Classical Hematology Journal club 1/13/22

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abelacimab for Prevention of Venous Thromboembolism

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Collaborators, Affiliations – collapse

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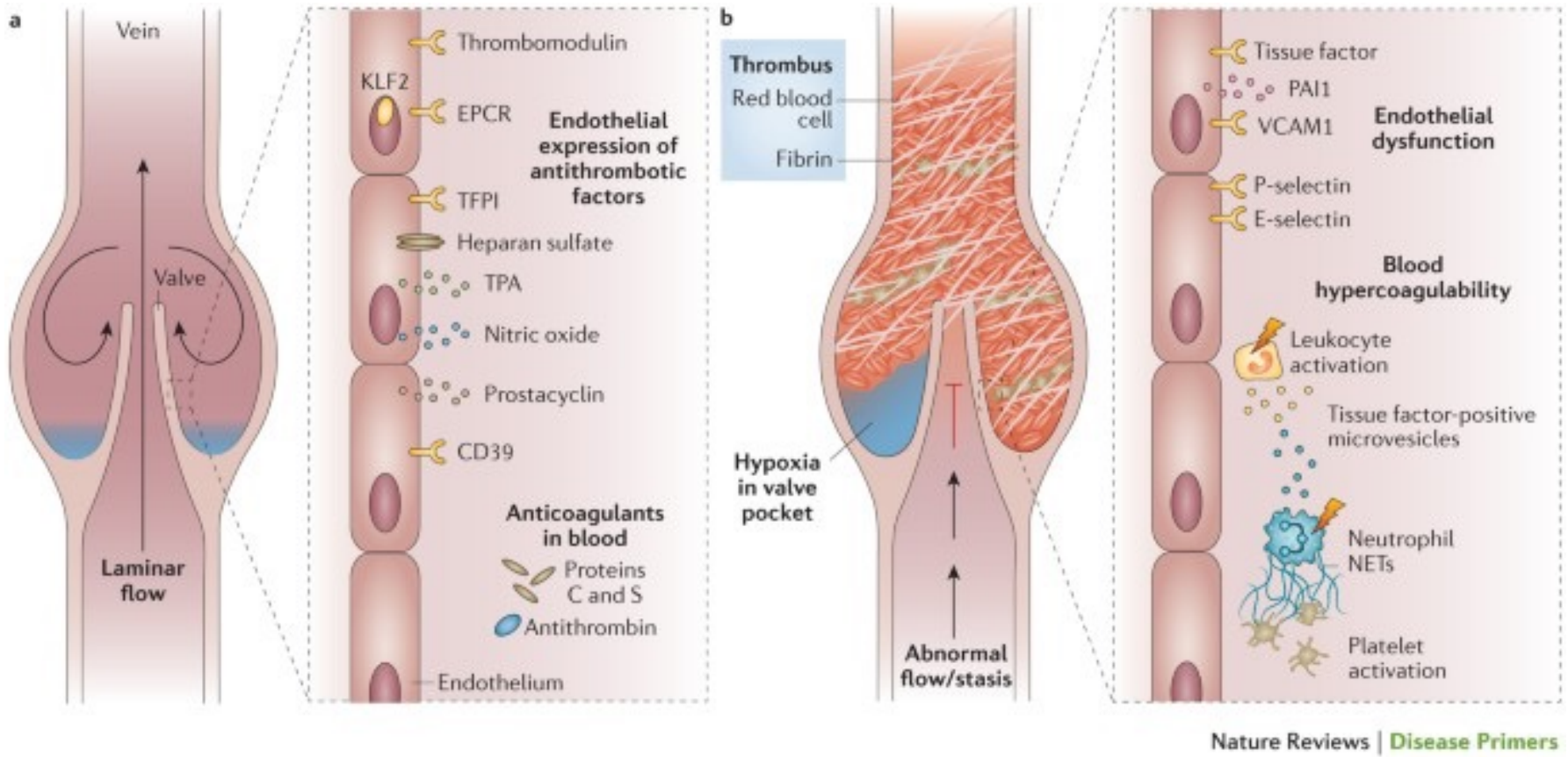

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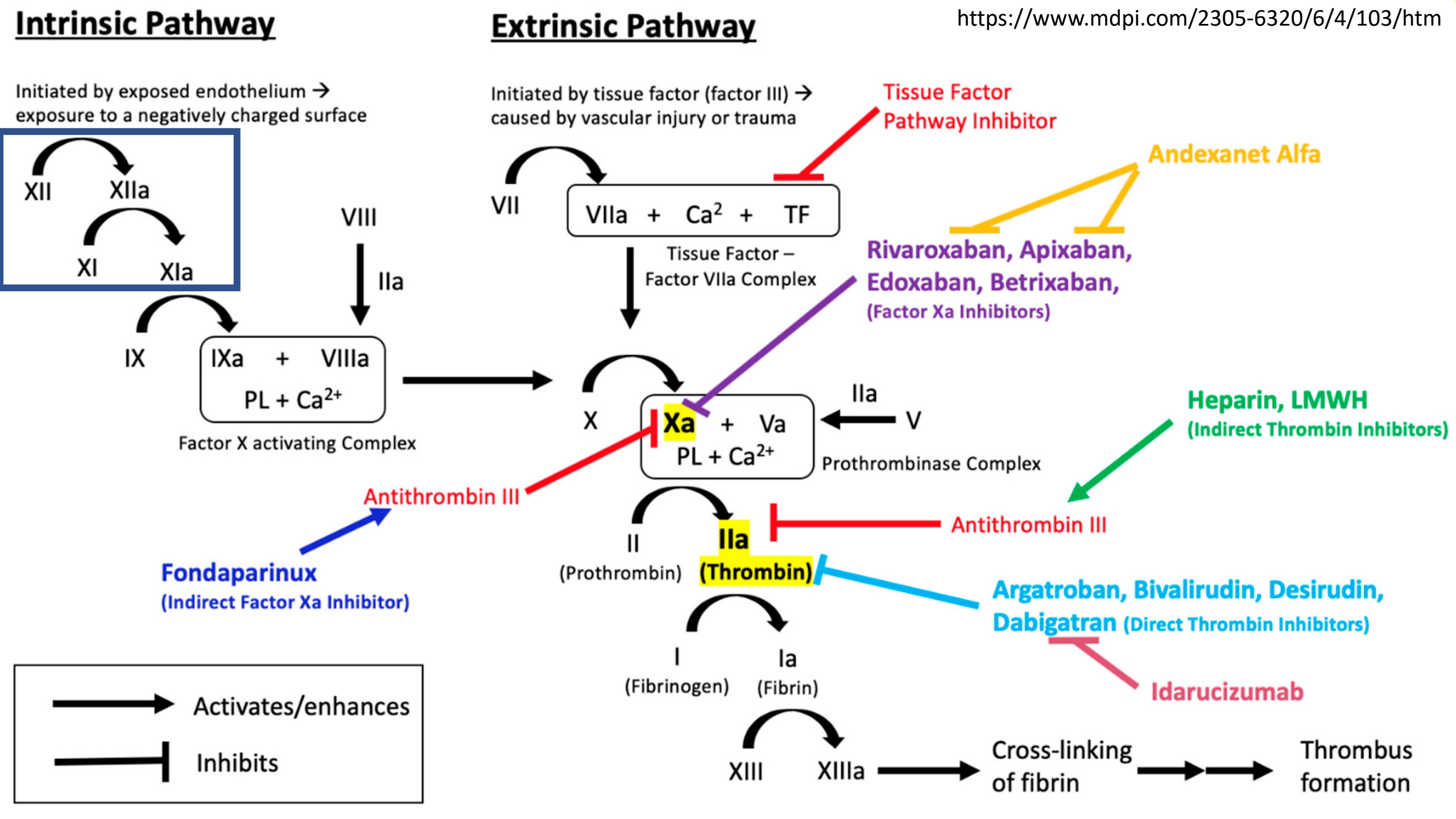

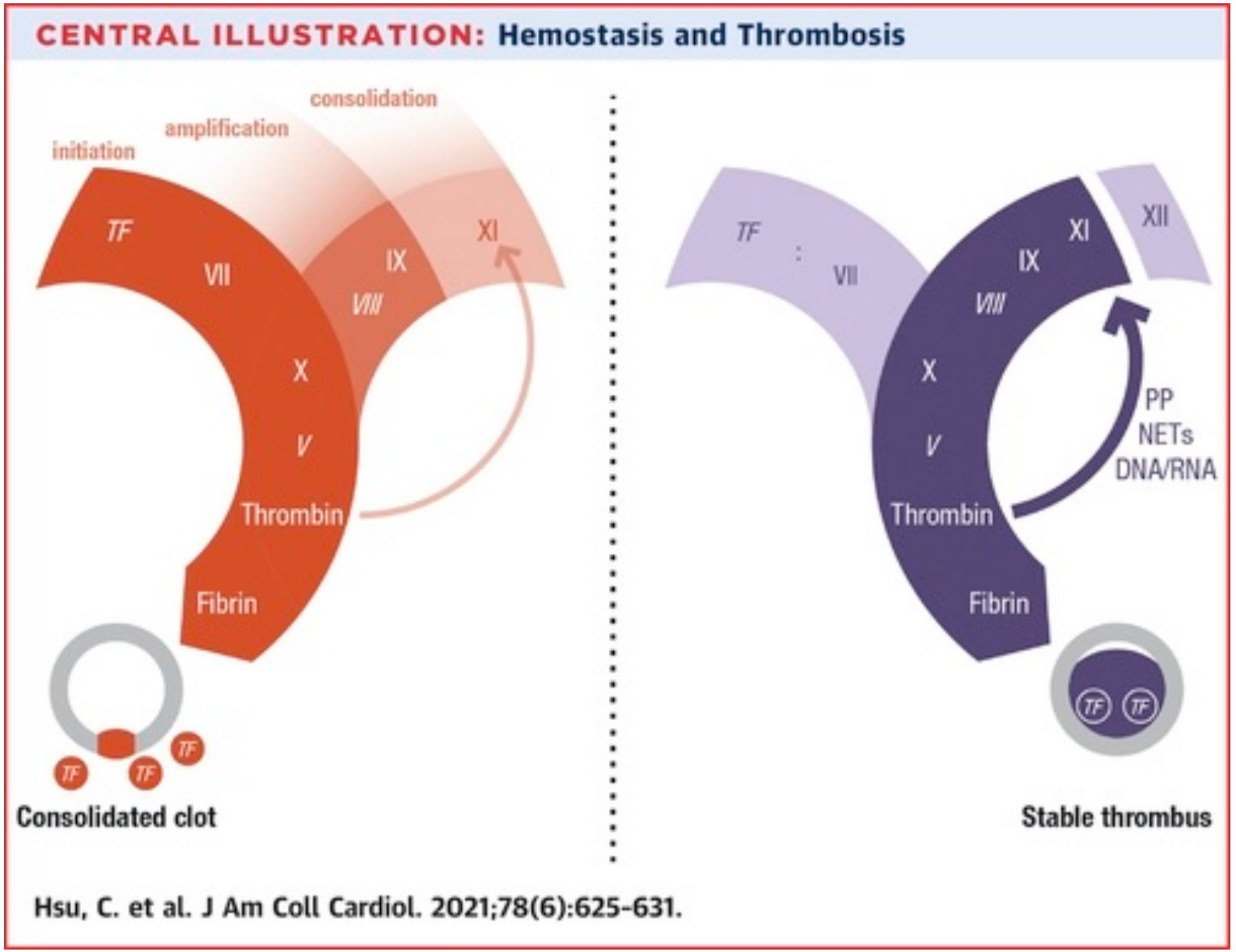

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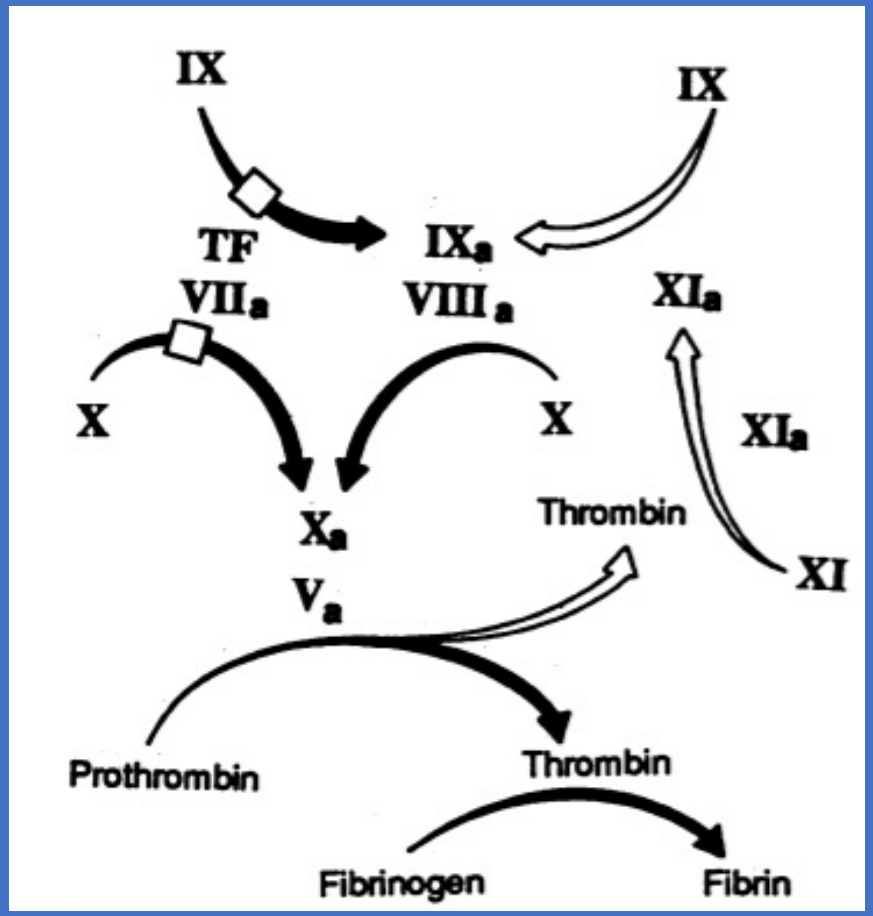

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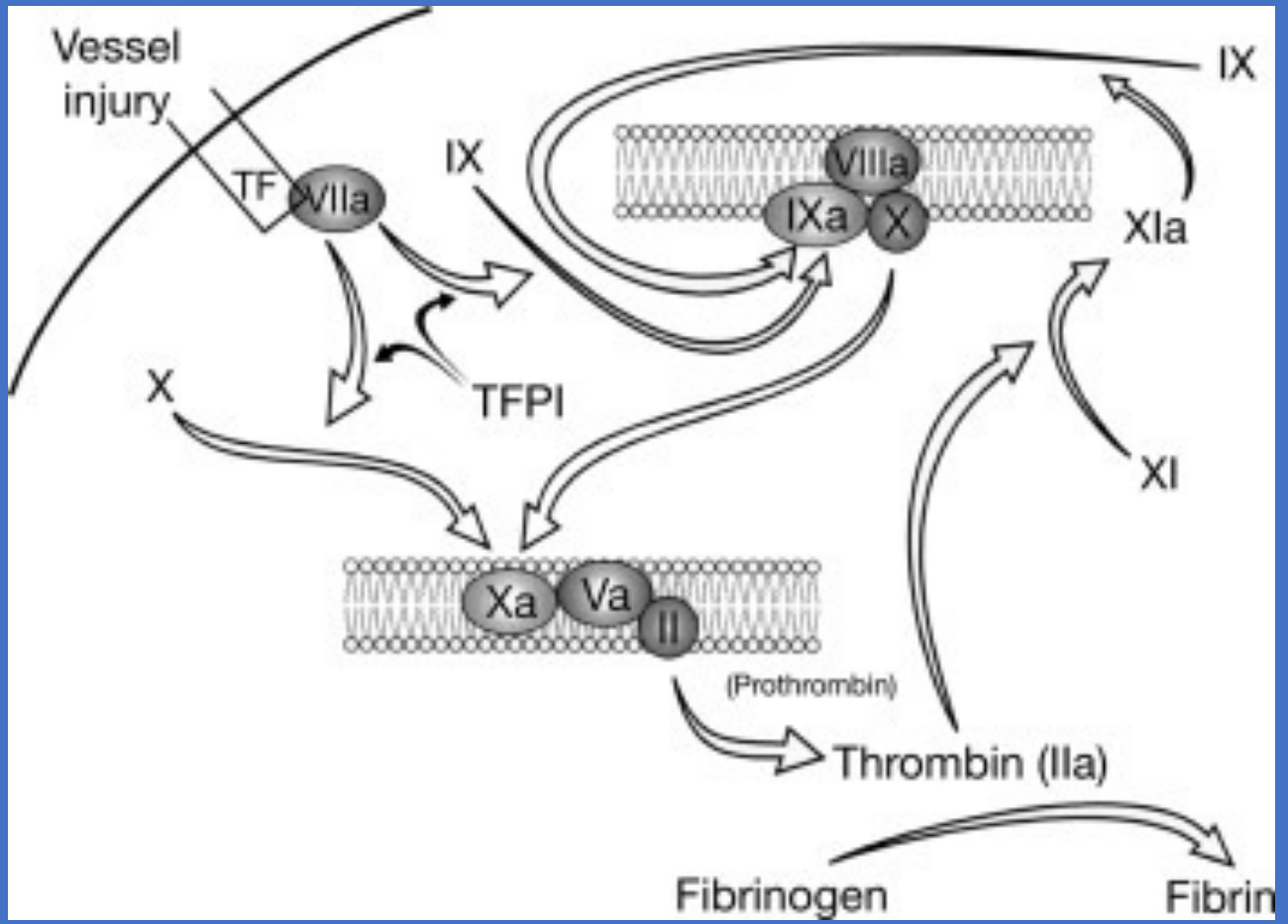

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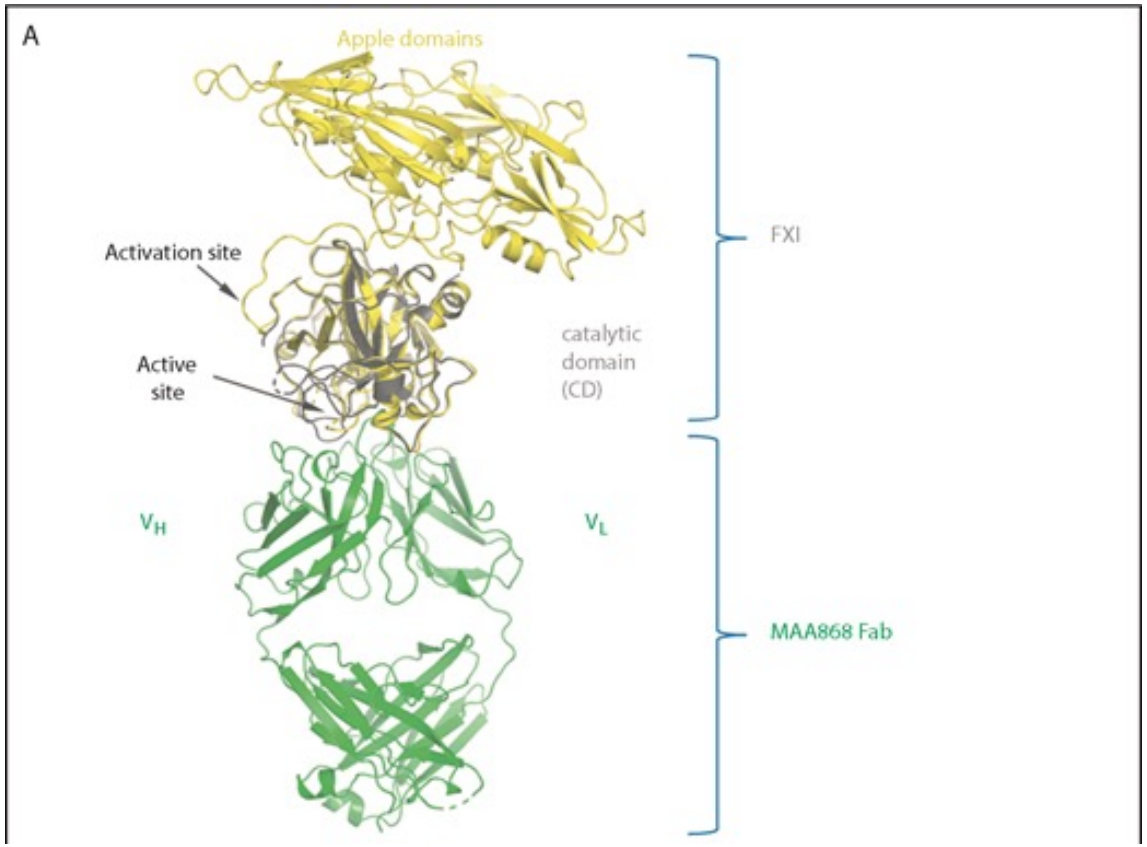
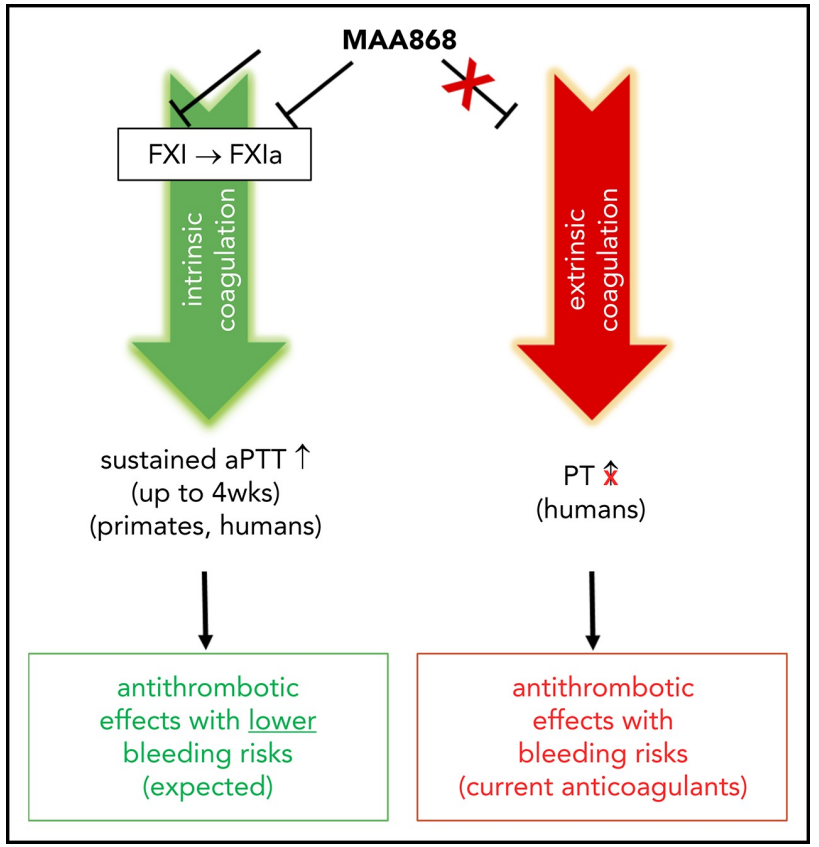
Abelacimab (MAA868)





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Research Question & Specific Aims

How does abelacimab reduce post-arthroplasty thrombosis?

Compare the efficacy and safety of abelacimab administered postoperatively with the efficacy and safety of enoxaparin in patients undergoing total knee arthroplasty.

HYPOTHESIS: non-inferiority

Power calculation: 600 patients, but pandemic changed that

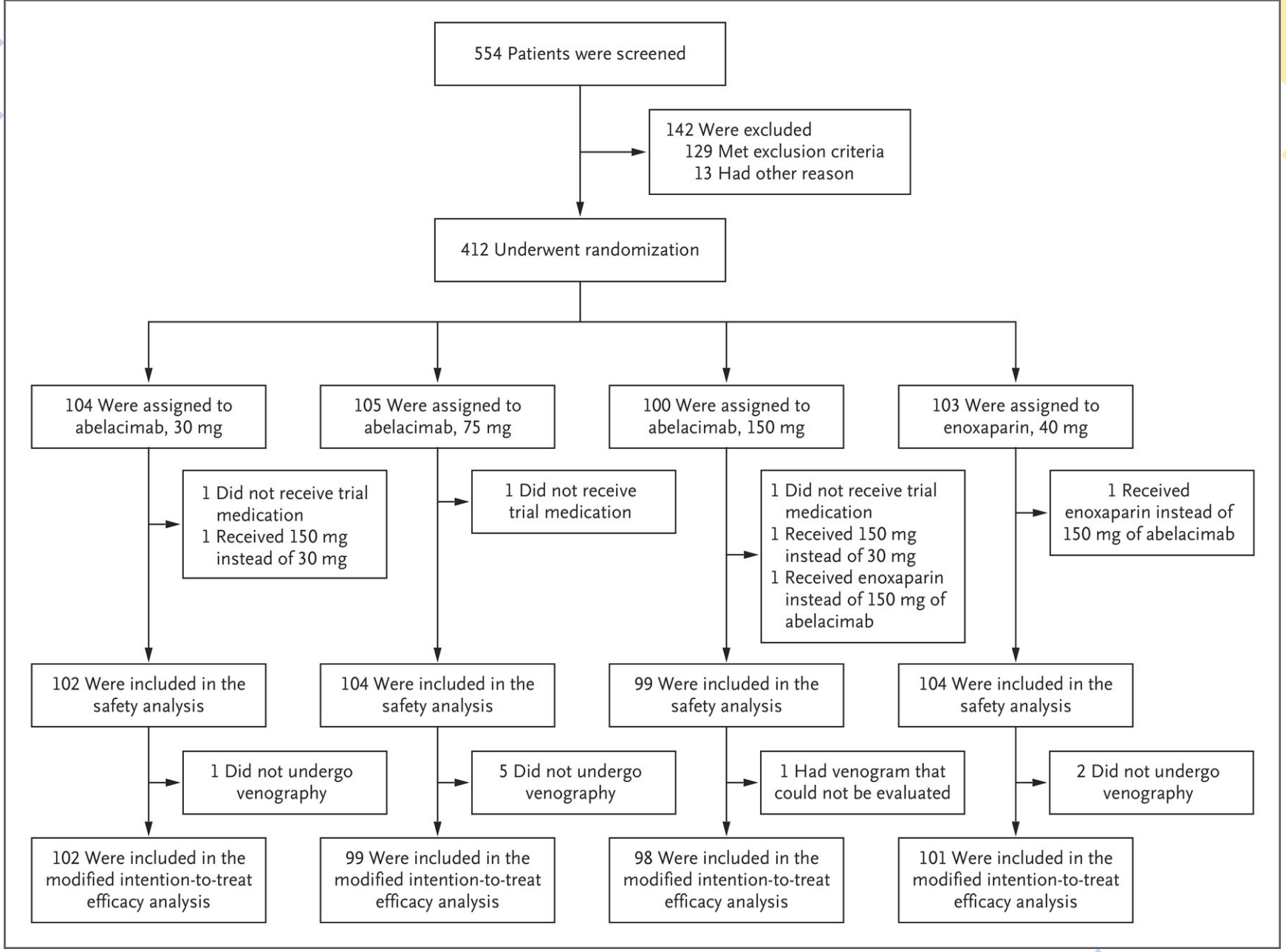
Efficacy

- Primary efficacy outcome = adjudicated VTE
  - Asymptomatic DVT
    - (detected by **mandatory unilateral ascending venography** performed after surgery, between day 8 and day 12)
  - Confirmed symptomatic VTE
    - (DVT/non-fatal PE)
  - Fatal pulmonary embolism
  - Unexplained death
    - (PE could not be ruled out)

Safety

- The principal safety outcome = adjudicated clinically relevant bleeding
  - Major bleeding
  - Clinically relevant nonmajor bleeding
- From randomization until venography was completed and from randomization through day 30.

- *Major bleeding = overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more or necessitated transfusion of 2 units of blood or more within 48 hours, occurred in a critical area or organ, or was fatal.*
  - *Bleeding at the surgical site was classified as major only if it resulted in an intervention, caused hemodynamic instability, or caused hemarthrosis that delayed mobilization or wound healing and resulted in prolonged hospitalization or deep wound infection.*
- *Clinically relevant nonmajor bleeding = overt bleeding that did not meet the criteria for major bleeding but resulted in a medical examination or an intervention or had clinical consequences*


554 Patients were screened
142 Were excluded
129 Met exclusion criteria
13 Had other reason
412 Underwent randomization
104 Were assigned to abelacimab, 30 mg
105 Were assigned to abelacimab, 75 mg
100 Were assigned to abelacimab, 150 mg
103 Were assigned to enoxaparin, 40 mg
1 Did not receive trial medication
1 Received 150 mg instead of 30 mg
1 Did not receive trial medication
1 Did not receive trial medication
1 Received 150 mg instead of 30 mg
1 Received enoxaparin instead of 150 mg of abelacimab
1 Received enoxaparin instead of 150 mg of abelacimab
102 Were included in the safety analysis
104 Were included in the safety analysis
99 Were included in the safety analysis
104 Were included in the safety analysis
1 Did not undergo venography
5 Did not undergo venography
1 Had venogram that could not be evaluated
2 Did not undergo venography
102 Were included in the modified intention-to-treat efficacy analysis
99 Were included in the modified intention-to-treat efficacy analysis
98 Were included in the modified intention-to-treat efficacy analysis
101 Were included in the modified intention-to-treat efficacy analysis

From June 2020 through November 2020, a total of 412 patients at 16 centers in five countries underwent randomization.

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Abelacimab, 30 mg	Abelacimab, 75 mg	Abelacimab, 150 mg	Enoxaparin, 40 mg
Modified intention-to-treat population				
No. of patients	102	99	98	101
Age — yr				
Median	67	67	68	67
Range	49–81	41–80	49–80	45–79
Female sex — no. (%)	89 (87)	80 (81)	77 (79)	81 (80)
Weight — kg				
Median	90	86	89	94
Range	51–129	50–130	57–126	62–127
Estimated glomerular filtration rate — ml/min/1.73 m^2				
Median	78	78	77	76
Range	40–123	48–125	36–161	46–120

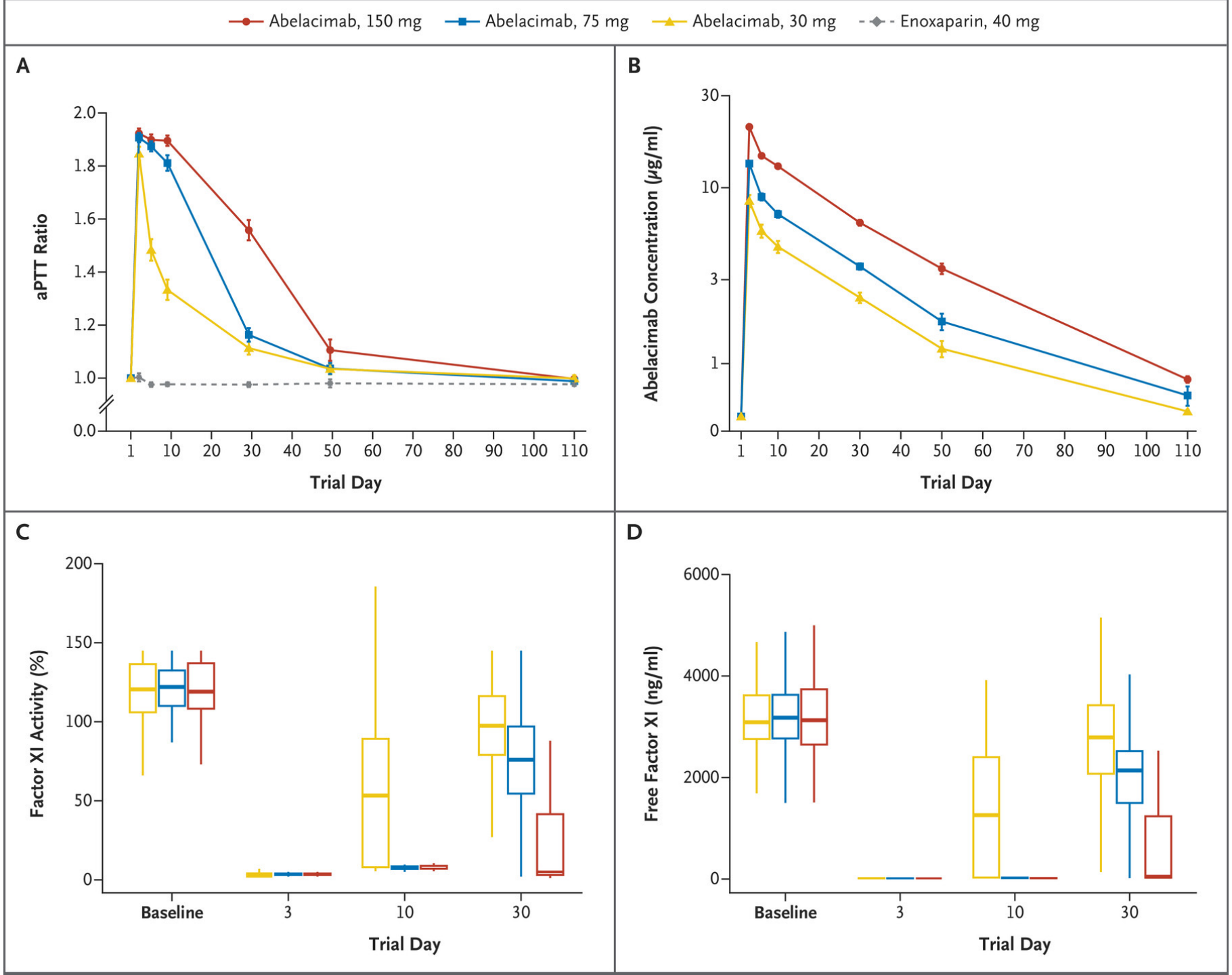
Type of anesthesia — no. (%)				
General	0	1 (1)	2 (2)	1 (1)
Spinal	88 (86)	90 (91)	86 (88)	88 (87)
Epidural	10 (10)	6 (6)	6 (6)	9 (9)
Duration of surgery — hr				
Median	1.3	1.3	1.3	1.3
Range	0.7–2.5	0.7–3.0	0.6–2.9	0.6–2.9
Tourniquet use — no. (%)	56 (55)	57 (58)	54 (55)	58 (57)
Duration of tourniquet use — min				
Median	53	50	50	60
Range	7–125	8–125	8–120	8–130
Time after surgery to ambulation — days				
Median	1	1	1	1
Range	0.5–5.0	0.5–1.0	0.5–2.0	0.5–2.0
Length of hospital stay — days				
Median	10	10	10	10
Range	7–15	3–18	6–17	4–16
Baseline factor XI activity — %†				
Median	118	121	117	120
Range	66–145	66–144	64–144	90–145
Baseline activated partial-thromboplastin time — sec‡				
Median	26	26	26	26
Range	22–32	21–35	22–40	20–38

Table 2. Efficacy and Safety Outcomes.*

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)‡
Extent of deep-vein thrombosis on venography — no.				
Confluent distal into proximal	1	0	0	2
Isolated proximal				
Large: ≥10 cm	0	0	0	0
Small: <10 cm	0	0	0	0
Isolated distal				
Extensive: ≥2 veins	2	0	2	8
Limited: <2 veins	10	5	2	12‡

	Abelacimab, 30 mg	Abelacimab, 75 mg	Abelacimab, 150 mg	Enoxaparin, 40 mg
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)
Adverse events — no. of patients (%)				
Serious adverse event	1 (1)‖	3 (3)	1 (1)	0
≥1 Adverse event	15 (15)	16 (15)	15 (15)	13 (13)

* Efficacy outcomes were assessed in the modified intention-to-treat population and safety outcomes in the safety population. CI denotes confidence interval, and NA not applicable.
† Venous thromboembolism is a composite of asymptomatic deep-vein thrombosis (detected by mandatory unilateral ascending venography), confirmed symptomatic venous thromboembolism (symptomatic deep-vein thrombosis of the leg or nonfatal pulmonary embolism), fatal pulmonary embolism, or unexplained death for which pulmonary embolism could not be ruled out.
‡ One patient in the enoxaparin group had calf pain on the day of venography; the venogram showed isolated distal deep-vein thrombosis.
§ Two patients in the 75-mg abelacimab group withdrew early from the trial (on day 6 and on day 30).
¶ One patient in the 75-mg abelacimab group had two bleeding events: clinically relevant nonmajor bleeding on day 6 and a joint infection and hemarthrosis on day 12 that led to surgical drainage and was classified as major bleeding.
‖ One patient in the 30-mg abelacimab group had two serious adverse events.


Abelacimab, 150 mg
Abelacimab, 75 mg
Abelacimab, 30 mg
Enoxaparin, 40 mg
A
aPTT Ratio
2.0
1.8
1.6
1.4
1.2
1.0
0.0
1
10
20
30
40
50
60
70
80
90
100
110
Trial Day
B
Abelacimab Concentration (μg/ml)
30
10
3
1
0
Trial Day
C
Factor XI Activity (%)
200
150
100
50
0
Baseline
3
10
30
Trial Day
D
Free Factor XI (ng/ml)
6000
4000
2000
0
Baseline
3
10
30
Trial Day

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Abelacimab for Prevention of Venous Thromboembolism

PHASE 2, OPEN-LABEL, PROSPECTIVE, RANDOMIZED TRIAL

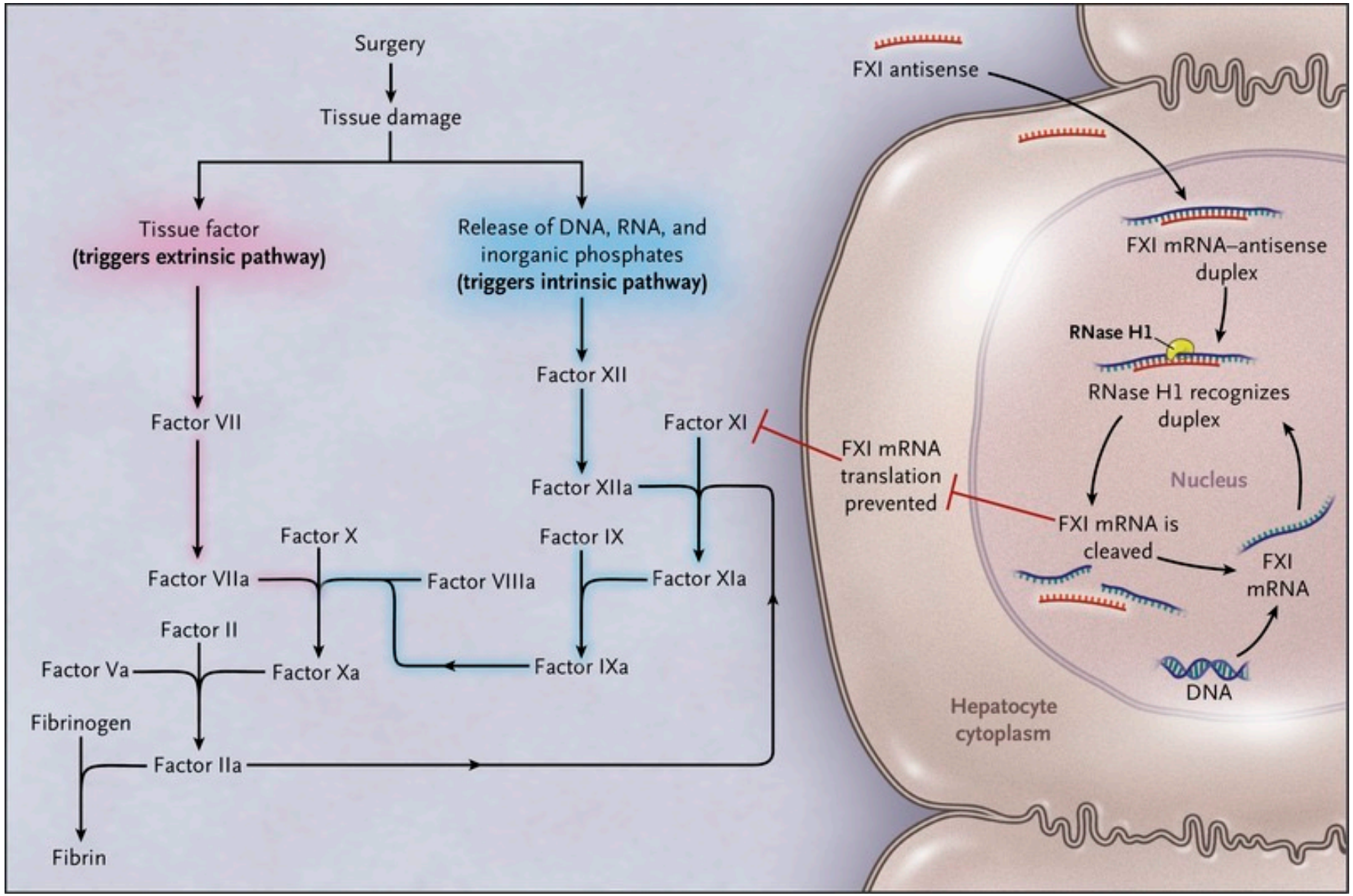
400
Patients undergoing total knee arthroplasty

	Abelacimab 30 mg N=102	Abelacimab 75 mg N=99	Abelacimab 150 mg N=98	Enoxaparin 40 mg N=101
	Single infusion 4–8 hours after surgery			Daily until 8–12 days after surgery
Incidence of venous thromboembolism	13% P=0.08 for superiority	5% P<0.001 for superiority	4% P<0.001 for superiority	22%
Major or clinically relevant nonmajor bleeding within 30 days	2%	2%	0%	0%

A single dose of abelacimab after knee arthroplasty was effective for prevention of VTE and was associated with a low risk of bleeding.

P. Verhamme et al. 10.1056/NEJMoa2105872

	Mylvexian	Abelacimab	Osocimab	FXI-ASO
MOA	Selective factor XIa inhibitor	Factor XI-directed monoclonal antibody	Factor XIa-directed monoclonal IgG1 ab	2nd generation anti-sense oligonucleotide
Route	Oral QD; post-surgery 14d, half life = 12 h	IV, 30-60 min post-op infusion, half life = 25-30 d	IV, 60-min pre-op infusion, half-life 30-44 d	subQ, 1st dose 35 days pre-op (7 doses pre-, 2 doses post-op)
Inclusion (TKA)	50+ yrs	18-80 yrs	18+	18-80 yrs.
Exclusion	CrCl < 30, cirrhosis, previous DVT, previous AC	eGFR < 45, cirrhosis Previous DVT	Recent surgery, HTN, > 135 kg, CrCl <60, cirrhosis, previous DVT	Recent surgery, < 50kg, CrCl < 60, cirrhosis, previous DVT
Study/arms	N=1242, 7 doses	N=412, 3 dose	N =600, 4 doses	N=300, 2 doses
Best dose efficacy	200 mg QD: 8/123 (7%) VTE	150 mg QD: 4/98 (4%)	1.8 mg/kg pre-op: 9/79 (11.3%)	300 mg QD: 3/71 (4%)
Enoxaparin efficacy (40 mg QD)	54/252 (21%)	22/101 (22%)	20/76 (26.3%) Apixaban 12/83 (14.5%)	21/69 (30%)
Bleeding (drug vs enoxaparin)	38/923 (4%) vs 12/296 (4%)	0% vs 0%	4.7% vs 5.9% (enoxaparin) vs 2% (apixaban)	3% vs 8%
Source	J. Weitz et al. NEJM 12/2021. Phase 2 RCT. AXIOMATIC-TKR. BMS/Janssen R&D.	P. Verhamme et al. NEJM 8/2021. ANT-005 TKA. Anthos Therap.	J. Weitz et al. JAMA 1/2020. Phase 2 FOXTROT RCT. Bayer AG.	H. Büller et al. NEJM 1/2015. Phase 2. FXI-ASO TKA. Isis pharma.



https://www.nejm.org/doi/10.1056/NEJMoa1405760

Limitations

Low rate of bleeding observed with abelacimab is limited by the modest sample size.

Open-label trial with respect to assignment to abelacimab or enoxaparin.

-To minimize bias, the trial was blinded with respect to assignment to an abelacimab regimen

- All outcomes were adjudicated by a committee whose members were unaware of the trial-group assignments.

98% of the patients had a venogram that could be evaluated for efficacy

- The small number of patients who did not have a venogram that could be evaluated were spread across the trial groups.

Patient recruitment was stopped early for *administrative* reasons

- Did not affect the assessment of the efficacy of abelacimab.

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- https://www.nejm.org/doi/10.1056/NEJMoa1405760

Table S2 Serious treatment-emergent adverse events

Safety population

	Abelacimab, 30mg (N = 102)	Abelacimab, 75mg (N = 104)	Abelacimab, 150mg (N = 99)	Enoxaparin, 40mg (N = 104)
Any – no. (%)	1 (1)	3 (2.9)	1(1)	0
Infections– no.	1*	1	1	0
Medical device site joint infection	0	1	1	
Coronavirus infection	1	0	0	
Wound infection	1	0	0	
Gastrointestinal disorder- no.	0	1	0	0
Ileus		1		
Reproductive system disorders - no	0	1	0	0
Ovarian cyst torsion		1		

* One patient had 2 serious adverse events