

The Future of Anticoagulation



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DISCLOSURES

Benjamin Brenner, MD

Declares receiving honoraria for lectures and advisory board contributions from Pfizer, LEO Pharma, Sanofi, ROVI Laboratories and Bayer Pharmaceuticals.

Historic Development of Anticoagulants

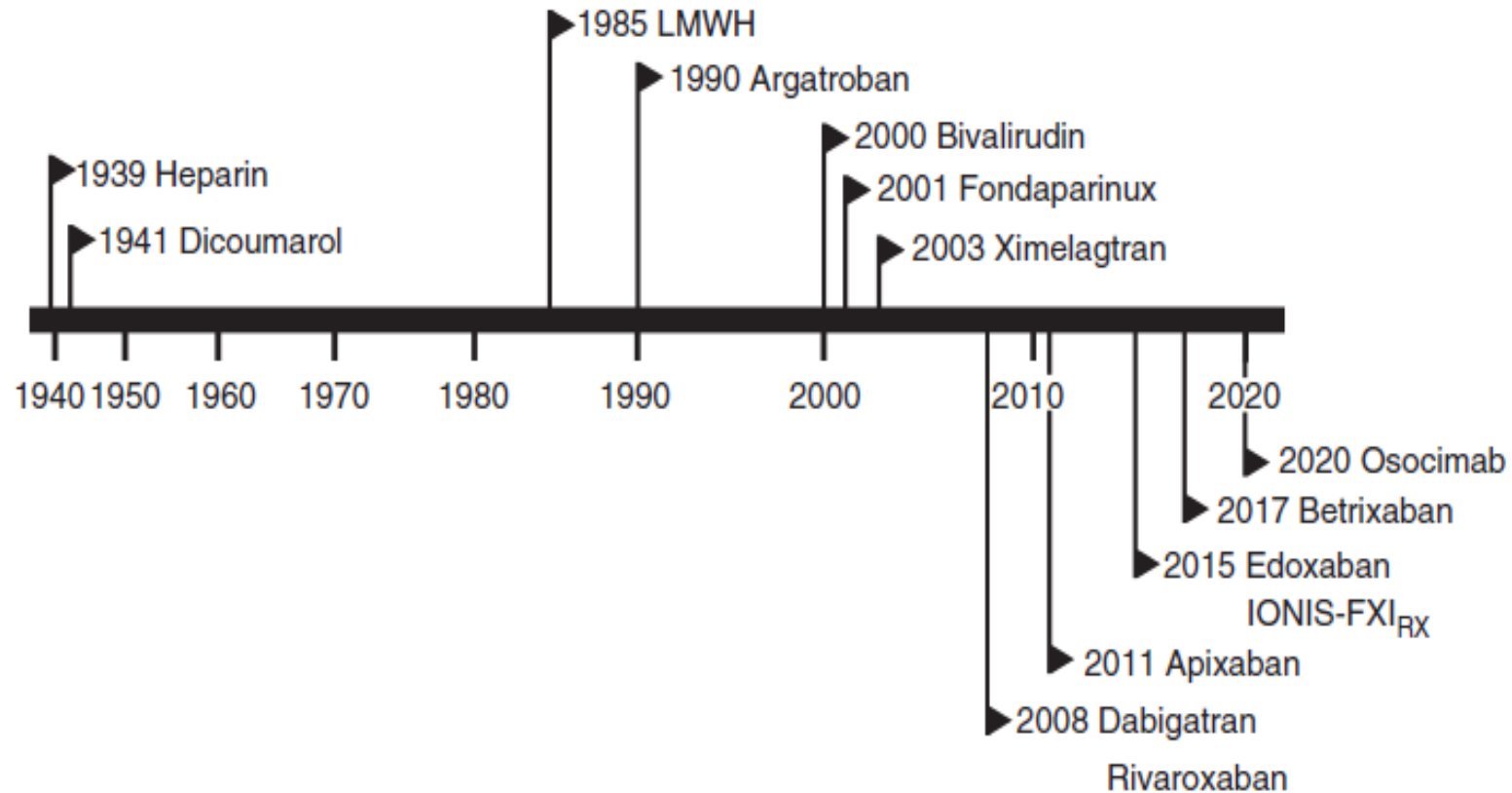
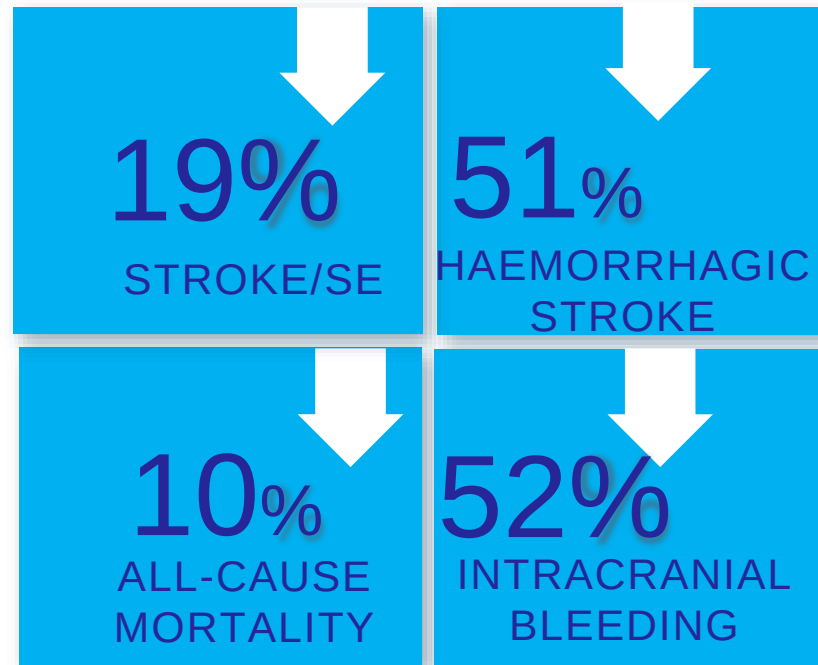


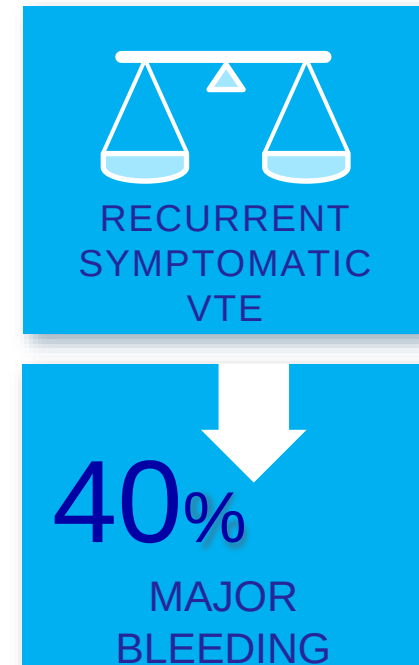
FIGURE 1 Timeline of major landmarks in the development of anticoagulants. The year of approval of drugs for therapeutic use or of completion of phase 2 trials with newer agents is shown

DOACs are an Advance over VKA

Stroke prevention in AF¹



DVT/PE treatment²



1. Ruff et al. Lancet 2013; 2. Hirschl and Kundi. Vasa. 2014

Why Do We Need New Targets?

Ultimate goal of anticoagulant therapy
is to attenuate thrombosis without
increasing the risk of bleeding

Less intracranial bleeding with DOACs,
but annual rates of major bleeding
remain at 2% to 3% in the AF population

Fear of Bleeding

**Underuse of anticoagulants for
stroke prevention in atrial fibrillation**

**Inappropriate use of low-dose DOAC
regimens**

Rose AJ, et al., *J. Am Heart. Assoc.* 2019; Mitchell A, et al., *BMC Med.* 2021; Leef GC, et al., *J. Pharm. Pract.* 2020; Fernandez CS, et al. *J. Comp Eff. Res.* 2020

DOACs are not Suitable for Every Patient

- **Hospitalized Medical patients:** 2 large phase III studies.
MAGELLAN (n = 8101 rivaroxaban) & ADOPT(n = 6528 apixaban).
- DOACs equally effective as enoxaparin with greater bleeding risk.
- **Valve replacement, mechanical valves:** Phase II study
RE-ALIGN (n=252 dabigatran) was terminated premature due to increase of thromboembolic and bleeding events in dabigatran group.
- Pregnancy and puerperium, infants, severe hepatic or renal failure
- Fragile Elders, Obese-Bariatric patients, Antiphospholipid syndrome,

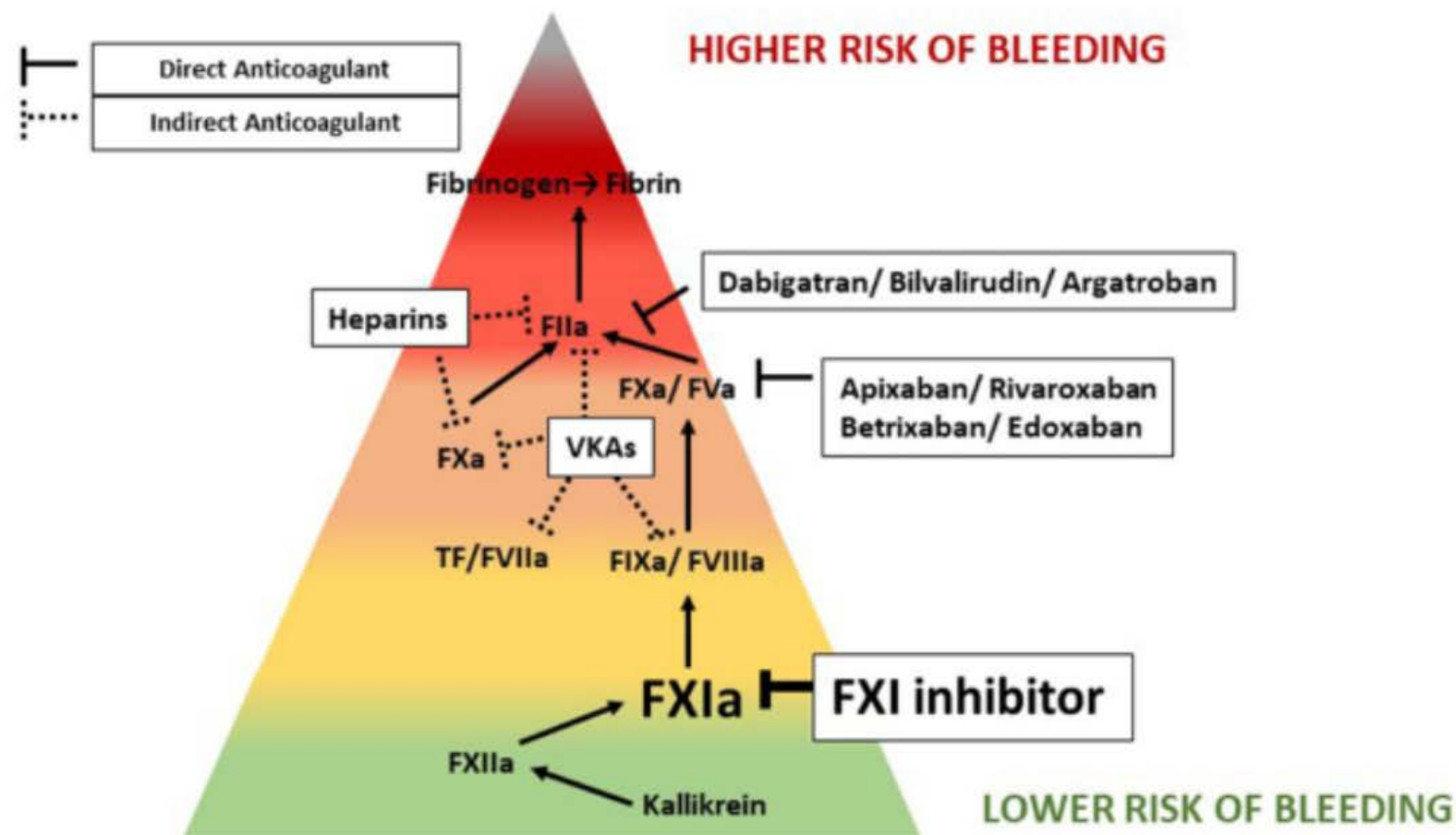
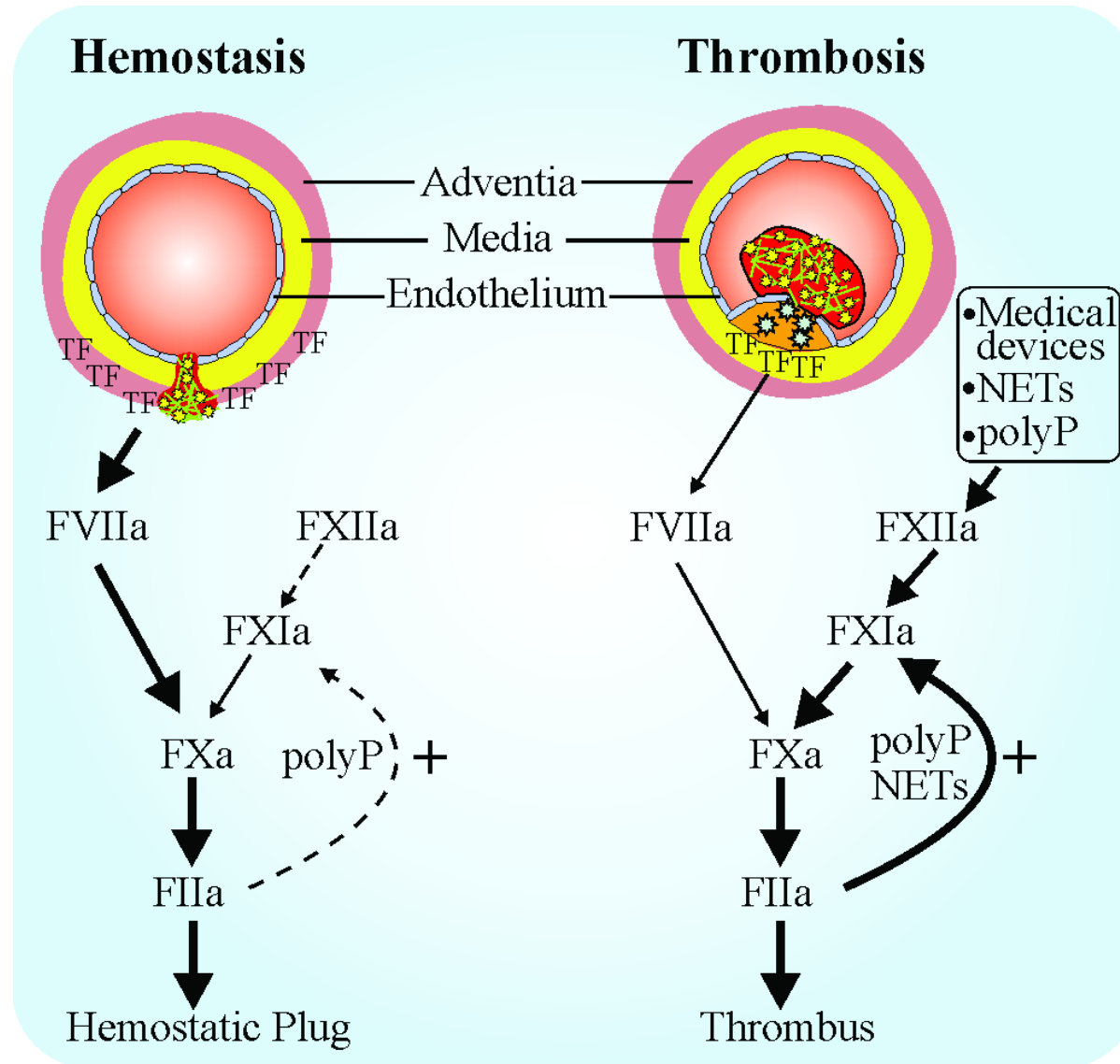


Figure I Anticoagulant associated bleeding risk.

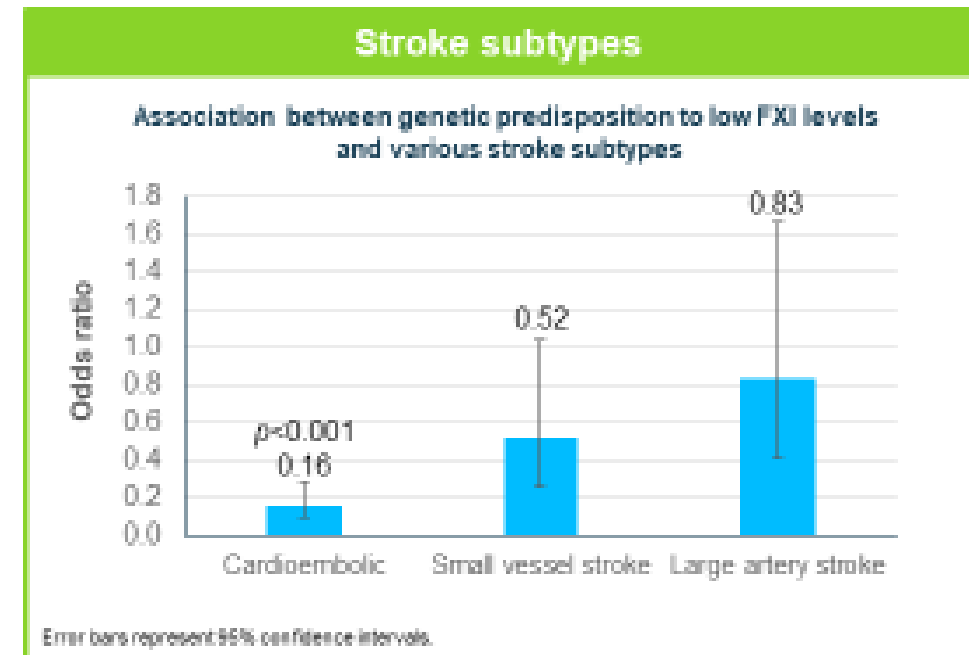
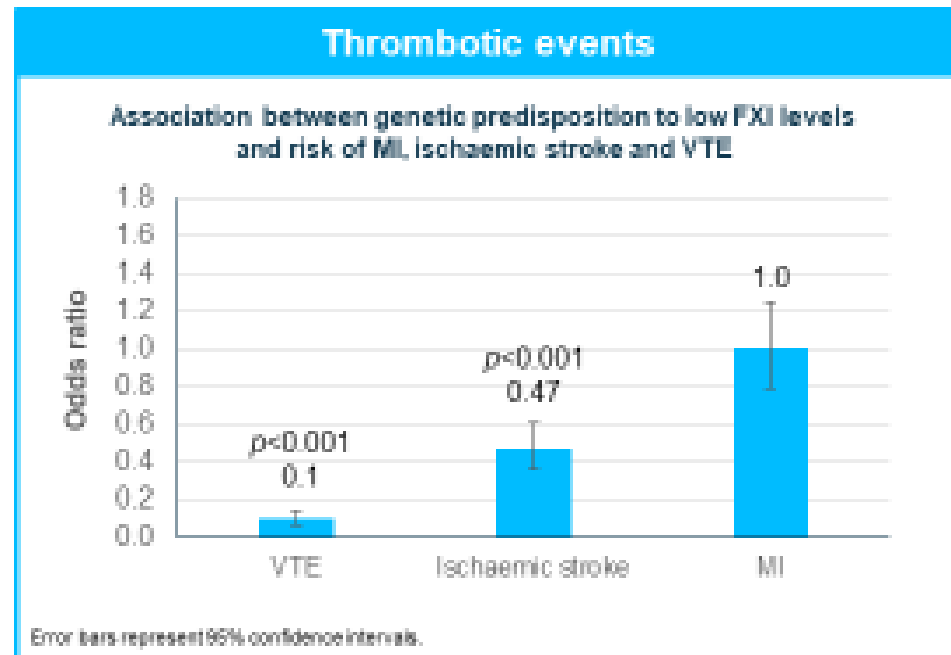
Factor XI in Hemostasis

- ❖ **Produced in liver** not being vitamin K dependent.
 - ❖ Has receptors for **thrombin, HK and FIX**
 - ❖ Circulates in plasma as a dimer with a half life of 52 hours.
 - ❖ Plasmatic concentration is 5 µg/mL, **bleeding is observed usually at FXI activity <10-20% after trauma or surgery**, setting a **safety activity limit** in case of pharmacologic inhibition.
-
- FXI exerts **procoagulant effect independent** of FIX activation .
 - FXIa **promotes thrombin generation** through FVIII & FV activation
 - FXIa affects the extrinsic pathway by **TFPI inhibition**
 - FXIa **inhibits fibrinolysis** by activating **TAFI**.

Role of FXI in Thrombosis and Hemostasis

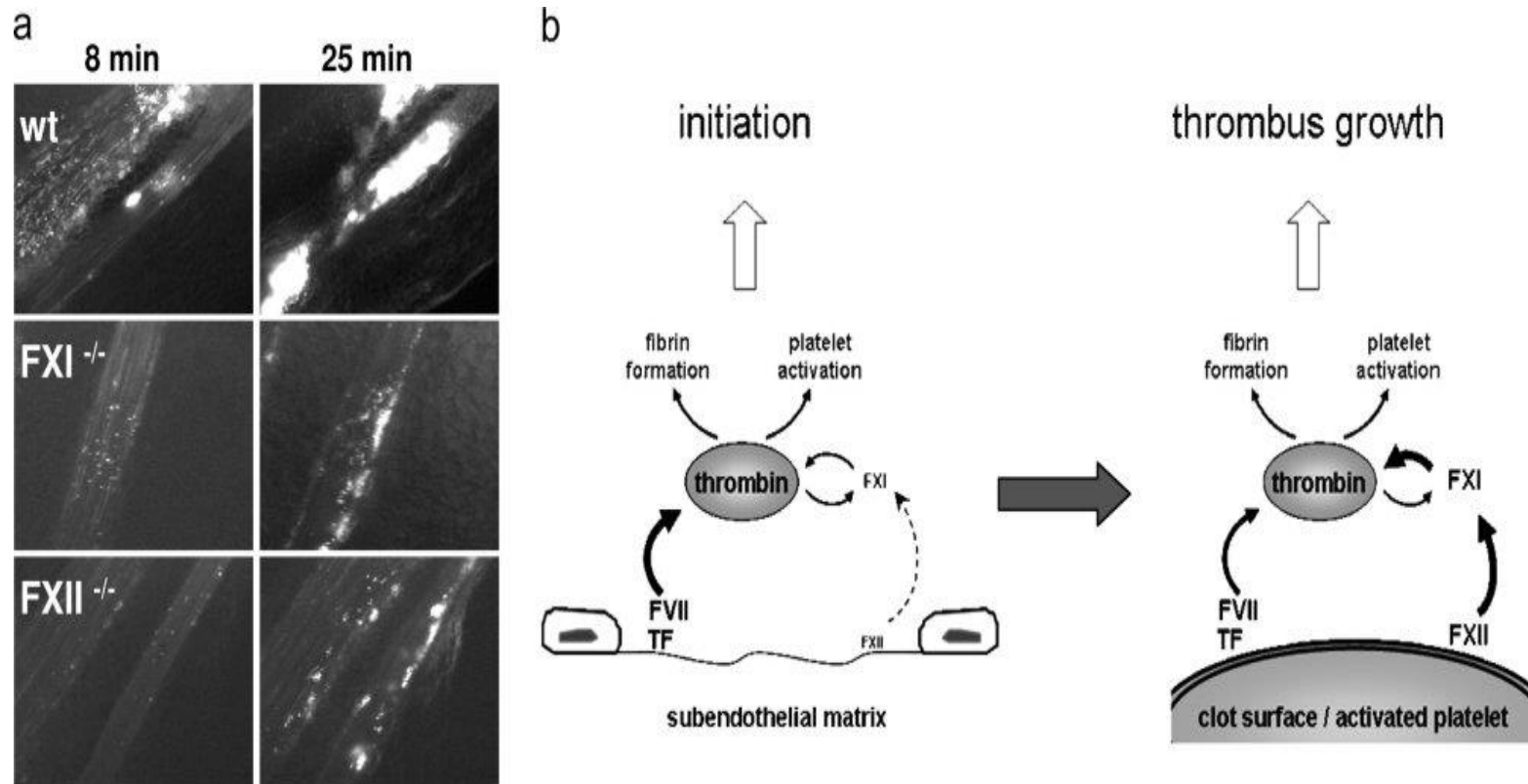


Genetic Predisposition to Low FXI Levels is Associated with Reduced Risk of Ischaemic Stroke



Odds ratios presented are for a 35% mean increase in aPTT (equivalent to pharmacological FXI lowering). Data are from 371,025 participants in the UK Biobank and two large genome-wide association studies. aPTT, activated partial thromboplastin time; F, factor; MI, myocardial infarction; VTE, venous thromboembolism. Georgi B *et al.* *Stroke* 2019;50:3804–3812.

Attenuated Thrombosis in Mice Deficient in FXII or FXI



Evidence Supporting Factor XII as a Target



Animal studies

FXII knockout or inhibition attenuates thrombosis in mouse, rat, rabbit, and baboon models with no increase in bleeding¹⁻⁴



Human genetic deficiency

No evidence that subjects with congenital FXII deficiency have a reduced risk of thrombosis



Genetic epidemiology

No evidence that the risk of thrombosis is increased in subjects with high FXII levels compared with those with normal levels, or that the risk is lower with reduced FXII levels

¹ Renné, T, et al.. *J Exp Med* ; 2005: 202: 271-281.

² Xu, Y, et al. *Thromb Haemostas*; 2014; 111: 694-704.

³ Yau, J. W., et al.. *Blood*; 2014; 123, 2102-2107.

⁴ Matafonov, A, et al. *Blood*, 2014: 123.: 1739-1746.

Evidence Supporting Factor XI as a Target



Human genetic deficiency

Subjects with severe congenital FXI deficiency (1 in 450 Ashkenazi Jews) have a reduced risk of thrombosis and rarely experience spontaneous bleeding¹



Genetic epidemiology

In large cohort studies, the risk of thrombosis was 2-fold higher in subjects with high FXI levels compared with those with normal levels,² and 40% to 90% lower in those with reduced FXI levels³



Animal studies

FXI inhibition attenuates thrombosis in mouse, rabbit, monkey, and baboon models with no increase in bleeding⁴

1 Asselta R et al. Blood 2017; 130(4):e1-e6

2 Meijers J et al. N Engl J Med 2000; 9;342(10):696-701

3 Preis M et al. Blood 2017; 129(9):1210-1215

4 Gailani D, Gruber A. Arterioscler Thromb Vasc Biol 2016; 36(7):1316-22

Targeting FXI (or FXII)

	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

Abbreviations: ASO, antisense oligonucleotide; CYP, cytochrome P450; FXI, factor XI; FXII, factor XII; IV, intravenous; SC, subcutaneous.

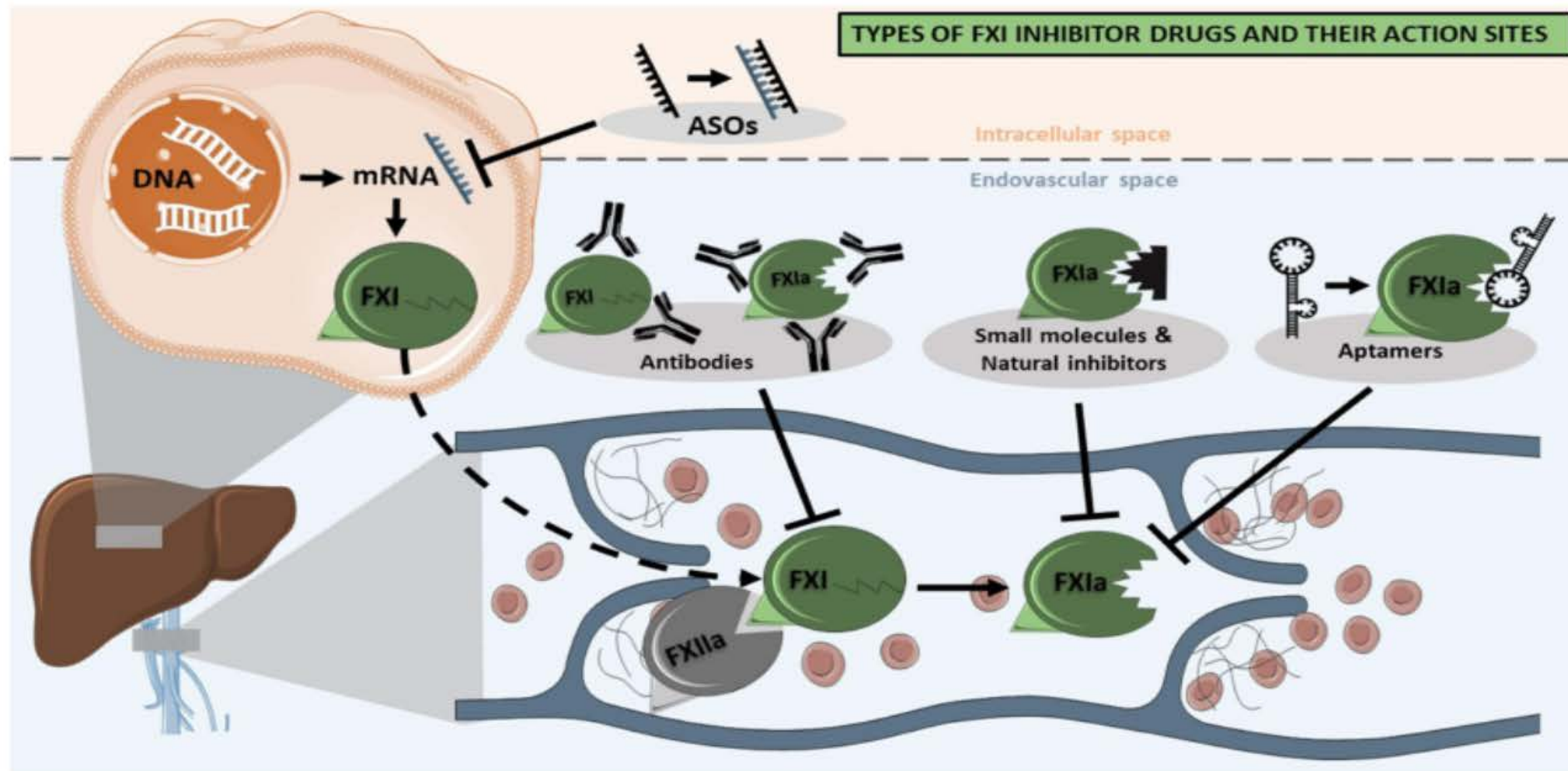


Figure 2 Types of FXI inhibitor drugs and their action sites.

FXI Inhibitors: IONIS-FXIRX/FXI-ASO

Antisense oligonucleotide ASO targeting FXI production in hepatic cells. Administered subcutaneous. (slow onset-slow offset)

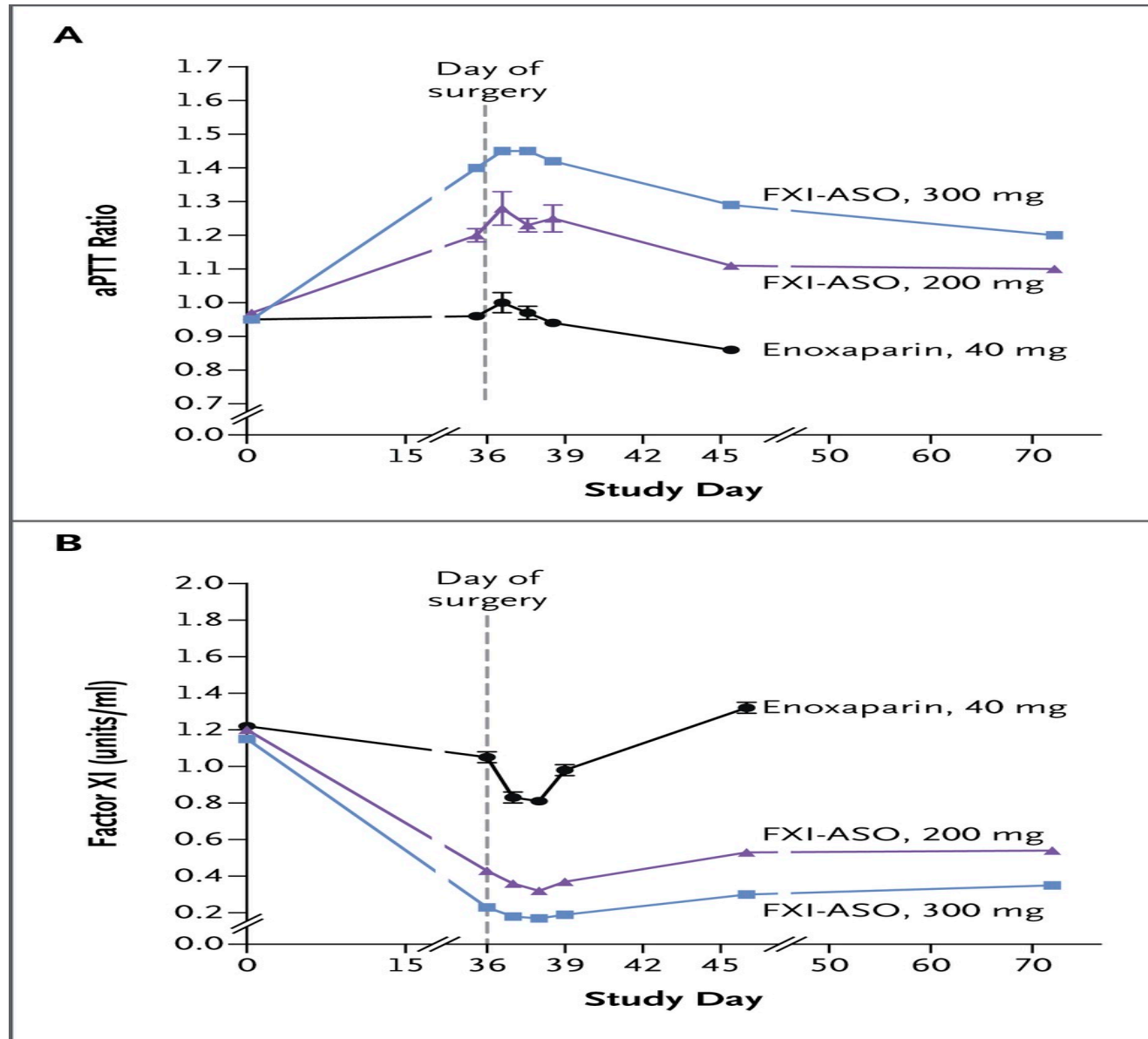
In a randomized study*[[FXI-ASO TKA 2015](#)] 300 patients received 36 hours before surgery doses of 100mg, 200mg and 300mg.

The 100mg dose was ineffective and was dropped.

The 200mg was non-inferior and the 300mg was superior to enoxaparin.

Bleeding was observed in 3% of patients receiving FXI-ASO compared to 8% of patients receiving enoxaparin.

IONIS - aPTT, FXI levels



Phase 2 Study of the Factor XI Antisense Inhibitor IONIS-FXI_{Rx} in Patients with ESRD



Multicenter



Double- blinded



43 patients on HD



12 weeks

Pharmacokinetics similar when given before or after HD



No accumulation of IONIS-FXI_{Rx} observed

Day 85: Factor XI activity

 200 mg Decreased 56.0%

 300 mg Decreased 70.7%

 Placebo Decreased 3.9%

Major Bleeding Events*:

200 mg 0.0%

300 mg 6.7%

Placebo 7.7%



Dose dependent prolongation of aPTT without changes in INR

***Serious adverse events were not considered related to treatment**



KI REPORTS
Kidney International Reports

Walsh M et al, 2022

Visual abstract by:
Brian Rifkin MD
 @brian_rifkin

Conclusion: IONIS-FXI_{Rx} reduced FXI activity in ESRD patients receiving HD. Further studies are needed to determine the benefit-risk profile of FXI as a therapeutic target for patients that require HD.

Oscimab – Foxtrot Study

Monoclonal antibody that binds and inactivates FXI and blocks activation to FXIa by FXIIa or thrombin.(fast onset-slow offset)

813 patients were randomized to receive osocimab (0.3, 0.6, 1.2, 1.8 mg/kg) before or after TKR surgery and were compared with patients that received enoxaparin 40 mg or apixaban 2.5 mg bid.

- Osocimab at **1.8** mg/dl was superior in VTE prevention.
- Major or CRNM bleeding were observed in **4.7%** of patients receiving osocimab, in **5.9%** receiving enoxaparin, and in **2%** of patients who received apixaban.

Abelacimab

Human monoclonal antibody that can be administered iv or sc.
(fast onset-slow offset).

It binds on FXI blocking activation to FXIa, In addition is a direct inhibitor of FXIa.

- 412 patients were randomized prior to TKR surgery to receive abelacimab postop. at 3 iv schemes (30, 75, 150 mg) and compared with patients receiving 40 mg enoxaparin*.
- Abelacimab was non-inferior to enoxaparin at 30mg , and appeared to be superior at 75mg and 150 mg doses.
- No major bleeding episodes were recorded.

Milvexian

Small molecule, direct, selective, reversible inhibitor of FXIa, administered orally with a $t_{1/2}$ of 12hrs.

APTT prolongation is observed and is dose dependent.

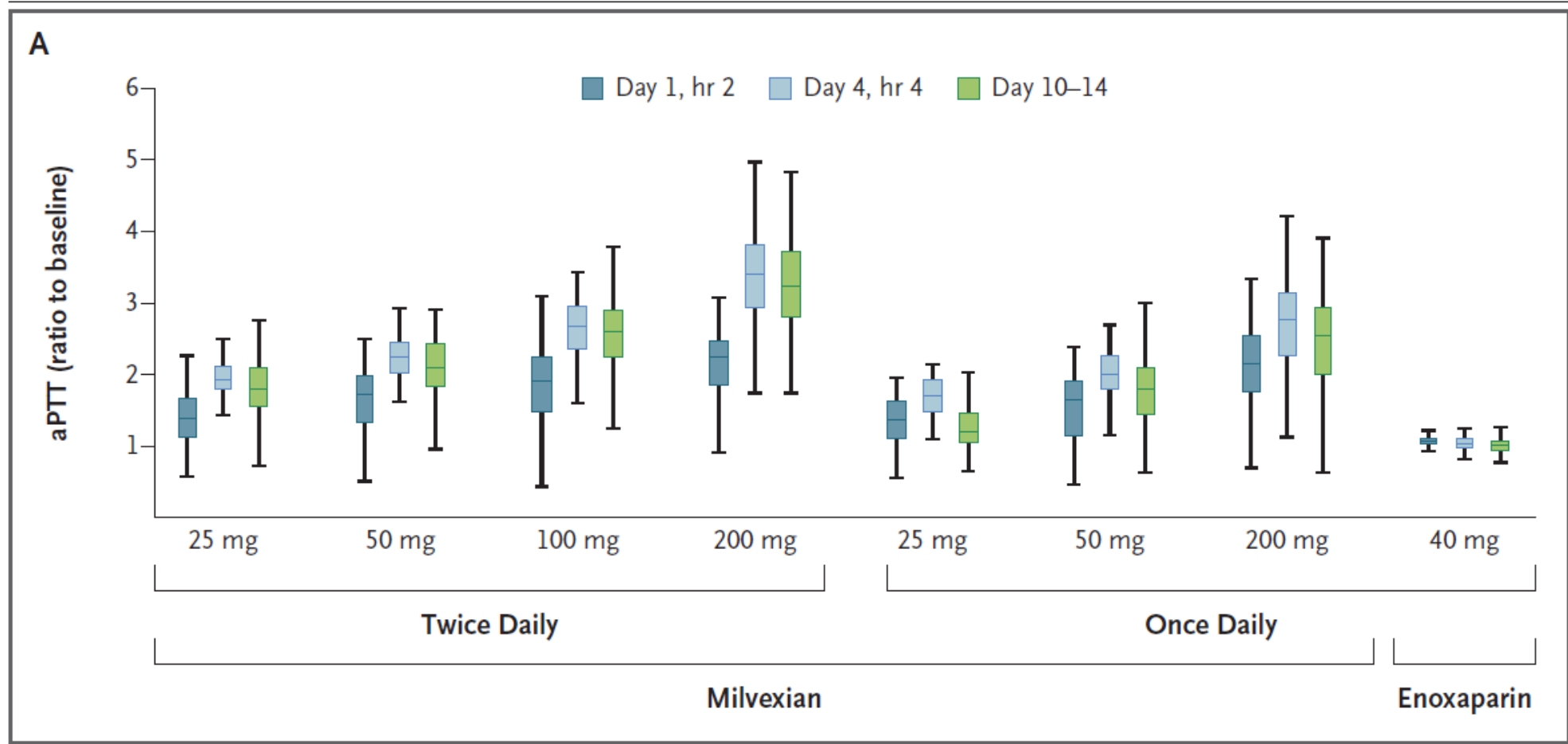
(Fast onset-fast offset)

In AXIOMATIC-TKR* study 1242 patients undergoing surgery were randomized to receive milvexian at 7 different dosing schedules or enoxaparin.

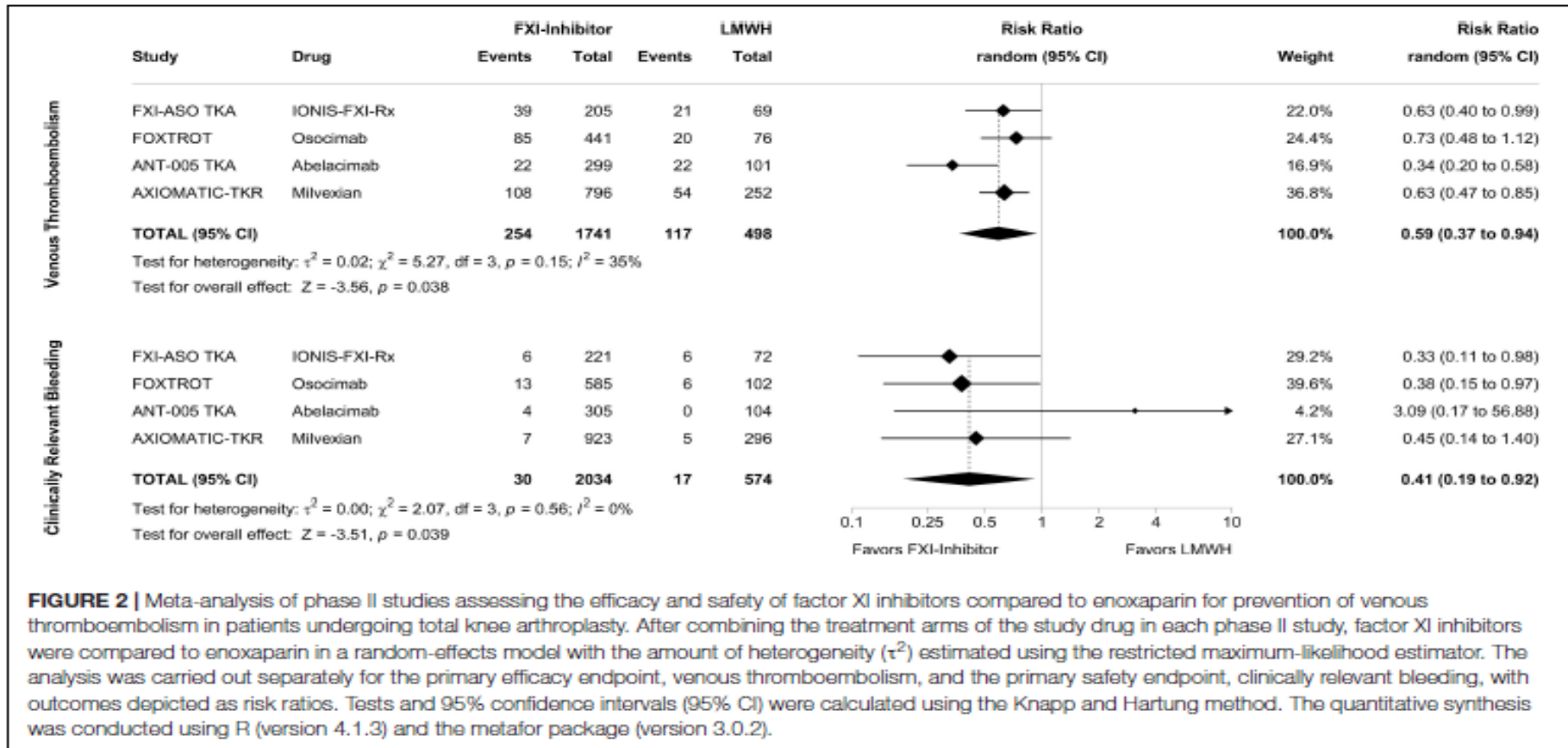
- Milvexian **was non-inferior** to enoxaparin and at 25;50;100 and 200mg dose.
- The 200mg bid dose **was superior** for VTE prevention.
- **No serious adverse reactions were reported**
- No differences in major(1%) or CRMM (2%) bleeding episodes were observed.

Milvexian dose dependent aPTT prolongation

The NEW ENGLAND JOURNAL of MEDICINE



Meta-analysis of Phase II Studies in Orthopedic Patients



AXIOMATIC-Secondary Stroke Prevention

Milvexian in addition to dual antiplatelet treatment was assessed in 2366 patients with stroke.

Patients were randomized to receive milvexian at 25, 50, 100, 200 mg bid., or 25 mg od or placebo for 90 days.

All patients received antiplatelet treatment (dual for 21 days)

- ✓ Although milvexian **did not decrease** cerebral infarcts or strokes at 90 days, it did **reduce the risk for symptomatic strokes**
- ✓ **Major bleeding episodes were infrequent** at all doses tested

Asundexian-Pacific AF Study

Small molecule, direct inhibitor of FXIa, administered orally with a $t_{1/2}$ of 17hrs, no interaction with P450 cytochrome and less than 15% renal clearance.

In the phase II PACIFIC-AF study*, 753 patients with atrial fibrillation and increased bleeding risk were randomized to receive two different schedules of asundexian od (20 mg or 50 mg) or apixaban for 12wks.

Bleeding episodes were observed at 1.2, 0.4 and 2.4% of patients receiving asundexian 20 mg, 50 mg and apixaban respectively.

Larger phase III studies are warranted for efficacy demonstration

FXII Inhibitors: Garadacimab

- ❖ Fully humanized **monoclonal antibody** against FXIIa
- ❖ Planned evaluation in cancer patients receiving **systemic chemotherapy** via a **percutaneously inserted central catheter** (PICC;NCT04281524).
- ❖ This **study was withdrawn** based on a company business decision.
- ❖ Garadacimab is being compared with placebo in patients with **COVID-19 pneumonia** with the primary outcome being the need for intubation or death (NCT04409509), and in the treatment of patients with **idiopathic Pulmonary fibrosis** (NCT05130970)
- ❖ In patients with **hereditary angioedema** deficient in **C1-esterase inhibitor**, garadacimab significantly reduced the number of monthly attacks.

Factor XII or Factor XI as Targets for New Anticoagulants

	Factor XII	Factor XI
Epidemiological data	Weak	Stronger
Risk of bleeding	None	Low
Potential for bypassing inhibition	Thrombin-mediated activation of factor XI could bypass factor XII inhibition	None
Potential for off target effects	May modulate inflammation by inhibiting bradykinin generation	Unlikely
Level of evidence for role in thrombosis	minimal Phase 2 data	Robust Phase 2 data

Ongoing Phase 3 Clinical Trials with FXI Inhibitors

Drug	Trial name (NCT)	Indication	Comparator	N	Sponsor
Abelacimab	LILAC-TIMI 76 (NCT05712200)	AF patients deemed unsuitable for oral anticoagulation	Placebo	1900	Anthos
	ASTER (NCT05171049)	Cancer-associated VTE	Apixaban	1655	
	MAGNOLIA (NCT05171075)	Gastrointestinal/genitourinary cancer associated VTE	Dalteparin	1020	
Asundexian	OCEANIC-AF (NCT05643573)	AF	Apixaban	18000	Bayer
	OCEANIC STROKE (NCT05686070)	Secondary stroke prevention	Placebo	9300	
Milvexian	LIBREXIA-AF (NCT 05757869)	AF	Apixaban	15500	BMS and Janssen
	LIBREXIA Stroke (NCT05702034)	Secondary stroke prevention	Placebo	15000	
	LIBREXIA ACS (NCT05754957)	ACS	Placebo	16000	

Novel Indications and Targets

- Angiogenesis and Inflammation in CAT -**Heparanase Inhibition** –no effect on hemostasis
- Thrombo-inflammation pathways- **COVID;IBD**
- Pregnancy complications
- Liver disease –LMWH attenuate progression
- Neuro-Psychiatric disorders
- Gene targeting -attenuation of coagulation factors activation

Patient-related

- Medical comorbidities
- Presence of varicose veins
- Prior VTE
- Hereditary risk factors (e.g. Factor V Leiden)

Tumor-related

- Site of cancer
- Very High: stomach, pancreas
- High: lung, hematologic, gynecologic, Brain, Renal, bladder
- Histological grade of a tumor
- Stage of cancer metastases
- Time since cancer diagnosis

Cancer Associated VTE Risk

Treatment-related

- Platinum based and other chemotherapy
- Anti-angiogenesis agents
- Hormonal therapy
- Surgery
- Radiotherapy
- Blood transfusion
- Central venous catheters
- Immobility and hospitalization

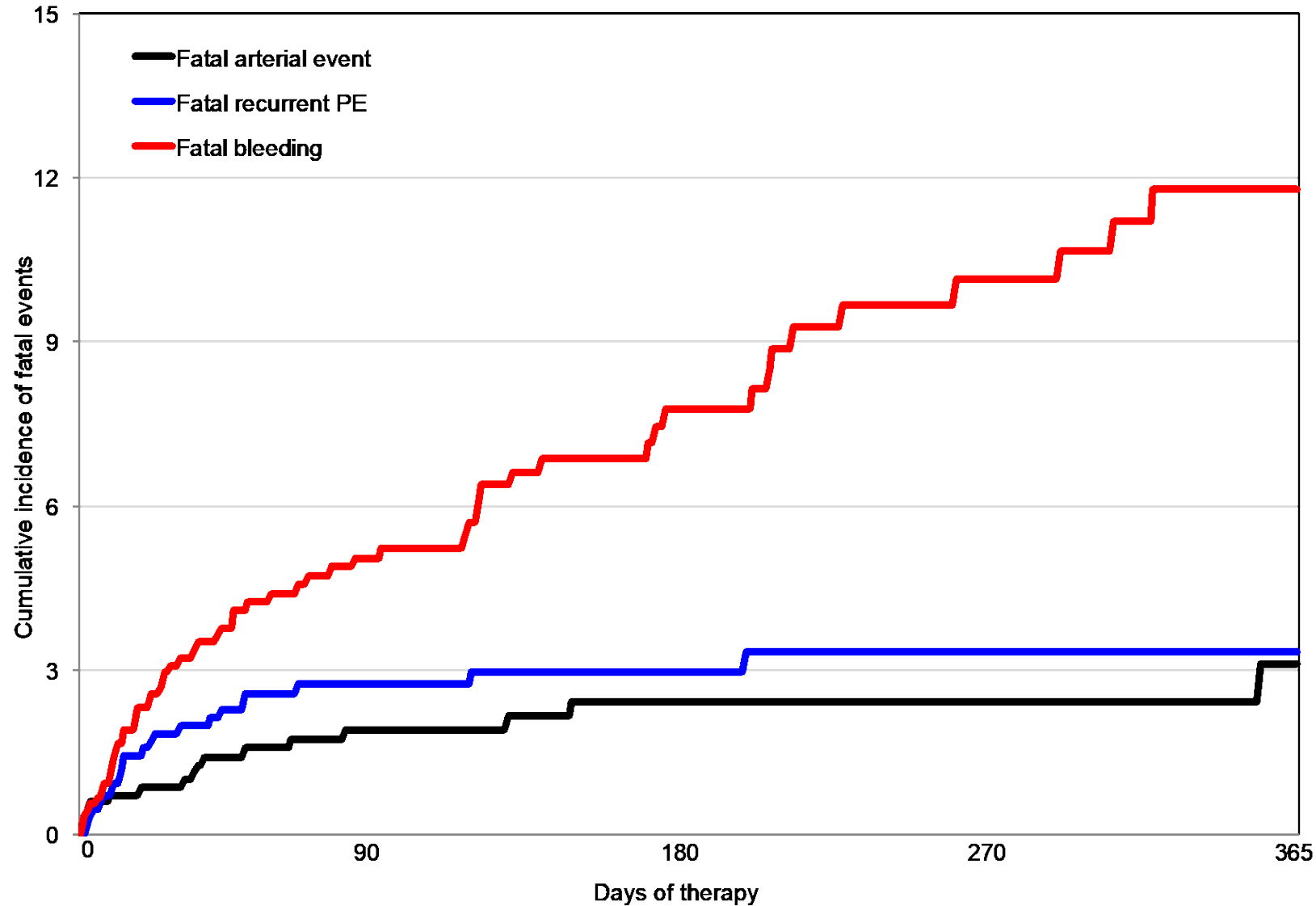
Biomarkers

- Hematologic biomarkers (e.g., platelet haemoglobin, leukocyte count)
- D-dimer
- P-selectin
- Prothrombin fragment 1+2
- Thrombin generation potential
- Microvesicle-tissue factor activity
- C-reactive protein

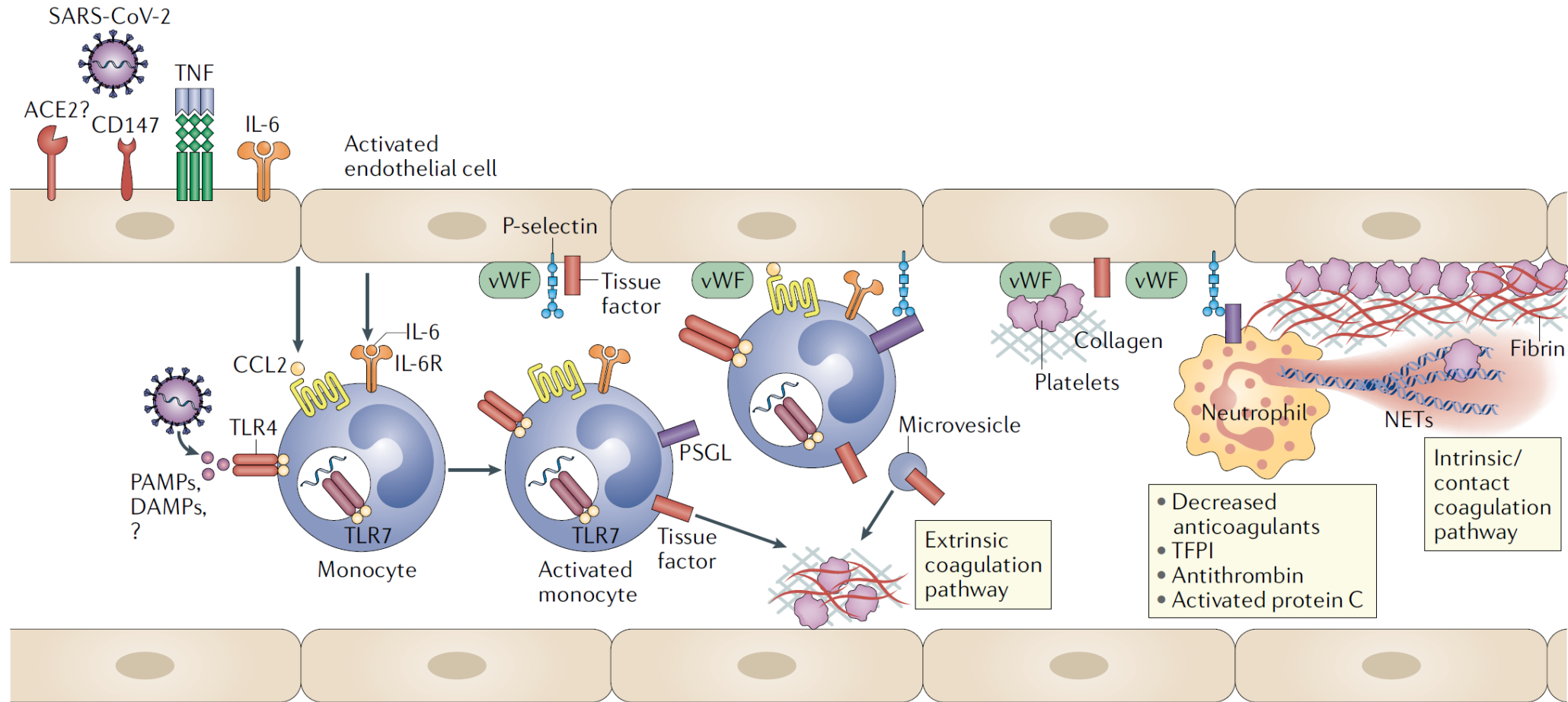
RAMs -The Future Goal

- The heterogeneity in risk, favors a targeted risk adaptive approach
- A need for adding sensitive and practical biomarkers into thrombosis and bleeding risk-models
- Apply in real time and repeat sequentially to optimize personalized decision making.

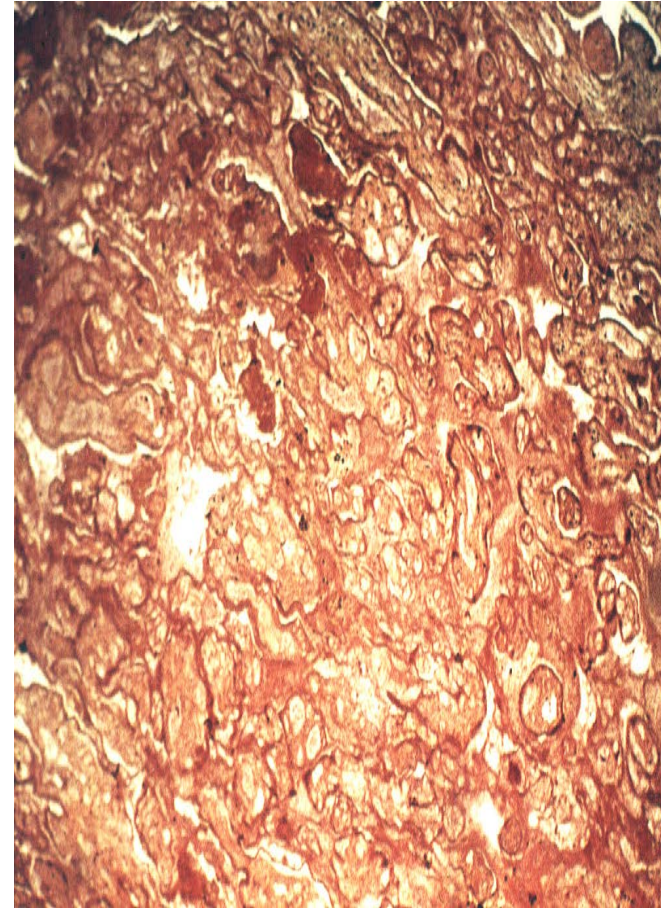
Cumulative Mortality in CAT Patients with Arterial Ischemic Event



COVID-19, INFLAMMATION AND COAGULATION: DELETERIOUS TRIO



Pathological Findings in Placenta of Thrombophilic Woman



Coagulation and Inflammation are major players in Pregnancy Complications

Sarig & Brenner, Lancet 2004

Maternal extracellular Vesicles and Platelets Promote Preeclampsia

- EVs cause placental sterile inflammation and preeclampsia
- Activation of maternal platelets.
- Purinergic inflammasome activation in trophoblast cells.
- Highlighting a novel thrombo-inflammatory mechanism at the maternal-embryonic interface.

Kohli, Blood 2016

Mechanisms of Action of LMWH

- Systemic anticoagulation in the maternal circulation
- TFPI release from endothelial cells and trophoblasts
- Anti-inflammatory properties
- Modulation of trophoblasts apoptosis and migration

RAM Score Vs. LMWH Dose

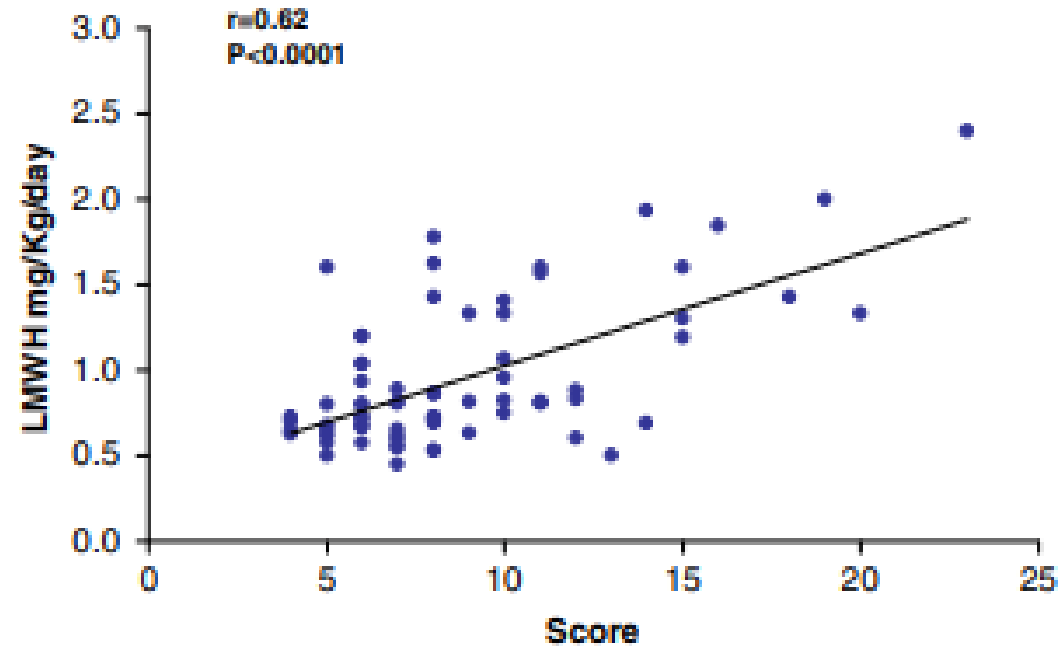
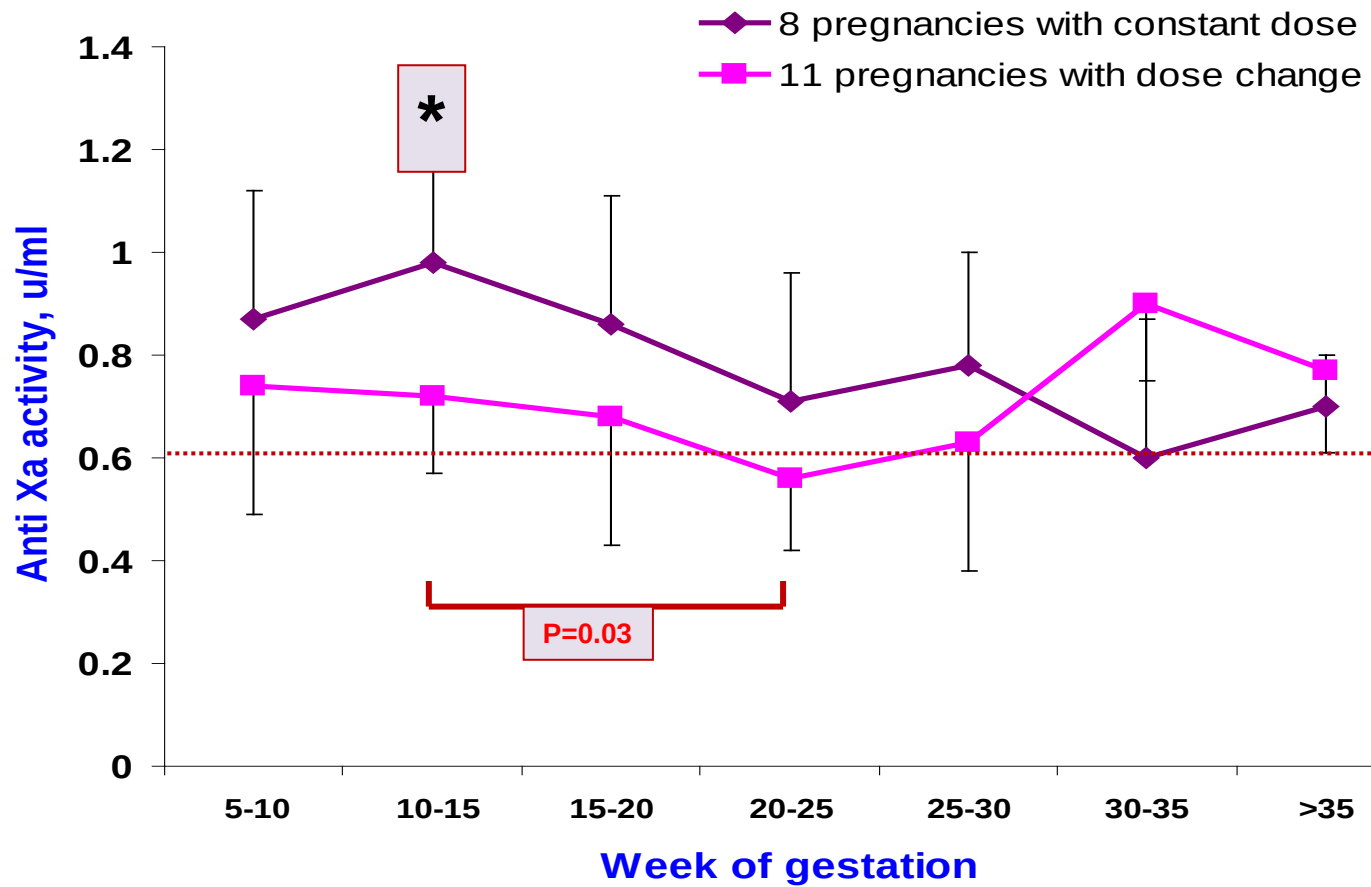


Fig. 1. Correlation between score and LMWH dosages in the live born group (n = 74).

Assessment-based management of placenta-mediated pregnancy complications: Pragmatism until a precision medicine approach evolves

- The management of pregnant women with thrombophilia and a history of gestational vascular complications remains debatable.
- The available guidelines are inconsistent in some situations, which reflects the limited evidence base.
- **RAMs**, taking into account obstetric and thrombotic history as well as thrombophilia status, **could drive a precision medicine approach**, based on disease mechanism, and guide individual therapeutic interventions in high-risk clinical settings.

Pregnancies treated with therapeutic dosages



Effects of anti-Xa activity monitoring on the outcome of high-risk pregnancies treated with a prophylactic dose of low-molecular-weight heparin

Objective: To evaluate if anti-Xa level monitoring and dose adjustment in women using a prophylactic dose of enoxaparin can decrease placenta-mediated pregnancy complications.

Main findings :

- The most prominent decrease in anti-Xa levels was observed in the second trimester.
- **Monitored women had significantly more term deliveries and demonstrated a trend toward higher birth weight and fewer placenta-mediated pregnancy complications.**
- Larger studies are needed to confirm improved pregnancy outcome in monitored women.

GVC-Future Directions

- Define patient groups based on:
 - Maternal and fetal characteristics
 - Disease mechanisms (such as maternal thrombo-genicity and placental thrombotic lesions)
- **Establish registries for thrombophilia and pregnancy complications**
- Evaluate relevant biomarkers (e.g., EV- TF/TFPI ratio, Protein C Global Assay)
- **Design specific intervention studies based on RAMs**

Incidence of venous thromboembolism in different ethnic groups: a regional direct comparison study

Europeans have a significantly higher incidence of VTE compared with Maori, Pacific Island and Asian populations.



However, beware of travel related thrombosis!

Coagulation in Psychiatric Disorders

- APLA, Homozygous PTM, (PS deficiency?) are associates with neuro-psychiatric presentations
- Dysfunction in the coagulation system and schizophrenia

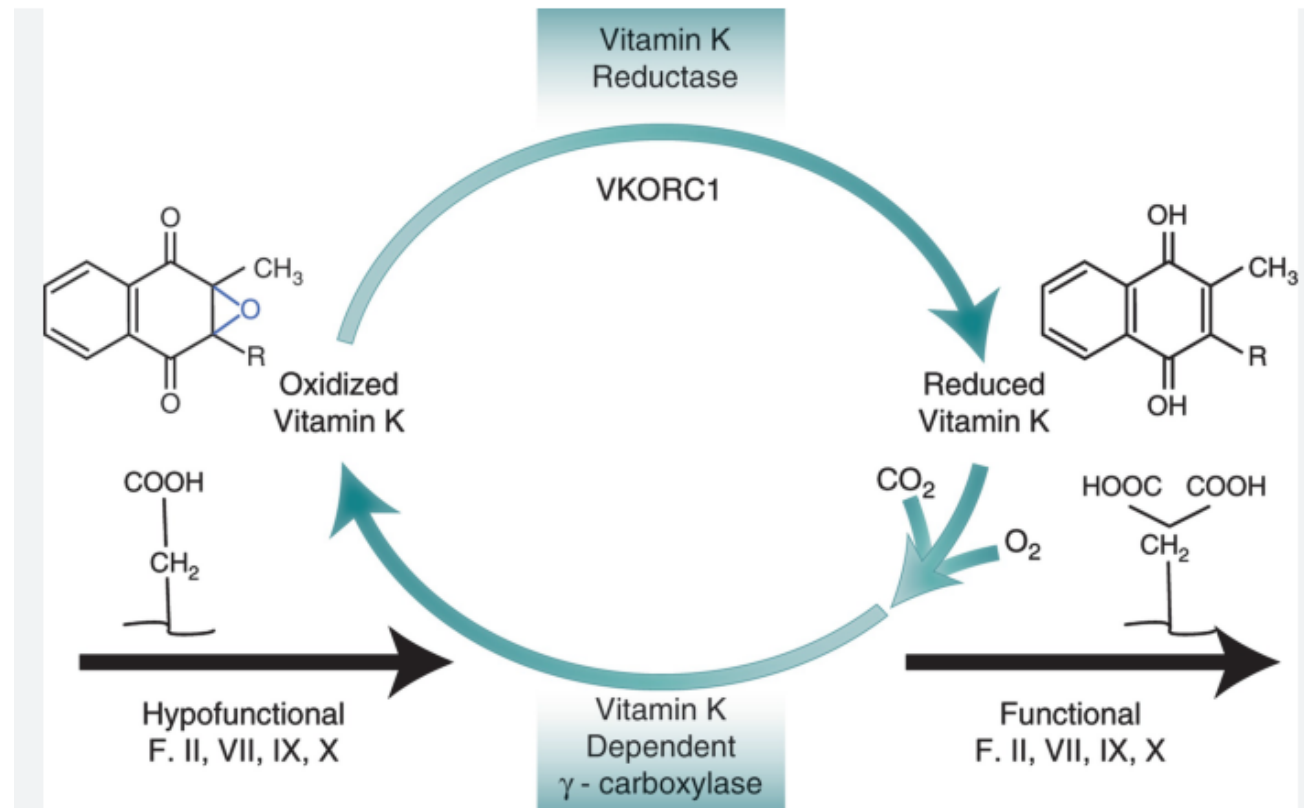
Psychotropic Drugs and Outcome in Patients Receiving Anticoagulant Therapy for Venous Thromboembolism - RIETE Study .
S. Hirsch-Clapauch Transl, Psychiatry 2016

During the course of anticoagulation for VTE, patients using psychotropic at baseline were at **increased risk for intracranial bleeding**.

Marchena PJ, Tzoran I, Brenner B Thromb Haemost. 2020

A Missense Mutation in γ -Glutamyl Carboxylase Gene Causes Combined Deficiency of All Vitamin K-Dependent Blood Coagulation Factors

Benjamin Brenner, Beatriz Sánchez-Vega, Sheue-Mei Wu, Naomi Lanir, Darrel W. Stafford, Jesus Solera



AI is the Future !(?)



Can Machine Learning from Real-World Data Support Drug Treatment Decisions? A Prediction Modeling Case for Direct Oral Anticoagulants

Meid Med Decis making, 2022

Using Artificial Intelligence to Reduce the Risk of Nonadherence in Patients on Anticoagulation Therapy

Labovitz DL Stroke 2017

THANK YOU!

