Nouveaux Anticoagulants : Quelles nouveautés en 2023 ?

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Innovations Thérapeutiques en Hémostase (IThEM)

INSERM_1140

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Liens d’intérêt

- Bayer
- Bristol-Myers squibb/Pfizer
- LEO-Pharma
- Viatris
- Sanofi
- LFB
- Stago
- Werfen

Nouveaux anticogulants : NACO encore ?

RECOMMENDATIONS AND GUIDELINES

Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH

G. D. BARNES,* W. AGENO,† J. ANSELL‡ and S. KAATZ,§ FOR THE SUBCOMMITTEE ON THE CONTROL OF ANTICOAGULATION

**Frankel Cardiovascular Center and Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA; †Division of Internal Medicine, University of Insubria, Varese, Italy; ‡Department of Internal Medicine, Lenox Hill Hospital, New York, NY; and §Hurley Medical Center, Michigan State University, Flint, MI, USA*

Recommendation statements for consensus around oral anticoagulation nomenclature and harm with NOAC

1 We suggest that consensus be reached on a single term to be used for describing the direct oral FIIa and FXa inhibitors.

2 We recommend that a single term be used consistently for all oral direct anticoagulants that have inherently different mechanisms and clinical properties from those of vitamin K antagonists.

3 We suggest that the abbreviation NOAC should not be used to describe any class of oral anticoagulant.

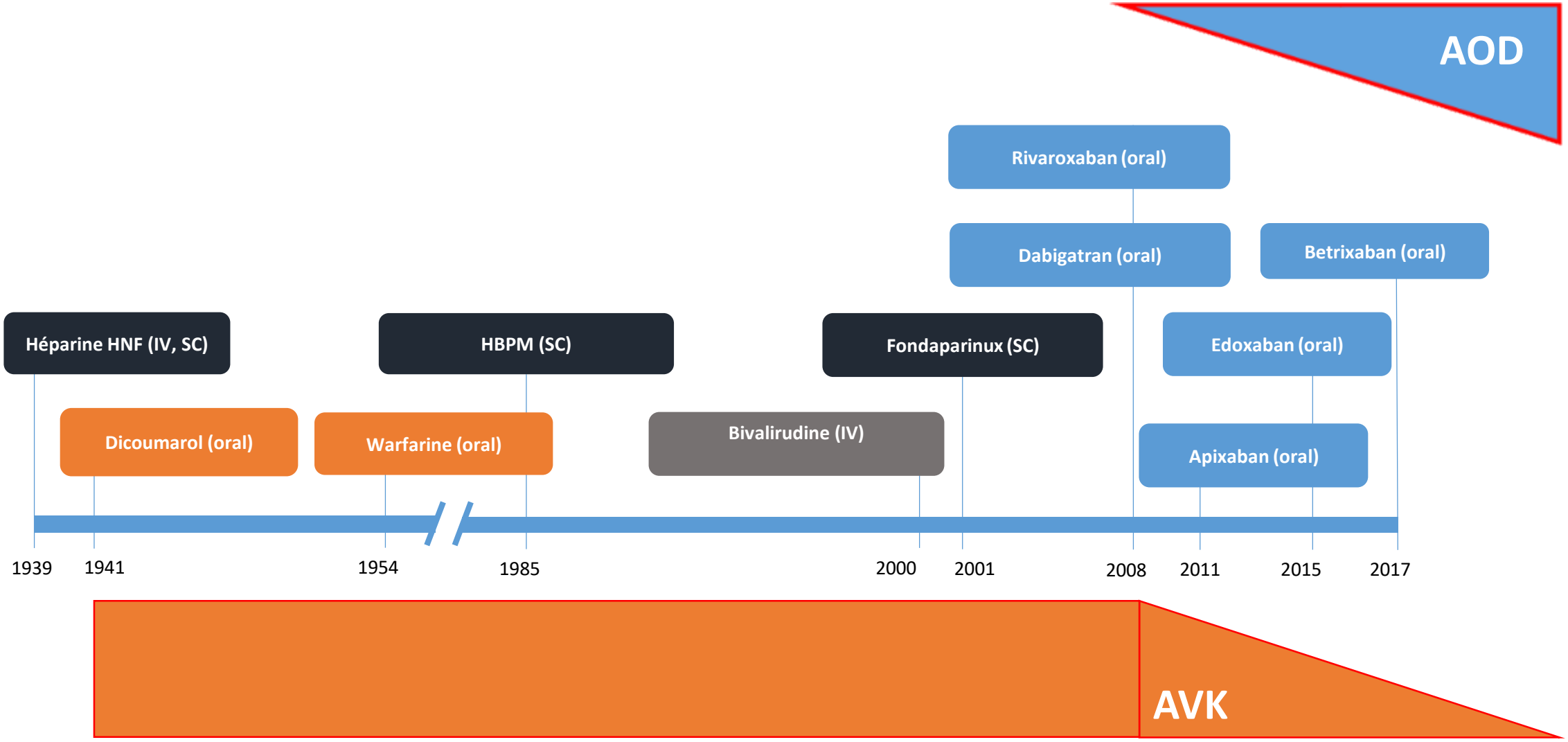
Recommendation statement for the use of DOAC

1 We suggest using the term 'direct oral anticoagulant' (DOAC) to reference the class of oral anticoagulants that directly inhibit a single target and have similar clinical properties (e.g. dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban).

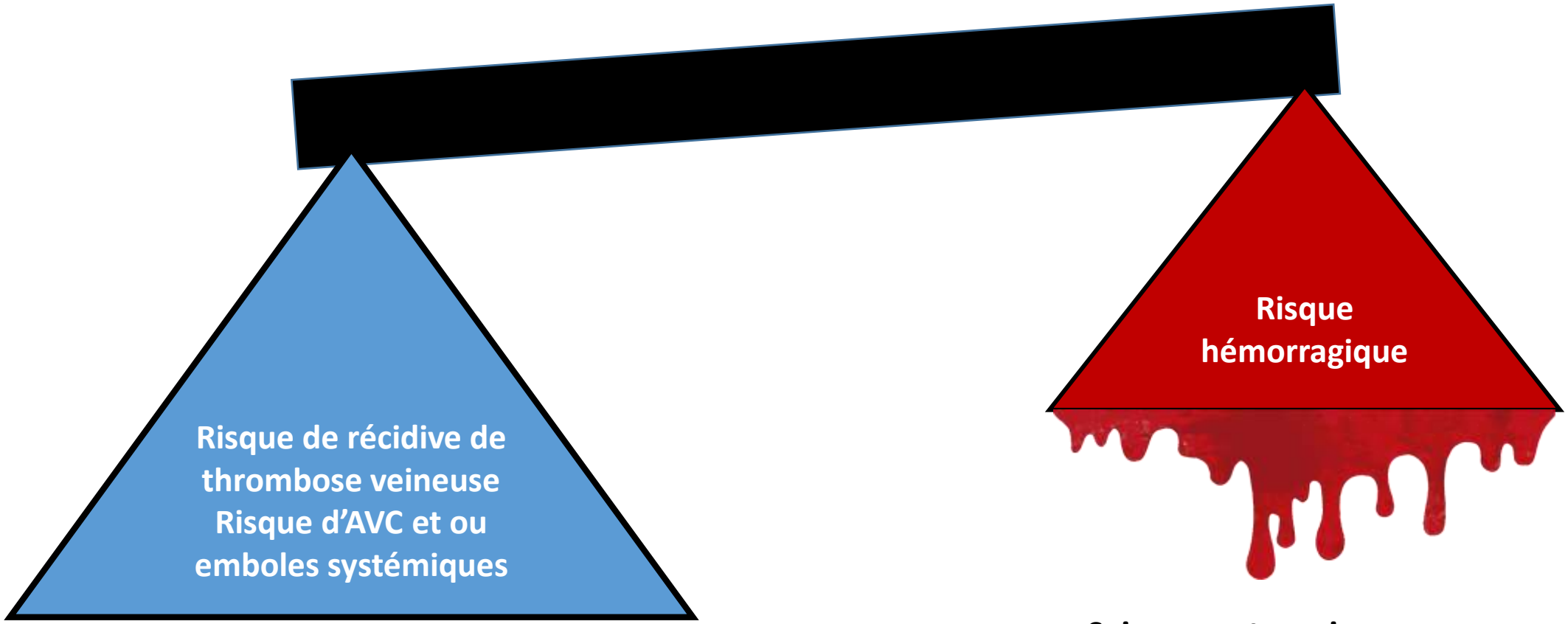
2 We suggest that a drug's specific mechanism of action (e.g. direct FXa inhibitor or direct thrombin inhibitor) should be used when it is clinically important to distinguish between the various DOAC medications.

Barnes GD et al. JTH 2015

Evolution de l'arsenal thérapeutique des anticoagulants



Pourquoi de nouveaux anticoagulants ?



Saignements majeurs :
2-4%/ an pour AOD < AVK
Mortalité : 8%

Mackman N et al, Nat Rev Drug Dis 2020

Kahn F et al., Ann Intern Med, 2021

Cibles des nouveaux anticoagulants

Name/company	Agent/route of administration	Target	Disease	Clinical trial	Trial ID	Comments
TB-402/ThrombGenics	Antibody/IV	FVIII	NA	Phase I	NCT00612196	Completed; safety study
			TKA	Phase II	NCT00793234	Completed; reduced VTE
			THA	Phase II	NCT01344954	Completed; no data
REG1/NHLBI/Regado Biosciences	RNA Aptamer/IV	FIX	NA	Phase I	NCT00113997	Completed; safety study
			CAD	Phase II	NCT01848106	Terminated early; allergic reaction
			ACS	Phase III	NCT00932100	Terminated early; allergic reaction
TTP889/vTv Therapeutics	Small molecule/oral	FIX	Hip repair	Phase II	NCT00119457	Completed; no effect
			LVAD	Phase II	NCT00909298	Terminated
Ionis-416858/Ionis Pharmaceuticals	ASO/SC	FXI	TKA	Phase II	NCT02553889	Ongoing
			ESRD on haemodialysis	Phase II	NCT03358030	Ongoing
BAY-1213790/Bayer	Antibody/IV	FXI	TKA	Phase II	NCT03276143	Ongoing
			ESRD on haemodialysis	Phase II	NCT03787368	Ongoing
MAA868/Novartis	Antibody/IV	FXI	AF	Phase II	NCT04213807	Ongoing
BMS-986177/BMS	Small molecule/oral	FXI	Recurrent stroke	Phase I	NCT02608970	Completed; safety study
				Phase II	NCT03766581	Ongoing
			TKA	Phase II	NCT03891524	Ongoing
AB023/Aronora	Antibody/IV	FXI	ESRD on haemodialysis	Phase I	NCT03097341	Completed; safety study
				Phase II	NCT03612856	Ongoing
CSL312/CSL Behring	Antibody/IV	FXII	Hereditary angioedema	Phase II	NCT03712228	Ongoing

Mackman N et al, Nat Rev Drug Dis 2020

Déficit en FXI constitutionnel

FXI deficiency :

- an autosomal genetic disorder that was historically known as hemophilia C[1]
- associated with **low FXI plasma activity levels** compared with the normal range of **70–150** %[1,2]
- Testing for FXI deficiency is typically performed when a patient presents with a **prolonged aPTT** in routine clinical testing[1]

Epidemiology

Congenital FXI deficiency is observed with a frequency of 1 per 1 million worldwide[3]

In Jews of Ashkenazi origin the heterozygote frequency is 8%[3]

Symptoms

- FXI deficiency can manifest as **bleeding following injury or trauma in areas of high fibrinolysis** like the oral cavity or urogenital tract; **bleeding is usually mild**[4,5]
- No clear association has been observed between FXI activity levels and bleeding[6]
- It has been speculated that the increased bleeding risk observed in some individuals with FXI deficiency may be a result of additional or other coagulopathies[4]
- **Incidence of CV and VTE events is lower in individuals with FXI deficiency**[6,7]

1. Gomez K et al. *Semin Hematol* 2004; 2. O'Connell NM. *Semin Hematol* 2004; 3. Berber E. *Clin Appl Thromb Hemost* 2011; 4. Bolton-Maggs PH. *Hematology Am Soc Hematol Educ Program* 2009
5. Seligsohn U. *J Thromb Haemost* 2009;6. Peyvandi F *et al. J Thromb Haemost* 2012 8. Preis M *et al. Blood* 2017; 8. Georgi B *et al. Stroke* 2019

Du déficit en FXI au développement des nouveaux anticoagulants

The role of FXI(a) in the intrinsic/contact-activated coagulation pathway

Epidemiological data from individuals with FXI deficiency

Israël, entre 2002 et 2014, étude rétrospective des patients avec mesure de FXI.

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

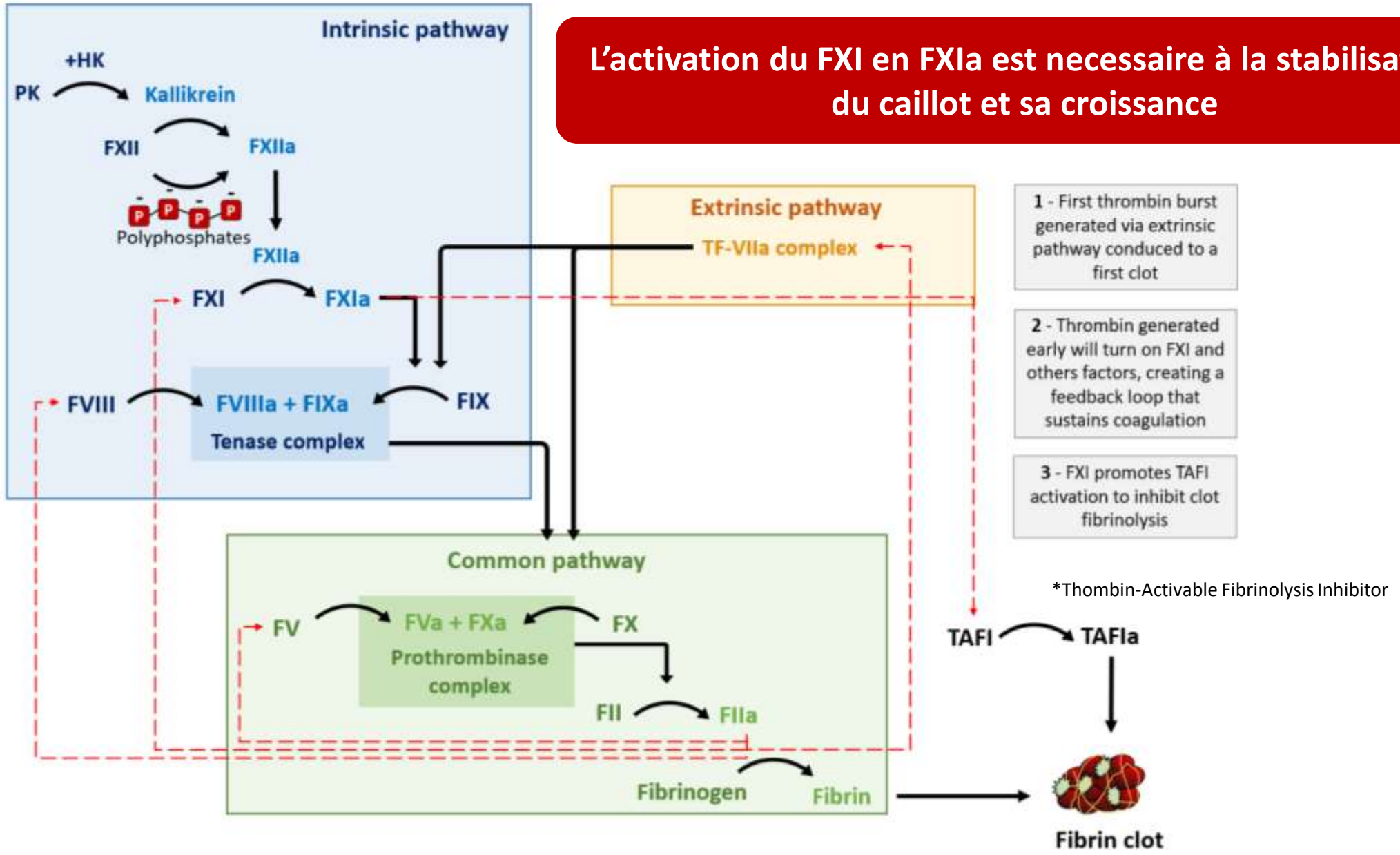
Study outcome	Factor XI activity	Number	Events	Age-adjusted model HR (95% CI)	Fully adjusted model HR (95% CI)
Cardiovascular event	≤30%	542	19	0.56 (0.35-0.91)	0.57 (0.35-0.93)
	30%-50%	693	16	0.57 (0.34-0.95)	0.52 (0.31-0.87)
	>50%	8958	230	Reference	Reference
VTE	≤50%	1235	3	0.14 (0.04-0.44)	0.26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

Déficit en FXI est associé à des risques plus faibles d'AVC ischémique, AIT, IDM et MVTE.

Preis M et al. Blood 2017

Du déficit en FXI au développement des nouveaux anticoagulants

L'activation du FXI en FXIa est necessaire à la stabilisation du caillot et sa croissance



Bentounes KN, et al. In press 2023

Du déficit en FXI au développement des nouveaux anticoagulants

The role of FXI(a) in the intrinsic/contact-activated coagulation pathway

Epidemiological data from individuals with FXI deficiency

Data from FXI-knockout mouse studies

Preclinical studies of FXI(a) inhibition

Clinical studies of FXI(a) inhibition

Séparer la thrombose de l'hémostase !

Le début des anti-FXI

Büller HR et al, NEJM 2015

ORIGINAL ARTICLE

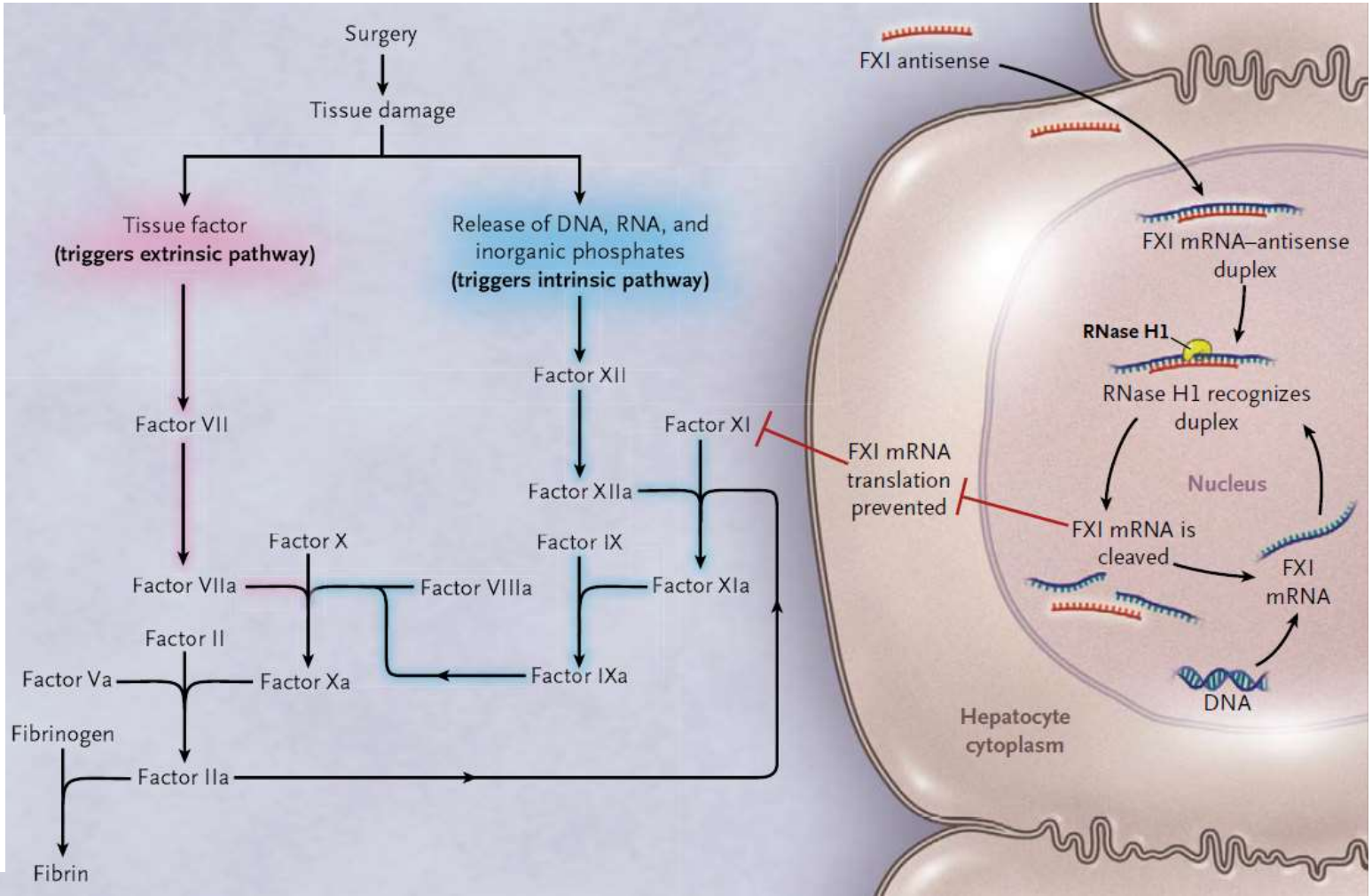
Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

Harry R. Büller, M.D., Claudette Bethune, Ph.D., Sanjay Bhanot, M.D., Ph.D., David Gailani, M.D., Brett P. Monia, Ph.D., Gary E. Raskob, Ph.D., Annelise Segers, M.D., Peter Verhamme, M.D., and Jeffrey I. Weitz, M.D., for the FXI-ASO TKA Investigators*

- **Treatment with FXI-ASO was initiated 36 days before surgery** (day 1 of the study).

Patients received 3 subcutaneous doses of FXI-ASO during the first week of treatment (**days 1, 3, and 5**) followed by **four once-weekly doses on days 8, 15, 22, and 29**. **On day 36**, the day of surgery, patients received a dose 6 hours postoperatively.
A final dose was given on **day 39**

- **Enoxaparin 4000 UI administered subcutaneously once daily, was initiated the evening before or 6 to 8 hours after surgery**, according to the investigator's preference, and was to be continued for at least 8 days postoperatively.



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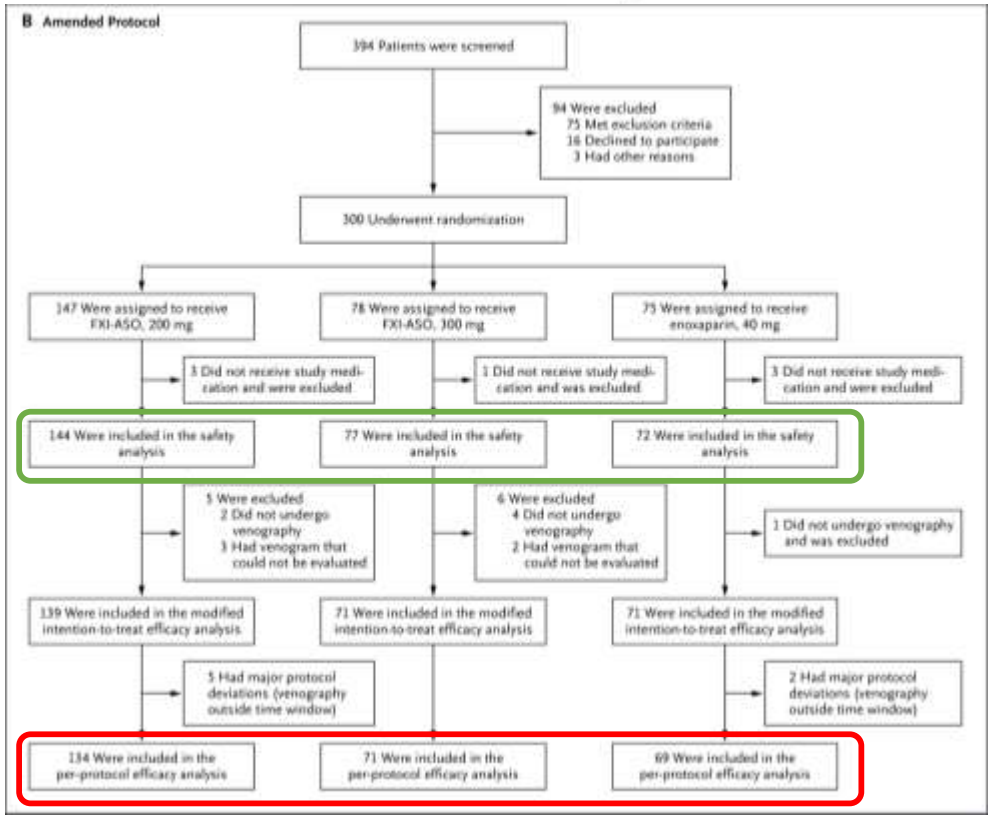
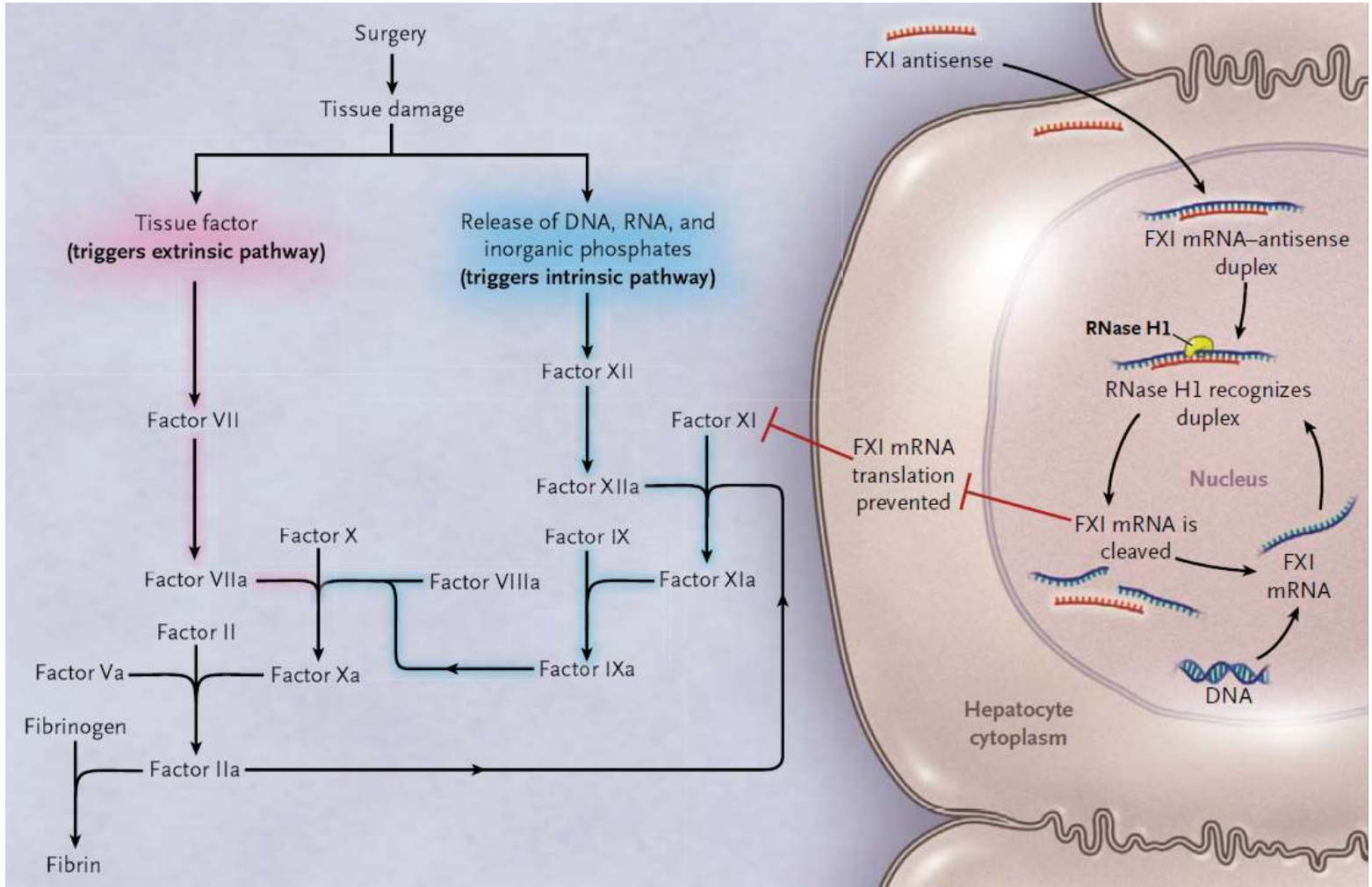




Le début des anti-FXI dans la PTG

Study Outcomes

- ✓ The primary efficacy outcome was the incidence of adjudicated **total venous thromboembolism**, which was a composite of asymptomatic deep-vein thrombosis (detected by mandatory bilateral venography), objectively confirmed symptomatic venous thromboembolism, fatal pulmonary embolism, or unexplained death for which pulmonary embolism could not be ruled out.
- ✓ **Venography** was to be performed **8 to 12 days after the surgery.**

Table 2. Efficacy and Safety Outcomes.*

Outcome	FXI-ASO, 200 mg (N=134)	FXI-ASO, 300 mg (N=71)	Enoxaparin, 40 mg (N=69)
Efficacy			
Primary efficacy outcome: total venous thromboembolism — no. (% [95% CI])†	36 (27 [20 to 35])	3 (4 [1 to 12])	21 (30 [20 to 43])
Risk difference, FXI-ASO vs. enoxaparin — % (upper limit of 90% CI)	−4 (5)	−26 (−18)	—
Risk difference, FXI-ASO vs. enoxaparin — % (upper limit of 95% CI)	−4 (8)	−26 (−16)	—
P value for superiority of FXI-ASO to enoxaparin	0.59	<0.001	—
Secondary efficacy outcomes: components of the primary efficacy outcome — no. (%)			
Symptomatic venous thromboembolism	2 (1)	0	1 (1)
Asymptomatic deep-vein thrombosis	34 (25)	3 (4)	20 (29)
Proximal deep-vein thrombosis	7 (5)	1 (1)	4 (6)
Distal deep-vein thrombosis	29 (22)	2 (3)	17 (25)

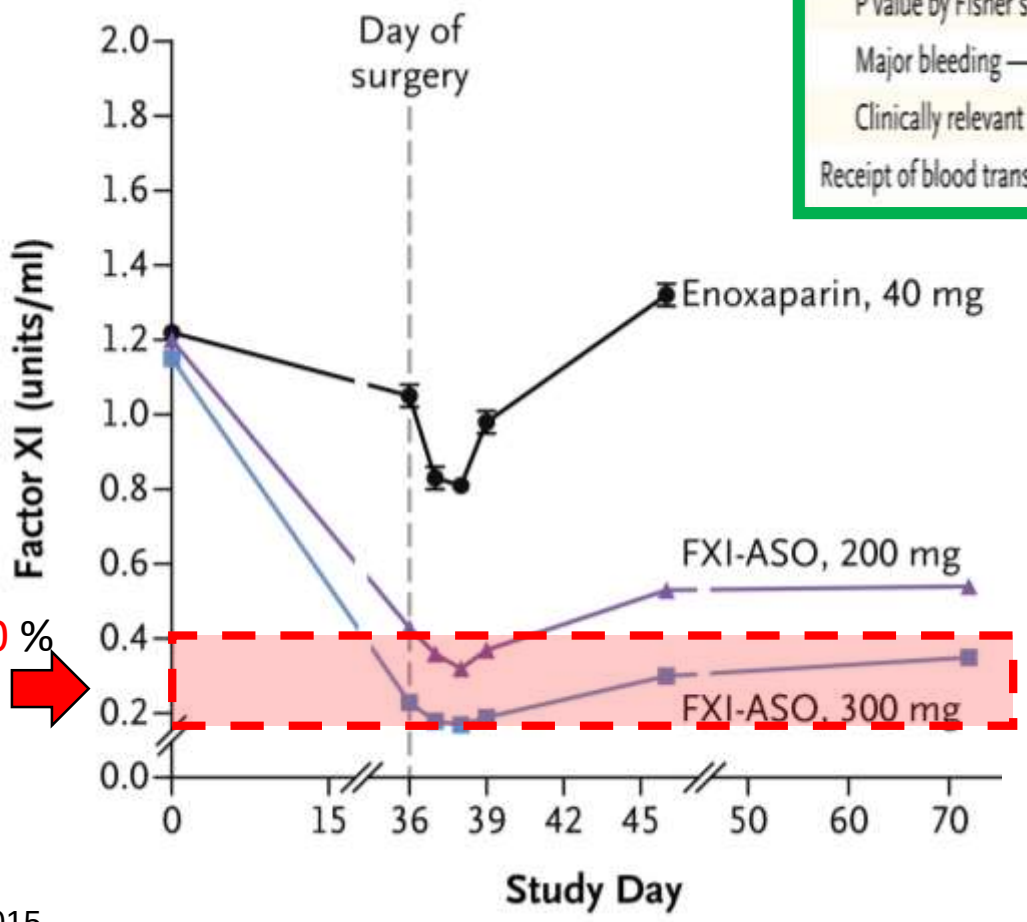
➔**Bonne efficacité de l'ARN antisens anti-FXI prévention de la MVTE post-PTG**

Büller HR et al, NEJM 2015

Le début des anti-FXI dans la PTG

❑ **Risque hémorragique ?**

Outcome	FXI-ASO, 200 mg (N=134)	FXI-ASO, 300 mg (N=71)	Enoxaparin, 40 mg (N=69)
Safety‖			
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])
Risk difference, FXI-ASO vs. enoxaparin — % (95% CI)	-6 (-12 to 1)	-6 (-13 to 2)	
P value by Fisher's exact test, FXI-ASO vs. enoxaparin	0.09	0.16	
Major bleeding — no. (% [95% CI])¶	0 [0 to 2.5]	1 (1 [<1 to 7])	0 [0 to 5.0]
Clinically relevant nonmajor bleeding — no. (% [95% CI])	4 (3 [1 to 7])	1 (1 [<1 to 7])	6 (8 [3 to 17])
Receipt of blood transfusion — no. (%)	55 (38)	22 (29)	23 (32)



FXI entre 20 et 40 % lors de la PTG

ARN antisens anti-FXI est une stratégie anticoagulante à faible risque hémorragique

similaire à l'enoxaparine dans la prévention de la MVTE post-PTG

Büller HR et al, NEJM 2015

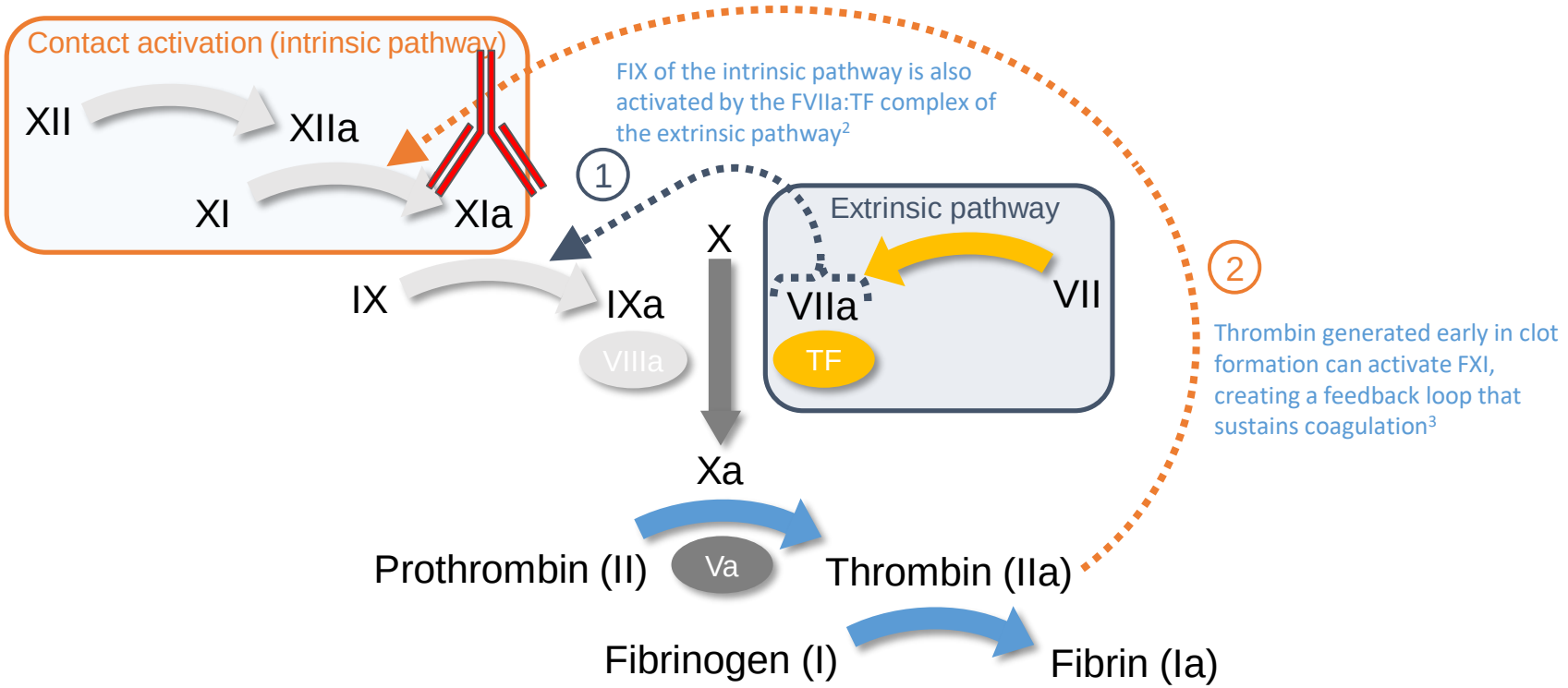
1er essai des anti-FXIa dans la PTG : osocimab

JAMA | Original Investigation

Effect of Osocimab in Preventing Venous Thromboembolism Among Patients Undergoing Knee Arthroplasty
The FOXTROT Randomized Clinical Trial

Jeffrey I. Weitz, MD; Rupert Bauersachs, MD; Bastian Becker, MSc; Scott D. Berkowitz, MD; Maria C. S. Freitas, MD, PhD; Michael R. Lassen, MD; Carola Metzig, MD; Gary E. Raskob, PhD

Osocimab : anticorps monoclonal humain **anti-FXIa**

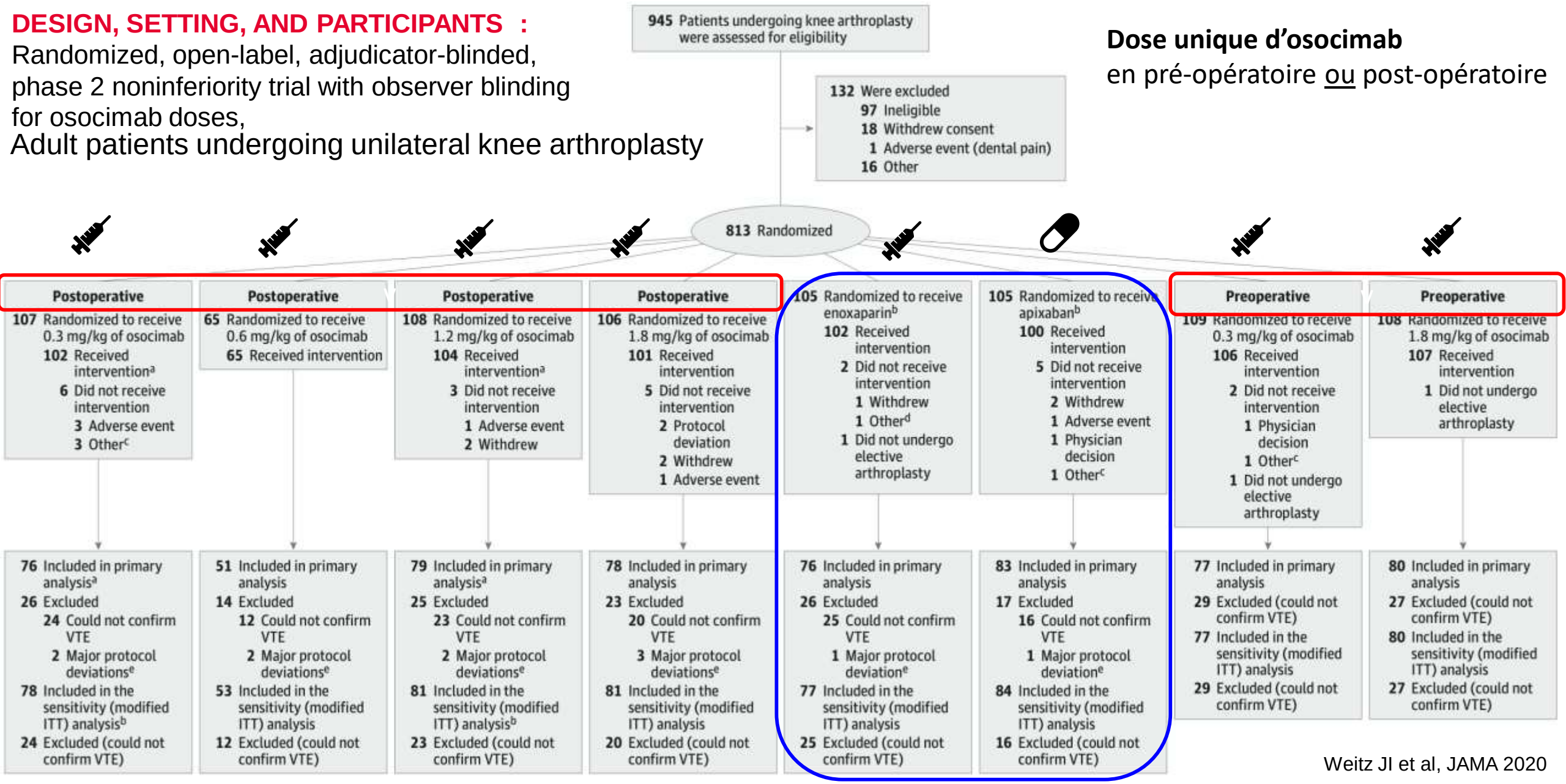


Weitz JI et al, JAMA 2020

1er essai des anti-FXIa dans la PTG : osocimab

DESIGN, SETTING, AND PARTICIPANTS :
Randomized, open-label, adjudicator-blinded, phase 2 noninferiority trial with observer blinding for osocimab doses,
Adult patients undergoing unilateral knee arthroplasty

Dose unique d'osocimab
en pré-opératoire ou post-opératoire



Weitz JI et al, JAMA 2020

1er essai des anti-FXIa dans la PTG : osocimab

- **Critère d'évaluation principal : composite, incidence de thrombose symptomatique ou asymptomatique mis en évidence par une phlébographie bilatérale** réalisée à 10 ou 13 jours après l'opération.

- **Critère d'évaluation secondaire** : **composite, saignements non majeurs mais cliniquement pertinents et de saignements majeurs** jusqu'à 150 jours après l'administration d'osocimab.

Weitz JI et al, JAMA 2020

1er essai des anti-FXIa dans la PTG : osocimab

Table 2. Rates of Venous Thromboembolism (Per-Protocol Analysis)[a]

	Postoperative Osocimab, mg/kg				Preoperative Osocimab, mg/kg			
	0.3 (n = 76)	0.6 (n = 51)	1.2 (n = 79)	1.8 (n = 78)	0.3 (n = 77)	1.8 (n = 80)	Enoxaparin (n = 76)	Apixaban (n = 83)
Primary VTE Outcome, No. (%) [90% CI][b]								
	18 (23.7) [15.9 to 33.1]	8 (15.7) [8.1 to 26.5]	13 (16.5) [10.0 to 24.9]	14 (17.9) [11.2 to 26.6]	23 (29.9) [21.4 to 39.6]	9 (11.3) [6.0 to 18.8]	20 (26.3) [18.2 to 35.9]	12 (14.5) [8.6 to 22.4]
Noninferiority of Osocimab vs Enoxaparin, % (1-Sided 95% CI)								
Risk difference	2.6 (-8.9 to ∞)	10.6 (-1.2 to ∞)	9.9 (-0.9 to ∞)	8.4 (-2.6 to ∞)	-3.6 (-15.5 to ∞)	15.1 (4.9 to ∞)		
P value	.14	.01	.01	.02	.42	<.001		
Superiority of Osocimab vs Enoxaparin, % (2-Sided 90% CI)[c]								
Risk difference		10.6	9.9	8.4		15.1		
P value		.07	.07	.10		.007		
Exploratory Comparison of Osocimab vs Apixaban, % (90% CI)[d]								
Risk difference	-9.2 (-19.5 to 1.0)	-1.2 (-11.7 to 9.3)	-2.0 (-11.3 to 7.4)	-3.5 (-13.1 to 6.1)	-15.4 (-26.1 to -4.7)	3.2 (-5.4 to 11.8)		
DVT Components of the Primary Outcome, No. (%)[b]								
Asymptomatic	18 (23.7)	7 (13.7)	13 (16.5)	14 (17.9)	22 (28.6)	9 (11.3)	20 (26.3)	11 (13.3)
Symptomatic	1 (1.3)	1 (2.0)	1 (1.3)	2 (2.6)	1 (1.3)	0	1 (1.3)	1 (1.2)
Proximal[e]	2 (2.6)	3 (5.9)	3 (3.8)	3 (3.8)	5 (6.5)	2 (2.5)	3 (3.9)	2 (2.4)
Distal[e]	18 (23.7)	8 (15.7)	13 (16.5)	13 (16.7)	24 (31.2)	9 (11.3)	19 (25.0)	12 (14.5)

Saignements majeurs et non majeurs mais cliniquement pertinents observés chez 4,7% des patients sous osocimab, contre 5,9% sous énoxaparine et 2% sous apixaban

- **Administrées en postopératoire, les doses de 0,6 mg/kg, 1,2 mg/kg et 1,8 mg/kg d'osocimab répondaient aux critères de non-infériorité par rapport à l'énoxaparine.**
- **Osocimab administré en préopératoire à 1,8 mg/kg répondait aux critères de supériorité par rapport à l'énoxaparine.**

Weitz JI et al, JAMA 2020

Confirmation des anti-FXI dans la PTG : abelacimab

ORIGINAL ARTICLE

Abelacimab for Prevention of Venous Thromboembolism

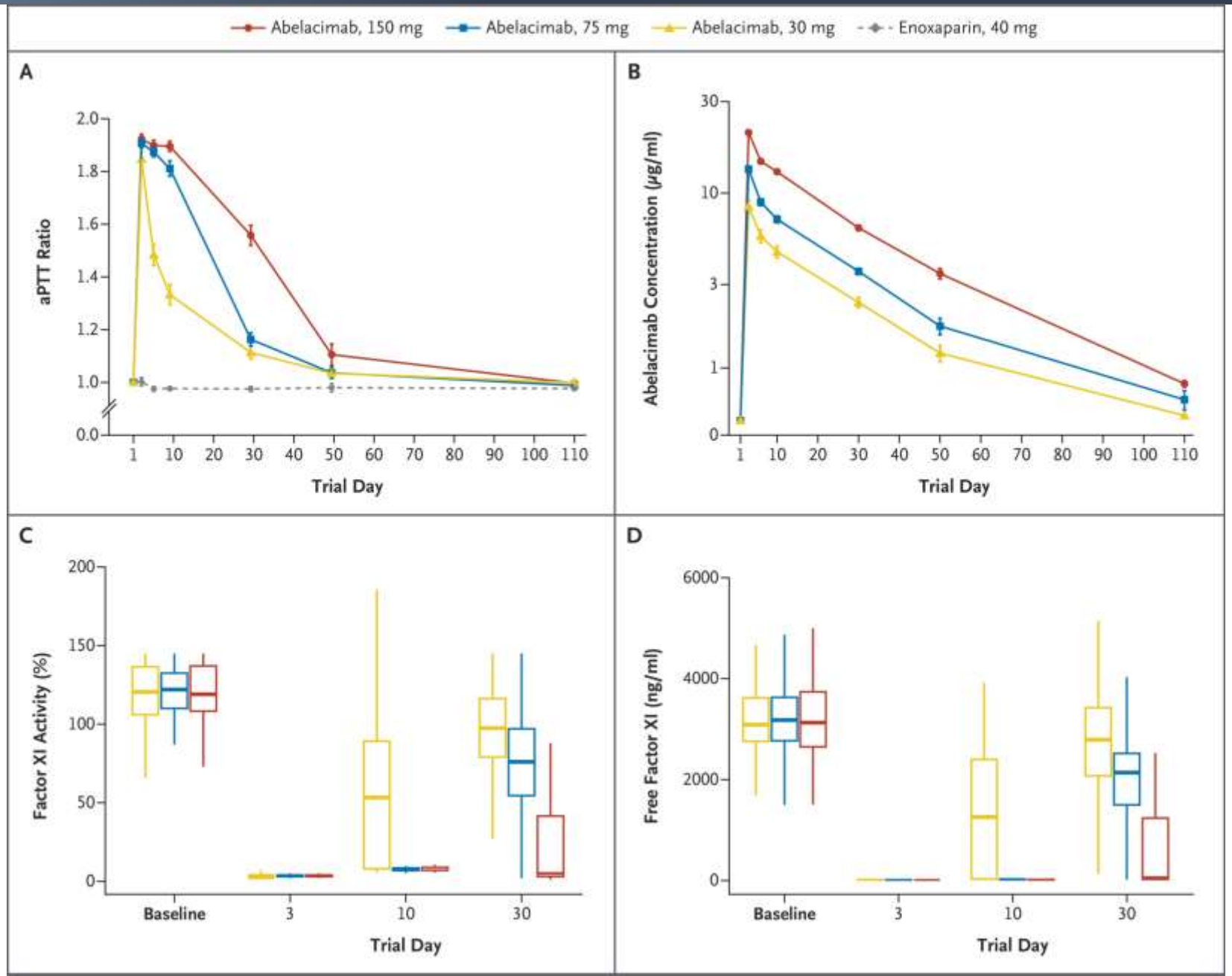
Peter Verhamme, M.D., B. Alexander Yi, M.D., Ph.D., Annelise Segers, M.D., Janeen Salter, B.S.N., Daniel Bloomfield, M.D., Harry R. Büller, M.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the ANT-005 TKA Investigators*

Abelacimab : anticorps monoclonal humain **anti-FXI**

- Open-label, parallel-group trial, we randomly 1:1:1:1 assigned patients who were undergoing TKA to receive :
  - One of 3 regimens of **abelacimab (30 mg, 75 mg, or 150 mg) administered postoperatively in a single intravenous dose**
  - **Enoxaparin 4000 UI** administered SC once daily.
- **Primary efficacy outcome** : **VTE** : detected by **mandatory venography (between Day 8 and Day 12) of the leg involved** in the operation **or objective confirmation of symptomatic events**.
- **Principal safety outcome** : composite of major or clinically relevant non-major bleeding up to 30 days after surgery.

Verhamme P et al, NEJM 2021

Confirmation des anti-FXI dans la PTG



Verhamme P et al, NEJM 2021

Confirmation des anti-FXI dans la PTG

Outcome	Abelacimab, 30 mg	Abelacimab, 75 mg	Abelacimab, 150 mg	Enoxaparin, 40 mg
Efficacy				
No. of patients evaluated	102	99	98	101
Primary efficacy outcome: venous thromboembolism†				
Any event — no. of patients (%)	13 (13)	5 (5)	4 (4)	22 (22)
Risk difference, abelacimab vs. enoxaparin — percentage points (95% CI)	−9.2 (−19.4 to 1.1)	−16.8 (−26.0 to −7.6)	−17.8 (−26.7 to −8.8)	NA
P value for superiority of abelacimab to enoxaparin	0.08	<0.001	<0.001	NA
Components of the primary efficacy outcome — no. (%)				
Symptomatic venous thromboembolism	0	0	0	1 (1)‡
Asymptomatic deep-vein thrombosis	13 (13)	5 (5)	4 (4)	21 (21)
Proximal deep-vein thrombosis	1 (1)	0	0	2 (2)
Distal deep-vein thrombosis	12 (12)	5 (5)	4 (4)	20 (20)‡

- ✓ **Dose unique de 30 mg de l'abelacimab était non inférieure à l'énoxaparine** pour la prévention de la MVTE postopératoire
- ✓ **Doses uniques de 75 mg et 150 mg de l'abélacimab étaient supérieures à l'énoxaparine**

Verhamme P et al, NEJM 2021

Confirmation des anti-FXI dans la PTG

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Components of the primary efficacy outcome — no. (%)				
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Proximal deep-vein thrombosis	1 (1)	0	0	2 (2)
Distal deep-vein thrombosis	12 (12)	5 (5)	4 (4)	20 (20)‡
Safety				
No. of patients evaluated	102	104§	99	104
Major or clinically relevant nonmajor bleeding				
From randomization until venography was completed				
Any event — no. of patients (%)	2 (2)	2 (2)	0	0
Risk difference, abelacimab vs. enoxaparin — percentage points (95% CI)	1.9 (−0.7 to 4.6)	1.9 (−0.7 to 4.5)	0	NA
Major bleeding — no. (%)	0	0	0	0
Clinically relevant nonmajor bleeding — no. (%)	2 (2)	2 (2)	0	0
From randomization through day 30 — no. (%)				
Any event	2 (2)	2 (2)¶	0	0
Major bleeding	0	1 (1)	0	0
Clinically relevant nonmajor bleeding	2 (2)	2 (2)	0	0
Receipt of blood transfusion through day 30 — no. (%)	6 (6)	8 (8)	9 (9)	7 (7)

✅

✅

Abelacimab = stratégie anticoagulante à faible risque hémorragique comme enoxaparine !

Verhamme P et al, NEJM 2021

Confirmation des anti-FXI dans la PTG

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Safety				
No. of patients evaluated	102	104§	99	104
Major or clinically relevant nonmajor bleeding				
From randomization until venography was completed				
Any event — no. of patients (%)	2 (2)	2 (2)	0	0
Risk difference, abelacimab vs. enoxaparin — percentage points (95% CI)	1.9 (−0.7 to 4.6)	1.9 (−0.7 to 4.5)	0	NA
Major bleeding — no. (%)	0	0	0	0
Clinically relevant nonmajor bleeding — no. (%)	2 (2)	2 (2)	0	0
From randomization through day 30 — no. (%)				
Any event	2 (2)	2 (2)¶	0	0
Major bleeding	0	1 (1)	0	0
Clinically relevant nonmajor bleeding	2 (2)	2 (2)	0	0
Receipt of blood transfusion through day 30 — no. (%)	6 (6)	8 (8)	9 (9)	7 (7)

✅

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Abelacimab = stratégie anticoagulante à faible risque hémorragique comme enoxaparine !

Verhamme P et al, NEJM 2021

L’arrivée des anti-FXIa oraux

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Milvexian for the Prevention of Venous Thromboembolism

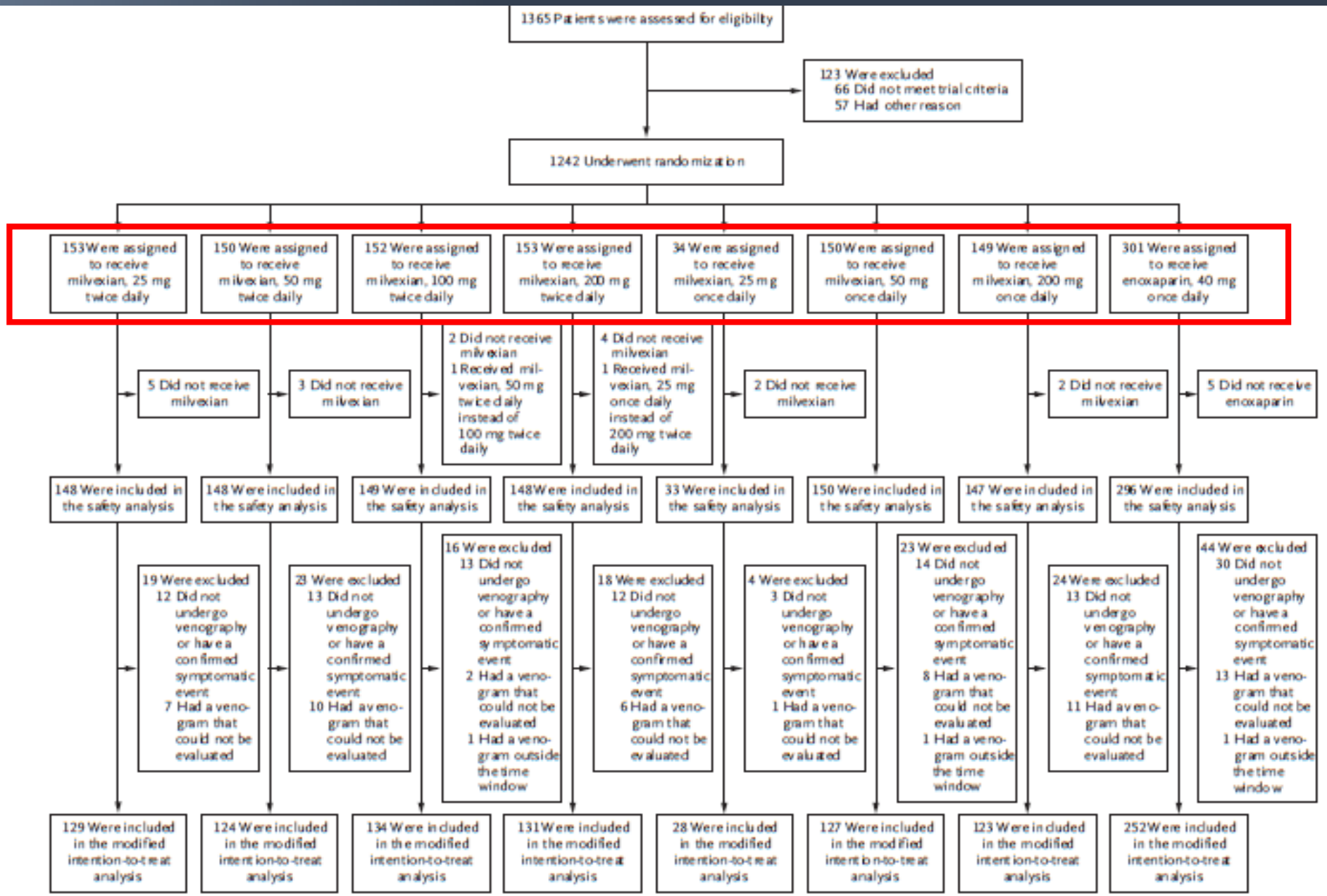
Jeffrey I. Weitz, M.D., John Strony, M.D., Walter Ageno, M.D., David Gailani, M.D., Elaine M. Hylek, M.D., Michael R. Lassen, M.D., Kenneth W. Mahaffey, M.D., Ravi S. Notani, M.B.A., Robin Roberts, M.S., Annelise Segers, M.D., and Gary E. Raskob, Ph.D., for the AXIOMATIC-TKR Investigators*

Milvexian : Petite molécule inhibiteur sélectif du facteur XIa.

- ✓ Plusieurs doses administrées par **voie orale** (25, 50, 100 ou 200 mg) selon des modalités différentes (une ou deux fois par jour)
- ✓ Plus de 1 000 patients opérés pour une arthroplastie totale

Weitz JI et al, NEJM, 2022

Anti-FXIa oral dans la PTG : milvexian



Weitz JI et al, NEJM, 2022

Anti-FXIa oral dans la PTG : milvexian

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)	
Primary efficacy outcome: venous thromboembolism†								
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)	—
Components of the primary efficacy outcome — no.‡								
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
Extent of deep-vein thrombosis on venography — no.								
Confluent distal into proximal	1	0	1	0	0	2	0	1
Isolated proximal								
Large: ≥10 cm	0	0	0	0	0	0	0	0
Small: <10 cm	0	0	0	0	0	0	0	1
Isolated distal								
Extensive: ≥2 veins	9	5	1	2	5	9	1	20
Limited: <2 veins	17	8	9	8	2	18	7	30

- ✓ La plus **faible incidence de MVTE** est de 7 % sous milvexian à 200 mg en une prise quotidienne, contre 21 % sous énoxaparine 4000 UI/jour.

Weitz JI et al, NEJM, 2022

Anti-FXIa oral dans la PTG : milvexian

Table 3. Safety Outcomes.*

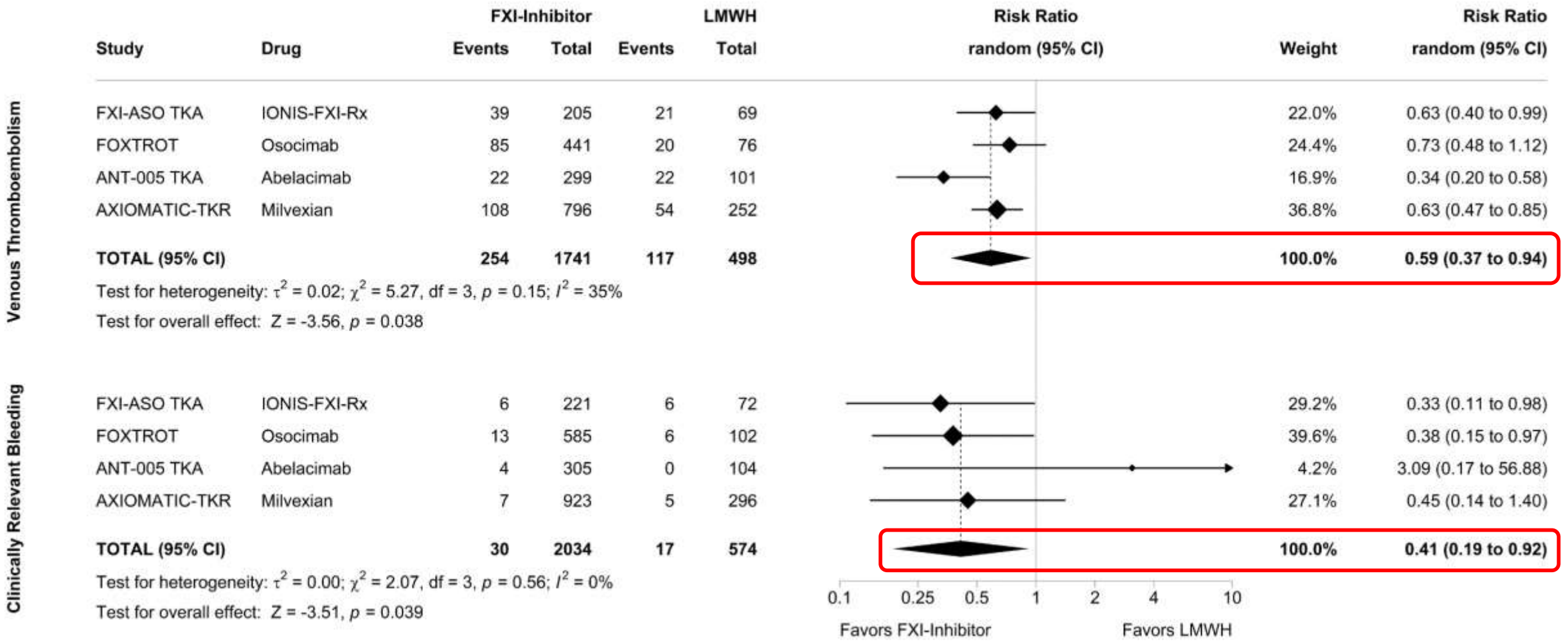
Outcome	Milvexian Twice Daily				Milvexian Once Daily			Enoxaparin (N=296)
	25 mg (N=148)	50 mg (N=148)	100 mg (N=149)	200 mg (N=148)	25 mg (N=33)	50 mg (N=150)	200 mg (N=147)	
Any bleeding — no. (%)	2 (1)	7 (5)	7 (5)	5 (3)	0	8 (5)	9 (6)	12 (4)
Relative risk vs. enoxaparin (95% CI)	0.33 (0.08–1.43)	1.15 (0.47–2.82)	1.14 (0.47–2.80)	0.81 (0.29–2.24)	0 (NA)	1.17 (0.50–2.72)	1.51 (0.66–3.43)	—
Major bleeding or clinically relevant nonmajor bleeding — no. (%)	0	2 (1)	1 (1)	1 (1)	0	2 (1)	1 (1)	5 (2)
Relative risk vs. enoxaparin (95% CI)	0 (NA)	0.79 (0.16–3.96)	0.39 (0.05–3.30)	0.39 (0.05–3.28)	0 (NA)	0.68 (0.14–3.39)	0.40 (0.05–3.34)	—
Major bleeding — no. (%)	0	0	0	0	0	0	0	1 (<1)†
Clinically relevant nonmajor bleeding — no. (%)	0	2 (1)	1 (1)	1 (1)	0	2 (1)	1 (1)	4 (1)
Serious adverse event — no. (%)	5 (3)	5 (3)	5 (3)	2 (1)	1 (3)	2 (1)	2 (1)	11 (4)
At least one adverse event — no. (%)	56 (38)	67 (45)	51 (34)	54 (36)	7 (21)	58 (39)	65 (44)	113 (38)
Adverse event leading to discontinuation of treatment — no. (%)	2 (1)	7 (5)	2 (1)	4 (3)	0	4 (3)	6 (4)	8 (3)

✅

✓ **Pas de sur-risque hémorragique** : 4 % sous milvexian et sous énoxaparine 4000 UI/jour

Weitz JI et al, NEJM, 2022

Efficacité et tolérance des anti-FXI ou FXIa *VS* énoxaparine dans la PTH



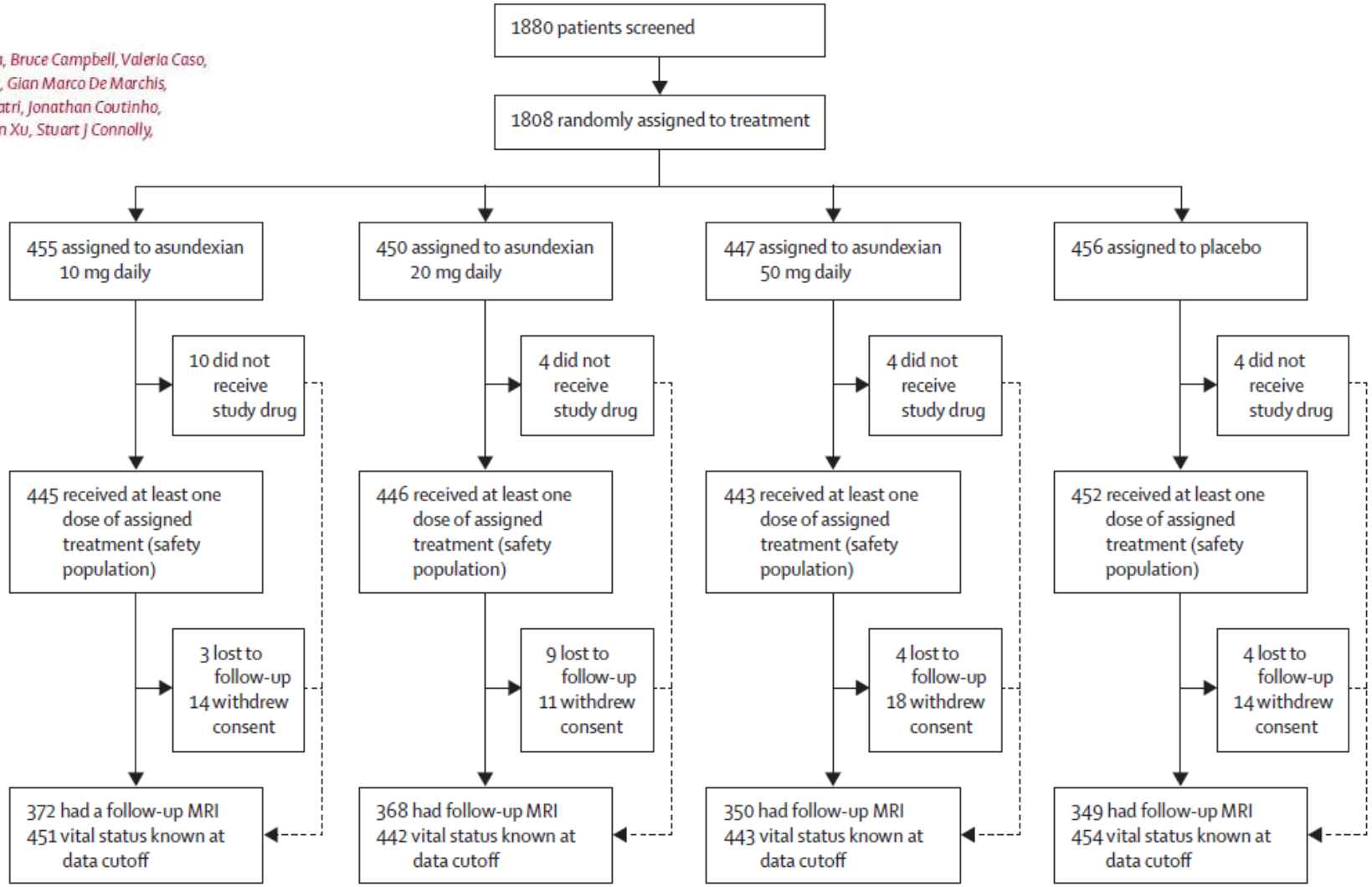
Nopp S et al, Frontiers CardioVasc Med, 2022

Asundexian en prévention secondaire de l'AVC

Factor XIa inhibition with asundexian after acute non-cardioembolic ischaemic stroke (PACIFIC-Stroke): an international, randomised, double-blind, placebo-controlled, phase 2b trial

Ashkan Shoamanesh, Hardi Mundl, Eric E Smith, Jaime Masjuan, Ivan Milanov, Teruyuki Hirano, Alina Agafina, Bruce Campbell, Valeria Caso, Jean-Louis Mas, Qiang Dong, Peter Turcani, Hanne Christensen, Jose M Ferro, Roland Veltkamp, Robert Mikulik, Gian Marco De Marchis, Thompson Robinson, Robin Lemmens, Adam Stepien, Stefan Greisenegger, Risto Roine, Laszlo Csiba, Pooja Khatri, Jonathan Coutinho, Arne G Lindgren, Andrew M Demchuk, Pablo Colorado, Bodo Kirsch, Christoph Neumann, Laura Heenan, Lizhen Xu, Stuart J Connolly, Robert G Hart, for the PACIFIC-Stroke Investigators

- 1808 patients atteints d'**AVC d'étiologie non cardio-embolique**
- **Traitement anti-agrégant plaquettaire** (mono ou bi-thérapie) associé à **asudenxian** (10 mg, ou 20 mg ou 40 mg ou **placebo**)



Shoamanesh A et al, Lancet, 2022

Asundexian en prévention secondaire de l'AVC

- **Absence de différence significative entre les deux groupes sur le critère de jugement principal incluant la récurrence à six mois des AVC silencieux ou symptomatiques.**

- **Pas plus d'événements hémorragique sous asundexian**, alors que l'association avec un traitement antiplaquettaire est une situation à haut risque hémorragique.

	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
Primary outcome							
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)
Secondary outcomes							
Components of the primary outcome*							
Incident covert brain infarcts on MRI†	64 (14%)	63 (14%)	0·99 (0·75–1·30)	74 (16%)	1·17 (0·90–1·51)	74 (17%)	1·17 (0·91–1·52)
Recurrent symptomatic ischaemic stroke*	23 (5%)	24 (5%)	1·05 (0·66–1·67)	25 (6%)	1·10 (0·69–1·75)	17 (4%)	0·75 (0·45–1·26)
Efficacy outcomes‡							
Recurrent symptomatic ischaemic stroke§	28 (6%)	26 (6%)	0·93 (0·59–1·45)	26 (6%)	0·94 (0·60–1·47)	22 (5%)	0·80 (0·50–1·27)
Any recurrent stroke§	30 (7%)	26 (6%)	0·86 (0·56–1·34)	26 (6%)	0·88 (0·56–1·36)	25 (6%)	0·85 (0·54–1·32)
Disabling stroke (mRS score of ≥4)§	3 (1%)	5 (1%)	1·67 (0·50–5·55)	5 (1%)	1·69 (0·51–5·62)	1 (<1%)	0·34 (0·05–2·27)
Recurrent symptomatic ischaemic stroke, vascular death, or myocardial infarction§	35 (8%)	33 (7%)	0·94 (0·63–1·40)	30 (7%)	0·87 (0·58–1·30)	33 (7%)	0·96 (0·64–1·43)
Recurrent symptomatic ischaemic stroke, incident covert brain infarct on MRI, cardiovascular death, myocardial infarction and systemic embolism*	79 (17%)	80 (18%)	0·95 (0·76–1·20)	87 (19%)	1·06 (0·85–1·33)	81 (18%)	1·03 (0·82–1·30)
All-cause mortality§	10 (2%)	10 (2%)	1·00 (0·48–2·09)	6 (1%)	0·60 (0·26–1·41)	17 (4%)	1·72 (0·89–3·32)

	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
Primary safety outcome*									
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)

Shoamanesh A et al, Lancet, 2022

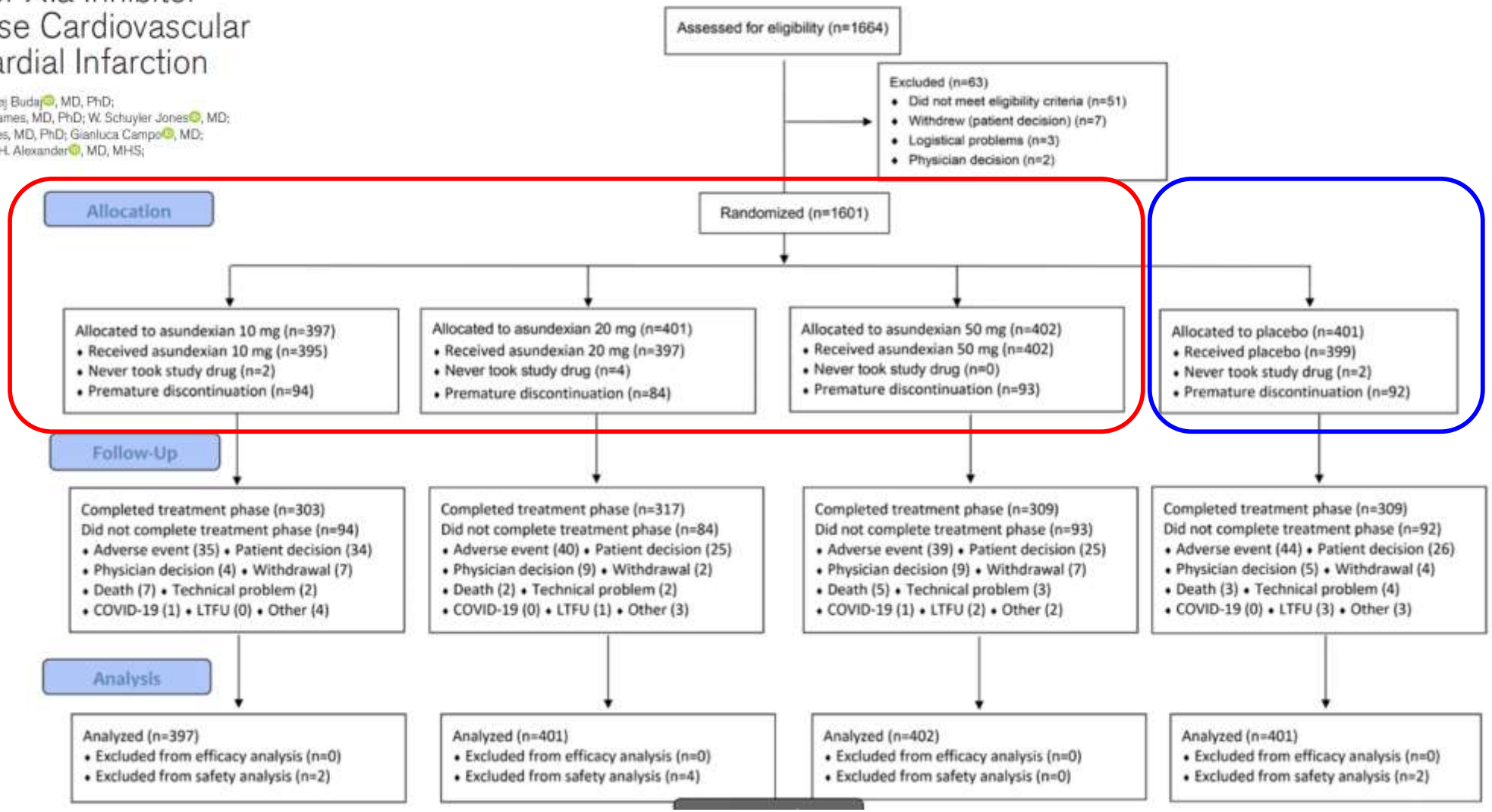
Asundexian en prévention secondaires après SCA

ORIGINAL RESEARCH ARTICLE

A Multicenter, Phase 2, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Dose-Finding Trial of the Oral Factor XIa Inhibitor Asundexian to Prevent Adverse Cardiovascular Outcomes After Acute Myocardial Infarction

Sunil V. Rao, MD; Bodo Kirsch, MSc; Deepak L. Bhatt, MD, MPH; Andrzej Budaj, MD, PhD; Rosa Coppolecchia, DO, MPH; John Eikelboom, MBBS, MSc; Stefan K. James, MD, PhD; W. Schuyler Jones, MD; Bela Merkely, MD, PhD, MSc, DSc; Lars Keller, MD; Renicus S. Hermanides, MD, PhD; Gianluca Campo, MD; José Luis Ferreiro, MD, PhD; Taro Shibasaki, MD; Hardi Mundl, MD; John H. Alexander, MD, MHS; on behalf of the PACIFIC AMI Investigators

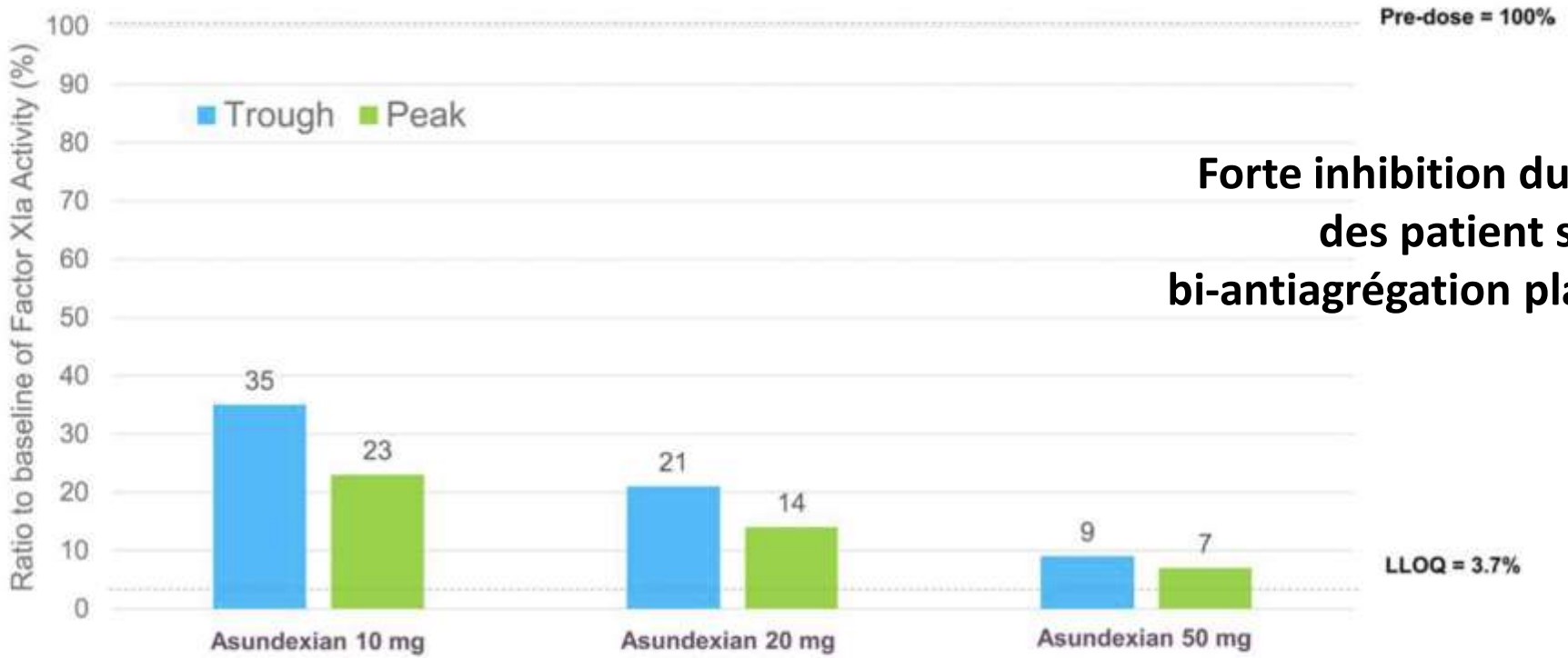
- ✓ Dans les 5 jours post-SCA
- ✓ **Asundexian** (x1/jour) vs **placebo** et **en association avec aspirine et anti-P2Y12** pendant au 6 -12 mois



Rao S et al, Circulation, 2022

Asundexian en prévention secondaires après SCA

- **4 semaines après la prise d'asundexian (1x/jour, per os)**



	Asundexian 10 mg		Asundexian 20 mg		Asundexian 50 mg	
	n=327	n=320	n=347	n=344	n=347	n=338
Analysis value (95% CI)	35.58 (28.68–32.48)	18.34 (13.34–23.34)	16.59 (15.55–17.64)	10.78 (5.96–15.61)	7.19 (6.39–7.99)	5.09 (4.11–6.07)
Mean ratio to baseline (95% CI)	0.35 (0.33–0.37)	0.23 (0.15–0.30)	0.21 (0.18–0.25)	0.14 (0.08–0.19)	0.09 (0.08–0.09)	0.07 (0.05–0.08)

Forte inhibition du FXIa chez des patient sous bi-antiagrégation plaquettaire !

Asundexian en prévention secondaires après SCA

	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)

Rao S et al, Circulation, 2022

Asundexian en prévention secondaires après SCA

	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)
Cardiovascular death	7 (1.76)	4 (1.00)	5 (1.24)	9 (1.12)	2 (0.50)	18 (1.12)
MI	18 (4.53)	20 (4.99)	18 (4.48)	38 (4.73)	17 (4.24)	73 (4.56)
Stroke	4 (1.01)	3 (0.75)	0	3 (0.37)	2 (0.50)	9 (0.56)
Ischemic stroke	4 (1.01)	2 (0.50)	0	2 (0.25)	2 (0.50)	8 (0.50)
Hemorrhagic stroke	0	1 (0.25)	0	1 (0.12)	0	1 (0.06)
Stent thrombosis	4 (1.01)	5 (1.25)	4 (1.00)	9 (1.12)	4 (1.00)	17 (1.06)
All-cause mortality	10 (2.52)	7 (1.75)	10 (2.49)	17 (2.12)	7 (1.75)	34 (2.12)

Rao S et al, Circulation, 2022

Asundexian en prévention primaire dans la FA

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*

Double aveugle, randomisé 1:1:1

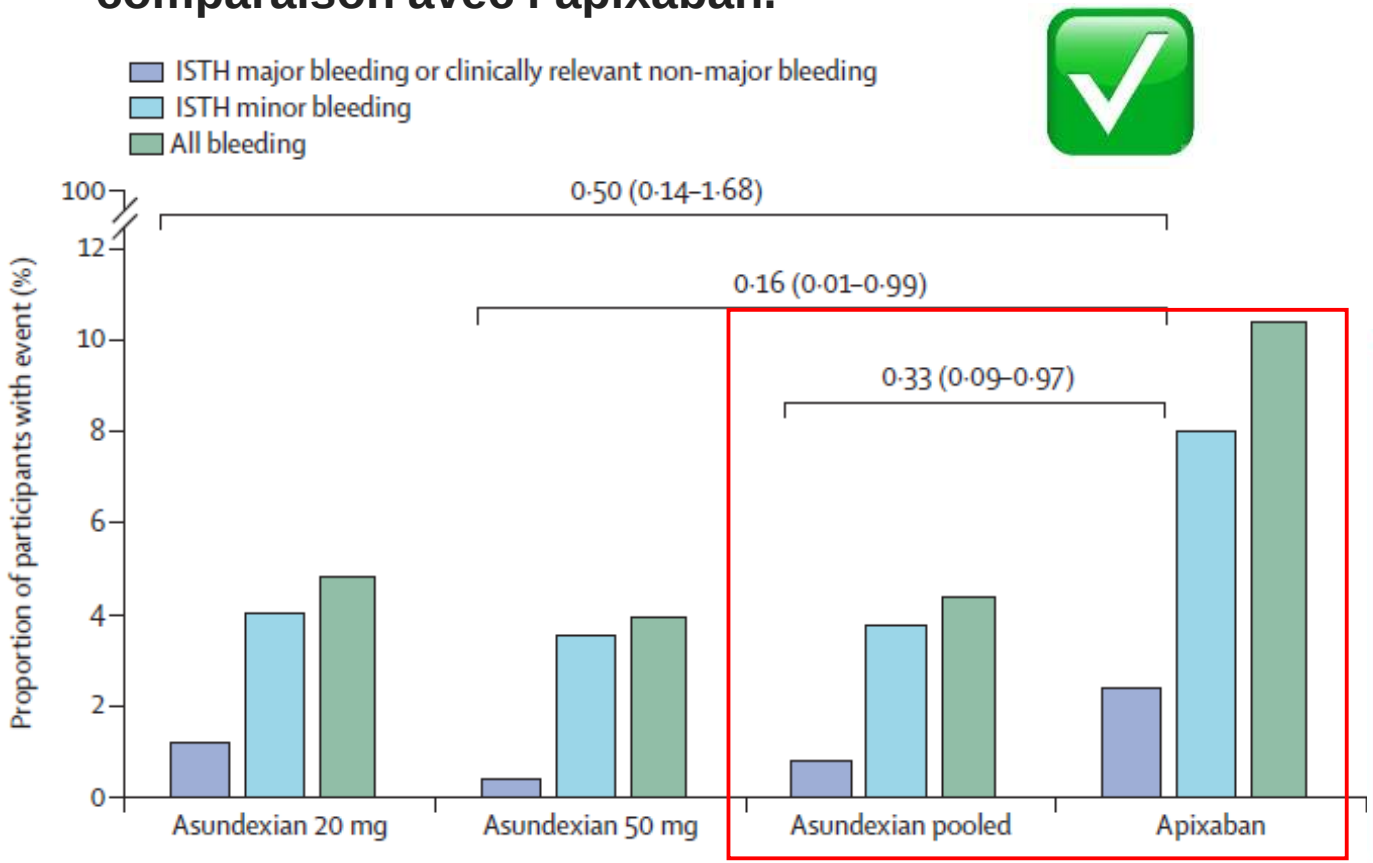
- ✓ Patients avec FA et au moins 1 facteur de risque hémorragique
- ✓ **Asundexian** (x1/jour) vs **Apixaban** pendant 12 semaines

	Asundexian 20 mg (n=251)	Asundexian 50 mg (n=254)	Apixaban (n=250)	Asundexian total (n=505)	Total (n=755)
Aspirin ≤100 mg	35 (14%)	33 (13%)	39 (16%)	68 (13%)	107 (14%)
Moderate renal dysfunction*	63 (25%)	76 (30%)	69 (28%)	139 (28%)	208 (28%)
Bleed within 12 months requiring medical attention	20 (8%)	24 (9%)	23 (9%)	44 (9%)	67 (9%)
CHA_2DS_2-VASc score	3·9 (1·4)	3·8 (1·3)	4·1 (1·4)	3·9 (1·3)	3·9 (1·3)
CHA_2DS_2-VASc score ≤3 (men) or ≤4 (women)	133 (53%)	138 (54%)	127 (51%)	271 (54%)	398 (53%)
Type of atrial fibrillation					
Paroxysmal	122 (49%)	115 (45%)	117 (47%)	237 (47%)	354 (47%)
Persistent	69 (27%)	70 (28%)	57 (23%)	139 (28%)	196 (26%)
Long-standing persistent	5 (2%)	3 (1%)	8 (3%)	8 (2%)	16 (2%)
Comorbidities					
Hypertension	226 (90%)	227 (89%)	220 (88%)	453 (90%)	673 (89%)
Hyperlipidaemia	142 (57%)	153 (60%)	152 (61%)	295 (58%)	447 (59%)
Heart failure	108 (43%)	107 (42%)	117 (47%)	215 (43%)	332 (44%)
Coronary artery disease	76 (30%)	71 (28%)	85 (34%)	147 (29%)	232 (31%)
Diabetes	83 (33%)	74 (29%)	87 (35%)	157 (31%)	244 (32%)
Chronic kidney disease	55 (22%)	84 (33%)	77 (31%)	139 (28%)	216 (29%)
Percutaneous coronary intervention	38 (15%)	46 (18%)	43 (17%)	84 (17%)	127 (17%)
Myocardial infarction	26 (10%)	41 (16%)	36 (14%)	67 (13%)	103 (14%)
Anaemia	26 (10%)	38 (15%)	26 (10%)	64 (13%)	90 (12%)
Stroke or transient ischaemic attack	22 (9%)	18 (7%)	25 (10%)	40 (8%)	65 (9%)
CABG surgery	22 (9%)	16 (6%)	17 (7%)	38 (8%)	55 (7%)

Picini JP, et al. Lancet, 2022

Asundexian en prévention primaire dans la FA

- **L'asundexian : risque hémorragique plus faible en comparaison avec l'apixaban.**



	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

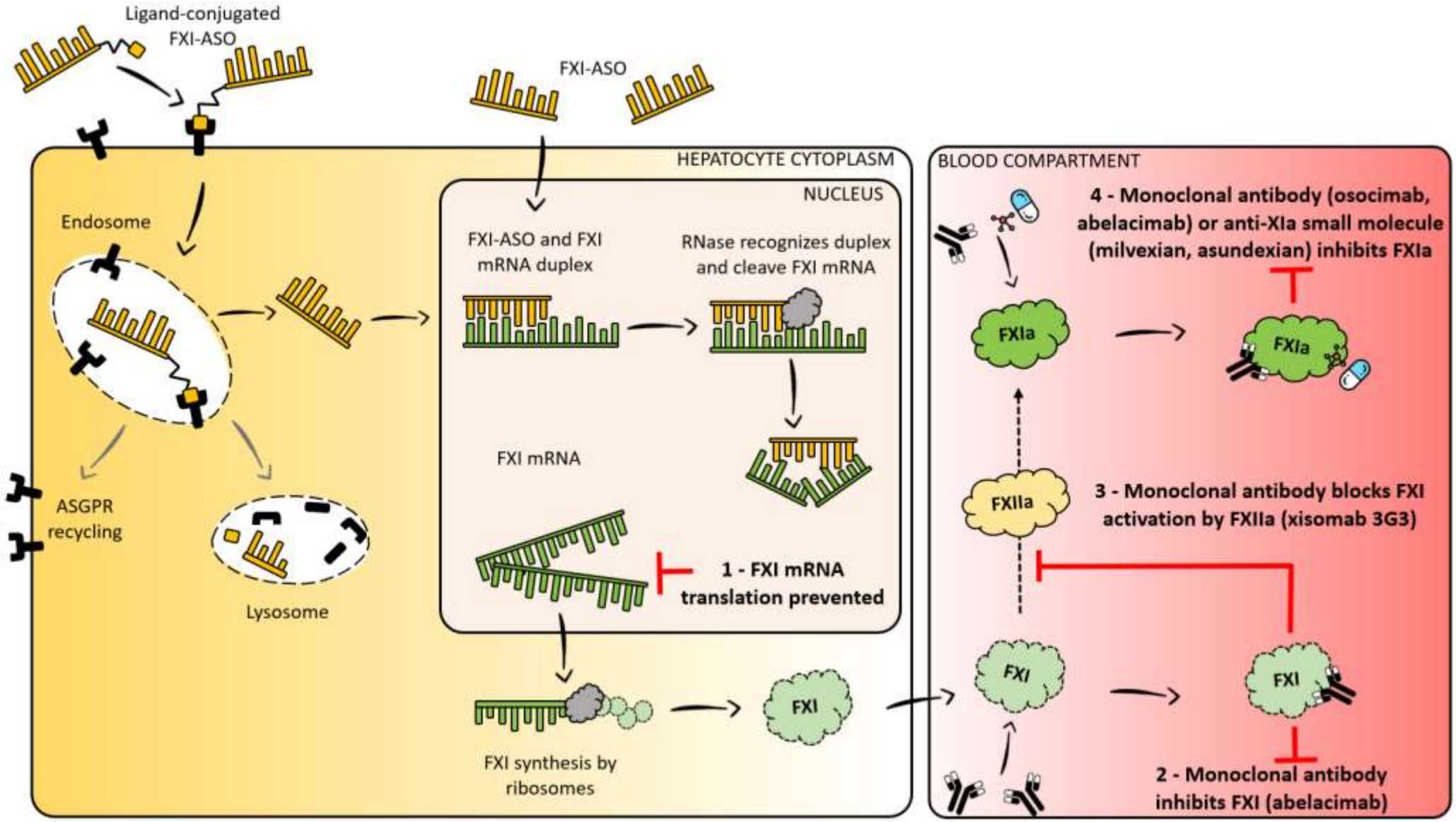
Data are numbers of participants.

Table 2: Exploratory thrombotic endpoints

- **Efficacité rassurante de l'asundexian comparée à l'apixaban.**
- **A valider en essai de Phase III**

Picini JP, et al. Lancet, 2022

Mécanismes d'action des nouveaux anticoagulants anti-FXI/FXIa



Bentounes KN, et al. In press 2023

PK/PD des nouveaux anticoagulants anti-FXI et FXIa

Drug	IONIS-FXI$_{Rx}$	Fesomersen	Osocimab	Abelacimab	Xisomab 3G3	Milvexian	Asundexian
Type	Antisense oligonucleotide	Antisense oligonucleotide	Monoclonal antibody	Monoclonal antibody	Monoclonal antibody	Small molecule inhibitor	Small molecule inhibitor
Mechanism	Inhibits **FXI** mRNA	Inhibits **FXI** mRNA	Binds and inhibits **FXIa**	Binds and inhibits **FXI** and **FXIa**	Binds **FXI** and blocks activation by FXIIa	Binds and inhibits **FXIa**	Binds and inhibits **FXIa**
APTT	↗	↗	↗	↗	↗	↗	↗
PT	No effect		No effect	No effect	No effect	No effect	No effect
TT				No effect			
Platelets	No effect		No effect			No effect	
Administration	Subcutaneous (weekly)	Subcutaneous (weekly)	Intravenous, subcutaneous (monthly)	Subcutaneous (monthly)	Intravenous (monthly)	Oral (OD)	Oral (OD)
Half life	20 days	1–122 hours	30–44 days	25 –30 days	20 – 28 days	11–18 hours	16–18h
Renal excretion	No	No	No	No	No	**20 % renal**	**15 % renal**
CYP metabolism	No	No	No	No	No	**CYP3A4**	**CYP3A4**

Bentounes KN, et al. In press 2023

Nomenclature des nouveaux anticoagulants en 2023

International Society on Thrombosis and Haemostasis

Table. Proposed Nomenclature for Anticoagulant Medications Currently Available or Under Investigation

	Vitamin K Antagonists	Heparins and Heparinoids	Thrombin Inhibitors	Factor Xa Inhibitors	Factor XI or XIa Inhibitors	Factor XII or XIIa Inhibitors
Parenteral		• Unfractionated heparin • Low molecular weight heparin • Fondaparinux • Danaparoid	• Argatroban • Bivalirudin		• Abelacimab • Fesomersen • Osocimab • Xisomab (AB023)	• Garadacimab
Oral	• Warfarin • Acenocoumarol • Phenprocoumon		• Dabigatran	• Apixaban • Edoxaban • Rivaroxaban	• Milvexian • Asundexian	

Barnes GD et al. JTH 2023

Perspectives

- **Résultats favorables dans la PTG +++** Nopp S et al, Frontiers CardioVasc Med, 2022
- **Quels résultats pour les indications d'anticoagulation au long cours** : FA & MVTE **?**
  - Résultats de Phase II favorables avec asundexian
- **Comparaisons aux AOD, nécessité de nombreux patients !**
  - Attention tolérance des anti-FXI/anti-FXIa chez femmes (ménorragie ?)

Perspectives des anti-FXI et anti-FXIa

TABLE 1 | Overview of factor XI inhibitors in clinical trials.

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

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

Nopp S et al, Frontiers CardioVasc Med, 2022

Perspectives

- **Résultats favorables dans la PTG +++** Nopp S et al, Frontiers CardioVasc Med, 2022
- **Quels résultats pour les indications d'anticoagulation au long cours** : FA & MVTE **?**
  - Résultats de Phase II favorables avec asundexian
- **Comparaisons aux AOD, nécessité de nombreux patients !**
  - Attention tolérance des anti-FXI/anti-FXIa chez femmes (ménorragie ?)

- **Nouvelles indications en cours d'évaluation** :
  - Patients IRC dialysés
  - Prévention thrombose circuit ECMO
  - Cathéter centraux dans le cancer.
- **Quelle efficacité dans les Indications résistantes aux AOD ? (SAPL, valve mécanique ?)**
- **Nouveaux antidotes ? Prise en charge hémorragique ?**

Bientôt dans nos pratiques ? A confirmer...

Hôpital européen Georges-Pompidou
AP-HP

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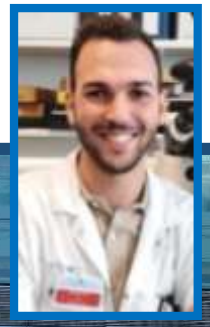

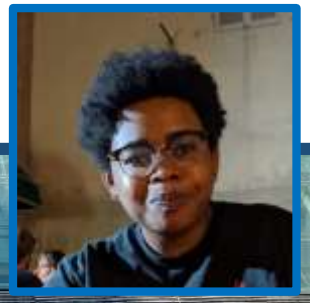

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