



Brigham and Women's Hospital

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FXI Inhibition: Rethinking risk, redefining benefit

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DISCLOSURES

Disclosures/Conflicts of Interest

Scientific Ad Boards and Consulting:

Abbott

Anthos

Alnylam

Cerus Corporation

Bristol Myers Squibb

Janssen

Perosphere Technologies

Pfizer

Regeneron

Steering committees and IDMC for FXI inhibitor development



OBJECTIVES

“Why do we need a new class of anticoagulants?”

“Why did they use a safety endpoint as the primary endpoint for a phase II clinical trial?”

“ FXI inhibitors aren’t going to make it, didn’t they halt that trial?”

Will describe data from patients with congenital FXI deficiency that suggest that we can separate physiologic hemostasis from pathologic thrombosis.

Will discuss published data for reported stage II and III FXIi clinical trial results



Populations that may benefit from anticoagulant with reduced bleeding profile

Reduction in bleeding the most important **unmet need** for many who are not treated with anticoagulants given bleeding risks:

- Older adults at risk for VTE
- Atrial fibrillation patients with bleeding concerns
- Patients with prior intracranial hemorrhage
- Patients with cancer associated thrombosis
- Medically ill or hospitalized patients
- Niche populations
 - Mechanical circulatory support and devices
 - Hemodialysis
 - HIT?
 - APS?

Why Factor XI Inhibitors?



Reduced bleeding
risk



Avoids disruption
of hemostasis

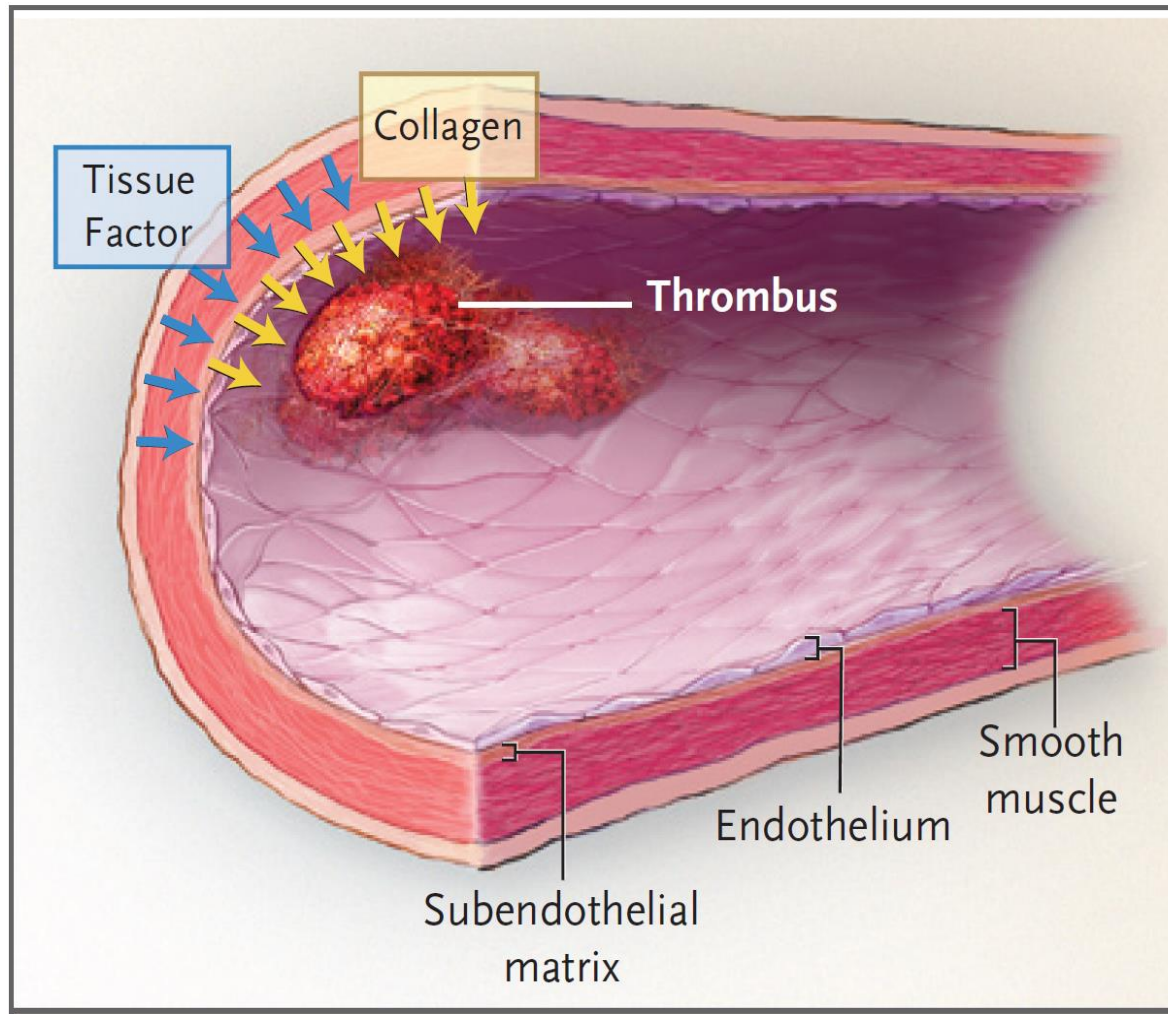


Efficacy in
preventing
thrombosis



Potential for a wide
therapeutic window

Thrombus formation



Need exposure to components to trigger thrombus formation

Collagen:

- **in subendothelial matrix**
- **binds VWF and platelets**

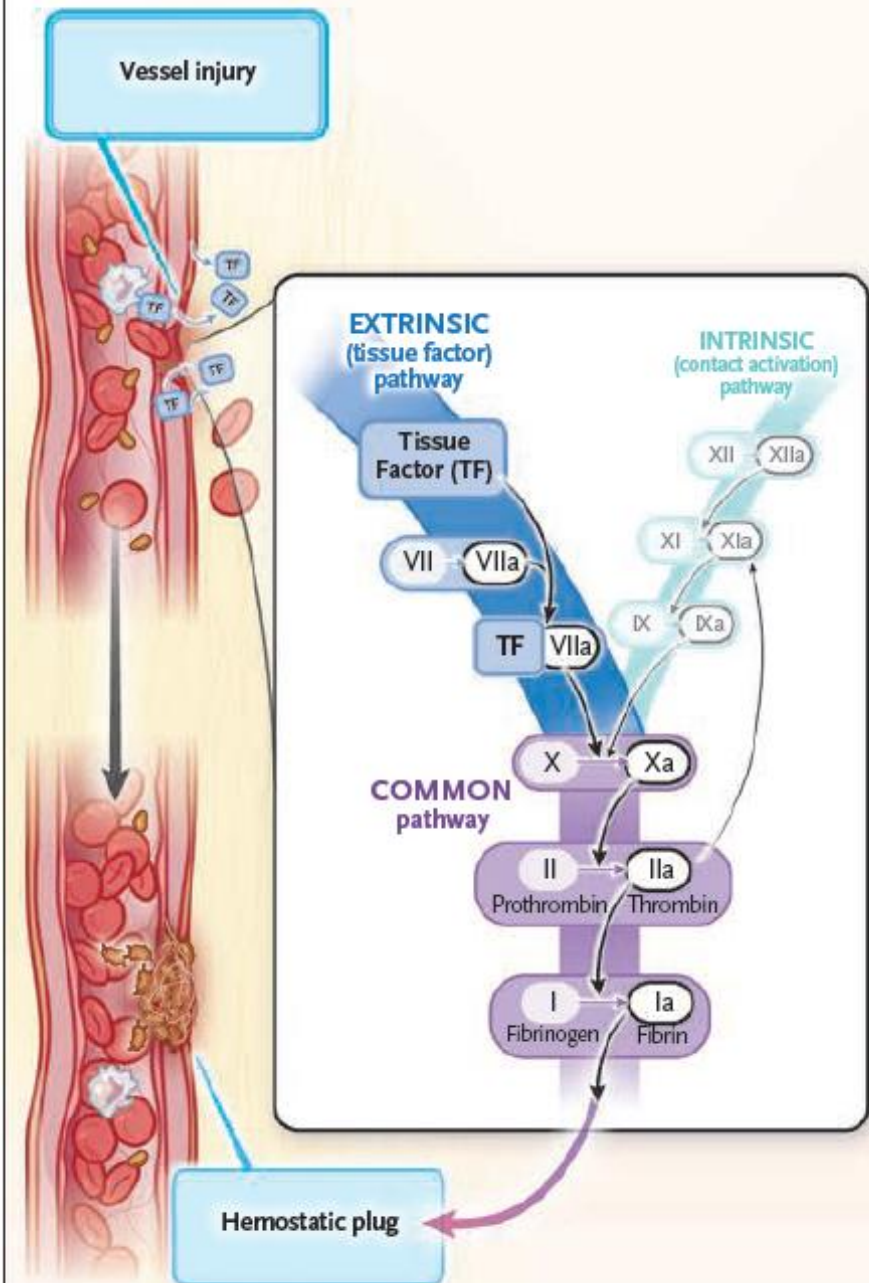
Tissue Factor:

- **in media and adventitia**
- **binds FVII → FVIIa**

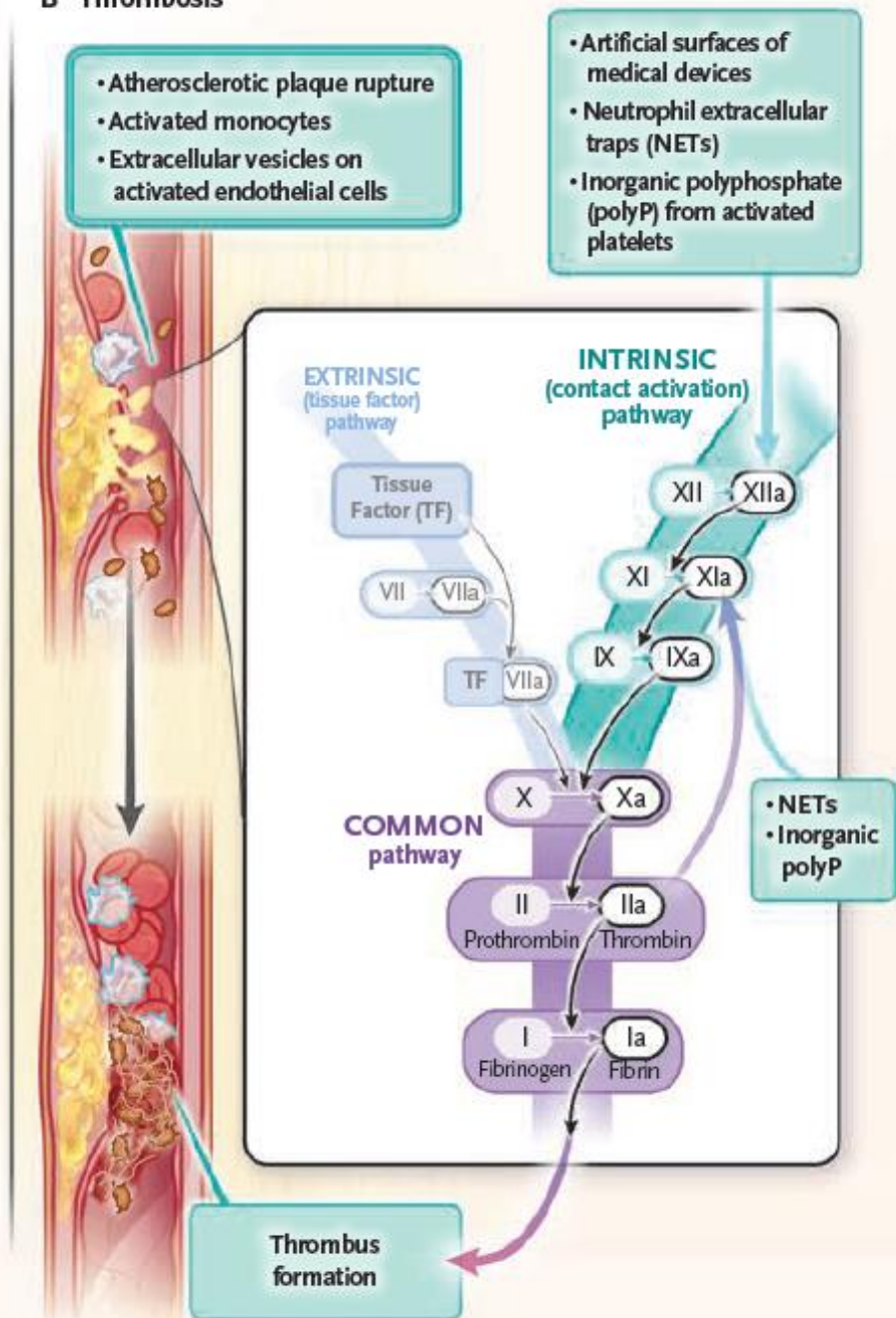
Extrinsic pathway critical for hemostasis in setting of trauma, surgery, childbirth

FXI not needed to initiate thrombin generation

A Hemostasis



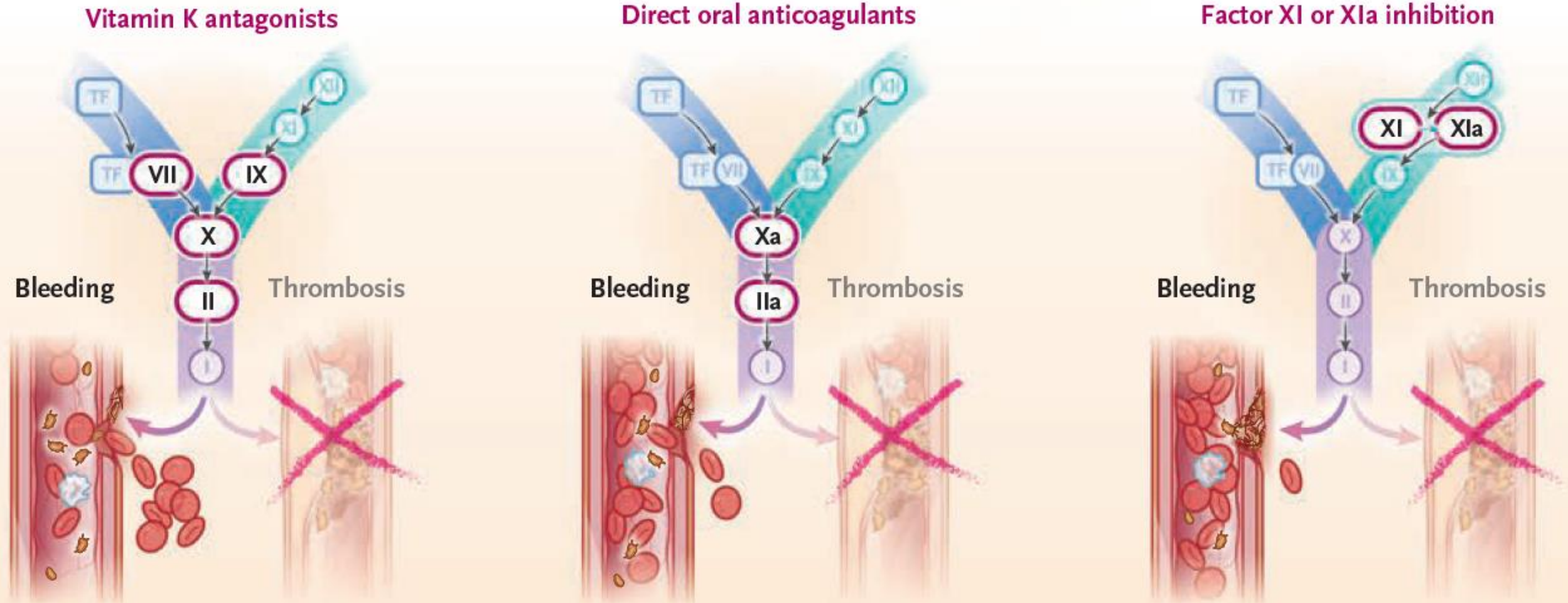
B Thrombosis



Can we truly separate physiologic hemostasis from pathologic thrombosis *in vivo*?

Current anticoagulants

C Targets of Anticoagulant Drugs and Effects on Hemostasis and Thrombosis



Congenital FXI deficiency

No spontaneous bleeding as with FVIII or FIX deficiency

- No joint or soft tissue bleeds or ICH despite aPTT often 70-80 seconds

Not like FXII deficiency which has no bleeding phenotype

Surgical or trauma related bleeding only

- Typically occurs hours to days after trauma or surgery
- Higher association with personal history of bleeding than family history
- Individual patient can have different degree of bleeding with different procedures
- Mucosal tissues with high fibrinolytic properties more likely to bleed
 - Nasopharyngeal, oropharynx, GI, GU tract
 - Menorrhagia frequent in women

Epidemiologic data to support FXI inhibition

Patients with congenital FXI deficiency have:

- Decreased risk of VTE
- Decreased risk of arterial events of stroke and MI (less well established)

Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events

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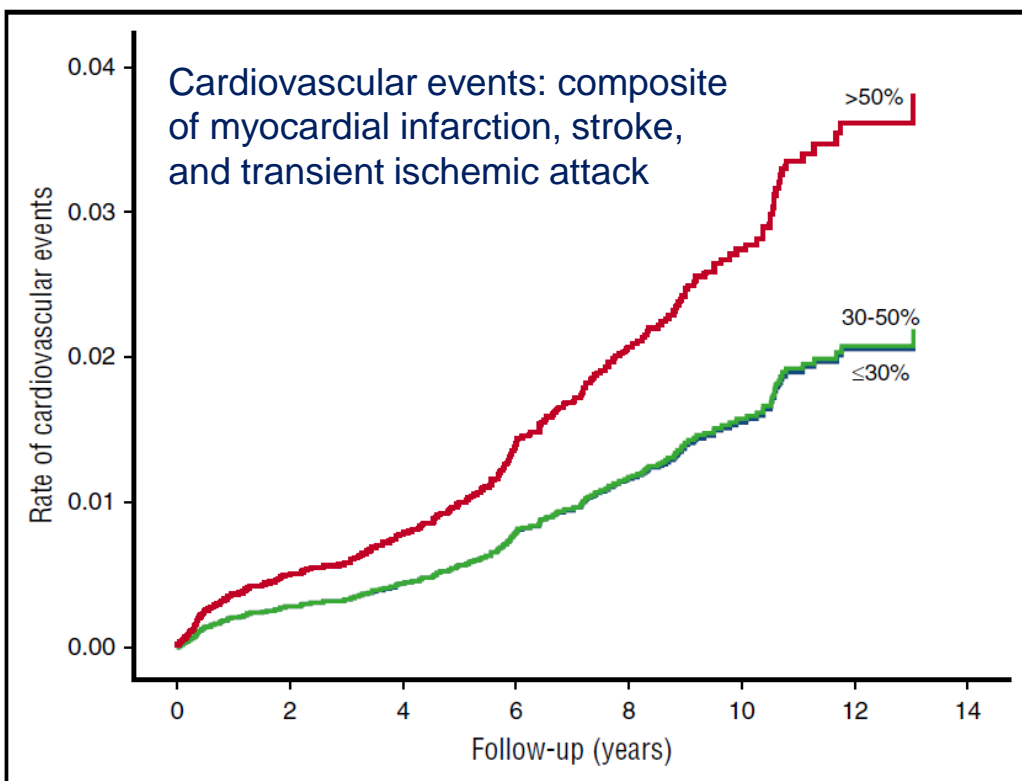


Figure 1. Age-adjusted survival function curves of patients with normal factor XI activity (>50%), mild deficiency (30%-50%), and moderate-severe deficiency (≤30%) for future cardiovascular events.

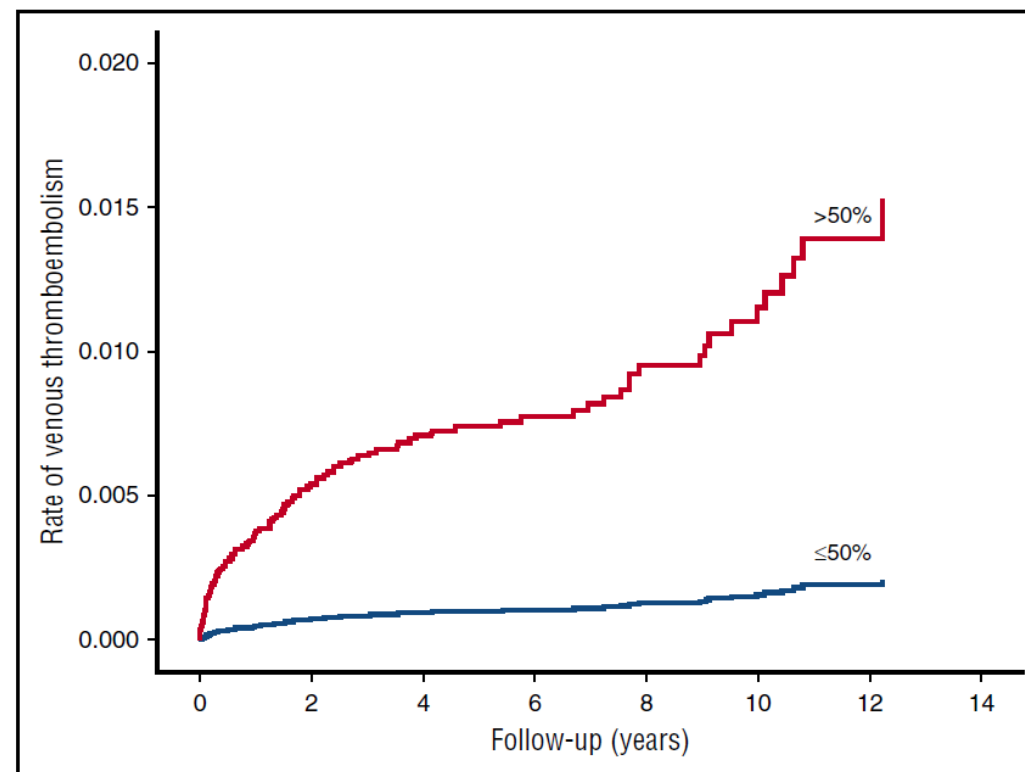


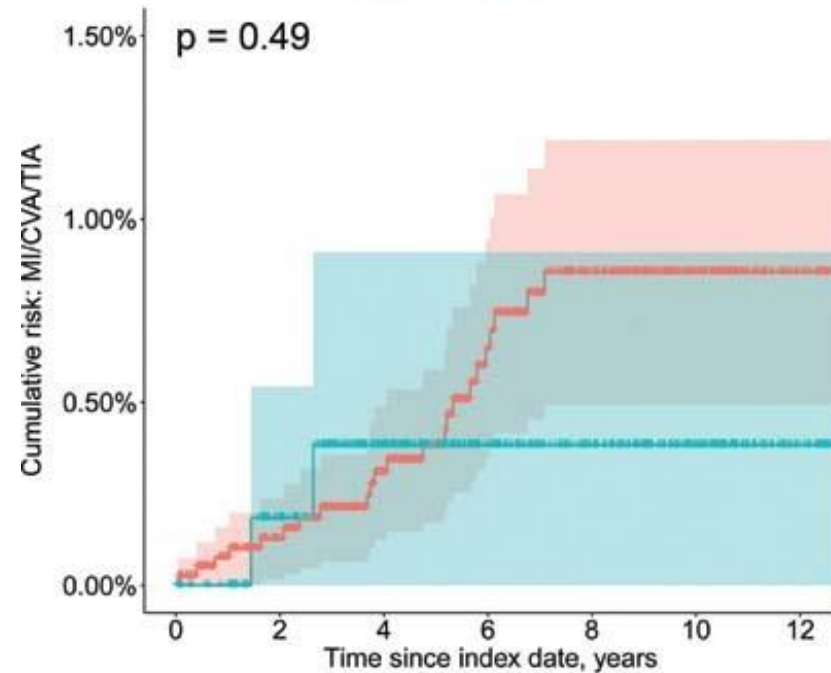
Figure 2. Age-adjusted survival function curves of patients with normal factor XI activity (>50%) and factor XI deficiency (≤50%) for future VTE events.

The Association between Factor XI Deficiency and the Risk of Bleeding, Cardiovascular, and Venous Thromboembolic Events

Sarah Sharman Moser¹ Gabriel Chodick^{1,2} Yan G. Ni³ Dan Chalothorn³ Ming-Dauh Wang³
 Alan R. Shuldiner³ Lori Morton³ Ophira Salomon^{2,4} Jessica J. Jalbert³

**CV (Stroke/TIA/MI) events,
Deficient (FXI<50%) vs GPRG**

Strata — GPRG — FXI deficient

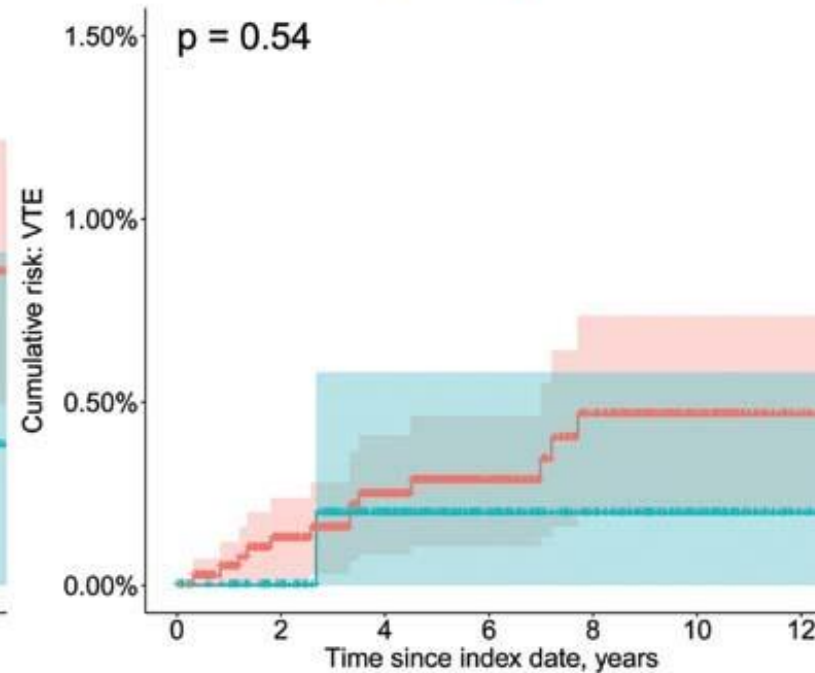


Number at risk (number of events)

GPRG	4039 (0)	3698 (5)	2947 (11)	2085 (19)	1506 (23)	897 (23)	246 (23)
FXI deficient	577 (0)	527 (1)	424 (2)	298 (2)	215 (2)	134 (2)	37 (2)

**VTE events,
Deficient (FXI<50%) vs GPRG**

Strata — GPRG — FXI deficient



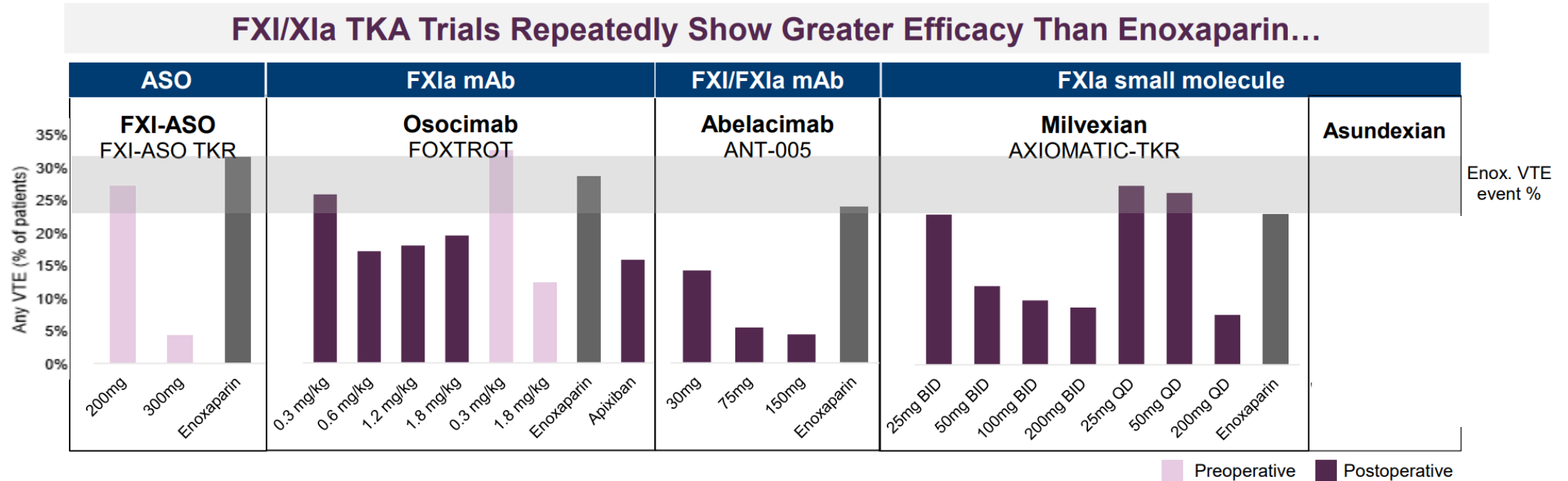
Number at risk (number of events)

GPRG	4081 (0)	3731 (5)	2968 (9)	2097 (10)	1507 (13)	896 (13)	247 (13)
FXI deficient	583 (0)	534 (0)	429 (1)	301 (1)	216 (1)	134 (1)	38 (1)

Strategies to Target Factor XI

Strategy	Drug Examples	Mechanism of Action	Route of Administration
Small Molecule Inhibitors	Asundexian, Milvexian	Reversibly bind the active site of FXIa, inhibiting enzymatic activity	Oral
Monoclonal Antibodies	Abelacimab, Osocimab, BAY 1831865	Bind to FXI or FXIa to block its activation or catalytic function	Intravenous / Subcutaneous
Antisense Oligonucleotides	IONIS-FXI(Rx), Fesomersen	Bind FXI mRNA in hepatocytes, reducing FXI protein synthesis	Subcutaneous
siRNA (Small Interfering RNA)	None in late-stage trials	Trigger degradation of FXI mRNA, leading to reduced FXI levels	Subcutaneous (anticipated)
Aptamers (experimental)	None in advanced trials	Structured oligonucleotides that bind FXIa, blocking its enzymatic activity	Intravenous (anticipated)

FXI/XIa TKA Trials: Greater Efficacy Than Enoxaparin



Phase II TKR trials

- Proof of concept against gold standard comparator enoxaparin
- Dose finding for efficacy and safety
 - Dose dependent increase in efficacy without increase in bleeding
 - Asundexian was not tested in TKR studies, used phase 2 stroke trial

Advanced stage clinical trials

Drug	moa	Trial	Indication	Phase	Status
Abelacimab	Monoclonal antibody	AZALEA-TIMI 71	AF	2	Stopped early (↓ bleeding)
Abelacimab		LILAC-TIMI 76	AF bleeding risk	3	Ongoing
Abelacimab		ASTER/MAGNOLIA	Cancer-associated VTE	3	Ongoing
Asundexian	Small molecule	OCEANIC-AF	AF	3	Stopped early (↓ efficacy)
Asundexian		OCEANIC-STROKE	Non-cardioembolic stroke	3	Ongoing
Milvexian	Small molecule	LIBREXIASTROKE	Stroke/TIA	3	Ongoing
Milvexian		LIBREXIA-ACS	ACS	3	Ongoing
Milvexian		LIBREXIA-AF	AF	3	Ongoing

FXI inhibition for SSE prevention in NVAF

Will discuss reported AF trials given large number of patients enrolled and global burden of AF and discrepant results

Abelacimab: monoclonal antibody binds catalytic domain both FXI and FXIa, locks in zymogen state

Phase II AZALEA TIMI-73 stopped early for efficacy*

- 1,280 participants

Asundexian: oral small molecule inhibitor of FXIa

Phase III OCEANIC-AF stopped early for inferiority*

- 14,810 participants analyzed

* Primary endpoints were different in these trials

AZALEA TIMI-71: Phase II Trial Design

1287 Patients with AF at Moderate-to-High

September 2023

AZALEA TIMI-71 study stopped early by IDMC due to overwhelming reduction in major and clinically relevant non-major bleeding observed with abelacimab compared to rivaroxaban.

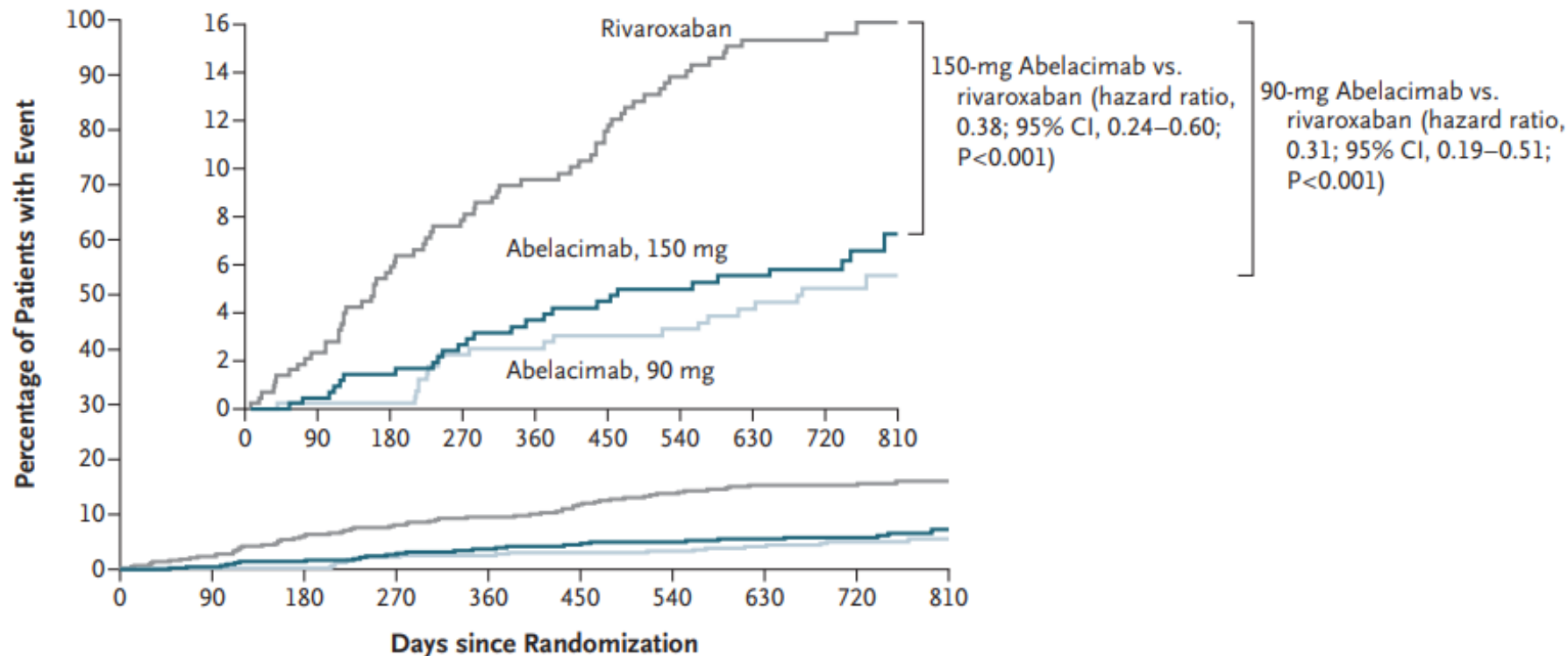
if CrCl ≤50 ml/min at
ization or during study

1° EP (Safety): Major or Clinically Relevant Non-Major Bleeding

AZALEA-TIMI 71: Outcomes

Endpoint	Rivaroxaban	Abelacimab 90 mg	Abelacimab 150 mg
PRIMARY ENDPOINT			
Major or CRNM Bleeding	15.4%	4.9%	6.1%
Hazard Ratio vs. Rivaroxaban	Reference	HR 0.31 p<0.001 (95% CI:0.19–0.51)	HR 0.38 p<0.001 (95% CI: 0.24–0.60)
SECONDARY* ENDPOINTS	*trial not designed to demonstrate efficacy for 2 nd endpoint events		
Major Bleeding	7.2%	1.9%	2.3%
GI Bleeding	4.2%	0.5%	0.5%
Intracerebral Hemorrhage	0.9%	0.9%	0.5%
Ischemic Stroke	1.2%	2.4%	2.3%
Stroke or Systemic Embolism	1.6%	2.6%	2.3%
All-Cause Mortality	7.0%	6.1%	5.2%

AZALEA TIMI-71: phase II primary endpoint result



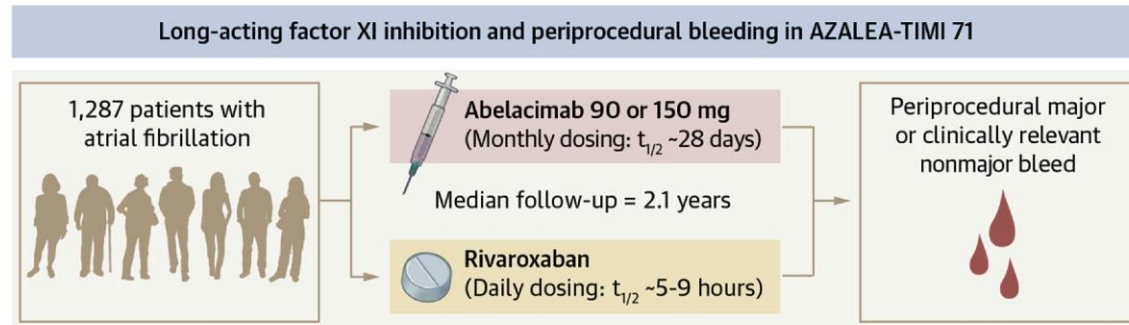
No. at Risk

Rivaroxaban	428	415	392	375	365	352	339	328	310	121
Abelacimab, 150 mg	427	419	404	386	375	363	353	343	324	117
Abelacimab, 90 mg	425	413	398	378	372	357	349	338	308	117

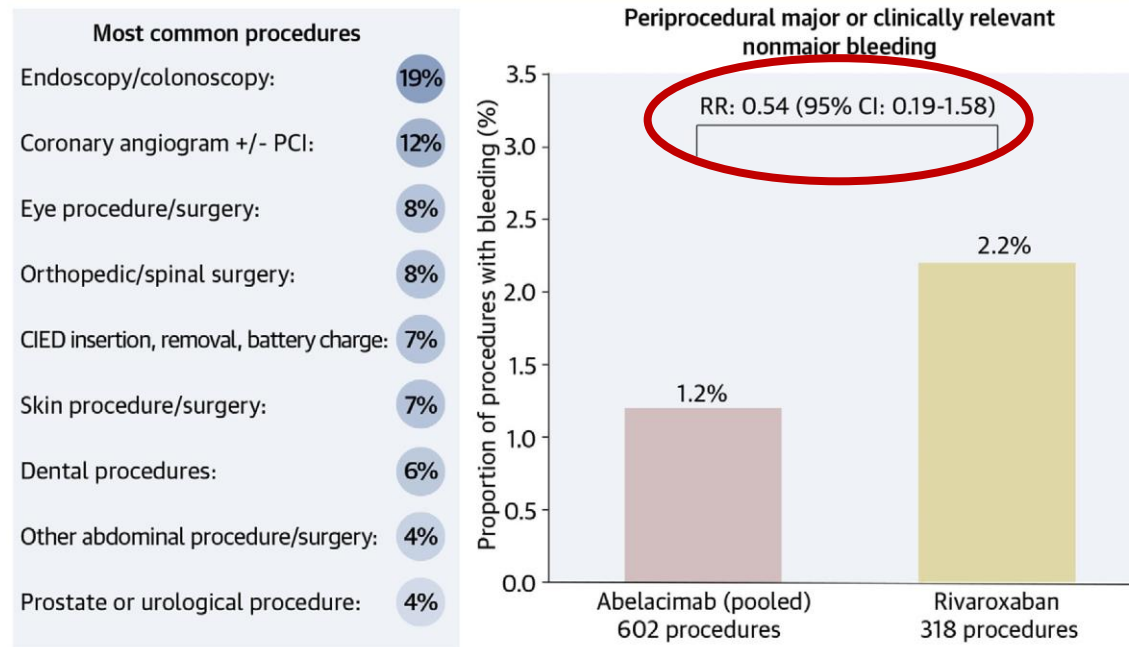
Figure 2. Major or Clinically Relevant Nonmajor Bleeding.

Shown is the cumulative incidence of the primary end point event of major or clinically relevant nonmajor bleeding. The inset shows the same data on an expanded y axis.

CENTRAL ILLUSTRATION: Long-Acting Factor XI Inhibition and Periprocedural Bleeding



Total of 920 procedures (~1 in 3 patients with a procedure in each treatment arm)



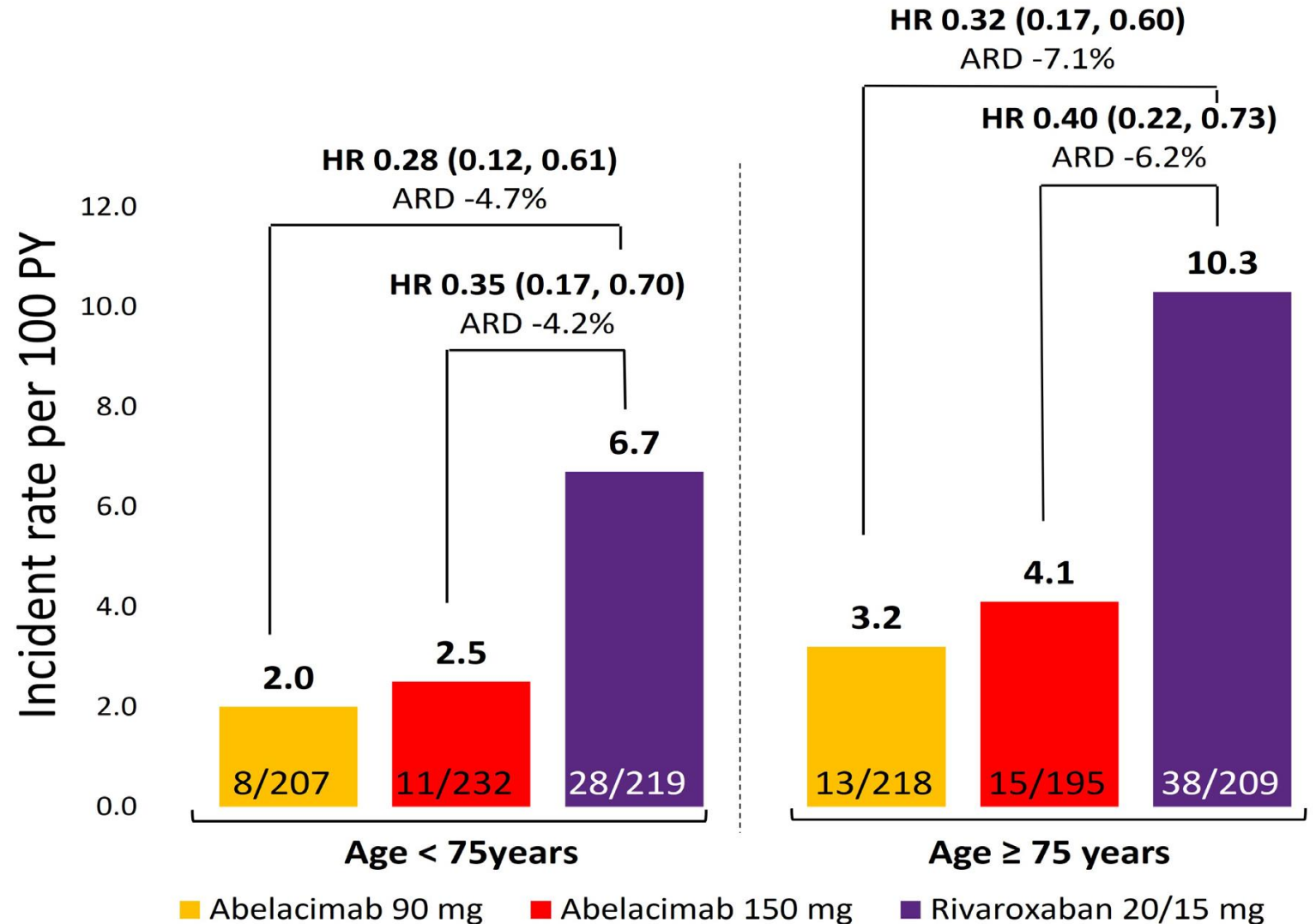
Rates of periprocedural bleeding were comparable among patients treated with the long-acting factor XI inhibitor abelacimab when compared to a standard-of-care interruption strategy with rivaroxaban.

Peri-procedure bleeding in AZALEA-TIMI 71

- median time procedure 29 days (IQR:Q1-Q3: 20-42 days) from last dose
- 336 of the 602 (55.8%) procedures within the monthly dosing interval
 - rate of major/CRNMB bleeds within the monthly dose interval: 3/336 (0.9%)
- No prophylaxis to prevent bleeding given

AZALEA TIMI-71: bleeding by age group

- 1,287 participants
- 625 (49%) ≥ 75 yrs



OCEANIC-AF: phase III trial in high-risk AF

November 2023

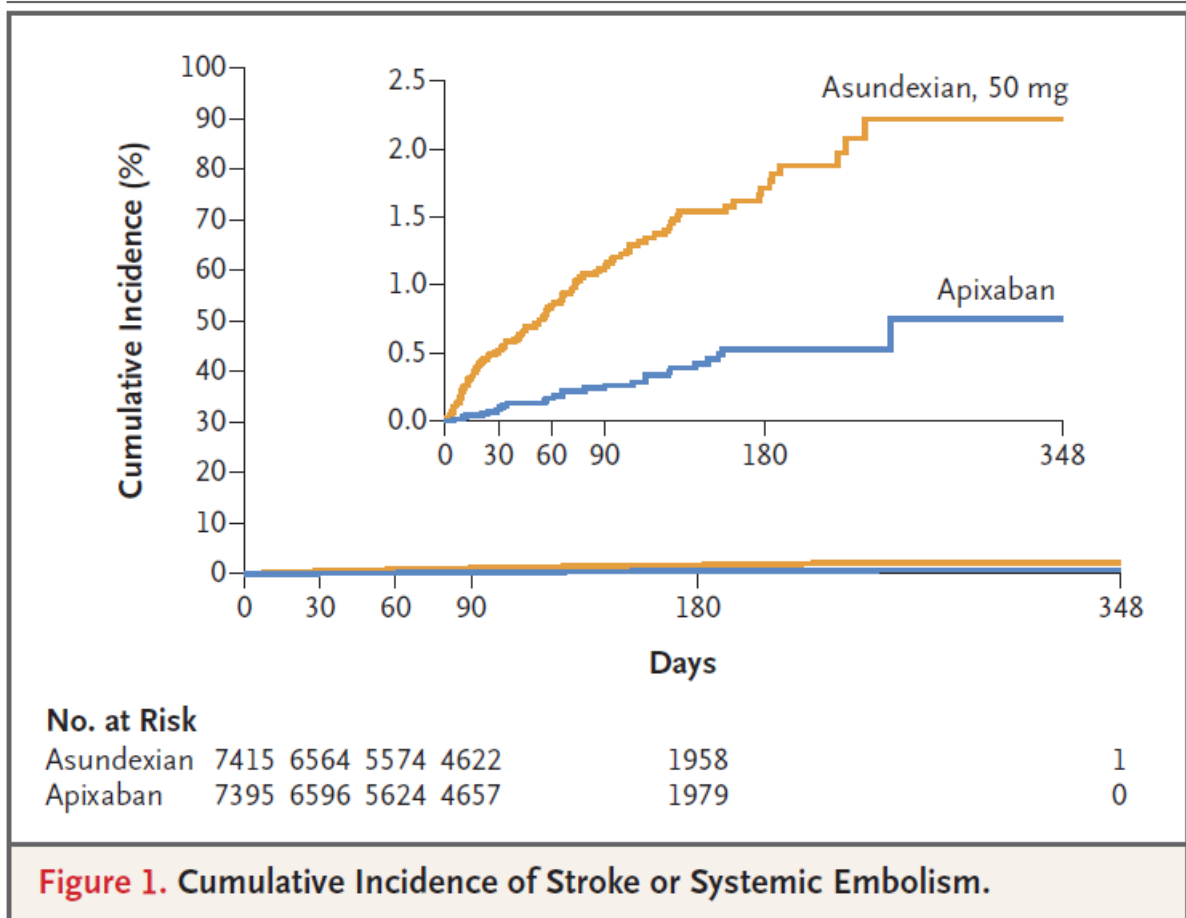
OCEANIC-AF study stopped early by IDMC due to an inferior efficacy of asundexian versus the control arm.

IDMC recommends continuing OCEANIC-STROKE trial as planned

- **Primary outcome:** Time to first occurrence of stroke or systemic embolism
- **Primary safety endpoint:** ISTH major bleeding
- **Secondary endpoint:** Net clinical benefit

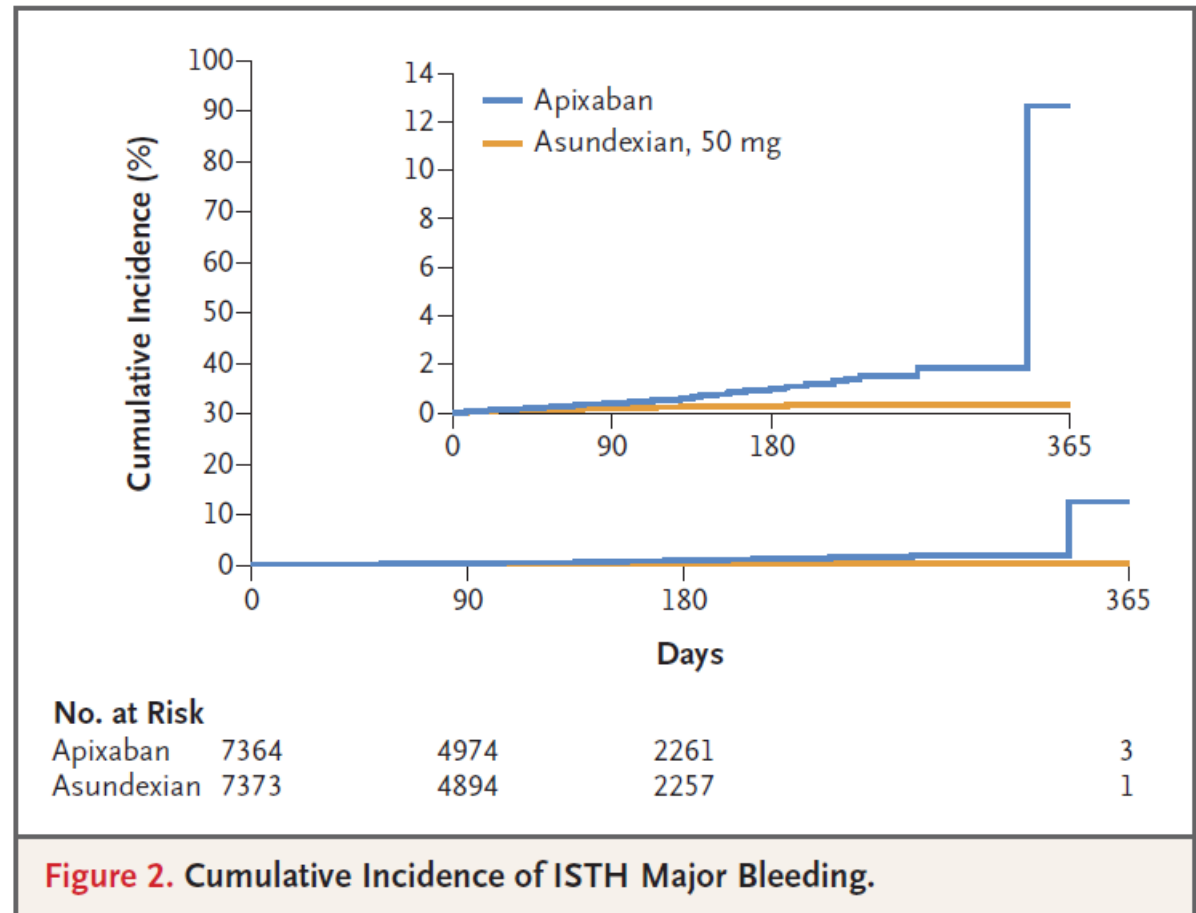
14,810 participants randomized

Oceanic-AF results



Primary efficacy endpoint: noninferiority **not** met: HR 3.79; 95% CI 2.46—5.83

Piccini, NEJM, 2024



Primary safety endpoint: not formally tested
HR 0.32; 95% CI 0.18—0.55

ISTH major and CRNMB: HR 0.44; 95% CI 0.34—0.57

Oceanic-AF

Why Inferior efficacy in this trial?

Class effect

- FX/FXIIa inhibition may not work?
- Escape mechanisms circumvent FXI inhibition?
- **But:** trials of other FXI/FXIIa inhibitors, including for AF, were continued after reviews by IDMC

DOAC work really well

- Stroke and SE rate was low with apixaban **1.27% over 1 year** in ARISTOTLE
(Granger, NEJM 2011)
- Apixaban stroke rate lower than expected/planned for in Oceanic AF
 - **0.4%** in apixaban arm median f/u 155 days or **1.02 events/100 patient-yr**
(Piccini, NEJM, 2024)
 - Better care for patients with AF than a decade ago?

Oceanic-AF

Why Inferior efficacy in this trial?

Specific characteristics of asundexian or trial design

Dose

- Once daily: peak and trough effect larger than twice daily
- Suppression of FXIa activity to 94% (peak) and 92% (trough) using a non-standard assay may not be sufficient degree of suppression
 - **Dose likely not sufficient**

PK/PD

- K_i for FXIa:
 - Asundexian 1.0 nM for FXIa (Heitmeier, JTH 2022)
 - Milvexian 0.11nM for FXIa (Dilger, J Med Chem, 2022)

Summary

FXI/FXIa inhibition is a promising new anticoagulant strategy

- Evidence of substantially decreased bleeding compared with DOAC or LMWH
- Efficacy for prevention of VTE demonstrated in small numbers in phase II TKR trials → translated to VTE and stroke prevention in AF with DOAC

Data from ongoing phase III trial trials are needed to identify efficacy

- Promising that IDMC have voted to keep trials open is setting of early closure of OCEANIC-AF asundexian trial
- Milvexian in Librexia-AF phase III trial has completed enrollment

Questions

Can we shift approach used for DOAC development, where efficacy combined with ease of use were the goals (achieved) but without substantially increasing safety in some patient populations to: **can we increase safety without sacrificing efficacy?**

FXI inhibitors may not have better efficacy than DOAC

- Hope is that they have similar or not much worse efficacy
 - must better than reduced dose DOAC which has been shown to result in decreased efficacy **without** decreased bleeding
 - How much lower efficacy will we tolerate?

Questions

LIBREXIA AF statistical considerations are stringent

primary efficacy endpoint: composite of stroke/SE with milvexian is non-inferior to apixaban

- Non-inferiority margin: 1.37
 - Caravaggio trial (apixaban vs dalteparin in cancer VTE) non-inferiority margin 2.00
- HR = 1.00 for milvexian compared to apixaban for stroke prevention

Principle safety endpoints: milvexian needs to be superior to apixaban for reducing the risk of major bleeding and composite of major and CRNM bleeding

Take home message

Net clinical benefit assessment will be critical for patient decision making, with likely larger reductions in bleeding but potentially smaller but hopefully not much lower differences in efficacy. (MOC statement)

If we can safely anticoagulate more people—even if with slightly lower efficacy—we may do more good overall than continuing to accept underuse of DOAC that patients or providers are afraid to use.

Post presentation question

Use of FXI/FXIa inhibitors to prevent thrombosis:

- a. Is being studied in advanced stage clinical development
- b. Has shown to result in dose dependent efficacy for all drugs studied in phase II clinical trials compared to enoxaparin for preventing VTE post knee replacement
- c. Have resulted lower rate of bleeding in a clinical trial for patients with AF compared to rivaroxaban
- d. Has been studied using drugs with different mechanisms of action
- a. All of the above

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