UPDATE IN CANCER-ASSOCIATED THROMBOSIS

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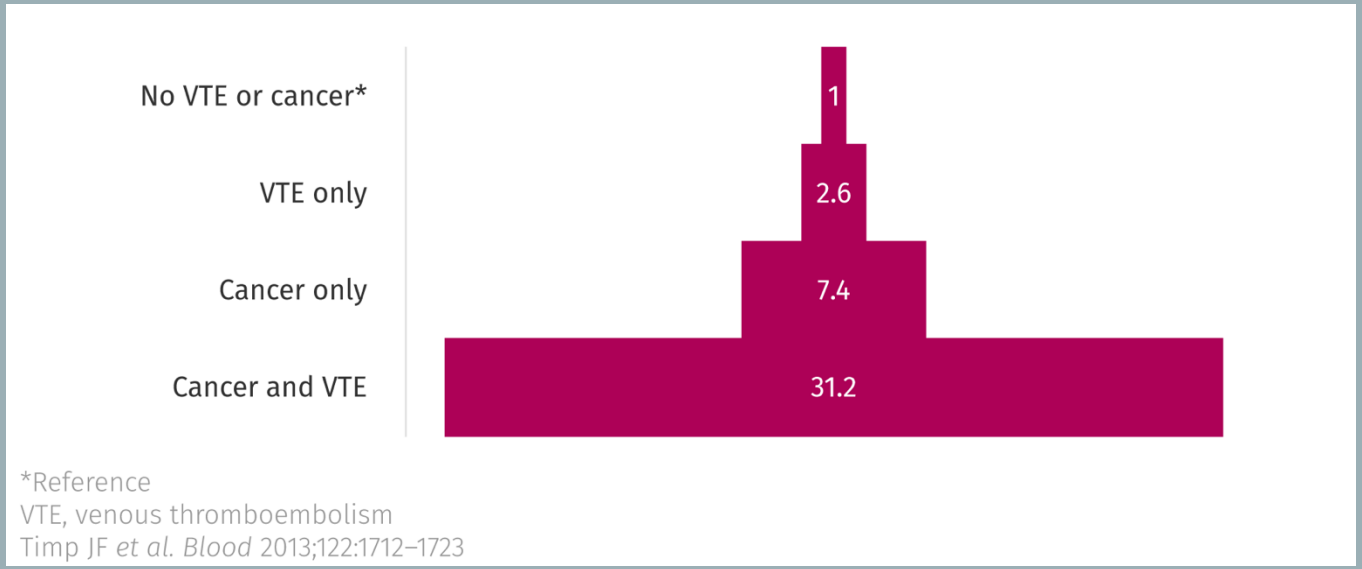
THE EPIDEMIOLOGY OF CANCER ASSOCIATED THROMBOSIS

Cancer accounts for nearly 20% of all VTE cases[1]

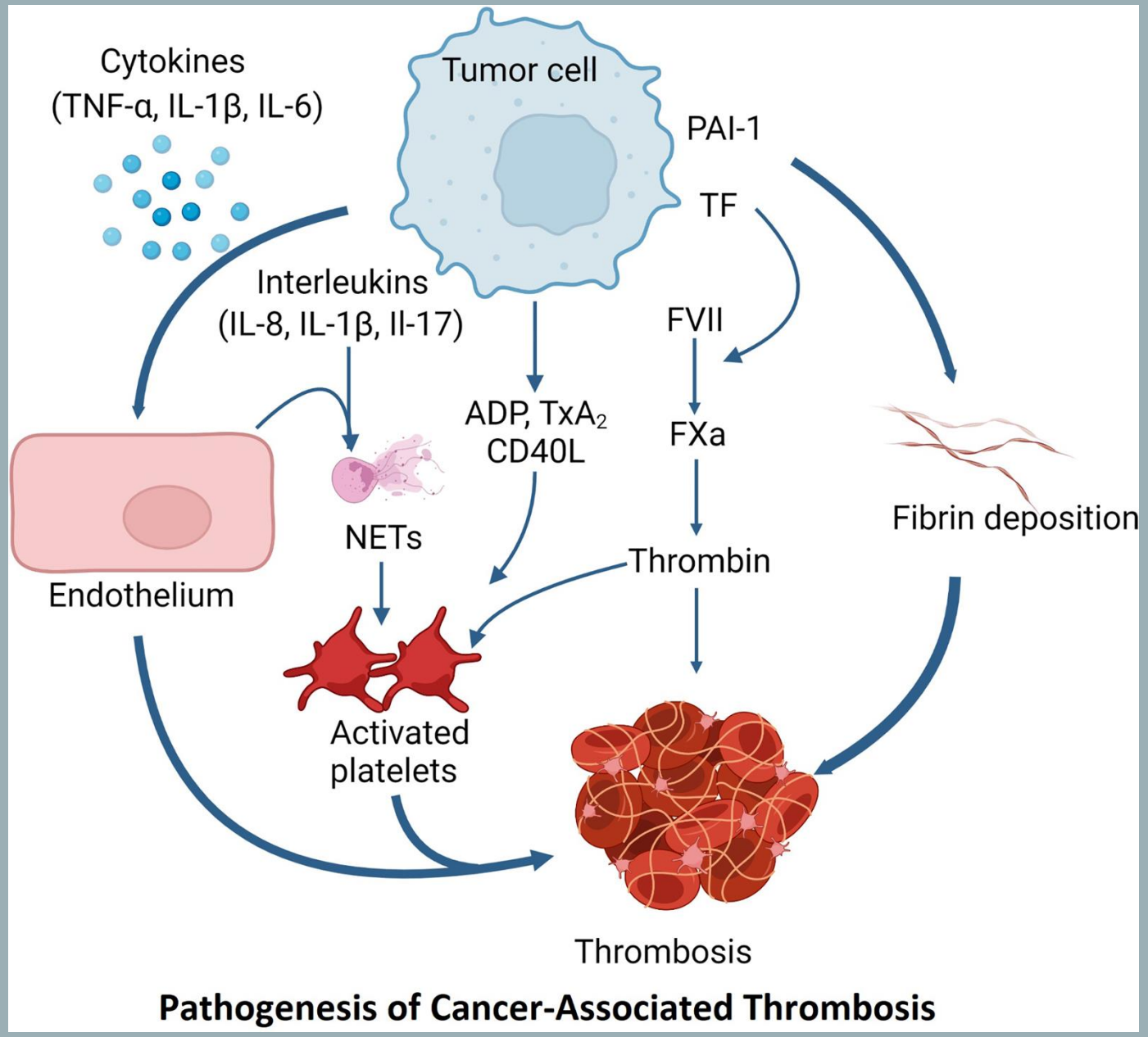
The risk of VTE in cancer patients is is ~5x greater than non-cancer controls[2]

Cancer is a known predictor of mortality in those with VTE[3]



Gender adjusted Hazard ratios of death in participants with and without cancer (The Tromso study 1994-2007)

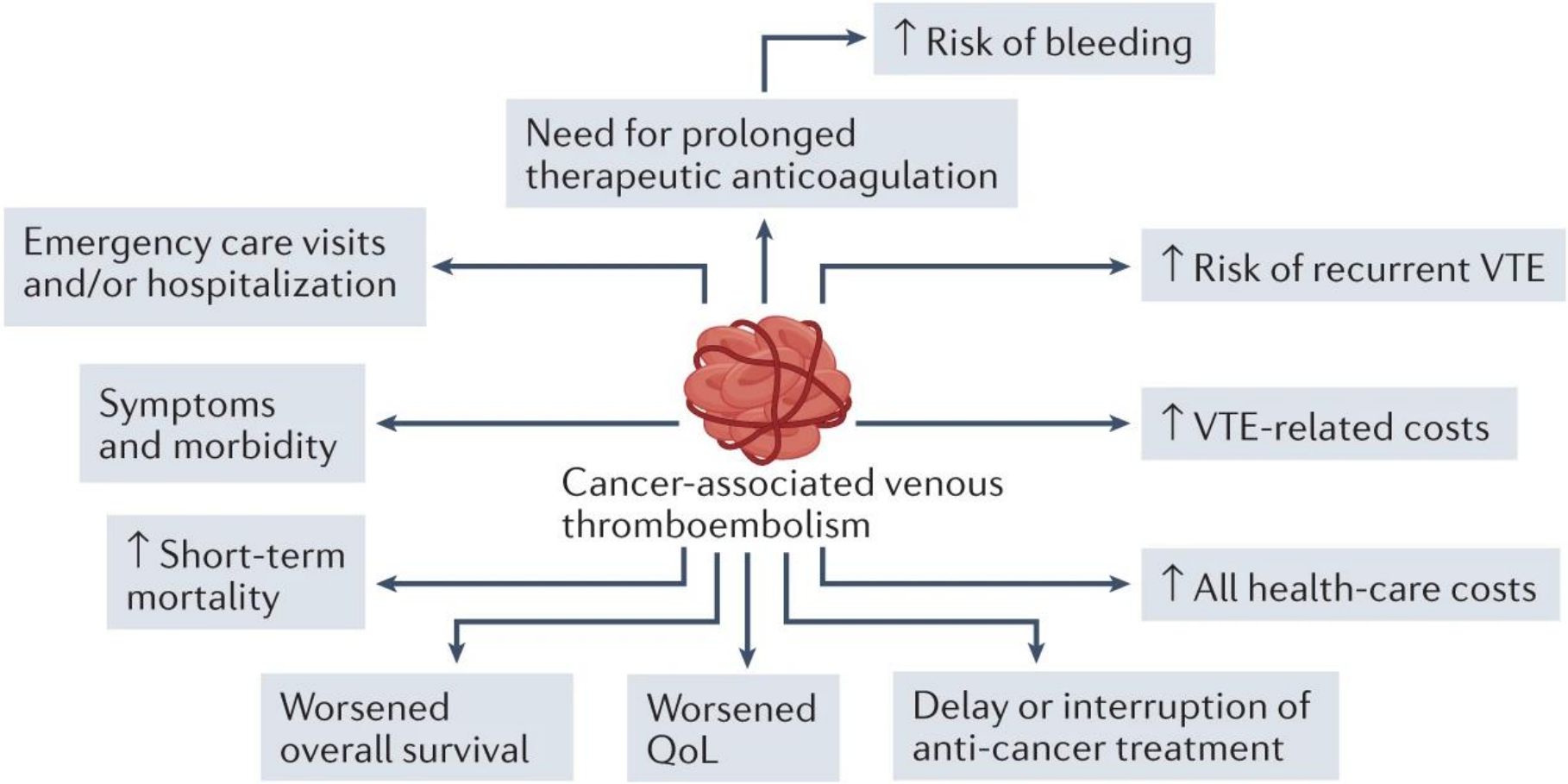
1. Heit JA, et al. Arch Intern Med 2002; 162: 1245–1248.
2. Cronin-Fenton et al. Br J Cancer 2010, 103 947-953
3. Braeken et al. Am J Empidemiology 2010, 171 (p 11069-1115)



Giardi et al. 2023 ATVB, Vol 43 (6):824-31

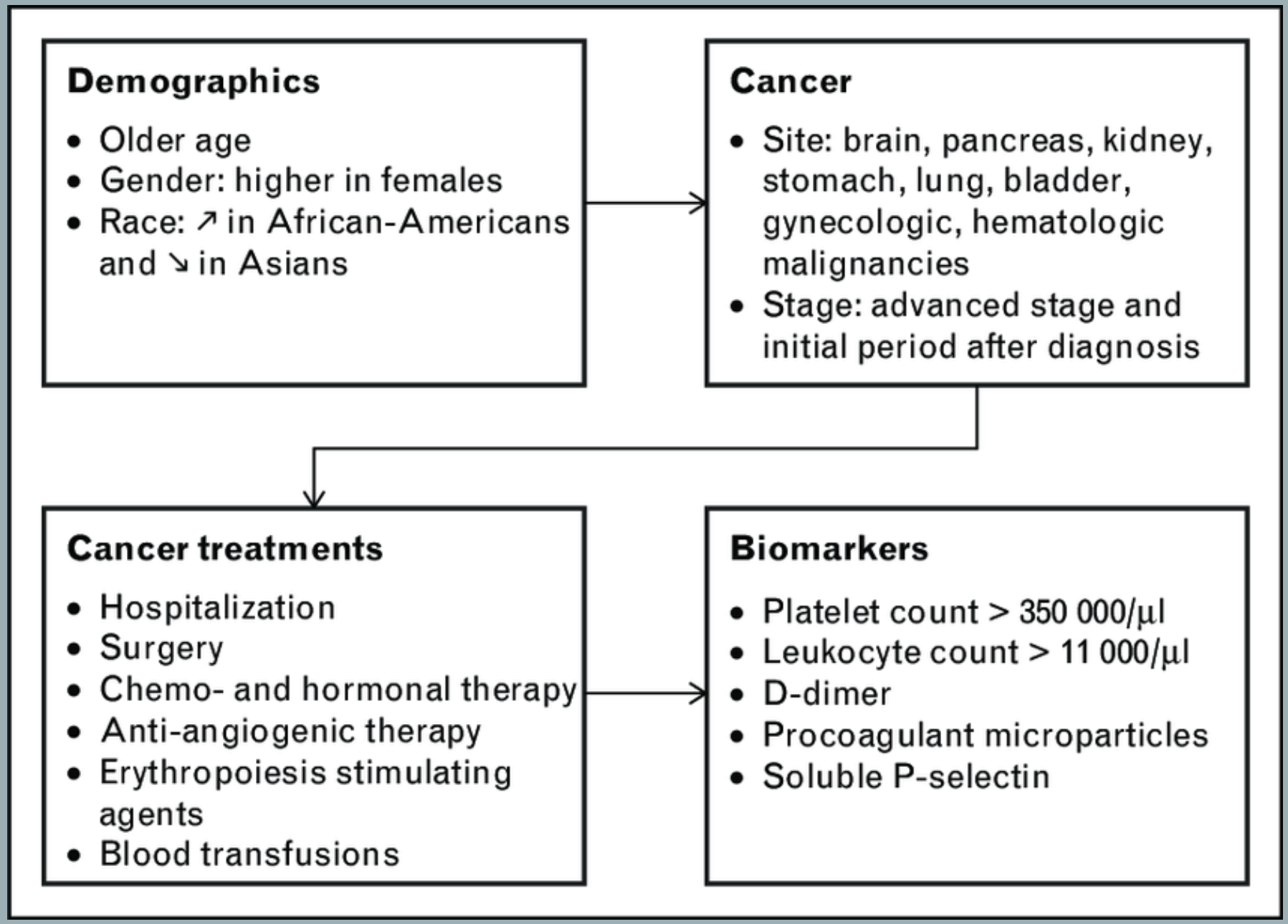
Fig. 1: Consequences of cancer-associated VTE.

From: Cancer-associated venous thromboembolism



The occurrence of cancer-associated venous thromboembolism (VTE) can lead to both direct and indirect consequences, which together add to the clinical burden already being experienced by patients with cancer. QoL, quality of life.

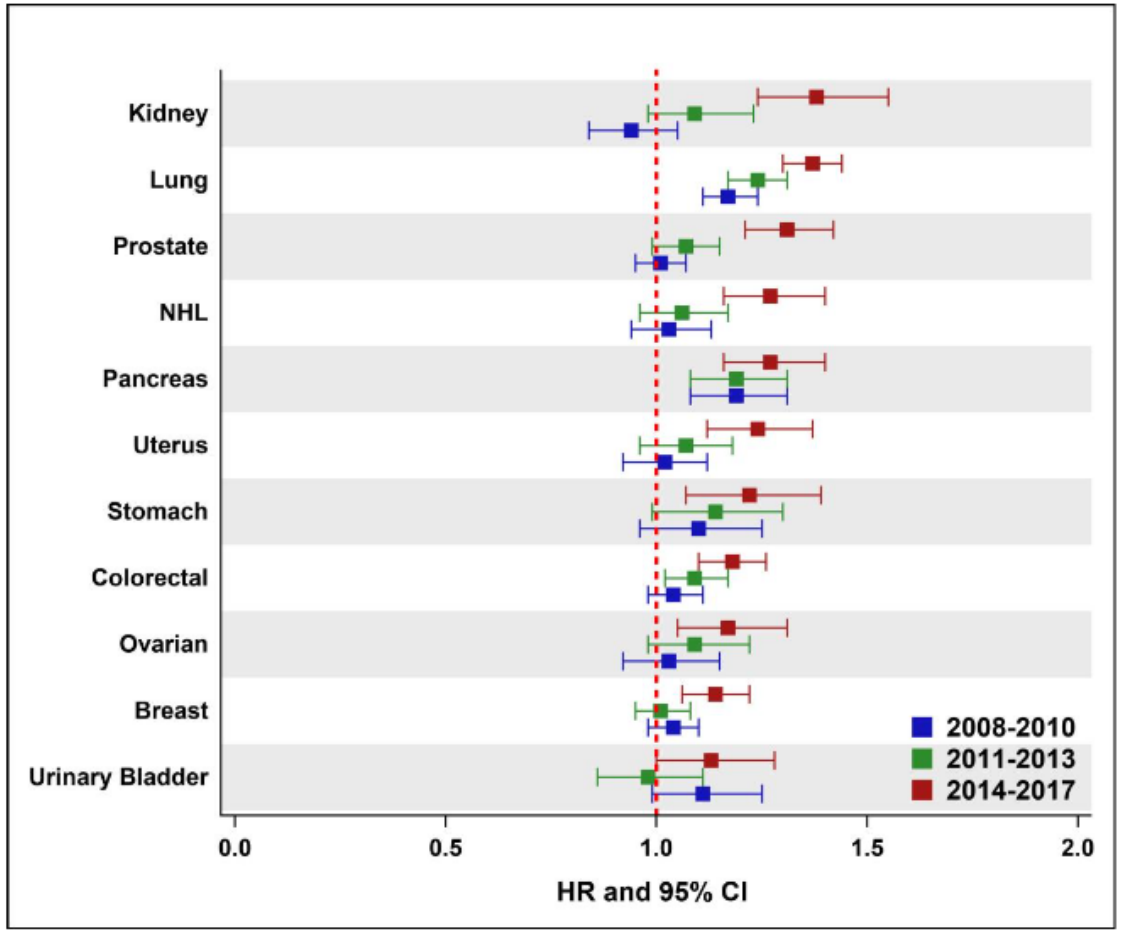
Khorana, A et al. 2022. Nature Rev Dis Primers (8):1 1

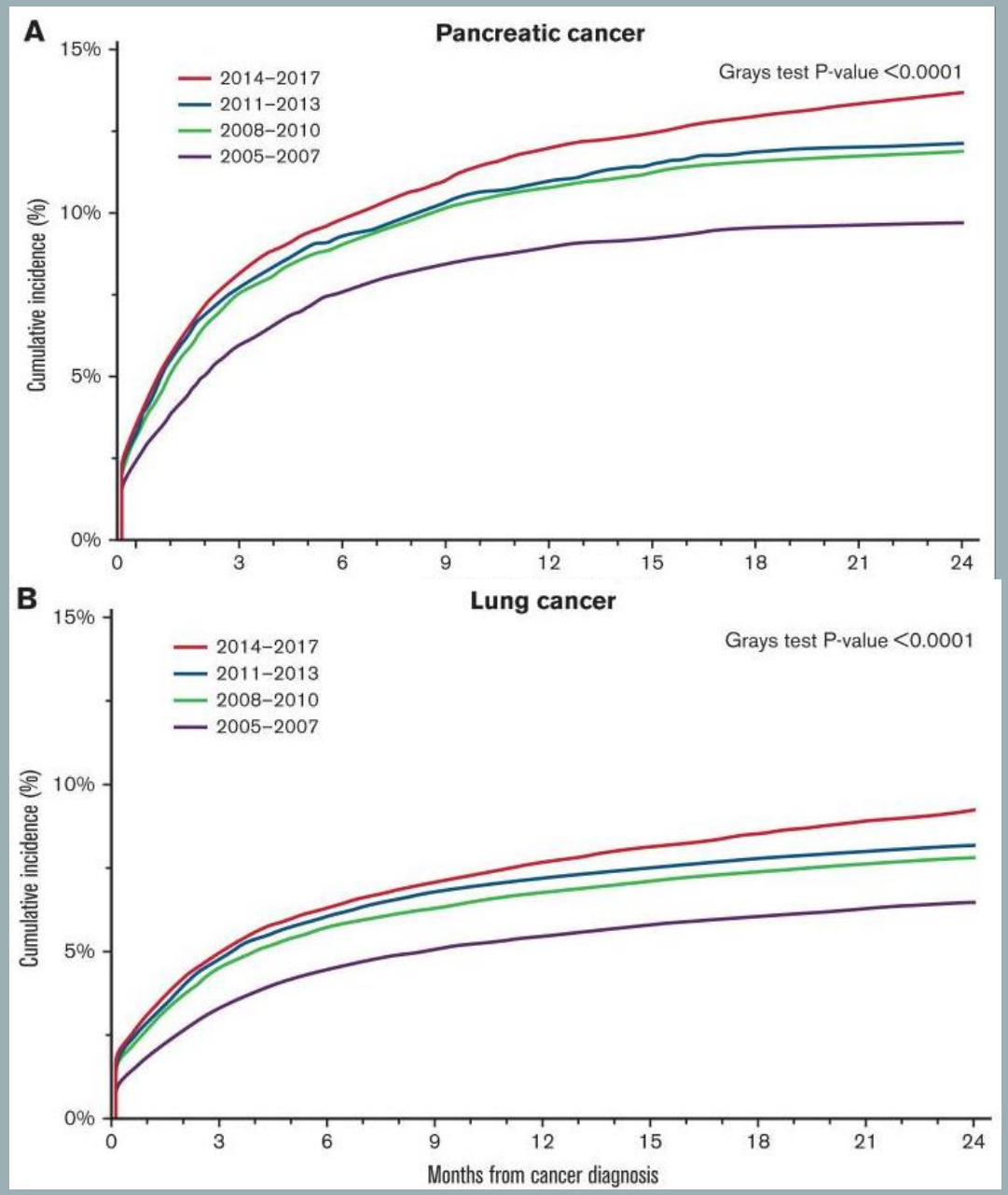


Ay et al. J Thromb and Haemostais, 2017, 117:219-230.

Risk of cancer-associated venous thrombosis (CAT) is increasing over time

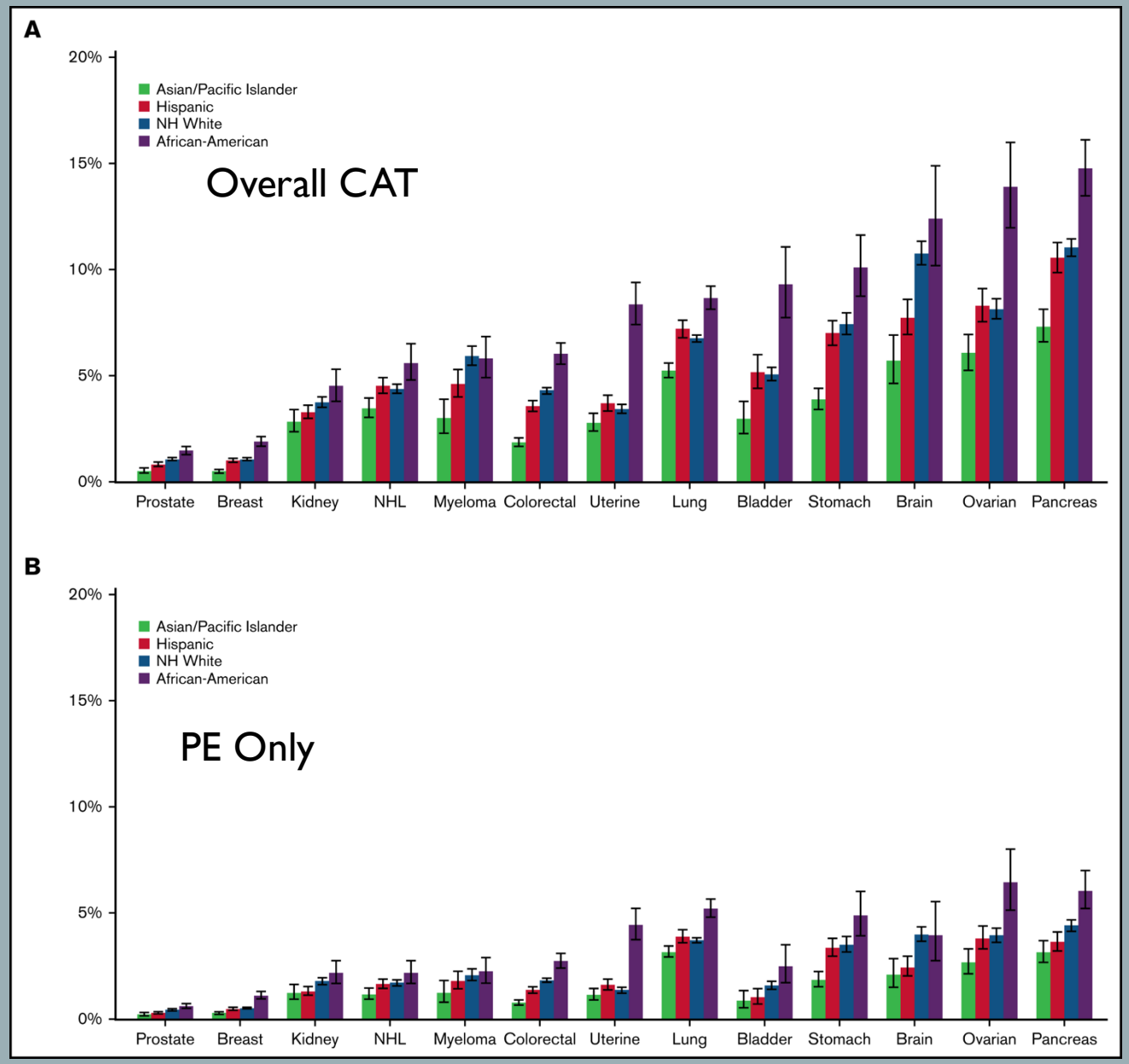
Hazard Ratio for CAT compared to 2005-2007





Mahajan et al, Blood Adv, 2022; 6(1):307-320

Racial disparities in cancer-associated thrombosis



Datta et al, Blood Adv, 2022; 6 (10):3167-77

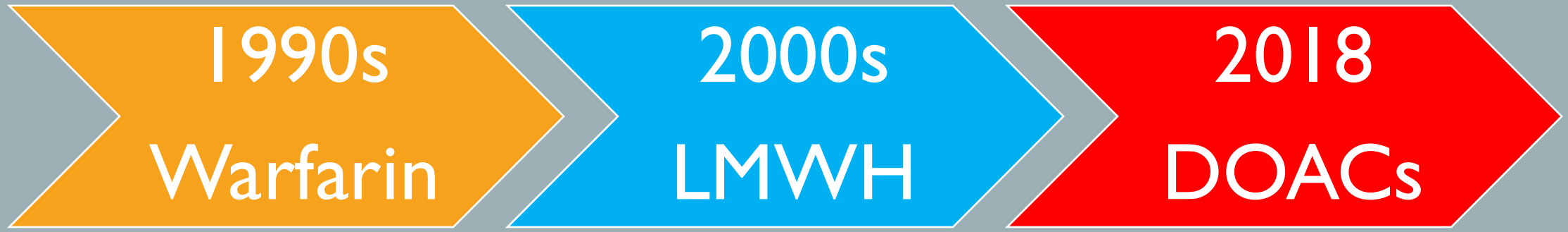
CLINICAL CASE

A 60-year-old woman with stage IV lung adenocarcinoma presents with right lower extremity swelling and pain.

She undergoes a venous duplex which shows thrombosis present in the right femoral vein

Which pharmacologic agent should you choose?

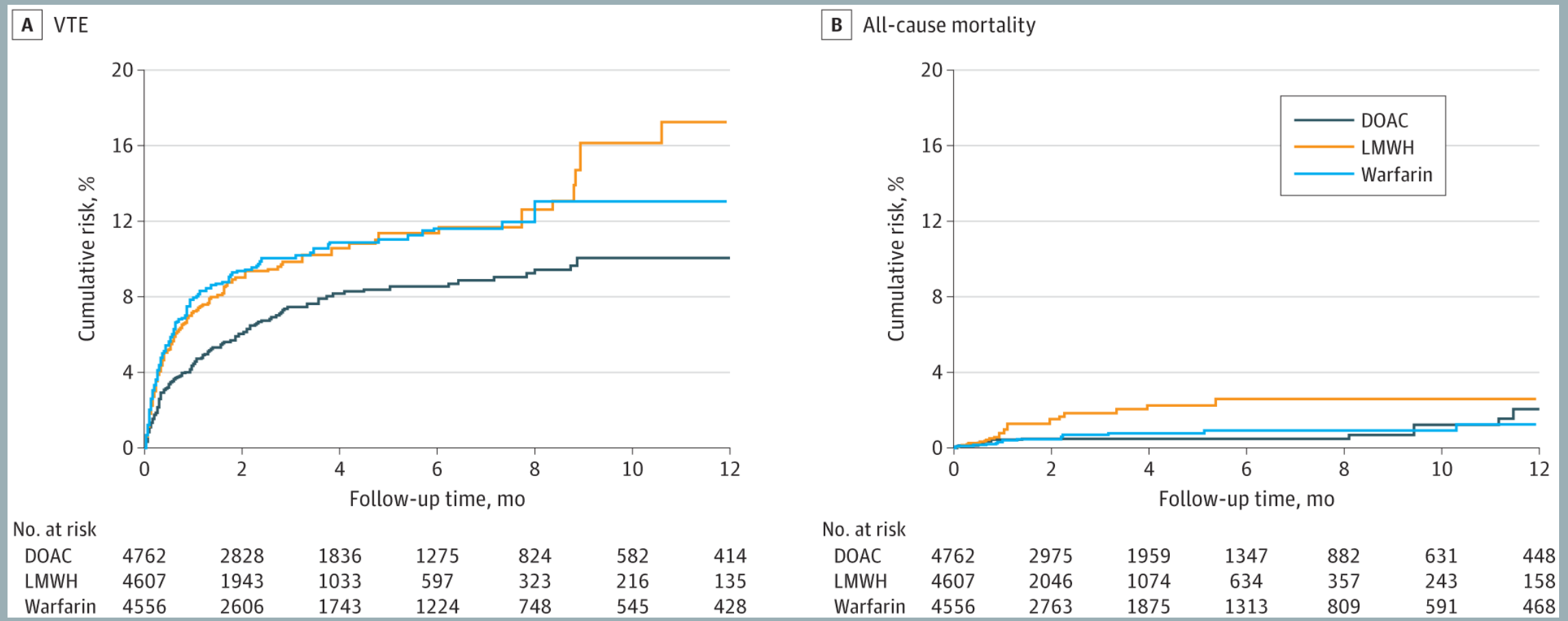
TREATMENT OF CANCER-ASSOCIATED THROMBOSIS



	Hokusai 2018 (Edoxaban)	Select D 2018 (Rivaroxaban)	Caravaggio 2020 (Apixaban)
Recurrent VTE	7.9% Edoxaban vs. 11.3% Dalteparin (HR 0.71; 95% CI 0.42-1.06, p=0.09)	4% rivaroxaban vs. 11% Dalteparin (HR 0.43, 95% CI 0.19-0.99)	5.6% apixaban vs 7.9% Dalteparin (HR 0.63, 95% CI 0.37-1.07; P<0.001)
Major Bleeding	6.9% edoxaban vs. 4.0% Dalteparin (HR 0.77; 95% CI 1.03-3.04, p=0.04) ***Highest bleeding risk in GI malignancy**	6% rivaroxaban vs. 4% Dalteparin (HR 1.83; 95% CI 0.68-4.96) ***Numerically higher rate of CRNM bleeding in rivaroxaban (13% versus 4%; Most bleeding events – GI bleeds)**	3.8% apixaban vs. 4% Dalteparin (HR 0.82, 95% CI 0.40-1.69) ***Excluded patients with brain tumors and included few with upper GI and hematologic cancers**

1. Rasko et al. NEJM. 2018;378:615-624
2. Young et al. J Clin Oncol. 2018; 36(20):2017-2023
3. Agnelli et al. NEJM. 2020; 382:1599-1607

LOWER RISK OF RECURRENT VTE WITH DOACS



Riaz (2023). JAMA Netw Open.;6(7):e2325283

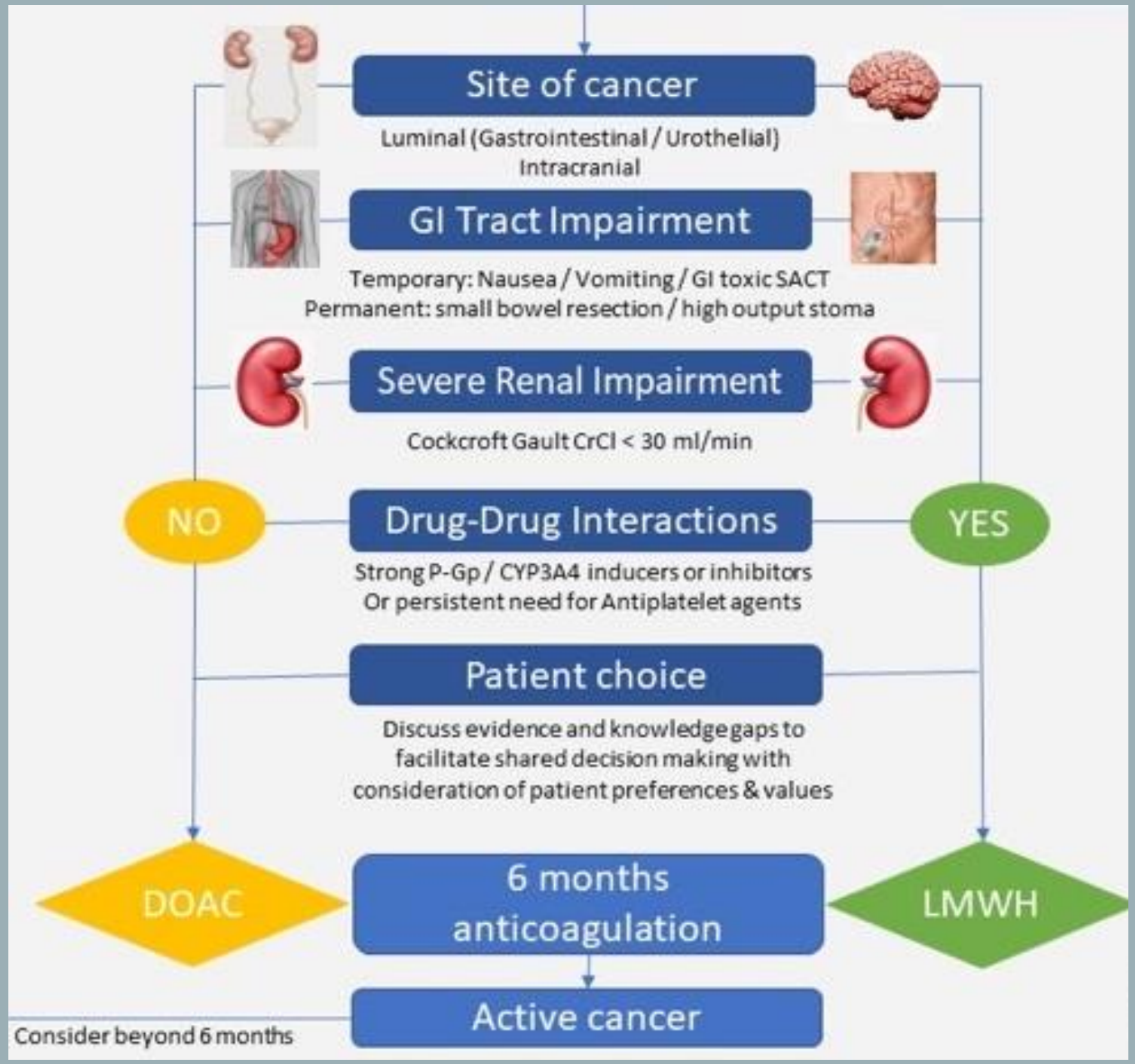
DOACS TO TREAT CANCER-ASSOCIATED THROMBOSIS?

DOACs may cause increased GI bleeding in those with intraluminal upper GI cancer and possibly increase in GU bleeding as well

Comparative effective analysis showed DOACs have lower risk of recurrent VTE

General lack of patients with brain malignancy and metastatic brain lesions in these trials

No head to head trials comparing the different DOACs



Alikhan, R. Res Pract Thromb Haemost. 2022, 6(5):e12747

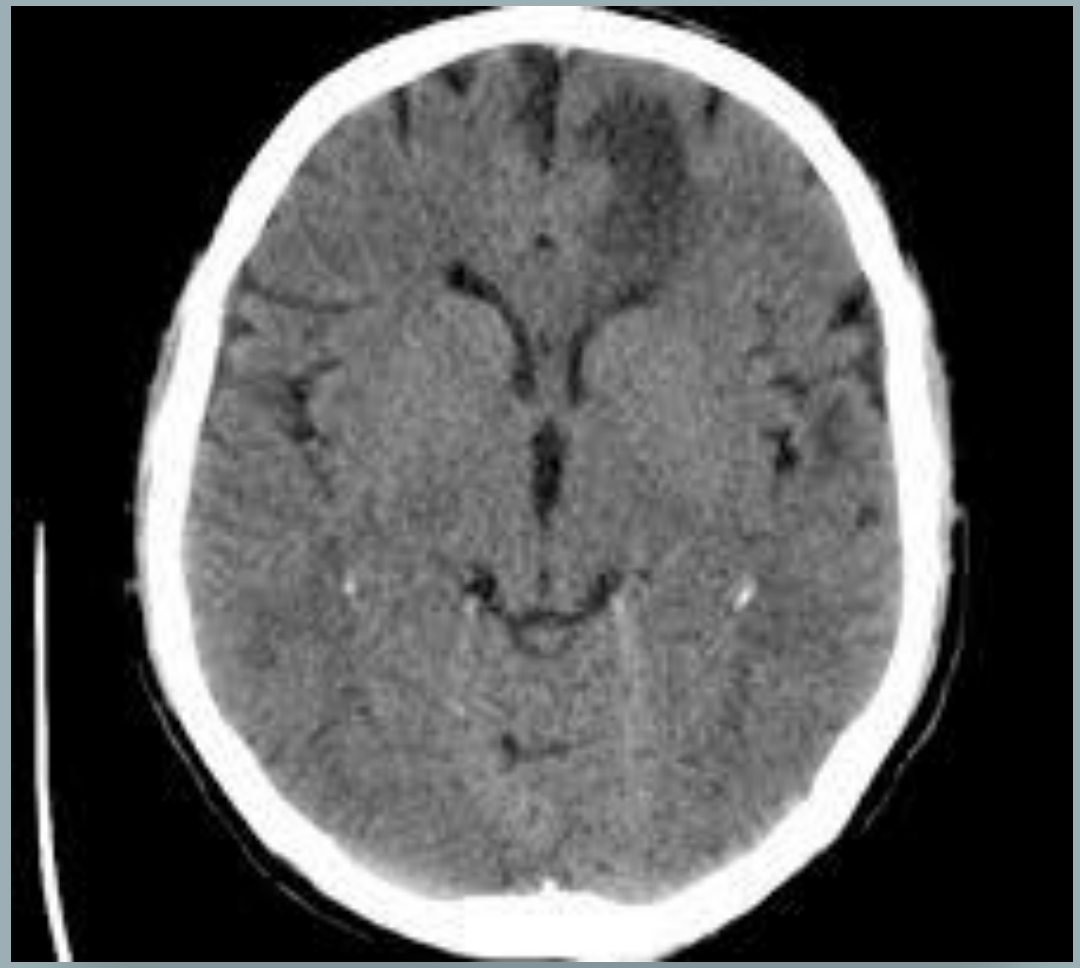
CLINICAL CASE CONTINUED

A 60-year-old woman with stage IV lung adenocarcinoma is diagnosed with cancer-associated thrombosis and is treated with Apixaban 5mg BID for 3 months.

She now presents with confusion and MRI shows metastatic disease

She is referred for radiation therapy

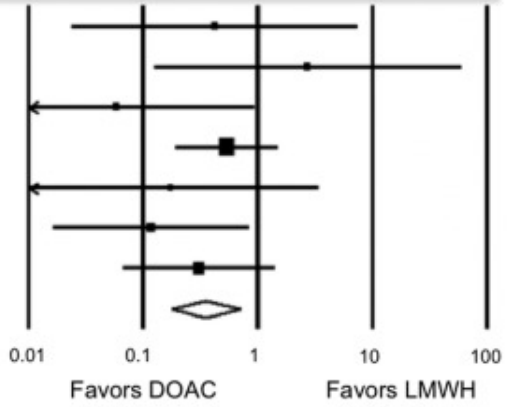
What is recommended for the treatment of CAT in the setting of brain metastases?



DOACS VS LMWH IN PRIMARY BRAIN TUMOR AND METASTATIC BRAIN CANCERS

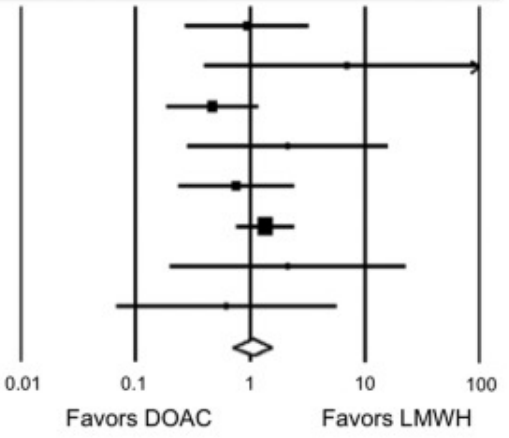
A

Study	DOAC Events	DOAC Total	LMWH Events	LMWH Total	M-H Risk Ratio (95% CI)
Abraham et al. (2018)	0	13	4	52	0.421 (0.024 – 7.358)
Burth et al. (2001)	1	9	0	8	2.700 (0.125 – 58.239)
Carney et al. (2019)	0	20	10	47	0.059 (0.004 – 0.926)
Leader et al. (2023)	4	61	22	179	0.534 (0.191 – 1.487)
Lee et al. (2021)	0	14	2	12	0.173 (0.009 – 3.292)
Reed-Guy et al. (2022	1	32	20	75	0.117 (0.016 – 0.836)
Swartz et al. (2021)	2	44	7	47	0.305 (0.067 – 1.391)
Total					**0.347 (0.175 – 0.690)**



B

Study	DOAC Events	DOAC Total	LMWH Events	LMWH Total	M-H Risk Ratio (95% CI)
Abraham et al. (2018)	4	32	5	38	0.950 (0.278 – 3.243)
Burth et al. (2001)	2	6	0	9	7.143 (0.402 – 127.072)
Carney et al. (2019)	4	21	34	84	0.471 (0.188 – 1.180)
Kewan et al. (2019)	1	7	5	75	2.143 (0.289 – 15.872)
Leader et al. (2020)	4	41	7	55	0.767 (0.240 – 2.445)
Leader et al. (2023)	21	203	23	305	1.372 (0.780 - 2.412)
Lee et al. (2021)	2	41	1	44	2.146 (0.202 – 22.788)
Swartz et al. (2021)	1	8	2	10	0.625 (0.068 – 5.715)
Total					**1.053 (0.711 - 1.560)**



Primary Brain Cancer

Metastatic Brain Cancer

Iyengar et al. 2024. J Thromb Haemost. Voll 22 (2) 432-29

WHAT ABOUT IVC FILTERS?

In a 2017 study among patients with the 10 most common malignancies[1]:

- 30-day mortality and subsequent PE was not decreased with IVCF placement
- IVCF associated with a higher risk of recurrent DVT (HR 2.10, 95% CI 1.53-2.89)

In an updated analysis of patients with melanoma, kidney, breast and lung cancer[2]

- Patients with brain metastases were more likely to receive an IVCF (OR 2.24; 95% confidence interval [CI], 2.01-2.50)
- No association was found between IVCF insertion and 180-day ICH

1. Brunson et al. 2017. Thromb Res.(153):57-64
2. Abrahao et al. 2024. Blood VTH 1(2):100011

TREATING CANCER-ASSOCIATED THROMBOSIS

More data is needed (including randomized trials) to evaluate use of DOACs in patients with CNS tumors (primary and secondary) but retrospective data suggests DOCAs are non-inferior to LMWH (and may reduce ICH in those with primary brain tumors)

If no contraindication to anticoagulation- DO NOT USE AN IVCF

TREATMENT CHALLENGES

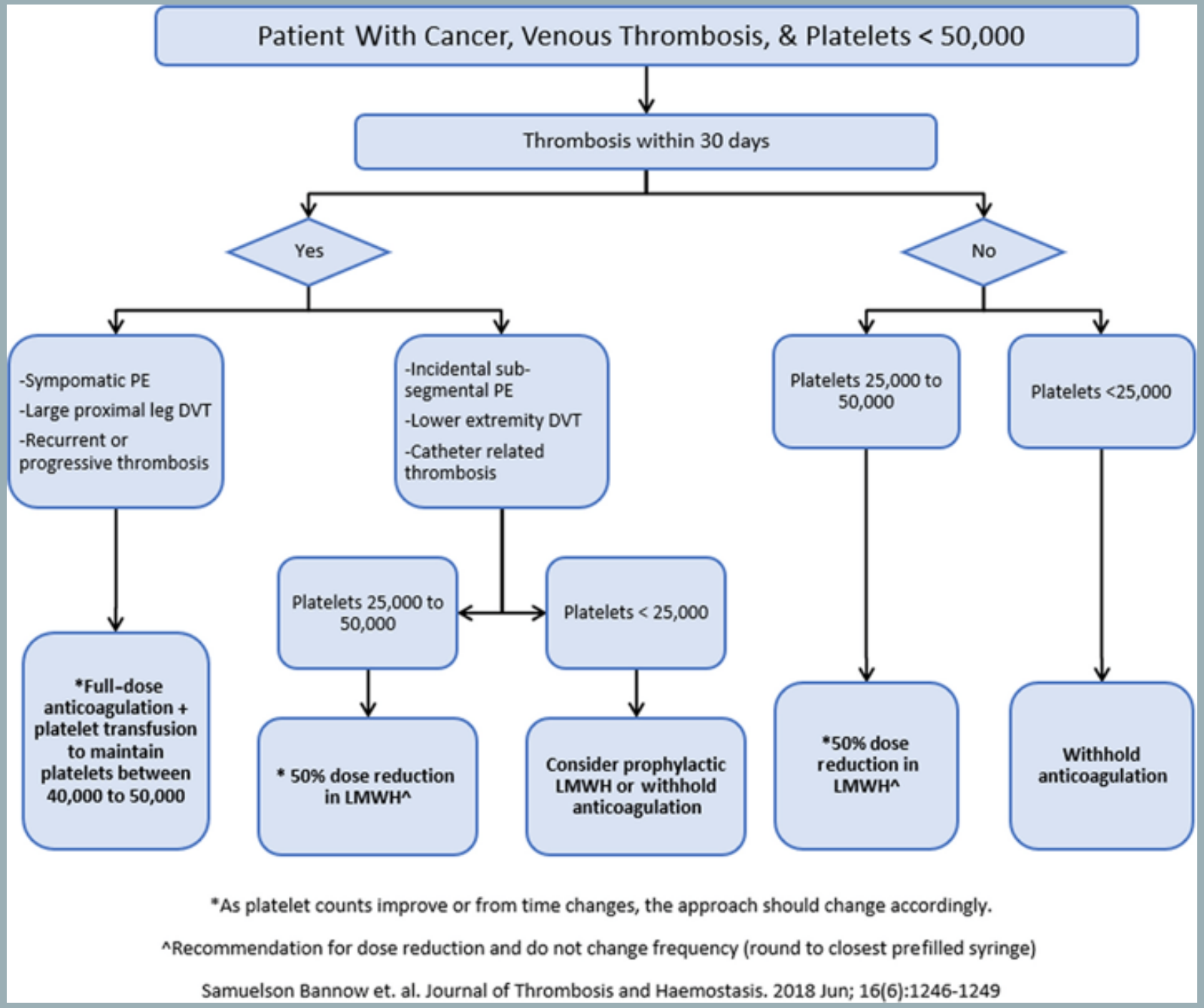
Managing Cancer Associated Thrombosis and Thrombocytopenia

Long term anticoagulation recommendations for those with metastatic cancer

CLINICAL CASE

A 40 yo man with AML admitted to the hospital for consolidation chemotherapy. He develops shortness of breath and a CT Angiogram shows an acute segmental PE.

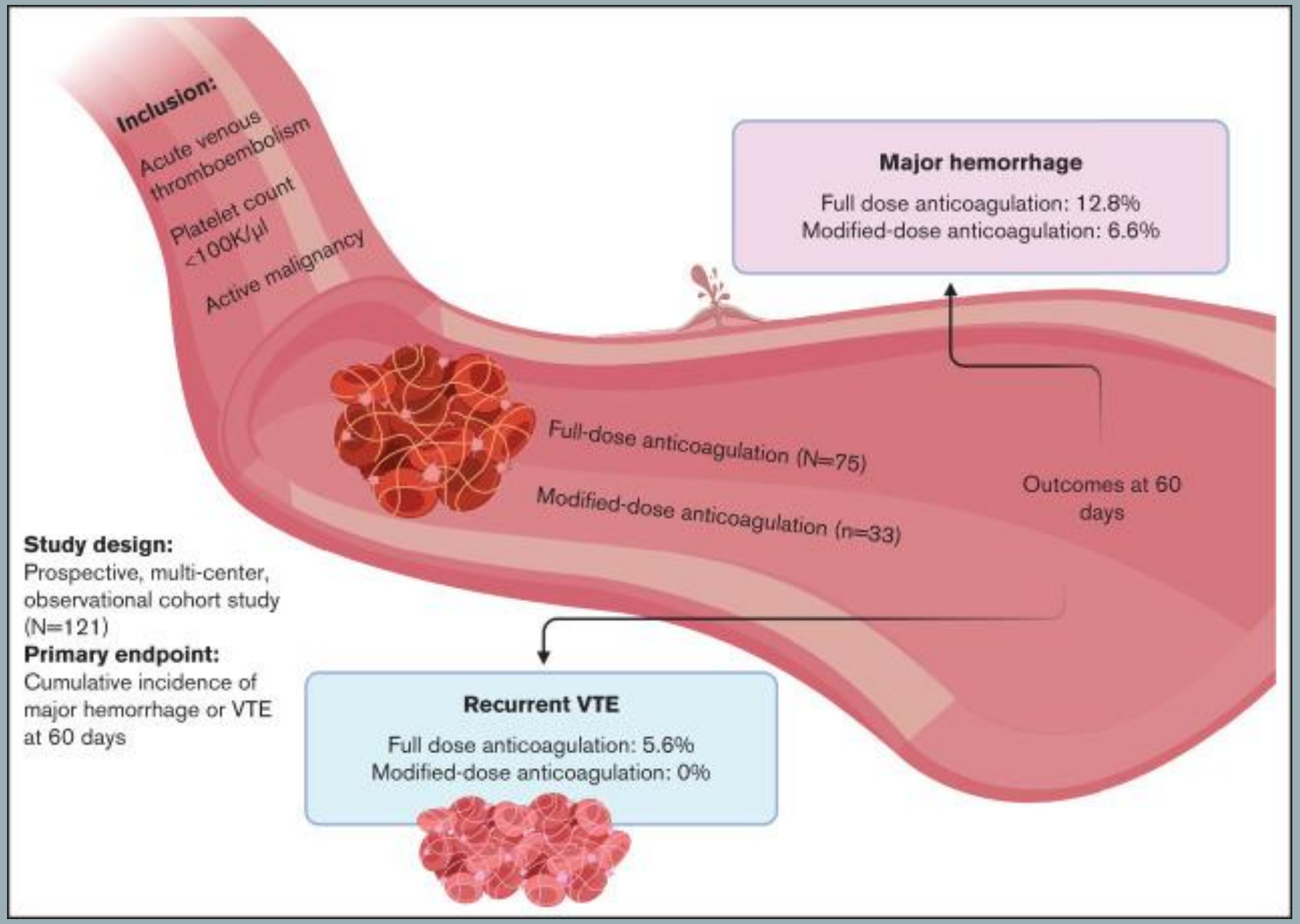
You treat him for 5 days with anticoagulation and then his platelet count drops to 25,000/μL. What do you recommend?



*As platelet counts improve or from time changes, the approach should change accordingly.

^Recommendation for dose reduction and do not change frequency (round to closest prefilled syringe)

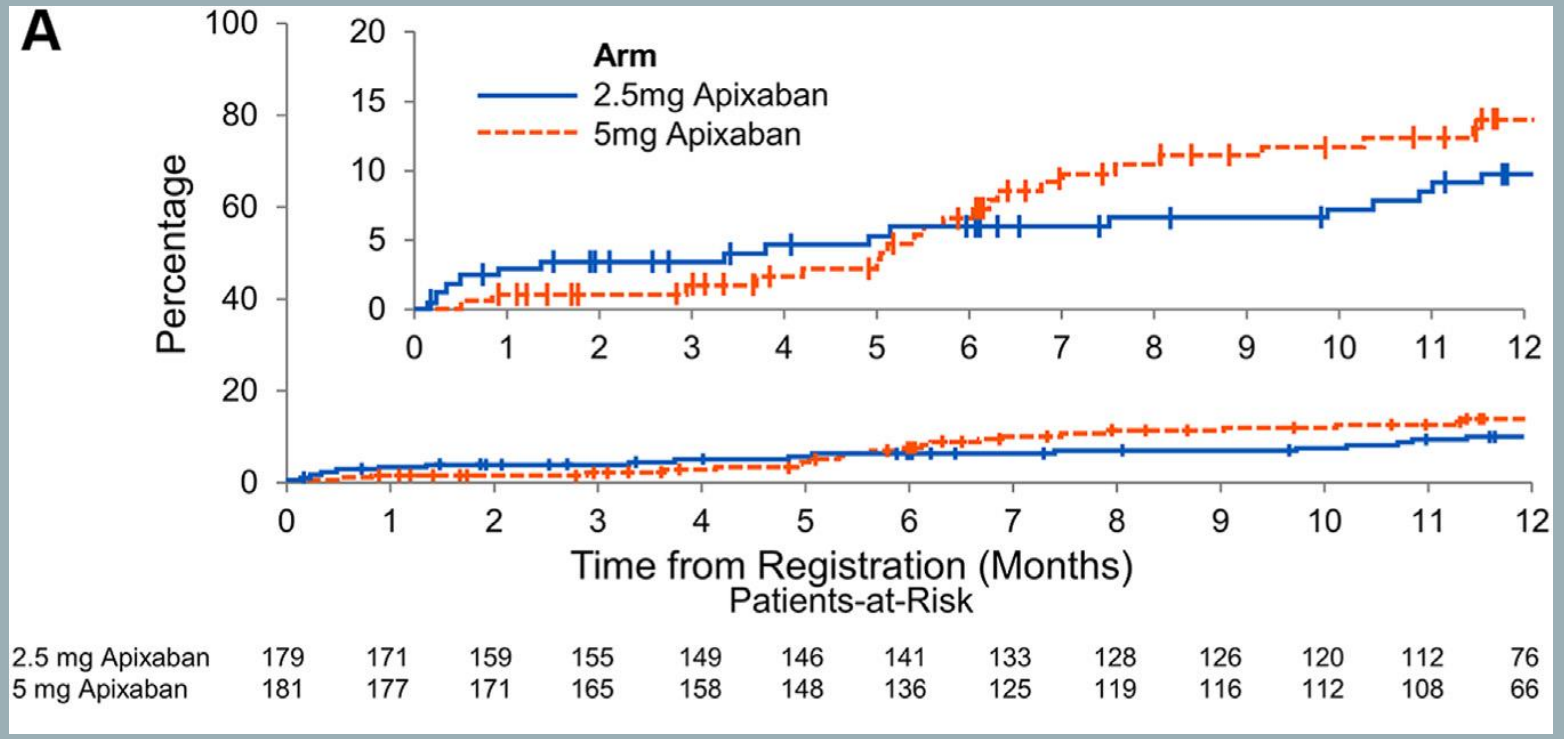
Samuelson Bannow et. al. Journal of Thrombosis and Haemostasis. 2018 Jun; 16(6):1246-1249



Carney et al Blood Adv. 2021(5)24; 5546-5553

What is the optimal dosing for secondary VTE prevention after cancer patients are treated for the minimum 6 months?

Role for low dose DOACs for secondary VTE prevention?



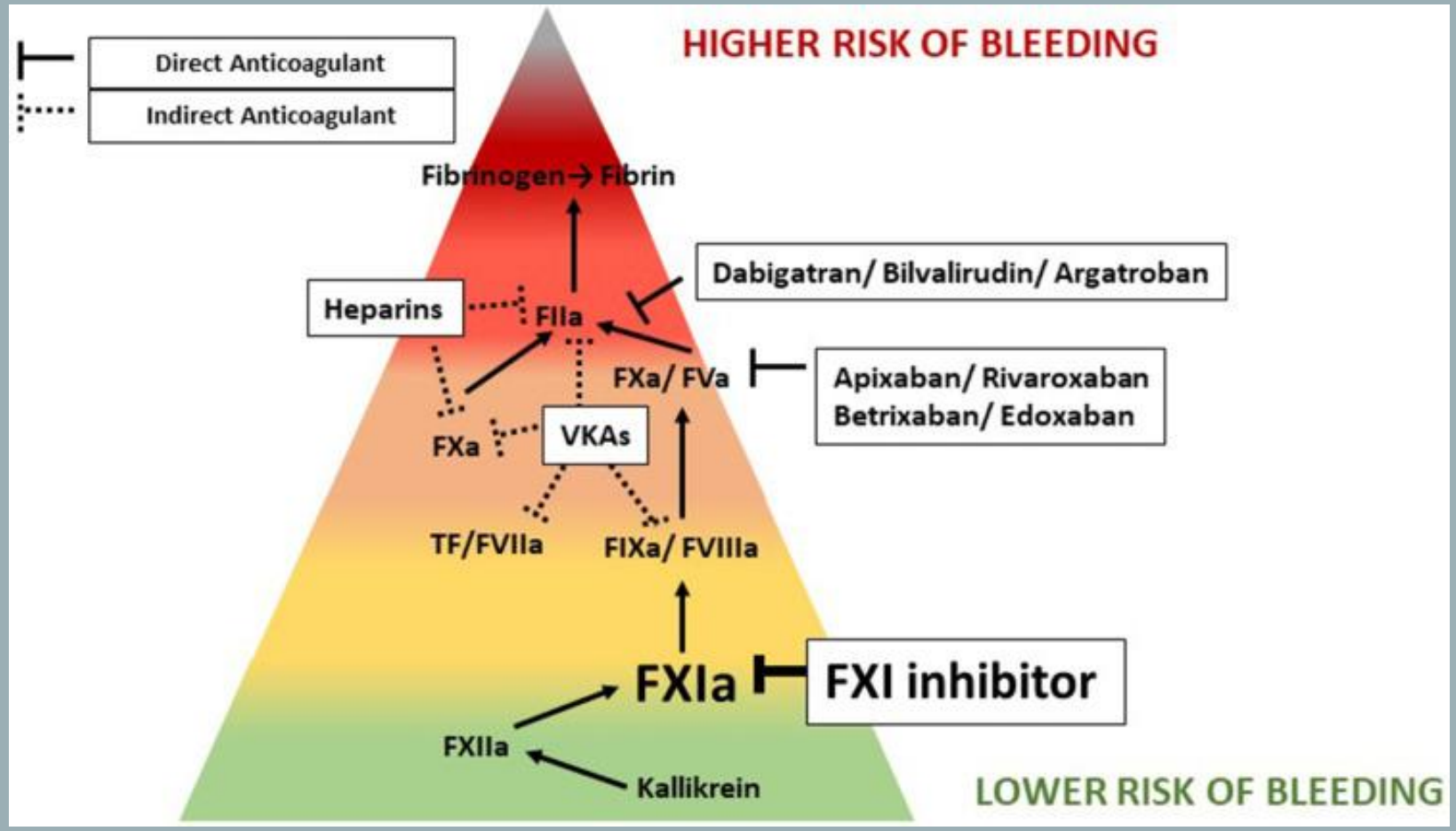
McBane et al. J Thromb Haemost. 2024; 22:1704-14

ON THE HORIZON

- **Better prediction models for cancer associated thrombosis to improve primary prevention**
  - CASSINI and AVERT studies (*NEJM 2019*) showed safety and efficacy of outpatient primary prophylaxis for high-risk cancer patients but this had not been widely adopted in clinical practice
    - Can we better identify high risk patients through implementation science and EMR tools?
    - Health system approach to improve patient education and consider implementing a cancer-associated thrombosis clinic
    - Use of biomarkers to aid in prediction models

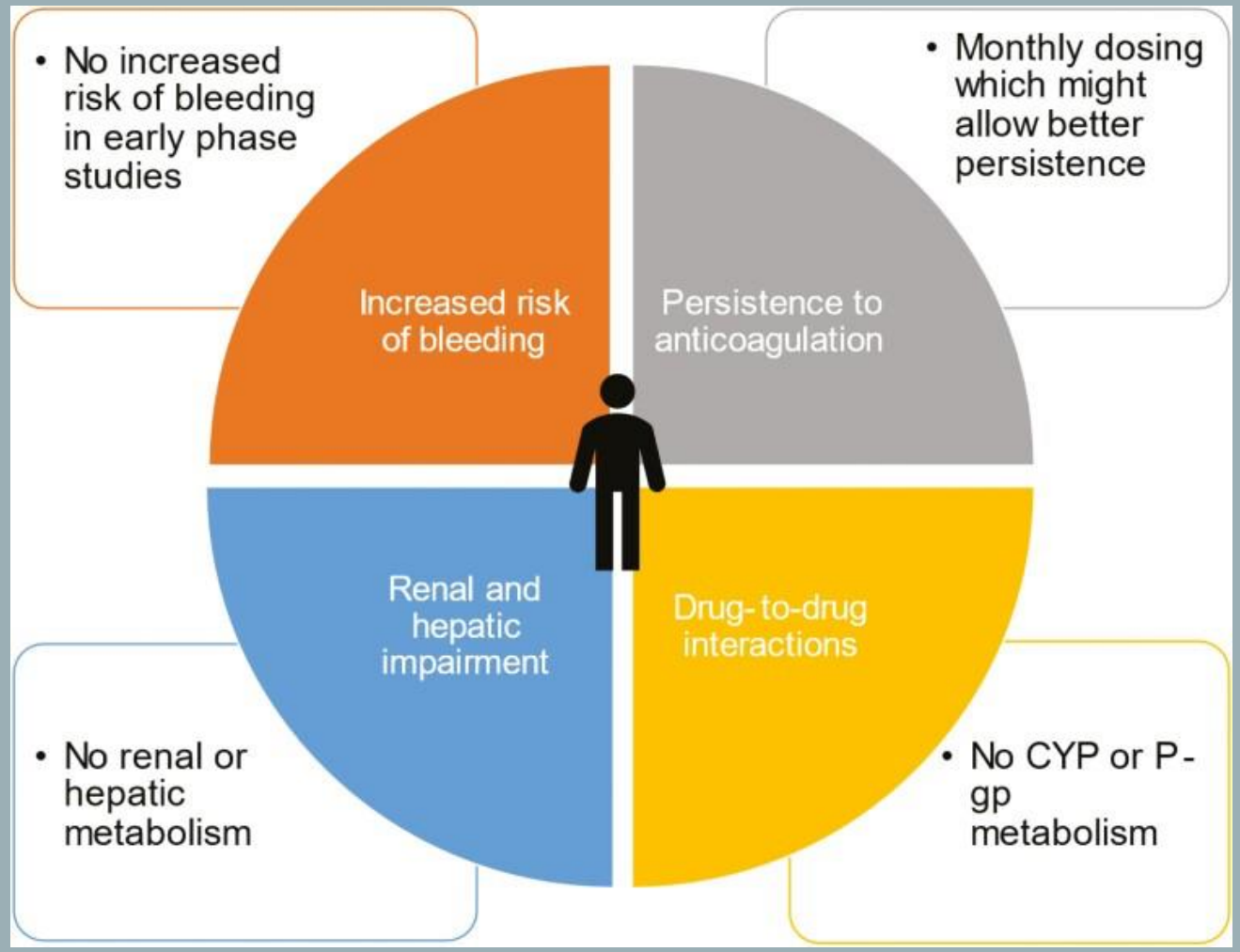
1. Khorana et al. NEJM.2019; 380:720-728
2. Carrier et al. NEJM.2019; 380:711-719

NOVEL THERAPEUTICS TO REDUCE BLEEDING RISK



Fredenburgh and Weitz. *Hematologica* 2021 (2):104-110

FXI INHIBITORS IN CAT



Oncologist 2023 May 12;28(7):555–564