitable for oral anticoagulation	Placebo	1900	Anthos
	ASTER (NCT05171049)	Cancer-associated VTE	Apixaban	1655	
	MAGNOLIA (NCT05171075)	Gastrointestinal/genitourinary cancer–associated VTE	Dalteparin	1020	
Asundexian	OCEANIC-AFINA (2023-505421-13)	AF	Placebo	Not yet recruiting	Bayer
	OCEANIC-STROKE (NCT05686070)	Secondary stroke prevention	Placebo	9300	
Milvexian	LIBREXIA-AF (NCT 05757869)	AF	Apixaban	15500	BMS and Janssen
	LIBREXIA-Stroke (NCT05702034)	Secondary stroke prevention	Placebo	15000	
	LIBREXIA-ACS (NCT05754957)	ACS	Placebo	16000	

ACS, acute coronary syndrome; AF, atrial fibrillation; VTE, venous thromboembolism.

Gragnano F, et al. *Eur Heart J Cardiovasc Pharmacother*. 2024;10(7):575-577. Updated per ClinicalTrials.gov Sept 2024.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

Summary

An unrestricted educational grant was provided by Anthos Therapeutics.
Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.

Unmet needs in AF

Protection from thrombosis is incomplete in the AF patient population

Physicians commonly underprescribe and underdose OACs

- Risk of bleeding is a substantial concern

Patients regularly skip doses

- Fear of major bleeding
- Quality of life impact associated with all bleeding
- Difficulty keeping up with medication regimens

PK/PD properties of DOACs exacerbate the clinical challenges

- Inter- and intra-patient drug responses are highly variable
- Most patients spend significant time out of therapeutic range

DOACs, direct-acting oral anticoagulants; OACs, oral anticoagulants; PK/PD pharmacokinetic/pharmacodynamic.

Factor XI/XIa inhibitors are investigational and not approved for use in any country.

The promise of FXI as a new therapeutic target

FXI inhibitors

- Target a different factor in the coagulation pathway
- Are theorized to be associated with less risk of bleeding

Parenterally administered FXI inhibitors may also provide

- Less burdensome treatment regimens for better adherence
- Fewer safety & dosing concerns related to renal/hepatic metabolism or DDI

Phase 3 trials are ongoing

An unrestricted educational grant was provided by Anthos Therapeutics
Factor XI/XIa inhibitors are investigational and not approved for use in any country.
Content created by the faculty as an educational service from the North American Thrombosis Forum (NATF). All opinions represent those of the faculty and the NATF.