11-13 SEPT. 2024
LILLE GRAND PALAIS
CONGRÈS FRANÇAIS D'HÉMOSTASE
SFTH SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE
GIHP

Les anti-FXI, mythe ou réalité complexe ?

Utilisation des anti-XI dans la fibrillation atriale

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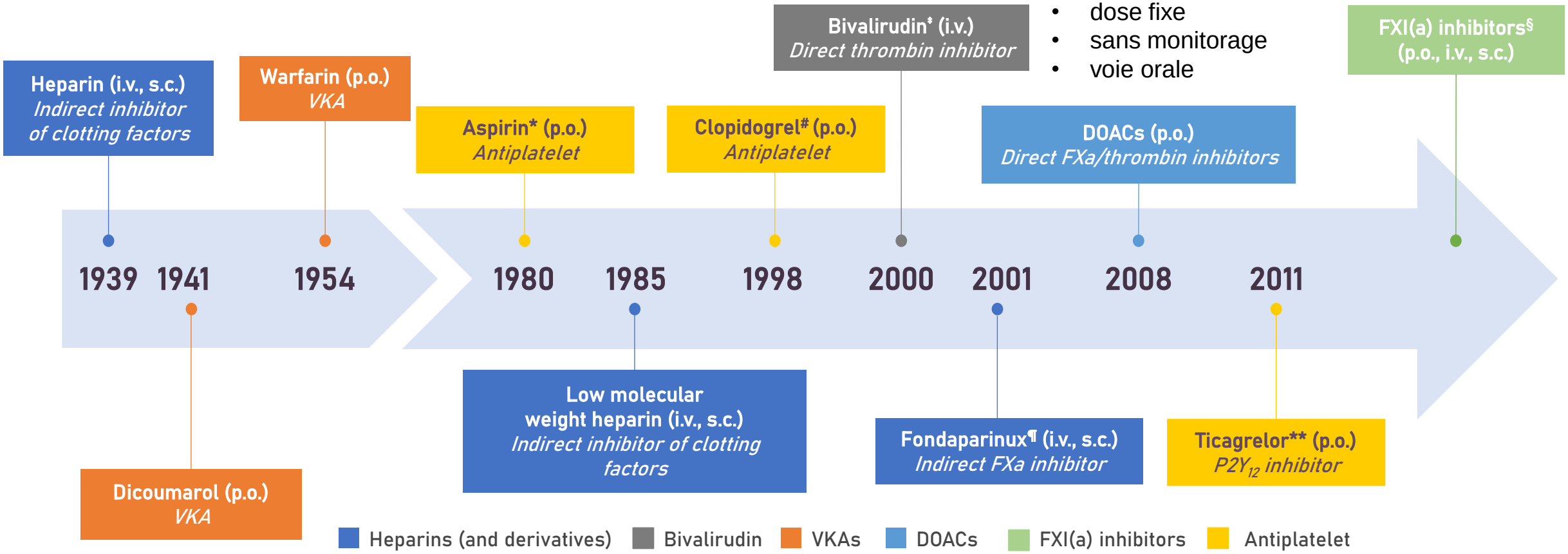
INSERM UMRS 1140 Thérapies Innovantes en hémostase
Université Paris Cité

Liens d'intérêt : Abbott, Alliance BMS-Pfizer, Bayer, Boehringer Ingenheim, Caramt, Novartis, Sanofi

Du mythe...

- 1 facteur de la coagulation
- dose fixe
- sans monitorage
- voie orale

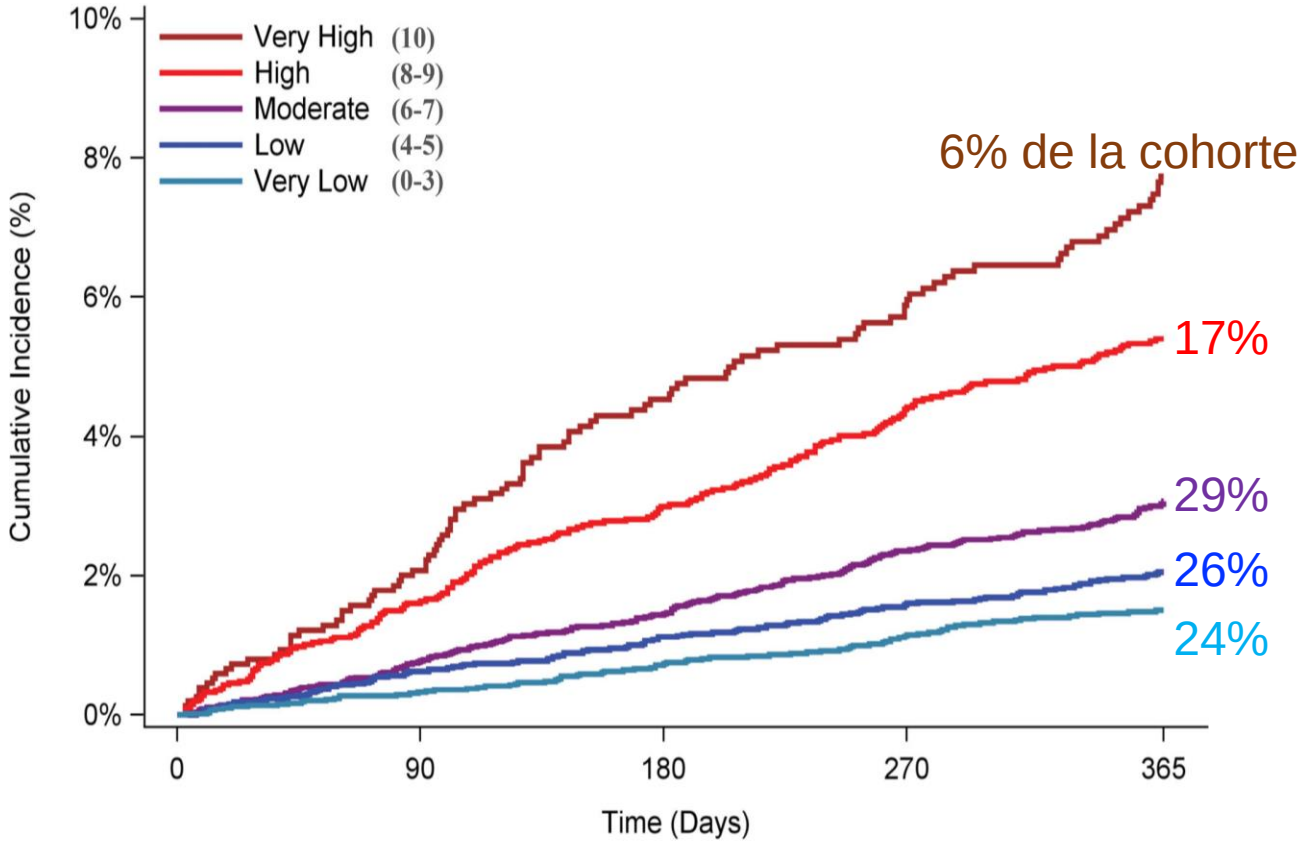


Efficace contre la thrombose, **qui ne fait pas saigner** !

Saignements majeurs sous AOD

DOAC score

COMBINE-AF (N=25 585)



→ Sous-traitement

< 66% of patients FA + CHA_2DS_2-VASc ≥ 2 reçoivent un anticoagulant

→ Sous-dosage

> 25% des patients sont sous-dosés

→ Faible compliance au traitement

1 patient sur 3 adhere au traitement

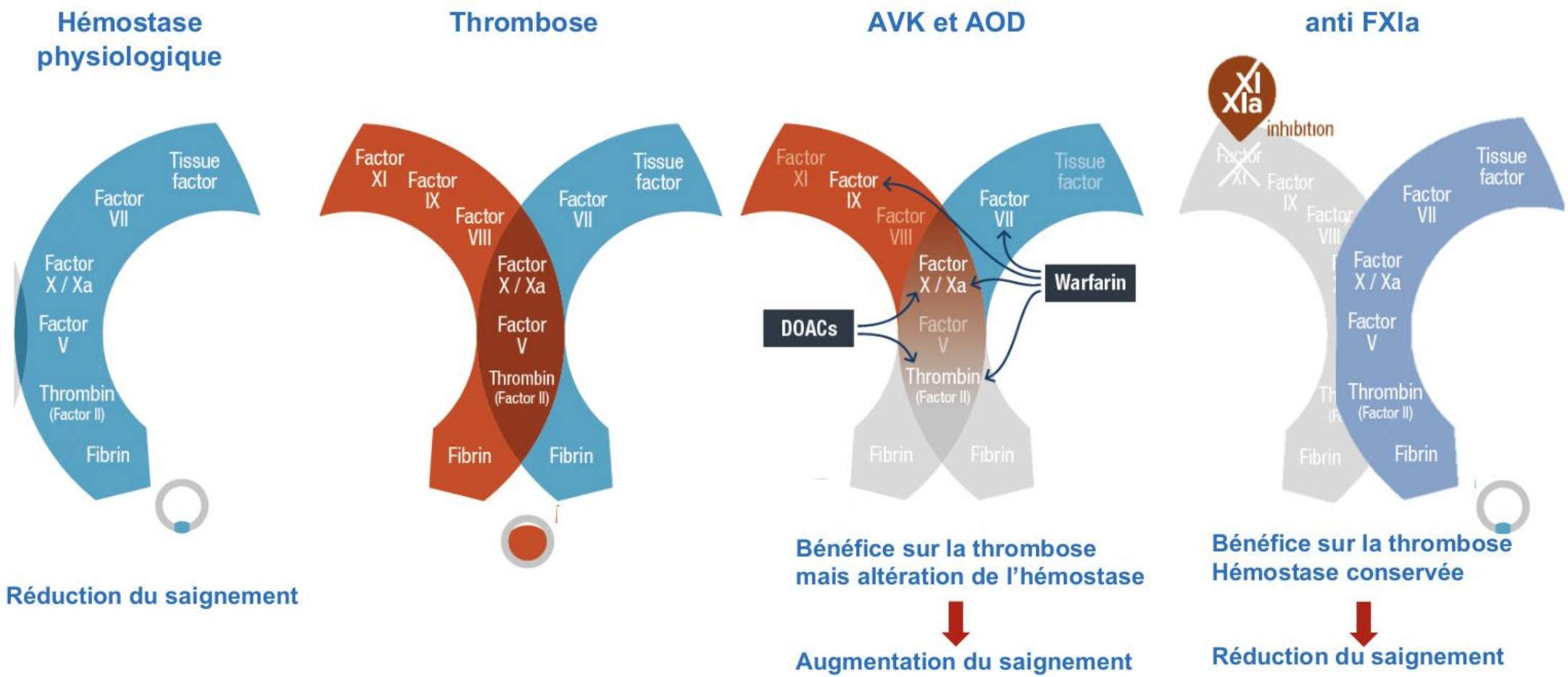
< 80%

Aggarwal R et al. Circulation 2023

Du mythe ...

Rôle du FXIa dans la cascade de la coagulation

Rôle du facteur XI dans la cascade de la coagulation: “Découplage” de l’hémostase et de la thrombose



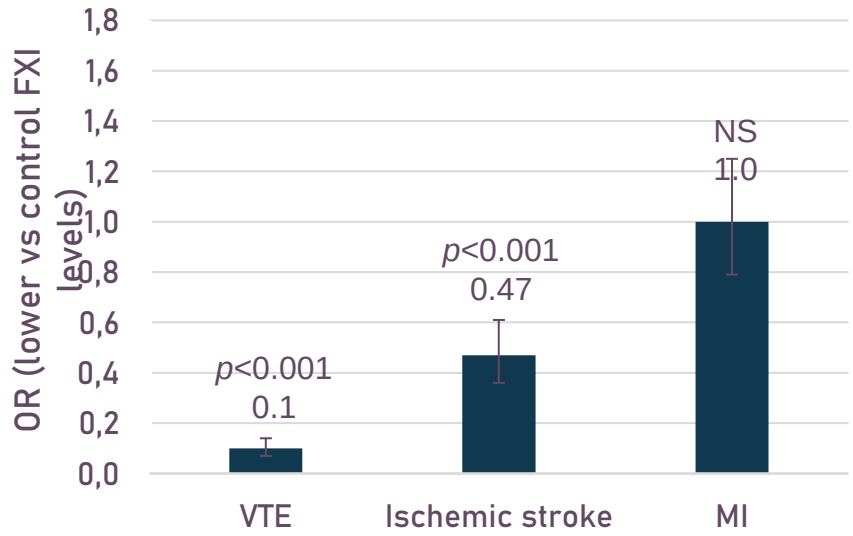
Du mythe ...

Rôle du FXIa dans la cascade de la coagulation

Données épidémiologiques d'individus avec un déficit en FXI

Georgi B *et al. Stroke* 2019
Gill D *et al. Stroke* 2018

Patients with genetically lower FXI levels show reduced risk of thrombotic events



Absence de saignement spontané
(même en cas de déficit sévère)

Saignement habituellement *modéré*

Saignement provoqué par une intervention invasive ou un traumatisme

Absence de corrélation entre le risque hémorragique et le déficit en FXI

Pas de surrisque d'hémorragie intracrânienne

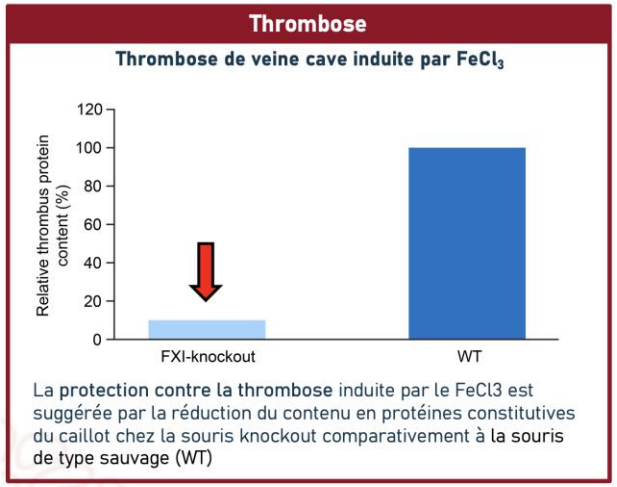
Pas de surrisque de saignement gastro-intestinal

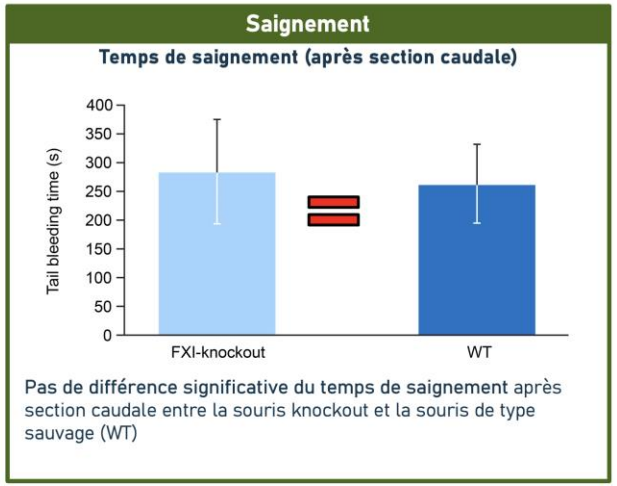
Du mythe ...

Rôle du FXIa dans la cascade de la coagulation

Données épidémiologiques d'individus porteurs d'un déficit en FXI

Etudes précliniques : souris knock-out pour le gène codant le FXI





Gailani D *et al. Blood Coag Fibrinol* 1997, Wang X *et al. J Thromb Haemost* 2005; Wang X *et al. J Thromb Haemost* 2006

Du mythe à la réalité

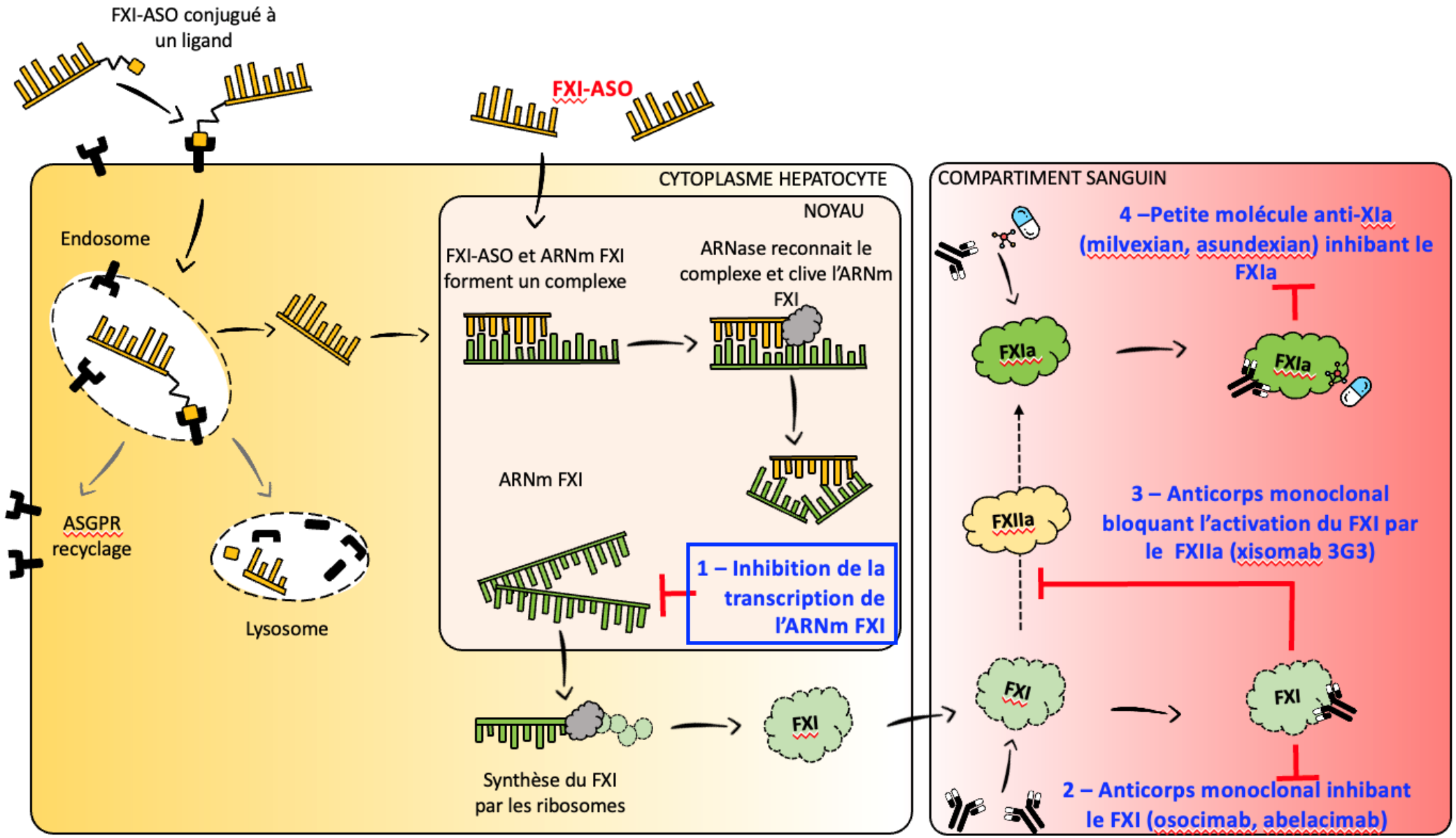
Rôle du FXIa dans la cascade de la coagulation

Données épidémiologiques d'individus porteurs d'un déficit en FXI

Etudes précliniques : souris knock-out pour le gène codant le FXI

Etudes de phase 2 en thromboprophylaxie après chir ortho résultats prometteurs sur la réduction de la thrombose sans augmentation du saignement

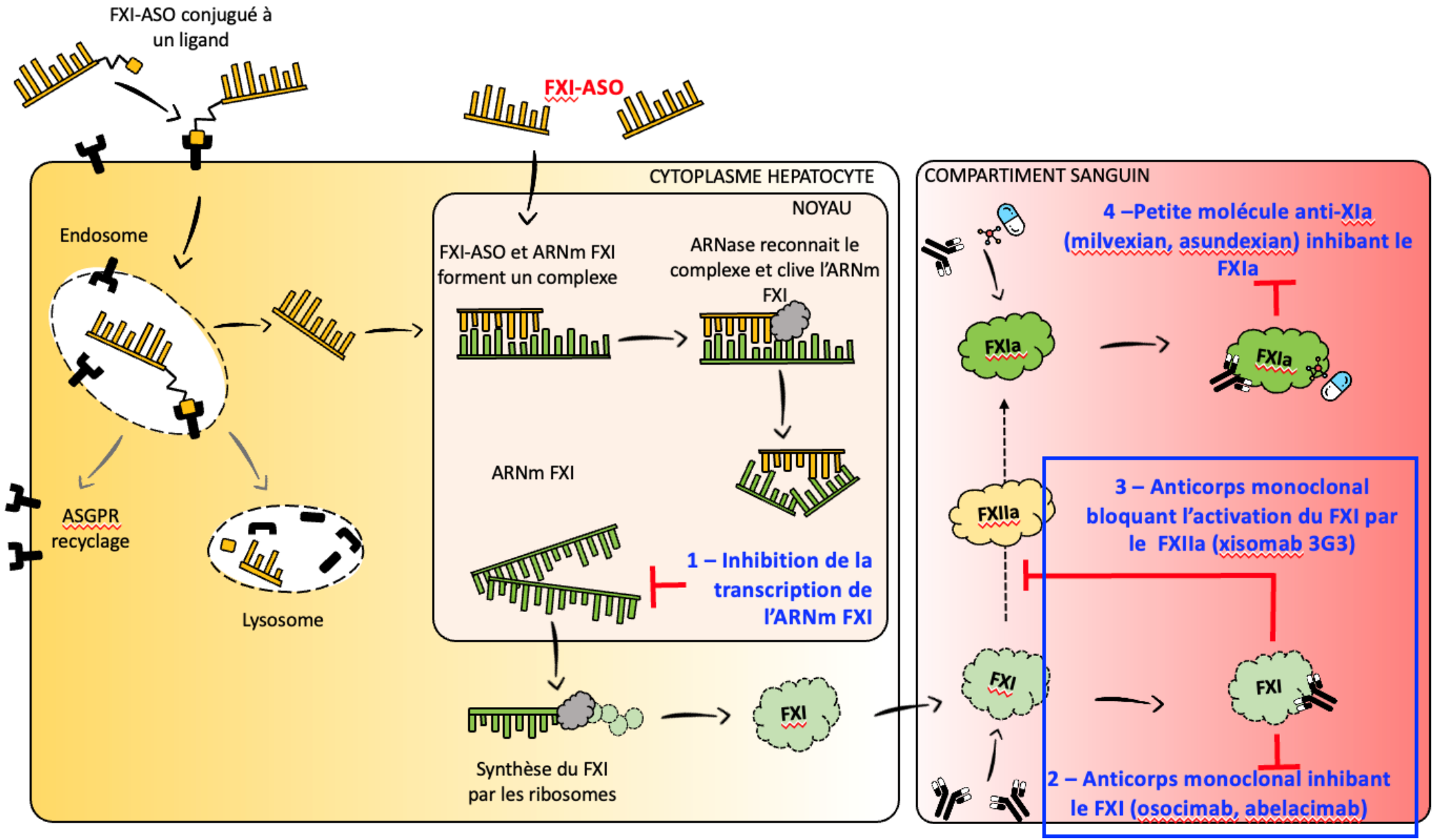
Inhibiteurs du Facteur XI/XIa



Inhibiteurs du Facteur XI/XIa

	Antisense oligonucleotide	**Monoclonal antibodies (IgG)**			**Small molecules**	
	IONIS-FXI-LRx Fesomersen	**Abelacimab**	Osocimab	Xisomab (gruticibart)	**Asundexian**	**Milvexian**
Mechanism of action	reduces FXI synthesis	binds to the catalytic domain of **FXI and FXIa**	binds to the catalytic domain of **FXIa**	binds to the apple 2 domain of **FXI(a)**	inhibits the FXIa catalytic active site	inhibits the FXIa catalytic active site
Administration route and frequency	Subcutaneous or IV, weekly to monthly	Subcutaneous or IV	Subcutaneous or IV	Subcutaneous or IV	Oral, once daily	Oral, twice daily
Half-life	Effect may persist for weeks to months after discontinuation	25-30 days	30-44 days	121h (for one dose of 5 mg/kg)	14.2 to 17.4 h	11.4 to 18.1 h
Indications under development	ESKD, TKR	**AF**, TKR, cancer associated VTE	TKR, ESKD	CRT, ESKD, TKR	, **AF,** AMI, stroke	**AF**, AMI, stroke

Inhibiteurs du Facteur XI/XIa



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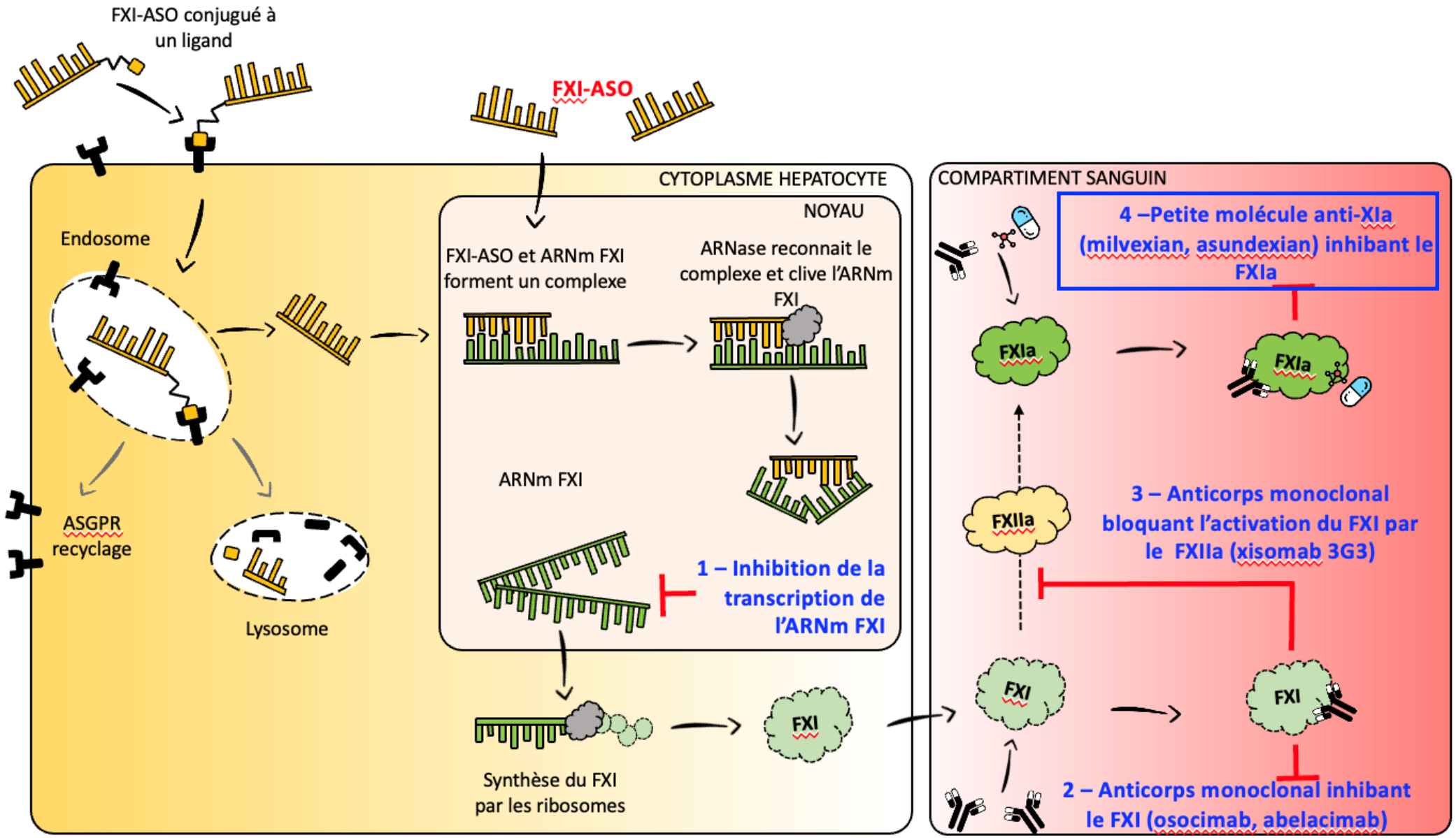

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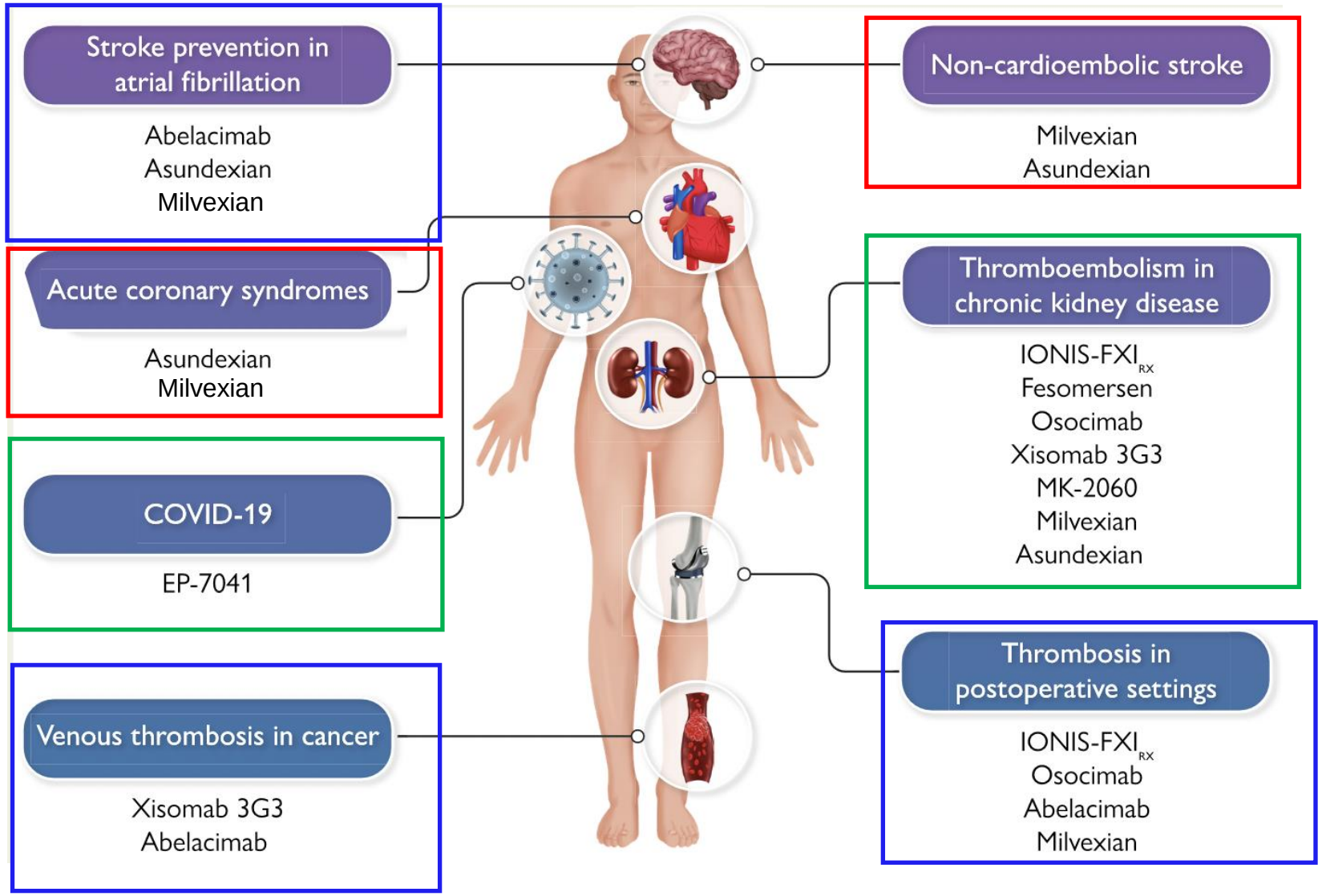
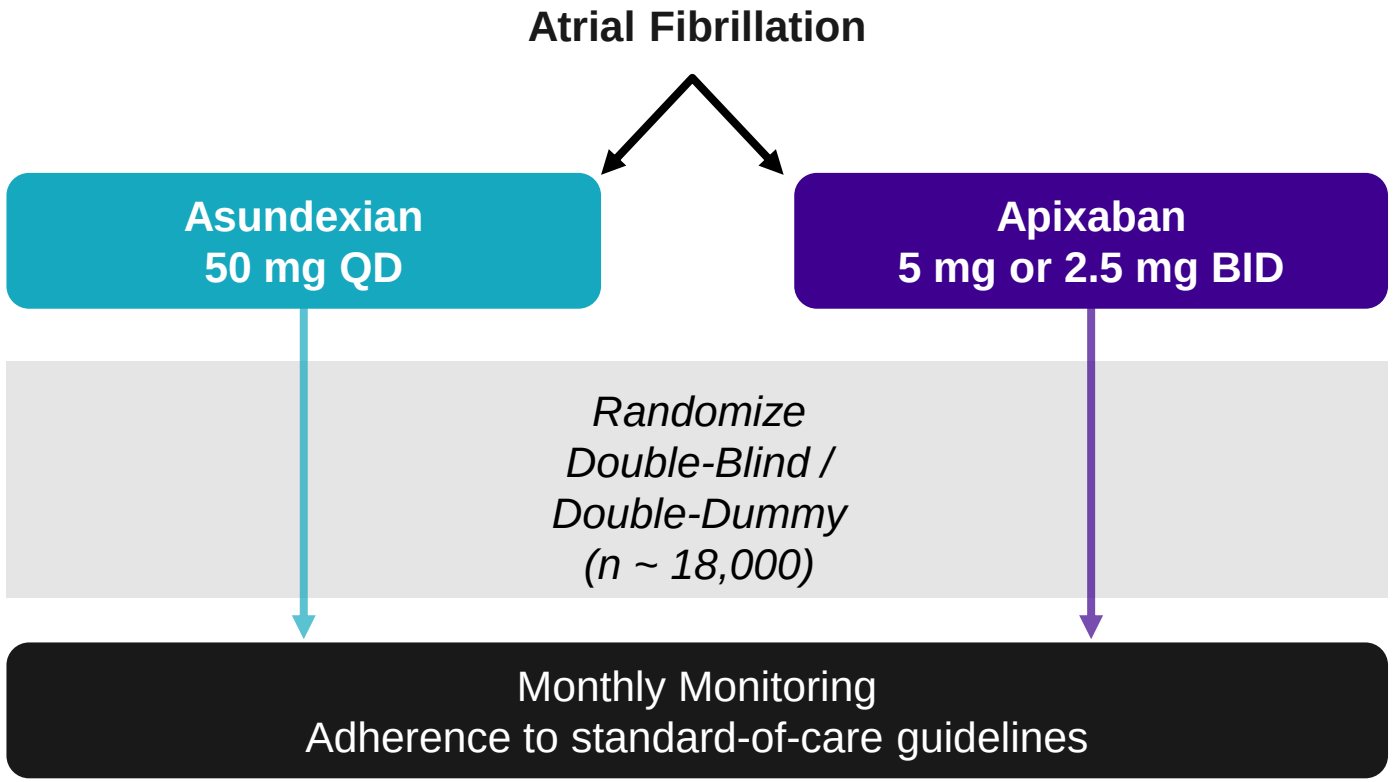
Factor XI inhibitors: cardiovascular perspectives

Raffaele De Caterina [1]*, Domenico Prisco [2], and John W. Eikelboom [3]



+ Surfaces artificielles : ***prothèse valvulaires meca,*** *circuits ECLS, dialyse,* ***LVAD****?*

Asundexian versus Apixaban in Patients with Atrial Fibrillation



Primary Efficacy Endpoint: Stroke or Systemic Embolism

Primary Safety Endpoint: ISTH Major Bleeding

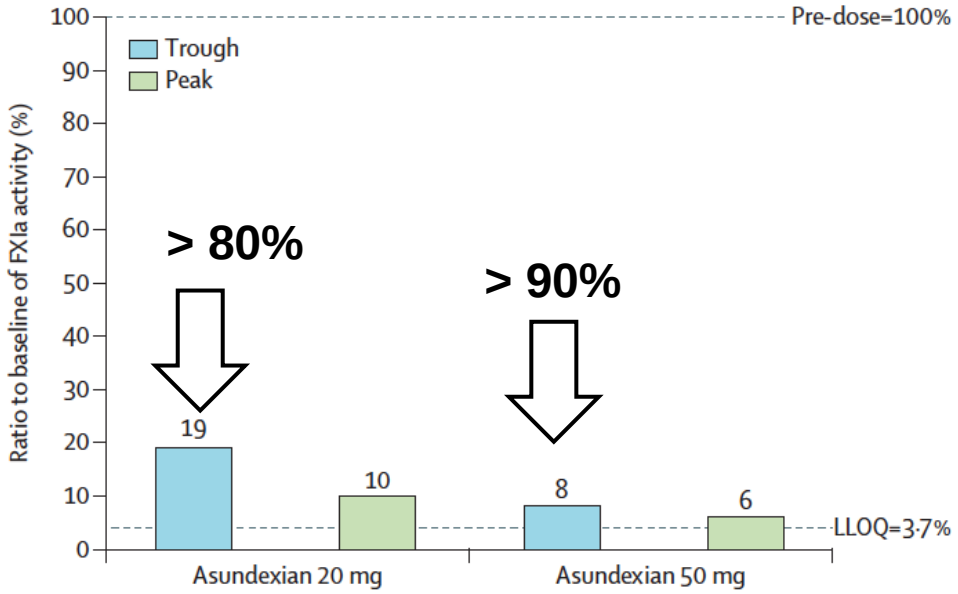
Primary Net Clinical Benefit Endpoint: Stroke or Systemic Embolism and ISTH Major Bleeding

- **Patients will be eligible for the study if they have:**
- Atrial fibrillation
- A CHA_2DS_2-VASc score ≥ 3 if male or ≥ 4 if female
- **OR**
- A CHA_2DS_2-VASc score of 2 if male or 3 if female **AND at least 1 of the following:**
  - age ≥ 70 years
  - previous stroke, transient ischemic attack, or systemic embolism
  - renal dysfunction with CKD-EPI eGFR < 50 mL/min/1.73m^2 within 14 days prior to randomization
  - prior episode of non-traumatic major bleeding
  - current single agent antiplatelet therapy planned for at least the next 6 months
  - ≤ 6 consecutive weeks of treatment with oral anticoagulant prior to randomization (OAC Naïve)

AsundeXIan – phase 2

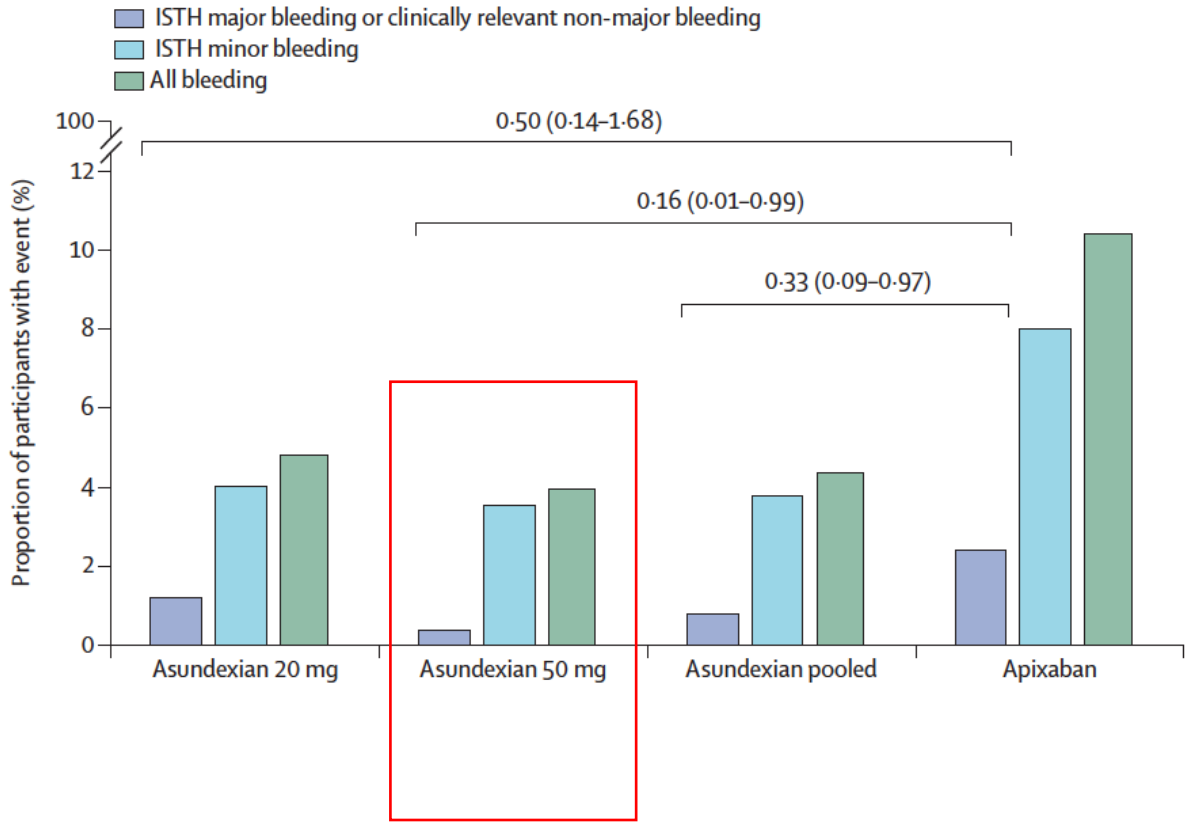
Piccini JP et al. The Lancet 2022, 399:383-1390

Inhibition activité du FXIa

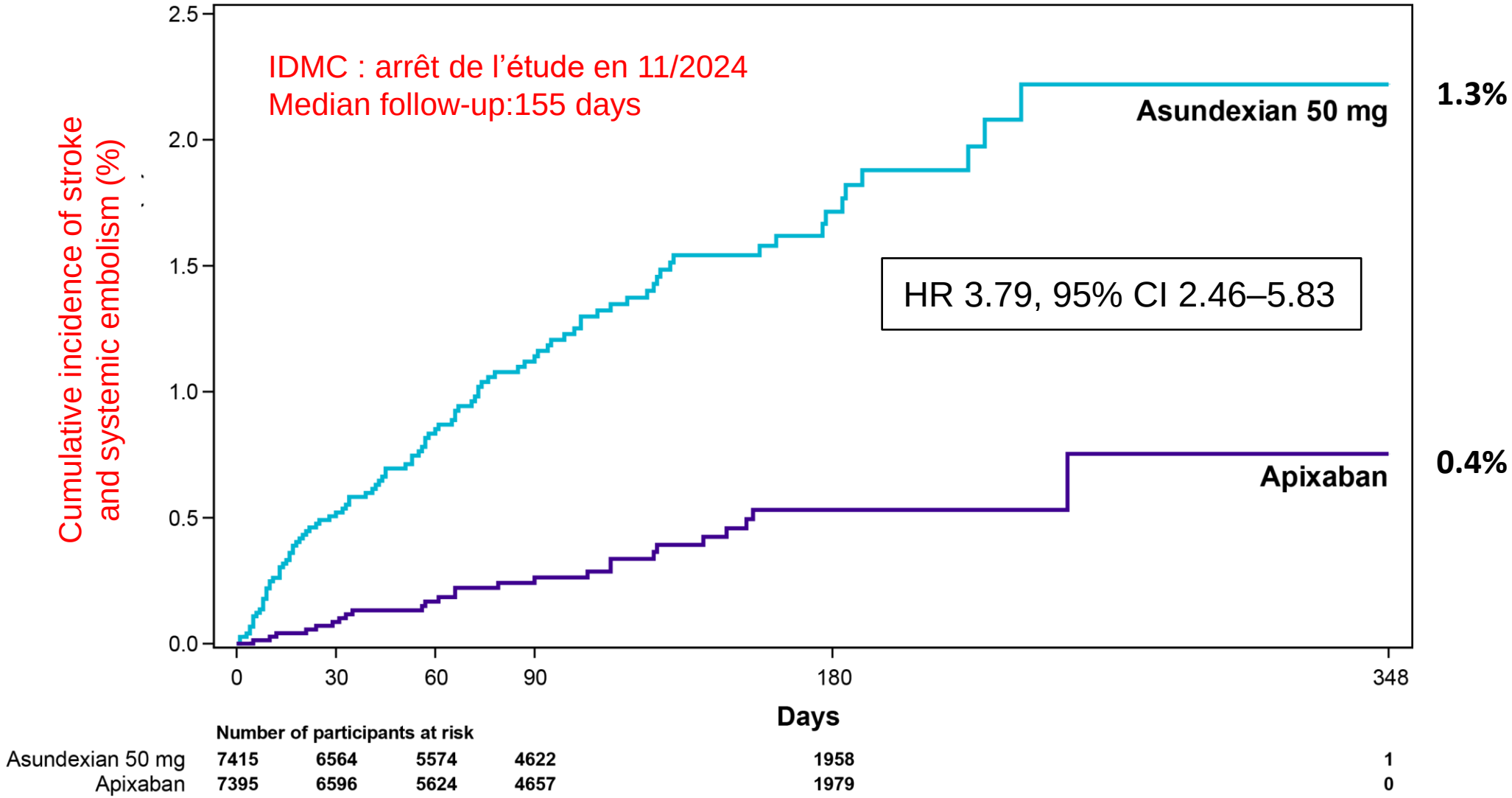


	Asundexian 20 mg		Asundexian 50 mg	
n	224	222	228	228
Analysis value (95% CI)	14·82 (12·65–16·99)	7·42 (6·33–8·51)	6·59 (5·15–8·02)	4·32 (3·60–5·05)
Mean ratio to baseline (95% CI)	0·19 (0·16–0·22)	0·10 (0·08–0·12)	0·08 (0·07–0·10)	0·06 (0·05–0·07)

Critère de SECURITE saignements (ISTH)



Asundexian versus Apixaban in Patients with Atrial Fibrillation



Critère de jugement principal EFFICACITE
AVC et embolie systémique

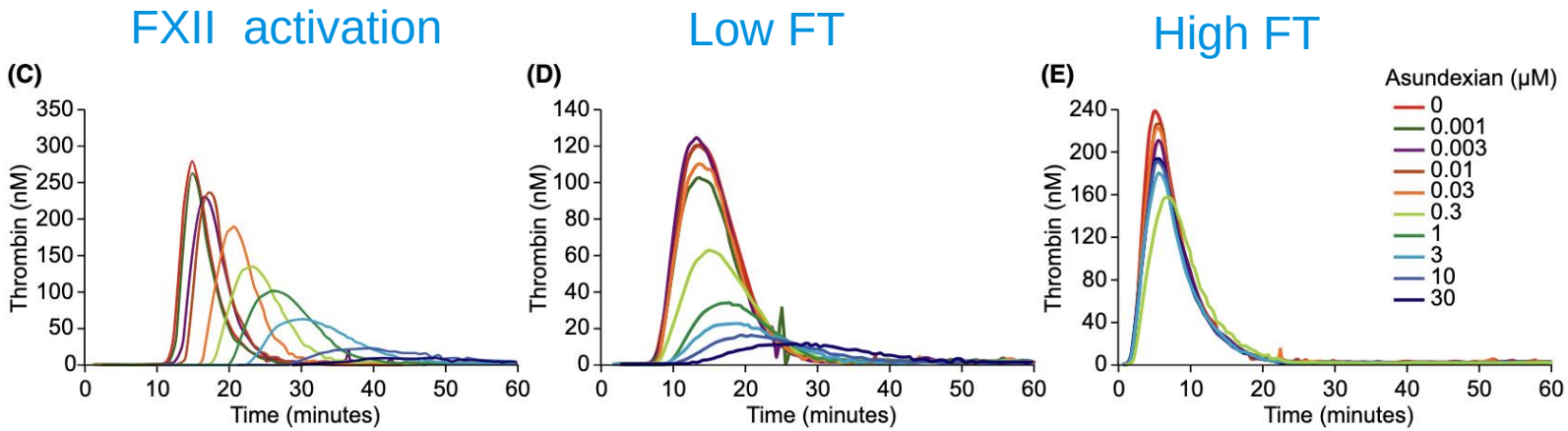
Efficacy Events According to ITT	Asundexian (N=7415)	Apixaban (N=7395)	Total (N=14,810)	csHR (95% CI)*
Stroke or SE	98 (1.3%)	26 (0.4%)	124 (0.8%)	3.79 (2.46–5.83)
Ischemic stroke or SE	96 (1.3%)	22 (0.3%)	118 (0.8%)	4.38 (2.76–6.96)
All-cause mortality	60 (0.8%)	71 (1.0%)	131 (0.9%)	0.84 (0.60–1.19)
Ischemic stroke	85 (1.1%)	21 (0.3%)	106 (0.7%)	4.06 (2.52–6.54)
CV death	48 (0.6%)	44 (0.6%)	92 (0.6%)	1.09 (0.72–1.64)
CV death, MI, or stroke	155 (2.1%)	77 (1.0%)	232 (1.6%)	2.02 (1.54–2.66)

Critère de jugement principal SECURITE saignements majeurs ISTH

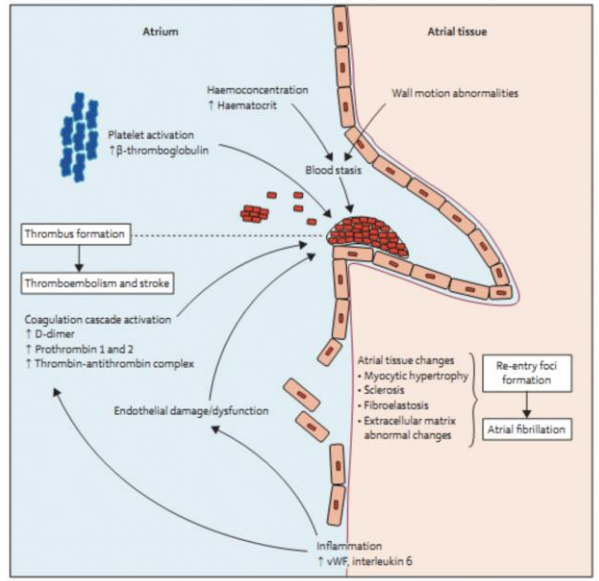
	Asundexian 50 mg (N=7373)	Apixaban (N=7364)	Total (N=14,737)	csHR (95% CI)†
ISTH major bleeding	17 (0.2%)	53 (0.7%)	70 (0.5%)	0.32 (0.18–0.55) ⇩ **68%**
ISTH major and CRNM bleeding	83 (1.1%)	188 (2.6%)	271 (1.8%)	0.44 (0.34–0.57)
ISTH CRNM bleeding	67 (0.9%)	140 (1.9%)	207 (1.4%)	0.48 (0.36–0.64)
Hemorrhagic stroke	1 (<0.1%)	6 (0.1%)	7 (<0.1%)	0.17 (0.02–1.42)
Symptomatic intracranial hemorrhage	3 (<0.1%)	18 (0.2%)	21 (0.1%)	0.16 (0.05–0.55)
Fatal bleeding	0 (0%)	4 (0.1%)	4 (<0.1%)	Not calculated
ISTH minor bleeding	187 (2.5%)	317 (4.3%)	504 (3.4%)	0.59 (0.49–0.70)
Stroke, SE, or ISTH major bleeding (net clinical benefit endpoint)	120 (1.6%)	75 (1.0%)	195 (1.3%)	1.61 (1.21–2.15)

Une réalité complexe

1/ l'inhibition du FXIa n'est pas efficace dans cette indication ?



Effect of asundexian on thrombin generation initiated by the FXII activating agent (C) or 0.1 pM or 5 pM tissue factor (D and E)



2/ la dose elle trop faible? le schéma d'administration non optimal?

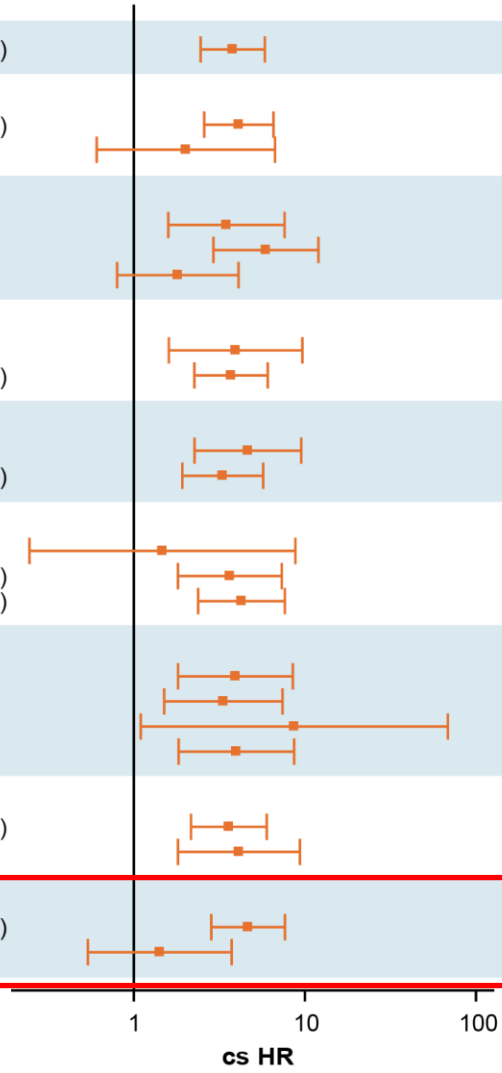
3/ ce n'est pas la bonne population?

4/ pas d'effet antiplaquettaire comme les antiXa?

5/ effet rebond à l'arrêt des antiXa?

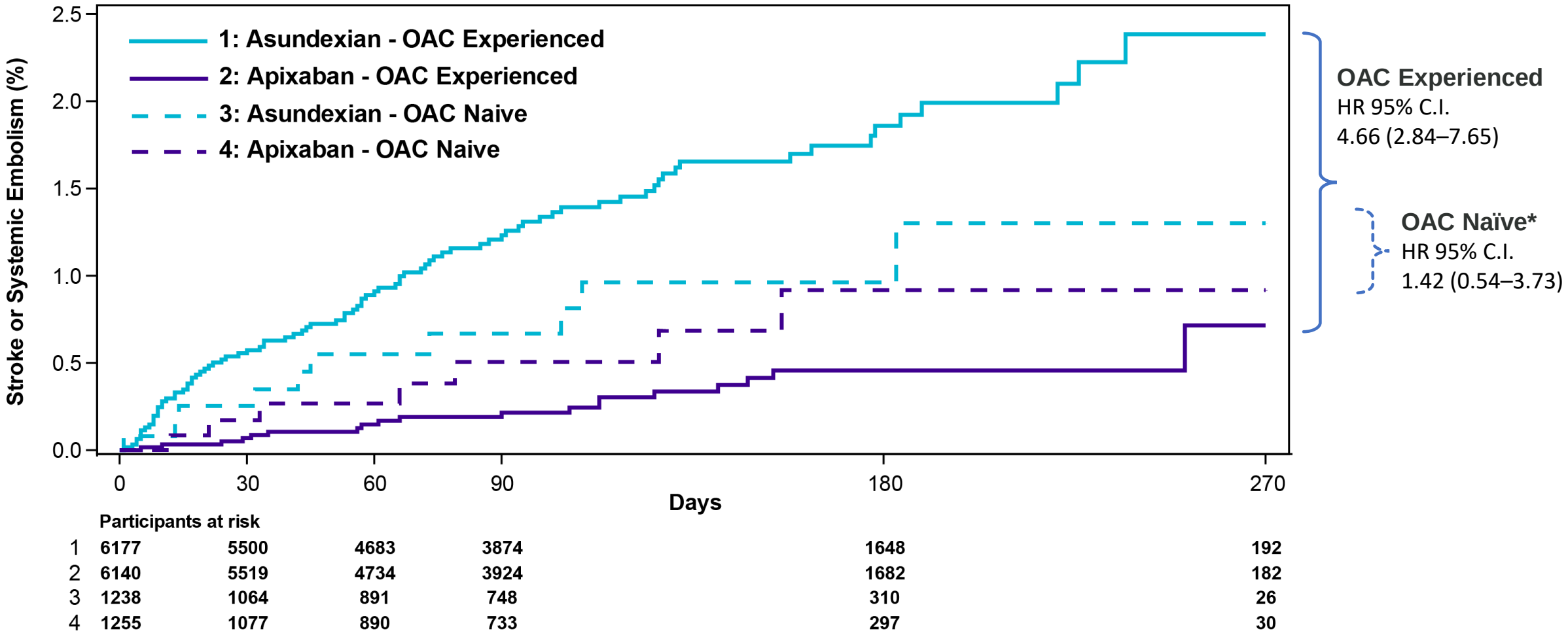
Analyse en sous-groupes

	Asundexian 50mg n/N (%)	Apixaban n/N (%)	CoxPH model csHR (95% CI)
Overall	98/7415 (1.3%)	26/7395 (0.4%)	3.79 (2.46, 5.83)
Single agent antiplatelet therapy planned to continue for ≥6 months after randomization			
No	90/6673 (1.3%)	22/6652 (0.3%)	4.11 (2.58, 6.55)
Yes	8/742 (1.1%)	4/743 (0.5%)	2.01 (0.61, 6.69)
eGFR group (mL/min/1.73m²)			
<50	29/1347 (2.2%)	8/1289 (0.6%)	3.48 (1.59, 7.60)
50 to 80	53/3854 (1.4%)	9/3854 (0.2%)	5.92 (2.92, 11.99)
>80	16/2133 (0.8%)	9/2162 (0.4%)	1.81 (0.80, 4.09)
Pooled CHA_2DS_2-VASc score Group 1			
≤3 for males and ≤4 for females	23/3077 (0.7%)	6/3132 (0.2%)	3.93 (1.60, 9.66)
>3 for males and >4 for females	75/4338 (1.7%)	20/4263 (0.5%)	3.70 (2.26, 6.06)
Sex			
Female	43/2656 (1.6%)	9/2558 (0.4%)	4.64 (2.26, 9.52)
Male	55/4759 (1.2%)	17/4837 (0.4%)	3.31 (1.92, 5.70)
Age group			
<65 years	3/730 (0.4%)	2/715 (0.3%)	1.47 (0.25, 8.80)
65–75 years	37/3455 (1.1%)	10/3403 (0.3%)	3.64 (1.81, 7.32)
>75 years	58/3230 (1.8%)	14/3277 (0.4%)	4.26 (2.38, 7.64)
Atrial fibrillation pattern			
Paroxysmal	33/2760 (1.2%)	8/2641 (0.3%)	3.93 (1.81, 8.50)
Persistent	25/1773 (1.4%)	8/1805 (0.4%)	3.34 (1.50, 7.40)
Long-standing persistent	9/436 (2.1%)	1/428 (0.2%)	8.67 (1.10, 68.48)
Permanent	31/2327 (1.3%)	8/2384 (0.3%)	3.97 (1.83, 8.65)
History of stroke or TIA			
No	67/6026 (1.1%)	19/6090 (0.3%)	3.59 (2.16, 5.98)
Yes	31/1389 (2.2%)	7/1305 (0.5%)	4.11 (1.81, 9.34)
≤6 consecutive weeks of treatment with oral anticoagulant prior to randomization			
No	88/6177 (1.4%)	19/6140 (0.3%)	4.66 (2.84, 7.65)
Yes	10/1238 (0.8%)	7/1255 (0.6%)	1.42 (0.54, 3.73)



P <0.05

Sous-groupe : Patients naïfs vs patients sous anticoagulants au moment de la randomisation



Participants at risk

1	6177	5500	4683	3874	1648	192
2	6140	5519	4734	3924	1682	182
3	1238	1064	891	748	310	26
4	1255	1077	890	733	297	30

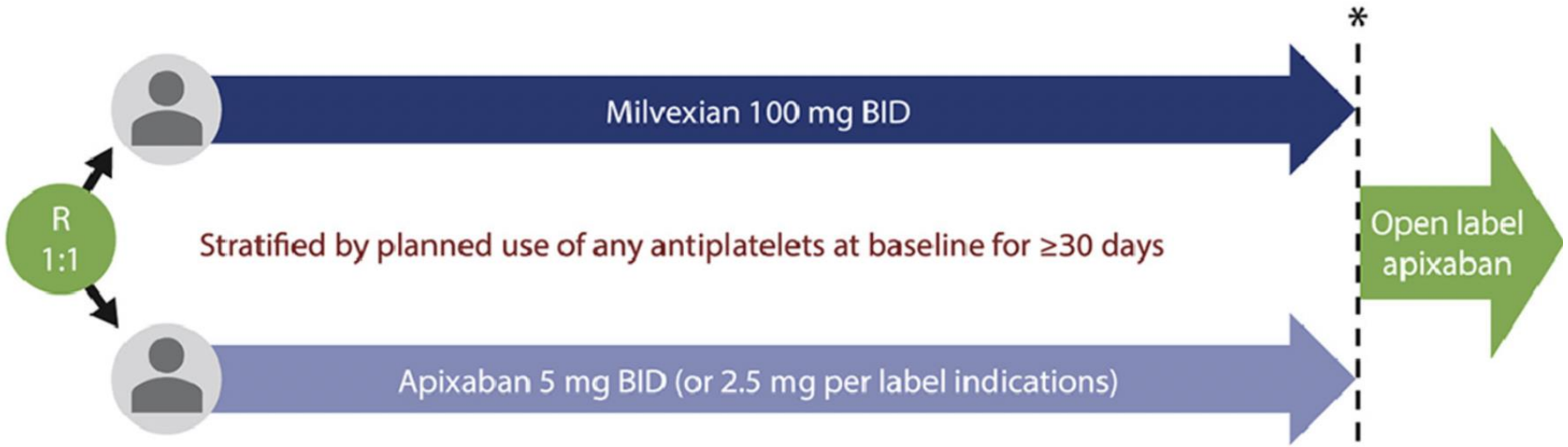
* ≤ 6 consecutive weeks of treatment with oral anticoagulant prior to randomization (OAC Naïve)

MilveXIan – phase 3

Global phase 3 event-driven trial

Inclusion criteria

- Age ≥18 years
- Atrial fibrillation or atrial flutter
- Eligible for anticoagulation
- One or both of the following categories of risk:
  a. One or more of the following:
     i. Age ≥75 years
     ii. History of stroke
  b. Two or more of the following:
     i. Age 65–74 years
     ii. Hypertension
     iii. Diabetes
     iv. Vascular disease (CAD, MI, PAD)
     v. Congestive heart failure



Primary Efficacy Objective

To evaluate if milvexian is non-inferior to apixaban for the prevention of stroke and systemic embolism

Principal Safety Objective

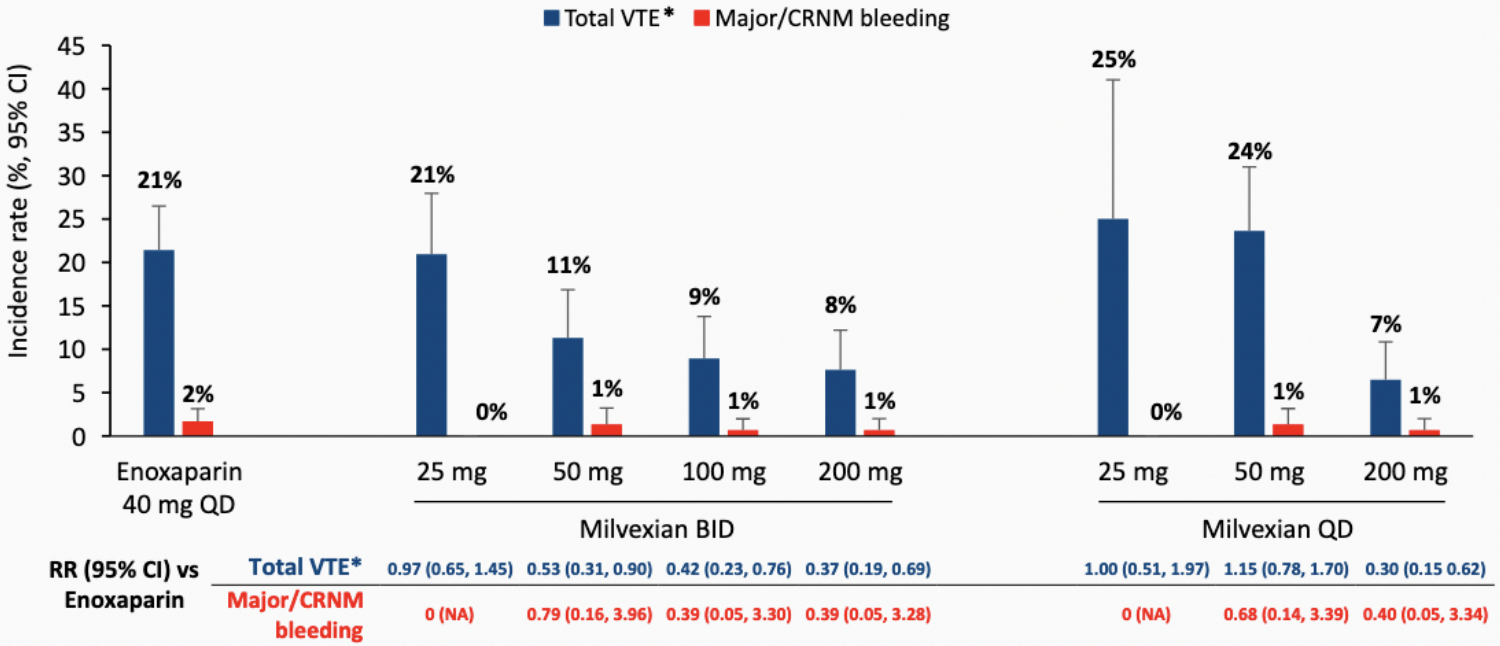
To evaluate if milvexian is superior to apixaban in reducing the endpoint of ISTH major bleeding and the composite endpoint of ISTH major and CRNM bleeding events

*Minimum of 13 weeks of treatment with study drug after the last patient is randomized.

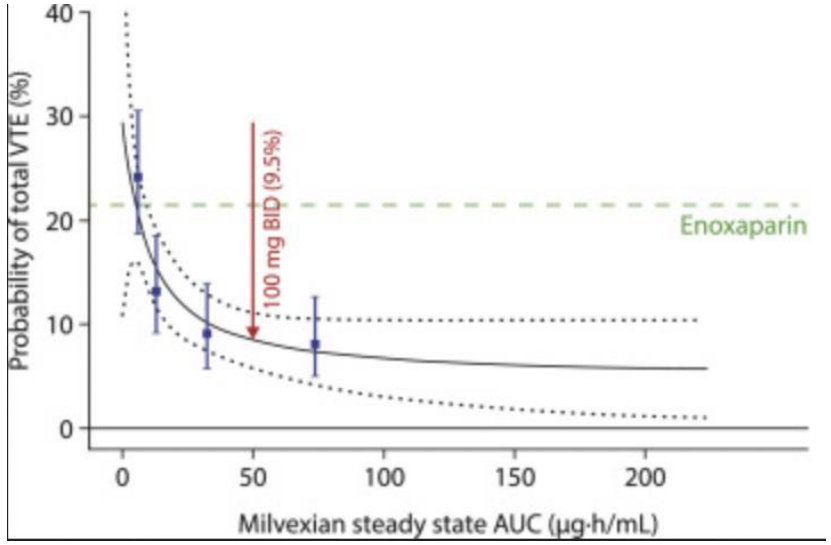
MilveXian – phase 2

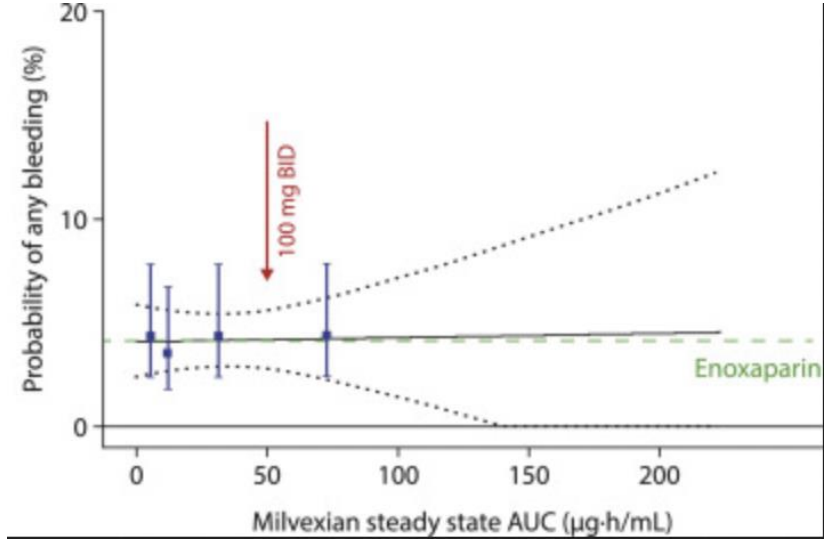
AXIOMATIC-TKR

N= 1242 PTG



RR (95% CI) vs Enoxaparin	25 mg BID	50 mg BID	100 mg BID	200 mg BID	25 mg QD	50 mg QD	200 mg QD
Total VTE*	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)
Major/CRNM bleeding	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)





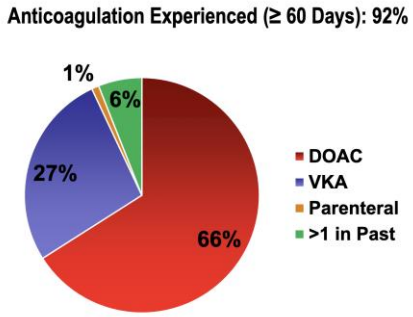
Abelacimab – phase 2

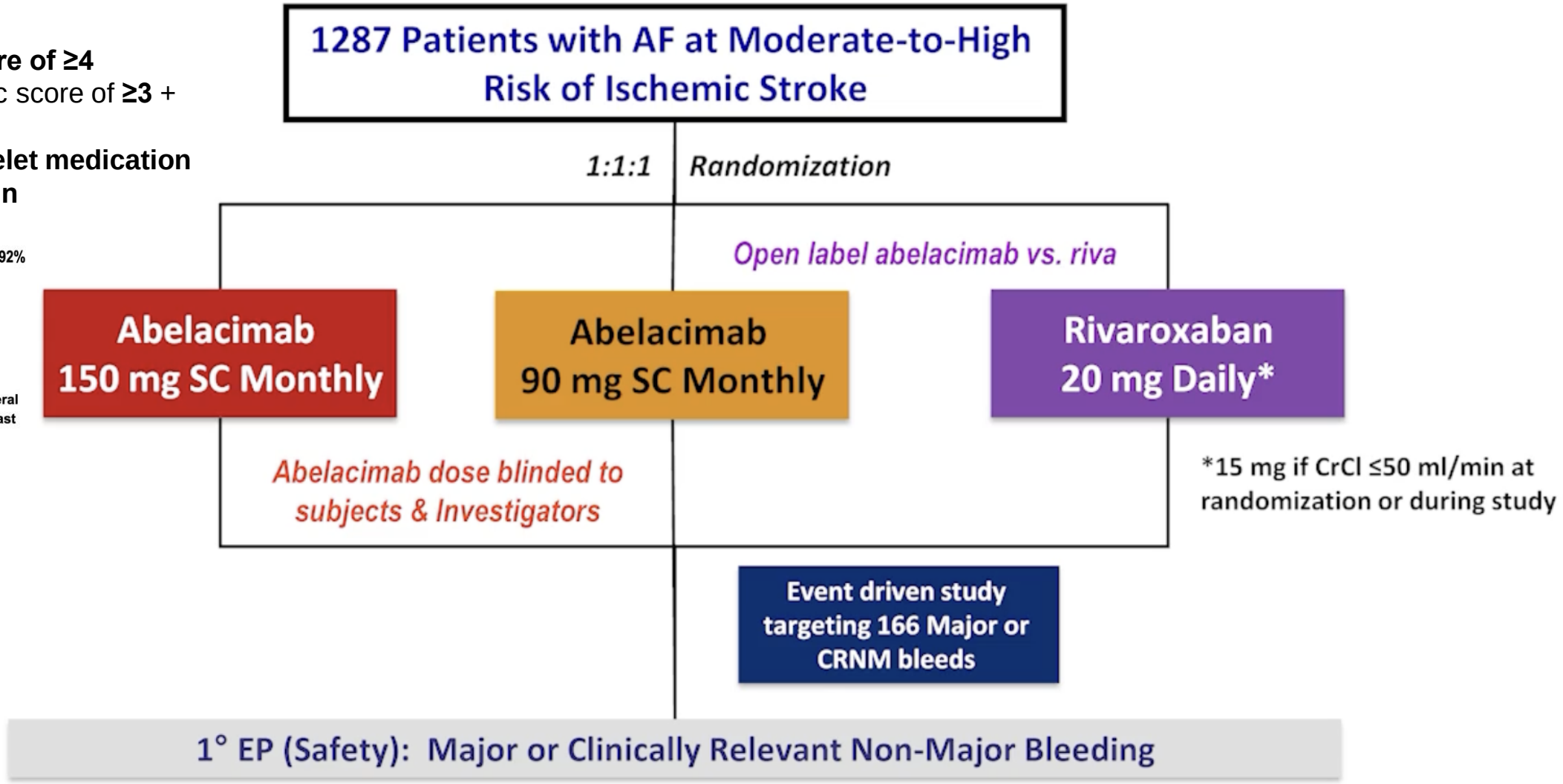
AZALEA TIMI 71

AHA 2023

Inclusion criteria:

- Age ≥55 years
- **CHA_2DS_2-VASc score of ≥4**
- OR a CHA_2DS_2-VASc score of **≥3** + ≥1 of the following:
  - **use of antiplatelet medication**
  - CrCl **≤50 mL/min**

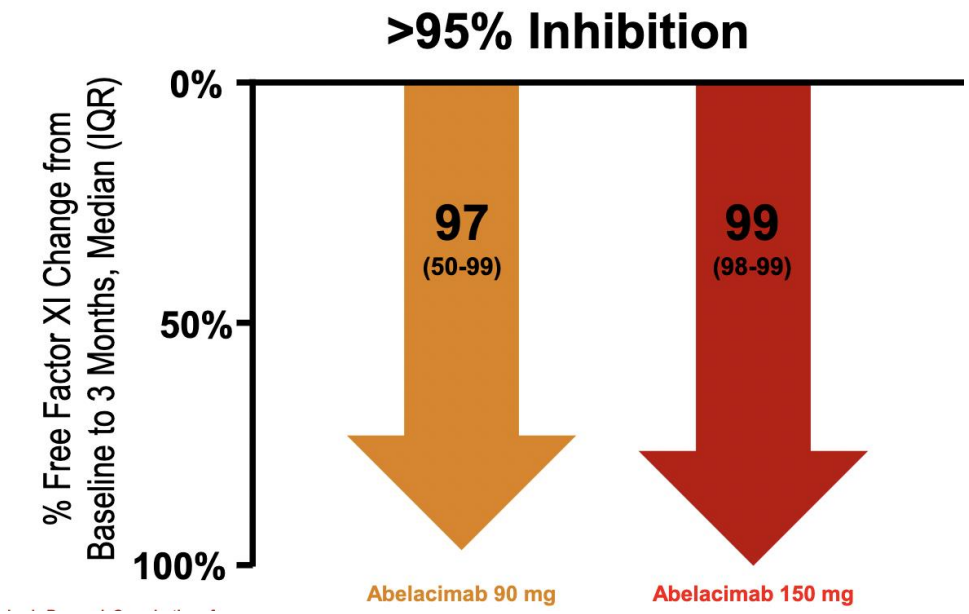




AZALEA TIMI 71

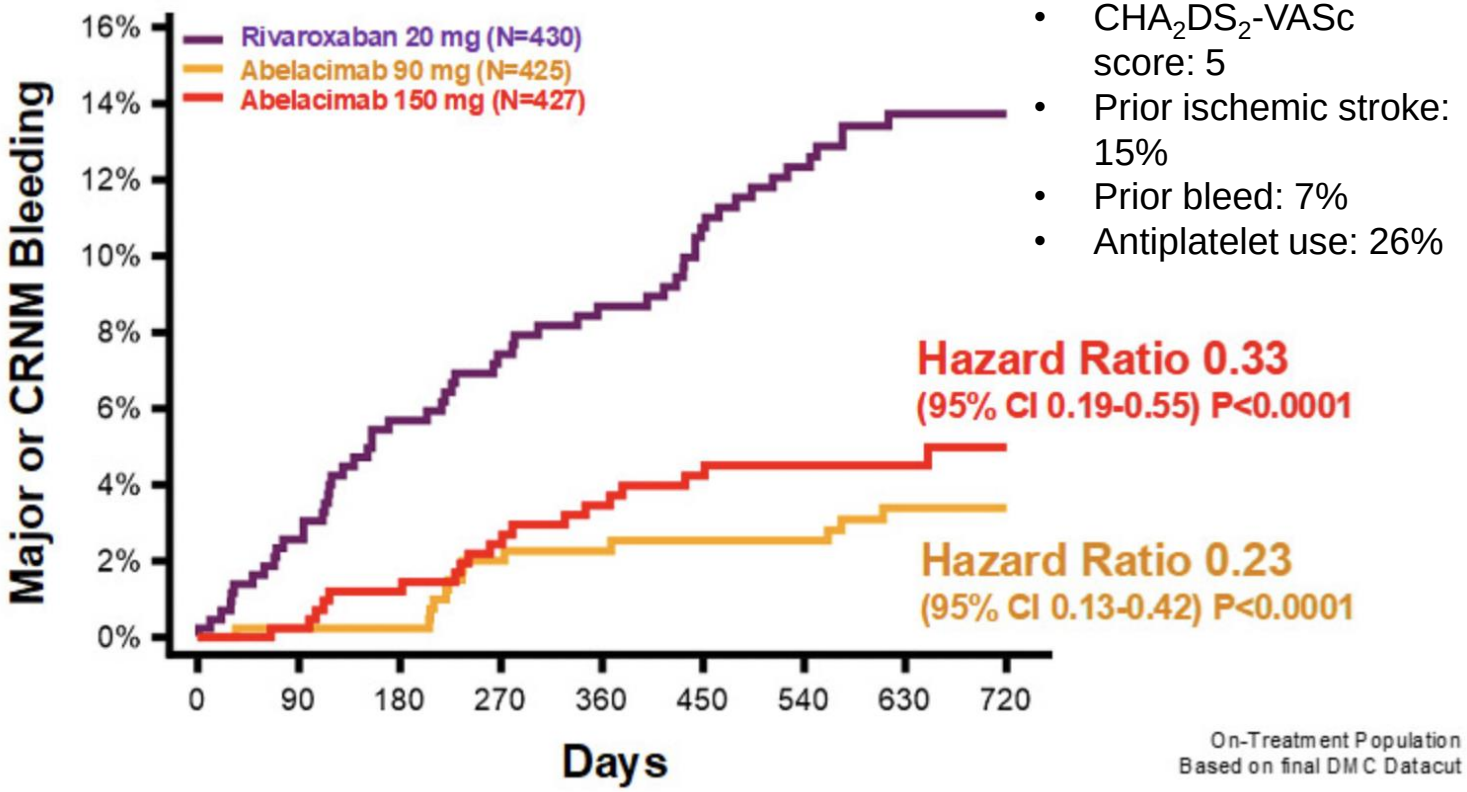
AHA 2023

Inhibition activité du FXIa



Critère de SECURITE saignements (ISTH)

- age 74 ans
- 44 % female
- CHA_2DS_2-VASc score: 5
- Prior ischemic stroke: 15%
- Prior bleed: 7%
- Antiplatelet use: 26%



Exploratoire EFFICACITE
AVC et embolies systémiques

AZALEA TIMI 71

AHA 2023

Endpoint	Riva 20 mg (N=430) Incidence Rate	Abelacimab 150 mg (N=427) Incidence Rate	HR (95% CI)	P Value	Abelacimab 90 mg (N=425) Incidence Rate	HR (95% CI)	P-Value
Stroke or SEE	1.0	1.1	1.13 (0.41-3.12)	0.81	1.4	1.45 (0.55-3.80)	0.45
Stroke	1.0	1.1	1.13 (0.41-3.12)	0.81	1.4	1.45 (0.55-3.80)	0.45
Ischemic	0.7	1.1	1.59 (0.52-4.85)	0.42	1.3	1.82 (0.61-5.45)	0.28
Hemorrhagic	0.3	0	N/A	N/A	0.1	0.51 (0.05-5.62)	0.58
All-Cause Death	3.1	2.4	0.77 (0.41-1.46)	0.43	2.8	0.93 (0.51-1.71)	0.83
Net Clinical Outcome	11.3	5.5	0.49 (0.33-0.71)	<0.001	5.6	0.49 (0.34-0.73)	<0.001

Exploratoire EFFICACITE
AVC et embolies systémiques

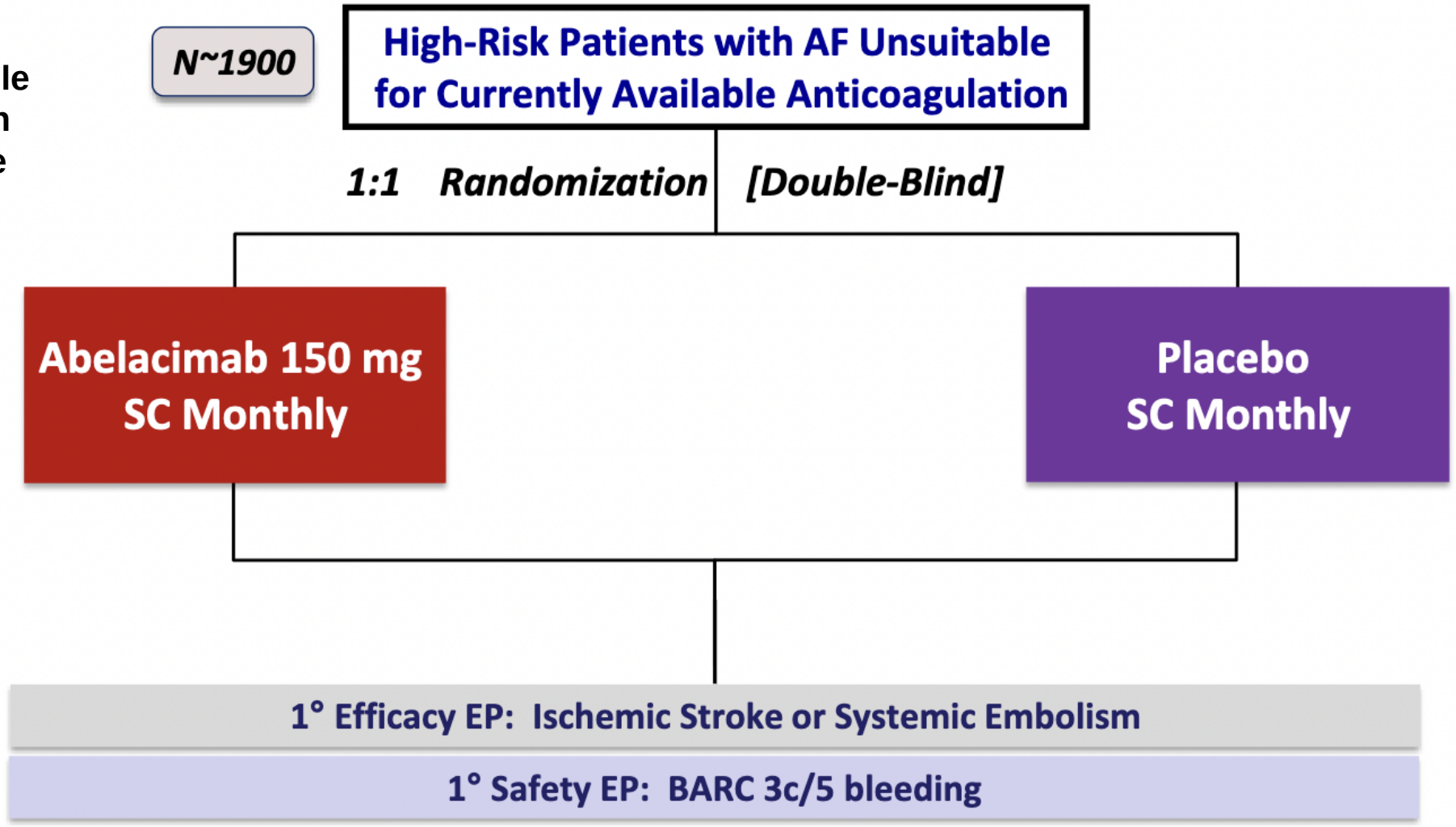
PACIFIC AF

Piccini JP et al. The Lancet 2022, 399:383-1390

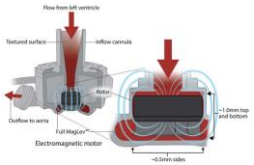
	Asundexian 20 mg N = 251 IR (90% CI)	Asundexian 50 mg N = 254 IR (90% CI)	Apixaban N = 250 IR (90% CI)	Total N = 755 IR (90% CI)
CV death, MI, ischemic stroke, or systemic embolism	2 (0.80 %)	4 (1.57 %)	3 (1.20 %)	9 (1.19 %)
CV death	1 (0.40 %)	3 (1.18 %)	3 (1.20 %)	7 (0.93 %)
MI	0	1 (0.39 %)	0	1 (0.13 %)
Ischemic stroke	2 (0.80 %)	1 (0.39 %)	0	3 (0.40 %)
Systemic embolism	0	0	0	0
All cause mortality (ITT)	2 (0.80 %)	4 (1.57 %)	4 (1.60 %)	10 (1.32 %)

Abelacimab – phase 3

Age 65-74 +
CHA2DS2VASc **≥5**
OR age ≥75 and a
CHA2DS2VASc **≥4**
Judged by the responsible physician or by their own decision to be unsuitable for oral anticoagulation



Ce n’est pas fini!



Stroke prevention in atrial fibrillation

Abelacimab
Asundexian
Milvexian

Acute coronary syndromes

Asundexian
Milvexian

COVID-19

EP-7041

Venous thrombosis in cancer

Xisomab 3G3
Abelacimab

Non-cardioembolic stroke

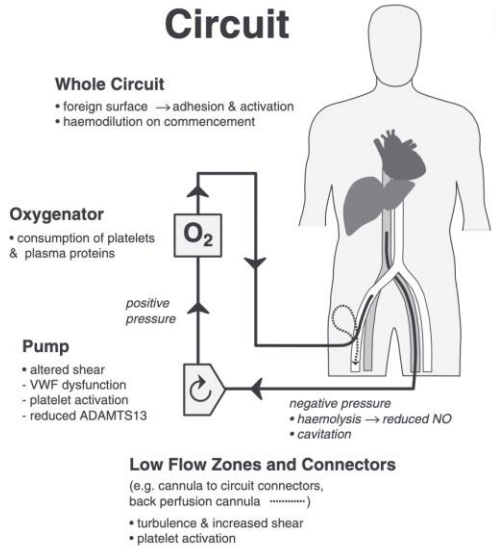
Milvexian
Asundexian

Thromboembolism in chronic kidney disease

IONIS-FXI$_{RX}$
Fesomersen
Osocimab
Xisomab 3G3
MK-2060
Milvexian
Asundexian

Thrombosis in postoperative settings

IONIS-FXI$_{RX}$
Osocimab
Abelacimab
Milvexian



+ Surfaces artificielles : ***prothèse valvulaires meca,*** *circuits ECLS, dialyse,* ***LVAD****?*

11-13 SEPT. 2024
CONGRÈS FRANÇAIS D'HÉMOSTASE
LILLE GRAND PALAIS

Les anti-FXI, mythe ou réalité complexe ?

Utilisation des anti-XI dans la fibrillation atriale

Anne-Céline Martin
Hôpital Européen Georges Pompidou, Paris
INSERM UMRS 1140 Thérapies Innovantes en hémostase
Université Paris Cité

MERCI

Liens d'intérêt : Abbott, Alliance BMS-Pfizer, Bayer, Boehringer Ingenheim, Caramt, Novartis, Sanofi