11° CONGRESSO NAZIONALE

CAMPUS Cuore

Quello che le Linee Guida Non Dicono

Napoli
5-6 aprile 2024

Inibitori del Fattore XI nella terapia antitrombotica in Cardioncologia

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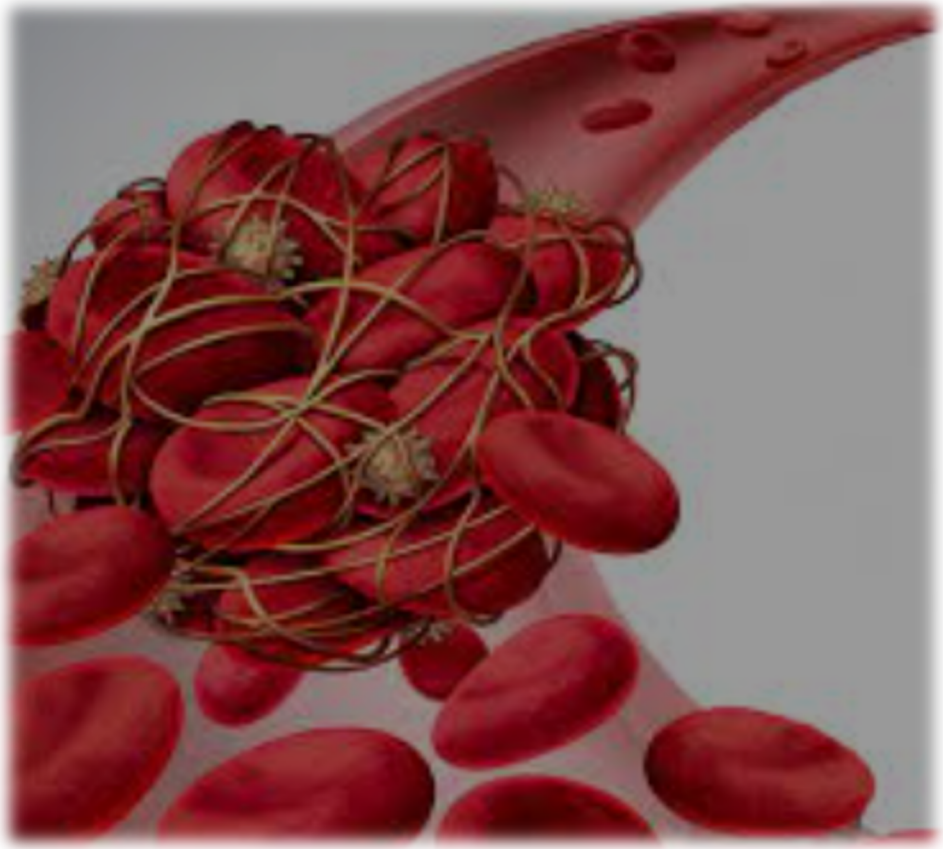
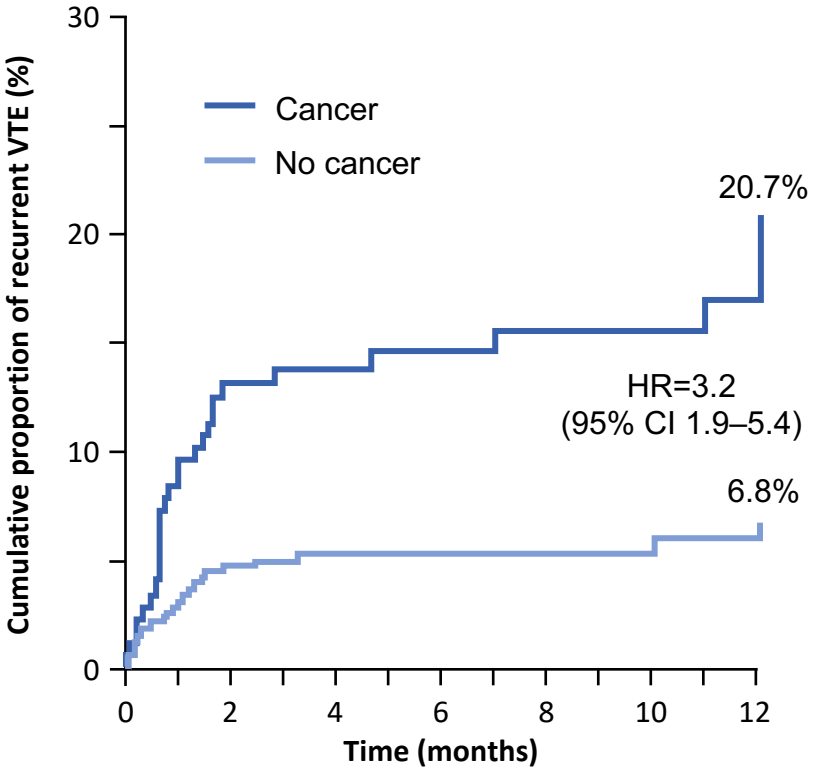
Presidente Associazione Italiana Cardioncologia(AICO)

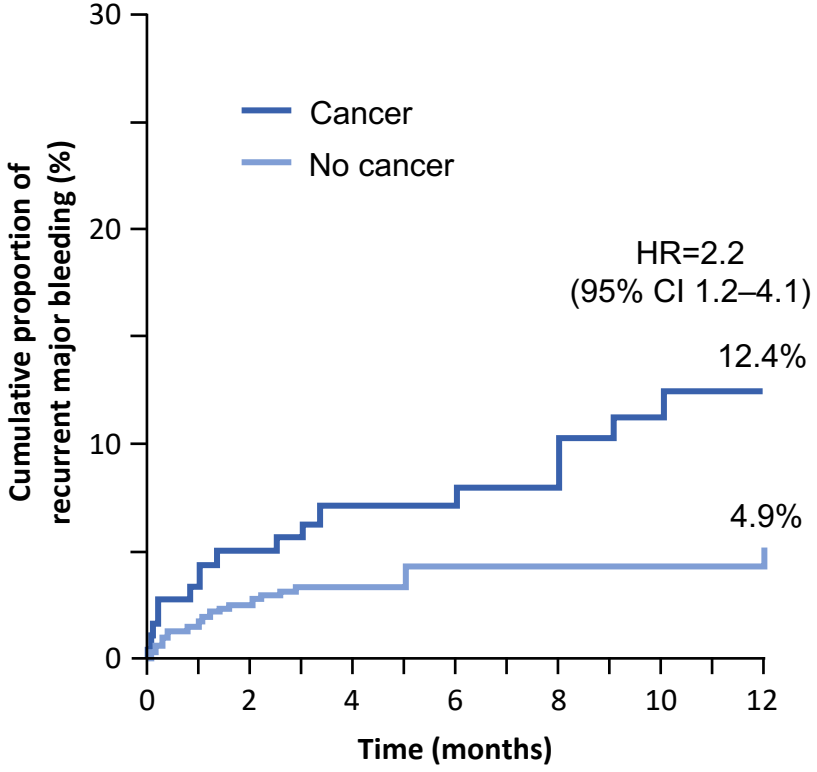
Treatment of VTE



Challenges of Anticoagulation in CAT Highlights the High Risk of VTE Recurrence and Major Bleeding

Risk of events in patients receiving anticoagulation therapy for VTE





*Defined as overt and associated with either a decrease in the haemoglobin level (at least 2.0 g/dl) or the need for transfusion (≥2 units of blood), if it was retroperitoneal or intracranial, or if the treatment had to be discontinued permanently.

Prandoni P et al. Blood 2002;100:3484–3488

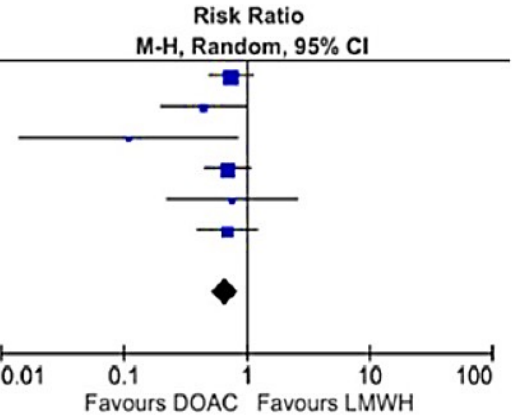
Data from RTCs comparing DOACS and LMWH in CAT

DOACs significantly decreased the risk of CAT recurrence (RR, 0.67; 95%CI, 0.52– 0.85), with a non-significant increase in the risk of major bleeding (RR, 1.17; 95%CI, 0.82–1.67).

Recurrent VTE

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	34	522	46	524	33.5%	0.74 [0.48, 1.14]
SELECT-D	8	203	18	203	9.3%	0.44 [0.20, 1.00]
ADAM-VTE	1	145	9	142	1.4%	0.11 [0.01, 0.85]
CARAVAGGIO	32	576	46	579	32.0%	0.70 [0.45, 1.08]
CASTA-DIVA	4	74	6	84	4.1%	0.76 [0.22, 2.58]
CANVAS	20	330	27	308	19.6%	0.69 [0.40, 1.21]
Total (95% CI)		**1850**		**1840**	**100.0%**	**0.67 [0.52, 0.85]**
Total events	99		152			

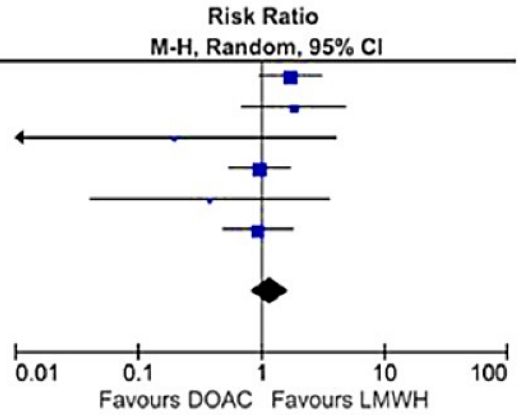
Heterogeneity: Tau² = 0.00; Chi² = 4.36, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 3.22 (P = 0.001)



Major Bleeding

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	29	522	17	524	29.2%	1.71 [0.95, 3.08]
SELECT-D	11	203	6	203	12.2%	1.83 [0.69, 4.86]
ADAM-VTE	0	145	2	142	1.4%	0.20 [0.01, 4.04]
CARAVAGGIO	22	576	23	579	30.3%	0.96 [0.54, 1.71]
CASTA-DIVA	1	74	3	84	2.5%	0.38 [0.04, 3.56]
CANVAS	17	330	17	308	24.5%	0.93 [0.49, 1.80]
Total (95% CI)		**1850**		**1840**	**100.0%**	**1.17 [0.82, 1.67]**
Total events	80		68			

Heterogeneity: Tau² = 0.02; Chi² = 5.66, df = 5 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.85 (P = 0.39)



RCT, randomized controlled trial.
Frere C, et al. J Hematol Oncol. 2022;15:69.

Data from RTCs comparing DOACS and LMWH in CAT

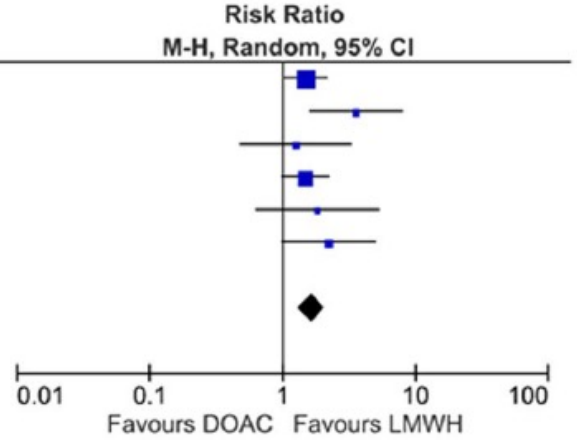
DOACS significantly increase the risk of clinically relevant nonmajor bleeding (RR 1.66; 95%CI, 1.31–2.09) and no difference in all-cause mortality rates.

C. Clinically relevant non major bleeding

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	64	522	43	524	40.6%	1.49 [1.04, 2.16]
SELECT-D	25	203	7	203	8.2%	3.57 [1.58, 8.07]
ADAM-VTE	9	145	7	142	5.9%	1.26 [0.48, 3.29]
CARAVAGGIO	52	576	35	579	32.1%	1.49 [0.99, 2.26]
CASTA-DIVA	8	74	5	84	4.8%	1.82 [0.62, 5.31]
CANVAS	19	330	8	308	8.3%	2.22 [0.98, 4.99]
Total (95% CI)		**1850**		**1840**	**100.0%**	**1.66 [1.31, 2.09]**
Total events	177		105			

Heterogeneity: Tau² = 0.00; Chi² = 4.82, df = 5 (P = 0.44); I² = 0%

Test for overall effect: Z = 4.23 (P < 0.0001)

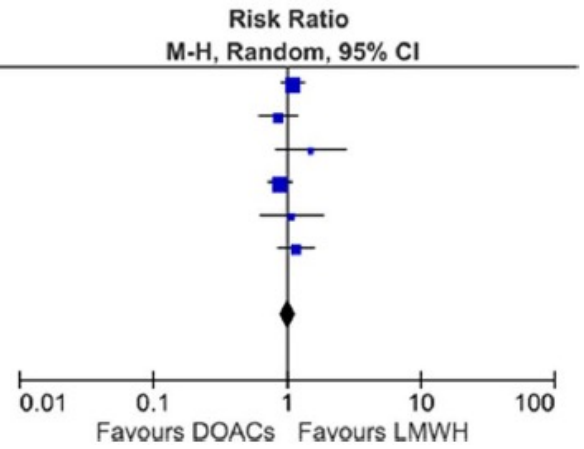


D. Overall Mortality

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	140	522	127	524	29.9%	1.11 [0.90, 1.36]
SELECT-D	48	203	56	203	13.6%	0.86 [0.61, 1.20]
ADAM-VTE	23	145	15	142	4.4%	1.50 [0.82, 2.76]
CARAVAGGIO	135	576	153	579	31.4%	0.89 [0.73, 1.08]
CASTA-DIVA	19	74	20	84	5.5%	1.08 [0.63, 1.86]
CANVAS	71	330	57	308	15.3%	1.16 [0.85, 1.59]
Total (95% CI)		**1850**		**1840**	**100.0%**	**1.02 [0.89, 1.16]**
Total events	436		428			

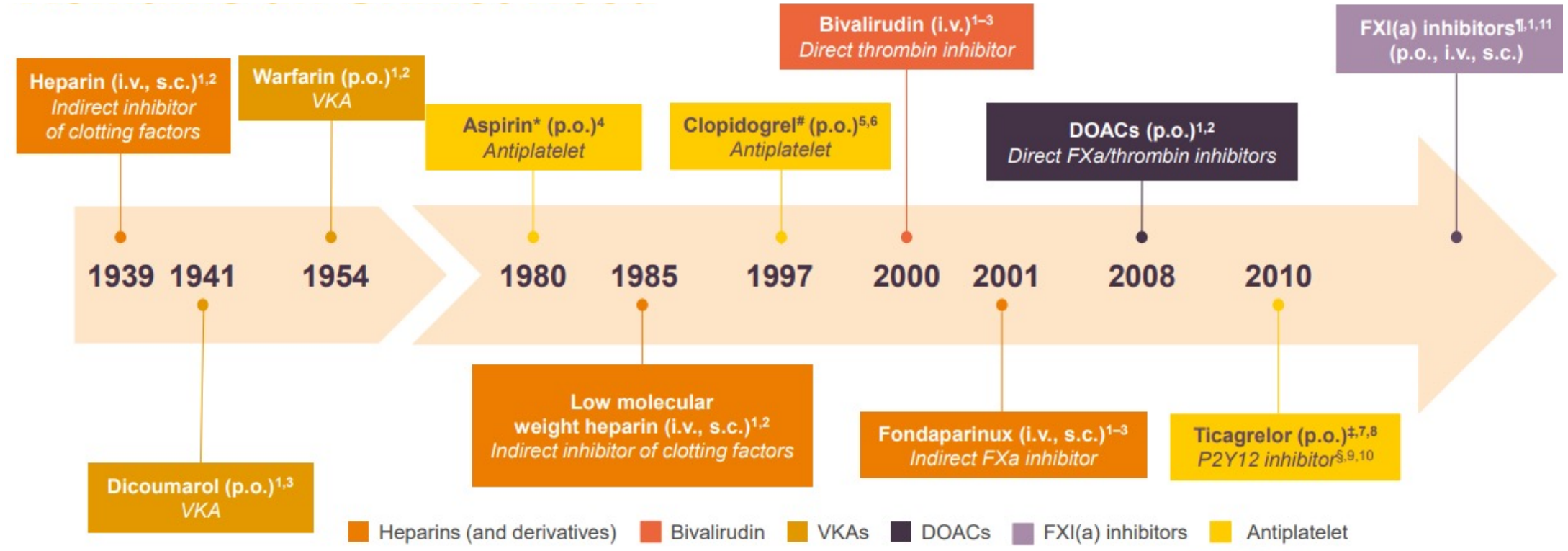
Heterogeneity: Tau² = 0.00; Chi² = 5.76, df = 5 (P = 0.33); I² = 13%

Test for overall effect: Z = 0.25 (P = 0.80)



Frere et al., Journal of Hematology & Oncology 2022

Antithrombotic Therapies Have Come Far, but There Remains an Unmet Need

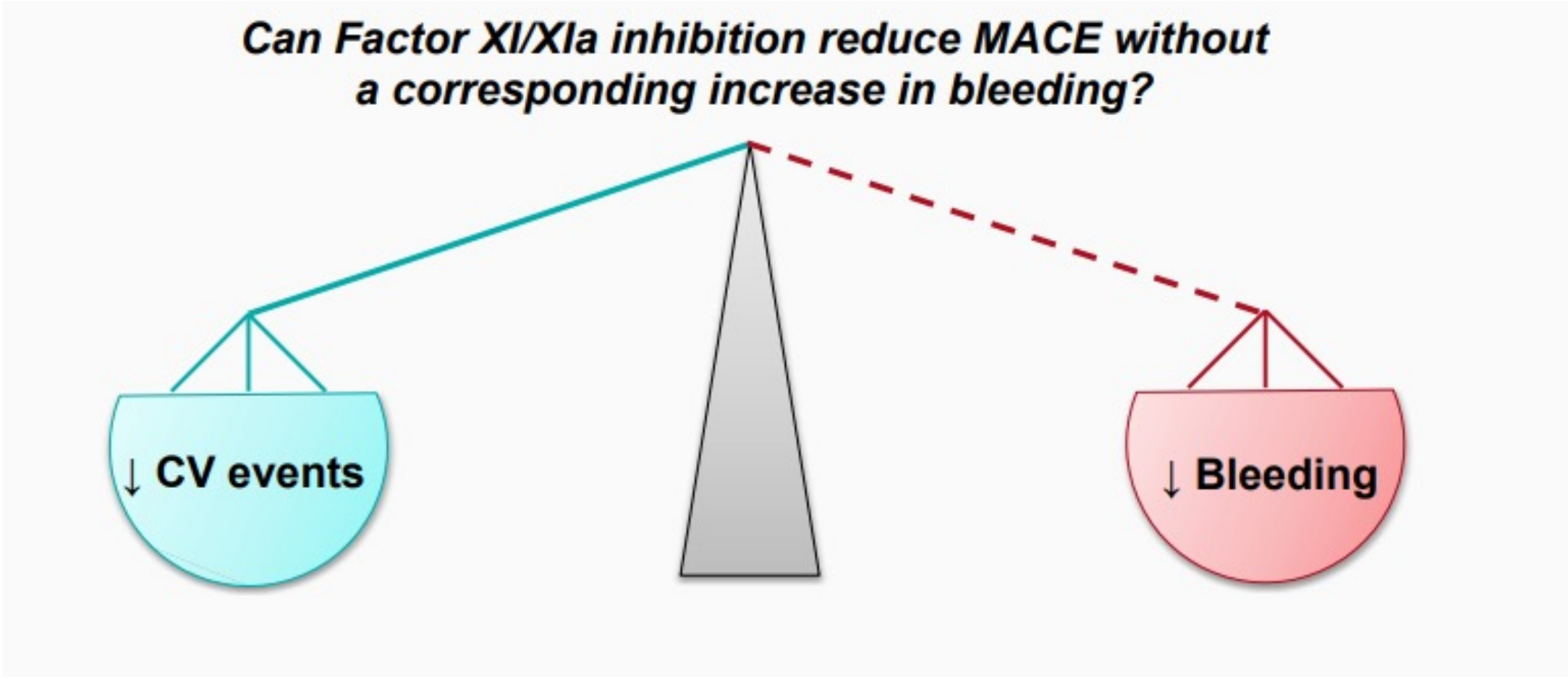


*Year aspirin approved for stroke prevention. #EU approval in 1998, FDA approval in 1997. ‡Ticagrelor received EU approval in 2010 and FDA approval in 2011. §Prasugrel received EU and FDA approval in 2009. ¶FXI(a) inhibitors are a class of antithrombotics that are currently being investigated in clinical trials; they are not approved for use in any country.
DOAC, direct oral anticoagulant; FDA, US Food and Drug Administration; FXa, activated factor X; FXI(a), activated Factor XI; i.v., intravenous; p.o., oral; s.c., subcutaneous; VKA, vitamin K antagonist.

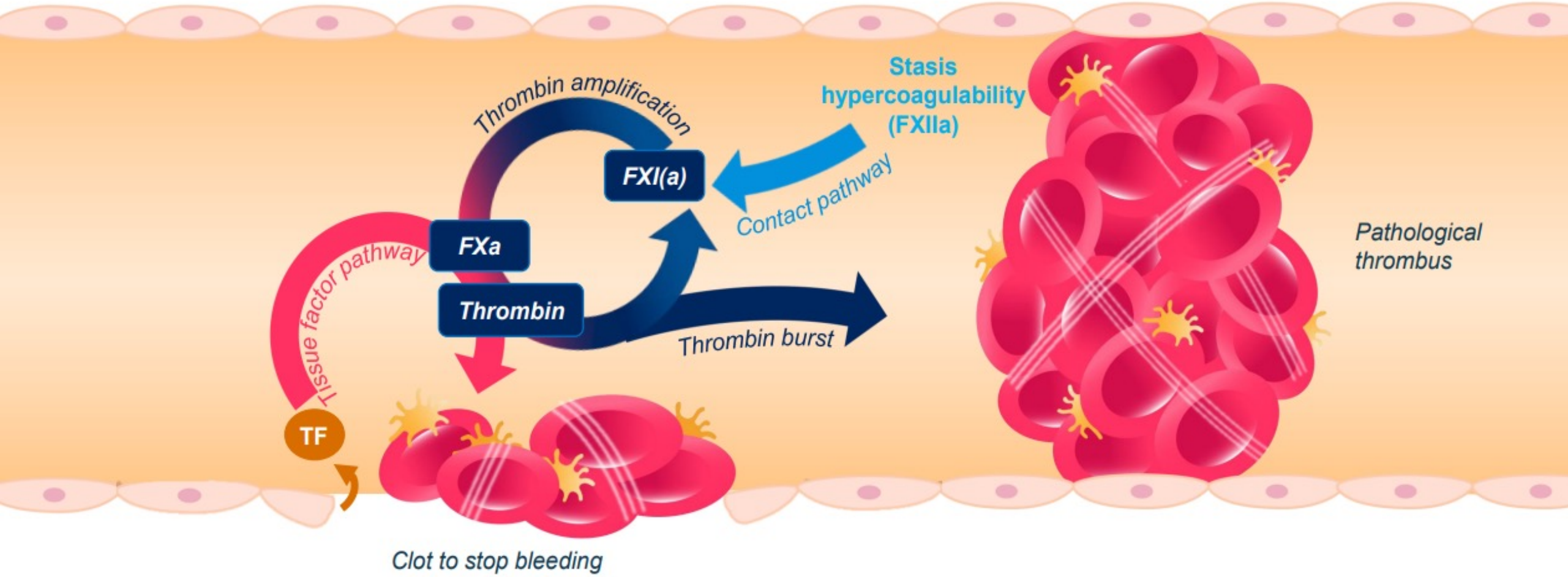
1. Weitz JI, Fredenburgh JC. *Arterioscler Thromb Vasc Biol* 2018;38:304–310. 2. Franchini M *et al. Blood Transfus* 2016;14:175–184. 3. Heestermans M *et al. Cells* 2022;11:3214.
4. Ugurlucan M *et al. Recent Pat Cardiovasc Drug Discov* 2012;7:71–76. 5. FDA. 1997. https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020839_plavix_toc.cfm.
6. Sanofi. 2021. https://www.sanofi.com/en/media-room/press-releases/2021/2021-02-09-06-00-00-2171820. 7. AstraZeneca. 2010. https://www.astrazeneca.com/media-centre/press-releases/2010/European-Commission-Approves-Brilique-06122010.html#. 8. AstraZeneca. 2011. https://www.astrazeneca.com/media-centre/press-releases/2011/fda-approves-new-medicine-brilinta--ticagrelor--for-use-in-the-us-20072011.html#. 9. Daiichi Sankyo. 2009. https://www.daiichisankyo.com/media/press_release/detail/index_3878.html. 10. Eli Lilly. 2009. https://investor.lilly.com/news-releases/news-release-details/european-commission-approves-efientr-prasugrel-patients-acute. 11. Campello E *et al. J Clin Med* 2022;11:6314. [all links accessed August 2023].


PAST
FUTURE
PRESENT

Factor XI/XIa inhibitors: Balance between efficacy and safety



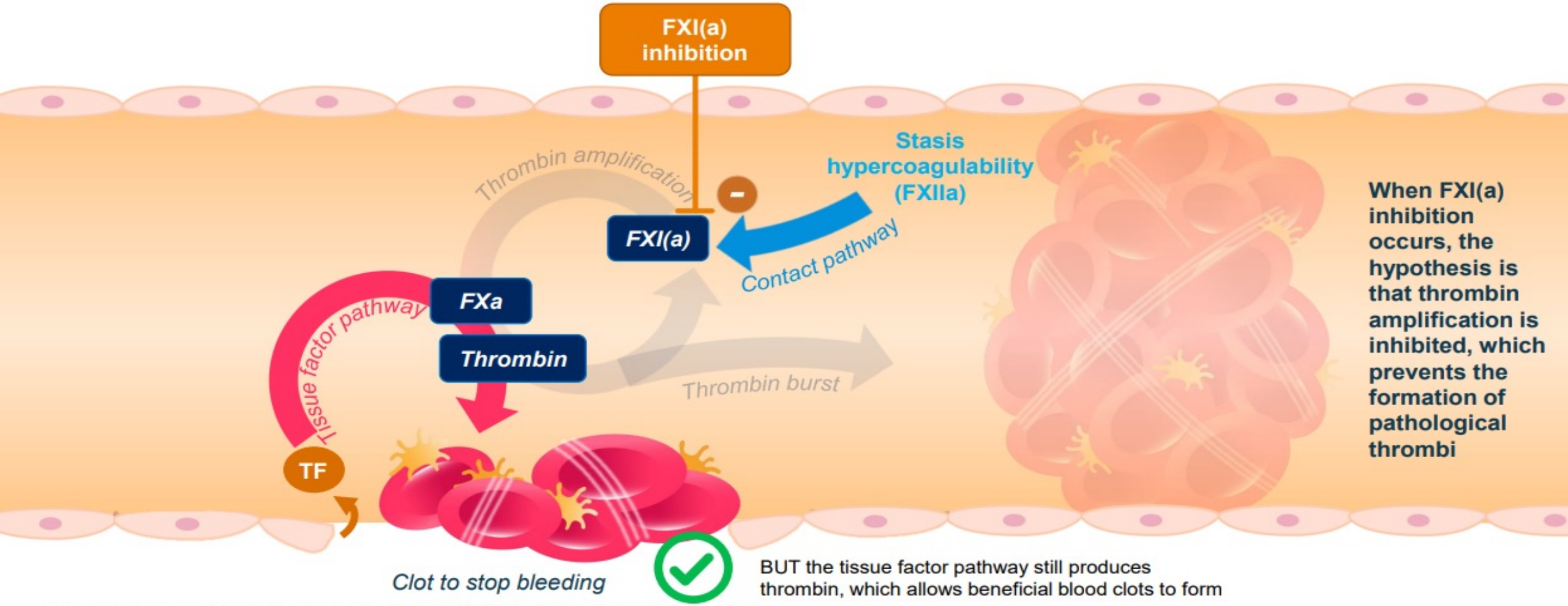
Normal Physiology: Central Role of Thrombin Amplification Without FXI(a) Inhibition



FXa, activated Factor X; FXI(a), activated Factor XI, FXII(a), activated Factor XII; TF, tissue factor.

1. Piccini JP *et al*. *Lancet* 2022;399:1383–1390. 2. Fredenburgh JC, Weitz JI. *Hamostaseologie* 2021;41:104–110.
3. Gailani D *et al*. *J Thromb Haemost* 2015;13:1383–1395.

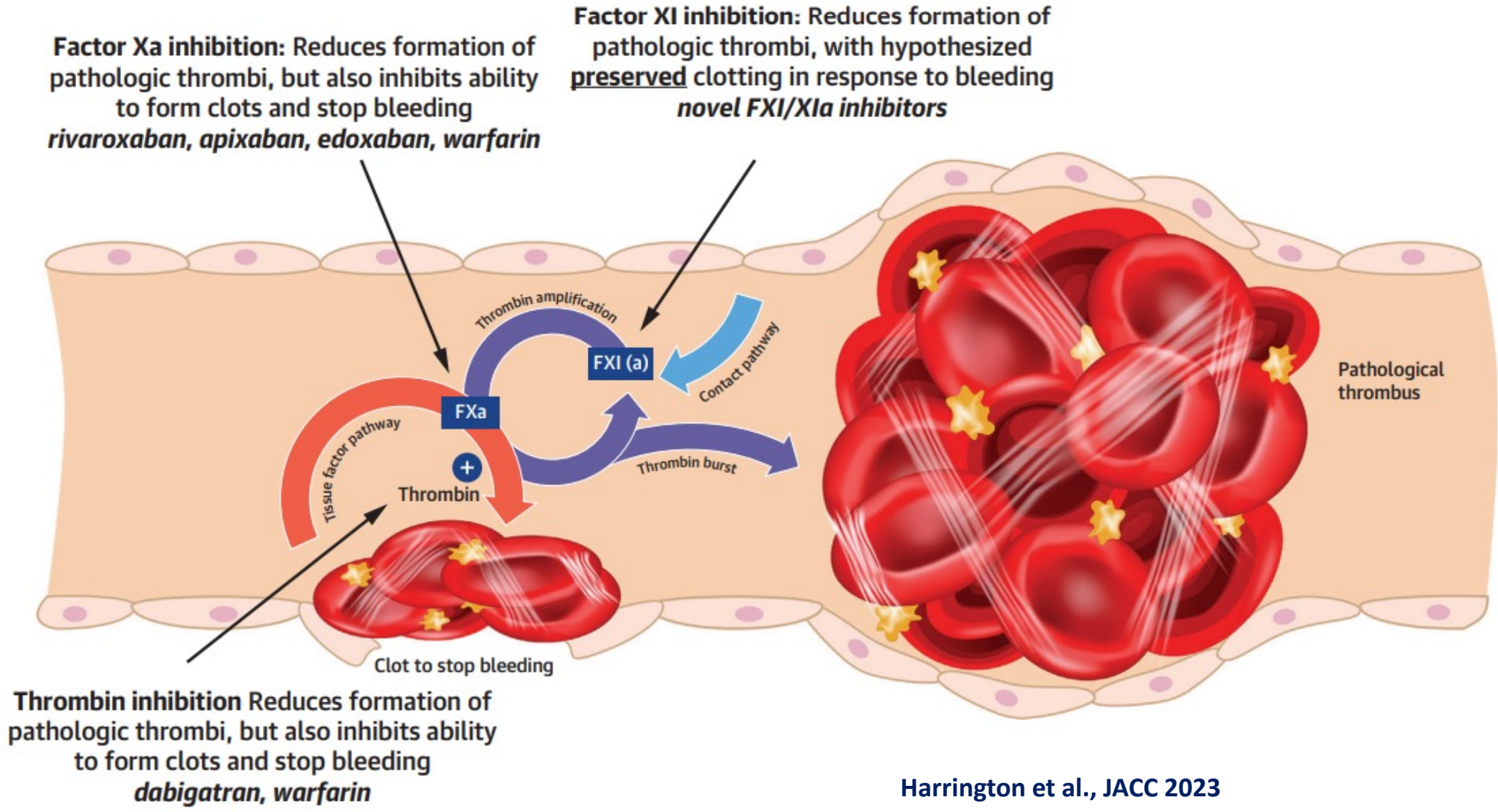
FXI(a) Inhibition: Hypothesized Uncoupling of Hemostasis From Thrombosis



FXa, activated Factor X; FXI(a), activated Factor XI, FXII(a), activated Factor XII; TF, tissue factor.

1. Piccini JP *et al*. *Lancet* 2022;399:1383–1390. 2. Fredenburgh JC, Weitz JI. *Hamostaseologie* 2021;41:104–110. 3. Gailani D *et al*. *J Thromb Haemost* 2015;13:1383–1395.

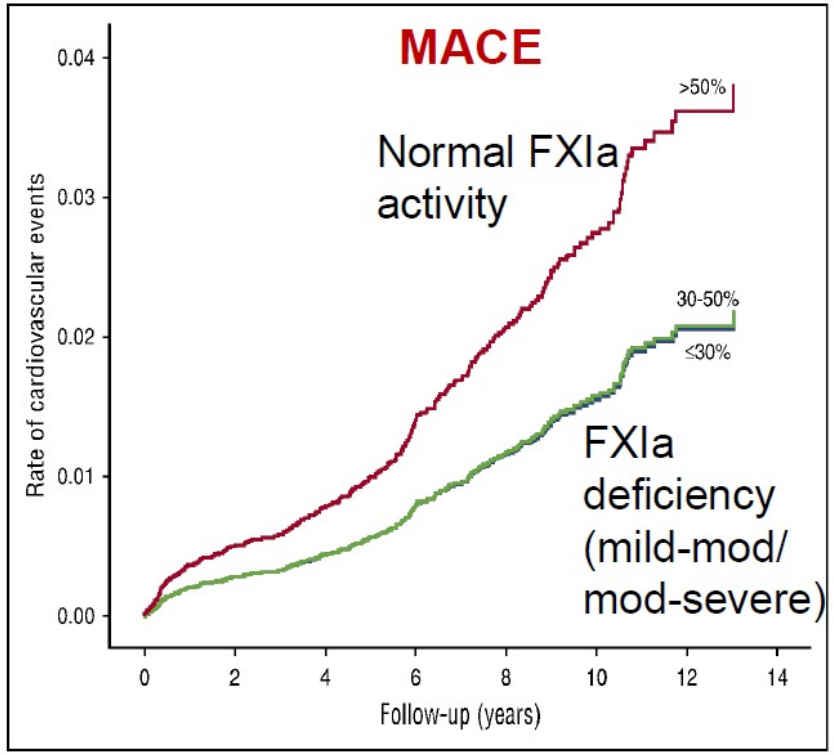
The Coagulation Cascade and Mechanism of Different Anticoagulant



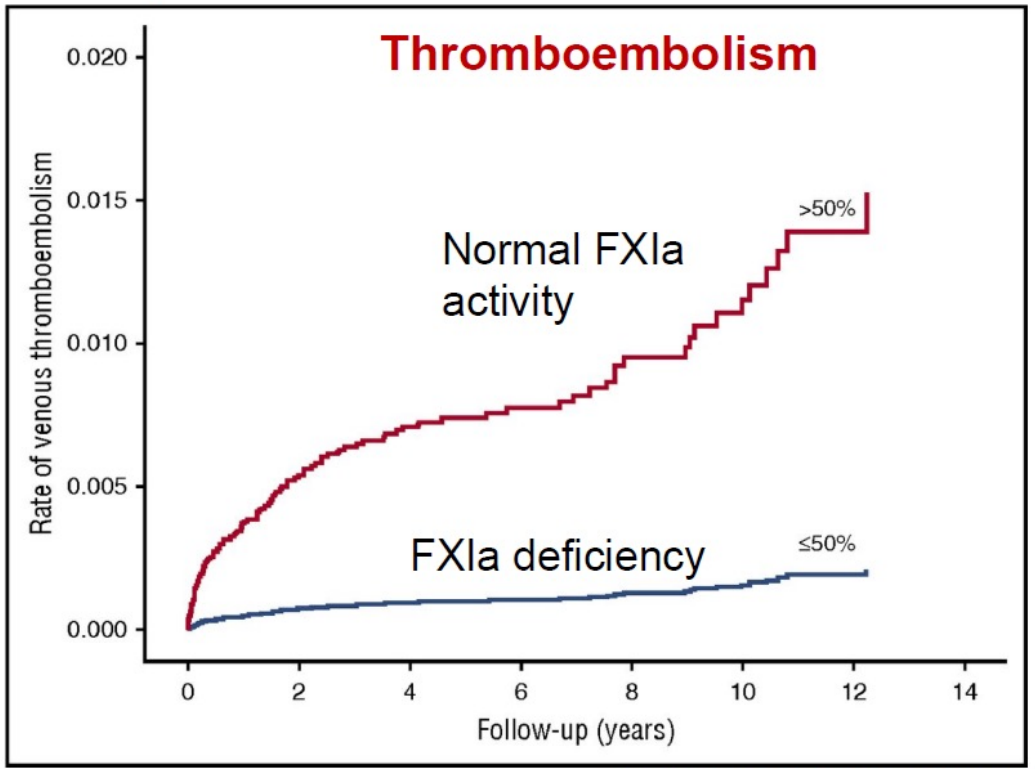
Harrington et al., JACC 2023

Lower factor XI Activity and Risk of CV Events and VTE

10,193 Individuals: Historical Cohort Study from Clalit Health Services in Israel



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.



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

Key Points

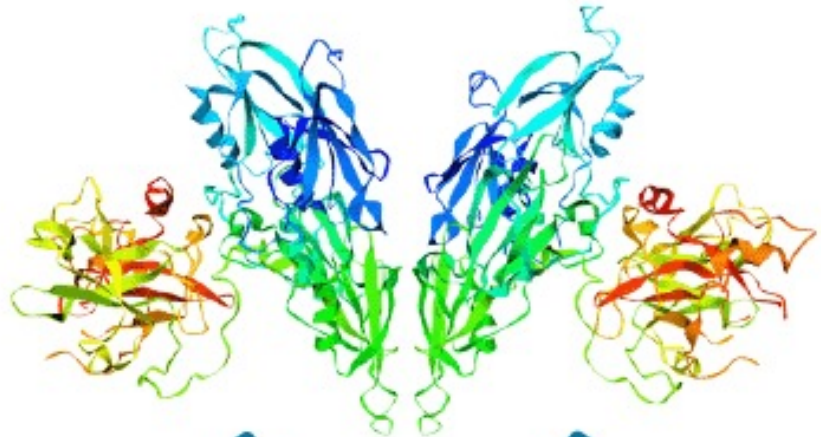
- Factor XI deficiency is associated with reduced risk of cardiovascular events.
- Factor XI deficiency is associated with reduced risk of VTE.

Preis et al., Blood 2017

Factor XI Inhibition: The Holy Grail of Haemostasis-Sparing Anticoagulation

Kakkar 2021

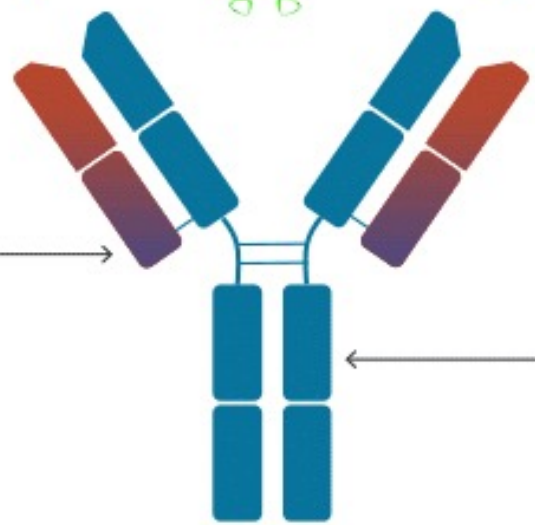
Abelacimab is a highly selective, fully human monoclonal antibody



Factor XI

Homodimeric structure[1]
(two identical subunits)

Binds to both Factor XI and Factor XIa with very high affinity and selectivity



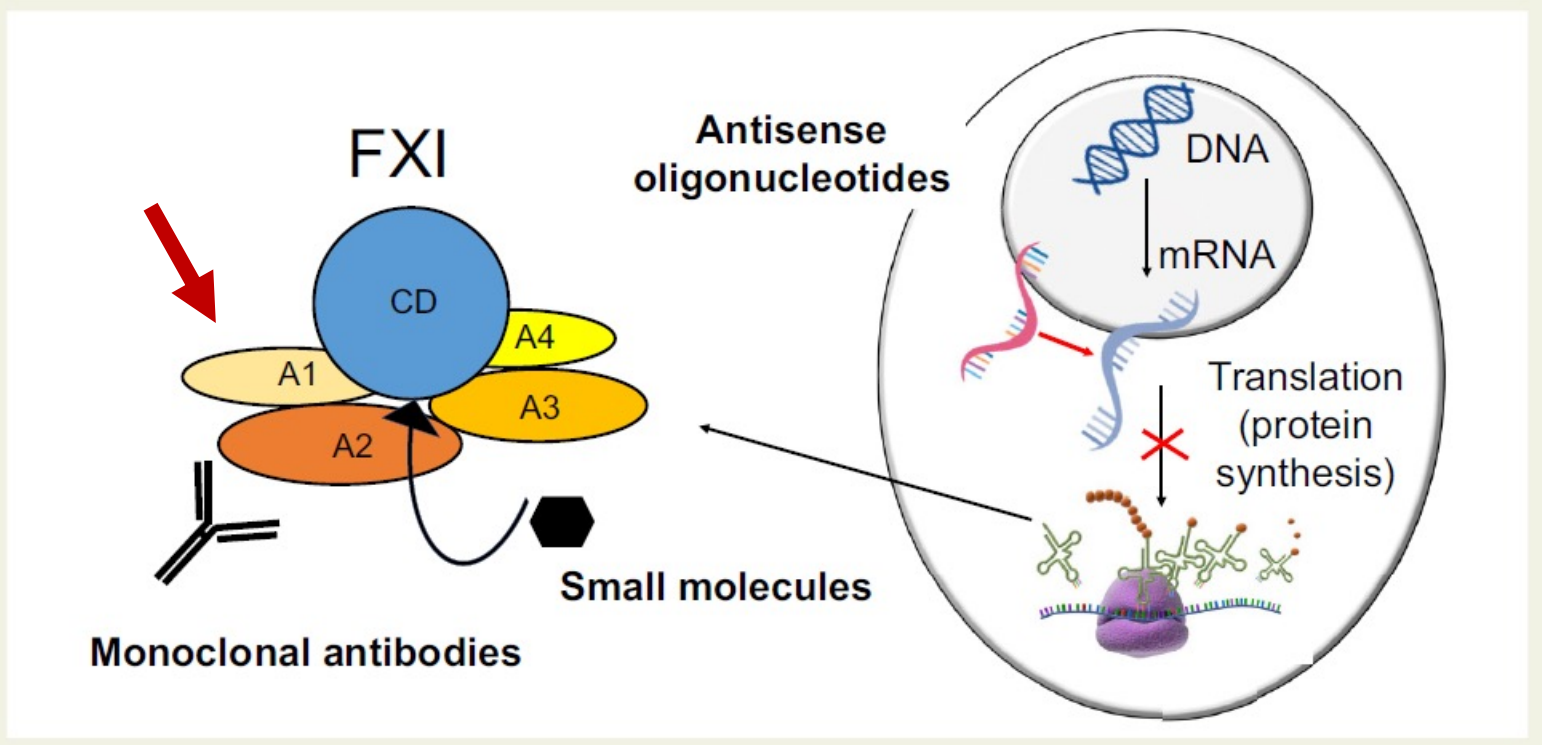
Modified to minimize the chances of off target effects

Abelacimab

Mechanism of action of FXI(a) inhibitors currently in development

Strategy	Mechanism of Action
Antisense oligonucleotides	Reduce hepatic synthesis of FXI
Aptamers	Bind FXI and block activity
Antibodies	Bind FXI and block activation or activity
Small molecules	Bind reversibly to active site of FXI and block activity

Fedenbourgh et al., Blood 2017



ASO: Inibisce l'espressione della proteina perché si lega all'acido nucleico

APTAMERO: agisce sulla proteina target

De Caterina et al., 2022 European Heart J

Properties of anticoagulants targeting FXI

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

Abelacimab
Osacimab

Asundexian
Milvexian

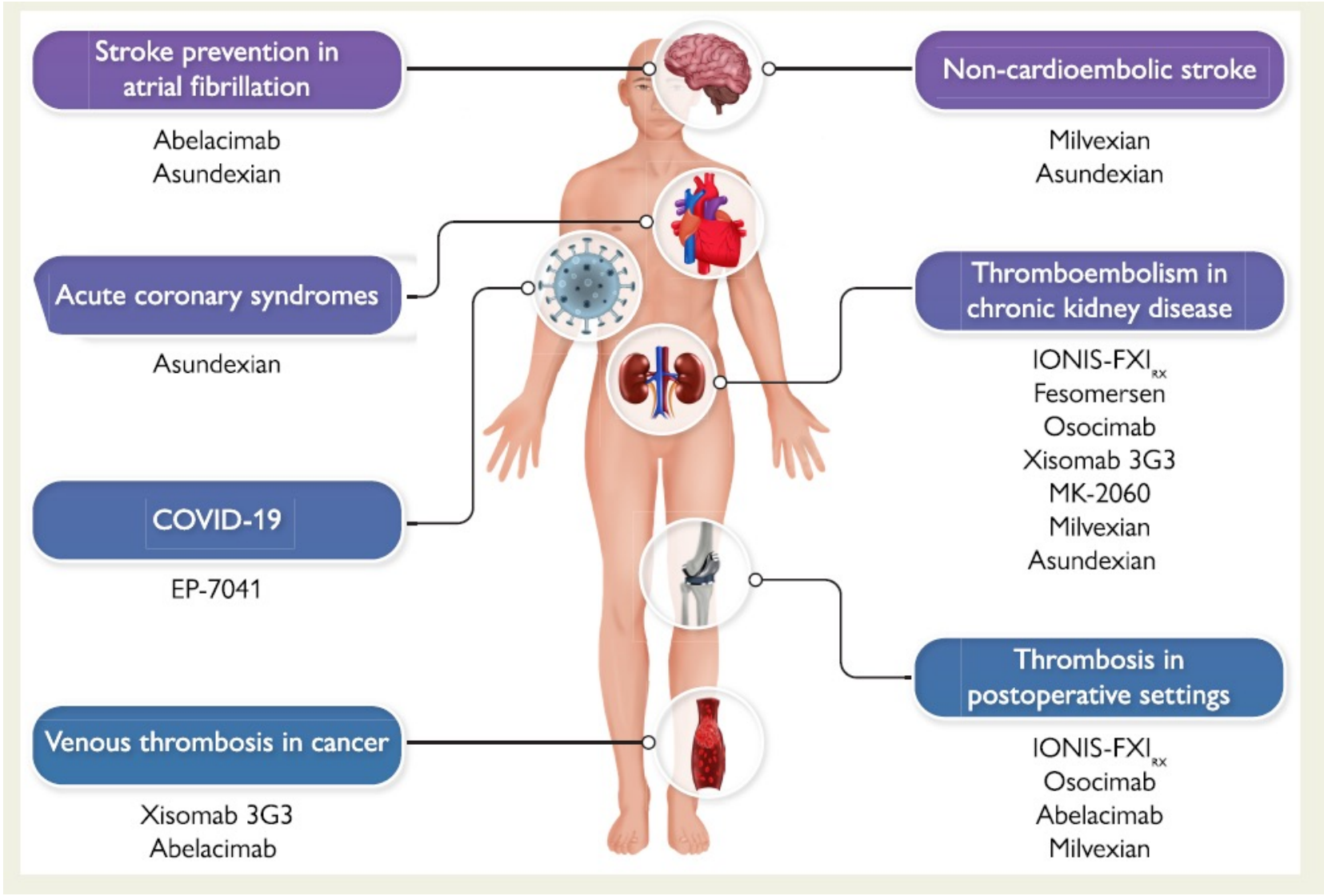
FXI - LICA

Fredenburgh et al., Hämostaseologie 2021;41:104–110.

Anthos Therapeutics Announces that Abelacimab has Received FDA Fast Track Designation for the Treatment of Thrombosis Associated with Cancer

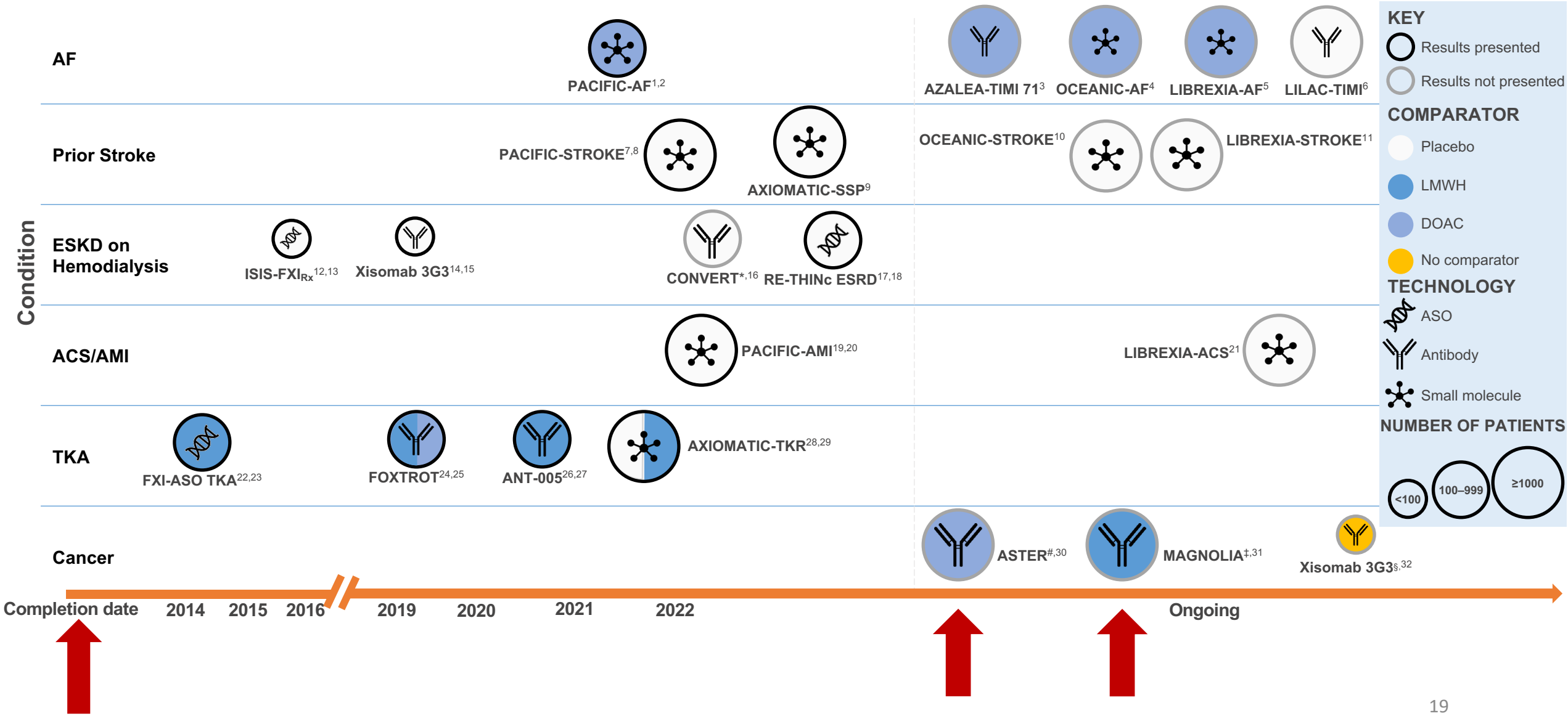
NEWS PROVIDED BY
Anthos Therapeutics →
Jul 11, 2022, 02:00 ET

Therapeutic Indications For FXI/Xia Inhibitors

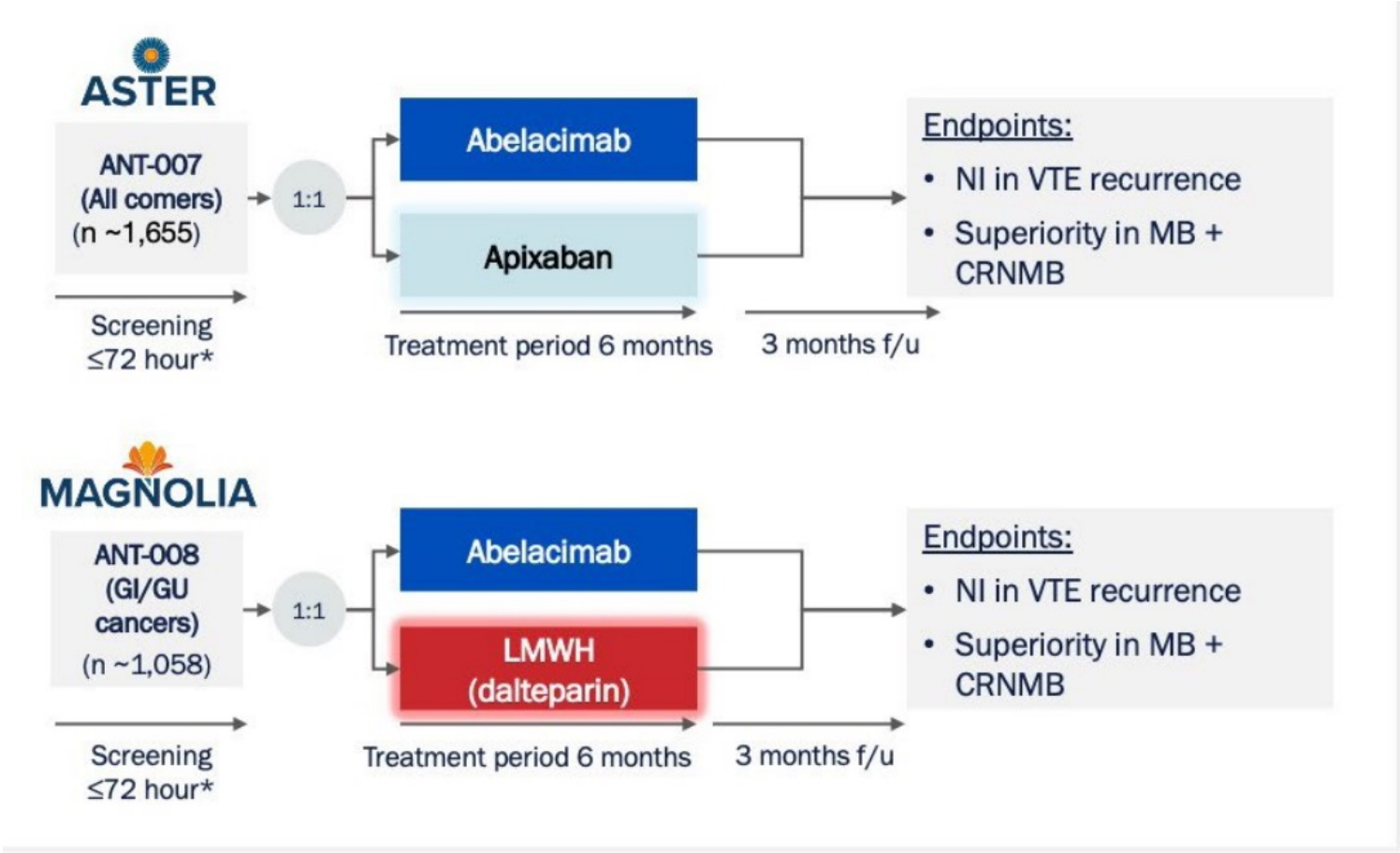


De Caterina et al, European Hearth of Journal; 2023

Overview of Clinical Trials Investigating FXI Inhibition



Abelacimab Phase III cancer-associated thrombosis programme



- DOACs are now Guideline-recommended therapy in large subset of CAT patients
- **Abelacimab may have safety and convenience advantages**

- High unmet need:
  - High bleeding rate with DOACs
  - Dalteparin is still SoC in this subset of patients
- **Abelacimab may have safety, efficacy, and convenience advantages**

Specific inclusion criteria for the ANT-007 and ANT-008

ANT-007

Confirmed diagnosis of cancer (by histology or adequate imaging modality), other than basal-cell or squamous-cell carcinoma of the skin alone with one of the following:

- Active cancer, defined as either locally active, regionally invasive, or metastatic cancer at the time of randomization

and/or

- Currently receiving or having received anticancer therapy (radiotherapy, chemotherapy, hormonal therapy, any kind of targeted therapy or any other anticancer therapy) in the last 6 months.

Anticoagulation therapy with a therapeutic dose of DOAC for at least 6 months is intended

ANT-008

Confirmed GI (colorectal, pancreatic, gastric, esophageal, gastro-esophageal junction or hepatobiliary) or confirmed GU (renal, ureteral, bladder, prostate, or urethra) cancers if:

- Unresectable, locally advanced, metastatic or non-metastatic GI/GU cancer

and

- No intended curative surgery during the study

Anticoagulation therapy with LMWH for at least 6 months is indicated.

STUDIO DI FASE 3

Multicentrico

Randomizzato

In aperto

Valutazione degli endpoint in cieco

Confronto dell'effetto di Abelacimab rispetto ad Apixaban/Dalteparina sulla recidiva di TEV ed eventi emorragici in pazienti con TEV associata a cancro

ANTHOS THERAPEUTICS

Area of Interest

- Potential for providing similar efficacy to standard of care with a reduced bleeding risk
- Particularly attractive for patients with high risk of bleeding
- Up to 72 hours from VTE diagnosis to randomization
- First dose will be administered through IV at randomization (if randomized to abelacimab)
- Subsequent doses will be subcutaneous injections
- Monthly dosing

Abelacimab: novel, fully human antibody targeting Factors XI and XIa

Abelacimab is SC injection administered after baseline IV dose

PI assessment of bleeding risk in GI/GU cancer patients drives comparator arm/trial selection

ANTHOS THERAPEUTICS

IQVIA BIOTECH

Study Design

ANT-007

Primary Objective:

- To assess whether abelacimab is non-inferior to apixaban for preventing VTE recurrence through 6 months post randomization in patients with cancer and recently diagnosed VTE

Secondary Objective:

- To assess whether abelacimab is superior to apixaban for preventing occurrence of the composite of major or CRNM bleeding at 6 months post randomization

ANT-008

Primary Objective:

- To assess whether abelacimab is non-inferior to dalteparin for preventing VTE recurrence through 6 months post randomization in patients with GI or GU cancer and recently diagnosed VTE

Secondary Objective:

- To assess whether abelacimab is superior to dalteparin for preventing occurrence of the composite of major or CRNM bleeding at 6 months post-randomization

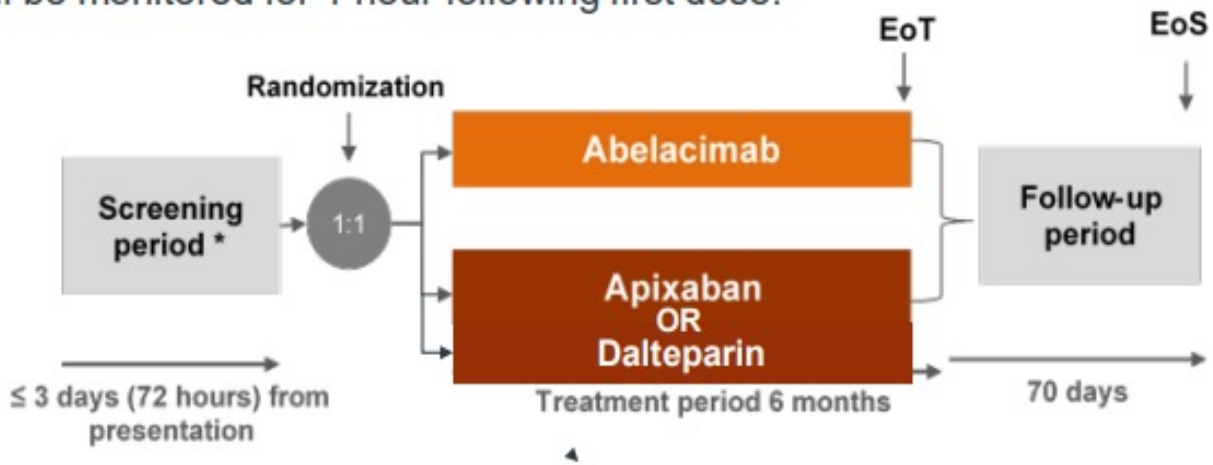
Key Inclusion Criteria

ANT-007	ANT-008
• Male or female subjects with age ≥18 • Confirmed diagnosis of cancer • Confirmed symptomatic or incidental proximal lower limb DVT and/or a confirmed symptomatic or incidental PE of, at least 2 subsegment, a segmental or larger pulmonary artery • Anticoagulation therapy with a therapeutic dose of DOAC for at least 6 months is anticipated.	• Male or female subjects with age ≥ 18 years • Confirmed diagnosis of GI or GU cancer • Confirmed symptomatic or incidental proximal lower limb DVT and/or a confirmed symptomatic, or incidental PE of , at least 2 subsegment, a segmental or larger pulmonary artery • Anticoagulation therapy with LMWH for at least 6-month is anticipated.

Study Duration – ANT-007 & ANT-008

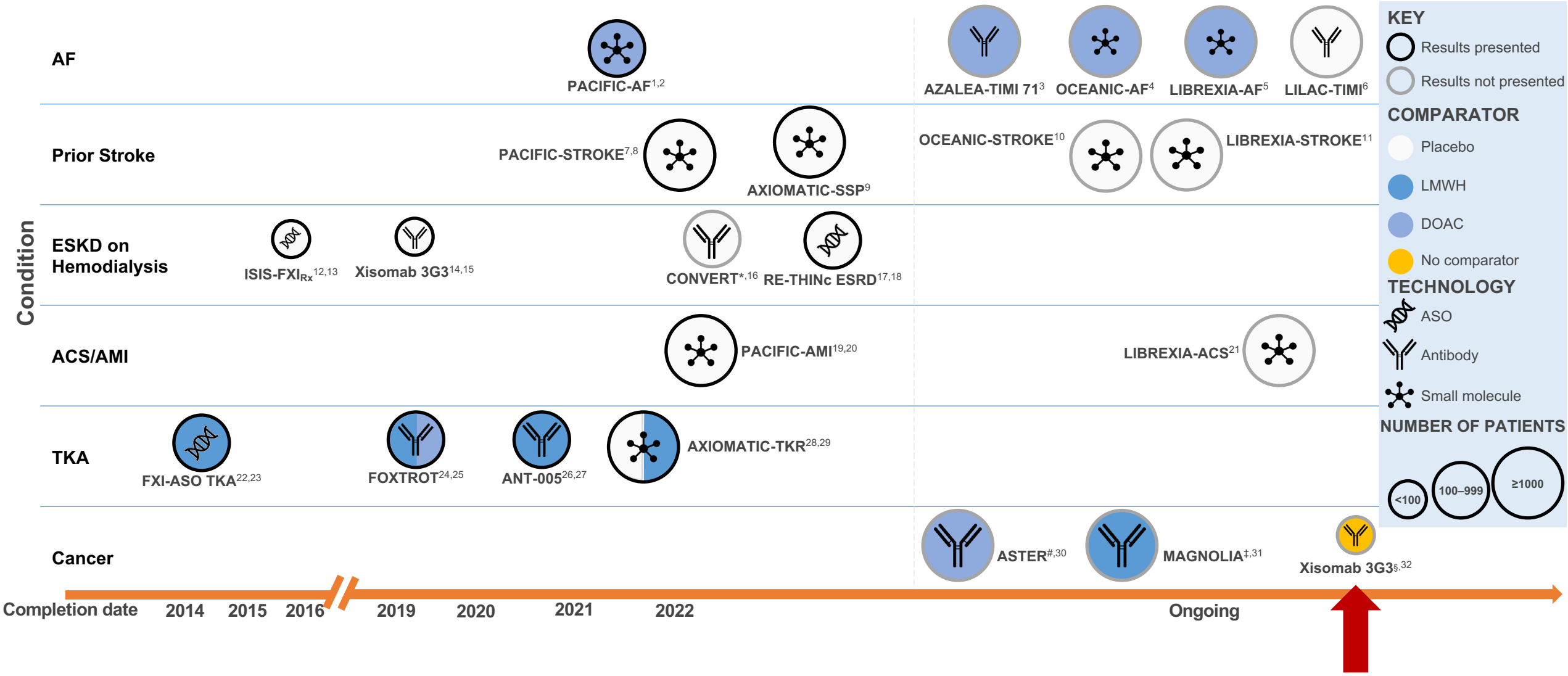
The study is comprised of 3 periods:

1) Screening (up to 3 days (72 hours ONLY))
2) First dose of abelacimab is administered through IV at randomization followed by monthly SC injection for 5 months (total of 6 months of treatment)
3) Patient will be monitored for 1 hour following first dose.



* Patients should receive standard of care treatment during the screening period (See Appendix 3 for recommended treatment during the screening period, and Table 3.1 for transition to study treatment)

Overview of Clinical Trials Investigating FXI Inhibition



RECRUITING

Xisomab 3G3 for the Prevention of Catheter-Associated Thrombosis in Patients With Cancer Receiving Chemotherapy

ClinicalTrials.gov ID NCT04465760

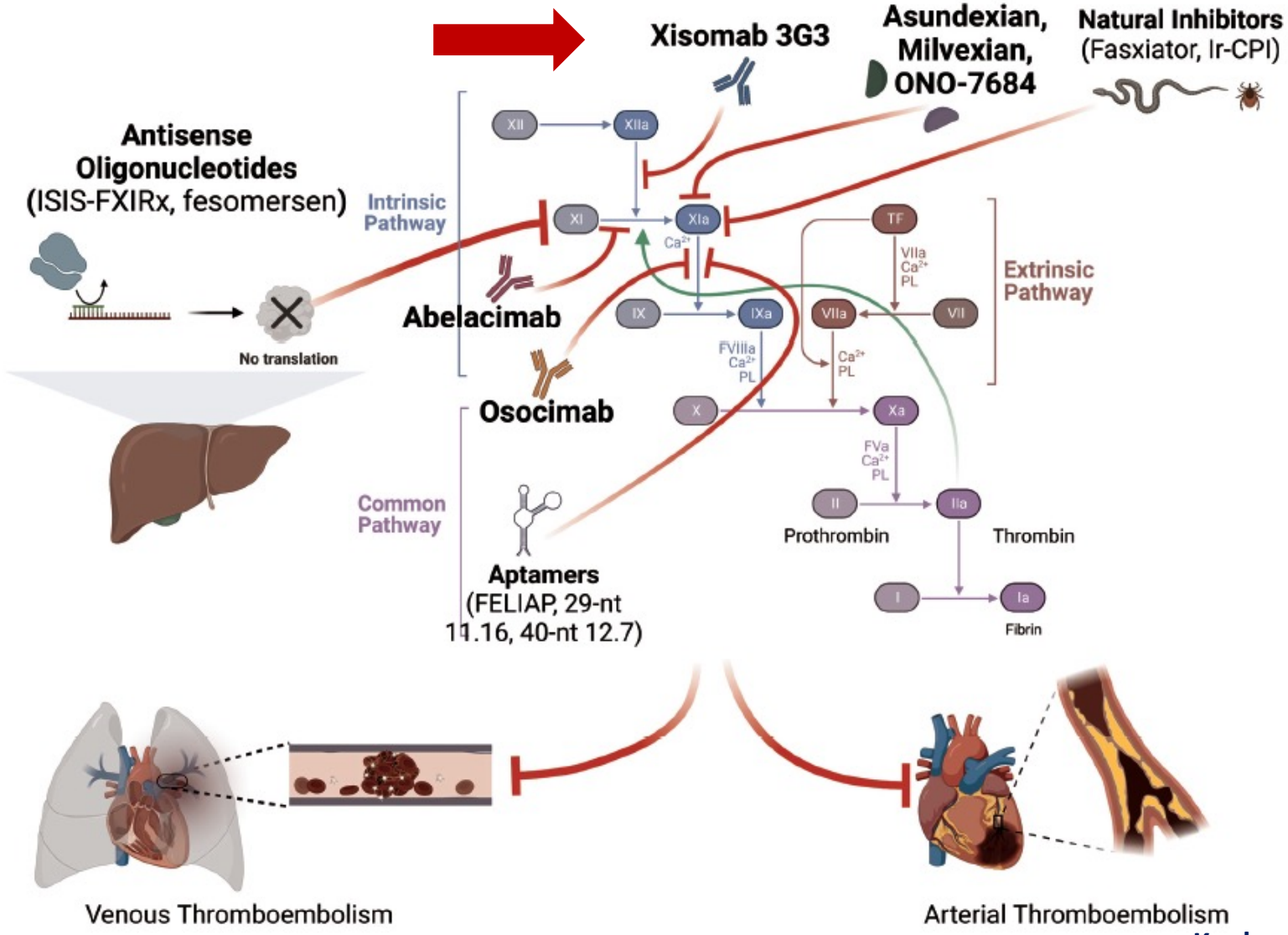
A Phase II Study of **Xisomab 3G3**, a Monoclonal Antibody Preventing the Activation of FXI by FXIIa, for the Prophylaxis of Catheter-Associated Thrombosis

OUTLINE:

Patients receive xisomab 3G3 intravenously (IV) or via catheter within 48 hours of catheter placement. Patients then receive standard of care chemotherapy 2 days later. After approximately 2 weeks, patients undergo standard of care ultrasound for possible CAT.

After completion of study, patients are followed up for 60 days.

Overview of factor XI/XIa inhibitors and their action site within the coagulation cascade



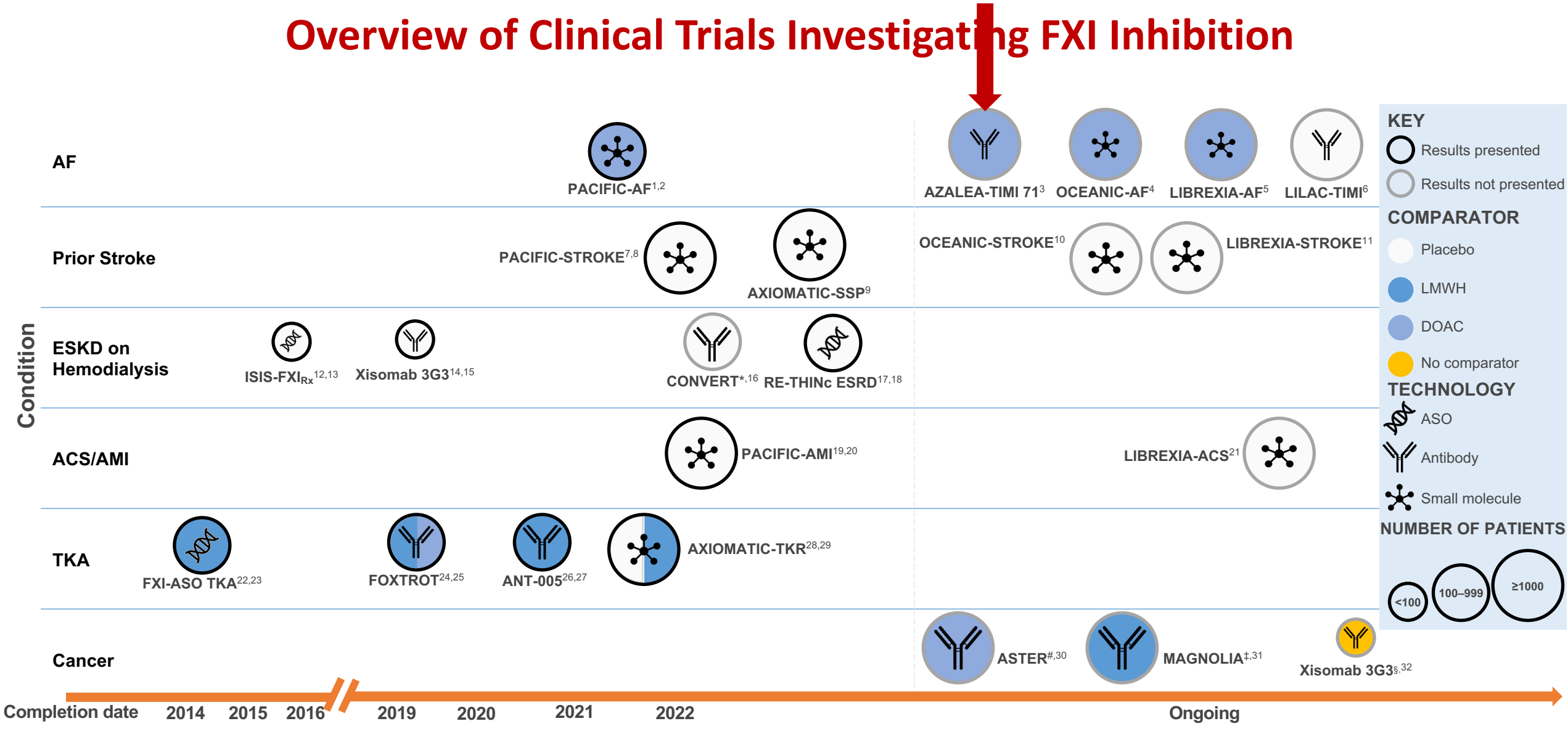
Koulas et al., Haemost 2023

Anthos Therapeutics Announces Abelacimab Received FDA Fast Track Designation for the Prevention of Stroke and Systemic Embolism in Patients with AFib

Anthos Therapeutics has announced that Abelacimab has received FDA Fast Track Designation for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

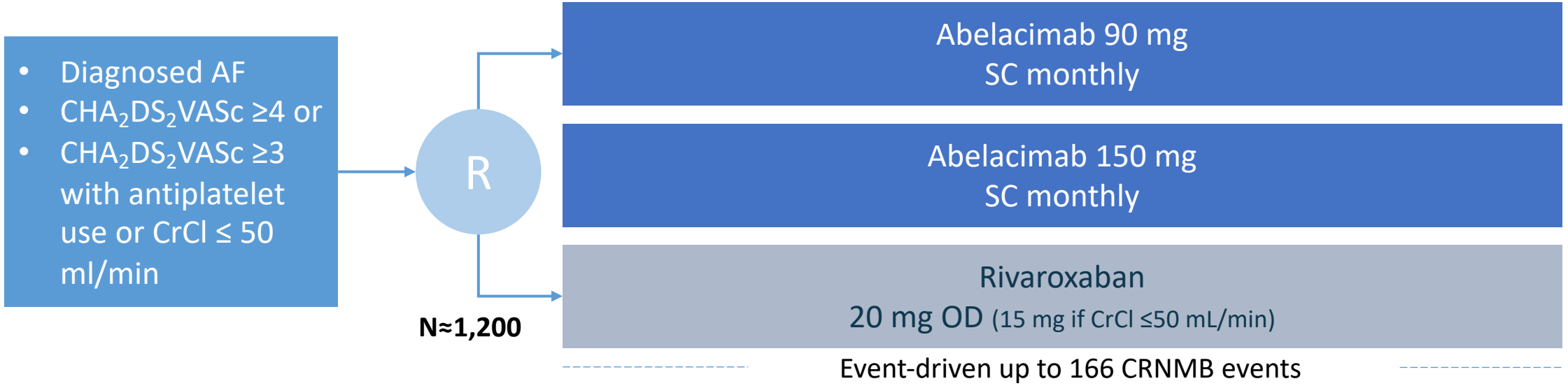
September 09, 2022

Overview of Clinical Trials Investigating FXI Inhibition



Phase IIb AZALEA-TIMI 71 Design[1,2]

Randomized, Active-Controlled Study to Evaluate the Safety and Tolerability of 2 Blinded Doses of the Novel FXI Inhibitor Abelacimab Compared With Open-Label Rivaroxaban in Patients With AF (active, not recruiting as of June-2023)



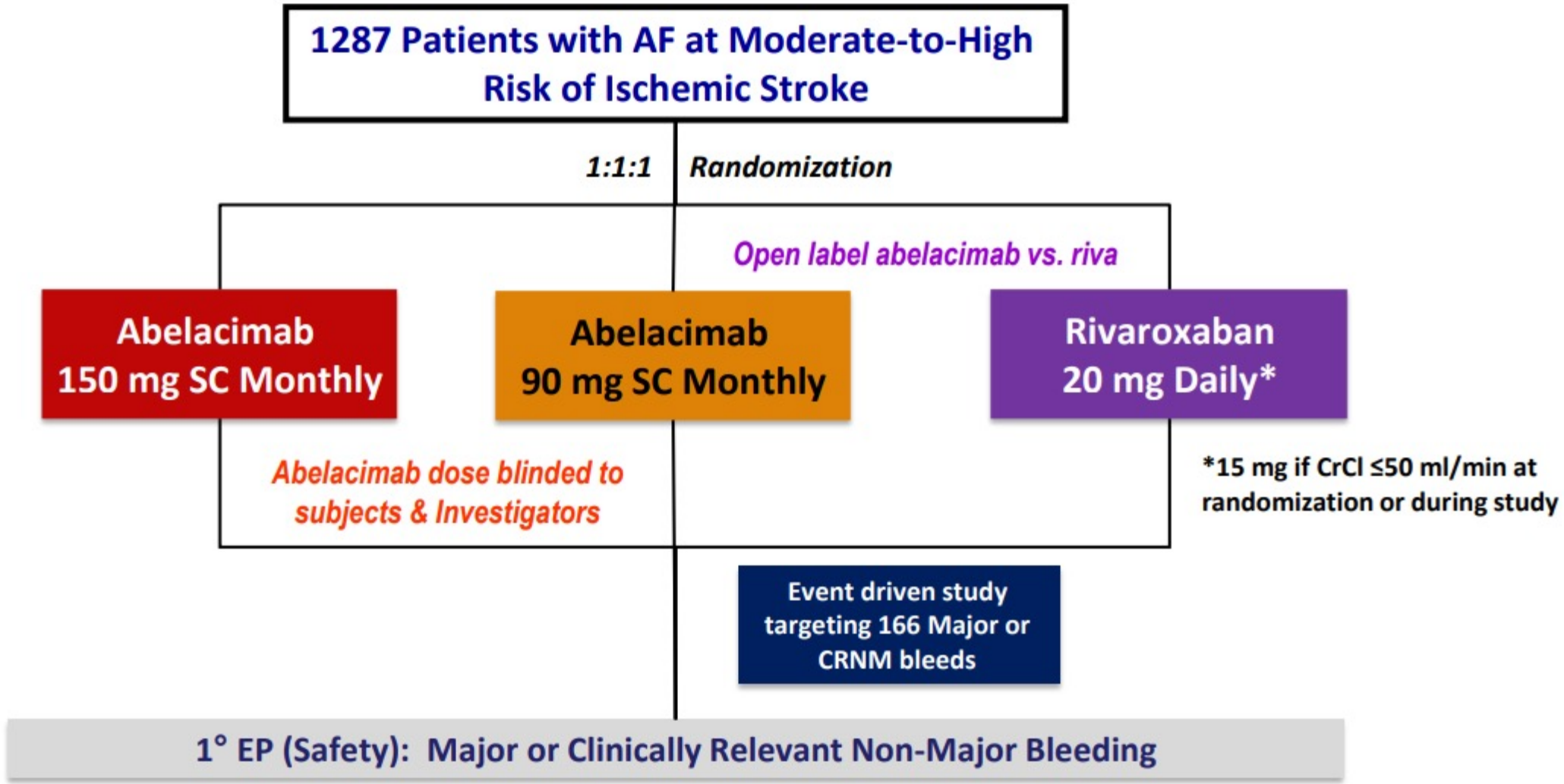
- **Primary outcome:** Time to first ISTH major bleeding or CRNMB events

- CrCl, creatine clearance; CRNMB, clinically relevant non-major bleeding.
- 1. ClinicalTrials.gov. NCT04755283. Accessed March 1, 2023. https://clinicaltrials.gov/ct2/show/NCT04755283. 2. TIMI.org. AZALEA-TIMI 71. Accessed March 1, 2023. https://timi.org/azalea-timi-71/

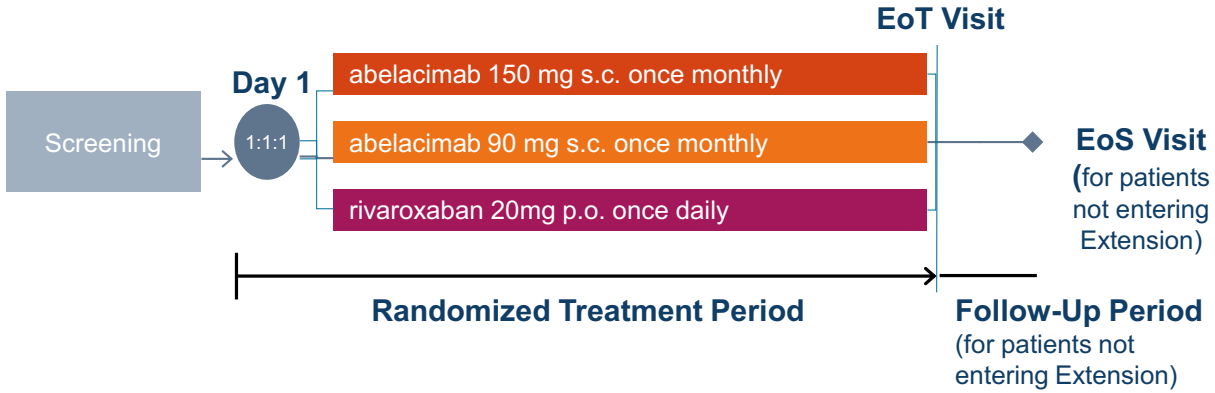
Objective

To evaluate the bleeding profile of abelacimab relative to rivaroxaban in patients with AF at moderate-to-high risk of stroke

Trial Design



ANT-006 (AZALEA) Open-Label Extension Amendment Long-Term Extension to the Protocol in Place

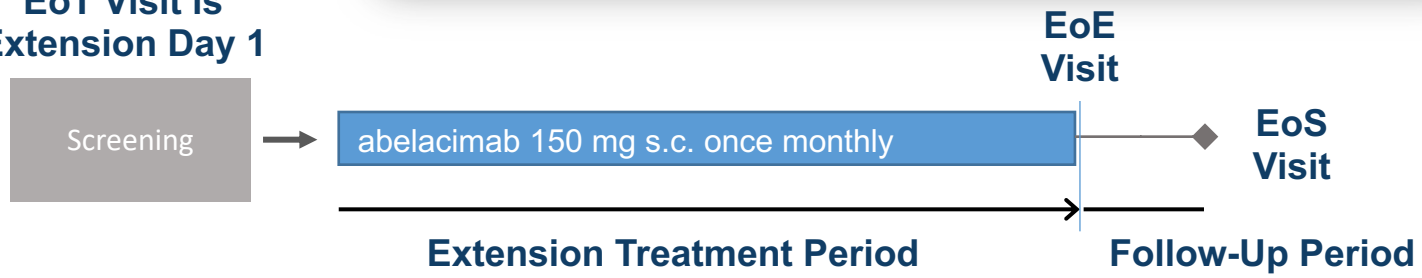


Atrial Fibrillation Study with Abelacimab Stopped Early by the Data Monitoring Committee Due to an Overwhelming Reduction in Bleeding as Compared to a DOAC (Direct Oral Anticoagulant)

ANTHOS THERAPEUTICS

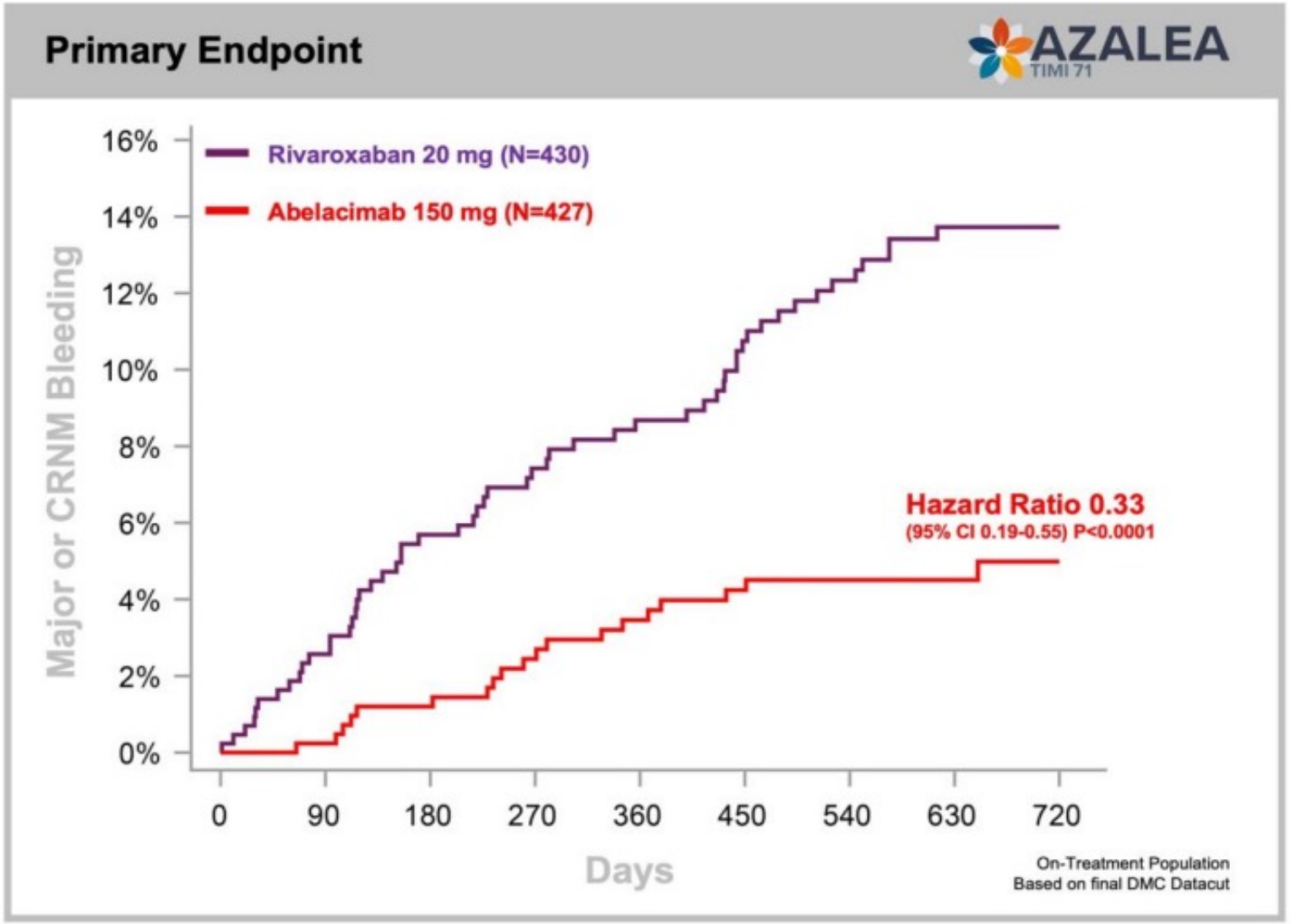
- Overwhelming reduction in bleeding events vs. rivaroxaban
- The 150 mg was selected for the OL extension study, highlighting the safety of this dose
- This confirms that robust and sustained FXI/FXIa inhibition has substantial safety advantages vs rivaroxaban

EoT Visit is Extension Day 1



Anthos Therapeutics' Novel Dual Acting Factor XI / XIa Inhibitor, Abelacimab 150 mg, Demonstrated a 67% Reduction in the Primary Endpoint of Major or Clinically Relevant Non-Major Bleeding Compared with Rivaroxaban in Patients with Atrial Fibrillation

- **Primary endpoint met with a 67% reduction in major or clinically relevant non-major bleeding (CRNM) with abelacimab 150 mg** compared with rivaroxaban 20 mg in patients with atrial fibrillation who are at moderate-to-high risk of stroke (P<0.0001, HR 0.33, 95% CI 0.19–0.55).



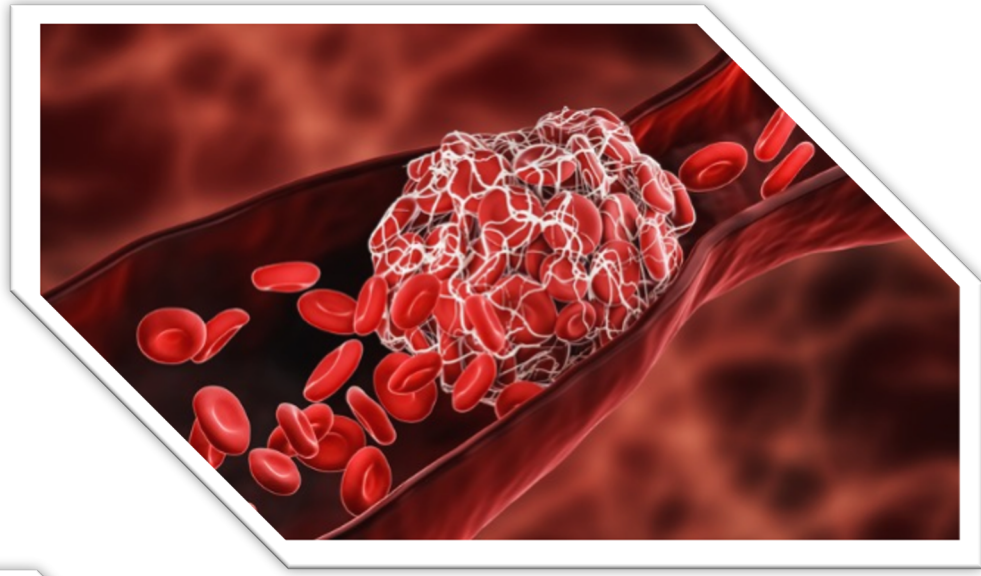
DMC Recommendation

September 14, 2023

"The IDMC members unanimously agreed to recommend termination of the AZALEA trial because of the substantially greater than anticipated reduction in major and clinically relevant non-major bleeds in the abelacimab arms compared to rivaroxaban and a benefit:risk favoring abelacimab."

Summary of Presented Results

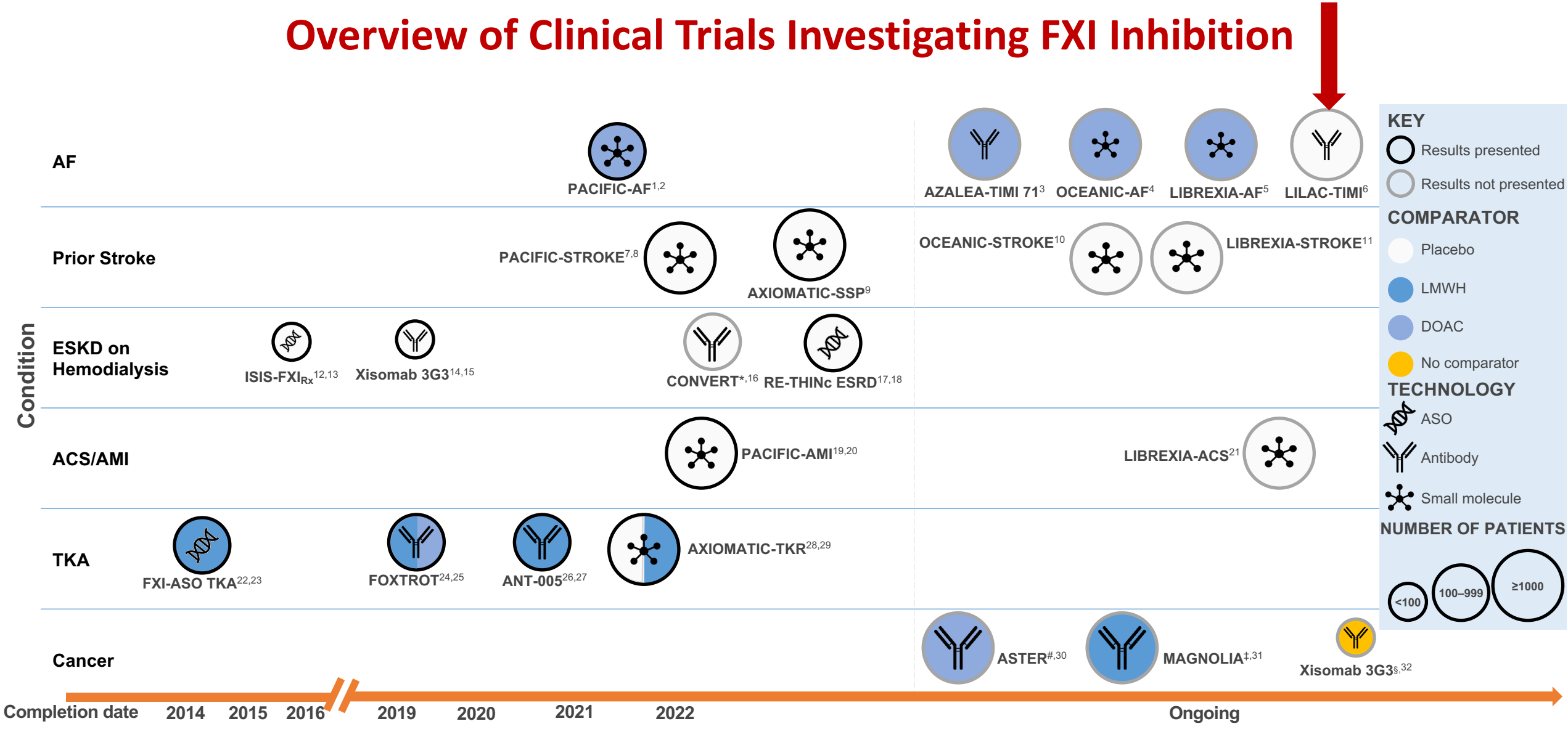
- Across all bleeding endpoints, abelacimab demonstrated a highly significant reduction versus rivaroxaban
- Factor XI inhibition of ~99% with abelacimab 150 mg dosed once monthly
- Abelacimab 150 mg dosed once monthly via subcutaneous injection has been selected for the Phase 3 clinical study program
- **Primary endpoint met with a 67% reduction in major or clinically relevant non-major bleeding (CRNM) with abelacimab 150 mg** compared with rivaroxaban 20 mg in patients with atrial fibrillation who are at moderate-to-high risk of stroke (P<0.0001, HR 0.33, 95% CI 0.19–0.55).



Other Bleeding Endpoints:

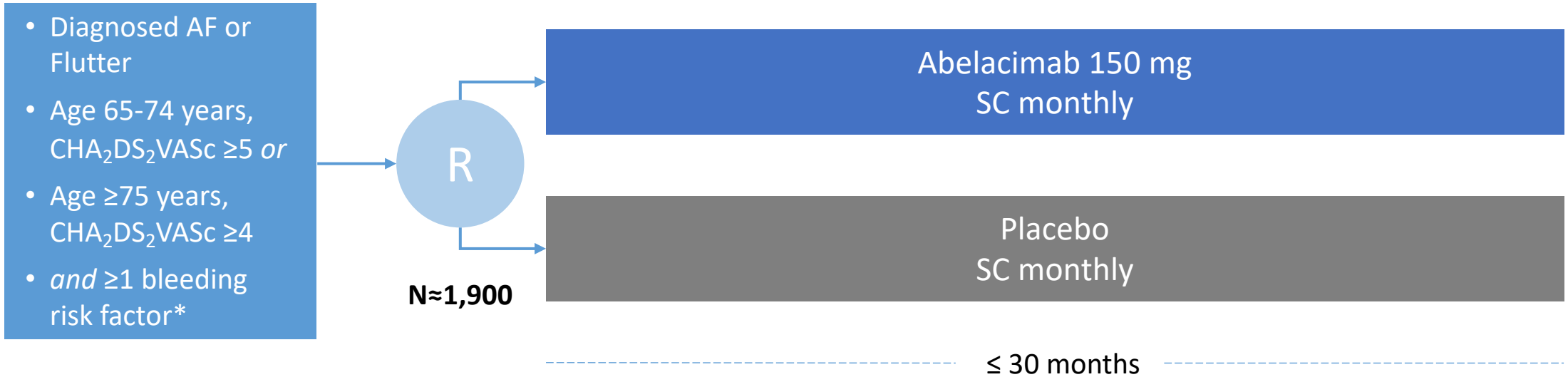
- **74% reduction in major bleeding alone with abelacimab 150 mg** vs rivaroxaban 20 mg. *(P=0.002, HR 0.26, 95% CI 0.11-0.61)*
- **93% reduction in gastrointestinal (GI) bleeding with abelacimab 150 mg** vs rivaroxaban 20 mg *(P=0.008, HR 0.07, 95% CI 0.01-0.50)*

Overview of Clinical Trials Investigating FXI Inhibition



Phase III LILAC-TIMI 76 Design[1,2]

Randomized, Double-Blind Placebo-Controlled Phase III Trial Investigating the Efficacy and Safety of the FXI Inhibitor **Abelacimab** in ~1900 **Patients With AF Deemed Unsuitable, by HCP or Patient, for Anticoagulation Therapy** (active, recruiting as of June-2023)

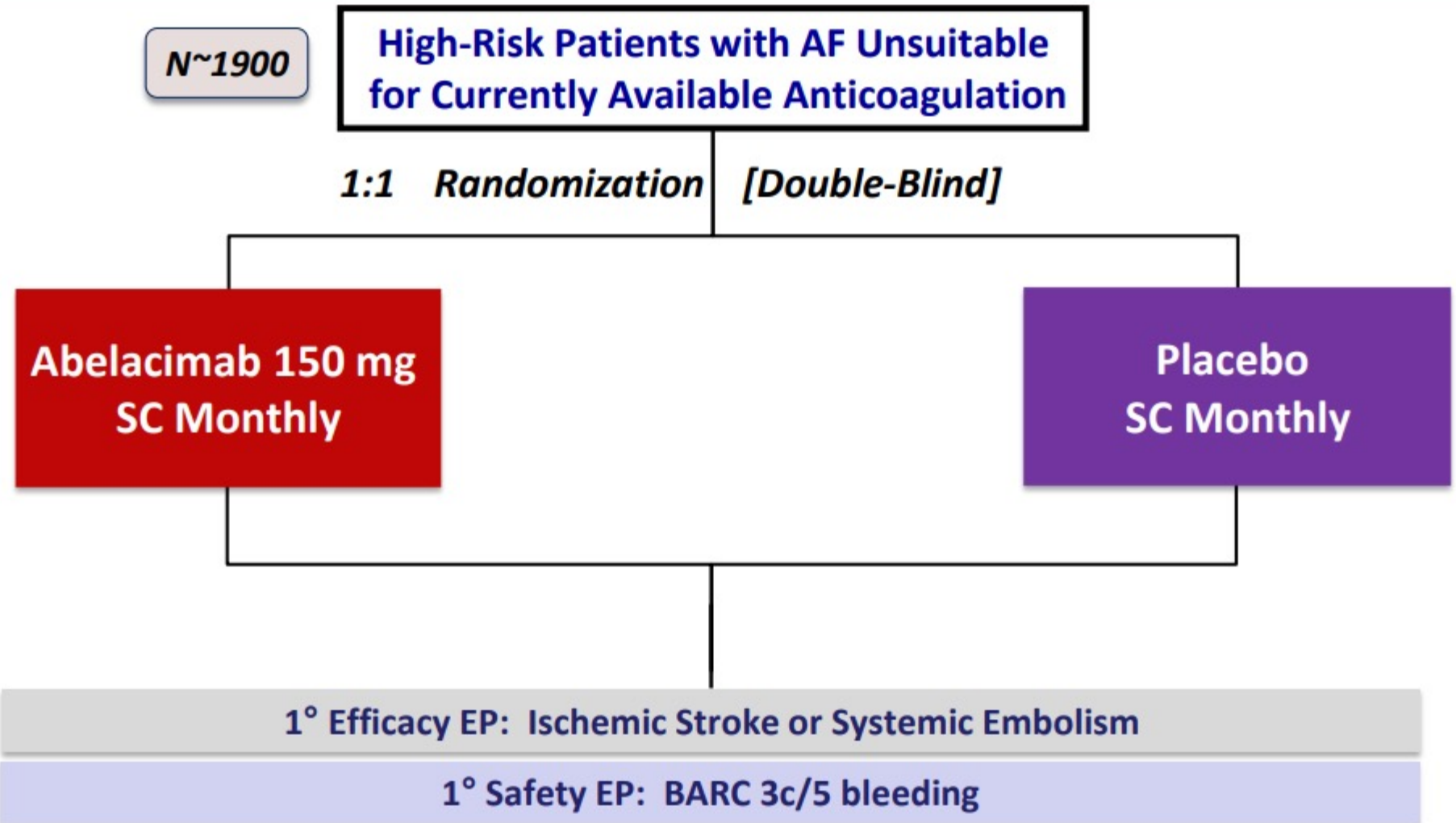


- **Primary efficacy outcome:** Ischemic stroke or systemic embolism
- **Primary safety outcome:** BARC 3c/5 bleeding

- BARC, Bleeding Academic Reserach Consortium; SC, subcutaneous; SE, systemic embolism. *severe renal insufficiency, antiplatelet use, history of critial area bleeding, NSAID use, frailty or multiple falls
- 1. ClinicalTrials.gov. NCT05712200. Accessed March 1, 2023. https://clinicaltrials.gov/ct2/show/NCT05712200. 2. TIMI.org. LILAC-TIMI 76. Accessed March 1, 2023. https://timi.org/lilac-timi-76/

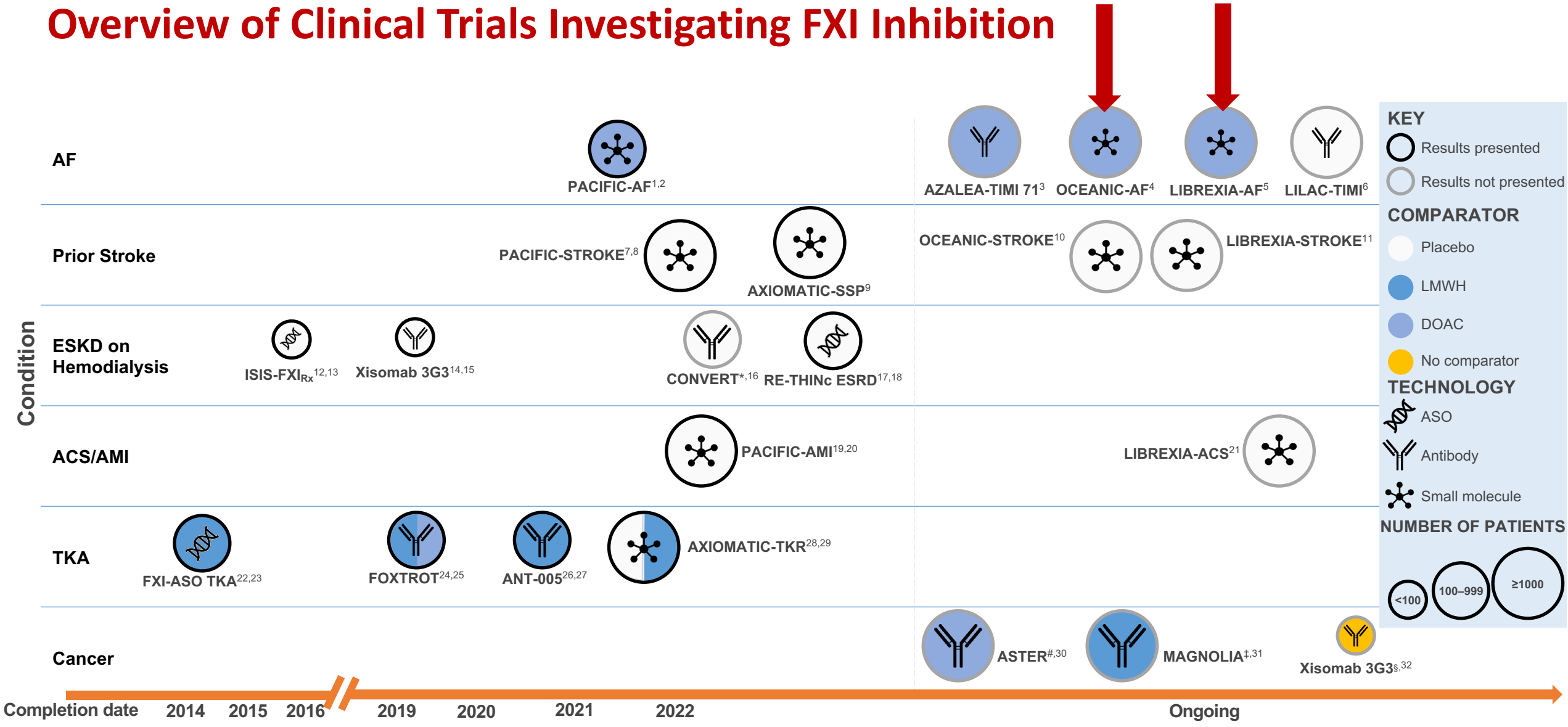
Ongoing Phase 3 Trial of Abelacimab in AF

TIMI 76 LILAC



NCT05712200

Overview of Clinical Trials Investigating FXI Inhibition



If in the ASTER and MAGNOLIA trials, Abelacimab will demonstrate non inferiority in terms of efficacy vs DOACs, and superiority in MB + CRNMB we might see that Abelacimab will be used also in AF in cancer patients similar to what occurred with DOACs.

Conclusioni e Prospettive

- Current anticoagulants are limited by th risk of bleeding that accompanies antithrombotic efficacy
- Factor XI/XIa inhibition may prevent thromboembolism and preserve hemostasis in response to vascular injury
- Data from phase 2 trial of FXI/XIa inhibitors suggest low rates of bleeding
- Phase 3 trials are underway to evaluate efficacy in patients at risk of thromboembolic events