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Venous Thromboembolism and Anticoagulation

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Disclosures

In compliance with ACCME policy, ASH requires disclosures to the session audience:

Speakers

David Garcia, MD

Disclosures

Consultancy: Abbott

Discussion of off-label drug use: N/A



Learning Objectives

Upon participation in this activity, attendees will be able to:

- Review evidence of anticoagulation in pregnant women with inherited thrombophilia and recurrent miscarriage
- Describe use of direct oral anticoagulants in the treatment of catheter related thrombosis in patients with cancer
- Discuss the use of novel anticoagulant (FXI inhibitors) in the prevention of catheter related thrombosis and other future potential applications



Overview – Thrombosis and anticoagulation at ASH 2022

- One potentially practice-changing abstract (ALIFE2)
- Several cohort studies provided data in the treatment and prevention of catheter-related thrombosis in patients with cancer and predicting VTE in cancer patients receiving immune checkpoint inhibitors
- Accumulating data on novel anticoagulants (FXI/FXII inhibitors) as treatment and prevention of thrombosis

Case 1

- A 32-year-old women with a history of two early pregnancy losses is now 6 weeks pregnant.
- Previous workup revealed heterozygous factor V Leiden mutation. All other thrombophilia workups were negative, including antiphospholipid antibodies. She has no personal history of thrombosis.
- Patient is concerned that she might have another miscarriage and asks what can be done to increase the success rate for this pregnancy.



Question

- How would you advise her?
 - A. She should use LMWH throughout pregnancy, primarily *to increase her chance of a live birth*
 - B. She should use LMWH antepartum and postpartum, primarily to *reduce the risk of DVT or PE*
 - C. She should use LMWH postpartum only, primarily to *reduce the risk of DVT or PE*
 - D. Neither she nor the developing fetus is likely to benefit from LMWH**



Low-molecular-weight heparin versus standard pregnancy care for women with recurrent miscarriage and inherited thrombophilia: an open-label, phase III randomized controlled trial (ALIFE2)

Executive writing committee:

Siobhan Quenby, M.D., Katie Booth, MSc, Louise Hiller, Ph.D, Arri Coomarasamy M.D., Paulien G. de Jong, M.D., Eva Hamulyák, M.D., Luuk Scheres, M.D., Thijs van Haaps, BSc, Lauren Ewington M.B.B.S., Shreeya Tewary M.D., Mariëtte Goddijn*, M.D., Saskia Middeldorp*, M.D., on behalf of the ALIFE2 block writing committee and ALIFE2 Investigators. *shared last authors

Inherited thrombophilia and recurrent miscarriages?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aspirin plus Heparin or Aspirin Alone in Women with Recurrent Miscarriage

No effect of aspirin and LMWH (RR 1.03, 0.85-1.25)

In women with thrombophilia:
Aspirin and LMWH (RR 1.31, 0.74-2.33)

ALIFE Study; Kaandorp et al, New Engl J Med 2010



ALIFE2 Study – Design

Investigator-initiated, international, open-label RCT

- 41 centers in 5 countries
- Two coordinating centers (Amsterdam & Warwick)
- Open-label
- Trial registration 2012 NTR3361/ EudraCT 2015-002357-35

Inclusion Criteria

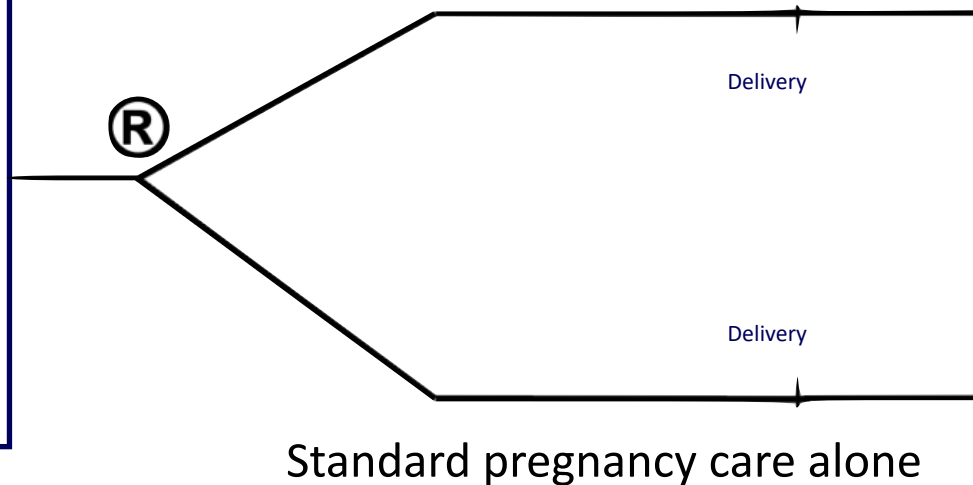


- History of 2 or more miscarriages
- Inherited thrombophilia
- Maximum 7 weeks gestational age

Once-daily LMWH, until delivery
Dalteparin 5000 IU
Enoxaparin 40 mg
Nadroparin 2850 IU
Tinzaparin 4500 IU



Plus standard pregnancy care



Outcomes

Primary efficacy

- Live birth

Secondary efficacy

- Miscarriage
- Adverse obstetric outcomes

Safety

- Bleeding episodes
- Thrombocytopenia
- Skin reactions
- Neonatal congenital malformations

Study design and rationale described previously: De Jong et al, Trials 2015

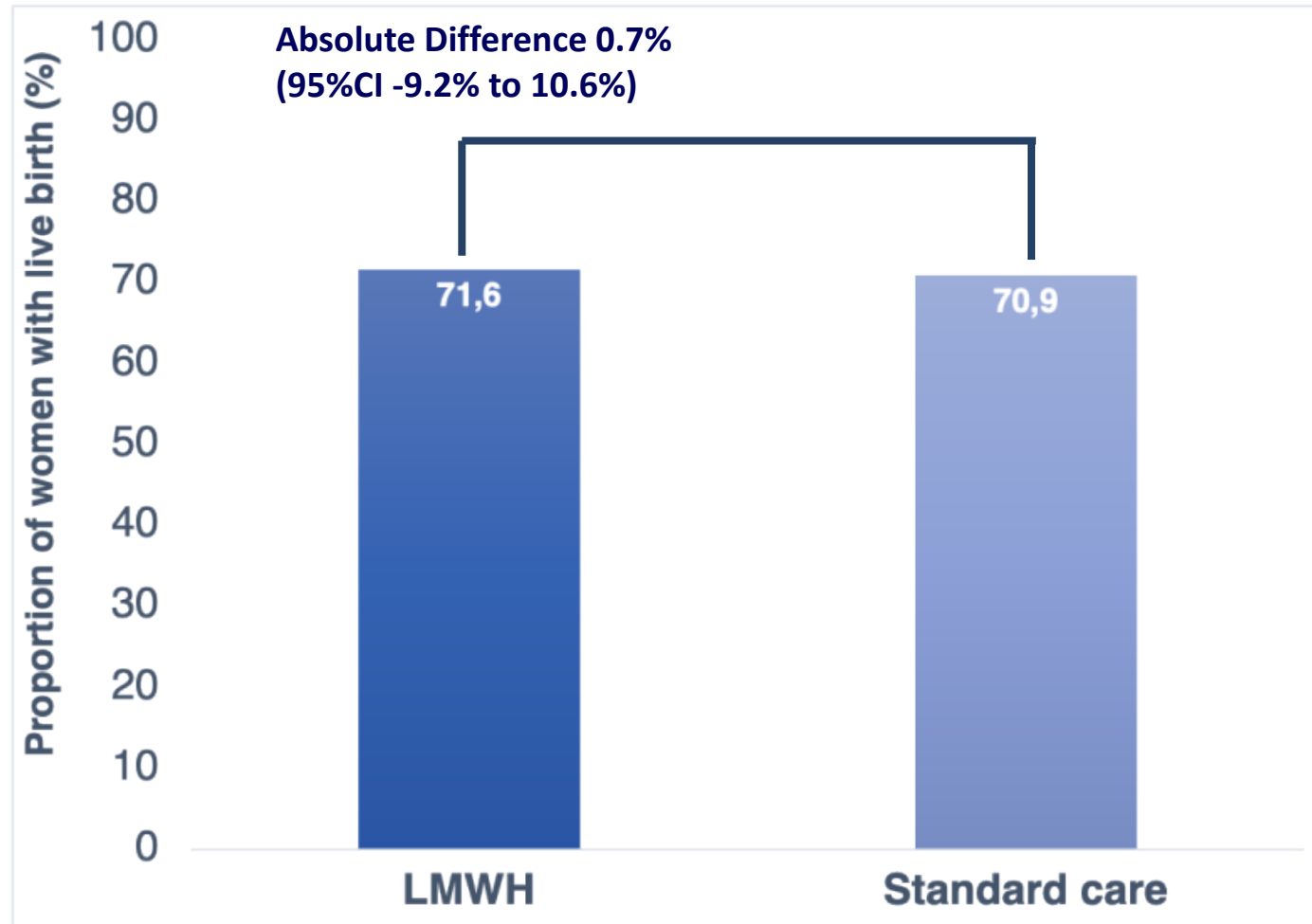


ALIFE2 Study – Baseline characteristics

| | LMWH (N=164) | Standard care (N=162) |
|--|-------------------------|----------------------------------|
| Mean age - years (SD) | 33.5 (5.2) | 33.3 (5.3) |
| Number of miscarriages - 3 or more | 118 (72%) | 110 (68%) |
| Factor V Leiden hetero/homozygous | 95 (58%) / 5 (3%) | 89 (55%) / 0 (0%) |
| Prothrombin mutation hetero/homozygous | 39 (24%) / 0 (0%) | 44 (27%) / 2 (1%) |
| Antithrombin deficiency | 2 (1%) | 5 (3%) |
| Protein C deficiency | 5 (3%) | 8 (5%) |
| Protein S deficiency | 23 (14%) | 21 (13%) |
| Combined thrombophilia | 5 (3%) | 7 (4%) |



ALIFE2 Study – Primary Outcome Live Birth



Odds Ratio 1.04
(95%CI 0.64 to 1.68)

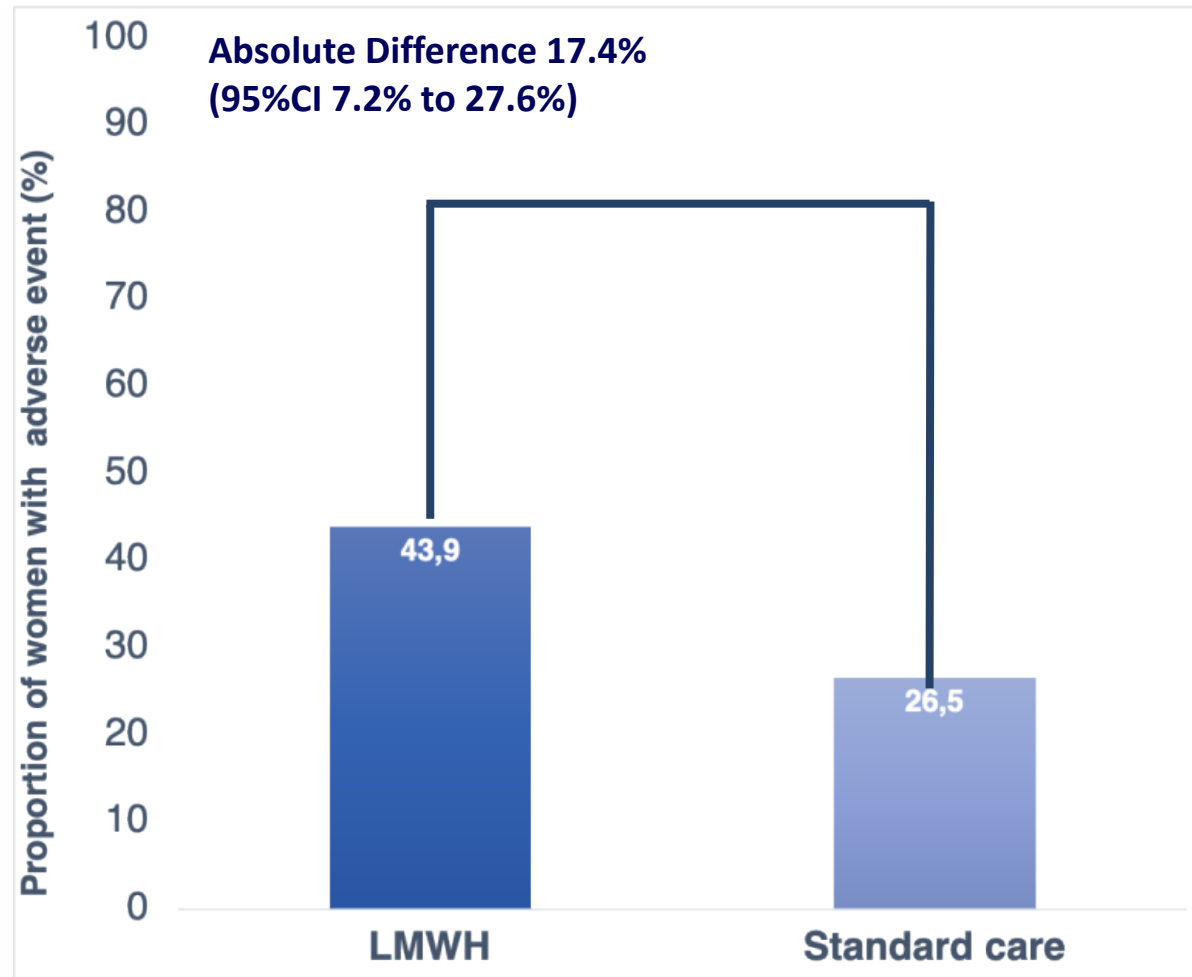
χ^2 p=0.99

Adjusted* Odds Ratio 1.08
(95%CI 0.65 to 1.78) p=0.770

*Adjusted for maternal age (<36, ≥36), number of miscarriages (2, ≥3), center (tertiary, non-tertiary) and randomizing country (UK, Netherlands)



ALIFE2 Study – Adverse events



Difference in adverse events

- Easy bruising
- Skin reactions at injection site
- Minor bleeding

Odds Ratio 2.17
(95% CI: 1.32 to 3.55)
 χ^2 p=0.0016



ALIFE2 Study – Strength and limitations

Strengths

- First RCT dedicated to women with recurrent miscarriage and inherited thrombophilia
- Careful documentation of efficacy and adverse events
- Intention to treat analysis
- Low rate of loss to follow-up
- International, multi-center, pragmatic LMWH choice, generalizable findings

Limitations

- Open-label design
- Cross-over to LMWH, 18 prior to 12 weeks
- Sample size modest
- A 10% absolute difference in live birth rate in either direction cannot be excluded
- Live birth rate higher than expected, in line with other studies in women with recurrent miscarriage



ALIFE2 Study – Conclusions and take home

In pregnant women with inherited thrombophilia and recurrent miscarriage

- The live birth rate is approximately 70% with standard pregnancy care
- LMWH does **not** increase live birth rate
- Do **not** treat women with recurrent miscarriage and inherited thrombophilia with LMWH to prevent miscarriage
- Do **not** test women with recurrent miscarriage for inherited thrombophilia in the absence of therapeutic consequences

Case 2

- A 76-year-old male with metastatic colon cancer recently started his first cycle of chemotherapy through a right arm PICC line.
- He has developed right arm pain, swelling, and redness.
- Doppler showed an acute upper extremity DVT in the right subclavian and axillary veins.
- The chemotherapy must be administered in a central vein and is considered pivotal for his chances to achieve a cure.



<https://www.hmpgloballearningnetwork.com/site/vdm/content/acoustic-assisted-catheter-directed-thrombolytic-therapy-upper-extremity-phlegmasia-cerulea>

Question

What management strategies would you recommend?

- A. Remove the line and repeat ultrasound in 5-7 days.
- B. Remove the line and initiate anticoagulant therapy with low molecular weight heparin.
- C. Leave the line in place and initiate anticoagulant therapy with an oral factor Xa inhibitor (rivaroxaban or apixaban).**
- D. Leave the line in place and initiate anticoagulant therapy with low molecular weight heparin.





A Prospective Study of Apixaban for Central Venous Catheter Associated Upper Extremity Deep Vein Thrombosis in Cancer Patients: Catheter 3

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Methods

- Multicentre prospective cohort trial in 3 tertiary centres in Canada
- Treatment: Dalteparin 200 IU/kg daily x 7d -> apixaban 5 mg bid x 11 weeks
- All events independently adjudicated, Patients were followed until 12 weeks
- Inclusion criteria:
 - ≥ 18 years with active malignancy and symptomatic proximal UEDVT +/- PE, associated with a CVC
- Main exclusion criteria:
 - Active bleeding, platelet count $<75 \times 10^9/L$, need for dual antiplatelet therapy (recent coronary stent)
 - Patient specific factors: dialysis catheters, acute leukemia or multiple myeloma with a bone marrow or stem cell transplant planned within 3 months, PE with hemodynamic instability, creatinine clearance <30 mL/min



Outcomes

- Primary: Catheter survival at 3 months
 - Loss includes infusion failure that does not respond to 2 mg of tPa, with physical removal of the CVC
- Secondary:
 - Symptomatic recurrent VTE, defined as objectively documented recurrent PE, DVT or death attributable to PE;
 - Major bleeding and clinically relevant non-major bleeding (CRNMB)
 - Death from all causes



Patient Demographics (n=70, 3 centres)

| Variable | Description |
|---------------------|--|
| Gender | Female, n=41 (59%) |
| Median Age | 62 years |
| Diagnostic Modality | Ultrasound, n=70 (100%), 2 pts (2.9%) had PE |
| Vein Involvement | Axillary, n=53 (76%) Subclavian, n=52 (74%) Internal Jugular, n=10 (14%) Others: Brachial, brachiocephalic, external jugular veins |
| CVC Type | Peripherally Inserted Central Catheter (PICC), n=56 (80%) Port-a-cath, n=14 (20%) |
| Type of Cancer | Breast, n=22 (31%) Colon, n=12 (17%) Colorectal, n=7 (10%), lung, n=4 (6%) Bladder, n=3 (4%), pancreatic, n=3 (4%) Other, n=19 (27%) |

Catheter Survival

| Variable | N (%) |
|-------------------------------|-------------------|
| Catheter survival at 12 weeks | 40 (57, CI 45-68) |
| Reason for Removal | |
| Failure to respond to tPA | 0 (0) |
| End of therapeutic need | 21 (30) |
| Fell Out | 3 (4.3) |
| Infection | 3 (4.3) |
| Death | 2 (2.9) |
| Patient Preference | 1 (1.4) |
| Recurrent DVT | 0 (0) |

Censored for failure to respond to tPa with removal, survival was 100% with apixaban therapy

Safety Outcomes

- Recurrent VTE: n=1 (1.4%) (95% CI 0.25 to 7.66)
 - 1 DVT in the same arm at day 10 in a breast Ca pt – line not removed
- Bleeding: n=6 events in 6 patients (8.6%, 95%CI 4 to 17)
 - 2 major (GI) and 4 CRNMB (GU, GI, skin, insertion site, one each)
 - All bleeding events happened during the first 56 days of treatment
- Deaths: n=2
 - 55y F from Adenocarcinoma of the duodenum at 77d
 - 69y F from Endometrial Cancer at 45d



Study Limitations

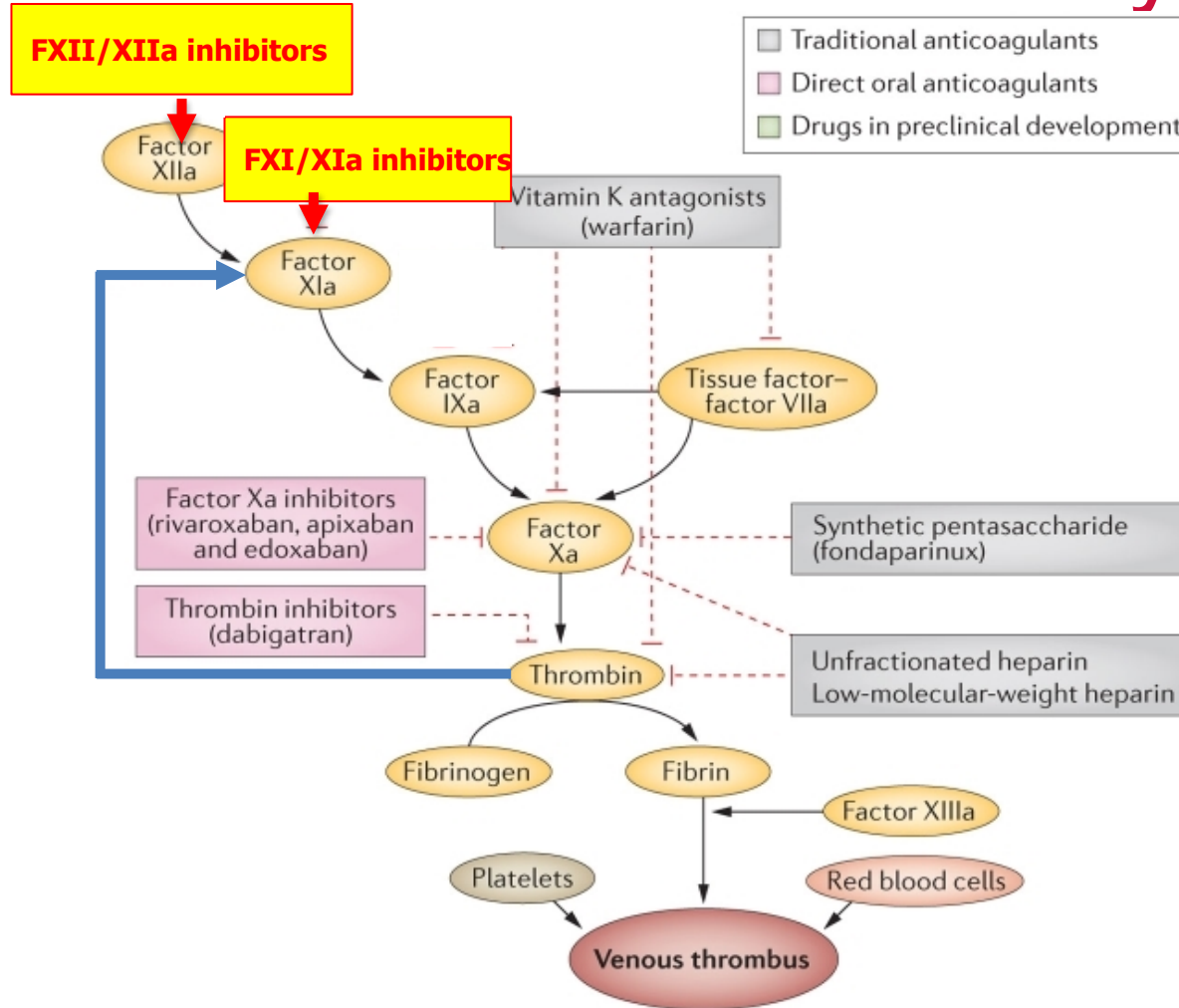
- Open label
- Single arm
- Patients included in our study were all outpatients so not as ill
- Follow up duration limited to 12 weeks

Conclusions

- Apixaban showed promise in treating CVC associated UEDVT in cancer patients, resulting in preserved CVC function
- The observed bleeding rates were less than with rivaroxaban but studies are small
- In a total of 214 pts in 3 catheter studies, no lines were removed due to DVT or infusion failure

| Study | N | Anticoagulant | Recurrent VTE | Total bleeding |
|------------------|----|---------------------------------|---------------|---|
| Catheter study | 74 | LMWH -> VKA | 0% | 4.7% (3/74) <ul style="list-style-type: none">▪ 3 MB |
| Catheter 2 study | 70 | Rivaroxaban | 1.4% (1/70) | 12.9% (9/70) <ul style="list-style-type: none">▪ 7 MB (10%)▪ 4 CRNMB |
| Catheter 3 study | 70 | Dalteparin x 7 days -> Apixaban | 1.4% (1/70) | 8.6% (6/70) <ul style="list-style-type: none">▪ 2 MB▪ 4 CRNMB |

The coagulation cascade: The Case for An Intrinsic Pathway Inhibitor



Rationale for the inhibition of Factors XI and XII

- These factors are involved in clot stabilization and expansion, not initiation
- Patients with very low FXI levels may be asymptomatic, bleeding is typically traumatic or surgical and occurs in mouth, nose, and urinary tract. Incidence of DVT and stroke are reduced
- FXII deficiency does not increase bleeding risk
- The relationship between FXII and thrombosis is not well established, but FXII has proinflammatory and prothrombotic properties



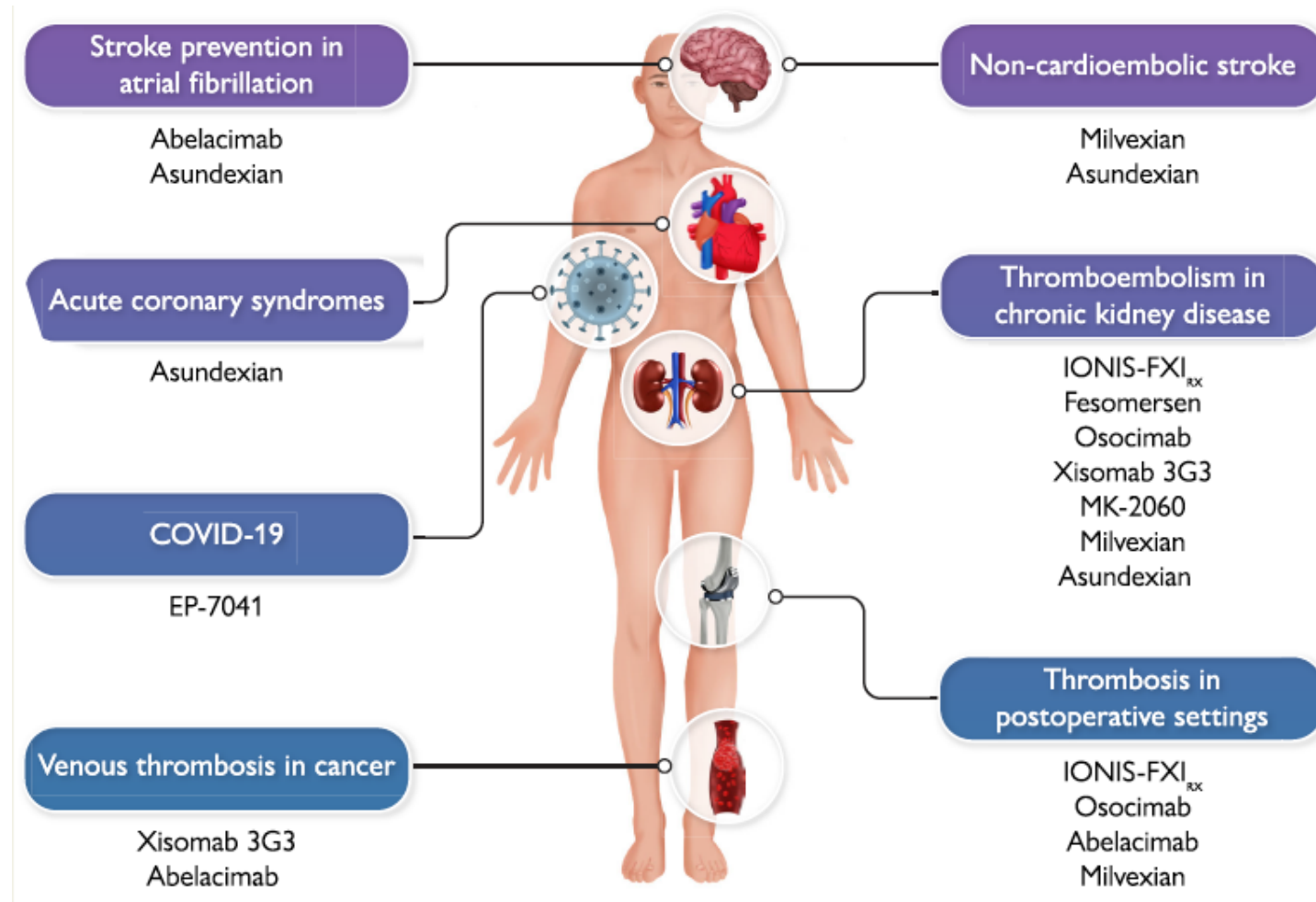
Factor XI/XIa inhibitors:

Characteristics of antibodies and small molecules

- ANTIBODIES
- **Abelacimab, osocimab**
- Intravenous or subcutaneous
- Rapid onset of action
- Long half-life (weeks)
- Monthly administration
- No renal excretion, **no** CYP metabolism, **no** drug interactions
- SMALL MOLECULES
- **Asundexian, milvexian**
- Intravenous or oral
- Rapid onset of action
- Short half-life
- Once or twice daily
- Renal excretion <20%, CYP metabolism, drug interactions



Possible future indications for FXI/FXIa inhibitors



Prevention of venous thromboembolism Elective major orthopedic surgery

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 Metzigg, MD; Gary E. Raskob, PhD

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*

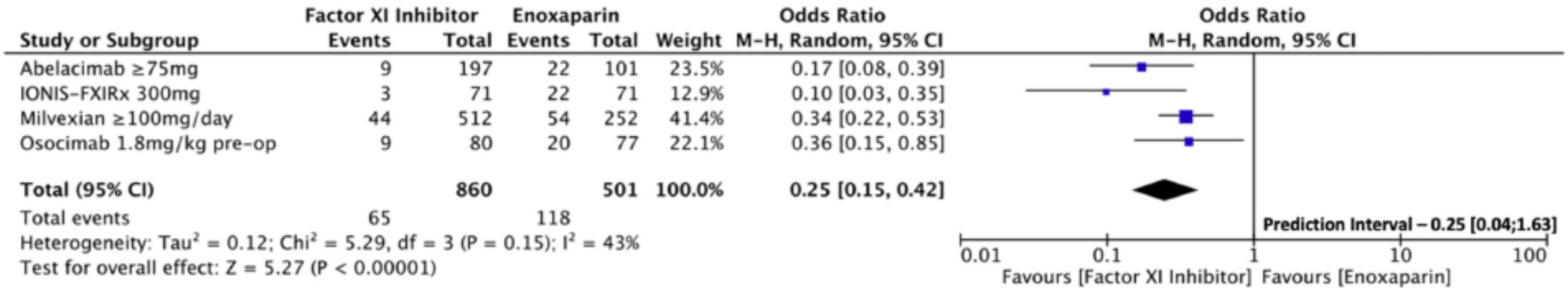
Milvexian for the Prevention of Venous Thromboembolism

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*

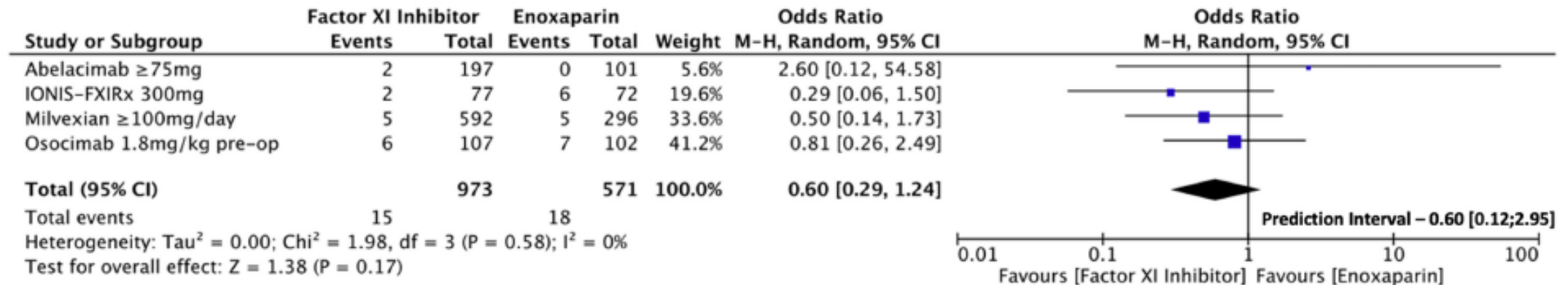


Factor XI inhibitors compared to enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis

Dosages that showed superior efficacy to LMWH: incidence of VTE

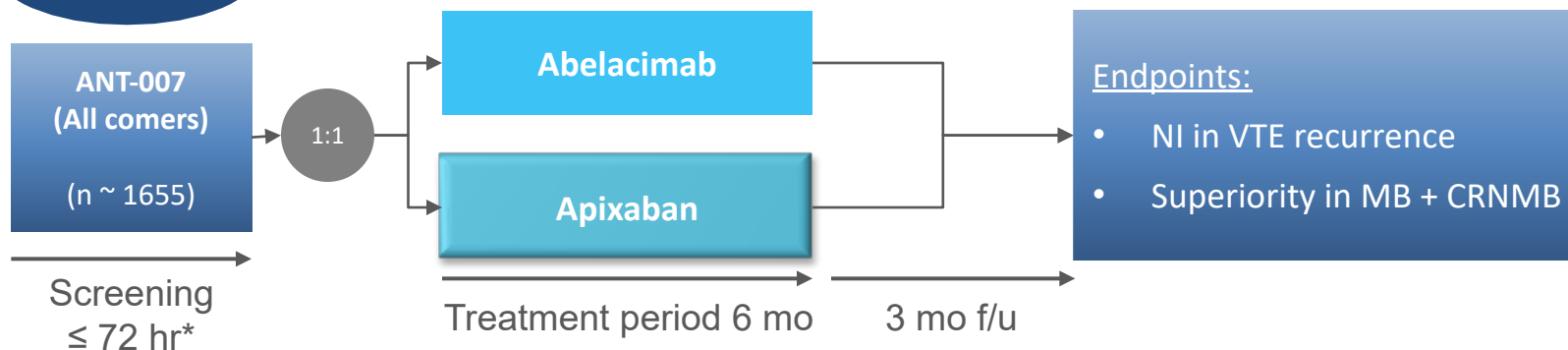


Dosages that showed superior efficacy to LMWH: incidence of major and clinically relevant non-major bleeding



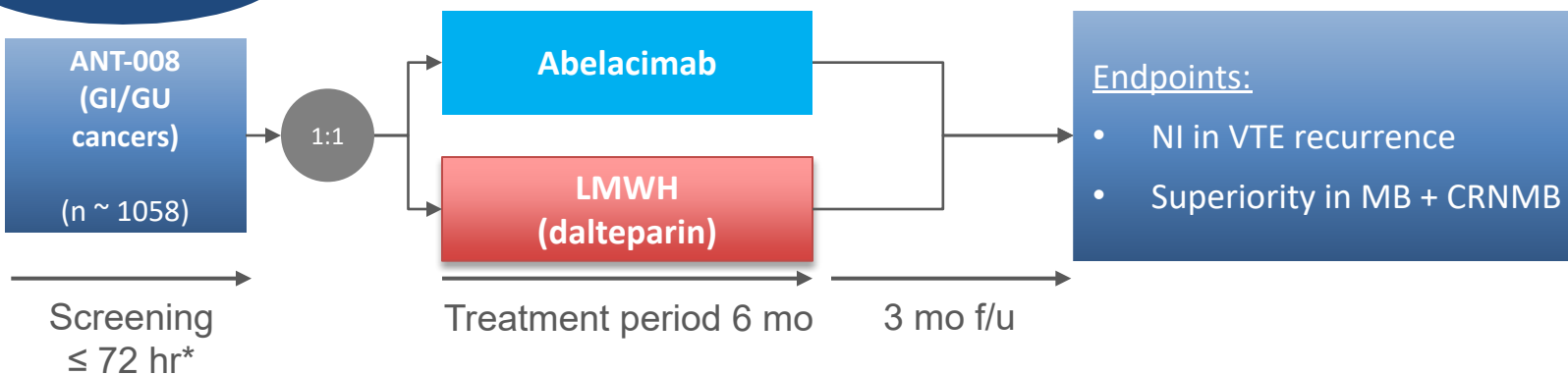
Abelacimab for the treatment of cancer-associated venous thromboembolism

Aster



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

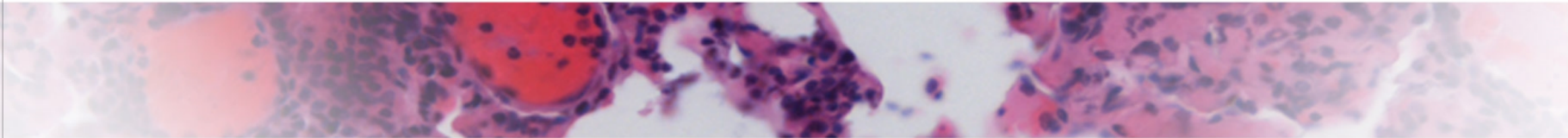
Magnolia



- 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



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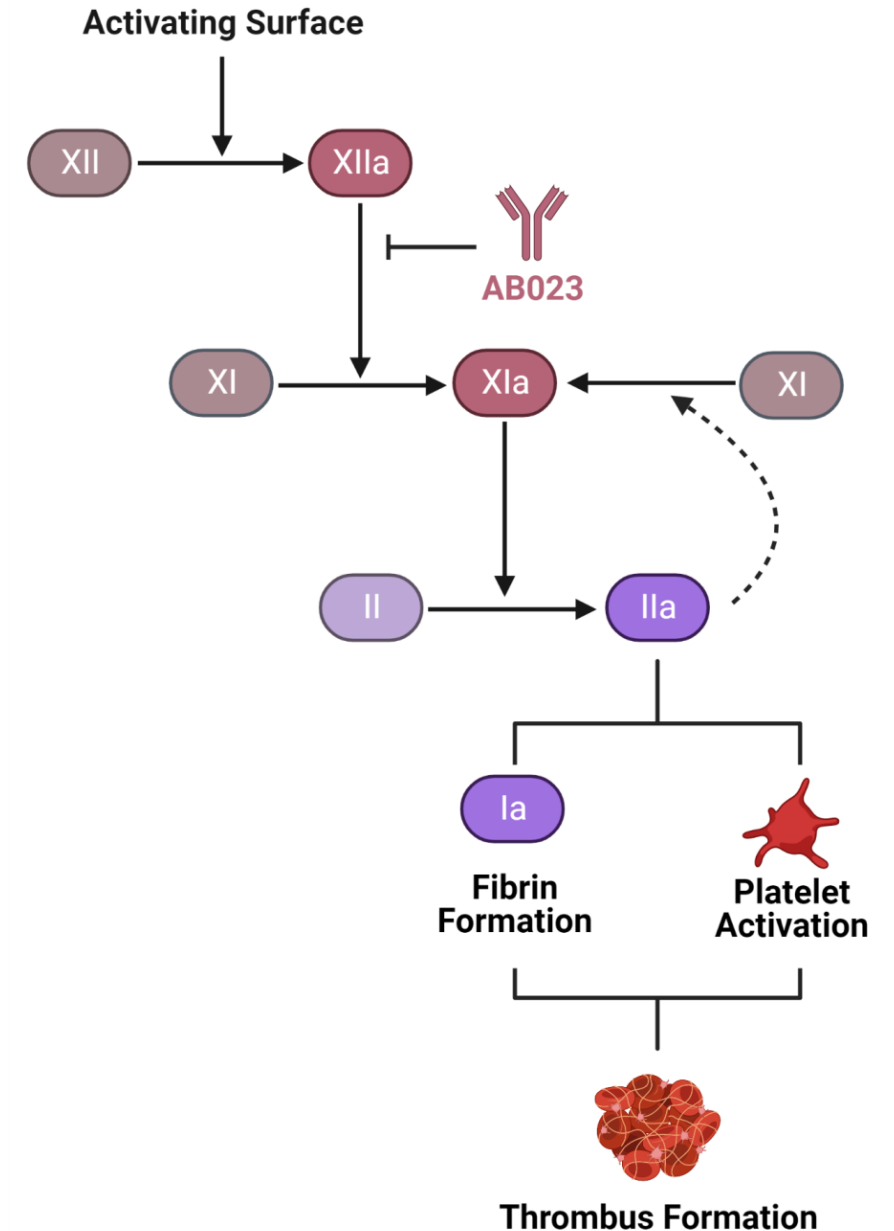


Factor XI Inhibition for the Prevention of Catheter-Associated Thrombosis in Cancer Patients Undergoing Central Line Placement: A Phase 2 Clinical Trial

Michael A. Pfeffer, MBBS

Overview of AB023

- Inhibits FXIIa-mediated activation of FXI
- Does **NOT** inhibit FXI activation by thrombin



Study Design

Inclusion Criteria

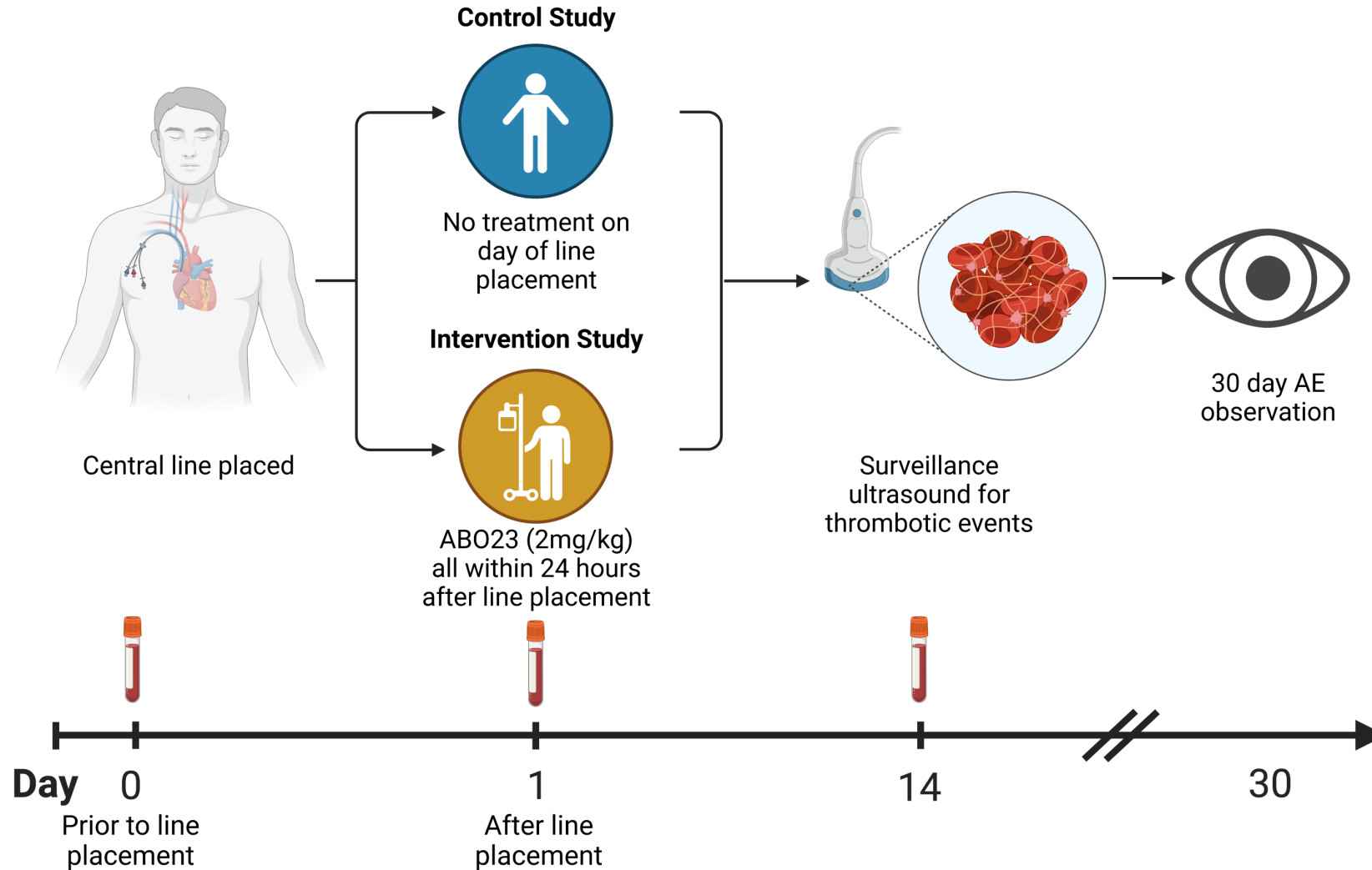
- ≥ 18 years
- Solid tumor malignancy
- ECOG < 2
- Life expectancy of > 6 months

Exclusion Criteria

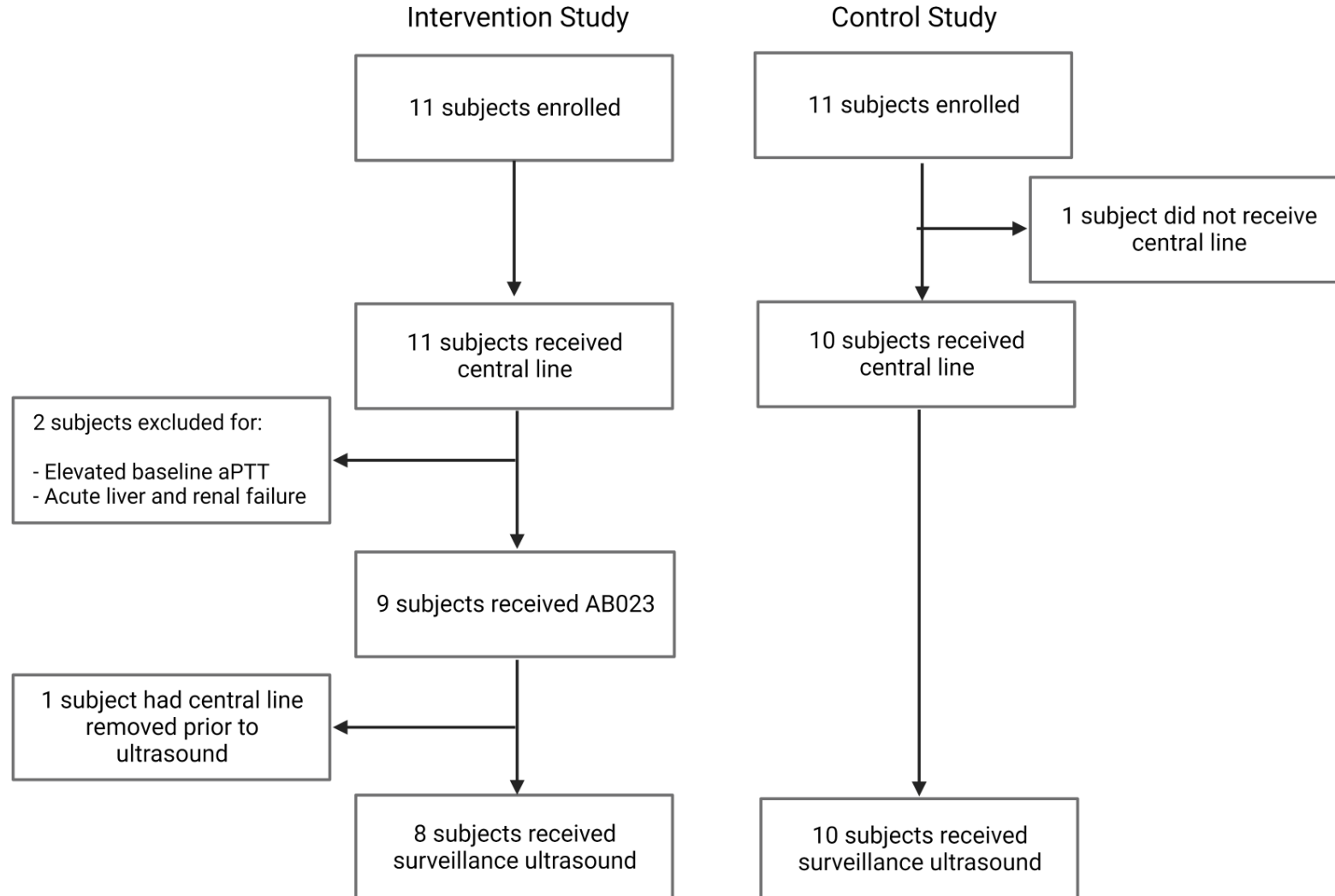
- Acute Leukemia
- Renal or liver dysfunction
- History of brain metastasis
- On anticoagulation or prolonged coagulation profile



Study Design



Study Design



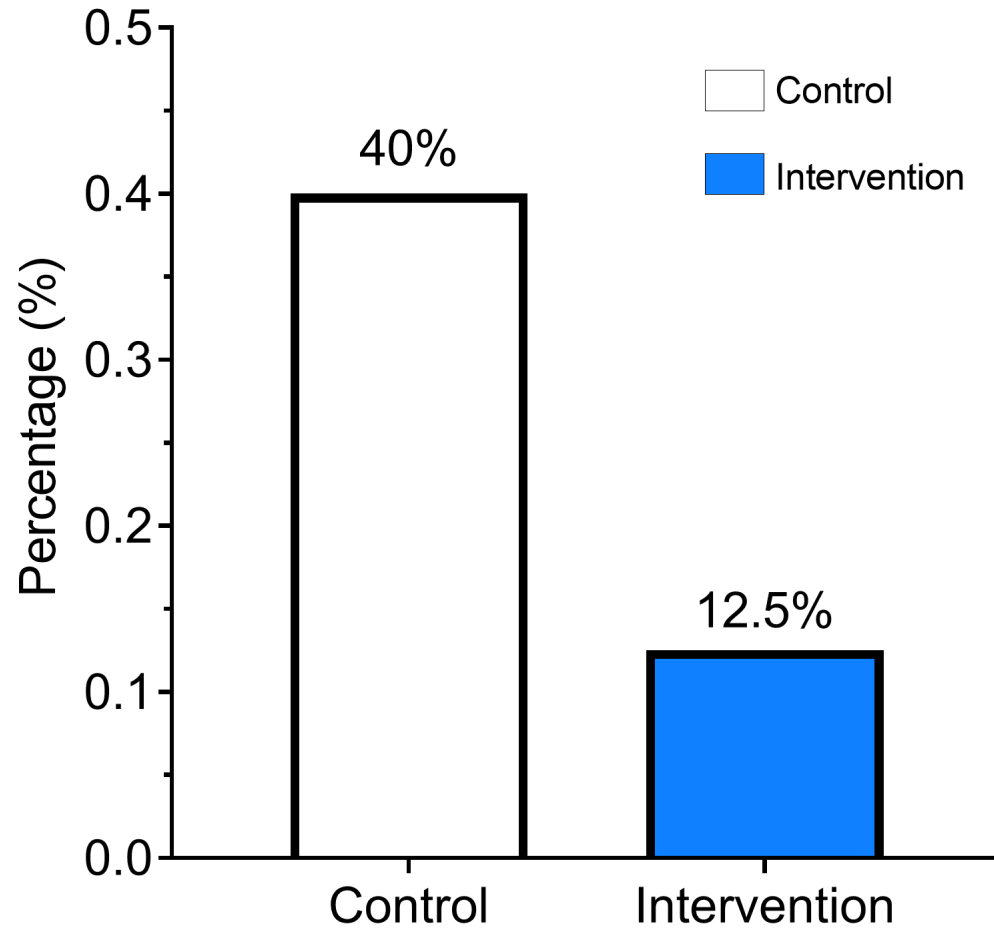
Patient Demographics

| | Participants | | |
|-------------------------------|----------------------|-----------------------|------------------|
| | Total (n = 22) | Intervention (n = 11) | Control (n = 11) |
| Age, median (IQR) | 60.5 (51.25 - 68.25) | 56 (50.5 - 67.5) | 64 (53 - 67.5) |
| Sex | | | |
| Male | 14 | 6 | 8 |
| Female | 8 | 5 | 3 |
| Weight (kg), mean (SD) | 92.25 | 98.03 | 86.48 |
| Tumor type | | | |
| Lung | 2 | 1 | 1 |
| Pancreatic | 5 | 4 | 1 |
| Colorectal | 5 | 3 | 2 |
| Lymphoma | 6 | 2 | 4 |
| Sarcoma | 2 | 1 | 1 |
| Head and Neck | 2 | 0 | 2 |
| Cancer stage | | | |
| I | 2 | 2 | 0 |
| II | 2 | 1 | 1 |
| III | 9 | 5 | 4 |
| IV | 9 | 3 | 6 |
| Khorana score | | | |
| 0 | 7 | 2 | 5 |
| 1 | 3 | 0 | 3 |
| 2 | 11 | 9 | 3 |
| ECOG | | | |
| 0 | 6 | 2 | 4 |
| 1 | 16 | 9 | 7 |

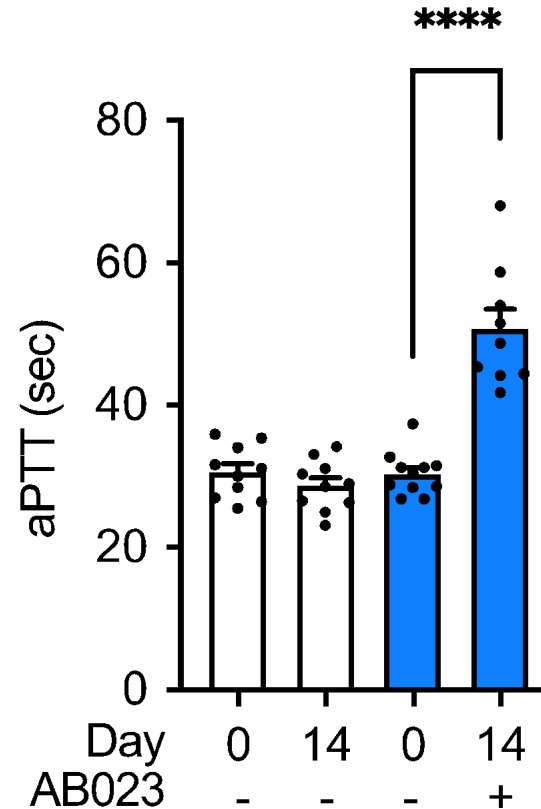


Central Access Outcomes

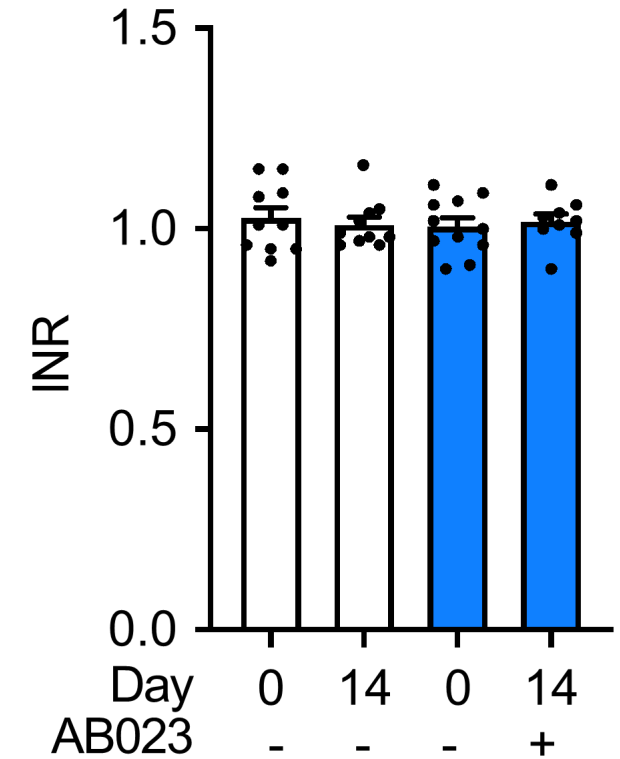
Catheter-associated thrombosis



aPTT



INR



Central Access Outcomes

Outcomes (Days 14 - Day 30)

| | Total | Intervention | Control |
|----------------------------------|-------|--------------|---------|
| TPA for luminal occlusion | 1 | 1 (18) | 0 |

Outcomes (Days 31 - 180)

| | Total | Intervention | Control |
|----------------------------------|-------|--------------|---------|
| VTE | 2 | 1 (99) | 1 (71) |
| Catheter thrombus | 1 | * 1 (81) | 0 |
| TPA for luminal occlusion | 6 | 4 (109) | 2 (43) |

Number (mean time in days)

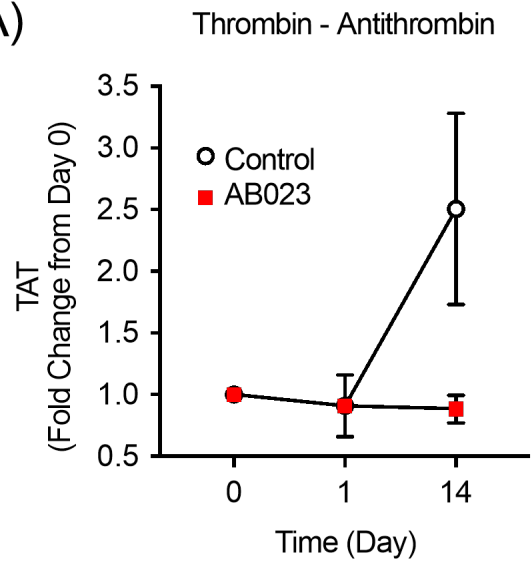
* Subject was a screen failure and did not receive AB023



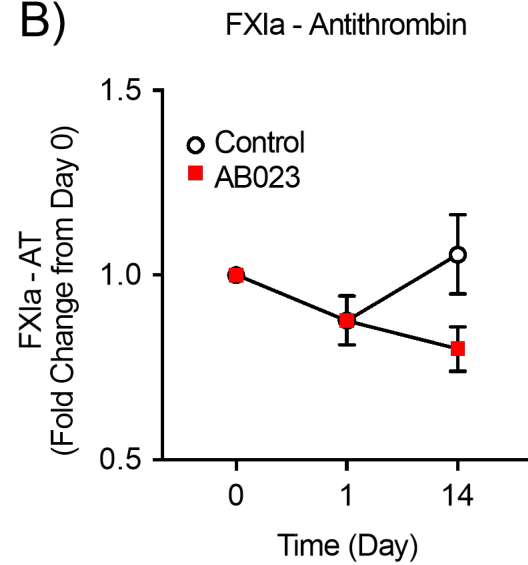
Sridhar et al. J Thrombosis Research 2020

Coagulation Activation

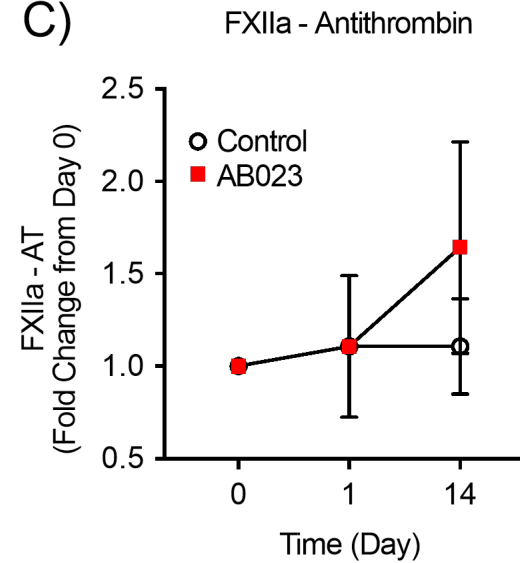
A)



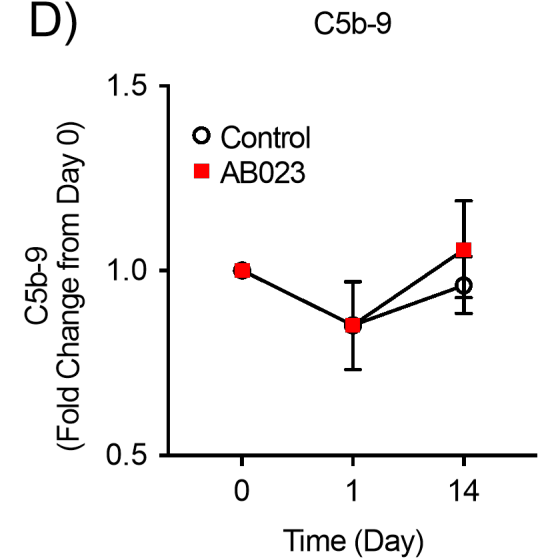
B)



C)



D)



AB023 Adverse Events

- No incidence of major or clinically relevant non-major bleeding
- No drug-related adverse events



Conclusions

- Lower than expected rate of catheter-associated thrombosis
- **No drug-related bleeding events**
- Blunting of prothrombotic complexes at Day 14
- No alteration in thrombin-dependent platelet activation
- Less elevation of systemic inflammation marker at Day 14
- Possibilities for larger trial



Summary

- In pregnant women with inherited thrombophilia and recurrent miscarriage
 - The live birth rate is ~70% with standard care
 - LMWH does **not** increase live birth rate
 - Do **not** test women with recurrent miscarriage for inherited thrombophilia
- In cancer patients with central venous catheters (CVC)
 - Apixaban showed promise in treating CVC associated upper extremity DVT and result in preserved CVC function (no need to remove catheters)
 - Novel agents such as factor XI inhibitors could have potential in the prevention of catheter related thrombosis

