What are the standards for the decision of optimal duration of anticoagulation in diverse clinical situations?

2023-04-29

경희대학교병원 호흡기내과 김태우

Contents

- Clinical case presentation
- Contributing factors to cancer-associated VTE
- Therapeutic principle of VTE
- Clinical challenges in management of VTE
- Development of New drug

Case (I)

- 65/F, RUQ pain으로 2020.07.08 소화기내과 입원하여 흉.복부 조영CT 검사 시행.

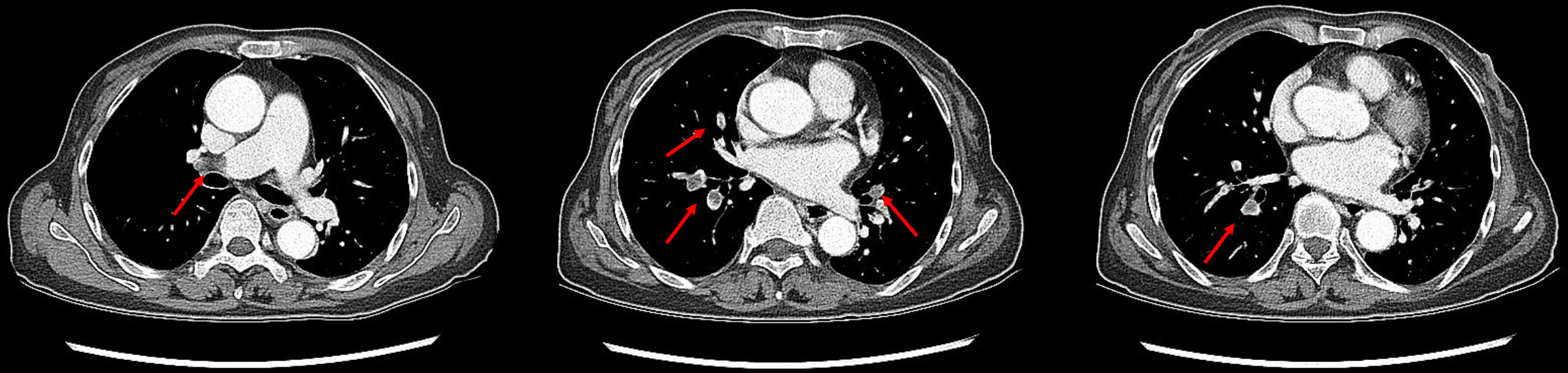
- Medical history

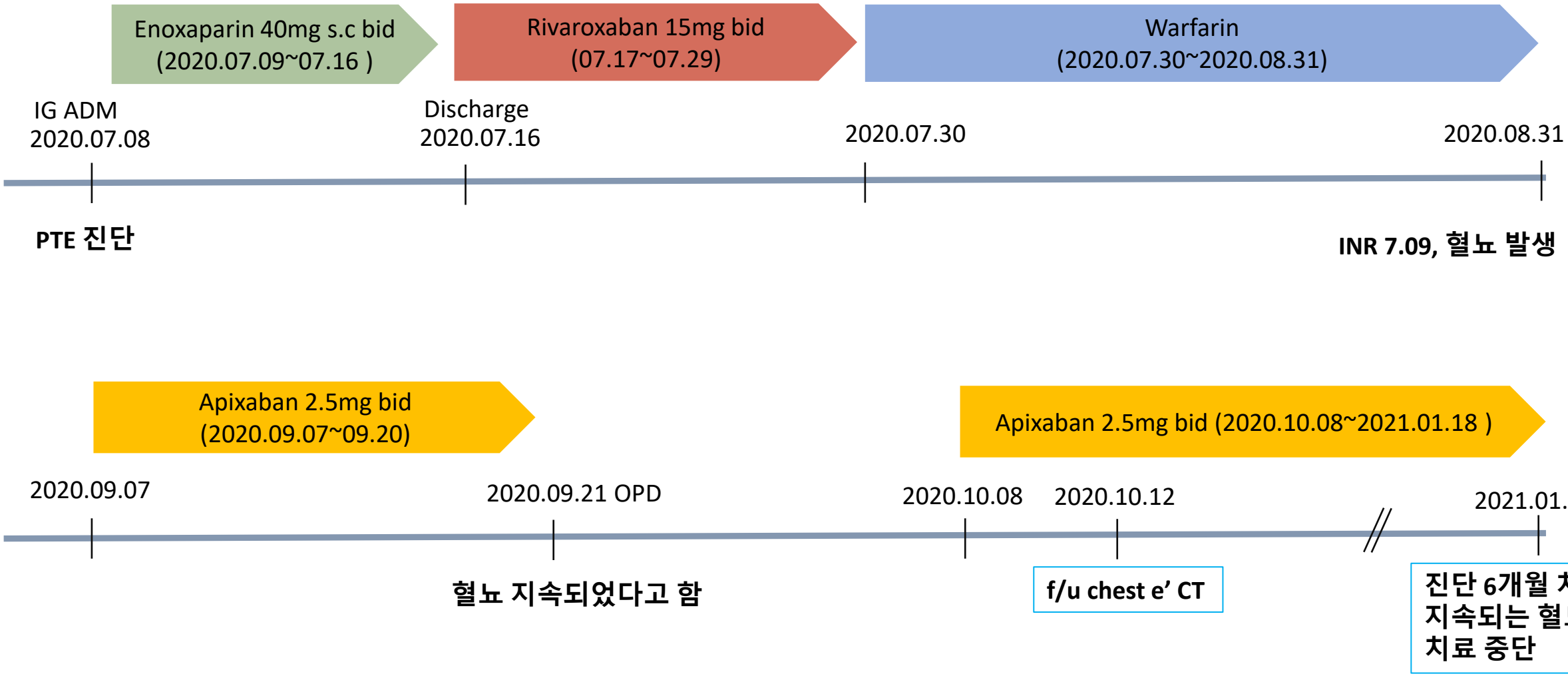
- CKD stage III (Cr 1.75mg/dL, CrCl 38ml/min)
- bladder cancer with peritoneal carcinomatosis (pStage IVA)

  s/p tans-urethral resection of bladder cancer and DJ stent

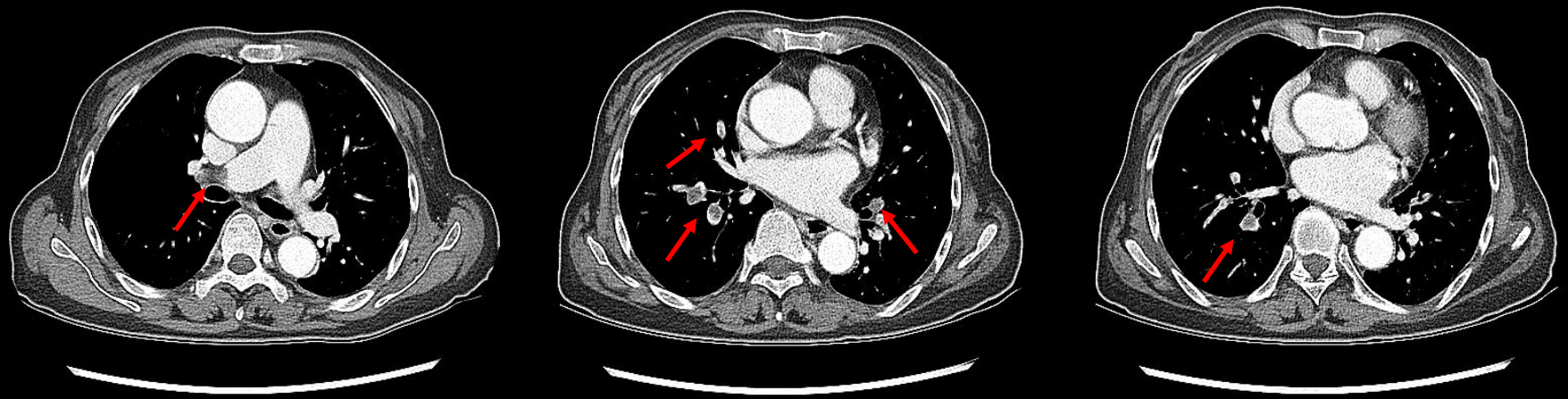
  on Gemcitabine + Cisplatin (2020.06.25~)

2020.07.08 chest e’ CT

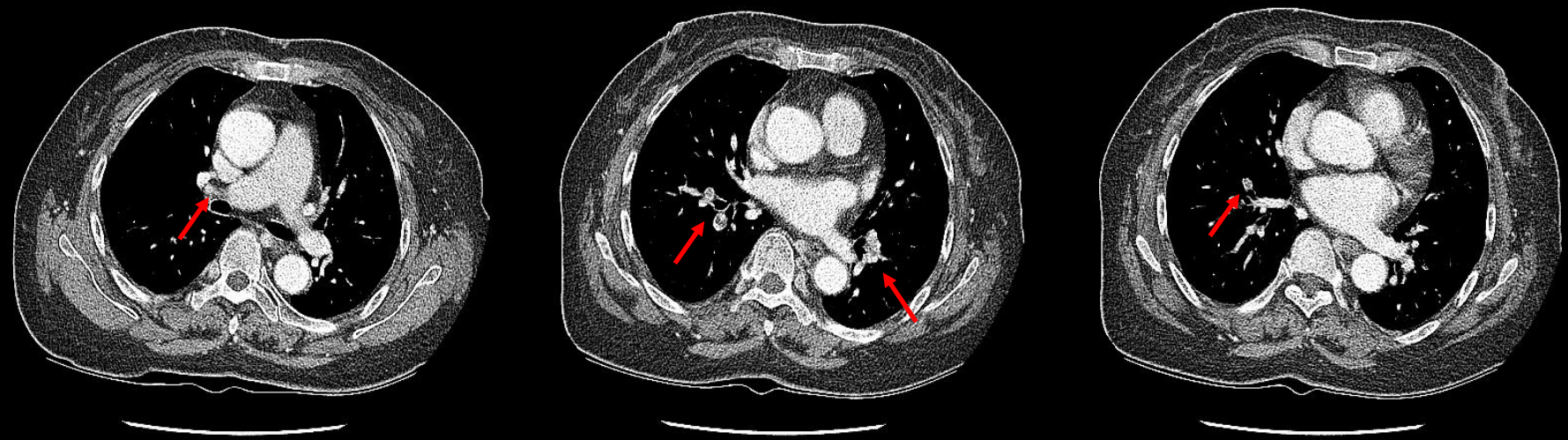



Enoxaparin 40mg s.c bid
(2020.07.09~07.16)
Rivaroxaban 15mg bid
(07.17~07.29)
Warfarin
(2020.07.30~2020.08.31)
IG ADM
2020.07.08
Discharge
2020.07.16
2020.07.30
2020.08.31
PTE 진단
INR 7.09, 혈뇨 발생
Apixaban 2.5mg bid
(2020.09.07~09.20)
Apixaban 2.5mg bid (2020.10.08~2021.01.18)
2020.09.07
2020.09.21 OPD
2020.10.08
2020.10.12
2021.01.18
혈뇨 지속되었다고 함
f/u chest e' CT
진단 6개월 차
지속되는 혈뇨
치료 중단

2020.07.08 chest e’ CT (진단 당시)

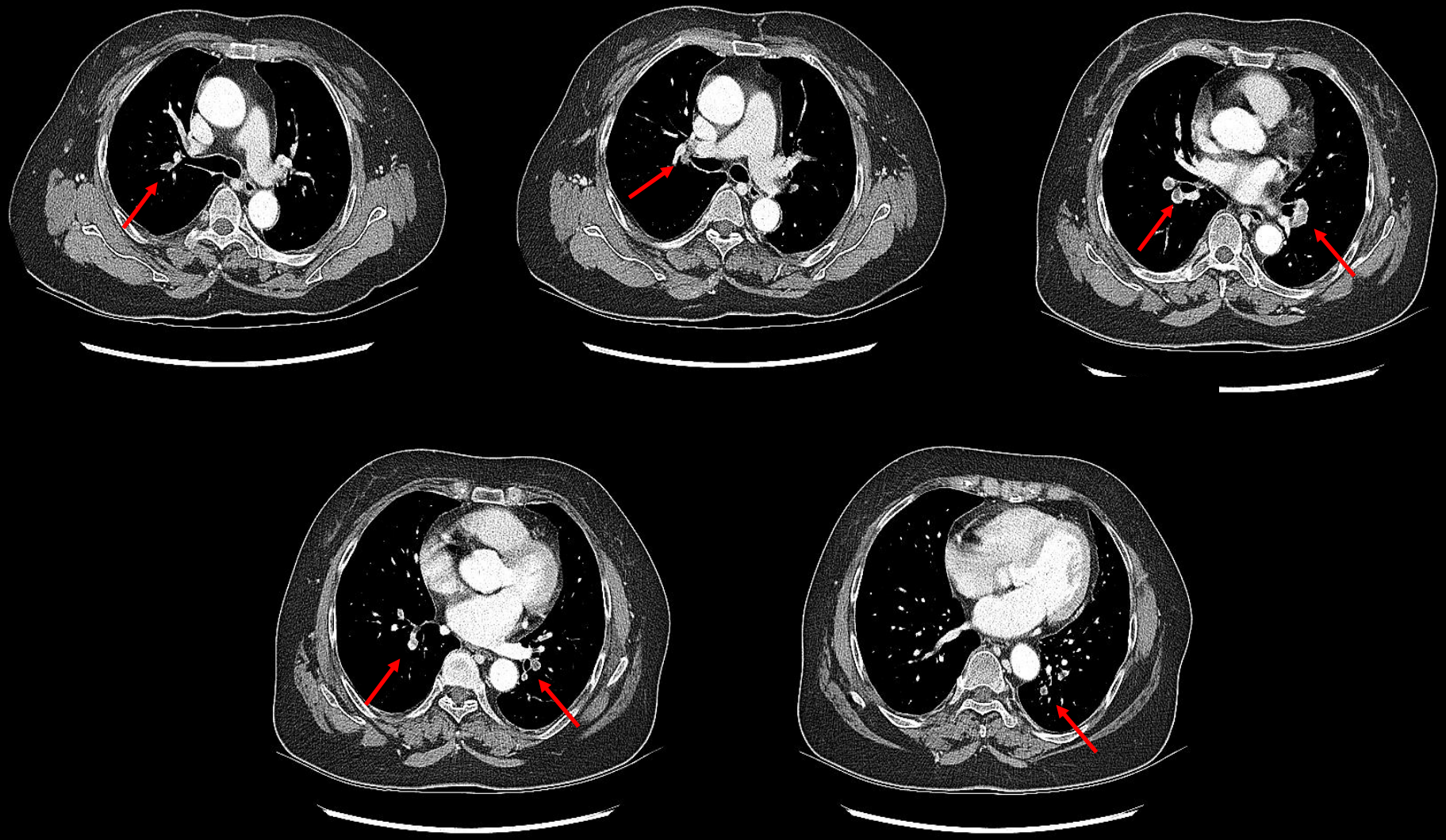


2020.10.12 chest e’ CT
(항응고요법 3개월 째)



2021.04.05 chest e' CT

(6개월 간 항응고 치료 중단 후 3개월 째)



Apixaban 2.5mg bid 로 재 치료 시작 (2021.04.22~)

Case (II)

- 80/M, 우측하지 방사통을 주소로 2019.06 정형외과 내원.
- Medical history

- h/o pulmonary tuberculosis (20대)
- spinal stenosis
- COPD
- hepatic flexure **colon cancer** with intra-abdominal lymph nodes

  s/p Lap. extended Rt. hemicolectomy (2019.04.01)

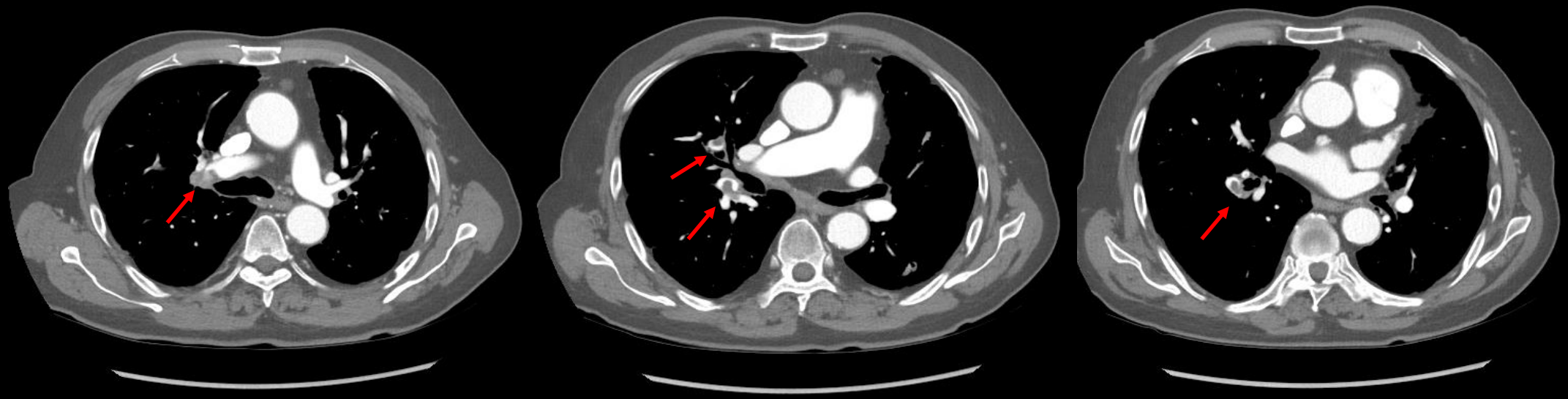
  on Adj. FOLFOX (2019.05.09~)

- **Dx.: infrarenal abdominal and Rt. femoral arterial thrombosis**

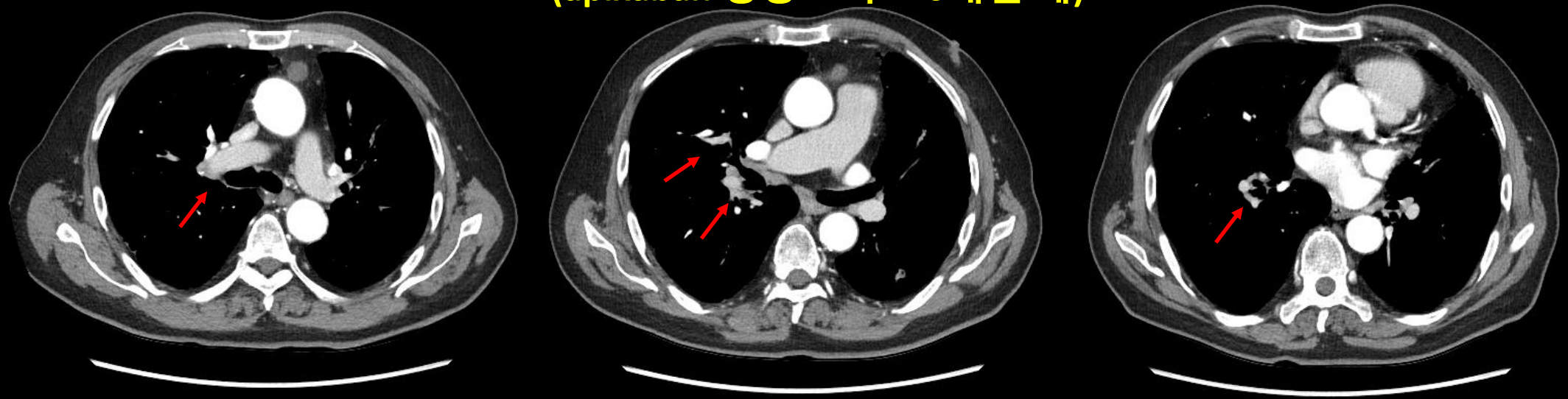
- colon cancer 치료 종료 6개월 차인 2021년 10월 경 부터
  Blood clot이 있는 소변이 6개월 간 지속되어 내원.

  - UA 상 혈뇨 +
  - AP enhanced CT: 2.3cm Lt. side **bladder tumor**
  - Chest enhanced CT: **PTE** at Right interlobar, RML, RLLobar and segmental pulmonary arteries

2022.03.31 chest e’ CT (진단 당시)

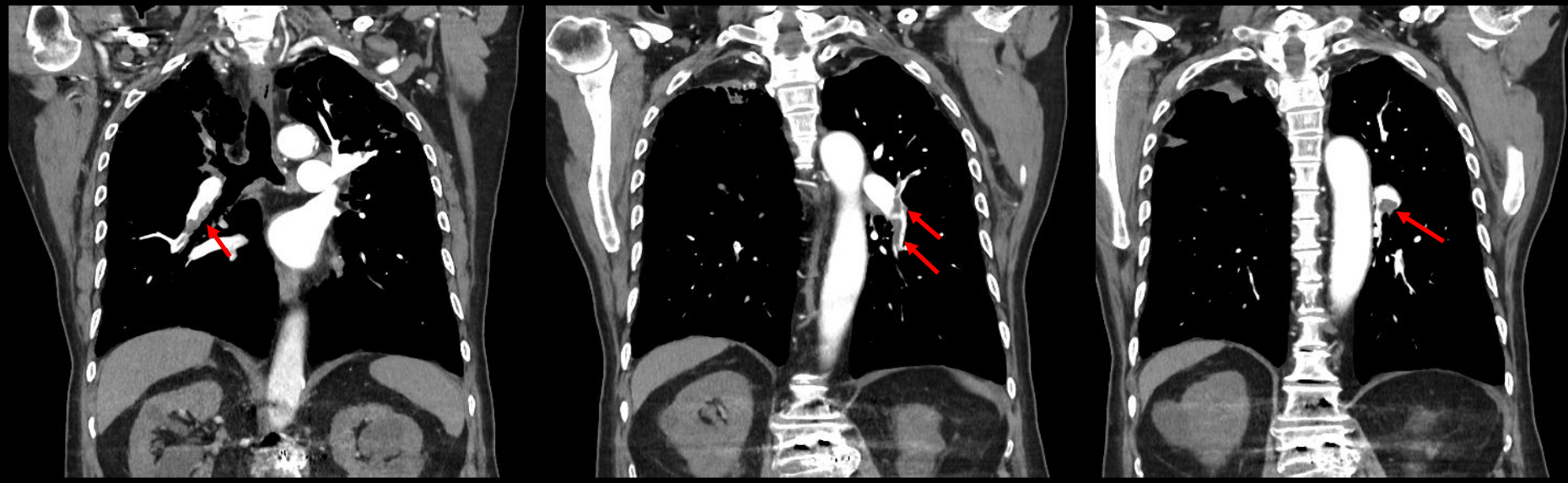


2022.09.27 f/u chest e’ CT
(apixaban 항응고치료 6개월 째)

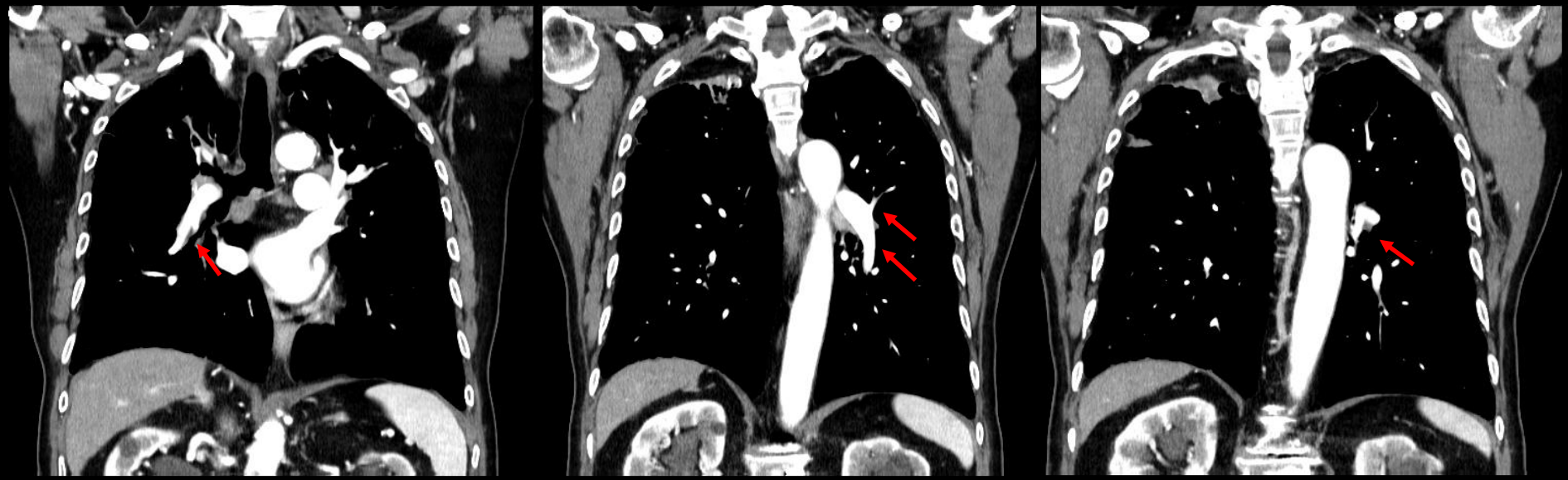


- Sudden onset Dyspnea 호소하며 2022.12.19 (치료 종료 3개월 째) IP opd 내원

2022.12.20 PTE-CT

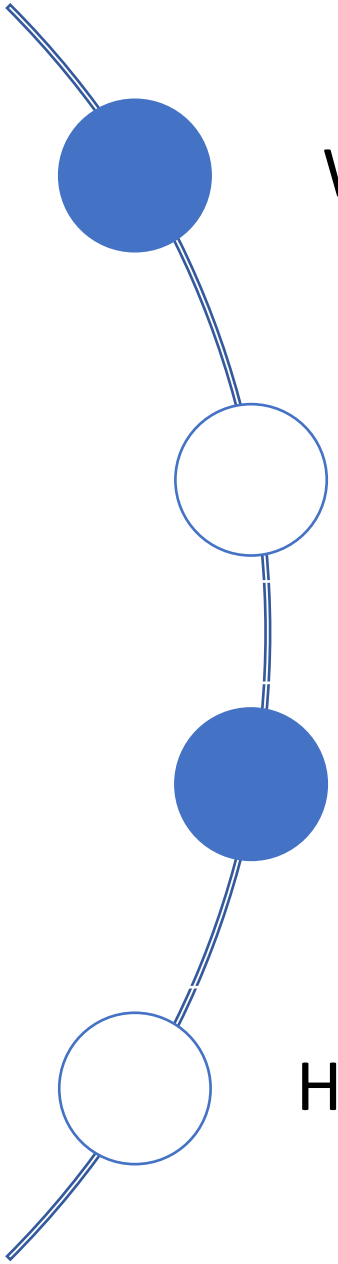


2023.03.28 (재 치료 3개월 차) f/u chest e’ CT



Case Summary

	CASE I	CASE II
Co-morbidity	CKD stageIII	COPD, h/o colon ca.
Cancer type and stage	**Bladder cancer (pStage IV A)**	**Bladder cancer (pStage I)**
Previous event of thrombosis	None	Arterial thrombosis of Rt. lower extremity and Abd. a.
Chemotherapy	Gemcitabine + Cisplatin	FOLFOX
Complications during Tx. or Recurrence	Frequent bleeding (non-major bleeding) → Tx. hold	Recurrence of VTE



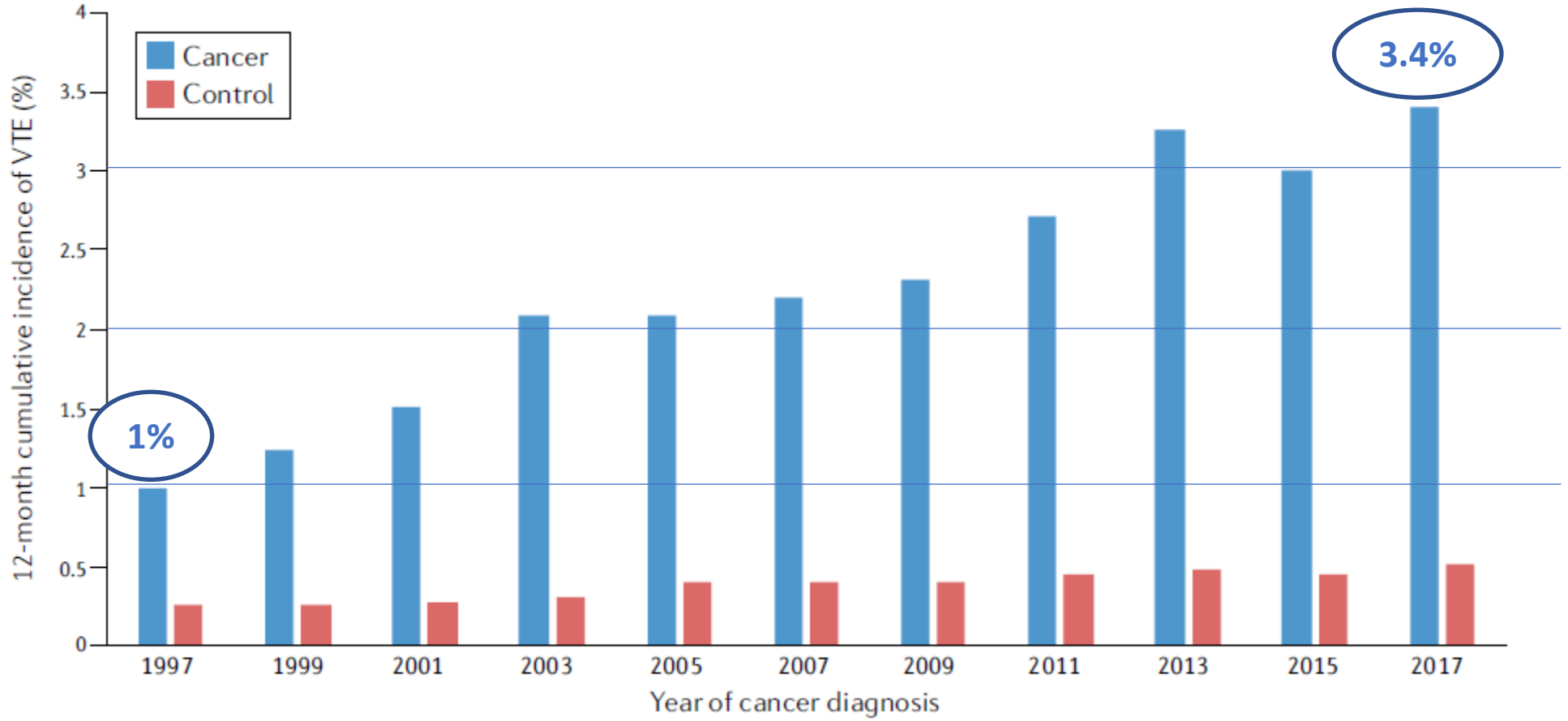
What makes thrombophilic condition in patients with active cancer?

How to treat VTE according to risk factors?

What problems are caused during anticoagulation treatment?

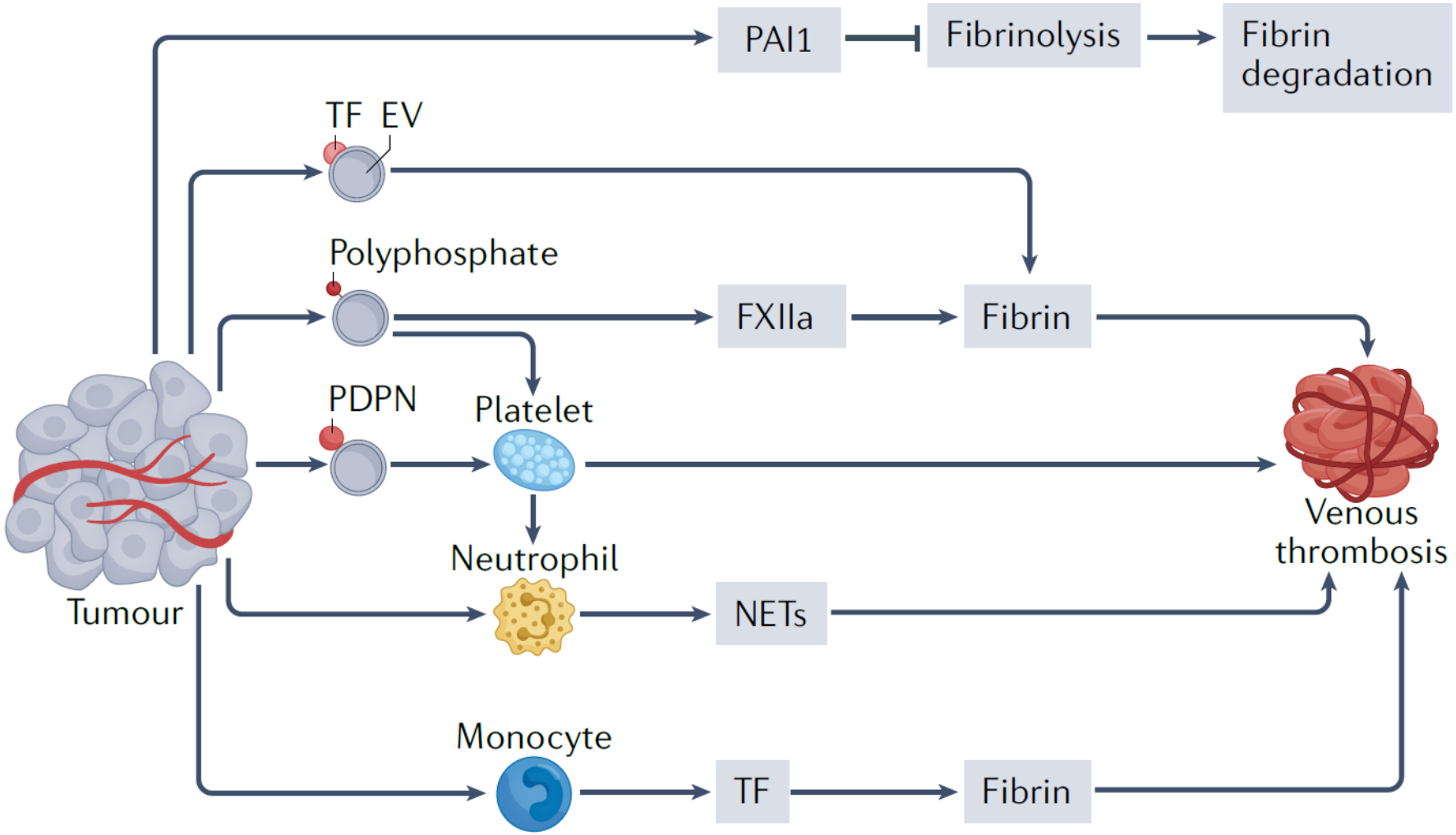
How to improve the problem and treat VTE?

1-yr cumulative incidence of VTE (1997~2017)



Nat Rev Dis Primers . 2022 Feb 17;8(1):11

Potential Mechanism of CAT



NETs: neutrophil extracellular traps, TF: tissue factor, EVs: extracellular vesicles,
PDPN: polyphosphate or podoplanin, FXII: factor XII, PAI1: plasminogen activator ingibitor 1

Nat Rev Dis Primers . 2022 Feb 17;8(1):11

Cancer-related factors

Patient characteristic	Khorana score	Risk score
Site of cancer		
Very high risk (stomach, pancreas)		2
High risk (lung, lymphoma, gynecologic, bladder, testicular)		1
Prechemotherapy platelet count 350 × 10^9/L or more		1
Hemoglobin level less than 100 g/L or use of red cell growth factors		1
Prechemotherapy leukocyte count more than 11 × 10^9/L		1
BMI 35 kg/m^2 or more		1

- Type (site): Pancreatic, stomach, brain, colorectal, lung, and ovarian cancer types
- Stage: Advanced cancer stage
- Histological high-grade tumors
- Timing relative to diagnosis
- Gene variants

  (e.g. ALK mutation or ROS1 rearrangement in lung cancer)

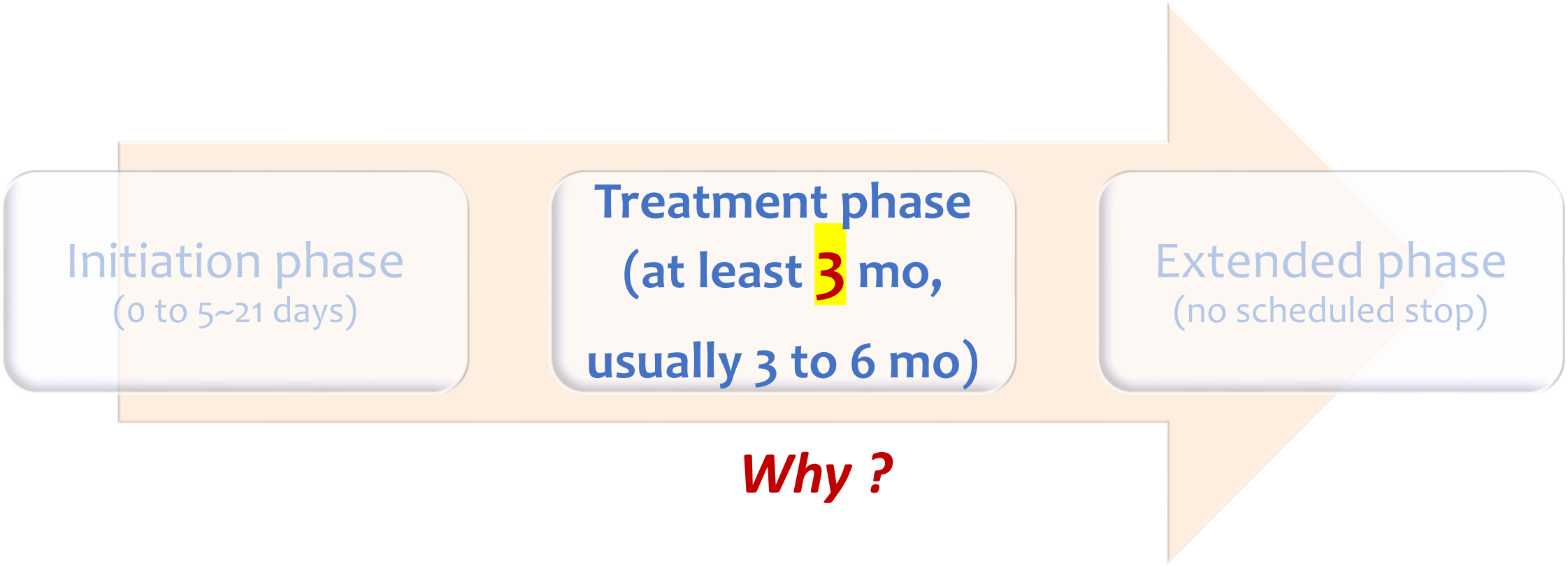
Thrombosis Research 191S1 (2020) S3–S11
European Journal of Cancer (2013) 49, 1404– 1413
Arch Intern Med. 2006;166:458-464
Thrombosis Research 186 (2020) 36–41

Therapy-related factors

- Chemotherapy (e.g. cisplatin)
- Hormonal therapies
  - selective estrogen receptor modulator (tamoxifen, raloxifene)
- Targeted and immunological therapies
  - immune checkpoint inhibitors (PD-L1 and CTLA4 inhibitors)
  - Chimeric antigen receptor T cell (CAR-T) therapy
  - inhibitors of cyclin-dependent kinase 4/6 (palbociclib, abemaciclib, and ribociclib)
  - anti-vascular endothelial growth factor (VEGF) monoclonal antibody (bevacizumab)
  - immunomodulatory drugs (IMiDs; thalidomide, lenalidomide) combined with glucocorticoids
- Surgery and Radiation therapy

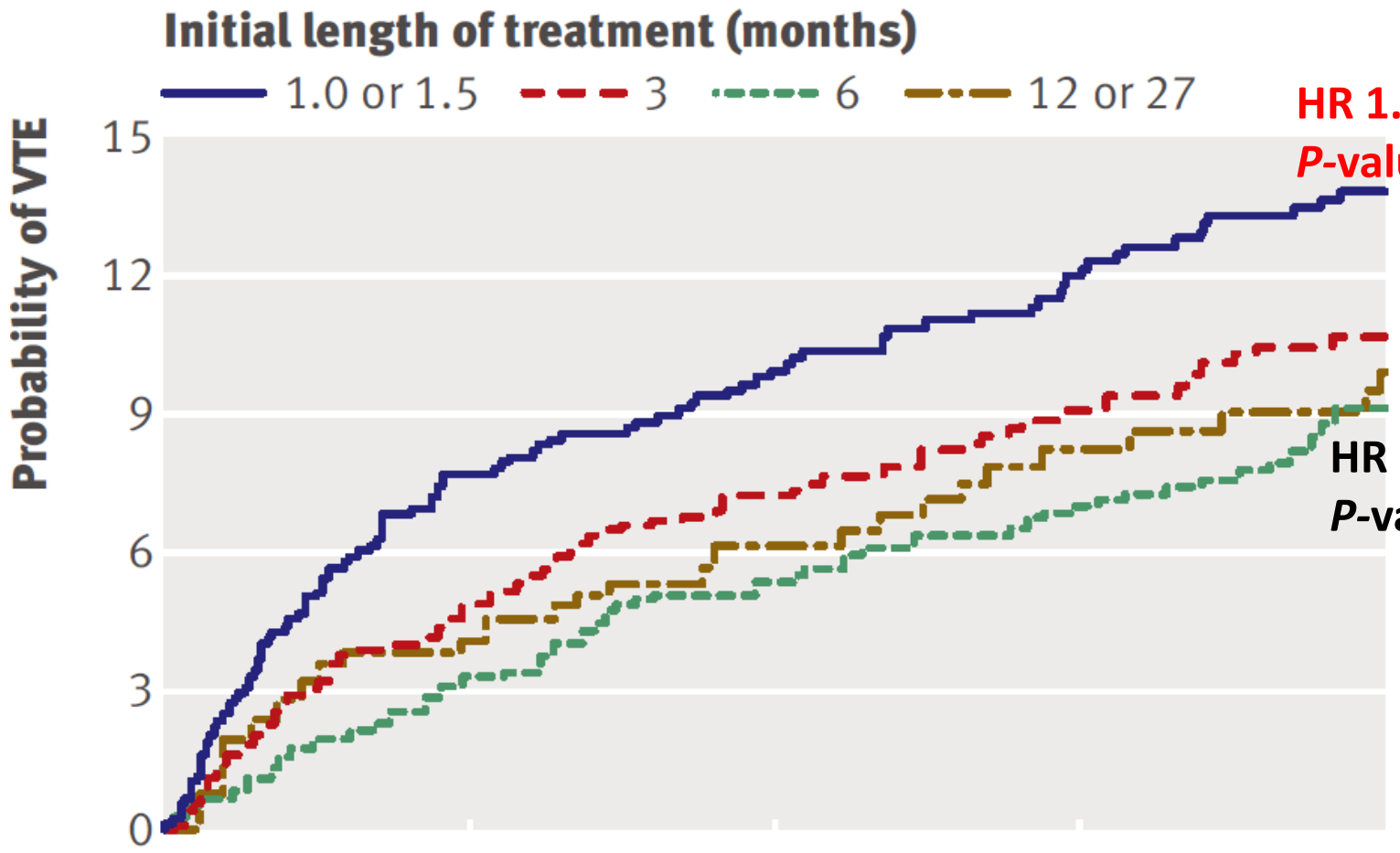
J Clin Oncol 30:4416-4426, Circulation. 2005;111:650-656, Eur J Haematol. 2021;106:634–642, Blood. 2001;98: 1614-1615, Eur J Haematol. 2022;108:271–277, Blood Adv . 2021 Nov 9;5(21):4465-4475

Therapeutic phase for VTE



CHEST 2021:160(6): e545-e608

Rationale for at least 3-month of treatment phase

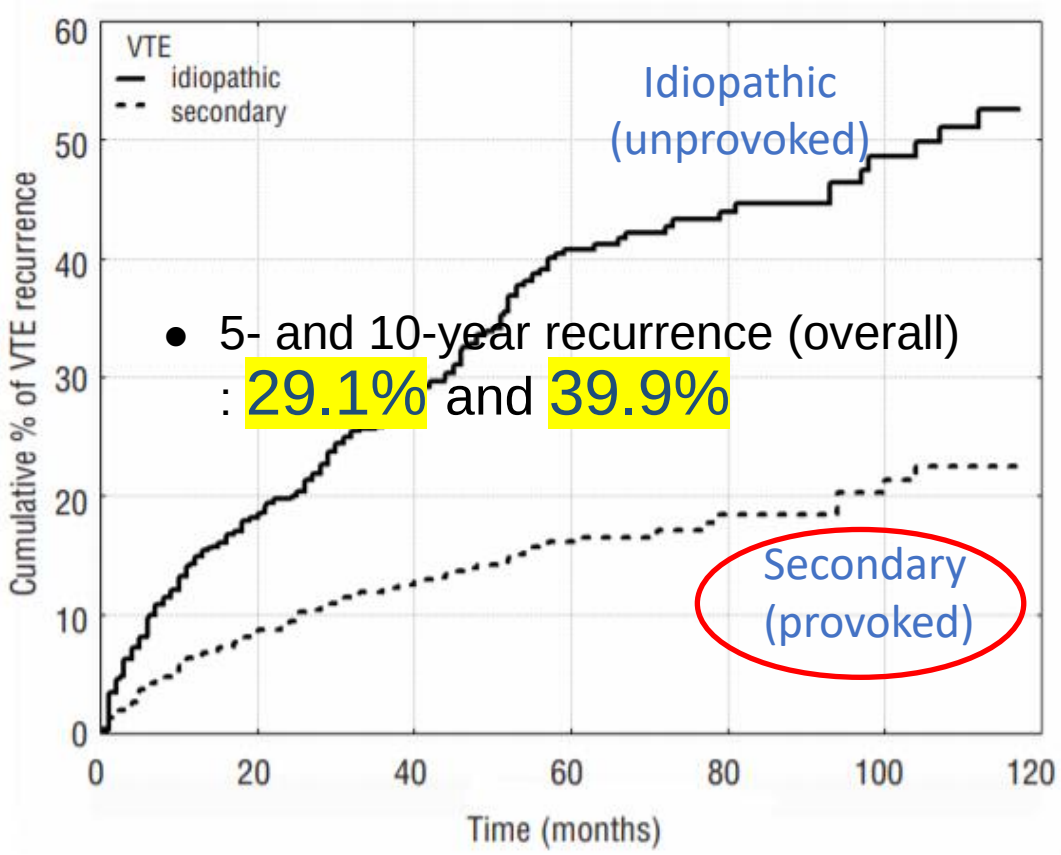


HR 1.52, 95% CI 1.14 to 2.02
***P*-value=0.004**

HR 1.19, 95% CI 0.86 to 1.65
***P*-value=0.29**

BMJ 2011;342:d3036

Risk of recurrence after discontinuation



- 5- and 10-year recurrence (overall) : 29.1% and 39.9%

Cumulative incidence of recurrent VTE in patients with idiopathic (unprovoked) and secondary (provoked) VTE

- 1,626 pts with VTE (Proximal DVT or PE)
- Unprovoked VTE (53%)
- 10 years F/U

	Overall of PE	Provoked	Unprovoked
5-year recurrence	21.5%	17%	27%

A significant proportion of patients experienced recurrence even in Asian (Korean)

Haematologica, 2007:92(02):199
Tuberc Respir Med 2019:82:341

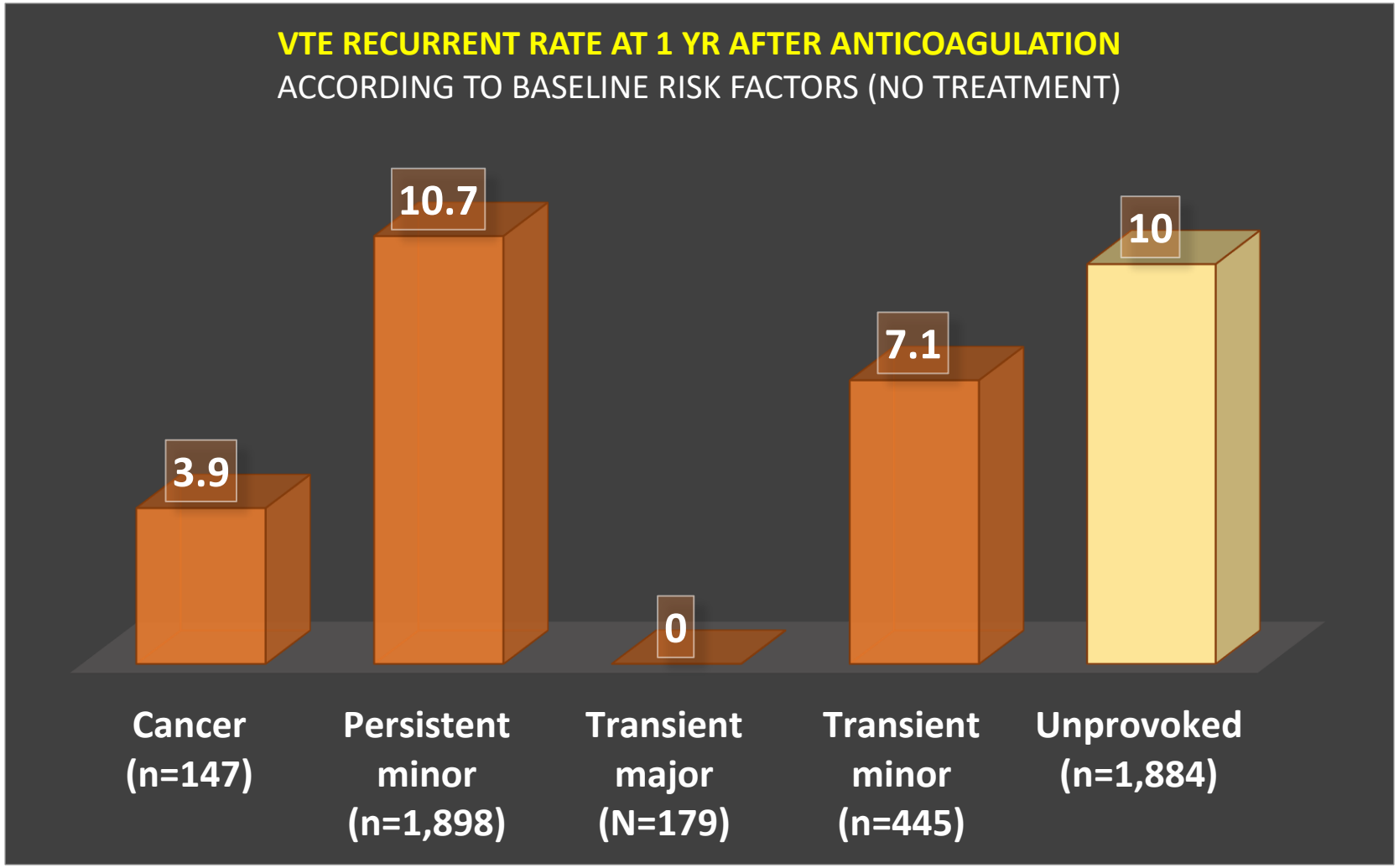
Messages from cohort studies

- **VTE recurrence is a highly significant problem.**
  - Even recurrence of provoked VTE is common
- **A substantial population** has higher recurrence risk

Therapeutic phase for VTE

CHEST 2021:160(6): e545-e608

Recurrence rate in patients with active cancer is significantly high



Modified from BLOOD 2018:2(7):788 (from EINSTEIN-EXT and EINSTEIN-Choice)

Categorization of risk factors for VTE based on the risk of recurrence over the long-term

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

stopping anticoagulation

Extended/Indefinite Tx.

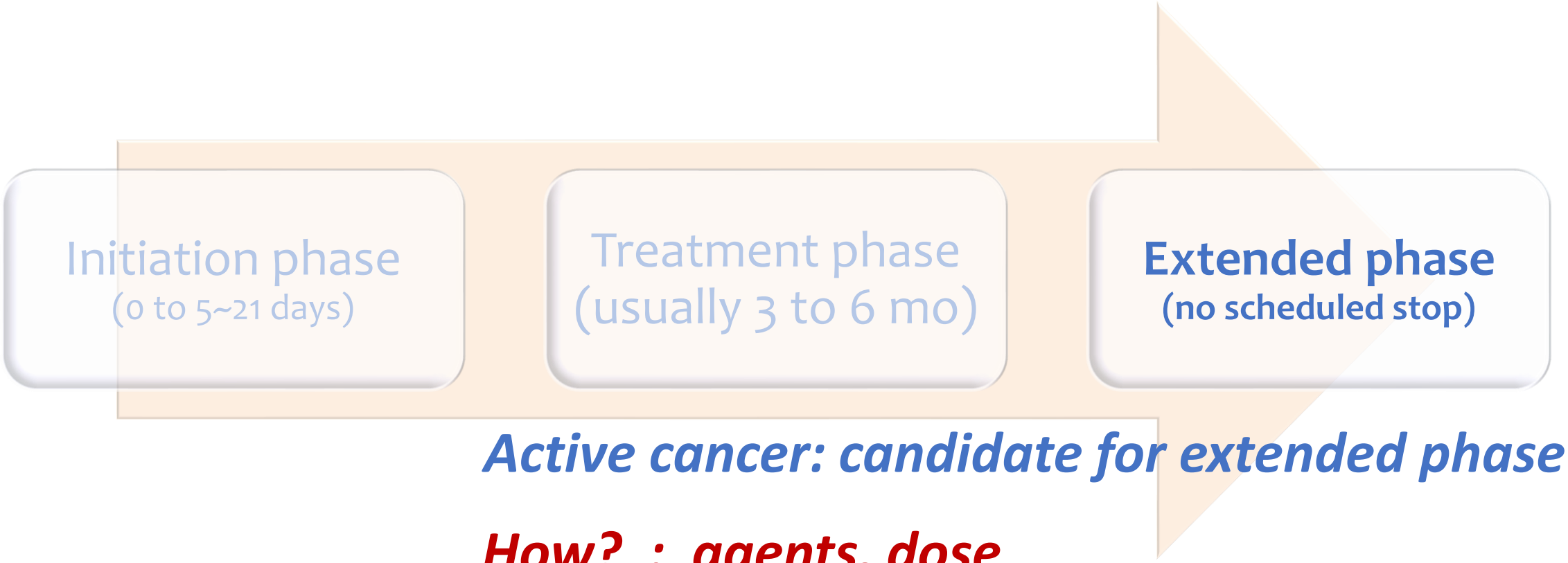
European Respiratory Journal 2019 54: 1901647

Transient risk factor (resolve after provoked VTE)		
Major	Surgery with general anesthesia (≥30 min)	**stopping anticoagulation**
	Confined to bed in hospital (≥3 d) w/ acute illness (only bathroom privileges)	
	Cesarean section	
Minor	Surgery with general anesthesia (<30 min)	Gray zone (stopping vs. indefinite Tx.)
	Hospital ADM for <3 d w/ acute illness	
	Estrogen Tx., Pregnancy, Puerperium	
	Confined to bed out hospital (≥3 d) w/ acute illness	
	Leg injury w/ decreased mobility for ≥3 d	
Chronic (persistent) risk factor (persist after VTE) ➔ Extended/Indefinite Tx.		
Active cancer - ongoing CTx., recurrent or progressive cancer IBD Autoimmune disorder (APS, RA) Chronic infections Chronic immobility		

* Recurrent **unprovoked** VTE: **indefinite antithrombotic Tx.**

Blood Adv (2020) 4 (19): 4693–4738

Therapeutic phase for VTE



Active cancer: candidate for extended phase

How? : agents, dose

CHEST 2021:160(6): e545-e608

Which agent is suitable for CAT?

LMWH *vs* VKA

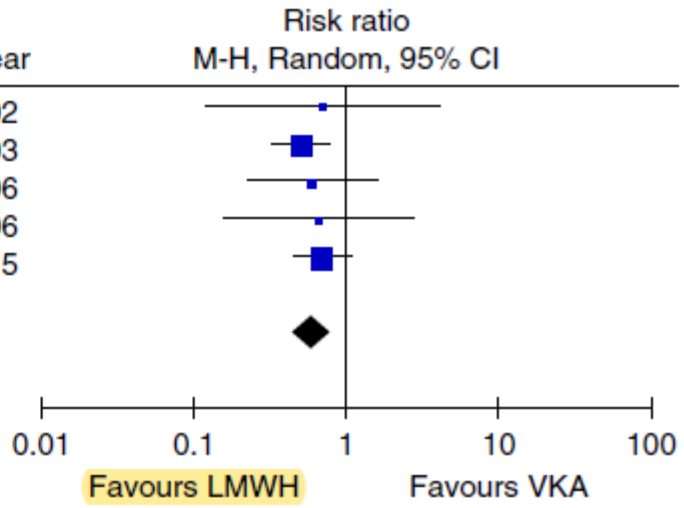
VTE recurrence

(A)

Study or subgroup	LMWH Events	LMWH Total	VKA Events	VKA Total	Weight	Risk ratio M-H, Random, 95% CI	Year
CANTHANOX	2	71	3	75	2.6%	0.70 [0.12, 4.09]	2002
CLOT	27	336	53	336	42.4%	0.51 [0.33, 0.79]	2003
MAIN-LITE	6	100	10	100	8.6%	0.60 [0.23, 1.59]	2006
ONCENOX	4	61	3	30	4.0%	0.66 [0.16, 2.74]	2006
CATCH	31	449	45	451	42.4%	0.69 [0.45, 1.07]	2015
Total (95% CI)		1017		992	100.0%	0.60 [0.45, 0.80]	
Total events	70		114				

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.99$, df = 4 ($P = .91$); $I^2 = 0\%$

Test for overall effect: $Z = 3.52$ ($P = .000$)



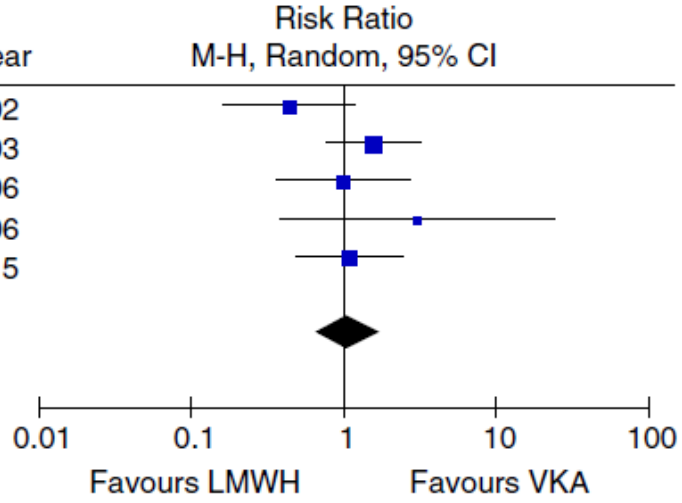
Major bleeding risk

(B)

Study or subgroup	LMWH Events	LMWH Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
CANTHANOX	5	71	12	75	19.2%	0.44 [0.16, 1.19]	2002
CLOT	19	338	12	335	31.0%	1.57 [0.77, 3.18]	2003
MAIN-LITE	7	100	7	100	18.6%	1.00 [0.36, 2.75]	2006
ONCENOX	6	67	1	34	5.3%	3.04 [0.38, 24.28]	2006
CATCH	12	449	11	451	25.9%	1.10 [0.49, 2.46]	2015
Total (95% CI)		1025		995	100.0%	1.07 [0.65, 1.75]	
Total events	49		43				

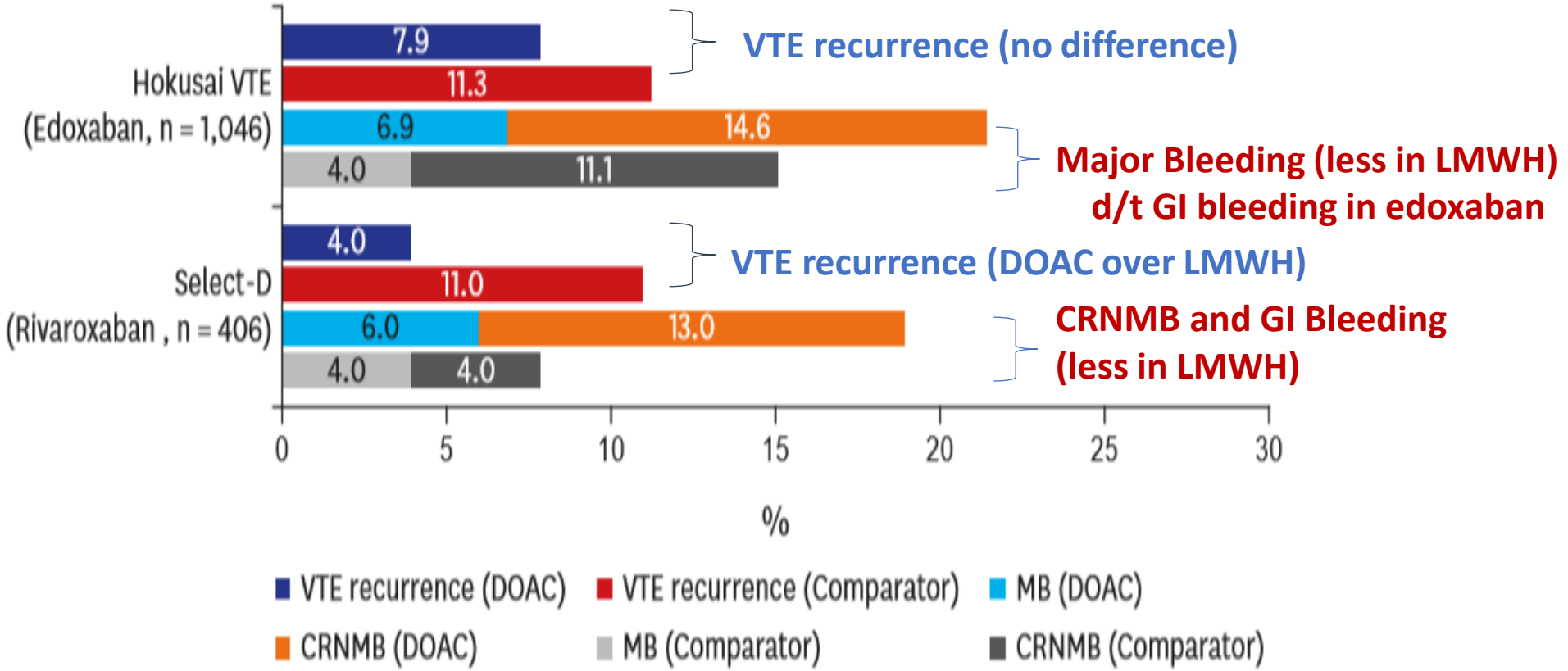
Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 5.20$, df = 4 ($P = .27$); $I^2 = 23\%$

Test for overall effect: $Z = 0.26$ ($P = .80$)



Res Pract Thromb Haemost. 2018;2:429–438.

Edoxaban and Rivaroxaban vs. LMWH



VTE recurrence (no difference)

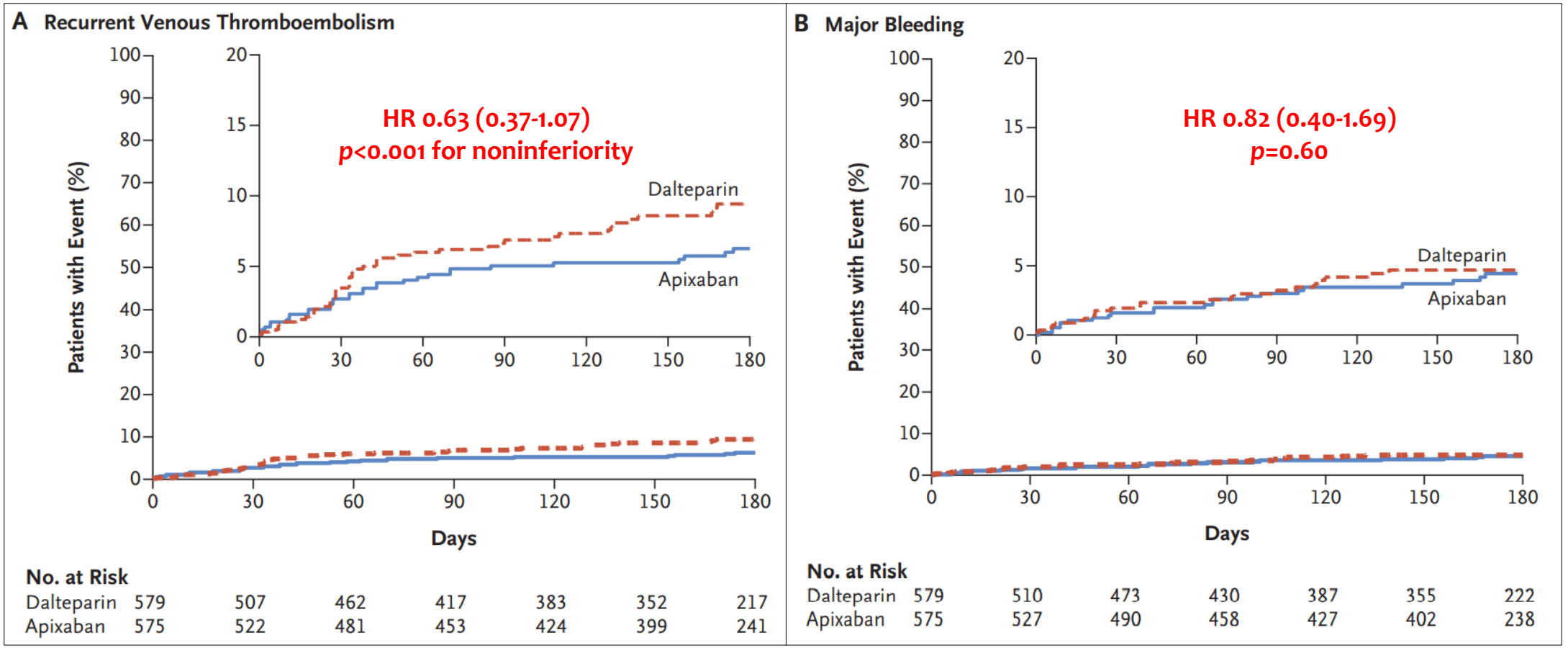
Major Bleeding (less in LMWH) d/t GI bleeding in edoxaban

VTE recurrence (DOAC over LMWH)

CRNMB and GI Bleeding (less in LMWH)

N Engl J Med 2018;378:615-24, J Clin Oncol 2018:36:2017-2023

Apixaban for Cancer-Associated Venous Thromboembolism (CARAVAGGIO study)



N Engl J Med 2020;382:1599-607

Major GI bleeding according to individual DOACs (DOAC vs. LMWH in CAT)

TABLE 10] Evidence Profile: Drug-Specific Direct-Acting Oral Anticoagulants vs Low-Molecular-Weight Heparin for Treatment of VTE in Patients With Cancer

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	DOACs	LMWH	Relative (95% CI)	Absolute (95% CI)
Major GI bleeding—edoxaban/rivaroxaban vs LMWH (follow-up: range, 6-12 mo)					GI/GU cancer = 38.1%					
1,452 (2 studies)	Not serious[a,b]	Not serious	Not serious	Serious[c]	None	⊕⊕⊕◯ MODERATE	28/725 (3.9%)	10/727 (1.4%)	RR, 2.81 (1.37-5.74)	25 more per 1,000 (from 5 more to 65 more)
Major GI bleeding—apixaban vs LMWH (follow-up: 6 mo)					GI/GU cancer = 32.8%					
1,442 (2 studies)	Not serious[a]	Not serious	Not serious	Very serious[c,d]	None	⊕⊕◯◯ LOW	11/721 (1.5%)	10/721 (1.4%)	RR, 1.11 (0.47-2.58)	2 more per 1,000 (from 7 fewer to 22 more)

Apixaban seems to have **less probability of GI/GU bleeding**, compared with Rivaroxaban or Edoxaban

Chest. 2021 Dec;160(6):e545-e608

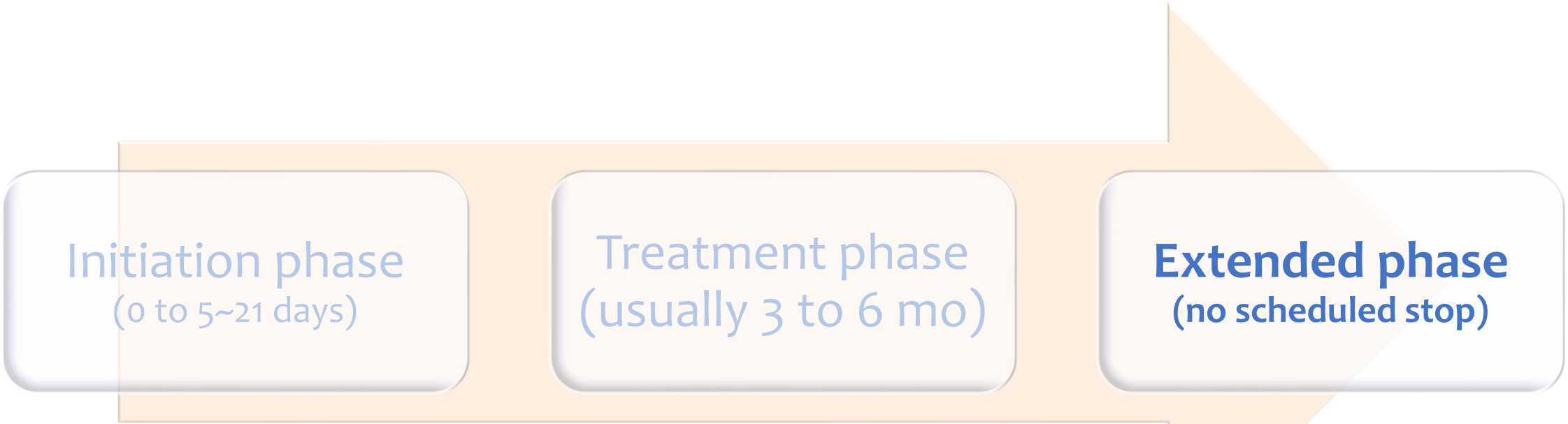
DOACs in Cancer-associated Thrombosis (CAT)

2016 ACCP through 2019 ESC/ERS	2021 ACCP
• LMWH (over VKA) • Edoxaban and Rivaroxaban : alternatives to LMWH in non-GI cancer	• Factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) over LMWH (Strong R, moderate-certainty evidence)

- Edoxaban and Rivaroxaban appear to be a/w a higher risk of GI major bleeding than LMWH
- Apixaban and LMWH may be the preferred option in patients with luminal GI malignancies
- Dabigatran does not have evidences in CAT

Chest. 2021 Dec;160(6):e545-e608

Therapeutic phase for VTE



Active cancer: candidate for extended phase

How? : agents (Factor Xa Inhibitors), dose

CHEST 2021:160(6): e545-e608

DOAC vs. Placebo in extended treatment

Study	Active	N*	Ext-Tx duration (months)	Risk reduction of recurrent VTE (HR 95% CI)	Major or CRNMB in active group (HR 95% CI)
EINSTEIN-choice	Rivaroxaban 20mg, qd	3396 (2.6%)	6~12	66%	No difference
	Rivaroxaban 10mg, qd		6~12	74%	No difference
AMPLIFY-Extension	Apixaban 5mg, bid	2486 (1.6%)	12	80%	No difference
	Apixaban 2.5mg, bid		12	81%	No difference

*: ( ) = proportion of patients with active cancer
CRNMB means clinically relevant non-major bleeding

N Engl J Med 2017;376:1211-22
N Engl J Med 2013;368:699-708

Really efficious even in CAT ?

- Rivaroxan: 20mg qd (initial 6 mo) → 10mg qd (after 6 mo)
- Apixaban: 5mg bid (initial 6 mo) → 2.5mg bid (after 6 mo)

Head-to-head RCT is underway

- REduced Dose Versus Full-dose of Direct Oral Anticoagulant After uNprOvoked Venous thromboEmbolism (The RENOVE)

Study type	Interventional clinical trial
phase	3
Estimated enrollment	2200
allocation	Randomized
Intervention model	Parallel assignment
Masking	Single (Outcomes Assessor)
Duration	24 months
Primary outcomes	Recurrent VTE
ClinicalTrials.gov identifier	NCT03285438
Completion date	Oct. 2023

https://clinicaltrials.gov/ct2/show/NCT03285438

Head-to-head RCT is underway

- Long-term Treatment of **Cancer Associated VTE**: Reduced vs Full Dose of Apixaban : API-CAT STUDY for APIxaban **Cancer Associated** Thrombosis

Study type	Interventional clinical trial
phase	3
Estimated enrollment	1722
allocation	Randomized
Intervention model	Parallel assignment
Masking	Double (Participant, Investigator)
Duration	12 months
Primary outcomes	Recurrent VTE or Death due to PE
ClinicalTrials.gov identifier	NCT03692065
Completion date	Aug. 2024

https://clinicaltrials.gov/ct2/show/study/NCT03692065

Scores estimating anticoagulation-related bleeding risk

Prediction model	population	Sensitivity, %	Specificity, %	PPV, %	NPV, %	C-statistic
RIETE	RIETE Registry	1.7 (0.0-4.0)	99.4 (99.1-99.7)	12.5 (0.0-28.7)	95.1 (94.5-96.2)	0.51 (0.49-0.52)
VTE-BLEED	RE-COVER and RE-COVER II	53.1 (43.9-62.3)	70.9 (69.1-72.8)	8.1 (6.1-10.1)	96.9 (96.1-97.7)	**0.61** (0.56-0.66)
HAS-BLEED	Atrial fibrillation	20.2 (12.8-27.5)	93.1 (92.0-94.1)	12.6 (7.8-17.4)	95.9 (95.1-96.8)	0.57 (0.53-0.61)
OBRI	VKA Tx. in general	3.4 (0.1-6.7)	98.5 (98.1-99.0)	10.3 (0.7-19.8)	95.4 (94.6-96.2)	0.51 (0.49-0.51)
CHAP	Non-active cancer	52.7 (43.4-61.9)	76.1 (74.3-77.9)	10.1 (7.6-12.5)	96.9 (96.1-97.7)	0.65 (0.60-0.70)

CHAP model: Cr, Hb, Age, use of antiplatelet agent

Blood Adv (2022) 6 (15): 4605–4616

New drug, Anti-Factor XI, for VTE

Patients with severe factor XI deficiency have a reduced incidence of deep-vein thrombosis

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Summary

Factor XI (FXI) plays a dual role in haemostasis and thrombosis. It contributes to thrombin generation and promotes inhibition of fibrinolysis. Severe FXI deficiency was shown to confer protection against arterial and venous thrombosis in animal models without compromising haemostasis. We have previously shown that patients with severe FXI deficiency have a low incidence of ischaemic stroke, but display the usual incidence of myocardial infarction. In the present study, we compared the incidence of deep-vein thrombosis (DVT) in 219 unrelated patients with severe FXI deficiency aged 20–94 to the incidence in a large population-based study. No cases of DVT were observed in the FXI-deficient cohort, a result that is significantly lower than the expected number (4.68) computed from the population-based study. The low incidence remains statistically significant when compared to three other population-based studies. These data suggest that severe FXI deficiency provides protection against DVT.

Keywords

Factor XI, factor XI deficiency, deep-vein thrombosis

Thromb Haemost 2011; 105: 269-73
Semin Thromb Hemost 2013; 39: 621-31

Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolic events

Table 2. Adjusted HRs for the association of factor XI activity with VTE and cardiovascular events (n=10 193)

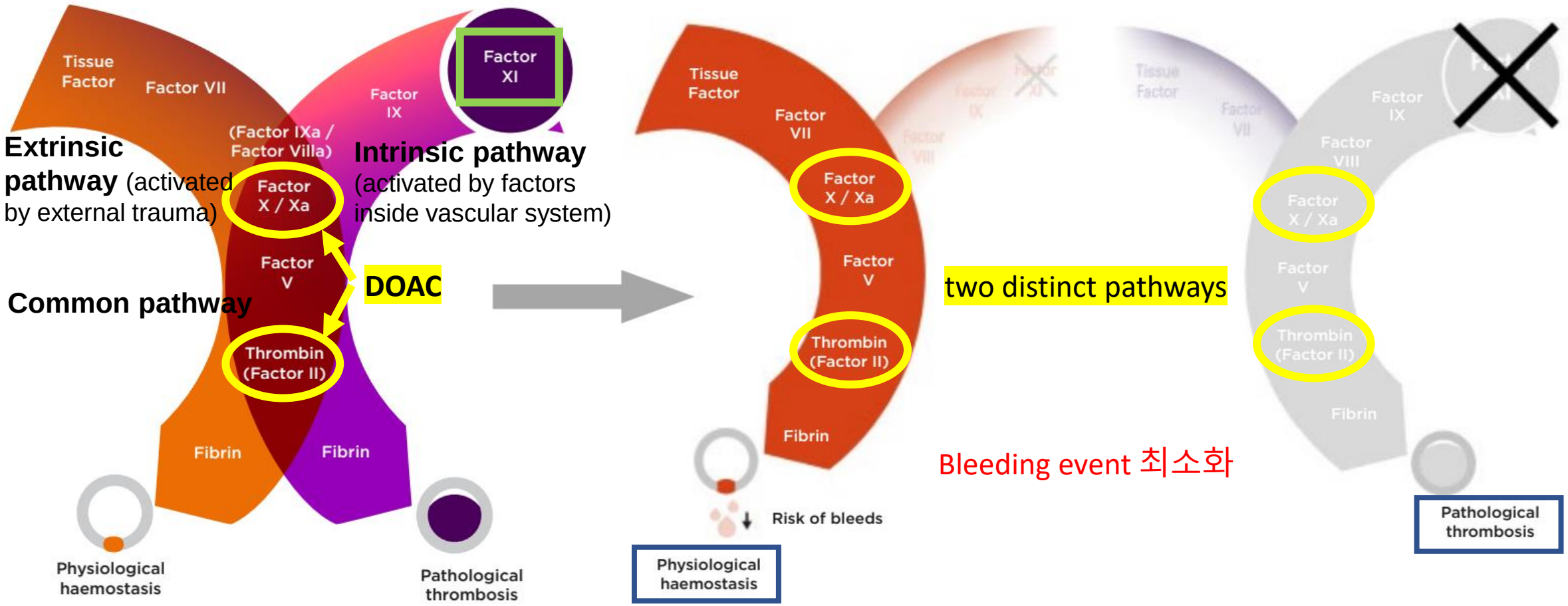
Study outcome	Factor XI activity	Number	Events	Age-adjusted model HR (95% CI)	Fully adjusted model HR (95% CI)
Cardiovascular event	≤30%	542	19	0.56 (0.35-0.91)	0.57 (0.35-0.93)
	30%-50%	693	16	0.57 (0.34-0.95)	0.52 (0.31-0.87)
	>50%	8958	230	Reference	Reference
VTE	≤50%	1235	3	0.14 (0.04-0.44)	0.26 (0.08-0.84)
	>50%	8958	94	Reference	Reference

All adults tested for factor XI activity between 2002 and 2014 were included in the study.
Factor XI activity was classified into 3 categories:

- normal (activity >50%), mild deficiency (activity : 30%-50%), and moderate–severe deficiency (activity < 30%).

Blood 2017:129(9):1210-15 (Israel)

New model of the coagulation cascade



Bleeding event 최소화

the International Society on Thrombosis and Haemostasis (ISTH) Virtual Congress 2021

TABLE 1 | Overview of factor XI inhibitors in clinical trials.

Drug	Type	Mechanism	Administration route	Studies (NCT)	Population (N)	Comparator	Status
IONIS-FXI$_{Rx}$	Antisense oligonucleotide of FXI	Inhibits FXI messenger RNA	Subcutaneous (weekly)	NCT01713361 NCT02553889 NCT03358030	TKA (300) ESKD (49) ESKD (200)	Enoxaparin Placebo Placebo	Published Published Completed
Osocimab	Monoclonal antibody to FXIa	Binds and inhibits FXIa	Intravenous, subcutaneous (monthly)	NCT03276143 NCT04523220	TKA (813) ESKD (686)	Enoxaparin/Apixaban Placebo	Published Ongoing
Abelacimab	Monoclonal antibody to FXI/FXIa	Binds and inhibits FXI and FXIa	Subcutaneous (monthly)	EudraCT 2019-003756-37 NCT04755283 NCT05171049 NCT05171075	TKA (412) AF (1,200) CAT (1,655) CAT (1,020)	Enoxaparin Rivaroxaban Apixaban Dalteparin	Published Ongoing Ongoing Ongoing
Milvexian	Small molecule inhibitor of FXIa	Binds and inhibits FXIa	Oral (daily)	NCT03891524 NCT03766581	TKA (1,242) Stroke (2,366)	Enoxaparin Placebo	Published Ongoing
Xisomab 3G3	Monoclonal antibody to FXI	Binds FXI and blocks activation by FXIIa	Intravenous (single dose)	NCT03612856 NCT04465760	ESKD (24) CRT (50)	Placebo None	Published Ongoing
Fesomersen	Antisense oligonucleotide of FXI	Inhibits FXI messenger RNA	Subcutaneous (weekly)	NCT04534114	ESKD (305)	Placebo	Ongoing
Asundexian	Small molecule inhibitor of FXIa	Binds and inhibits FXIa	Oral (daily)	NCT04218266 NCT04304534 NCT04304508	AF (753) AMI (1,592) Stroke (1,790)	Apixaban Placebo Placebo	Published Completed Ongoing

AF, atrial fibrillation; CAT, cancer-associated thrombosis; CRT, catheter-related thrombosis in cancer patients; ESKD, end-stage kidney disease; TKA, total knee arthroplasty.

Phase III

ASTER
MAGNOLIA

Front. Cardiovasc. Med. 9:903029

Summary

- Anticoagulation therapy for at least 3 months is recommended.
- The tumor cells induce thrombogenic state and bleeding complication.
- If anticoagulation therapy is stopped, the risk for recurrent thrombosis in patients with active cancer is increased.
- Extended anticoagulation therapy be considered in patients with active cancer.
- Nowadays, DOACs are the first-line choice for CAT.
- The effect of the half-dose DOACs in extended treatment for CAT is to be considered.

Summary

- The rate of bleeding, particularly GI bleeding is higher with DOACs than with LMWH.
- Apixaban is associated with less bleeding risk than other DOACs.
- Factor XI has now emerged as a new antithrombotic target that appears non-essential for hemostasis.
- New model of the coagulation cascade suggests they are more independent than previously realized.
- Development of new drugs for VTE to decrease bleeding risk is ongoing.

Thank you