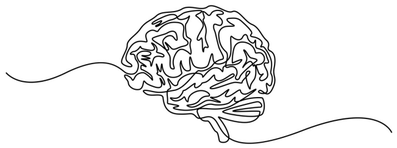
THE WARREN ALPERT Medical School
BROWN UNIVERSITY

Jointly Provided By

Comprehensive Stroke Center
Rhode Island Hospital
BROWNHealth UNIVERSITY

Factor XI Inhibition in Stroke Prevention

Jeffrey Weitz, OC, MD, FRCP(C), FRSC, FACP
Professor of Medicine and Biochemistry, and Biomedical Sciences
Executive Director
Thrombosis and Atherosclerosis Research Institute
McMaster University
Ontario, Canada



Disclosures

- Consultant: Alnylam, Anthos, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Ionis, Johnson & Johnson, Merck, Novartis, Pfizer, Regeneron, Servier
- Research support/PI: Canadian Institutes of Health Research, Heart and Stroke Foundation, Canadian Fund for Innovation
- Advisory Board: Alnylam, Anthos, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Ionis, Johnson & Johnson, Merck, Novartis, Pfizer, Regeneron, Servier

My talk will include off-label discussion

Anticoagulation Therapy Through the Years
Why Do We Need New Targets?

High rates of major and clinically relevant nonmajor bleeding (4% to 20%) in Phase 3 and observational studies in the AF population[2-4]

The ultimate goal of anticoagulant therapy is to attenuate thrombosis without increasing the risk of bleeding

DTI, direct thrombin inhibitor; IV, intravenous.

1. Fredenburgh JC, Weitz JI. et al. J Thromb Haemost. 2021;19:20-29; 2. Franco L, et al. Blood Transfus. 2018 Jul;16(4):387-391. 3. Ruff CT, et al. Lancet. 2014;383:955-962; 4. Carnicelli AP, et al;. Circulation. 2022;145:242-255.

Prior Bleeding History or Perceived Bleeding Risk Leads to . . .

UNDERUSE OF ANTICOAGULANTS
for stroke prevention in AF patients

INAPPROPRIATE USE
of low-dose DOAC regimens

. . . unprotected patients

1. Rose AJ, et al. J Am Heart Assoc. 2019;8:e012656; 2. Mitchell A, et al. BMC Med. 19:189; 3. Leef GC, et al. J Pharm Pract. 2020;33:647-653; 4. Fernandez CS, et al. J Comp Eff Res. 2020;9:509-523.

A considerable proportion of at-risk patients are not receiving recommended anticoagulation treatment[1,2]

In a meta-analysis of patients with elevated stroke risk[1]

were not treated

were undertreated

Across **ORBIT-AF II** and **GARFIELD** registries (N = 62,872),

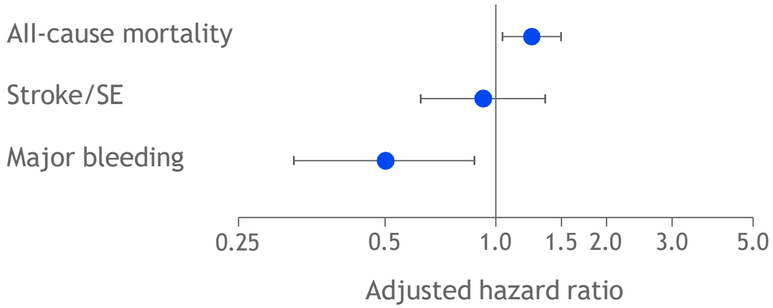
one-third

of high-risk patients with a CHA_2DS_2-VASc ≥ 2 did not receive recommended OAC therapy[2]

In **ORBIT-AF I**, patients **without OAC** had higher rates of[2,3]

- **Death**
- **Stroke, non-CNS embolisms**
- **Transient ischemic attacks**

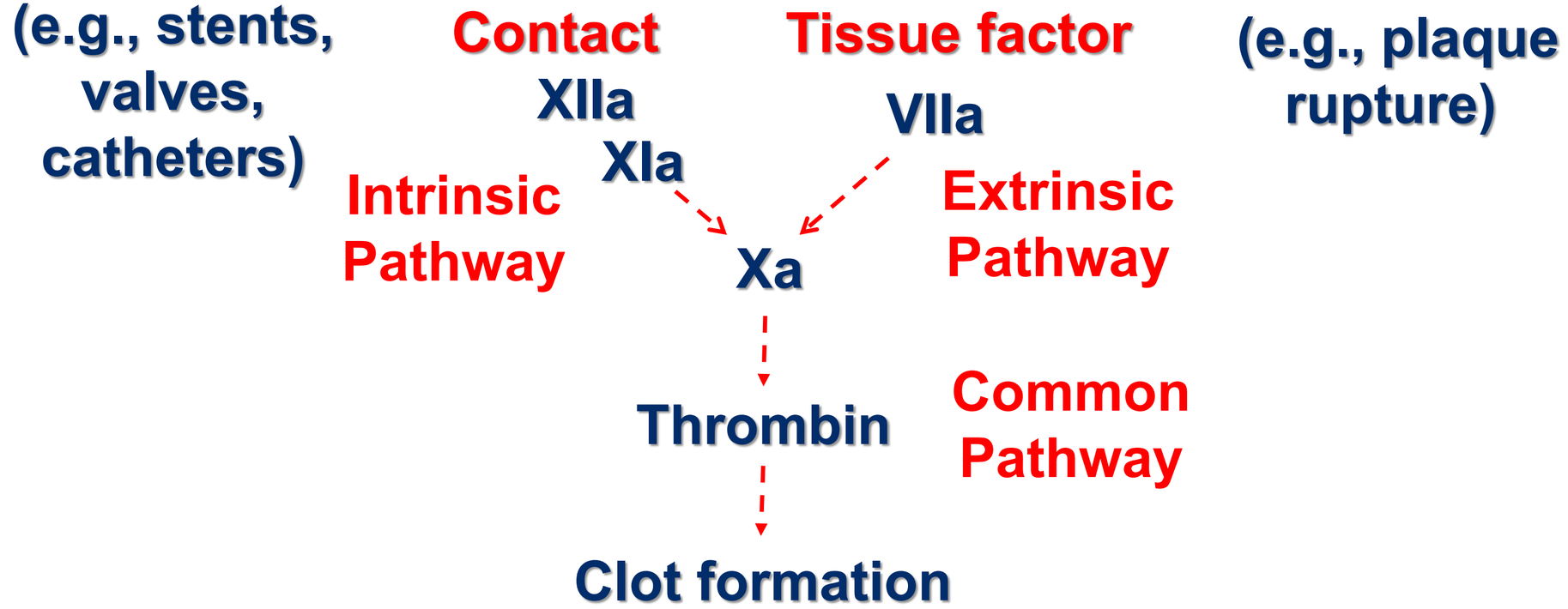
Relevant findings were also seen in **GARFIELD** among patients with **nonrecommended low dosing**[4]



Adapted from *J Am Coll Cardiol*.[4]

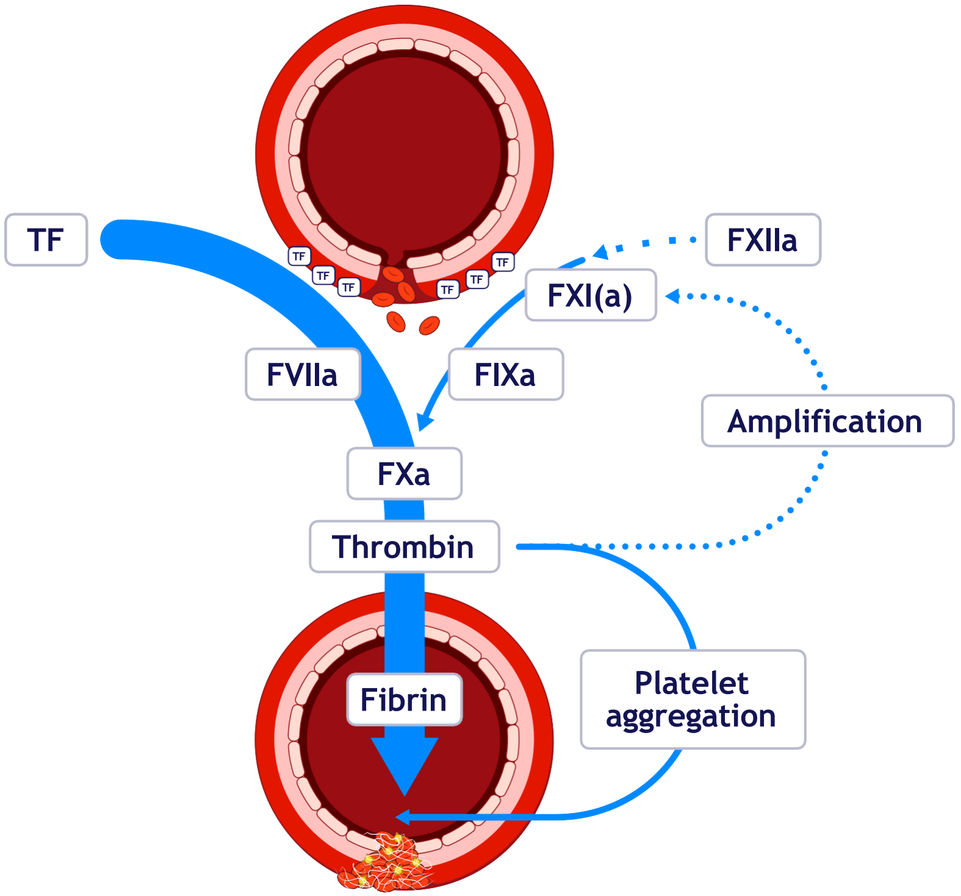
1. Sussman M et al. *Curr Med Res Opin*. 2022;38:7-18. 2. Steinberg BA et al. *Am Heart J*. 2017;194:132-140. 3. Hess PL et al. *Am J Med*. 2017;130:449-456. 4. Camm AJ et al. *J Am Coll Cardiol*. 2020;76:1425-1436.

Triggers of Coagulation Activation

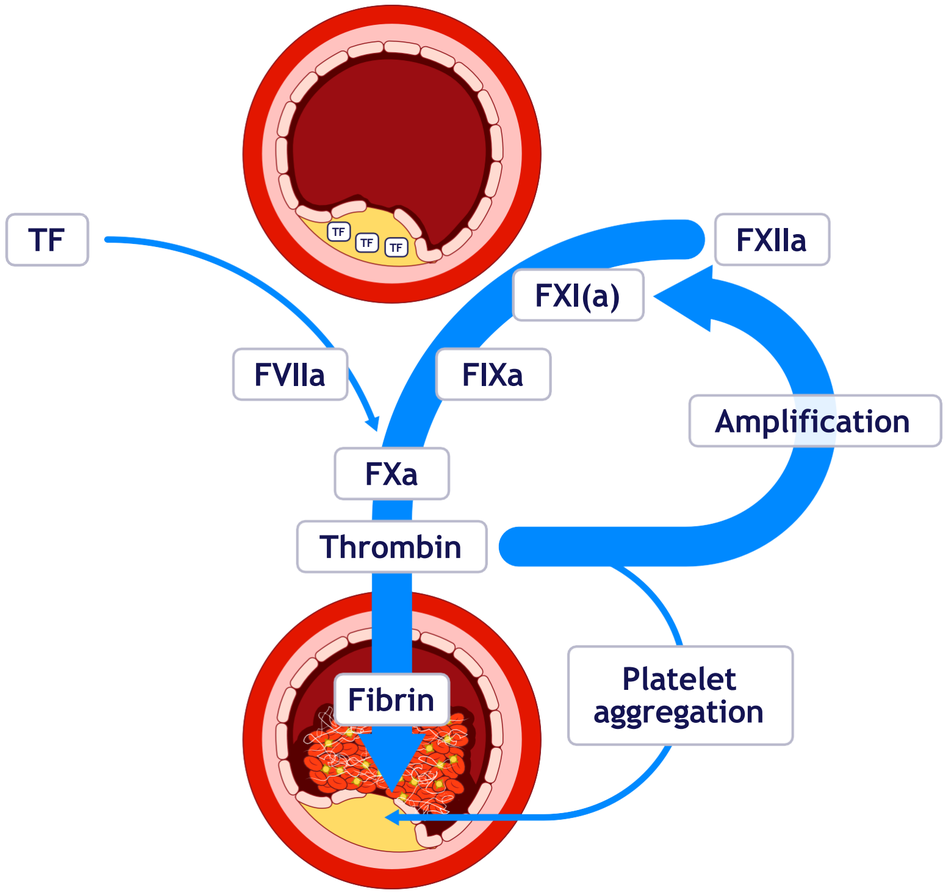


Chaudhry R, et al. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482253/

Pathological thrombosis and physiological haemostasis are linked through the common pathway[1-4]



Haemostasis



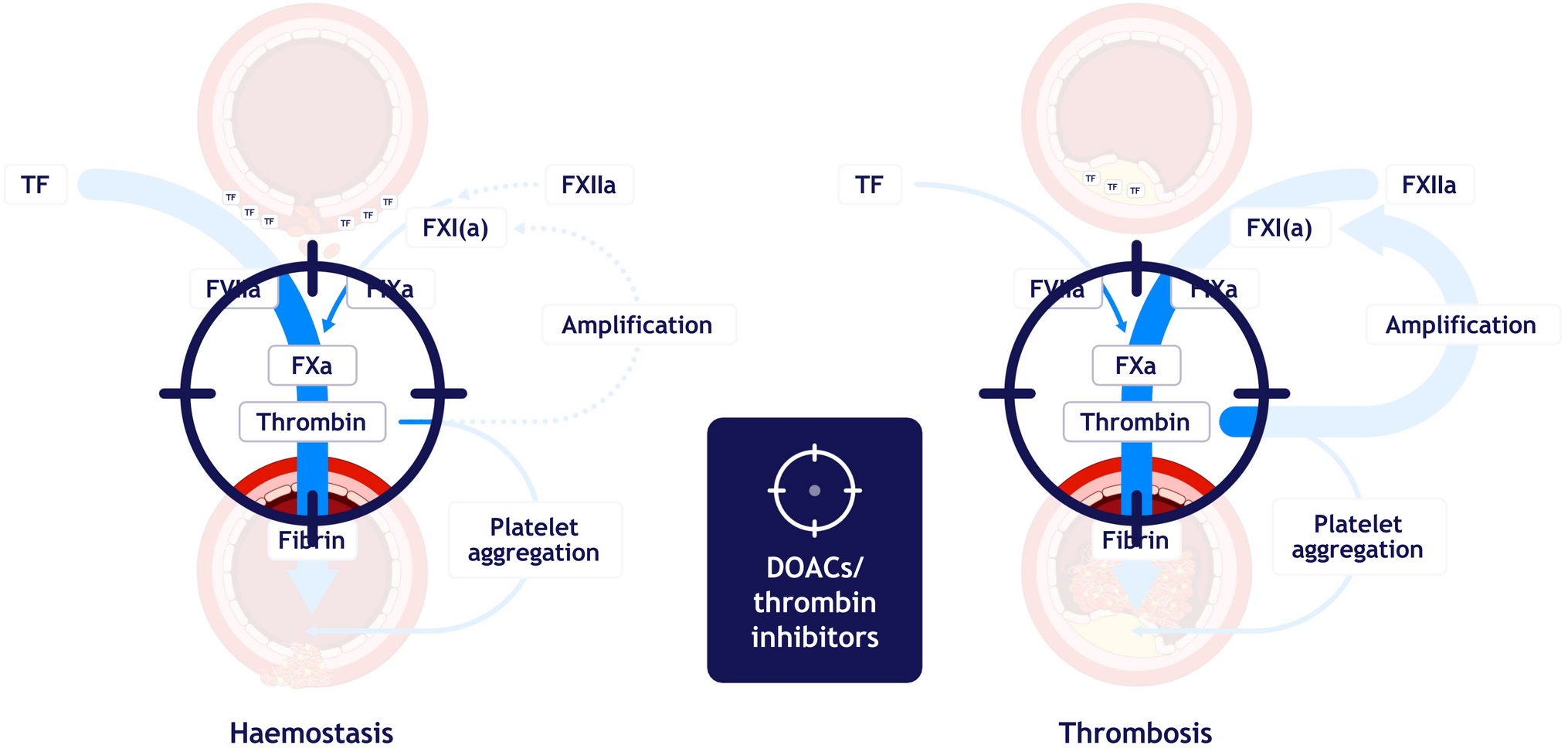
Thrombosis

Adapted with permission from *Hämostaseologie*.[1]

1. Fredenburg JC, Weitz JI. *Hämostaseologie*. 2021;41:104-110. 2. Greco A et al. *Circulation*. 2023;147:897-913. 3. Harrington J et al. *J Am Coll Cardiol*. 2023;81:771-779. 4. Coughlin SR. *Nature*. 2000;407:258-264.

FXI(a) INHIBITORS ARE INVESTIGATIONAL AGENTS WHICH HAVE NOT YET BEEN APPROVED FOR USE, AND THE SAFETY AND EFFICACY OF THESE INVESTIGATIONAL AGENTS HAVE NOT BEEN ESTABLISHED

Current anticoagulants target factors mainly within the common pathway[1-4]

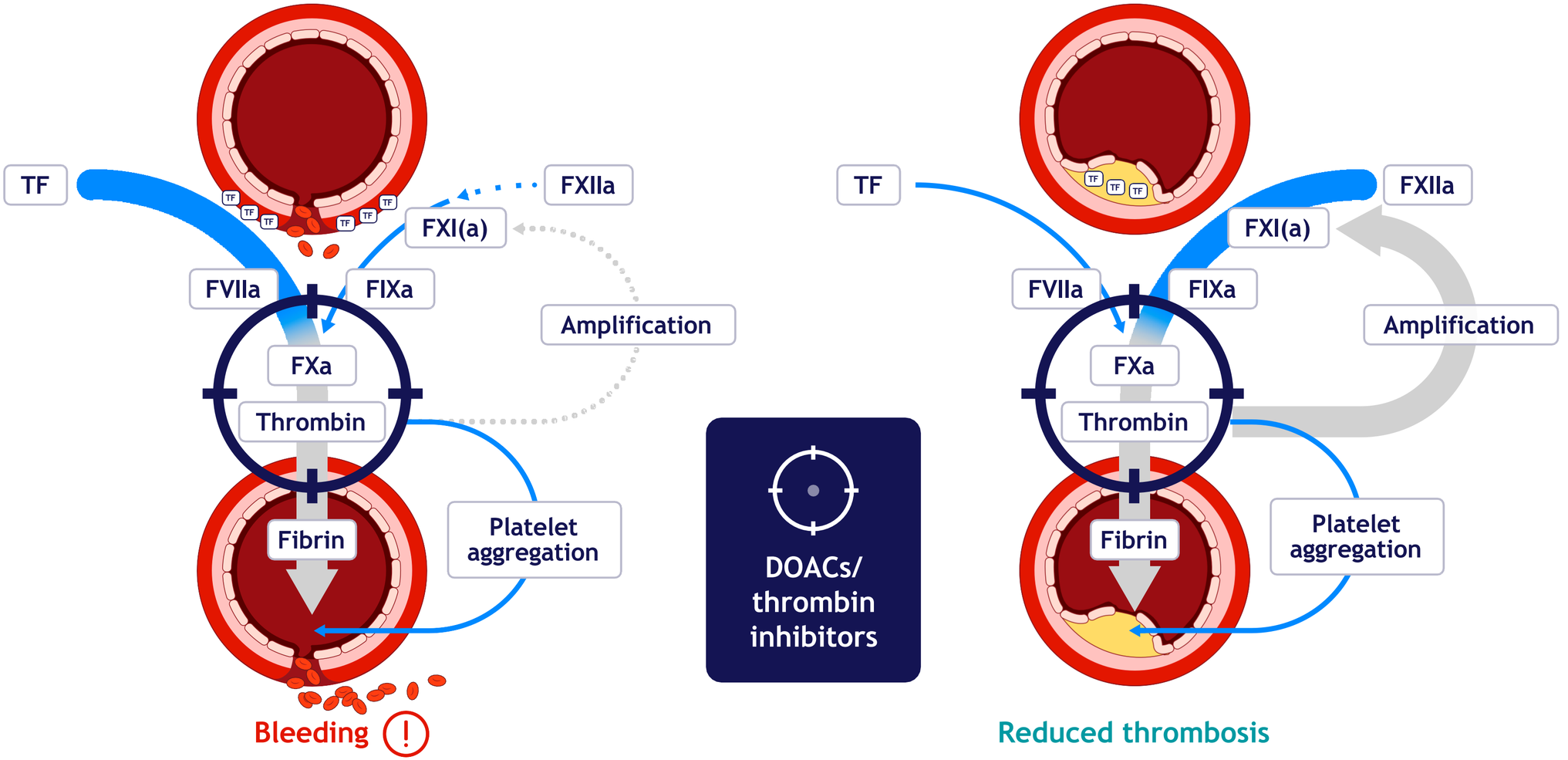


Adapted with permission from *Hämostaseologie*.[1]

1. Fredenburg JC, Weitz JI. *Hämostaseologie*. 2021;41:104-110. 2. Greco A et al. *Circulation*. 2023;147:897-913. 3. Harrington J et al. *J Am Coll Cardiol*. 2023;81:771-779. 4. Coughlin SR. *Nature*. 2000;407:258-264.

FXI(a) INHIBITORS ARE INVESTIGATIONAL AGENTS WHICH HAVE NOT YET BEEN APPROVED FOR USE, AND THE SAFETY AND EFFICACY OF THESE INVESTIGATIONAL AGENTS HAVE NOT BEEN ESTABLISHED

While these anticoagulants prevent pathological thrombosis, they also inhibit the ability to form clots and stop bleeding[1-5]

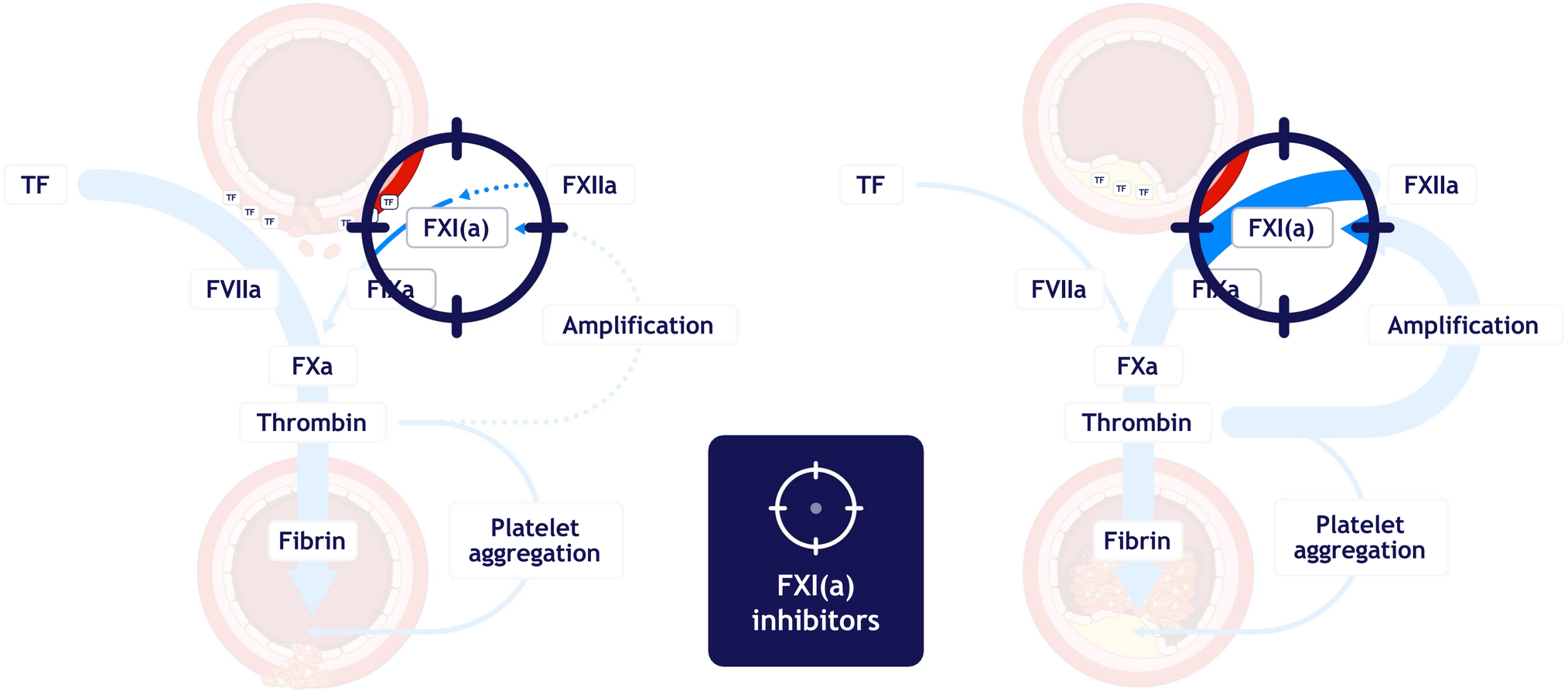


Adapted with permission from *Hämostaseologie*.[1]

1. Fredenburg JC, Weitz JI. *Hämostaseologie*. 2021;41:104-110. 2. Greco A et al. *Circulation*. 2023;147:897-913. 3. Harrington J et al. *J Am Coll Cardiol*. 2023;81:771-779. 4. Coughlin SR. *Nature*. 2000;407:258-264. 5. Monroe DM et al. *Atherioscler Throm Vasc Biol*. 2002;22:1361-1389.

FXI(a) INHIBITORS ARE INVESTIGATIONAL AGENTS WHICH HAVE NOT YET BEEN APPROVED FOR USE, AND THE SAFETY AND EFFICACY OF THESE INVESTIGATIONAL AGENTS HAVE NOT BEEN ESTABLISHED

Can targeting factor XI(a) uncouple thrombosis from haemostasis and thereby potentially reduce the risk of bleeding?[1-9]

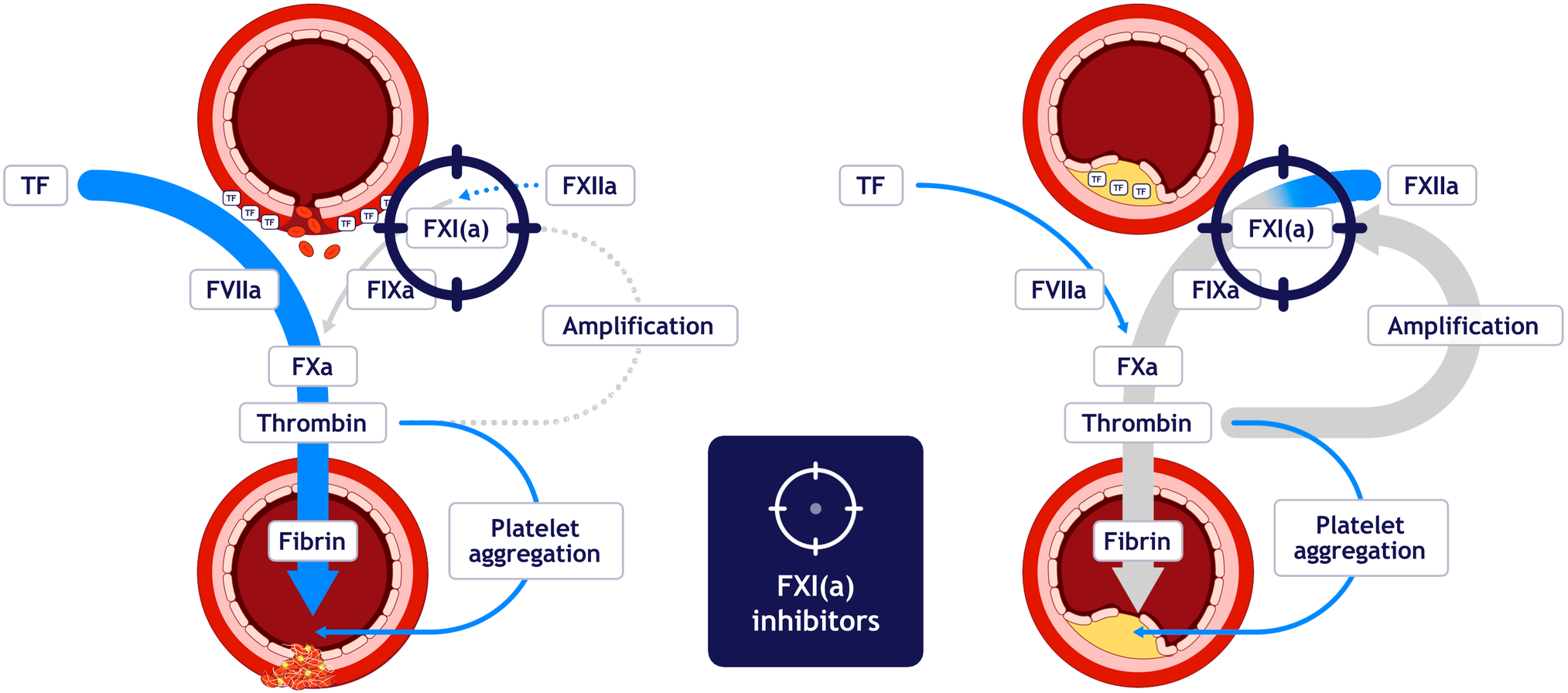


Adapted with permission from *Hämostaseologie*.[1]

1. Fredenburg JC, Weitz JI. *Hämostaseologie*. 2021;41:104-110. 2. Greco A et al. *Circulation*. 2023;147:897-913. 3. Harrington J et al. *J Am Coll Cardiol*. 2023;81:771-779. 4. Coughlin SR. *Nature*. 2000;407:258-264. 5. Monroe DM et al. *Atherioscler Throm Vasc Biol*. 2002;22:1361-1389. 6. Hsu C et al. *J Am Coll Cardiol*. 2021;78:625-631. 7. Nopp S et al. *Front Cardiovasc Med*. 2022;9:903029. 8. Ali AE, Becker RC. *J Thromb Thrombolysis*. 2024. [Epub ahead of print]. doi:10.1007/s11239-024-02972-5. 9. Galli M et al. *Eur Heart J*. 2023;44:Suppl 2.

FXI(a) INHIBITORS ARE INVESTIGATIONAL AGENTS WHICH HAVE NOT YET BEEN APPROVED FOR USE, AND THE SAFETY AND EFFICACY OF THESE INVESTIGATIONAL AGENTS HAVE NOT BEEN ESTABLISHED

Can targeting factor XI(a) uncouple thrombosis from haemostasis and thereby potentially reduce the risk of bleeding?[1-9]



Haemostasis

Reduced thrombosis

Adapted with permission from *Hämostaseologie*.[1]

1. Fredenburg JC, Weitz JI. *Hämostaseologie*. 2021;41:104-110. 2. Greco A et al. *Circulation*. 2023;147:897-913. 3. Harrington J et al. *J Am Coll Cardiol*. 2023;81:771-779. 4. Coughlin SR. *Nature*. 2000;407:258-264. 5. Monroe DM et al. *Atherioscler Throm Vasc Biol*. 2002;22:1361-1389. 6. Hsu C et al. *J Am Coll Cardiol*. 2021;78:625-631. 7. Nopp S et al. *Front Cardiovasc Med*. 2022;9:903029. 8. Ali AE, Becker RC. *J Thromb Thrombolysis*. 2024. [Epub ahead of print]. doi:10.1007/s11239-024-02972-5. 9. Galli M et al. *Eur Heart J*. 2023;44:Suppl 2.

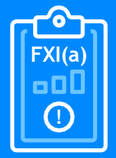
FXI(a) INHIBITORS ARE INVESTIGATIONAL AGENTS WHICH HAVE NOT YET BEEN APPROVED FOR USE, AND THE SAFETY AND EFFICACY OF THESE INVESTIGATIONAL AGENTS HAVE NOT BEEN ESTABLISHED

Published evidence suggests that factor XI is essential for thrombosis but mostly dispensable for haemostasis

Human genetic deficiency

Individuals with severe congenital FXI deficiency have a reduced risk of thrombosis and rarely experience spontaneous bleeding[1-3]

Genetic epidemiology



Large cohort studies show that risk of thrombosis is 2-fold higher in individuals with high FXI(a) levels compared with those with normal levels, and 43%–74% lower in those with reduced FXI levels[4,5]

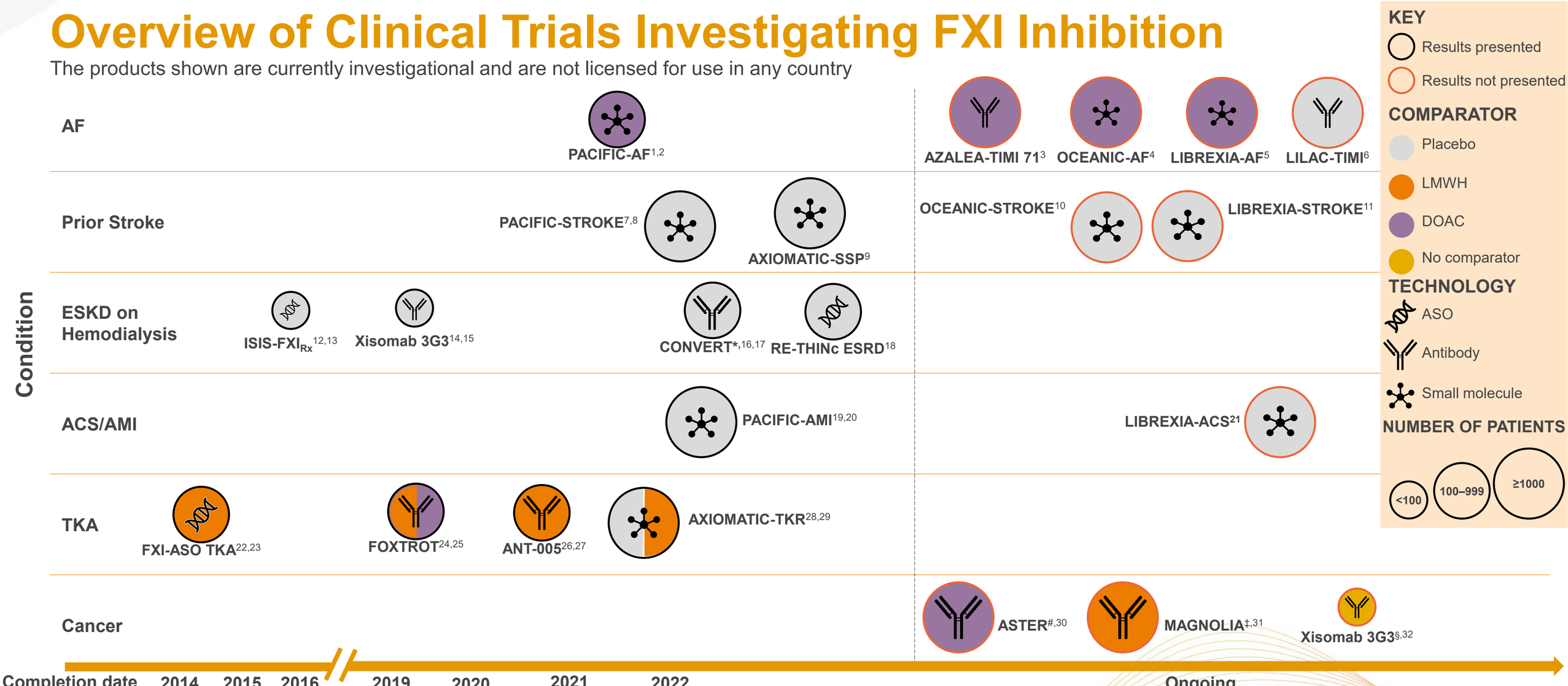
Animal studies

FXI inhibition attenuates thrombosis in murine, rabbit, and primate models with no increase in bleeding[6,7]

1. Asselta R et al. *Blood*. 2017;130:e1-e6. 2. Salomon O et al. *Blood*. 2008;111:4113-4117. 3. Salomon O et al. *Thromb Haemost*. 2011;105:269-273. 4. Meijers J et al. *N Engl J Med*. 2000;342:696-701.
5. Preis M et al. *Blood*. 2017;129:1210-1215. 6. Gailani D, Gruber A. *Arterioscler Thromb Vasc Biol*. 2016;36:1316-22. 7. Woodruff RS et al. *J Thromb Thrombolysis*. 2011;32:9-20.

Overview of Clinical Trials Investigating FXI Inhibition

The products shown are currently investigational and are not licensed for use in any country



*Osocimab. #Patients with CAT currently receiving or having received anticancer therapy in the last 6 months. ‡Patients with GI or GU cancer and CAT receiving LMWH for ≥6 months. §Patients with cancer receiving chemotherapy. ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ASO, antisense oligonucleotide; CAT, cancer-associated thrombosis; DOAC, direct oral anticoagulant; ESKD, end-stage kidney disease; FXI, Factor XI; GI, gastrointestinal; GU, genitourinary; LMWH, low molecular weight heparin; TKA, total knee arthroplasty.

1. Bayer. 2022. https://clinicaltrials.gov/ct2/show/NCT04218266. 2. Piccini JP *et al. Lancet* 2022;399:1383–1390. 3. Anthos Therapeutics, Inc. 2022. https://www.clinicaltrials.gov/ct2/show/NCT04755283. 4. Bayer. 2022. https://clinicaltrials.gov/ct2/show/NCT05643573. 5. Bristol Myers Squib. 2023. https://clinicaltrials.gov/ct2/show/NCT05757869. 6. Anthos Therapeutics, Inc. 2023. https://clinicaltrials.gov/ct2/show/NCT05712200. 7. Bayer. 2022. https://clinicaltrials.gov/ct2/show/NCT04304508. 8. Shoamanesh A *et al. Lancet* 2022;400:997–1007. 9. Bristol-Myers Squibb. 2022. https://clinicaltrials.gov/ct2/show/NCT03766581. 10. Bayer. 2023. https://clinicaltrials.gov/ct2/show/NCT05686070. 11. Janssen Research & Development, LLC. 2023. https://clinicaltrials.gov/ct2/show/NCT05702034. 12. Ionis Pharmaceuticals, Inc. 2016. https://clinicaltrials.gov/ct2/show/NCT02553889. 13. Walsh M *et al. Kidney Int Rep* 2021;7:200–209. 14. Aronora, Inc. 2022. https://clinicaltrials.gov/ct2/show/NCT03612856. 15. Lorentz U *et al. Blood* 2021;138:2173–2184. 16. Winkelmayer W. ERA. Milan, Italy, 15–18 June 2023, Presentation 499140. https://era-apps.m-anage.com/era23/en-GB/pag/presentation/499140. 17. Bayer. 2022. https://clinicaltrials.gov/ct2/show/NCT04523220. 18. Bayer. 2023. https://clinicaltrials.gov/ct2/show/NCT04534114. 19. Bayer. 2022. https://clinicaltrials.gov/ct2/show/NCT04304534. 20. Rao SV *et al. Circulation* 2022;146:1196–1206. 21. Janssen Research & Development, LLC. 2023 https://clinicaltrials.gov/ct2/show/NCT05754957 22. Ionis Pharmaceuticals, Inc. 2014. https://clinicaltrials.gov/ct2/show/NCT01713361. 23. Büller HR *et al. N Engl J Med* 2015;372:232–240. 24. Bayer. 2020. https://clinicaltrials.gov/ct2/show/NCT03276143. 25. Weitz JI *et al. JAMA* 2020;323:130–139. 26. Anthos Therapeutics, Inc. 2022. https://www.clinicaltrialsregister.eu/ctr-search/search?query=ANT-005 27. Verhamme P *et al. N Engl J Med* 2021;385:609–617. 28. Janssen Research & Development, LLC. 2022. https://clinicaltrials.gov/ct2/show/NCT03891524. 29. Weitz JI *et al. N Engl J Med* 2021;385:2161–2172. 30. Anthos Therapeutics, Inc. 2023. https://clinicaltrials.gov/ct2/show/NCT05171049. 31. Anthos Therapeutics, Inc. 2023. https://clinicaltrials.gov/ct2/show/NCT05171075. 32. OHSU Knight Cancer Institute. 2022. https://clinicaltrials.gov/ct2/show/NCT04465760 [all links accessed August 2023].

Factor XI(a) inhibitors with completed Phase 2 trials[1-9]

Class	Antisense oligonucleotide		Monoclonal antibody				Small molecule		
Inhibitor	**Fesomersen**	**IONIS-FXIRx**	**Abelacimab**	**Gruticibart**	**Osocimab**	**REGN9933**	**Asundexian**	**Milvexian**	**SHR2285**
Mechanism of action	FXI synthesis inhibition	FXI mRNA degradation	FXI and FXIa inhibition	FXI activation inhibition by Factor XIIa	FXIa inhibition	FXI inhibition	FXIa inhibition	FXIa inhibition	FXIa inhibition
Route	SC	SC	IV, SC	IV	IV, SC	IV	PO	PO	PO
Phase 2 indication	ESRD	TKA, ESRD	TKA, AF[a]	ESRD	TKA, ESRD	TKA	AF, stroke, AMI	TKA, stroke	TKA
Phase 2 doses	40, 80, 120 mg	200, 300 mg	30, 75, 150 mg	0.25, 0.5 mg/kg	0.3, 0.6, 1.2, 1.8 mg/kg	Not reported	10, 20, 50 mg	25, 50, 100, 200 mg BID; 25, 50, 200 mg QD	Not reported
Half-life	20 d	≈ 2 wk	20-30 d	11-121 h	30-44 d	Not reported	14-21 h	11-18 h	≈ 13 h
Renal clearance	No	Some	No	No	No	No	Some	Some	Yes
Drug-drug interactions	No	No	No	No	No	No	Possible	Possible	Possible

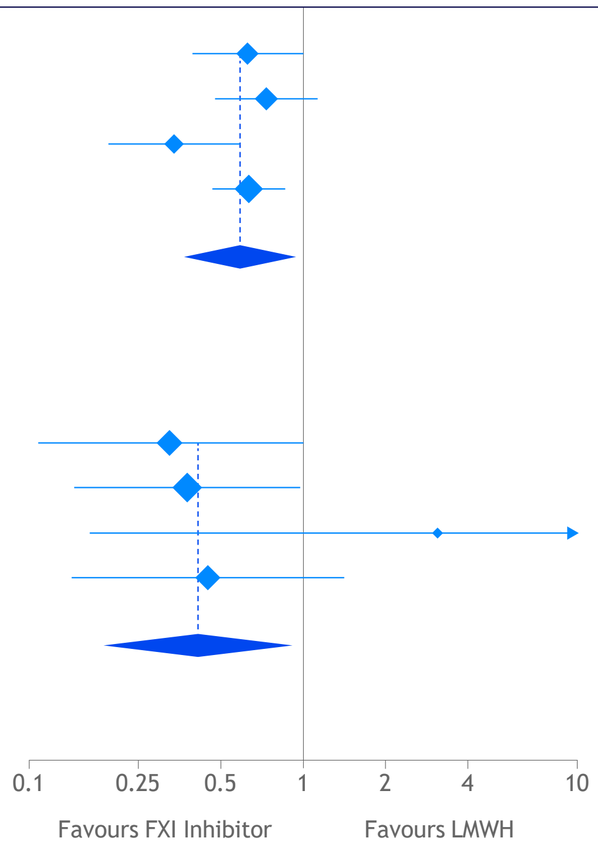
[a]AZALEA-TIMI 71, the Phase 2 study of abelacimab in AF, was terminated before study completion.[9]

1. Greco A et al. *Circulation*. 2023;147:897-913. 2. Fredenburgh JC, Weitz JI. *Hemostaseologia*. 2021;41:104-110. 3. Fredenburgh JC, Weitz JI. *J Thromb Haemost*. 2023;21:1692-1702. 4. Engelen MM et al. *Thromb Update*. 2024;15:100171.
5. Campello E et al. *J Clin Med*. 2022;11:6314. 6. Weitz JI et al. *Nature Med*. 2024;30:435-442. 7. ClinicalTrials.gov. NCT05618808. https://clinicaltrials.gov/study/NCT05618808. Accessed August 2024.
8. ClinicalTrials.gov. NCT05203705. https://clinicaltrials.gov/study/NCT05203705. Accessed August 2024. 9. Healio. https://www.healio.com/news/cardiology/20230918/abelacimab-trial-for-af-stopped-early-due-to-overwhelming-reduction-in-bleeding. Published September 2023. Accessed June 2024.

FXI(a) INHIBITORS ARE INVESTIGATIONAL AGENTS WHICH HAVE NOT YET BEEN APPROVED FOR USE, AND THE SAFETY AND EFFICACY OF THESE INVESTIGATIONAL AGENTS HAVE NOT BEEN ESTABLISHED

Meta-analysis of Phase 2 studies comparing factor XI(a) inhibitors with enoxaparin in total knee arthroplasty

	Study	Drug	FX Inhibitor Events	FX Inhibitor Total	LMWH Events	LMWH Total	Risk ratio (95% CI)	Weight
Venous thromboembolism	FXI-ASO TKA	IONIS-FXI-RX	39	205	21	69	0.63 (0.40-0.99)	22.0%
	FOXTROT	Osocimab	85	441	20	76	0.73 (0.48-1.12)	24.4%
	ANT-005 TKA	Abelacimab	22	299	22	101	0.34 (0.20-0.58)	16.9%
	AXIOMATIC-TKR	Milvexian	108	796	54	252	0.63 (0.47-0.85)	36.8%
	Total (95% CI)		**254**	**1741**	**117**	**498**	**0.59 (0.37-0.94)**	**100.0%**
	Test for overall effect: *P* = 0.038							
Clinically relevant bleeding	FXI-ASO TKA	IONIS-FXI-RX	6	221	6	72	0.33 (0.11-0.98)	29.2%
	FOXTROT	Osocimab	13	585	6	102	0.38 (0.15-0.97)	39.6%
	ANT-005 TKA	Abelacimab	4	305	0	104	3.09 (0.17-56.88)	4.2%
	AXIOMATIC-TKR	Milvexian	7	923	5	296	0.45 (0.14-1.40)	27.1%
	Total (95% CI)		**30**	**2034**	**17**	**574**	**0.41 (0.19-0.92)**	**100.0%**
	Test for overall effect: *P* = 0.039							

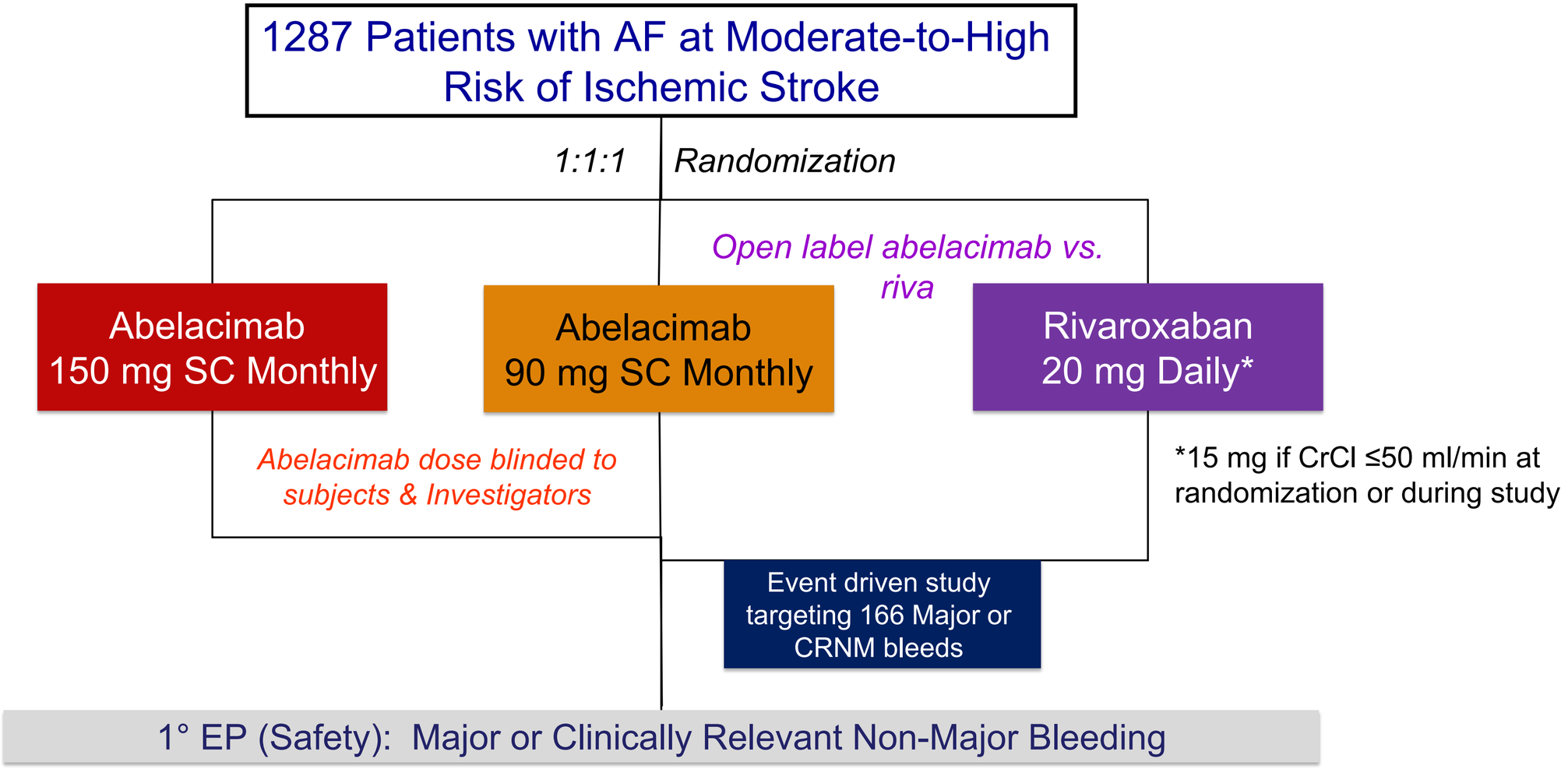


Reproduced from *Front Cardiovasc Med*.

Nopp S et al. *Front Cardiovasc Med*. 2022;9:903029.

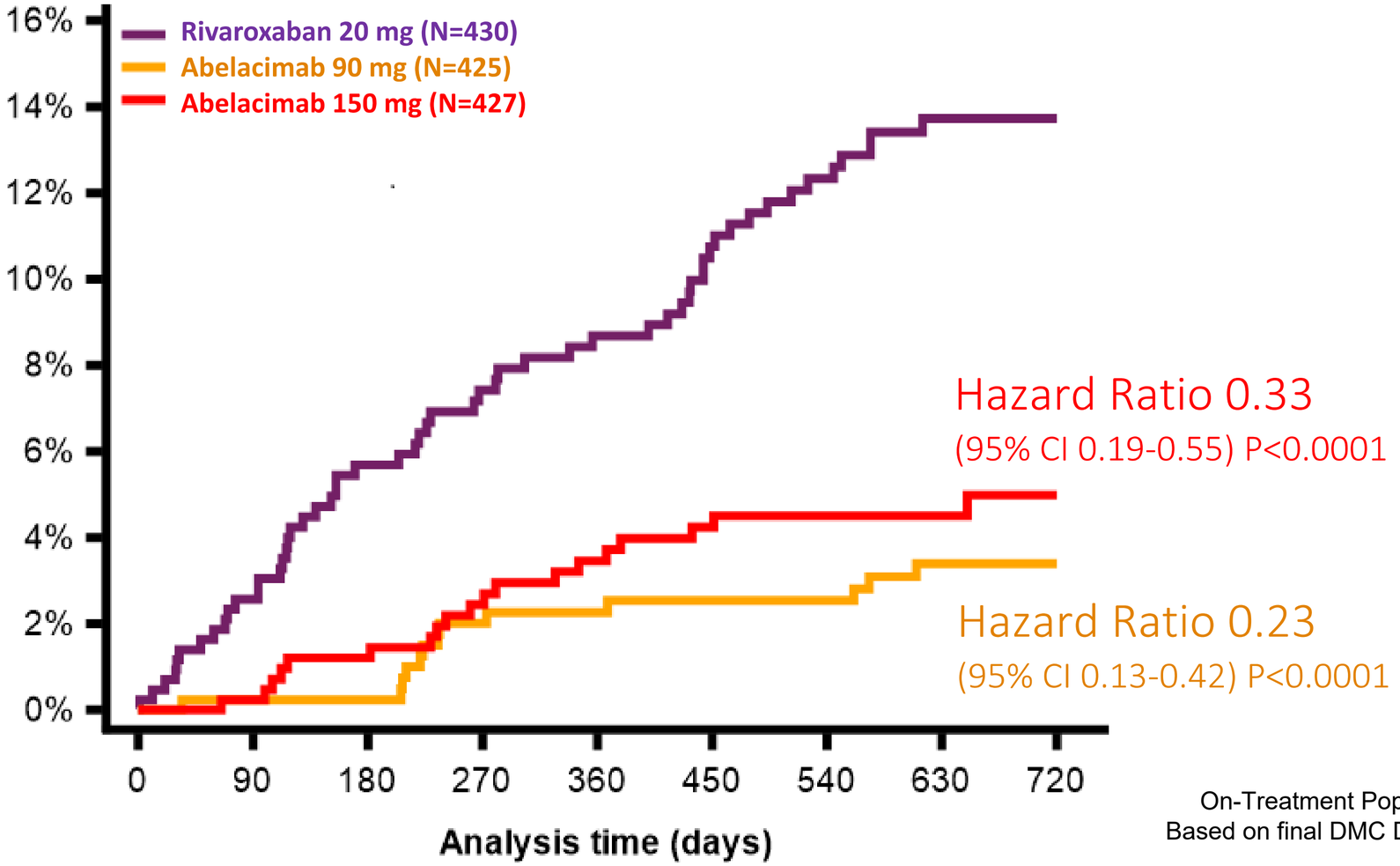
FXI(a) INHIBITORS ARE INVESTIGATIONAL AGENTS WHICH HAVE NOT YET BEEN APPROVED FOR USE, AND THE SAFETY AND EFFICACY OF THESE INVESTIGATIONAL AGENTS HAVE NOT BEEN ESTABLISHED

AZALEA Trial



Primary Endpoint

Major or Clinically Relevant Non-major Bleeding



On-Treatment Population
Based on final DMC Datacut

Asundexian: PACIFIC Phase 2 Clinical Trial Program

PACIFIC AF

Atrial fibrillation[1]

- Asundexian 20 mg, 50 mg QD
- Apixaban 5 mg BID
- *Aspirin (≤ 100 mg) was permitted*

Primary endpoint: composite of major or clinically relevant non-major bleeding

755 patients with AF randomized

Asundexian 20 mg and 50 mg once daily doses resulted in:

- ✓ Lower rates of bleeding compared with standard dosing of apixaban
- ✓ Near-complete FXIa inhibition

PACIFIC AMI

Acute myocardial infarction[2]

- Asundexian 10 mg, 20 mg, 50 mg QD
- Placebo
- *+ DAPT*

Safety outcome: composite of BARC 2, 3, or 5 bleeding
Efficacy outcome: composite of cardiovascular death, MI, stroke, or stent thrombosis

1601 patients with recent MI randomized

Results for all pooled asundexian doses vs placebo. When added to aspirin and a P2Y12 inhibitor, treatment with asundexian resulted in:

- ✓ Dose-dependent, near-complete inhibition of FXIa activity
- ✓ No significant increase in bleeding
- ✓ Low rate of ischemic events

PACIFIC STROKE

Non-cardioembolic ischemic stroke[3]

- Asundexian 10 mg, 20 mg, 50 mg QD
- Placebo
- *+ background antiplatelet therapy*

Primary endpoints: dose-response effect on composite of covert brain infarcts and recurrent symptomatic ischemic stroke; major or CRNMB

1880 patients with AIS randomized

- ✓ No reduction of the composite of covert brain infarction or ischemic stroke
- ✓ No increase of the composite of major or CRNMB compared with placebo
- ✓ 50 mg once daily reduced recurrent symptomatic ischemic stroke and TIAs, particularly among those with atherosclerosis (exploratory, post-hoc)

Asundexian was well tolerated in all 3 trials: 50 mg resulted in > 90% factor XI(a) inhibition

AIS, acute, non-cardioembolic ischemic stroke; BARC, Bleeding Academic Research Consortium; BID, twice daily; CRNMB, clinically relevant non-major bleeding; DAPT, dual antiplatelet therapy; TIA, transient ischemic attack; QD, daily.

1. Piccini JP, et al. Lancet. 2022;399:1383-1390; 2. Rao SV, et al. Circulation. 2022;146:1196-1206; 3. Shoamanesh A, et al. Lancet. 2022;400:997-1007.

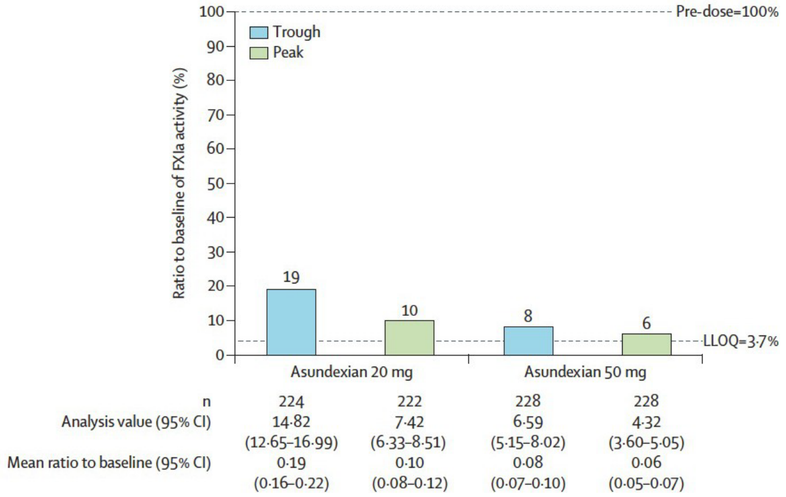
PACIFIC-AF: Phase 2 Study in Patients with Atrial Fibrillation

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

*Jonathan P Piccini, Valeria Caso, Stuart J Connolly, Keith A A Fox, Jonas Oldgren, W Schuyler Jones, Diana A Gorog, Václav Durdil, Thomas Viethen, Christoph Neumann, Hardi Mundl, Manesh R Patel, on behalf of the PACIFIC-AF Investigators**

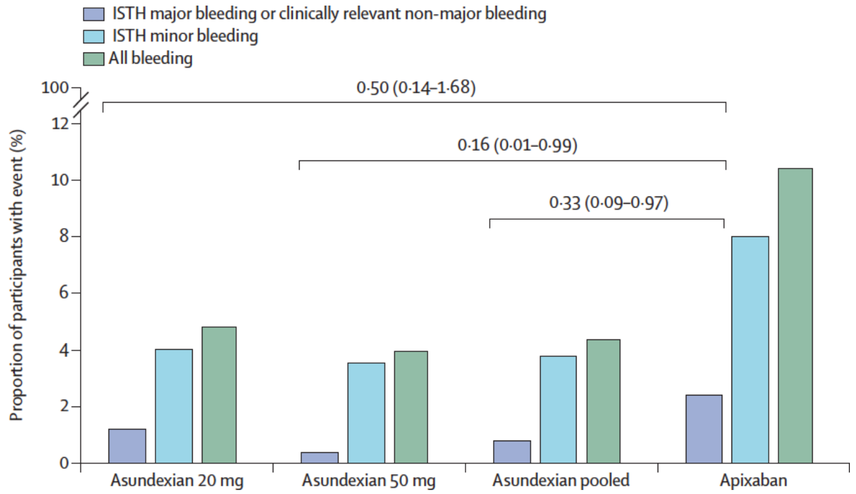
OCEANIC AF

FXIa Activity — Inhibition Data



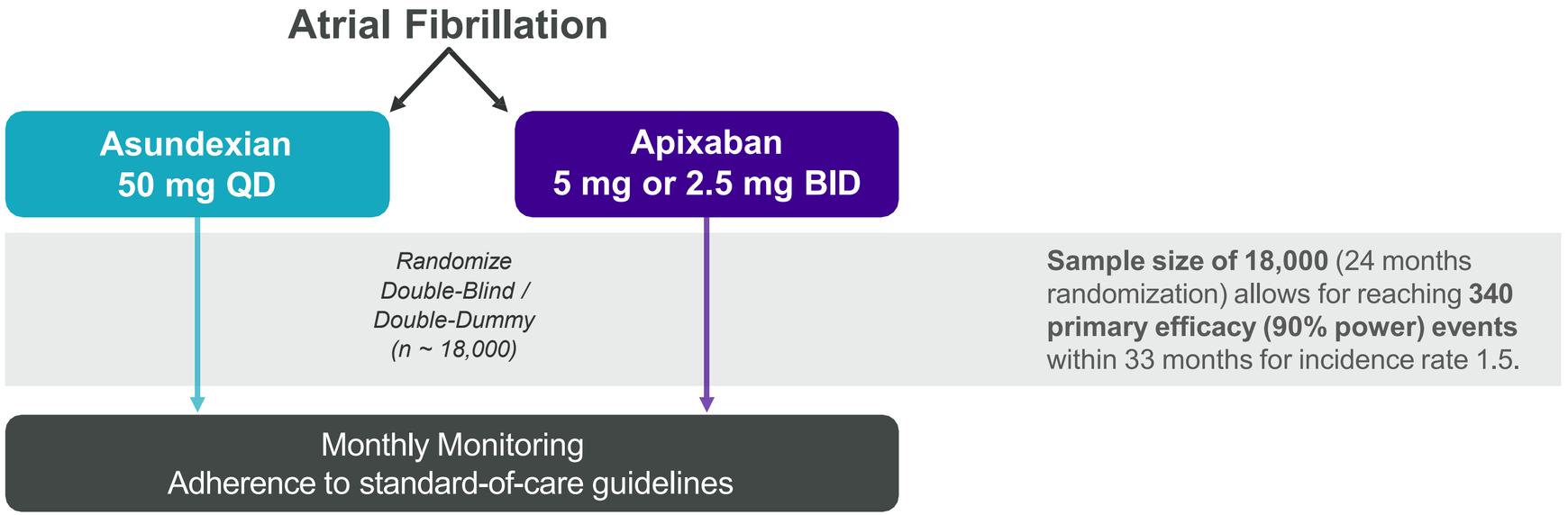
	Asundexian 20 mg		Asundexian 50 mg	
n	224	222	228	228
Analysis value (95% CI)	14·82 (12·65–16·99)	7·42 (6·33–8·51)	6·59 (5·15–8·02)	4·32 (3·60–5·05)
Mean ratio to baseline (95% CI)	0·19 (0·16–0·22)	0·10 (0·08–0·12)	0·08 (0·07–0·10)	0·06 (0·05–0·07)

Primary Safety Outcome (ISTH bleeding classification)



Duke Clinical Research Institute

OCEANIC-AF Study Design



Primary Efficacy Endpoint: Stroke or Systemic Embolism

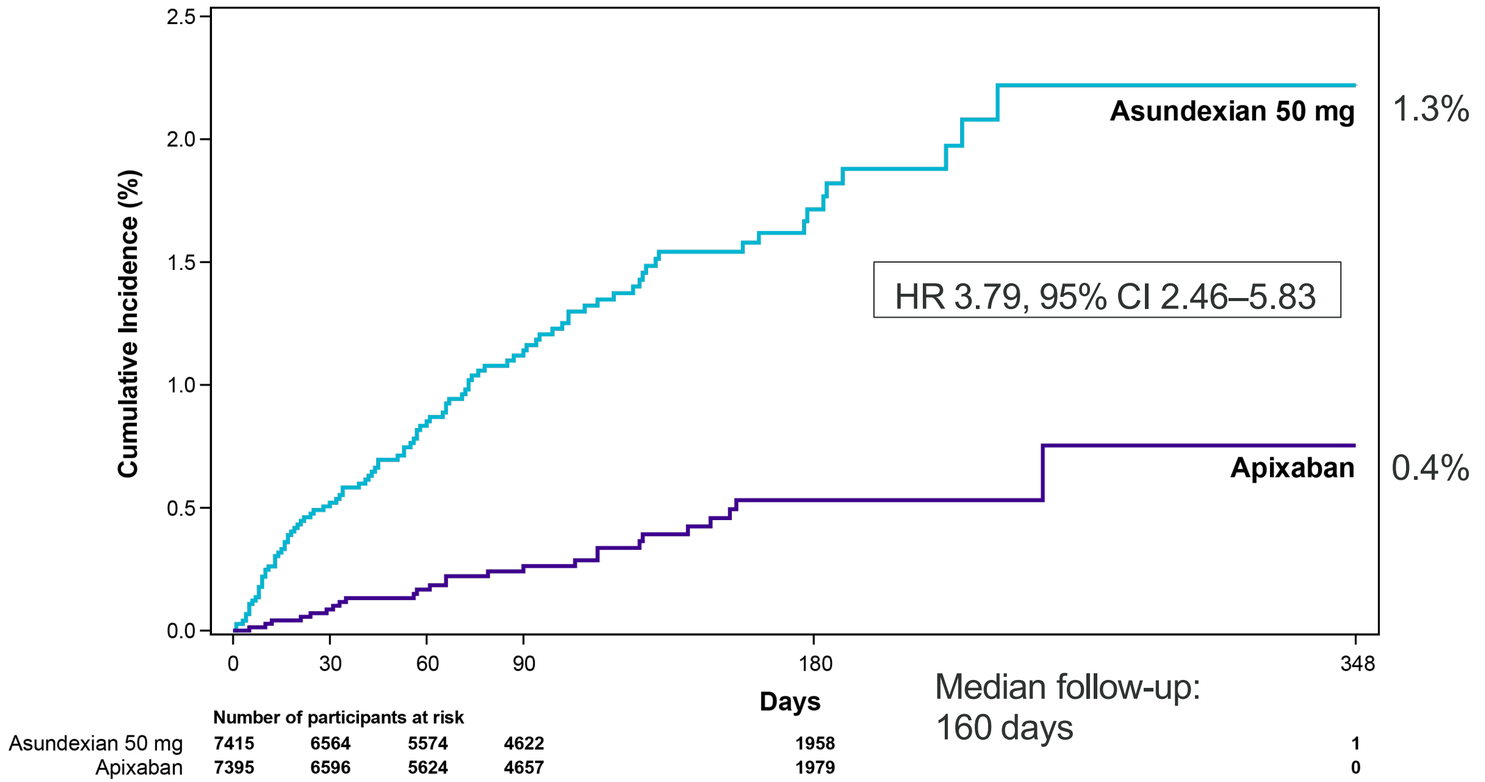
Primary Safety Endpoint: ISTH Major Bleeding

Primary Net Clinical Benefit Endpoint: Stroke or Systemic Embolism and ISTH Major Bleeding

Duke Clinical Research Institute

Piccini JP et al. N Engl J Med. DOI: 10.1056/NEJMoa240710

Cumulative Event Rate for the Primary Efficacy Endpoint



Duke Clinical Research Institute

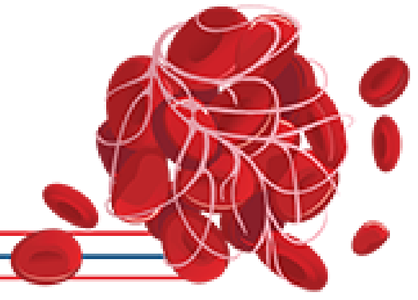
Piccini JP et al. N Engl J Med. DOI: 10.1056/NEJMoa240710

OCEANIC-AF: Inferior Efficacy or Low Dosing?

Inferior efficacy due to?

- **Class effect**
  - FXI may not contribute to thrombosis in AF
  - However, trials of other FXI/FXIa inhibitors, including for AF, continuing after recent reviews by IDMC
- **Specific characteristics of asundexian**
  - Dose
    - Reduced FXIa activity by 94% (peak) and 92% (trough) using a non-standard assay—not clear how this correlates with the aPTT
    - Less inhibition of thrombin generation with asundexian than with milvexian at concentrations achieved in the phase III AF trials (Vassart, Thromb Res 2024)
  - PK/PD
    - Ki for FXIa
      - Asundexian 1.0 nM (Heitmeier, JTH 2022)
      - Milvexian 0.1 nM (Dilger, J Med Chem, 2022)

aPTT, activated partial thromboplastin time; Piccini JP, et al. *N Engl J Med*. Published online September 1, 2024.



Milvexian Development Program

Phase II Program

AXIOMATIC-SSP
Secondary Stroke Prevention (SSP) Study
(N = 2366)

AXIOMATIC TKR
Total Knee Replacement (TKR) Study
(N = 1242)

Phase III Program
N = 46,500

Across distinct patient groups with different unmet needs for prevention of major thrombotic events

LIBREXIA STROKE
AIS and High-Risk TIA
15,000 pts/818 sites/47 countries
Efficacy endpoint: Ischemic stroke
Safety endpoints: BARC 3c and 5

LIBREXIA AF
Atrial Fibrillation
15,500 pts/1000 sites/43 countries
Efficacy endpoints: Stroke and non-CNS systemic embolism
Safety endpoints: ISTH major, composite of ISTH major and CRNM

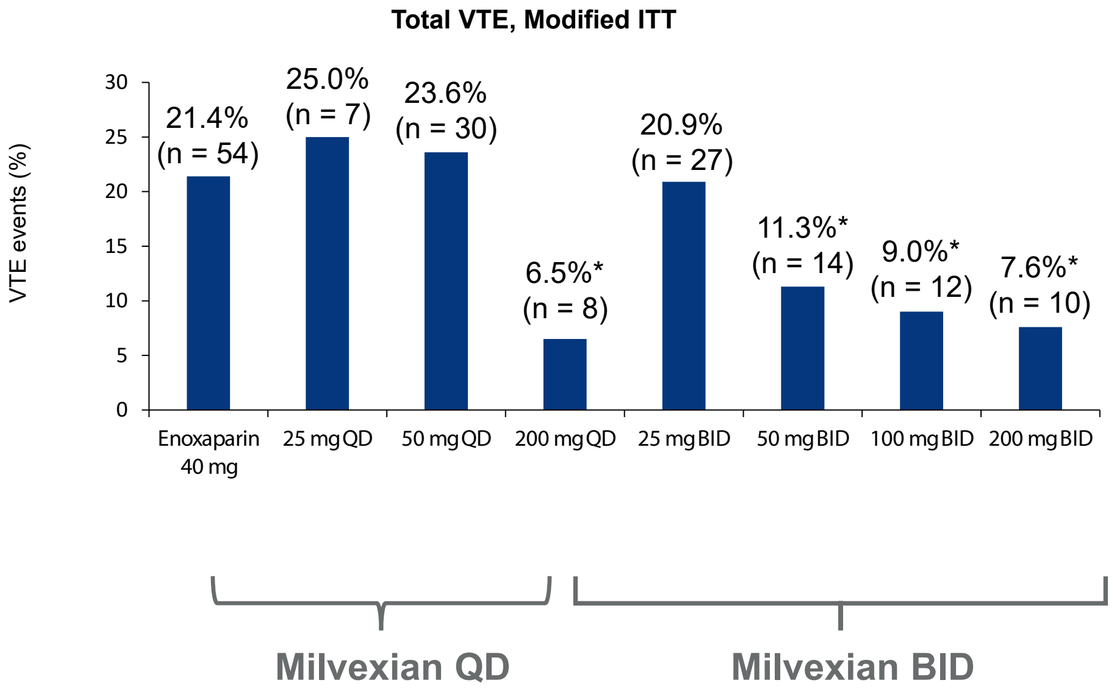
LIBREXIA ACS
Acute Coronary Syndrome
16,000 pts/1000 sites/45 countries
Efficacy endpoint: MACE CVD/MI/IS
Safety endpoints: BARC 3c and 5

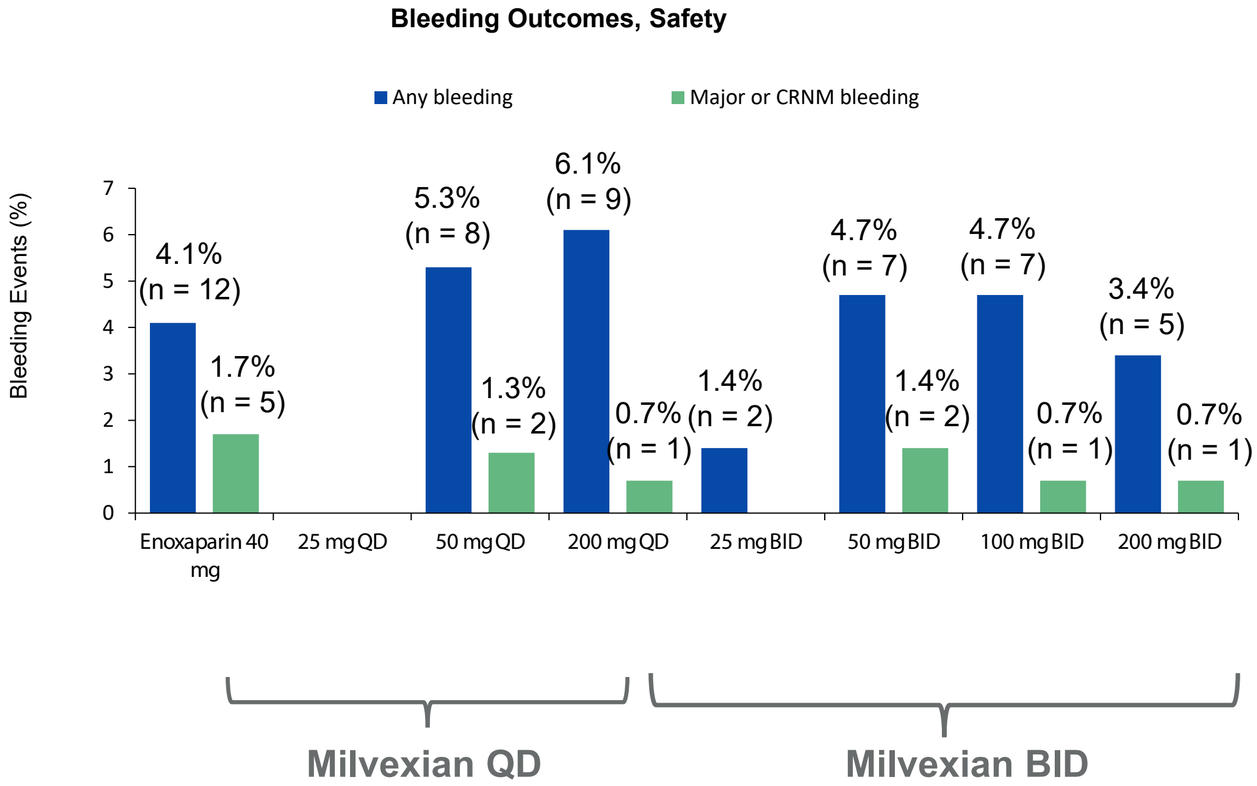
Pediatric Development

ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CNS, central nervous system; CRNM, clinically relevant non-major; CVD, cardiovascular disease; ISTH, International Society on Thrombosis and Haemostasis; MACE, major adverse cardiovascular event.
ClinicalTrials.gov. NCT05702034; NCT05757869; NCT05754957.

Milvexian TKR Phase 2 Key Efficacy and Safety Results

- Milvexian significantly reduced VTE events in a dose-dependent manner
- No meaningful relationship between milvexian dose and bleeding events
- No major bleeding was observed





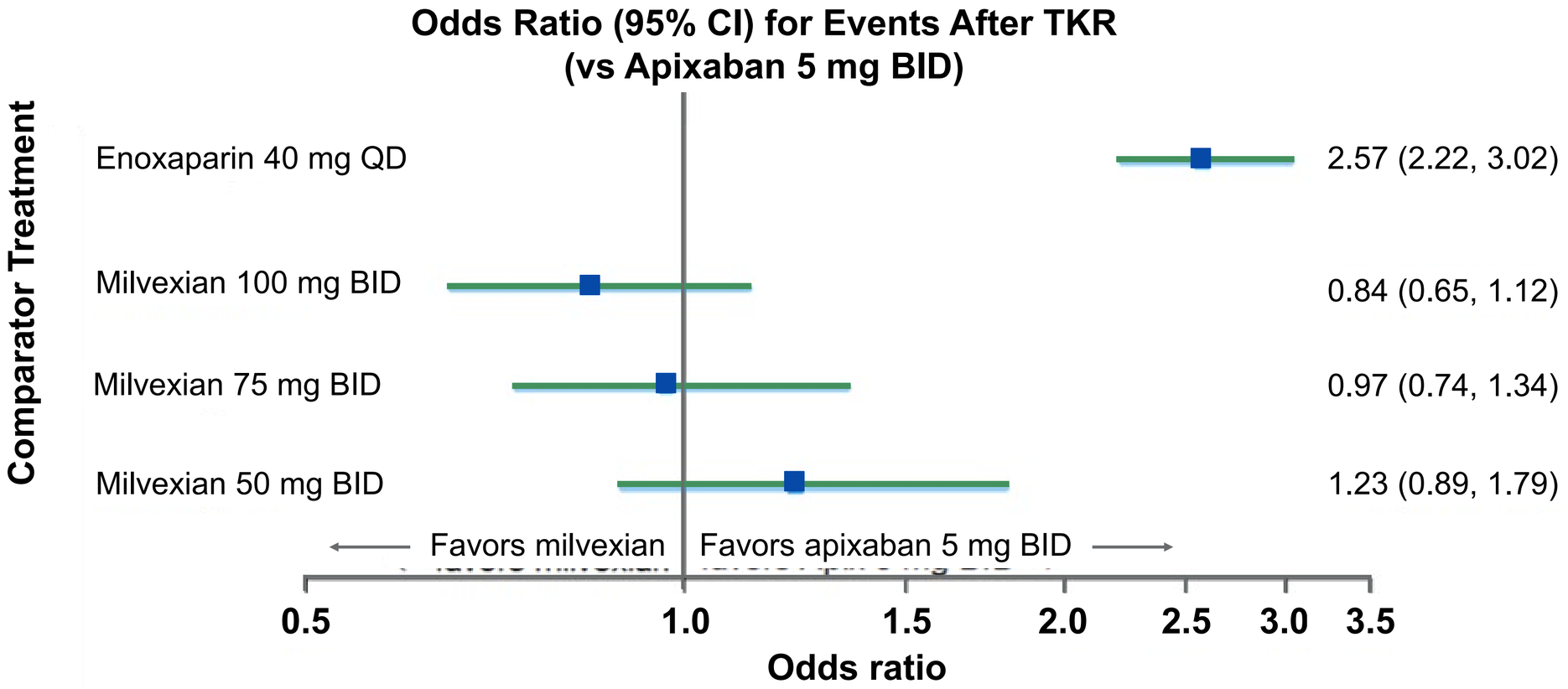
*$P < .01$

BID, twice daily; ITT, intent-to-treat; QD, once daily.

Weitz JI et al. N Engl J Med. 2021;385:2161-2172.

Model-Based Meta-Analysis of Anticipated VTE Outcomes for Milvexian vs Apixaban

The median VTE odds ratio showed a dose-dependent response favoring milvexian (investigational) over apixaban for doses ≥ 75 mg BID[a]



[a]**Results should be interpreted with caution due to high variability in results and model limitations.**

Zhou W, et al. Presented at: ISTH 2024 Congress; June 22-26, 2024; Bangkok, Thailand.

Dose Selection for Phase 3 LIBREXIA-AF and OCEANIC-AF Trials

	LIBREXIA-AF[1,2] (milvexian)	OCEANIC-AF[3,4] (asundexian)
Phase 2 dose range	16-fold	5-fold
Phase 2 background study	AXIOMATIC TKR	PACIFIC AF
Phase 2 evidence	Dose response in TKR	Safety outcomes in AF
Basis for dose selection	▪ Clinical event data ▪ Clinical assay: aPTT ▪ Meta-analysis	In vitro FXIa target engagement assay
Dose chosen from Phase 2	Middle dose 100 mg BID	Highest studied 50 mg QD

aPTT, activated partial thromboplastin time.
Courtesy of Carolyn Lam, MBBS, PhD.
1. Weitz JI, et al. N Engl J Med. 2021;385:2161-2172; 2. ClinicalTrials.gov.NCT05757869; 3. Piccini JP, et al. Lancet. 2022;399:1383-1390; 4. ClinicalTrials.gov. NCT05643573.

Phase 3 trials of factor XI(a) inhibitors[1-7]

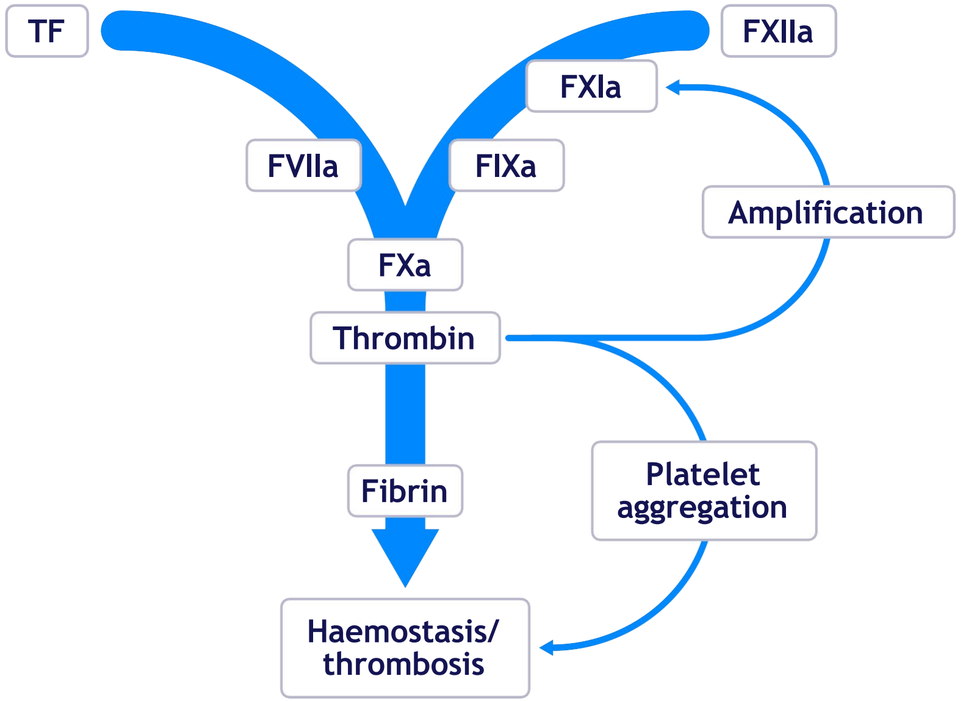
Inhibitor	Abelacimab			Asundexian		Milvexian		
Trial name	LILAC-TIMI 76	ASTER	MAGNOLIA	OCEANIC-AF (Terminated)	OCEANIC-STROKE	LIBREXIA-AF	LIBREXIA-STROKE	LIBREXIA-ACS
Indication	AF	Cancer-associated VTE	Cancer-associated VTE (GI/GU)	AF	Secondary stroke prevention	AF	Secondary stroke prevention	ACS
Comparator	Placebo	Apixaban	Dalteparin	Apixaban	Placebo	Apixaban	Placebo	Placebo
N	≈ 1900	≈ 1655	≈ 1020	≈ 15,000	12,300	≈ 17,500	≈ 15,000	≈ 16,000
Dosing	150 mg SC	150 mg SC	150 mg SC	50 mg QD	50 mg QD	100 mg PO BID	25 mg PO BID	25 mg PO BID

Adapted from *J Thromb Haemost*.[1]

1. Fredenburgh JC et al. *J Thromb Haemost*. 2023;21:1692-1702. 2. Shoamanesh A et al. Presented at 10th European Stroke Organisation Conference; May 15-17, 2024; Basel, Switzerland. Abstract P2296. 3. Presume J et al. *Cardiol Ther*. 2024;13:1-16. 4. ClinicalTrials.gov. NCT05757869. https://clinicaltrials.gov/study/NCT05757869. Accessed July 2024. 5. ClinicalTrials.gov. NCT05702034. http://clinicaltrials.gov/study/NCT05702034. Accessed July 2024. 6. ClinicalTrials.gov. NCT05754957. https://clinicaltrials.gov/study/NCT05754957. Accessed July 2024. 7. Bayer Press Release. https://www.bayer.com/media/en-us/oceanic-af-study-stopped-early-due-to-lack-of-efficacy/. Released September 2023. Accessed August 2024.

Conclusions

- Targeting FXI(a) has the potential to reduce the burden of thromboembolic cardiovascular diseases while preserving haemostasis[1-5]
- Phase 3 trial data are needed to establish the benefit-risk profiles of FXI(a) inhibitors[6]



Adapted with permission from *Hämostaseologie*.[1]

1. Fredenburg JC, Weitz JI. *Hämostaseologie*. 2021;41:104-110. 2. Harrington J et al. *J Am Coll Cardiol*. 2023;81:771-779. 3. Greco A et al. *Circulation*. 2023;147:897-913. 4. Ali AE, Becker RC. *J Thromb Thrombolysis*. 2024. [Epub ahead of print]. doi:10.1007/s11239-024-02972-5. 5. Galli M et al. *Eur Heart J*. 2023;44:Suppl 2. 6. Fredenburgh JC et al. *J Thromb Haemost*. 2023;21:1692-1702.