Gli Inibitori del fattore XI nella terapia antitrombotica della fibrillazione atriale

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Acute Cardiovascular Care Association
A Registered Branch of the ESC

Disclosure

Speaker fee: BMS, Pfizer, Novartis

Advisory board member: Amarin, BMS, Daiichi Sankyo

Overview

- Why to look for new direct anticoagulants?
- New drugs and results so far achieved
- Ongoing trials: a new perspective in AF treatment?

DOACs: Pros and Cons

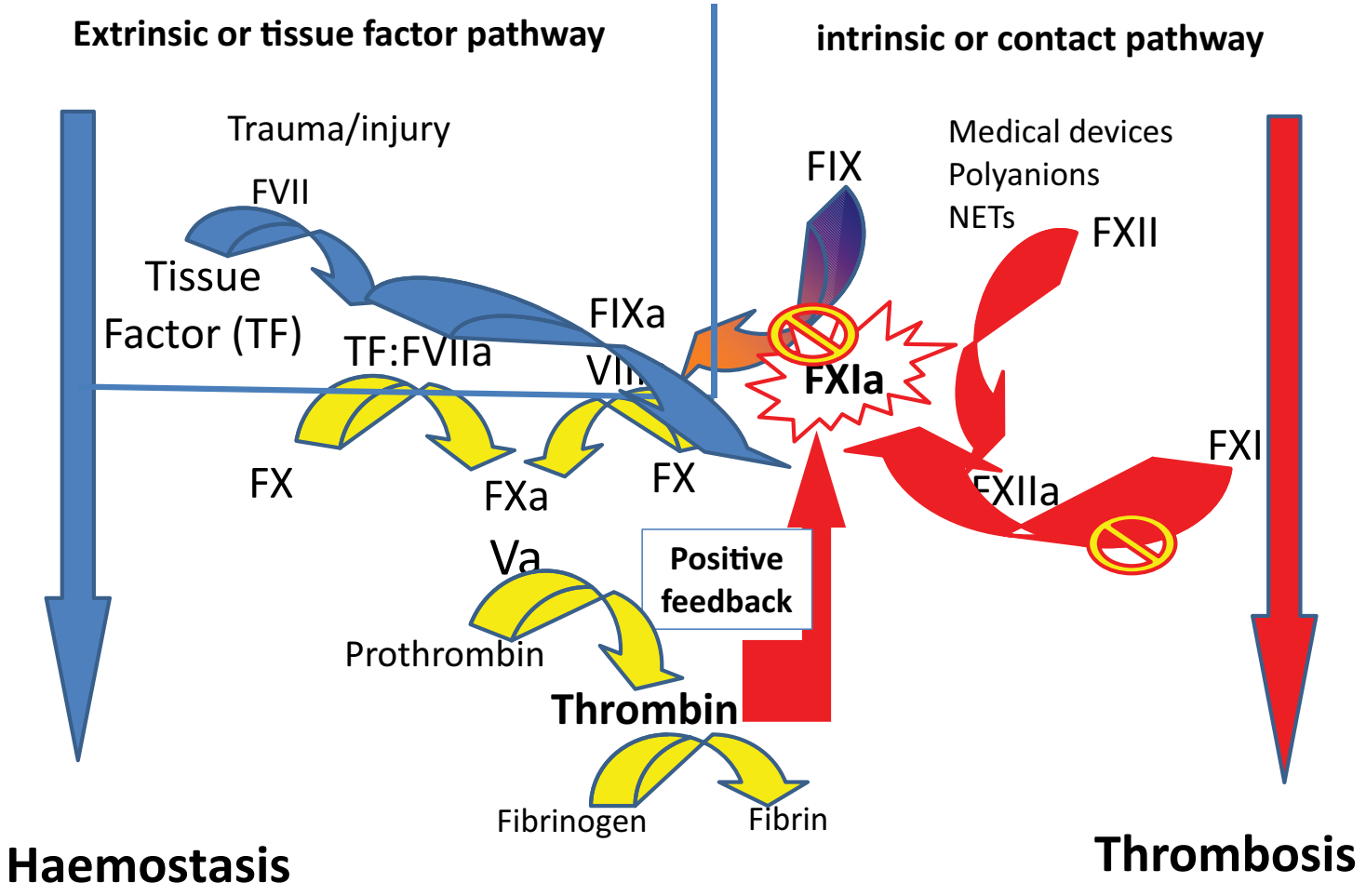
Plus

- ✓ Reduction of bleeding
- ✓ Reduction of intracranial haemorrhage
- ✓ No need for monitoring
- ✓ Few food/drug interactions

Limitations

- ✓ Unfavourable results reported in mechanical heart valves, antiphospholipid syndrome, high GI bleeding risk
- ✓ Setting with inadequate testing (severe renal impairment, extreme body wights, liver disease)
- ✓ Still non-negligible interactions with drugs

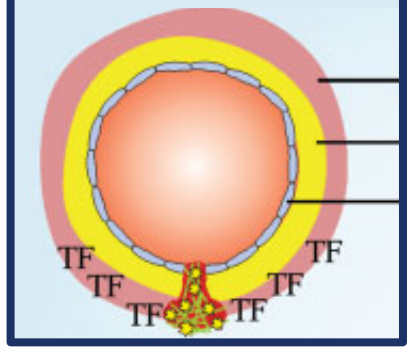
The coagulation cascade



Muscente F, De Caterina R. Eur Heart J Suppl 2023; 25: B 65

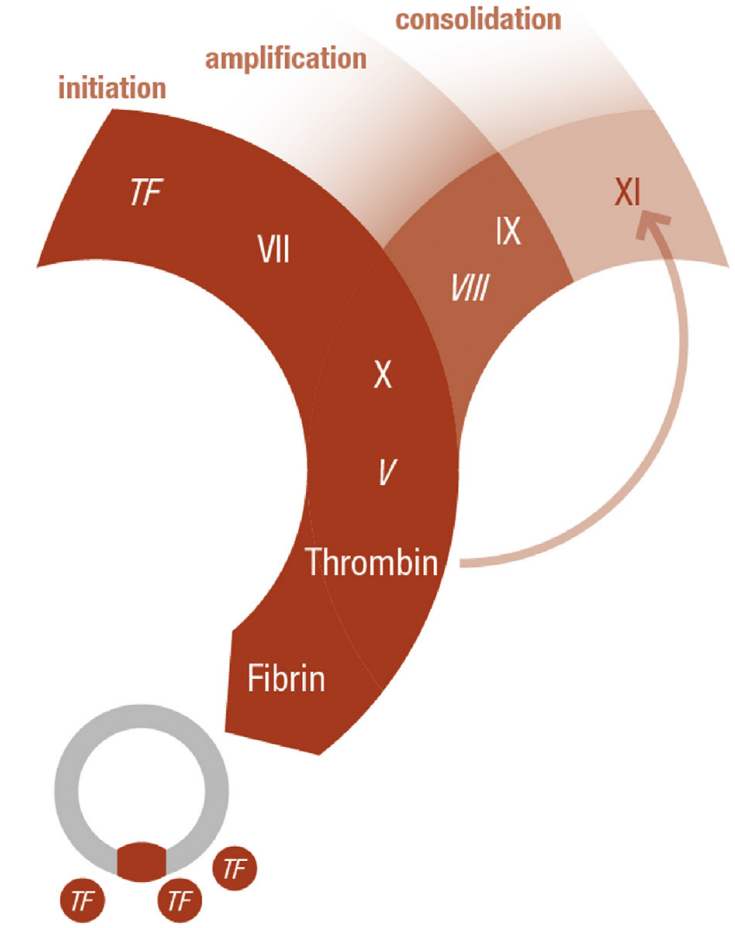
Uncoupling Haemostasis and Thrombosis

Haemostasis

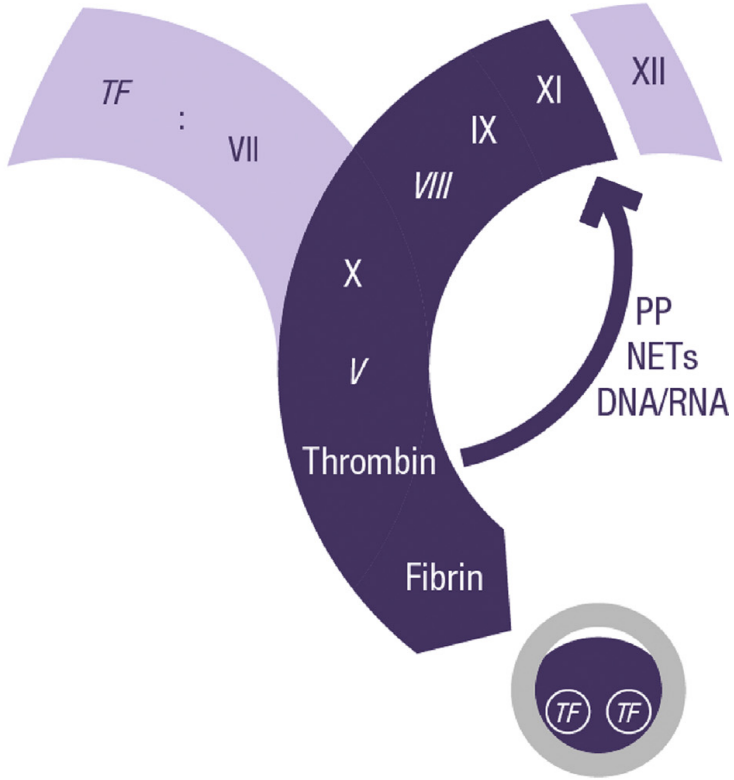


Thrombin Burst ++++

Clot consolidation is sufficient if FXI level is 10-20%

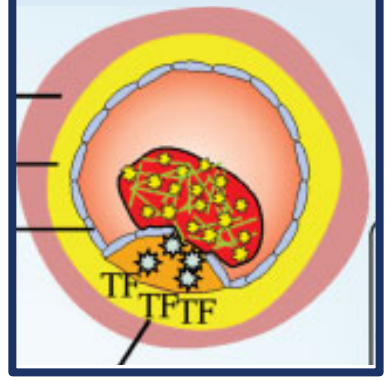


Consolidated clot



Stable thrombus

Thrombosis



Thrombin Burst +++

FXIa mediated amplification plays critical role

Hsu et al. JACC 2021

Why targeting Intrinsic Coagulation pathway to develop new antithrombotic drugs?

Let's learn from Hemophilia C, a fXI deficiency-related disease

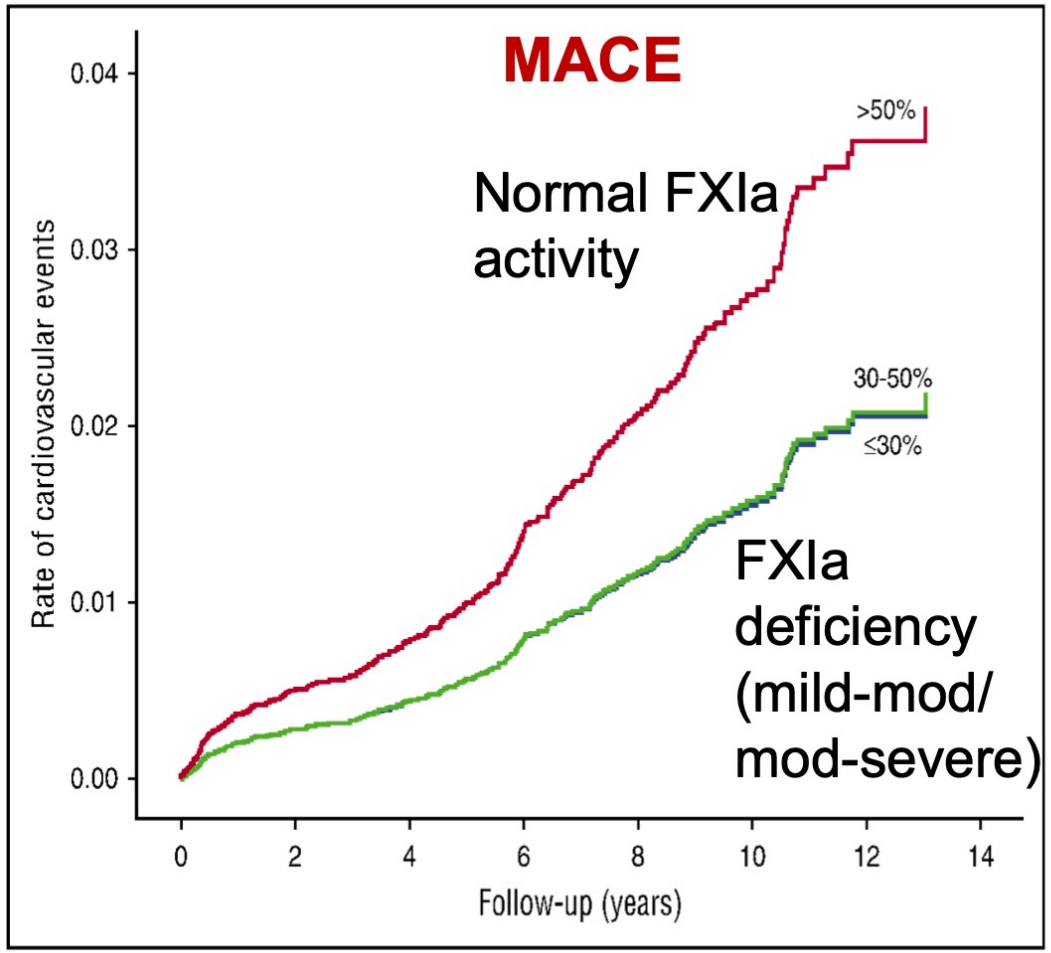
Also named Rosenthal disease, different from Hemophilia A (f VIII def) and Hemophilia B (f IX def)

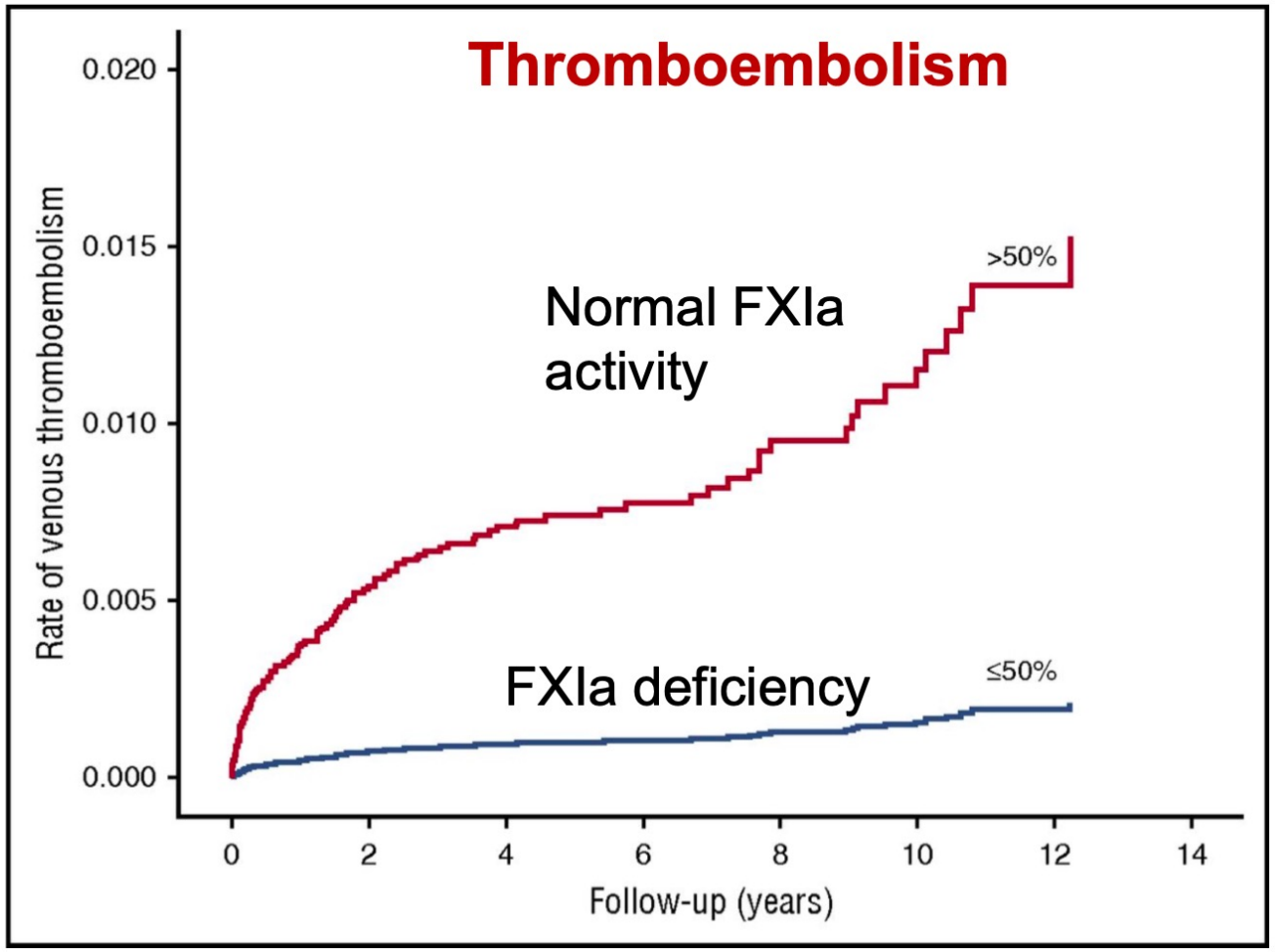
Described in the 50s' In pts bleeding for surgery or dental extraction

Very rare (1/1M people), more prevalent among the Iraqi and Ashkenazi Jews

Unpredictable level of bleeding, despite very severe deficiency of fXI

Lower Factor XI Activity and Risk of CV Events and VTE

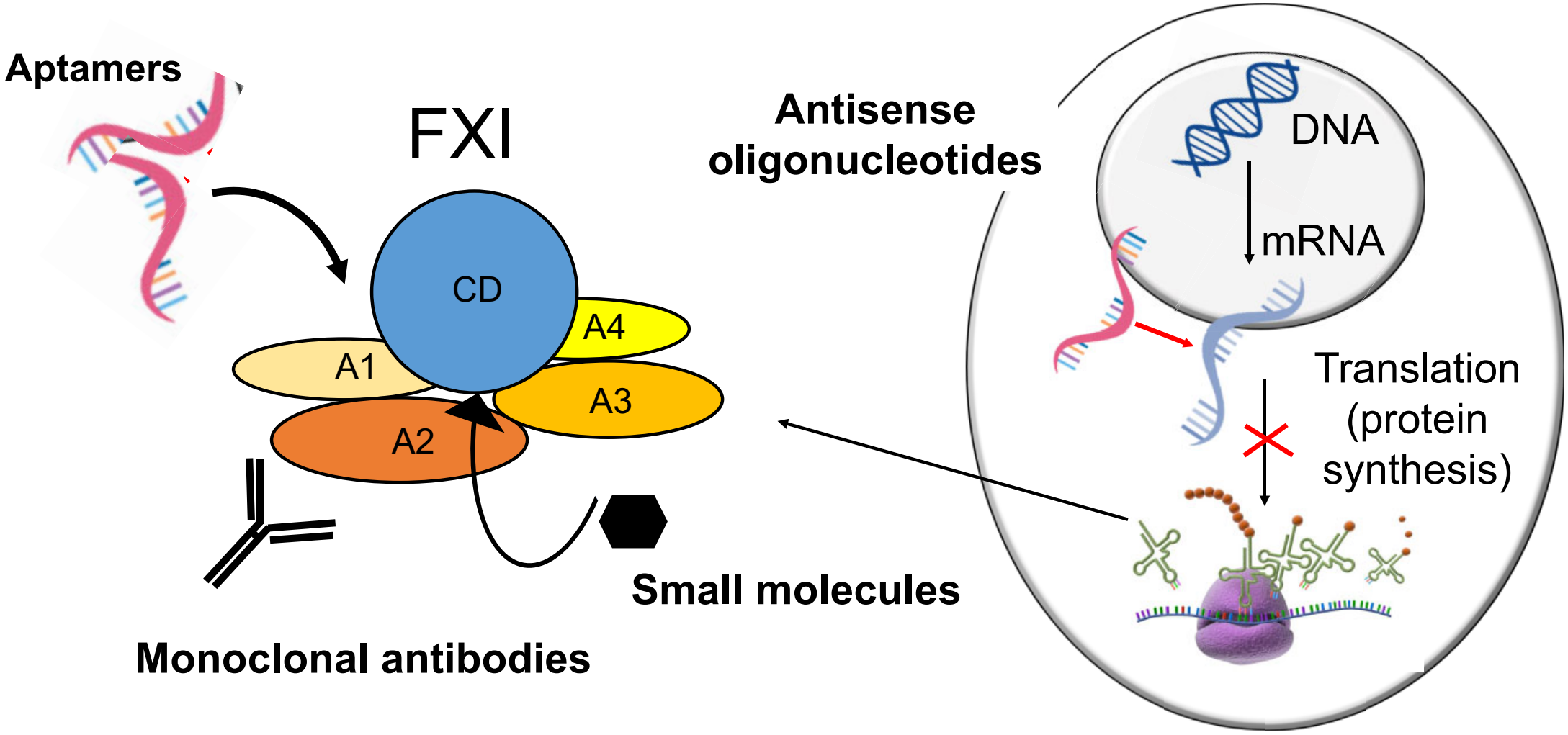




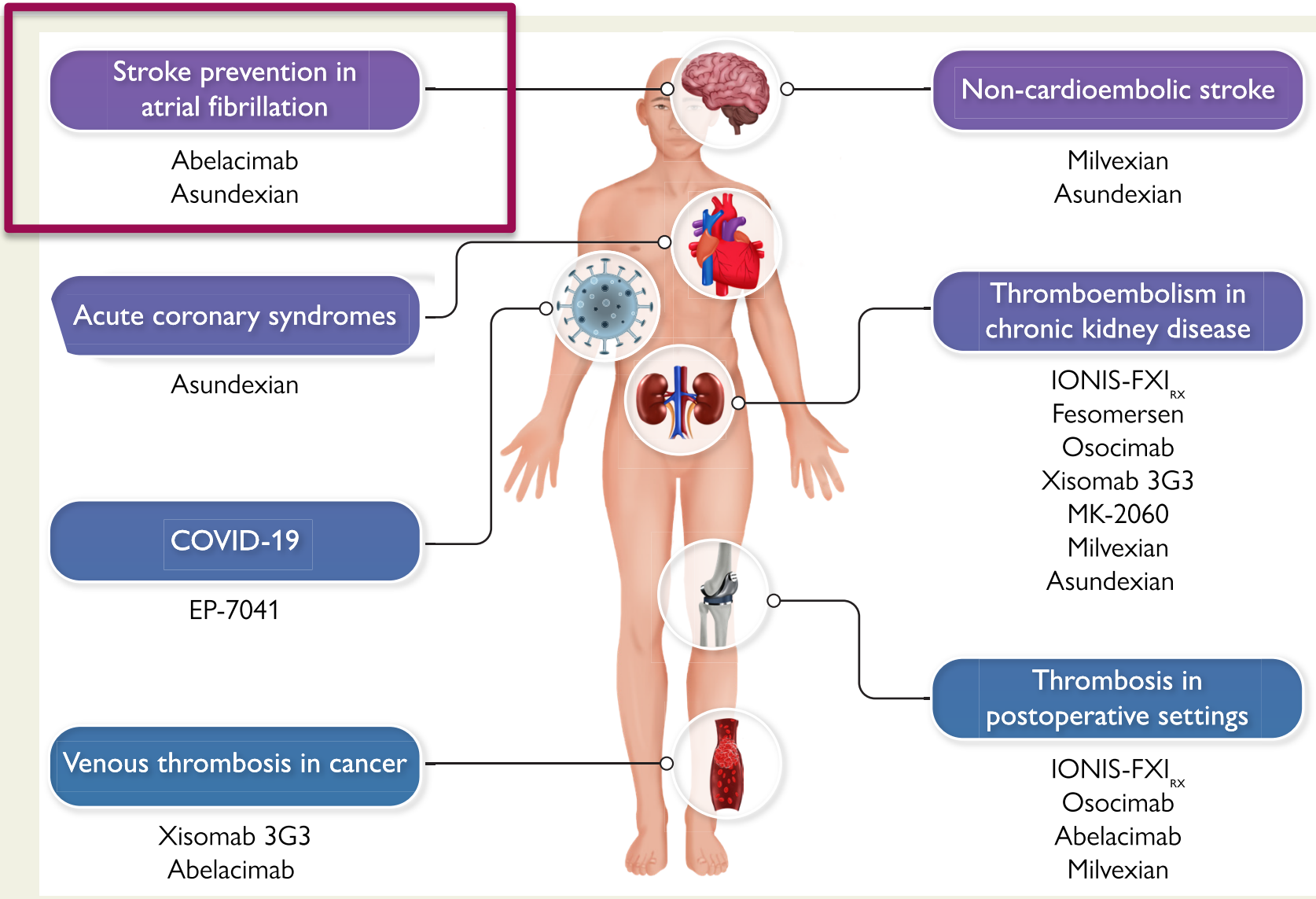
10,193 individuals Historical Cohort Study from Clalit Health Service in Israel

Preis M. et al. Blood 2017

Mechanism of action of FXI inhibitors



De Caterina R. et al Eur Heart J 2023; 44: 280



Possible forthcoming therapeutic indications for FXI/XIa inhibitors.

De Caterina R et al. Eur Heart J 2023; 44: 280

Novel Factor XI Inhibitors

	Antibodies	Small molecules	Natural inhibitors	ASOs	Aptamers
Mechanism	Bind target protein	Bind target protein	Bind target protein	Block biosynthesis	Bind target protein
Administration route	IV or SC	IV or oral	IV	SC	IV or SC
Administration frequency	Monthly	Daily	Daily	Weekly to monthly	Daily
Onset of action	Rapid (hours to days)	Rapid (minutes to hours)	Rapid (minutes)	Slow (weeks)	Rapid (minutes to hours)
Offset of action	Slow (weeks)	Rapid (minutes to hours)	Rapid (hours)	Slow (weeks)	Rapid (minutes to hours)
Renal excretion	No	Yes	Uncertain	No	No
CYP metabolism	No	Yes	No	No	No
Potential for drug–drug interactions	No	Yes	Unknown	No	No
	Abelacimab Osacimab	Asundexian Milvexian		FXI-LICA	

Fredenburgh JC. et al. Hämostaseologie 2022

AHA, November 11, 2023

A Multicenter, RandomiZed, Active-ControLled Study to Evaluate the Safety and Tolerability of Two Blinded Doses of Abelacimab Compared With Open-Label Rivaroxaban in Patients With Atrial Fibrillation - AZALEA-TIMI 71

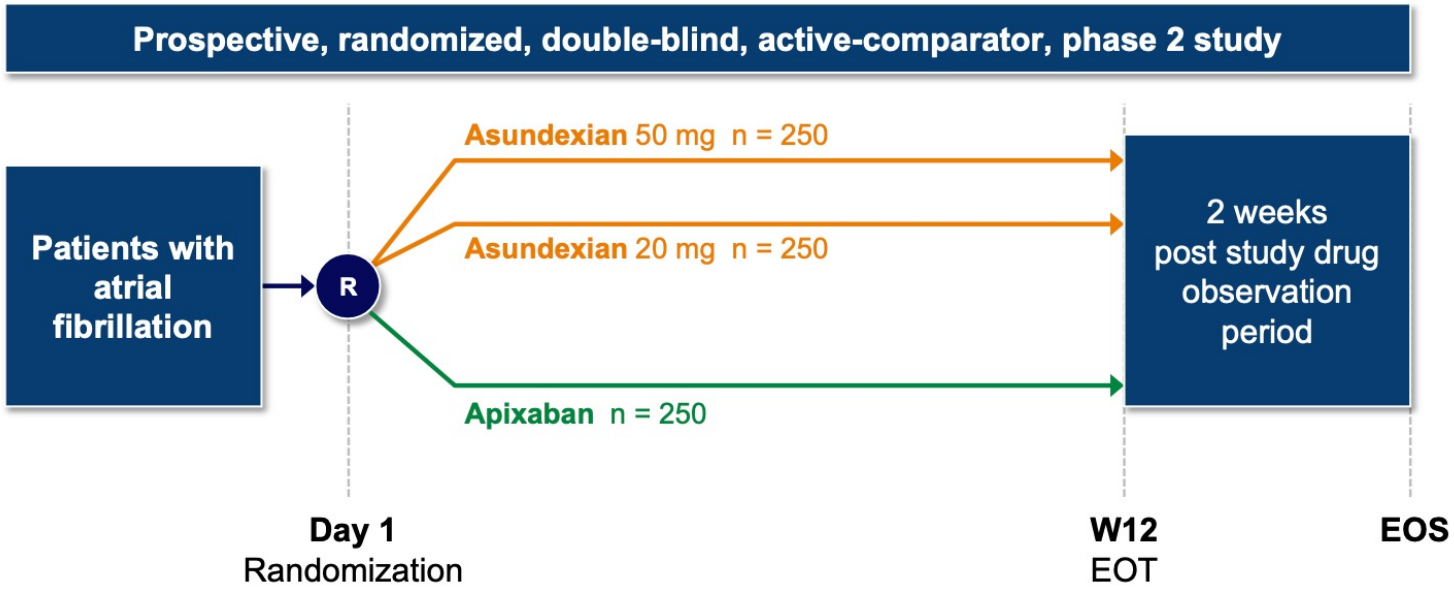
The results of this phase II trial indicate that both the tested doses of abelacimab (90 mg and 150 mg monthly) are superior to rivaroxaban 20 mg daily in reducing bleeding events among patients with AF and a high CHA_2DS_2-VASc score.

PACIFIC AF Trial: randomized double-blind, active comparator

PACIFIC AF

Atrial fibrillation
20mg asundexian
50mg asundexian
apixaban

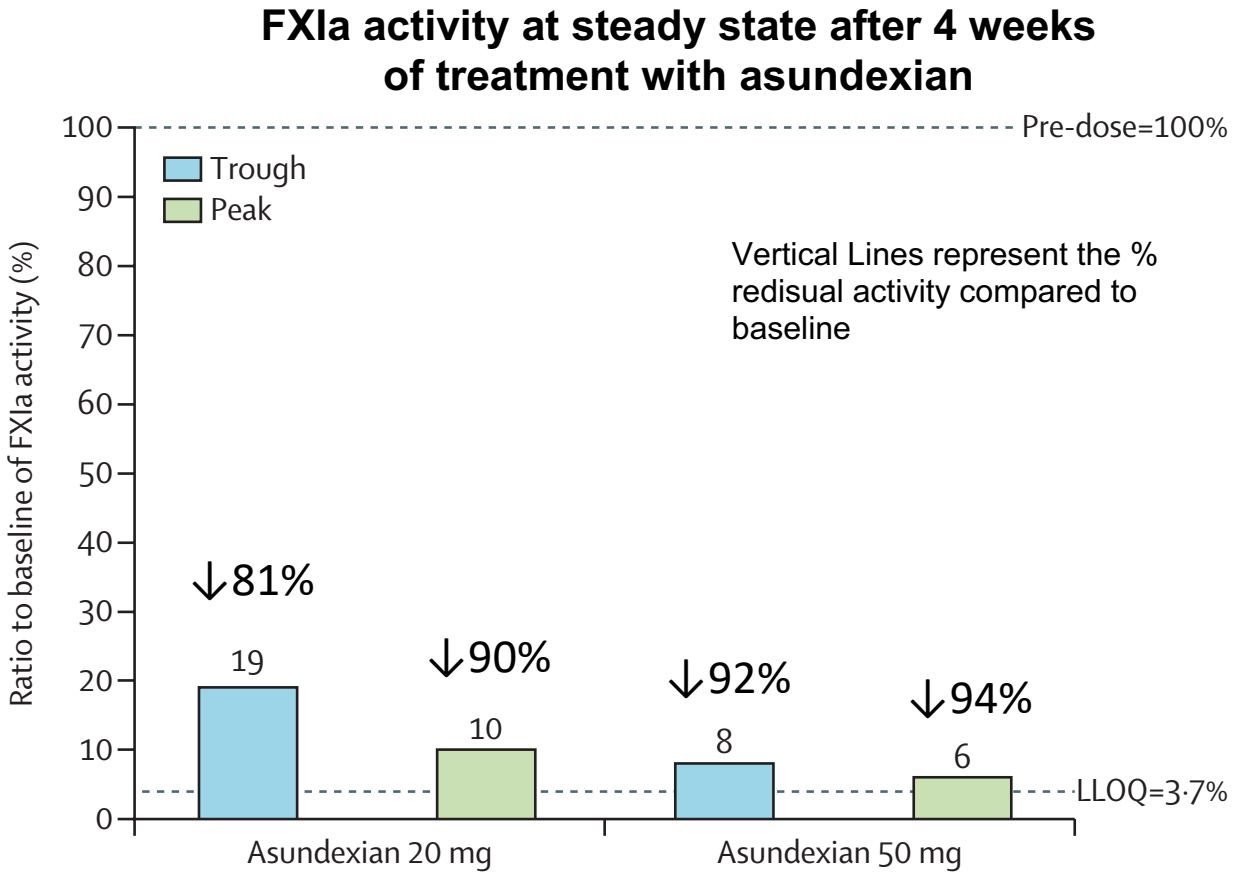
750 patients randomized
Results at ACC 2022

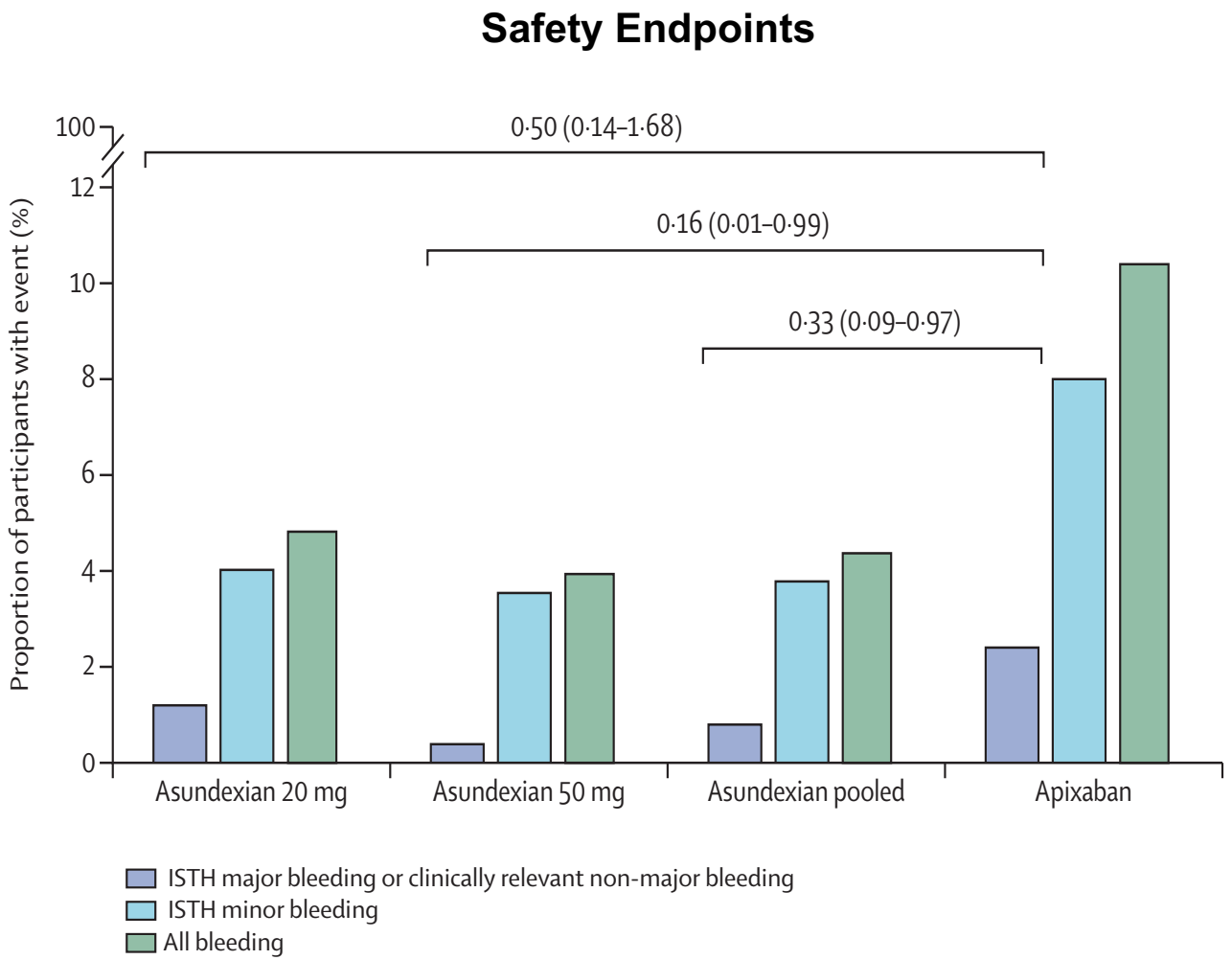


Primary safety EP= ISTH major and NM clinically relevant bleeding
Quantification of fXI inhibition
Exploratory efficacy EP= stroke, SE, CV death, MI

Piccini JP et al. Lancet 2022

PACIFIC AF Trial: randomized double-blind double dummy





Piccini JP et al. Lancet 2022; 399: 1383

PACIFIC AF Trial: exploratory efficacy EPs

	Asundexian 20 mg (n=251)	Asundexian 50 mg (n=254)	Apixaban (n=250)	Total (n=755)

- ✓ First study testing Asundexian vs. Active comparator (Apixaban)
- ✓ Near complete inhibition of FactorXIa with both dosages
- ✓ Asundexian well tolerated with few adverse effects
- ✓ Reduced bleeding compared to apixaban with both dosages of asundexian

Piccini JP et al. Lancet 2022; 399: 1383

Phase III trials with small molecules Factor XI(a)

Asundexian (Bayer)

Milvexian (BMS, Janssen)

Failure of OCEANIC-AF trial may not dampen future of fXIa inhibitors

On Nov. 19, Bayer announced that OCEANIC-AF was stopped due to failure of efficacy compared with apixaban

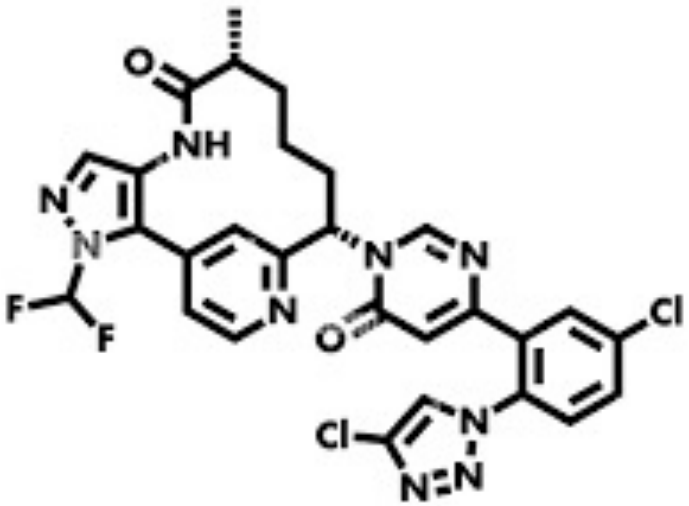
"I think OCEANIC-AF reflects a problem with the dose, not a problem with the [factor XI] hypothesis."

Jeffrey I. Weitz, MD

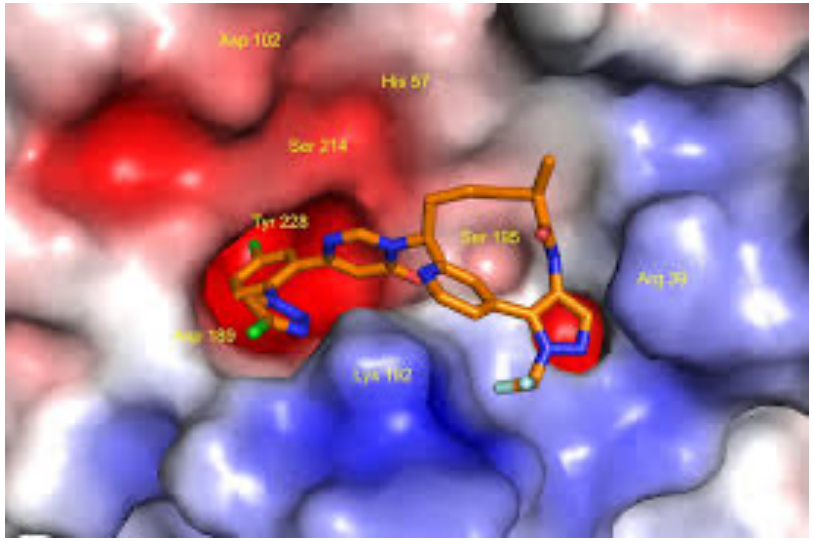
The news came as a surprise, as phase 1 and 2 studies of factor XI and factor XIa inhibitors, including asundexian, milvexian & abelacimab had been successful

McMaster University, Hamilton, Ontario, Canada

MILVEXIAN



milvexian



Milvexian is a direct-acting, reversible, high affinity inhibitor of activated fXI; orally administered determines concentration-dependent prolongation of aPTT

MILVEXIAN

Properties	Clinical Results
T_{max} after oral administration	4 hours
T1/2	13 to 16 hours
Metabolism	Substrate of cyt P450 3A4 &P-gp, No significant circulating metabolite
Hepatic impairment	Mild impairment: ↑30% C_{max} & AUC Moderate: ↑41% C_{max} and 23% AUC
Renal Impairment	C_{max} similar for all renal function groups
Time to reach steady-state condition	3-6 days of oral administration twice daily

LIBREXIA-AF

A Phase 3 Active-controlled Study of Milvexian for Prevention of Cardioembolic Events in Participants with Atrial Fibrillation

Protocol 70033093AFL3002; Phase 3

Version: Original

JNJ-70033093; BMS-986177 (Milvexian)

Diagnostic Assessments

18. Any of the following laboratory results, based on local laboratory, outside of the ranges specified below prior to randomization, confirmed by repeat:
    a. Platelet count <50,000 mm^3
    b. ALT >3x ULN
    c. Total bilirubin ≥1.5x ULN unless an alternative causative factor such as Gilbert's syndrome is identified
    d. Hemoglobin <8.0 g/dL

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate if milvexian is non-inferior to apixaban for the composite of stroke and non-CNS systemic embolism.	Time to the first occurrence of composite endpoint of stroke and non-CNS systemic embolism.
Secondary	
To evaluate if milvexian is superior to apixaban in reducing risk of the principal safety endpoint family: • ISTH major bleeding • Composite of ISTH major and CRNM bleeding	• Time to the first occurrence of ISTH major bleeding • Time to the first occurrence of the composite of ISTH major and CRNM bleeding
To evaluate if milvexian is superior to apixaban for the composite of CV death, MI, stroke and non-CNS systemic embolism.	Time to the first occurrence of composite endpoint of CV death, MI, stroke, and non-CNS systemic embolism.
To evaluate if milvexian is superior to apixaban as assessed by CV death.	Time to CV death.
To evaluate if milvexian is superior to apixaban as assessed by the composite of all-cause death, MI, stroke and non-CNS systemic embolism.	Time to the first occurrence of composite endpoint of all-cause death, MI, stroke and non-CNS systemic embolism.

In conclusion

- Epidemiological and experimental evidence suggests that inhibiting the contact pathway and especially factor XI (FXI) achieves thrombosis prevention with minimal interference on the haemostatic process

- FXI inhibitors will not necessarily replace currently available direct oral anticoagulants, but provide drugs in those clinical settings in which DOACs are contraindicated or in which their usefulness has not been fully established

- Finally, an equally effective treatment strategy, but with a better safety profile, will be particularly useful in clinical contexts with a higher bleeding risk