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# Factor XI in arterial thrombosis

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## My Conflicts of Interest:

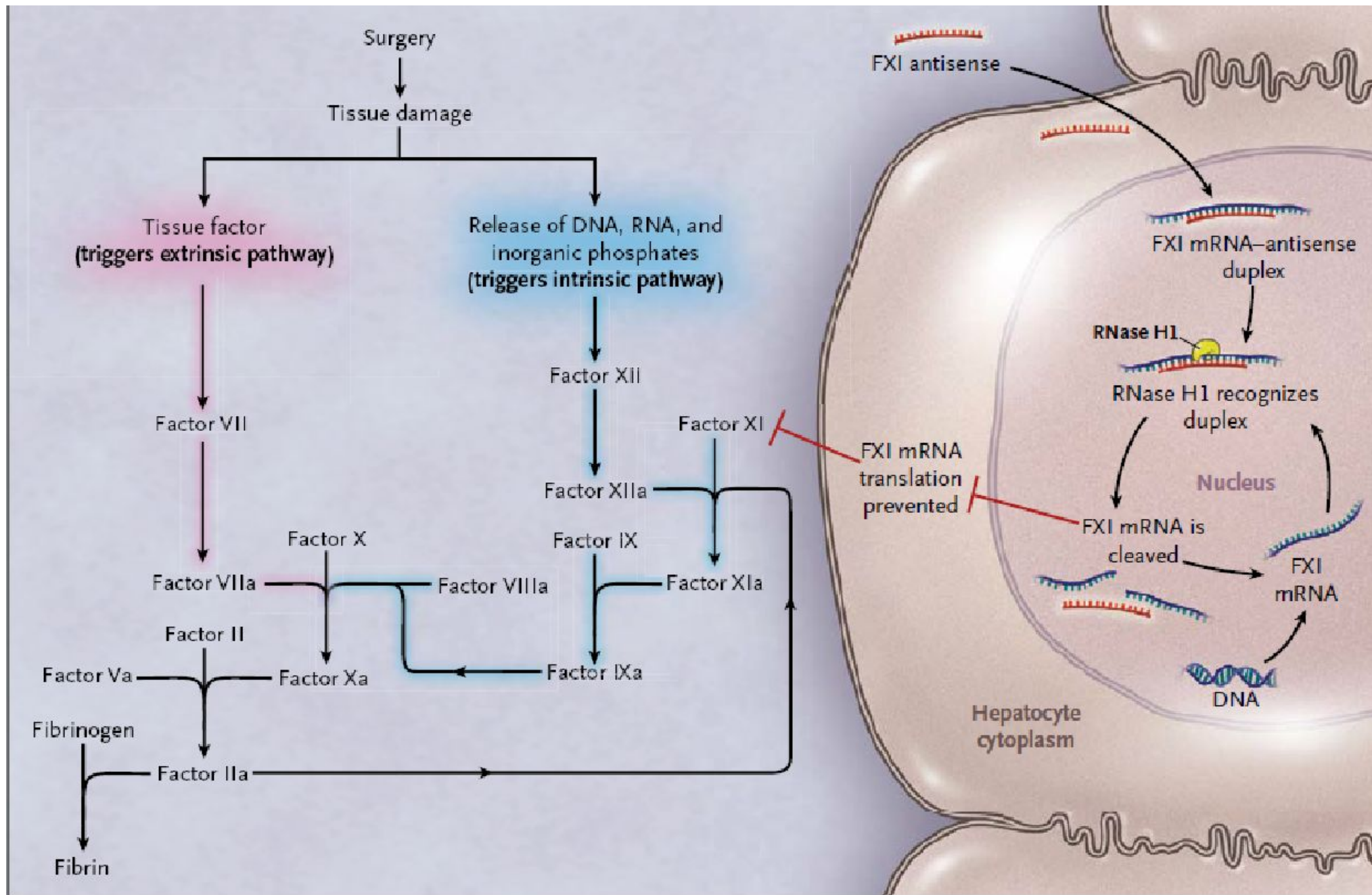
- Research grant from the Italian Medicines Agency (AIFA) for studies on acetylsalicylic acid in Essential Thrombocythemia
- Research grant from Cancer UK for studies on acetylsalicylic acid in cancer
- Investigator-initiated research grant from Bayer AG for rivaroxaban in diabetes
- Consulting fee from Aboca SRL for substance-based medical devices

# Challenge or Chimera?

**Effective inhibition** of thrombus formation  
on **pathological vascular lesions**

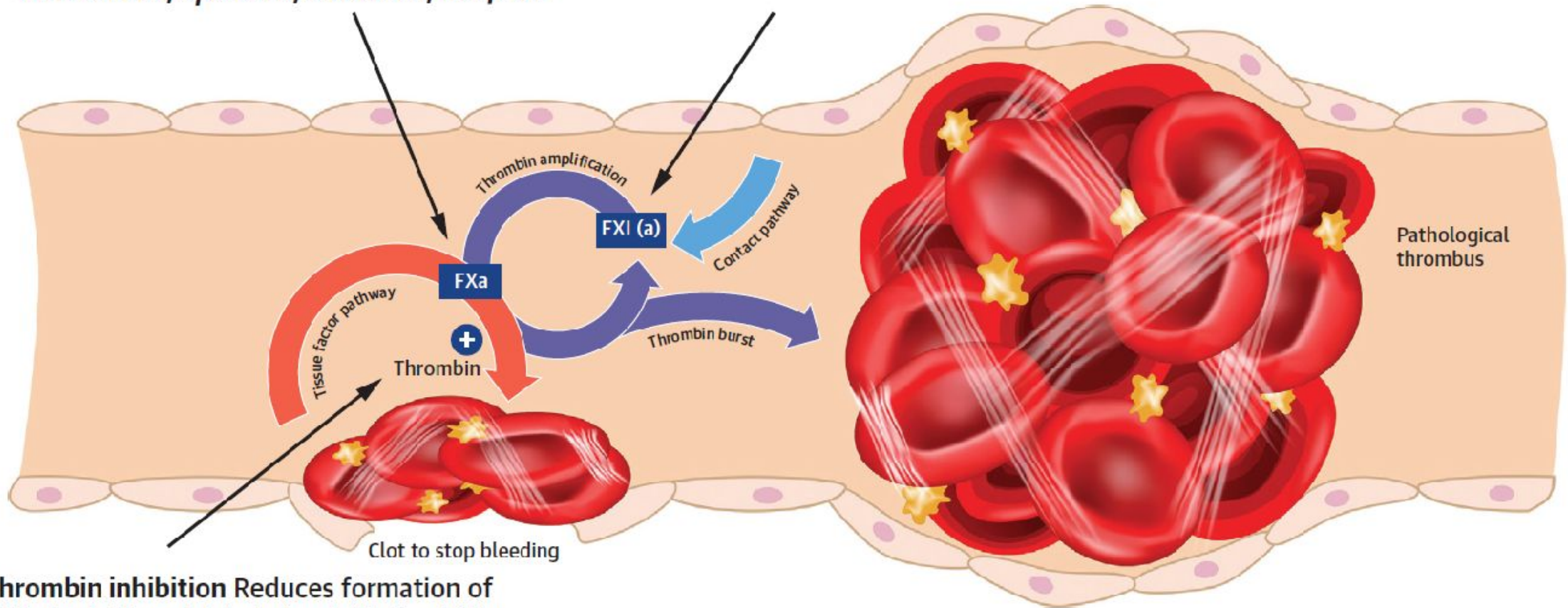
**No effect** on physiological haemostasis (i.e. no bleeding)





**Factor Xa inhibition:** Reduces formation of pathologic thrombi, but also inhibits ability to form clots and stop bleeding  
*rivaroxaban, apixaban, edoxaban, warfarin*

**Factor XI inhibition:** Reduces formation of pathologic thrombi, with hypothesized preserved clotting in response to bleeding  
*novel FXI/XIa inhibitors*



**Thrombin inhibition** Reduces formation of pathologic thrombi, but also inhibits ability to form clots and stop bleeding  
*dabigatran, warfarin*

# Factor XI deficiency: a rare bleeding disorder

**Table 2** Number of patients included in the European Network of Rare Bleeding Disorders database by diagnosis

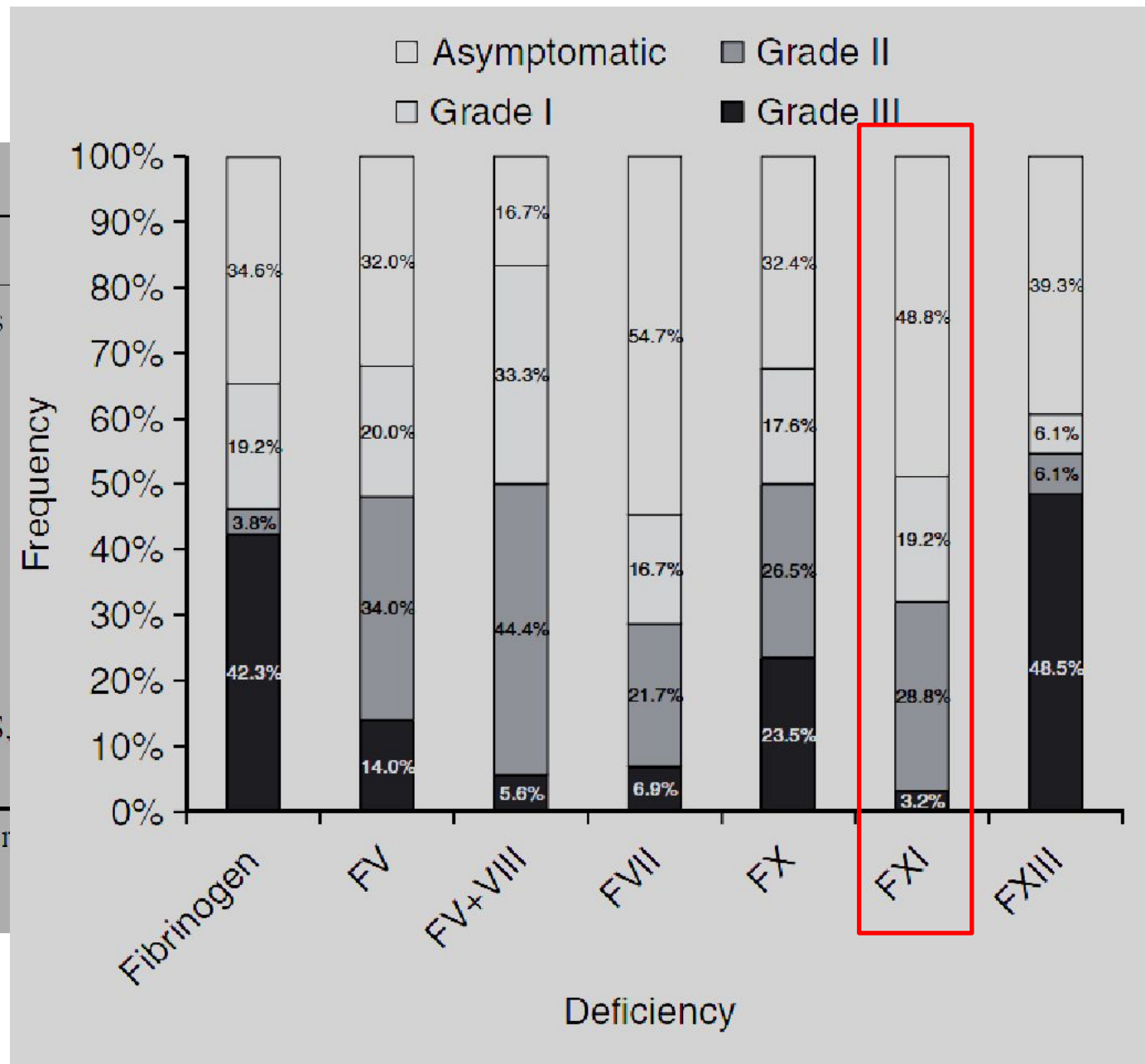
Type of deficiency	<i>n</i> (%)
FVII	224 (38)
FXI	133 (22)
FV	60 (10)
Fibrinogen	46 (8)
FX	45 (8)
FXIII	42 (7)
Combined FV + VIII	20 (3)
FII	6 (1)
FXII	6 (1)
Other combined	10 (2)

# Factor XI deficiency: phenotypic bleeding characteristics

**Table 1** Assigned categories of clinical bleeding severity

Clinical bleeding severity	Definition
Asymptomatic	No documented bleeding episodes
Grade I bleeding	Bleeding that occurred after trauma or drug ingestion (antiplatelet or anticoagulant therapy)
Grade II bleeding	<i>Spontaneous minor bleeding:</i> bruising, ecchymosis, minor wounds, oral cavity bleeding, epistaxis and menorrhagia
Grade III bleeding	<i>Spontaneous major bleeding:</i> hematomas*, hemarthrosis, CNS, GI and umbilical cord bleeding

CNS, central nervous system; GI, gastrointestinal. \*Intramuscular requiring hospitalization.

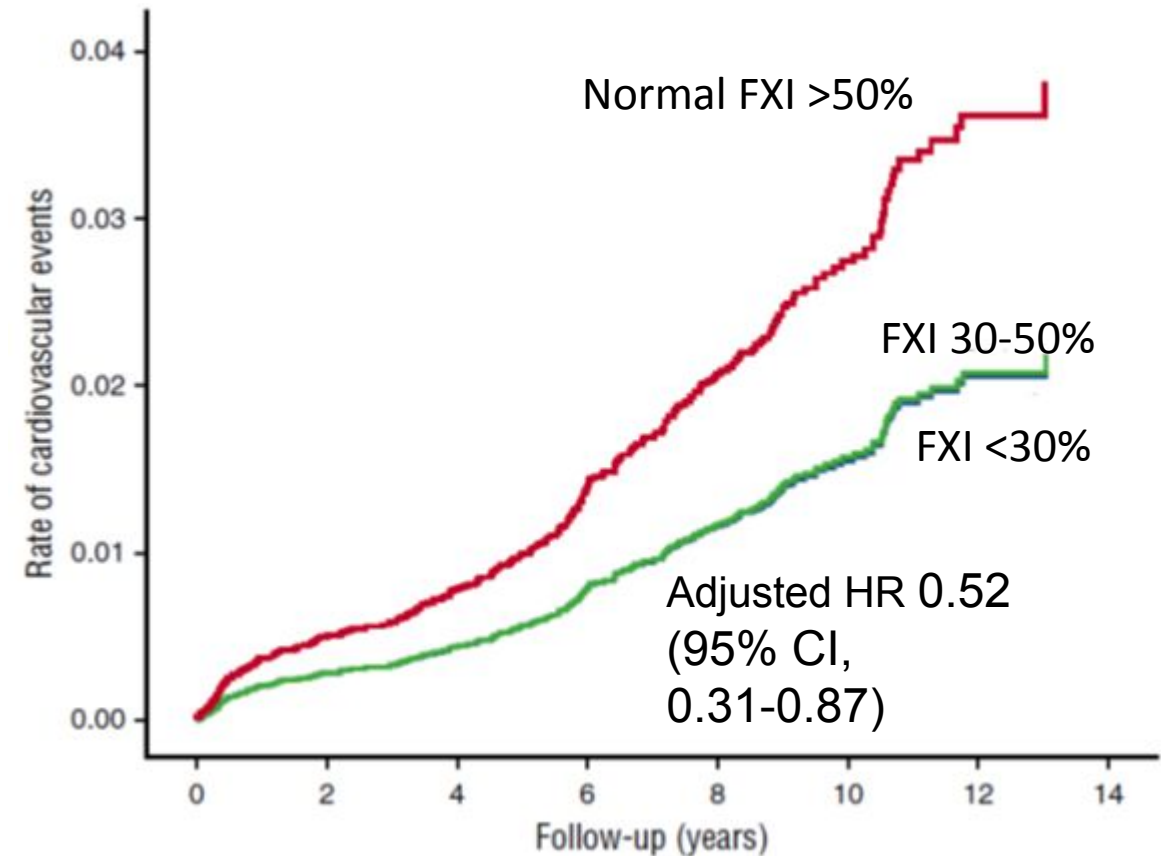
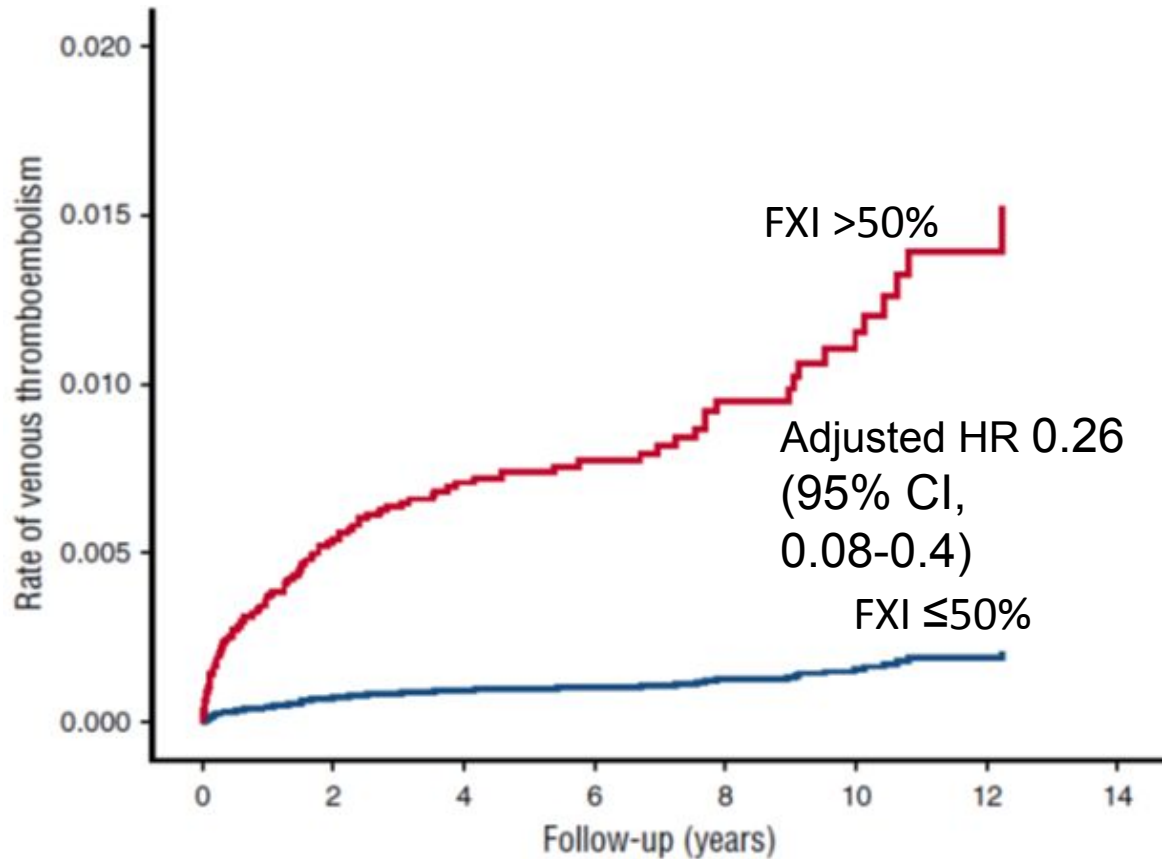


# Factor XI deficiency: a weak relationship between factor's activity and bleeding severity

**Table 3** Linear regression analysis of coagulation factor activity and clinical bleeding severity\*

Factor deficiency	Beta (95% CI)	Factor activity for asymptomatic patients (95% CI)	Factor activity for Grade I bleeding (95% CI)	Factor activity for Grade II bleeding (95% CI)	Factor activity for Grade III bleeding (95% CI)
Fibrinogen, mg dL <sup>-1</sup> (n = 26)	-40.22 (-54.24 to -26.19)	113.40 (22.80–204.01)	73.19 (0–164.14)	32.97 (0–126.39)	0 (0–90.61)
FV, U dL <sup>-1</sup> (n = 50)	-5.96 (-10.74 to -1.19)	11.94 (0–33.73)	5.98 (0–27.71)	0.01 (0–22.72)	0 (0–18.63)
FV + VIII, U dL <sup>-1</sup> (n = 18)	-9.52 (-15.07 to -3.96)	43.38 (24.90–61.86)	33.87 (15.71–52.02)	24.35 (4.87–43.82)	14.83 (0–36.98)
FVII, U dL <sup>-1</sup> (n = 203)	-5.74 (-8.33 to -3.15)	24.87 (14.88–34.86)	19.13 (8.48–29.78)	13.39 (1.54–25.25)	7.66 (0–21.11)
FX, U dL <sup>-1</sup> (n = 34)	-15.45 (-21.62 to -9.28)	55.91 (28.69–83.12)	40.45 (13.99–66.91)	25.00 (0–52.12)	9.55 (0–38.66)
FXI, U dL <sup>-1</sup> (n = 125)	-0.35 (-4.02 to 3.32)	26.05 (13.56–38.54)	25.70 (12.97–38.43)	25.35 (11.38–39.32)	25.00 (9.03–40.97)
FXIII, U dL <sup>-1</sup> (n = 33)	-14.22 (-18.18 to -10.26)	31.07 (10.83–51.31)	16.85 (0–37.13)	2.63 (0–23.71)	0 (0–10.97)

# Venous thromboembolism and cardiovascular events are reduced in a cohort of 10,193 individuals tested for levels of FXI activity



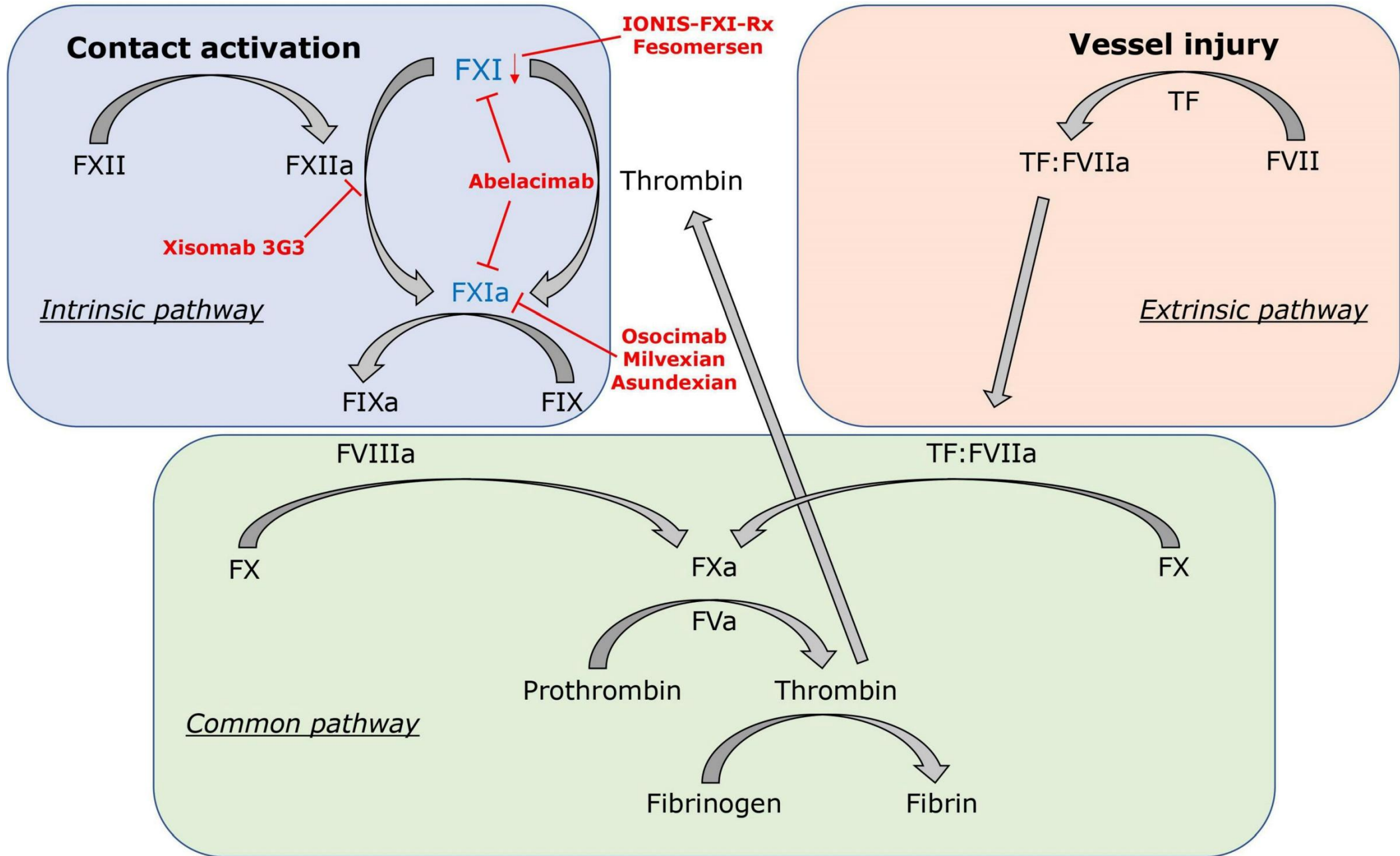
# Cardiovascular events and venous thromboembolism weak dose-dependance with Factor XI activity in 10,193 individuals

Table 2. Adjusted HRs for the association of factor XI activity with VTE and cardiovascular events (n=10 193)

Study outcome	Factor XI activity	Number	Events	Age-adjusted model HR (95% CI)	Fully adjusted model HR (95% CI)
Cardiovascular event	≤30%	542	19	0.56 (0.35-0.91)	0.57 (0.35-0.93)
	30%-50%	693	16	0.57 (0.34-0.95)	0.52 (0.31-0.87)
	>50%	8958	230	Reference	Reference
VTE	≤50%	1235	3	0.14 (0.04-0.44)	0.26 (0.08-0.84)
	>50%	8958	94	Reference	Reference

Patients with factor XI deficiency (<50% activity) had **more prior gastrointestinal bleeding** compared with patients with normal factor XI activity, **2.9% and 0.6%**, respectively (P <0.001)

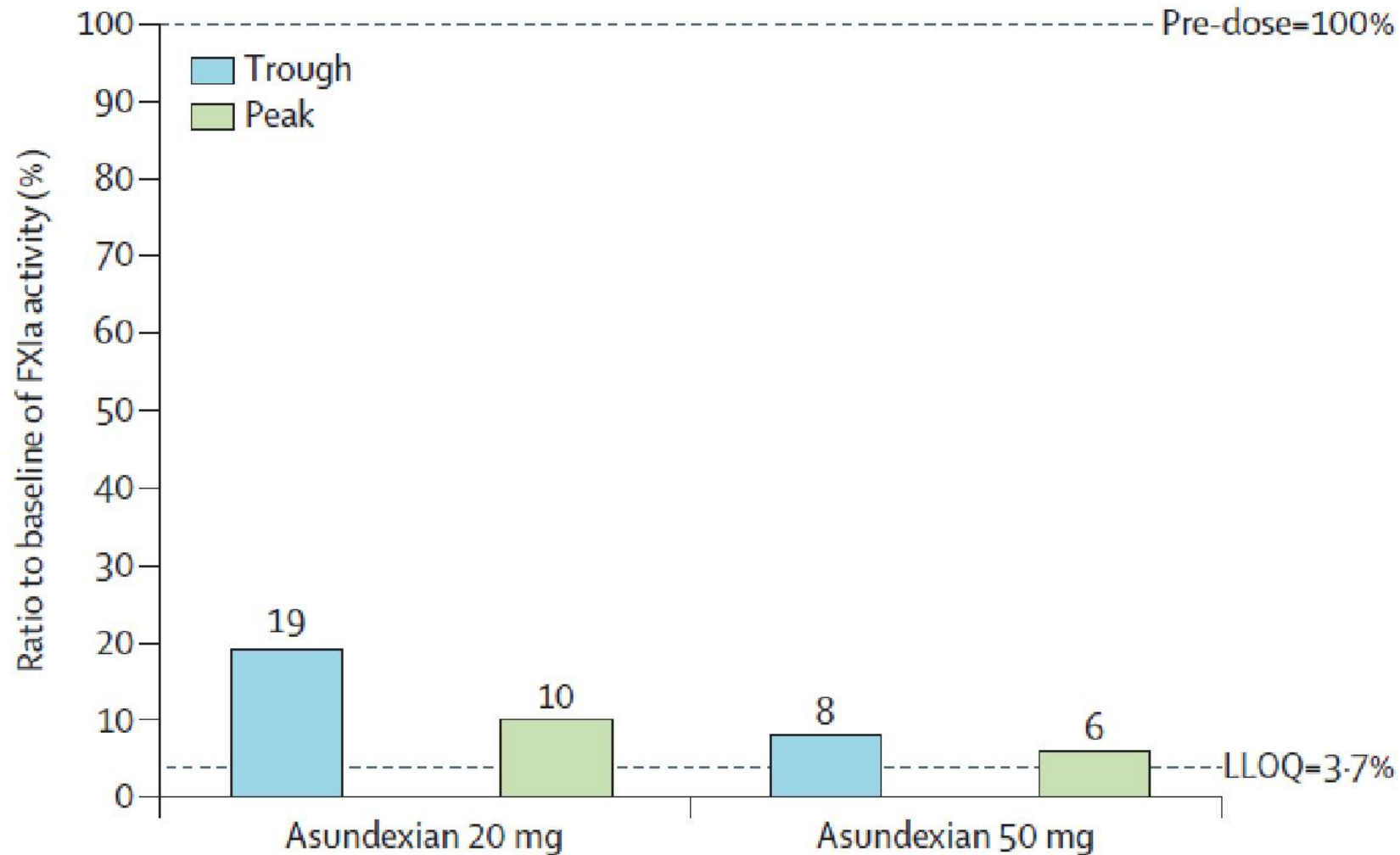
Prior history of intracerebral hemorrhage was observed in 3.3% of patients with factor XI deficiency (<50% activity) compared with 3.1% in patients with normal factor XI activity (P 0.689).



## Asundexian (small FXIa inhibitor) in AF a dose-finding, phase II trial

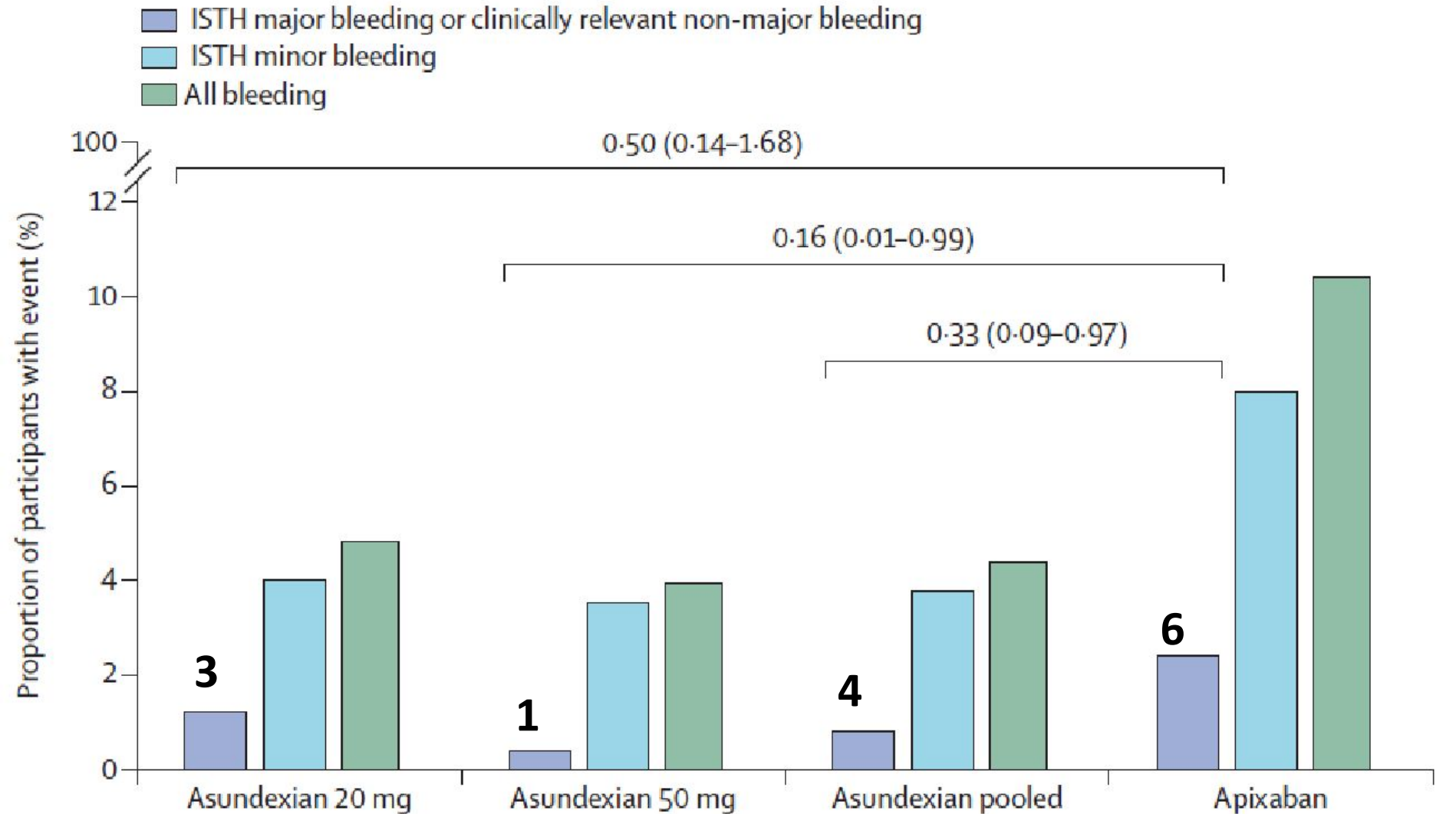
- Inclusion criteria: CHA2DS2-VASc score of 2+ if male or 3+ if female with an indication oral anticoagulant, age 45+ years and at least one bleeding risk feature
- Randomization 1:1:1 asundexian 25 or 50 mg od or apixaban for 12 weeks
- Primary outcome: composite of major and clinically relevant bleeding (ISTH definition); no primary or secondary thrombotic endpoints were formally analyzed
- Statistical hypothesis: assumed 4% events in the apixaban group over 12 weeks, and a relative risk reduction with asundexian (all doses) of 50% vs. apixaban. Approx 250 patients/group

# Asundexian in AF dose-dependent effect on FXIa activity



# Asundexian in AF primary safety endpoint

**Major bleed= 0**  
**CRNM= 10**  
**All bleed= 48**



## Asundexian in AF: CV events

	Asundexian 20 mg (n=251)	Asundexian 50 mg (n=254)	Apixaban (n=250)	Total (n=755)
Cardiovascular death, myocardial infarction, ischaemic stroke, or systemic embolism	2	4	3	9
Cardiovascular death	1	3	3	7
Myocardial infarction	0	1	0	1
Ischaemic stroke	2	1	0	3
Systemic embolism	0	0	0	0
All-cause mortality	2	4	4	10

Data are numbers of participants.

**Table 2:** Exploratory thrombotic endpoints

# Asundexian in stroke in a dose-finding, phase II trial: primary efficacy and safety endpoints

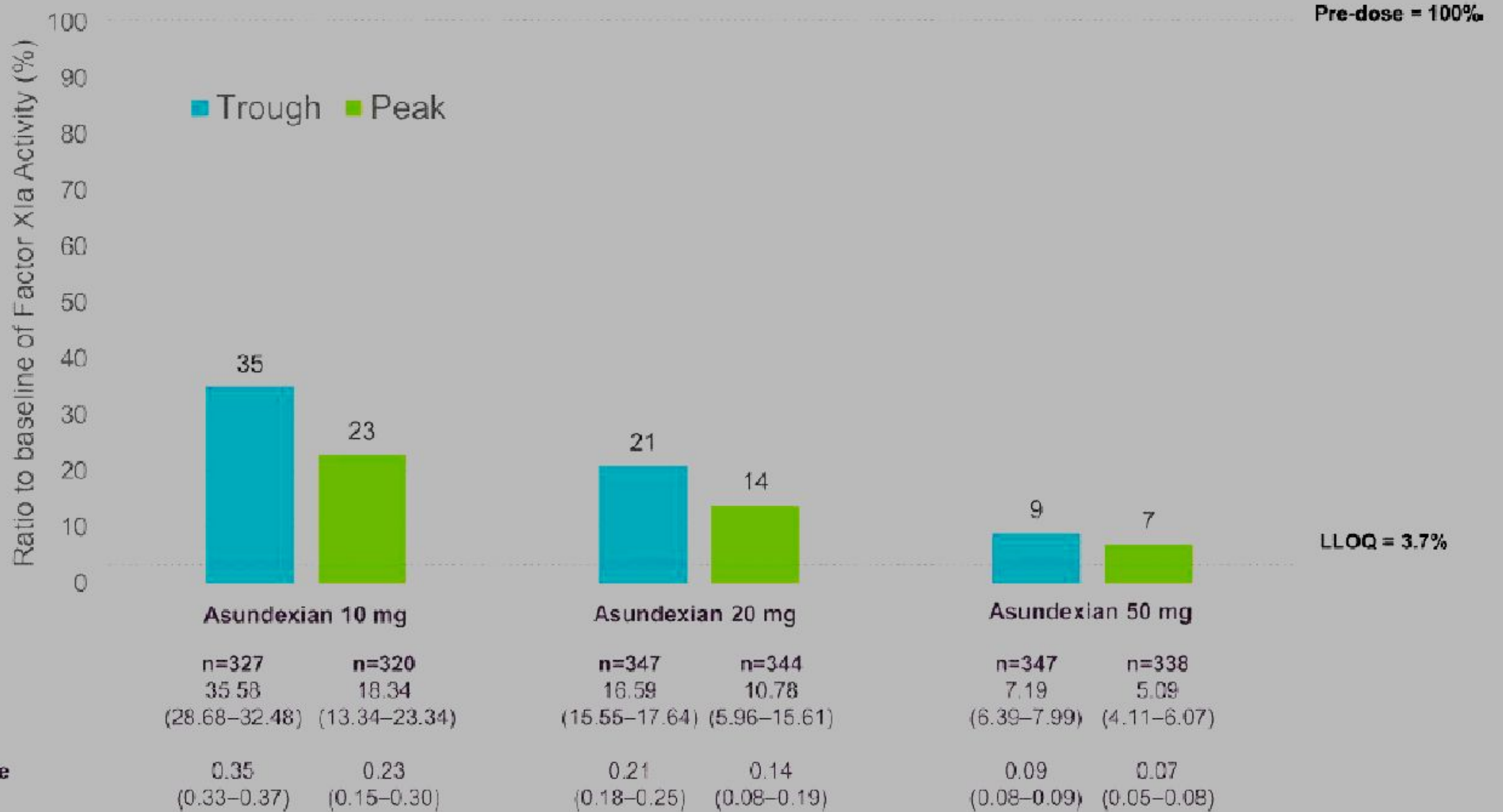
	Placebo (n=456)	Asundexian 10 mg group (n=455)	Asundexian 10 mg vs placebo	Asundexian 20 mg group (n=450)	Asundexian 20 mg vs placebo	Asundexian 50 mg group (n=447)	Asundexian 50 mg vs placebo
<b>Primary outcome</b>							
Ischaemic stroke or covert infarcts*	87 (19%)	86 (19%)	0.99 (0.79-1.24)	99 (22%)	1.15 (0.93-1.43)	90 (20%)	1.06 (0.85-1.32)

	Placebo group (n=452)	Asundexian 10 mg group (n=445)	Asundexian 10 mg vs placebo	Asundexian 20 mg group (n=446)	Asundexian 20 mg vs placebo	Asundexian 50 mg group (n=443)	Asundexian 50 mg vs placebo	Asundexian all doses (n=1334)	Asundexian all doses vs placebo
<b>Primary safety outcome*</b>									
ISTH-defined major and clinically relevant non-major bleeding	11 (2%)	19 (4%)	1.71 (0.91-3.18)	14 (3%)	1.27 (0.66-2.47)	19 (4%)	1.74 (0.93-3.24)	52 (4%)	1.57 (0.91-2.71)

# Asundexian in acute MI in a dose-finding, phase II trial

- 1601 patients randomized to asundexian 10, 20, or 50 mg or placebo od for 6 to 12 months within 5 days of their qualifying MI, on DAPT (aspirin plus a P2Y12 inhibitor). Approx 400 patients/group
- The trial designed for safety without any formal hypothesis testing, as specified in the protocol. The main safety outcome was BARC type 2, 3, or 5 bleeding comparing all pooled asundexian doses with placebo.
- The prespecified efficacy outcome was a composite of cardiovascular death, MI, stroke, or stent thrombosis comparing pooled asundexian 20 and 50 mg doses with placebo.

# Asundexian in acute MI: effect on FXIa activity



## Asundexian in acute MI: effect on BARC 2-5 bleeding and thromboses

	Asundexian 10 mg (n=395)	Asundexian 20 mg (n=397)	Asundexian 50 mg (n=402)	Asundexian total (n=1194)	Placebo (n=399)	Total (n=1593)
Safety outcomes						
BARC bleeding, type 2, 3, or 5	30 (7.59)	32 (8.06)	42 (10.45)	104 (8.71)	36 (9.02)	140 (8.79)
Type 2	27 (6.84)	29 (7.30)	39 (9.70)	95 (7.96)	31 (7.77)	126 (7.91)
Type 3	5 (1.27)	3 (0.76)	3 (0.75)	11 (0.92)	5 (1.25)	16 (1.00)
Type 5	0	0	0	0	0	0
All bleeding	70 (17.72)	75 (18.89)	82 (20.40)	227 (19.01)	85 (21.30)	312 (19.59)
	Asundexian 10 mg (n=397)	Asundexian 20 mg (n=401)	Asundexian 50 mg (n=402)	Asundexian 20 mg + 50 mg (n=803)	Placebo (n=401)	Total (n=1601)
Efficacy outcomes						
Cardiovascular death, MI, stroke, or stent thrombosis	27 (6.80)	24 (5.99)	22 (5.47)	46 (5.73)	22 (5.49)	95 (5.93)

## Asundexian in MI conclusions of the Authors

**CONCLUSIONS:** In patients with recent acute MI, 3 doses of asundexian, when added to aspirin plus a P2Y12 inhibitor, resulted in dose-dependent, near-complete inhibition of FXIa activity without a significant increase in bleeding and a low rate of ischemic events. These data support the investigation of asundexian at a dose of 50 mg daily in an adequately powered clinical trial of patients who experienced acute MI.

<b>Drug</b>	<b>Type</b>	<b>Mechanism</b>	<b>Administration route</b>	<b>Studies (NCT)</b>	<b>Population (N)</b>	<b>Comparator</b>	<b>Status</b>
IONIS-FXI <sub>Rx</sub>	Antisense oligonucleotide of FXI	Inhibits FXI messenger RNA	Subcutaneous (weekly)	NCT01713361	TKA (300)	Enoxaparin	Published
				NCT02553889	ESKD (49)	Placebo	Published
				NCT03358030	ESKD (200)	Placebo	Completed
Osocimab	Monoclonal antibody to FXIa	Binds and inhibits FXIa	Intravenous, subcutaneous (monthly)	NCT03276143	TKA (813)	Enoxaparin/Apixaban	Published
				NCT04523220	ESKD (686)	Placebo	Ongoing
Abelacimab	Monoclonal antibody to FXI/FXIa	Binds and inhibits FXI and FXIa	Subcutaneous (monthly)	EudraCT 2019-003756-37	TKA (412)	Enoxaparin	Published
				NCT04755283	AF (1,200)	Rivaroxaban	Ongoing
				NCT05171049	CAT (1,655)	Apixaban	Ongoing
				NCT05171075	CAT (1,020)	Dalteparin	Ongoing
Milvexian	Small molecule inhibitor of FXIa	Binds and inhibits FXIa	Oral (daily)	NCT03891524	TKA (1,242)	Enoxaparin	Published
				NCT03766581	Stroke (2,366)	Placebo	Ongoing
Xisomab 3G3	Monoclonal antibody to FXI	Binds FXI and blocks activation by FXIIa	Intravenous (single dose)	NCT03612856	ESKD (24)	Placebo	Published
				NCT04465760	CRT (50)	None	Ongoing
Fesomersen	Antisense oligonucleotide of FXI	Inhibits FXI messenger RNA	Subcutaneous (weekly)	NCT04534114	ESKD (305)	Placebo	Ongoing
Asundexian	Small molecule inhibitor of FXIa	Binds and inhibits FXIa	Oral (daily)	NCT04218266	AF (753)	Apixaban	Published
				NCT04304534	AMI (1,592)	Placebo	Completed
				NCT04304508	Stroke (1,790)	Placebo	Ongoing

*AF, atrial fibrillation; CAT, cancer-associated thrombosis; CRT, catheter-related thrombosis in cancer patients; ESKD, end-stage kidney disease; TKA, total knee arthroplasty.*

# Conclusions

Congenital factor XI deficiency is described as a bleeding disorder milder than other congenital defects, and with a reduced, mostly venous, thrombosis tendency.

Congenital FXI deficiency do not show a clear relationship between FXI levels and bleeding intensity, but  $<20\%$  FXI activity seems associated with spontaneous bleeding

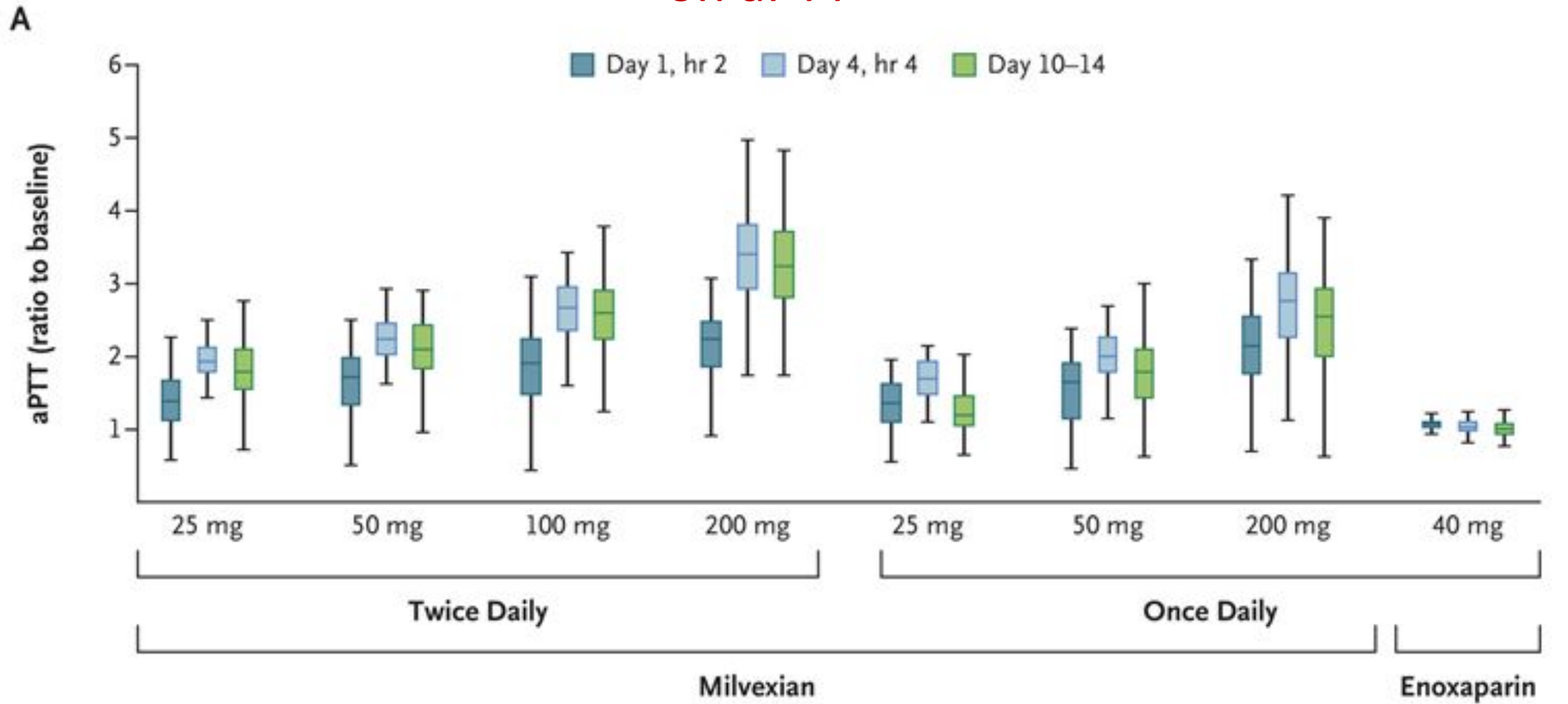
Several pharmacological strategies have been developed to block FXI or FXIa, on the assumption to increase bleeding-free thrombosis protection.

Dose finding, phase II trials in different settings have inconsistently shown a dose-dependency with coagulation biomarkers (aPTT or FXI activity) and with bleeding. Events are too low (and largely minor) to prove any hypothesis

Only phase III trials in different conditions (TKA, CKD, AF, MI, non-cardioembolic stroke) with FXI(a) blockade alone or as add-on (atherothrombosis) will finally prove the hypothesis of a bleeding-free antithrombotic strategy



# Milvexian in total knee arthroplasty: dose-dependent effect on aPTT

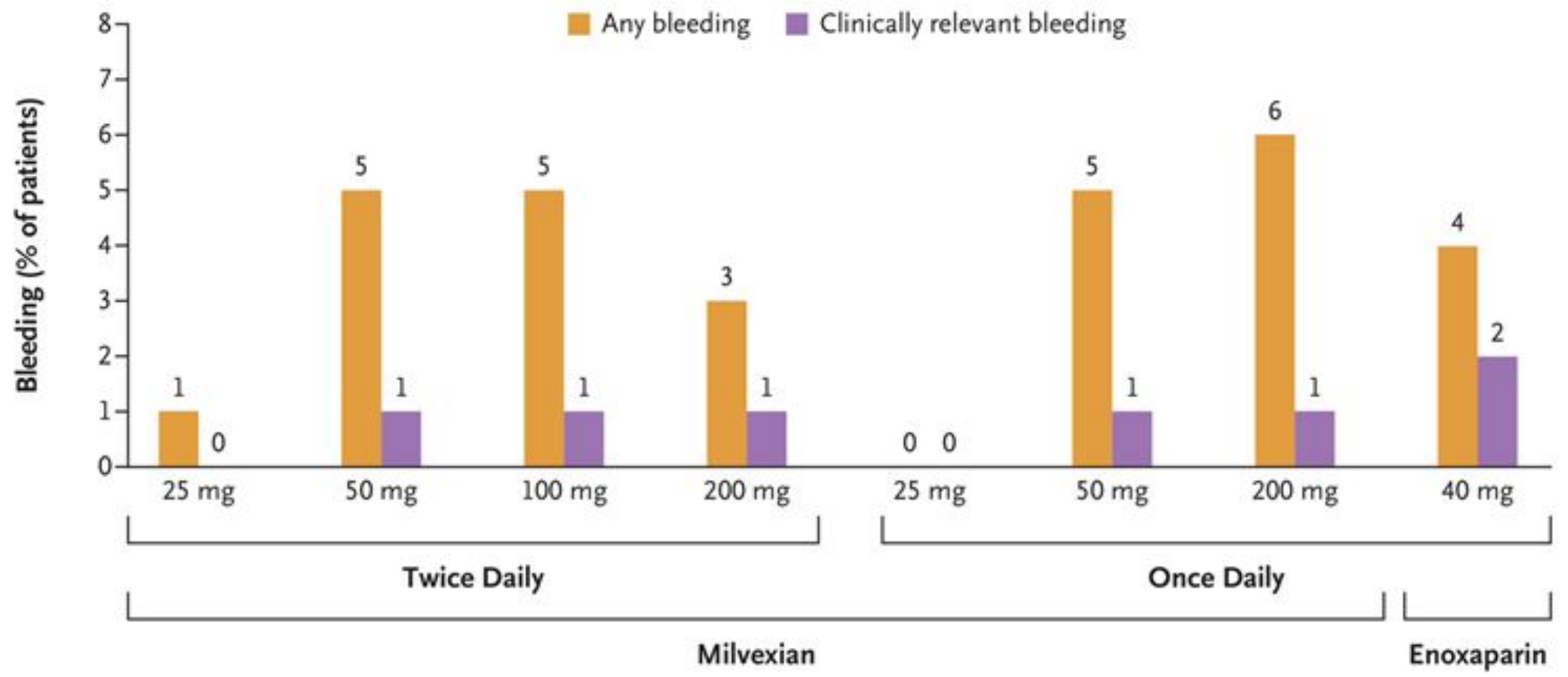


## Milvexian in total knee arthroplasty: phase II dose finding vs. enoxaparin

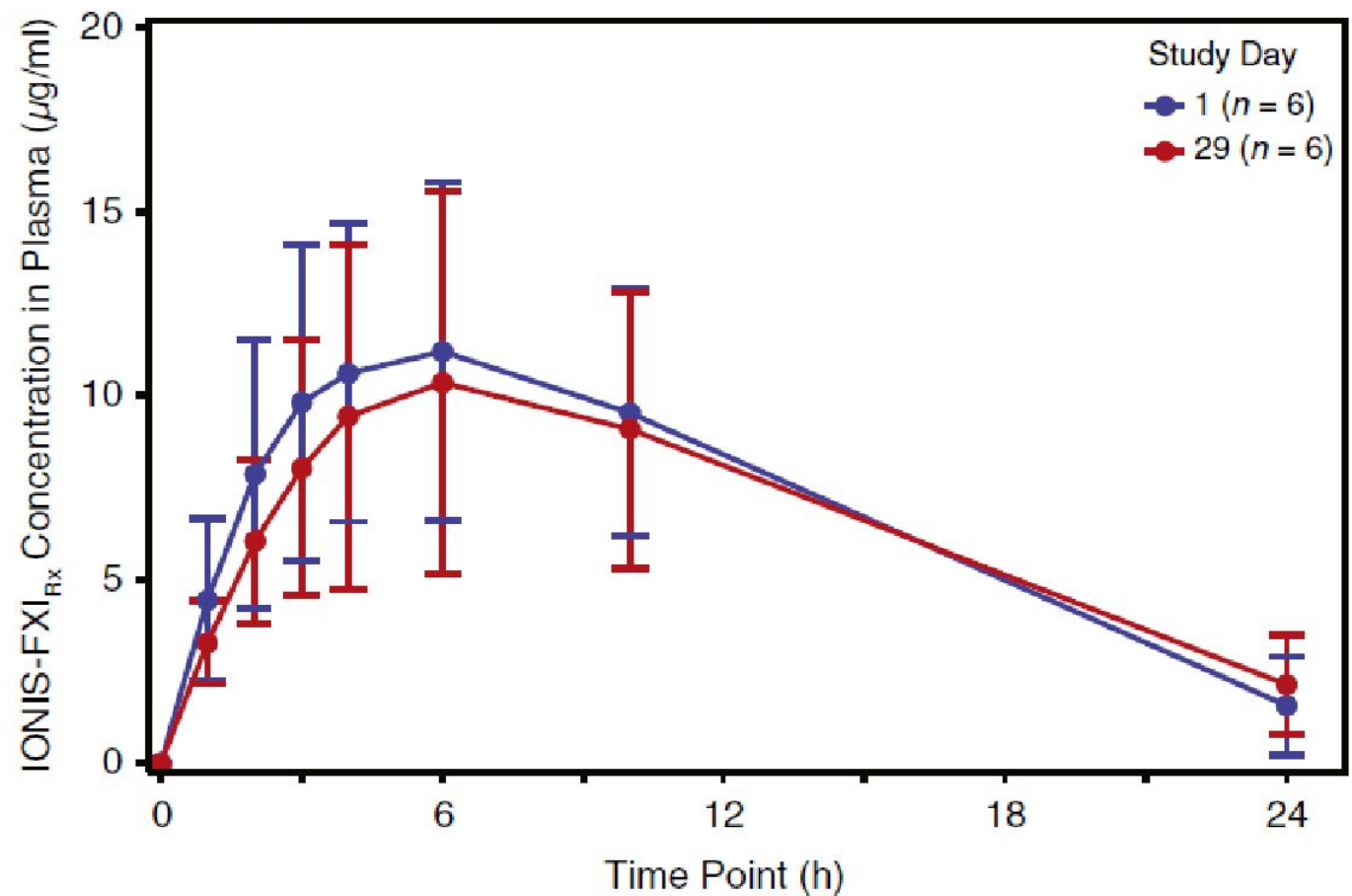
**Table 2. Efficacy Outcomes.\***

Outcome	Milvexian Twice Daily				Milvexian Once Daily			Enoxaparin (N = 252)
	25 mg (N = 129)	50 mg (N = 124)	100 mg (N = 134)	200 mg (N = 131)	25 mg (N = 28)	50 mg (N = 127)	200 mg (N = 123)	
<b>Primary efficacy outcome: venous thromboembolism†</b>								
Any event — no. (%)	27 (21)	14 (11)	12 (9)	10 (8)	7 (25)	30 (24)	8 (7)	54 (21)
Relative risk vs. enoxaparin (95% CI)	0.97 (0.65–1.45)	0.53 (0.31–0.90)	0.42 (0.23–0.76)	0.37 (0.19–0.69)	1.00 (0.51–1.97)	1.15 (0.78–1.70)	0.30 (0.15–0.62)	—
<b>Components of the primary efficacy outcome — no.‡</b>								
Death from any cause	0	0	0	0	0	0	0	1
Nonfatal pulmonary embolism	0	1	1	0	0	0	0	1
Symptomatic distal deep-vein thrombosis	0	0	1	0	0	2	0	0
Asymptomatic proximal deep-vein thrombosis	1	0	1	0	0	2	0	2
Asymptomatic distal deep-vein thrombosis	26	13	9	10	7	26	8	50

**B**



# Ionis (ASO) concentrations in ESKD patients after and before dialysis (phase II trial)



# Outcome in 49 patients with ESKD on dialysis with FXI-ASO or placebo for 12 weeks

**Table 2.** Bleeding events (safety population)

Outcome	PK cohort IONIS-FXI <sub>Rx</sub> 300 mg ( <i>n</i> = 6)	Randomized cohorts		
		Pooled placebo ( <i>n</i> = 13)	IONIS-FXI <sub>Rx</sub> 200 mg ( <i>n</i> = 15)	IONIS-FXI <sub>Rx</sub> 300 mg ( <i>n</i> = 15)
Major bleeding, <i>n</i> (%)	1 (16.7)	1 (7.7)	0 (0.0)	1 (6.7)
[95% CI] <sup>a</sup>	[0.4%–64.1%]	[0.2%,–6.0%]	[0.0%–21.8%]	[0.2%–31.9%]
Minor bleeding, <i>n</i> (%)	0 (0.0)	1 (7.7)	1 (6.7)	6 (40.0)
[95% CI] <sup>a</sup>	[0.0%–45.9%]	[0.2%–36.0%]	[0.2%–31.9%]	[16.3%–67.7%]
Any bleeding, <i>n</i> (%)	1 (16.7)	2 (15.4)	1 (6.7)	7 (46.7)
[95% CI] <sup>a</sup>	[0.4%–64.1%]	[1.9%–45.4%]	[0.2%–31.9%]	[21.3%–73.4%]

PK, pharmacokinetics.  
<sup>a</sup>Exact binomial 95% CI.

# Safety and efficacy outcome in 300 patients undergoing total knee arthroplasty randomized to FXI-ASO vs. enoxaparin: phase II, dose finding trial

Outcome	FXI-ASO, 200 mg (N=144)	FXI-ASO, 300 mg (N=77)	Enoxaparin, 40 mg (N=72)
<b>Safety§</b>			
Principal safety outcome: major or clinically relevant nonmajor bleeding — no. (% [95% CI])	4 (3 [1 to 7])	2 (3 [<1 to 9])	6 (8 [3 to 17])
<b>Efficacy</b>			
Primary efficacy outcome: total venous thromboembolism — no. (% [95% CI])†	36 (27 [20 to 35])	3 (4 [1 to 12])	21 (30 [20 to 43])

FXI-ASO administered @ days 1, 3, and 5, 8, 15, 22, 29, then 6 hours postoperatively.

Day 36: surgery

Repeated on day 39