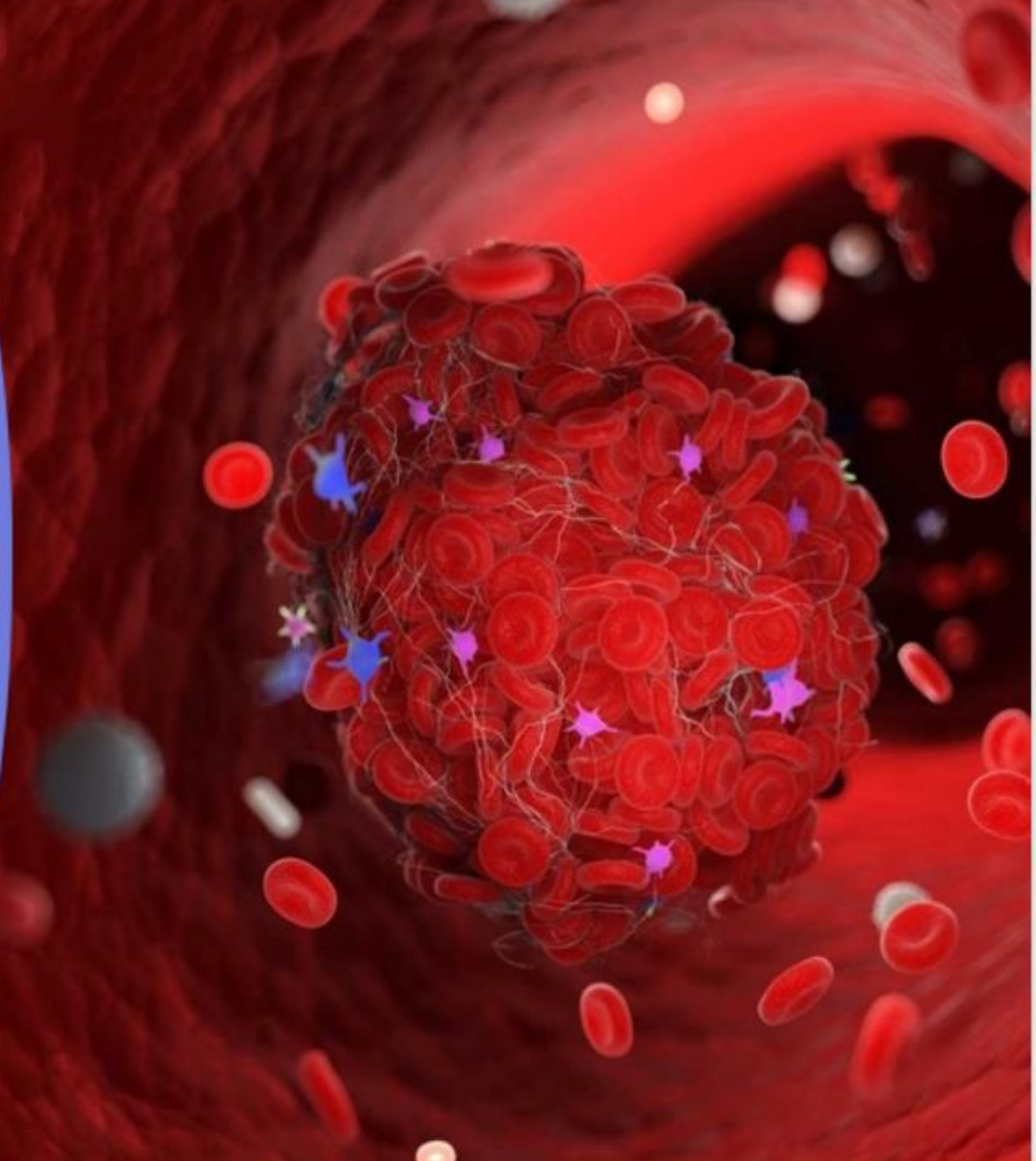

بسم الله الرحمن الرحیم

A Medscape LIVE! EVENT

Approach to the Patient With Cancer-Associated VTE



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CAT-DOACs

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A CASE OF DAILY CLINICAL PRACTICE

- A 67-year-old man receiving palliative chemotherapy for metastatic colon carcinoma is admitted to the acute medical assessment unit complaining of **dyspnea** and **pleuritic chest pain**

- He undergoes a CT pulmonary angiogram (CTPA) which confirms a **pulmonary embolism**

THROMBOSIS AND CANCER

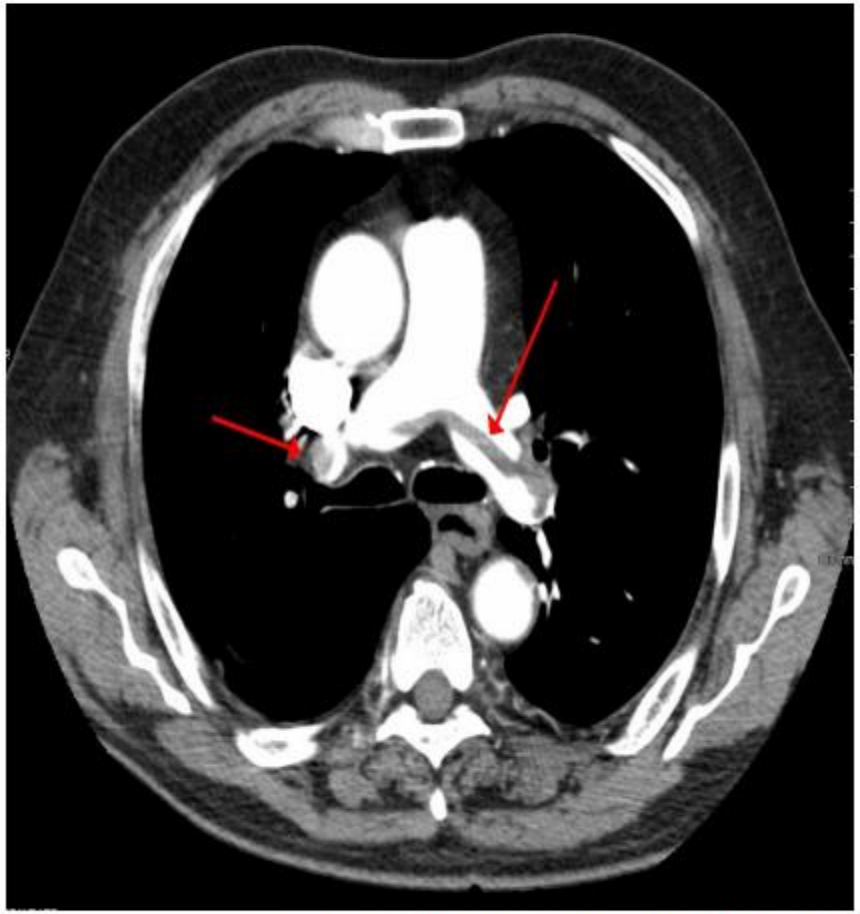
Questions?

1. Why did this occur?
2. What is the influence in patient's prognosis?
3. What is the optimal management of this patient?
4. Should this patient be managed differently if this were an incidental finding?
5. Could this have been prevented?

THROMBOSIS AND CANCER

Question 1

Why did this occur?



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THE LEGACY OF ARMAND TROUSSEAU

Cancer and Venous Thromboembolism (VTE)

(1801–1867)

Professor Armand Trousseau
Lectures in Clinical Medicine

"I have always been struck with the frequency with which cancerous patients are affected with **painful edema** of the superior or inferior extremities…"

New Syndenham Society – 1865

Armand Trousseau first described this finding in the 1860s; he later found the same sign in himself, was subsequently diagnosed with gastric cancer and died soon thereafter.

Clinique Medicale de l'Hotel-Dieu de Paris. 1865;3.

VTE AND CANCER: EPIDEMIOLOGY

Of all cases of VTE:

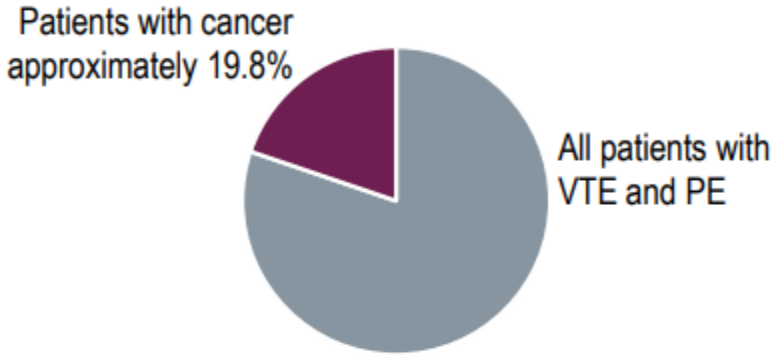
- About 20% occur in cancer patients

Of all cancer patients:

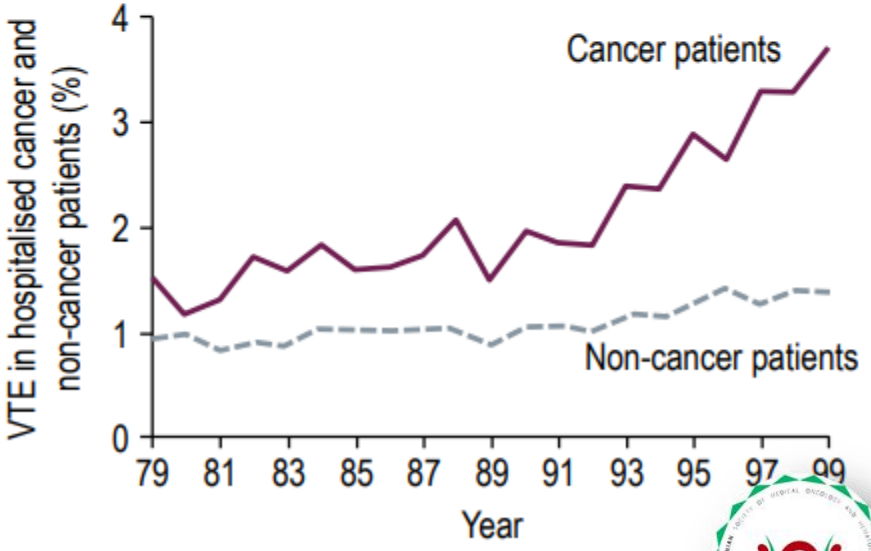
- **20% will have symptomatic VTE**
- 50% have VTE at autopsy

Compared with patients without cancer:[2]

- Higher risk of first and recurrent VTE (3.2-fold)
- Higher risk of bleeding on anticoagulants (2.2-fold)
- Higher risk of dying (2.2-fold)
- VTE is the **second leading cause of death in cancer**
- Incidence of Cancer Associated Thrombosis (CAT) increasing

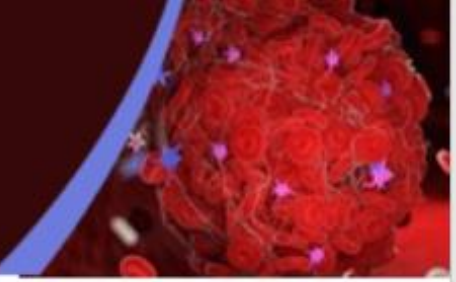


Incidence of VTE in patients hospitalised with cancer increasing significantly compared with non-cancer patients[2,3]



1. Lee AY, Levine MN. Circulation 2003;107:23 Suppl 1:I17–I21;
2. Noble S, *et al.*, Br J Cancer 2010;102:S2–S9; 3. Stein PD, *et al.*, Am J Med 2006;119: 60–68.

Cancer and Thrombosis

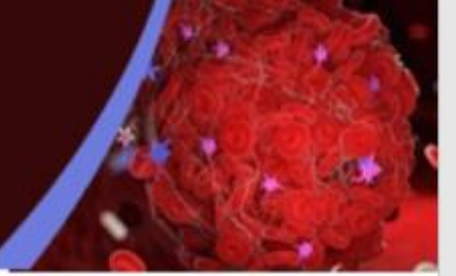


Patients with cancer have an increased risk of thrombosis

- associated with increased morbidity and mortality

Patients with cancer and VTE treated with anticoagulation have an increased risk of both recurrent thrombosis and major bleeding compared to patients without cancer

Risk of Recurrent VTE Versus Major Bleeding

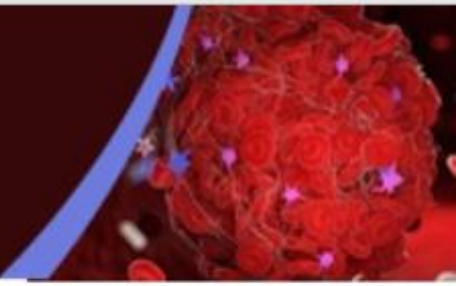


In patients with cancer, the risk of recurrent VTE is greater than the risk of major bleeding despite anticoagulation

- Prandoni[a]
  - 12 month risk of recurrent VTE 20.7% vs major bleeding 12.4%
- RIETE[b]
  - at 3 months, risk of fatal PE 2.6% vs fatal bleed 1.0%

a. Prandoni P, et al. *Blood*. 2002;100:3484-3488. b. Monreal M, et al. *J Thromb Haemost*. 2006;4:1950-1956.

Risk of Recurrent VTE Versus Major Bleeding



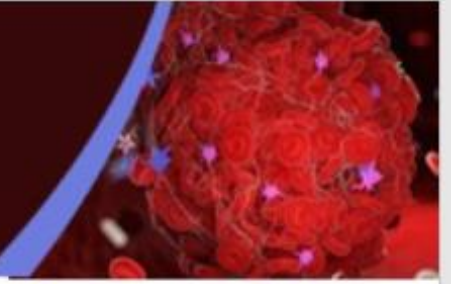
Despite advances in anticoagulants, incidence of bleeding remains higher in patients with cancer than without cancer, no matter which anticoagulant is used in this large health systems data analysis:

- Warfarin 20.2% vs 12.6%
- Rivaroxaban 16.7% vs 12.1%
- LMWH 13.2% vs 9.7%
- Apixaban 14.5% vs 9.3%,
  - $P < .001$ for all comparisons

Dedicated RCT in patients with cancer required to accurately assess DOAC

Angelini DE, et al. *Am J Hematol*. 2019;94:780-785.

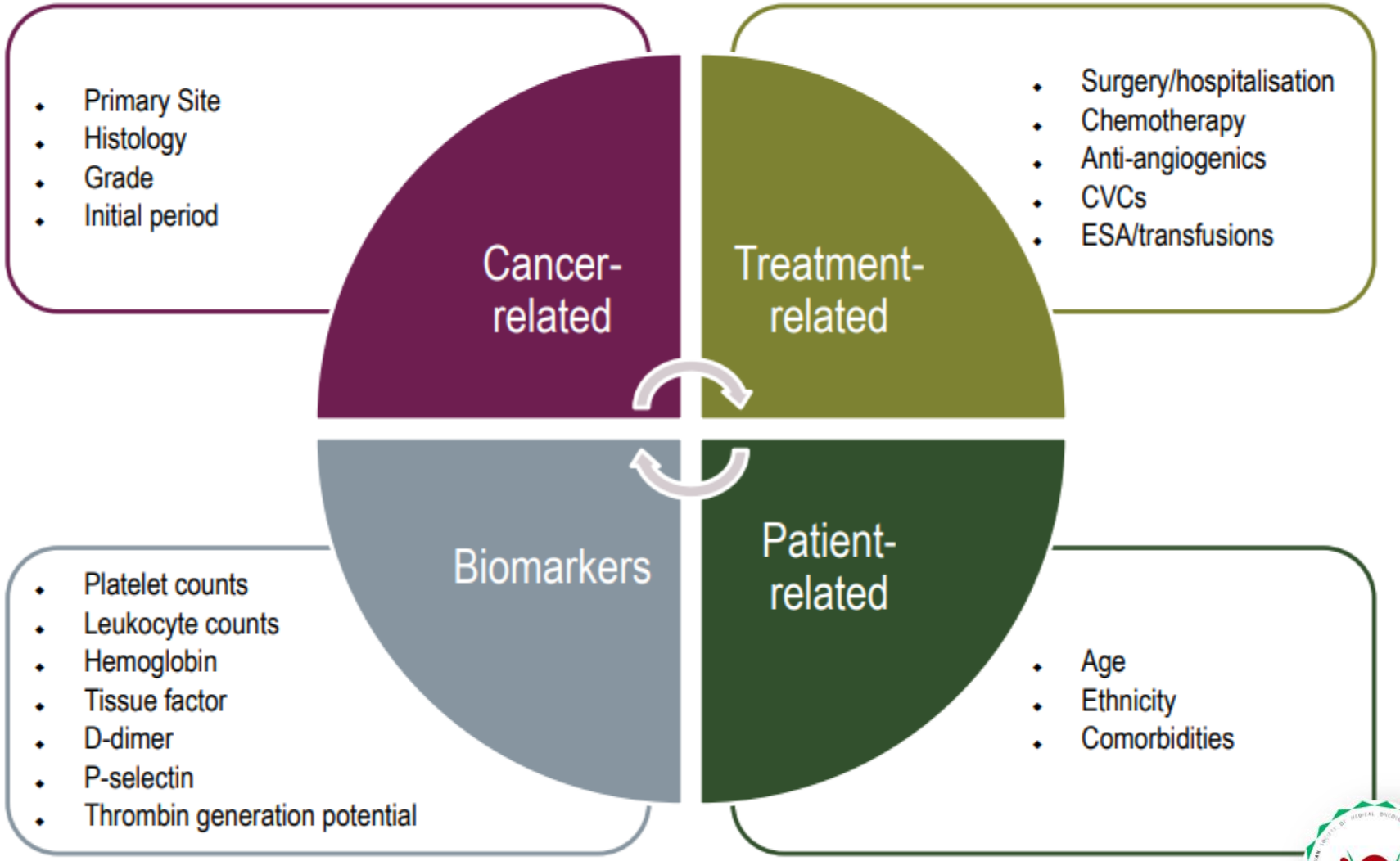
Thromboembolism and Cancer



LMWH has been the gold standard for acute treatment of VTE since publication of the CLOT trial 2003

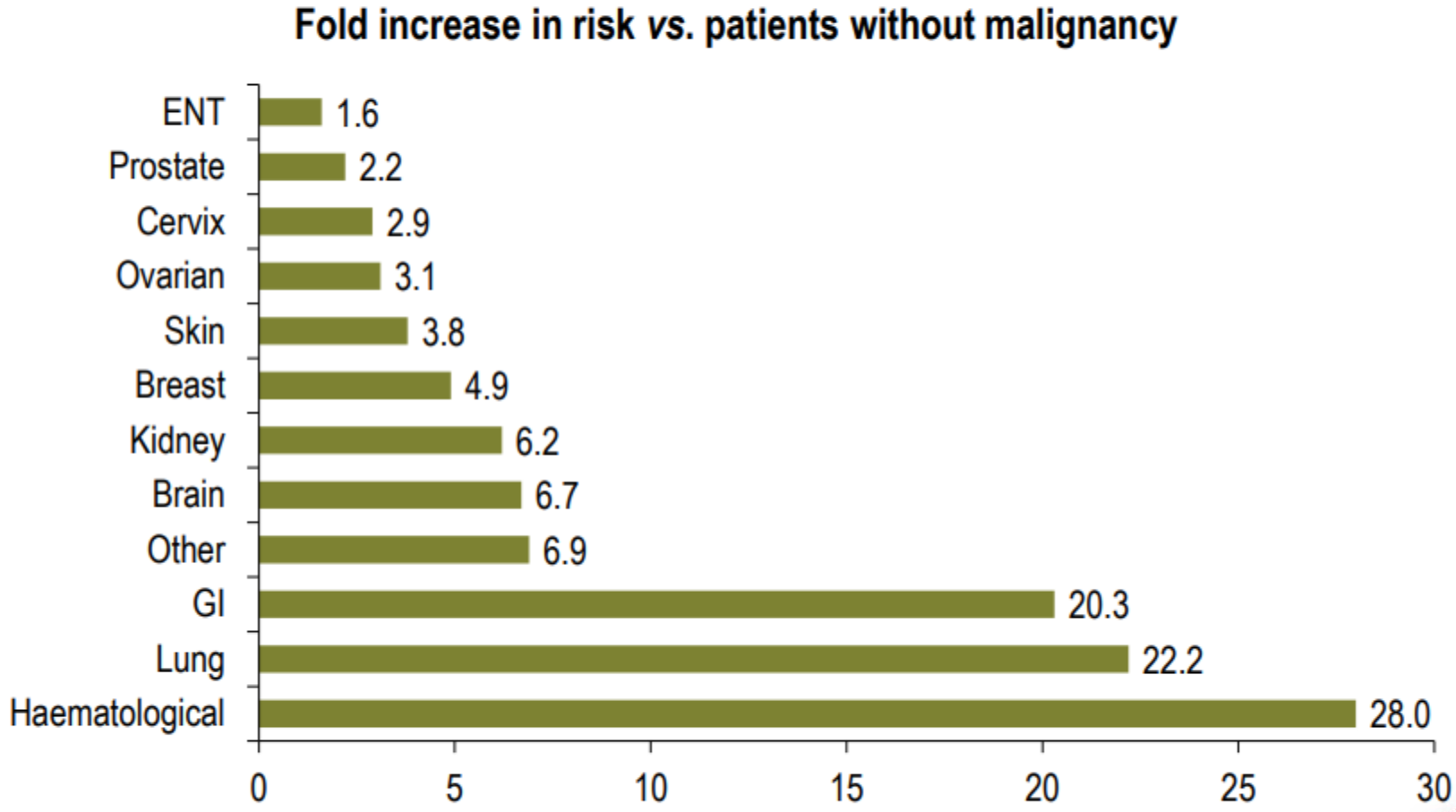
Data for DOAC use in cancer patients with VTE are now available as of December 2017

RISK FACTORS



Khorana presentation in HeSMO Conference 2017, Athens

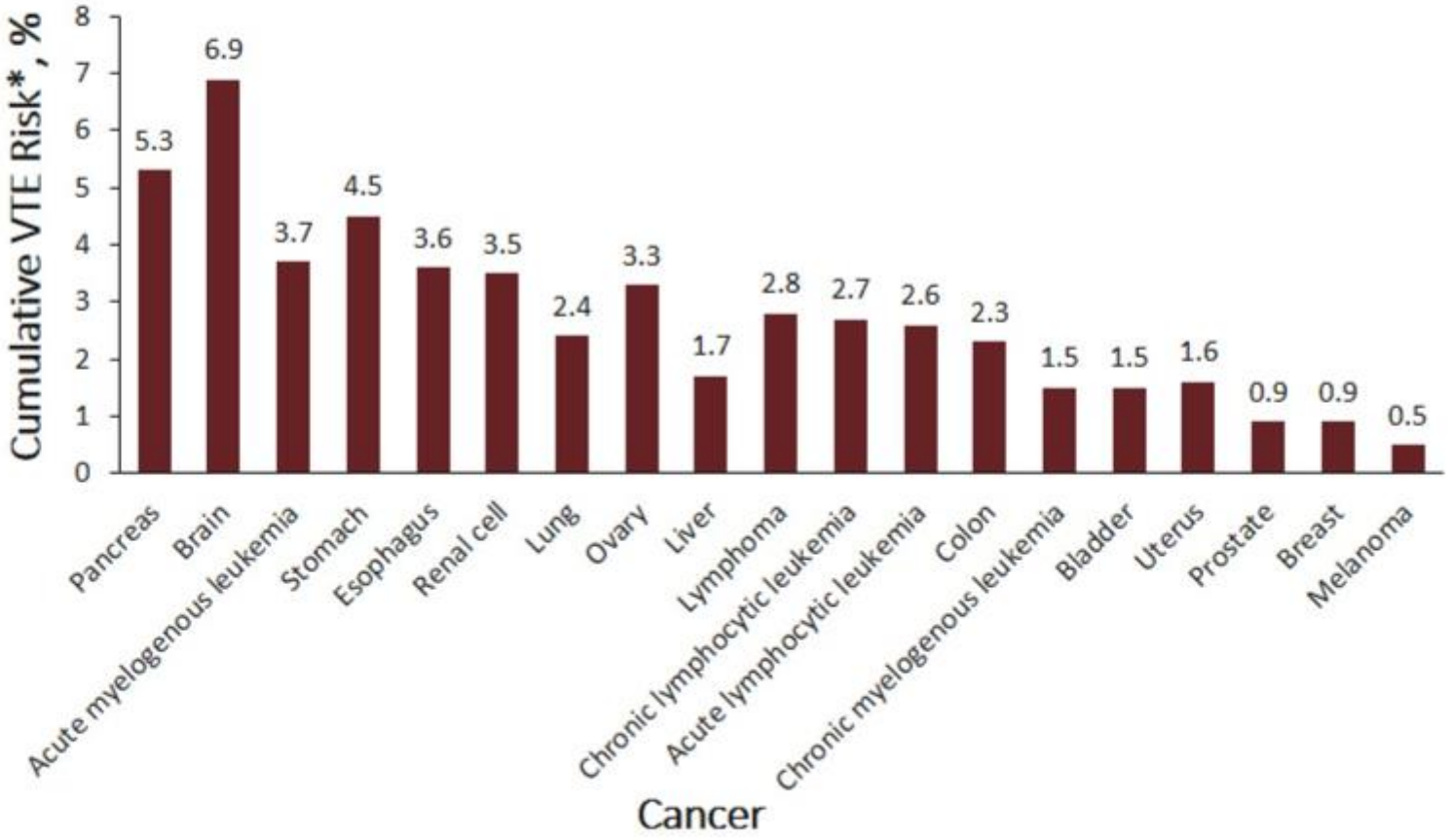
RISK FOR VTE BY TYPE OF MALIGNANCY



Lyman GH, *et al.*, J Clin Oncol 25:5490–5505; Blom JW, *et al.*, JAMA 2005;293:715–22.

VTE According to Cancer Type

- For the majority of cancers, VTE risk is further increased when the tumor is metastatic



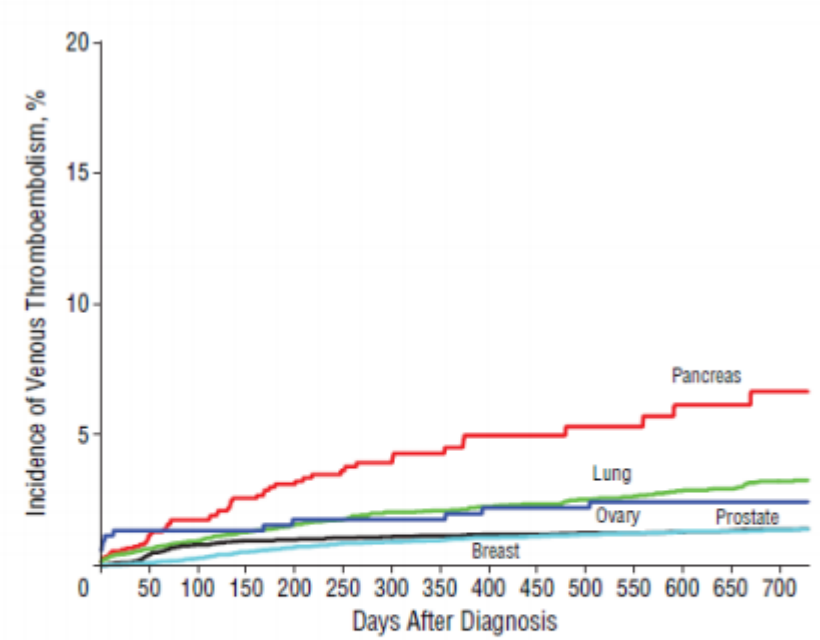
*In the US (California).

Wun T, et al. *Best Pract Res Clin Haematol*. 2009;22:9-23.

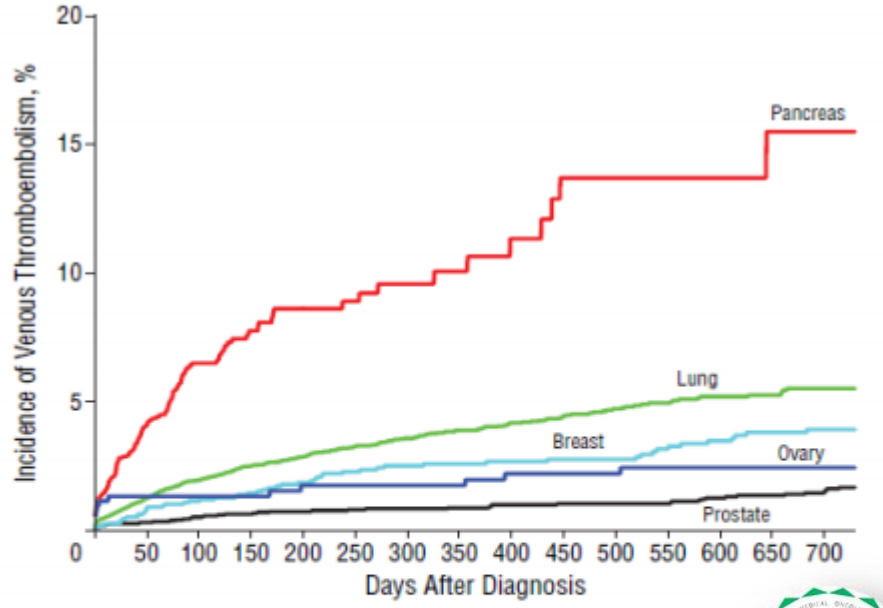
VTE WITHIN 2 YEARS OF DIAGNOSIS OF 5 DIFFERENT TYPES OF CANCER

(235,149 cancer cases)

Regional-stage
disease at the time of diagnosis

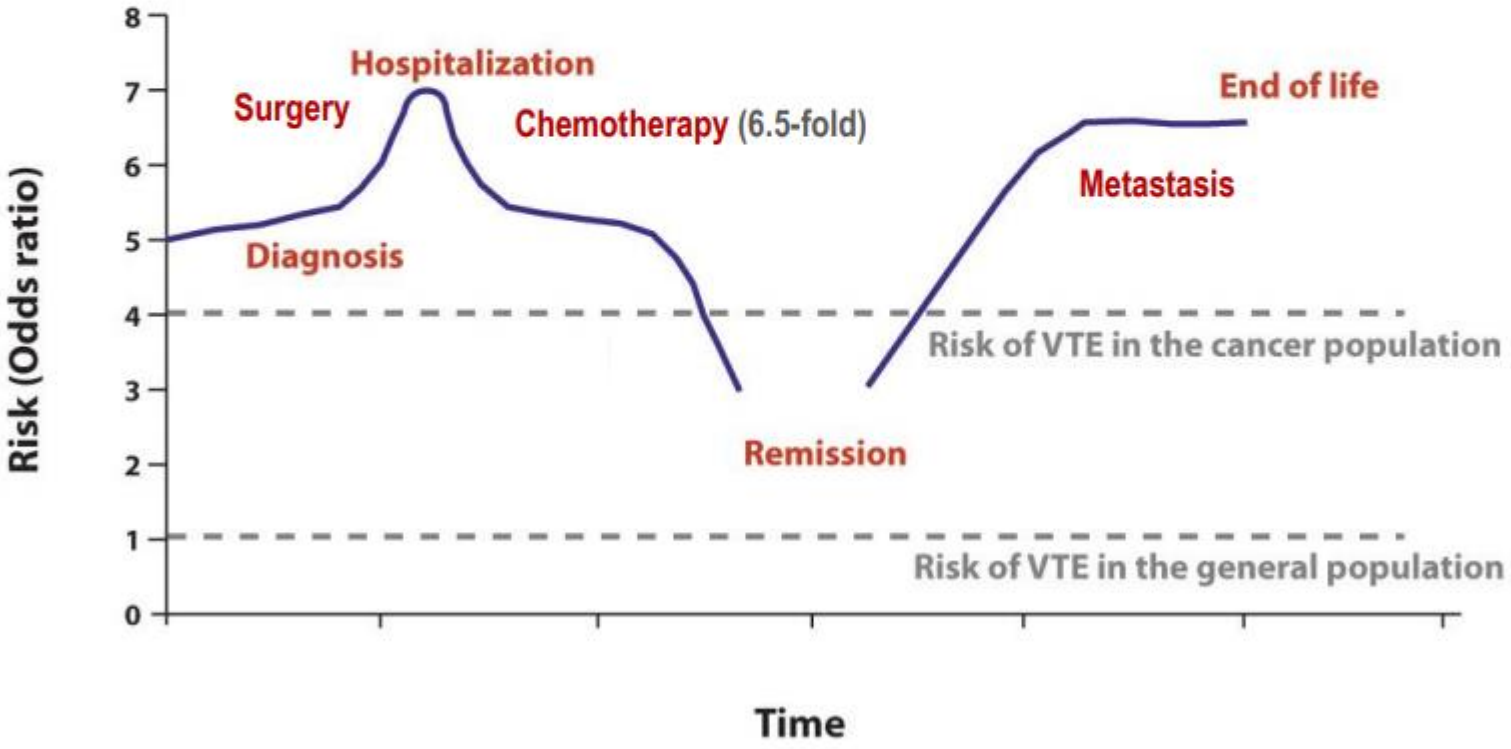


Metastatic-stage
disease at the time of diagnosis



CHANGES IN RISK FOR VTE IN A TYPICAL CANCER PATIENT

- Patients with cancer have a **4- to 6-fold increased risk for VTE**
- Risk factor assessment is an **ongoing process**



Blom JW, *et al.*, JAMA 2005;293:715–22; Heit JA, *et al.*, Arch Intern Med 2002;162:1245–8; Heit JW, *et al.*, Arch Intern Med 2000;60:809–15.

OCCULT CANCER IN UNPROVOKED VENOUS THROMBOEMBOLISM

- Unprovoked VTE may be **the earliest sign** of cancer
- Up to **10% of patients** will be diagnosed with cancer **in the year after**
- More **than 60% of occult cancers** are diagnosed shortly after the diagnosis of unprovoked VTE
- The incidence rate of cancer diagnosis returns to the rate in the general population after 1 year

Carrier M, *et al.*, N Engl J Med 2015;373:697–704.

PATHOPHYSIOLOGY

The pathogenesis of a prothrombotic state in cancer involves:

- Production of procoagulants by tumour cells
- Suppression of fibrinolytic activity
- Platelet activation

There is a close link between **malignant transformation, tumour angiogenesis, metastasis and thrombosis**

ESMO Handbook of Oncological Emergencies 2016

PATHOPHYSIOLOGY

- Cancer-mediated hypercoagulability occurs as a consequence of direct activation of procoagulant pathways by cancer cells (mediated by aberrant tumour cell TF expression, release of tumour cell-derived, TF-expressing microparticles, cancer procoagulant and other cell surface proteases) or from indirect systemic effects of cancer on a variety of cell types, including leucocyte, endothelial cells and platelets

- In various malignancies, neutrophils are “primed” to release their contents in the form of NETs, resulting in direct activation of procoagulant pathways, platelet activation and inhibition of naturally occurring anticoagulant pathways, including tissue factor pathway inhibitor. As a consequence of these various direct and indirect mechanisms, patients with cancer have an elevated risk for venous thromboembolism

FXa, factor Xa; NET, neutrophil extracellular trap; TF, tissue factor.

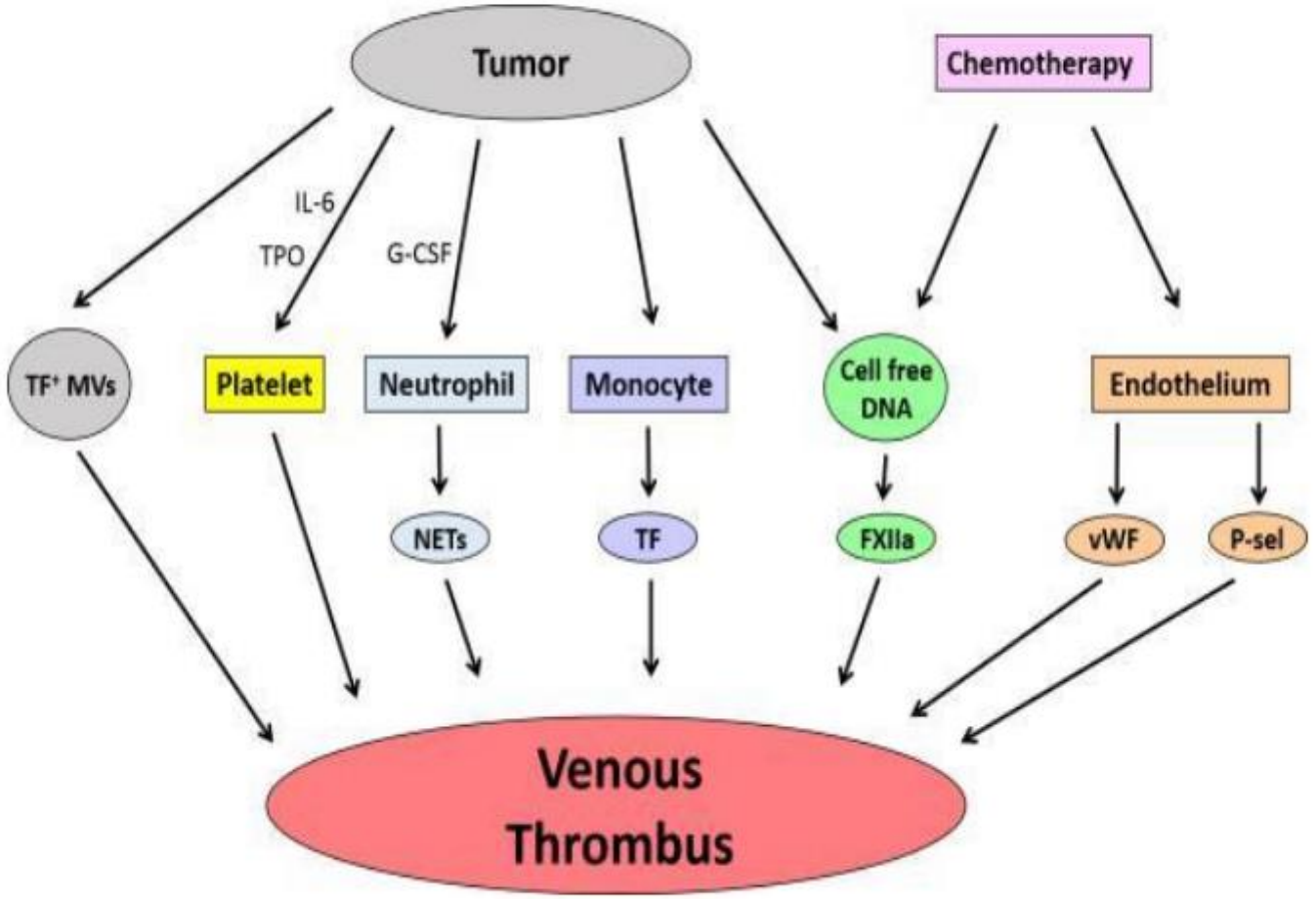
Donnellan E, Khorana AA, Oncologist 2017;22(2):199–207.

PATHOPHYSIOLOGY

- **Tissue factor (TF),** a transmembrane glycoprotein, is a procoagulant expressed by tumour cells
- Over expression of TF spontaneously releases **microparticles** into the bloodstream and these microparticles are procoagulant
- TF induces production of vascular endothelial growth factor **(VEGF)** in human tumour cells, independently of its ability to activate factor Xa-catalysed conversion of prothrombin

ESMO Handbook of Oncological Emergencies 2016

CANCER CELLS EXERT A PROCOAGULANT ACTIVITY IN THEIR MICROENVIRONMENT



Hisada Y, *et al.*, J Thromb Haemost 2015;13:1372–82. Published by John Wiley and Sons. © 2015 International Society on Thrombosis and Haemostasis.

PATHOPHYSIOLOGY

- The **TF–VIIa complex and factor Xa** are among the known activators of G-protein-coupled protease-activated receptor-2 (PAR-2) in tumour cells, while the **TF–VIIa–Xa complex** and **thrombin** efficiently activate PAR-1
- **Both PARs** have been implicated in signalling pathways leading to **angiogenesis and metastasis**
- The genetic mechanism responsible for malignant transformation, such as **oncogene activation** (RAS or MET), or **tumour suppressor gene inactivation** (P53 or PTEN), also directly induces the expression of genes regulating **haemostasis**

ESMO Handbook of Oncological Emergencies 2016

PATHOPHYSIOLOGY

- **Plasminogen activator inhibitor-1** is a potent inhibitor of the fibrinolytic system, promoting tumour growth and angiogenesis
- **Proinflammatory cytokines** such as tumour necrosis factor, interleukin-1, interleukin-6 and interferons activate coagulation
- **Platelet P-selectin** leads to platelet aggregation and platelet-rich thrombus formation
- **Chemotherapy** induces endothelial cell activation, leading to increased TF expression, elevated levels of plasma von Willebrand factor and factor VIII coagulant protein, and decreased level of antithrombin and protein C and S

ESMO Handbook of Oncological Emergencies 2016

THROMBOSIS AND CANCER

Question 2

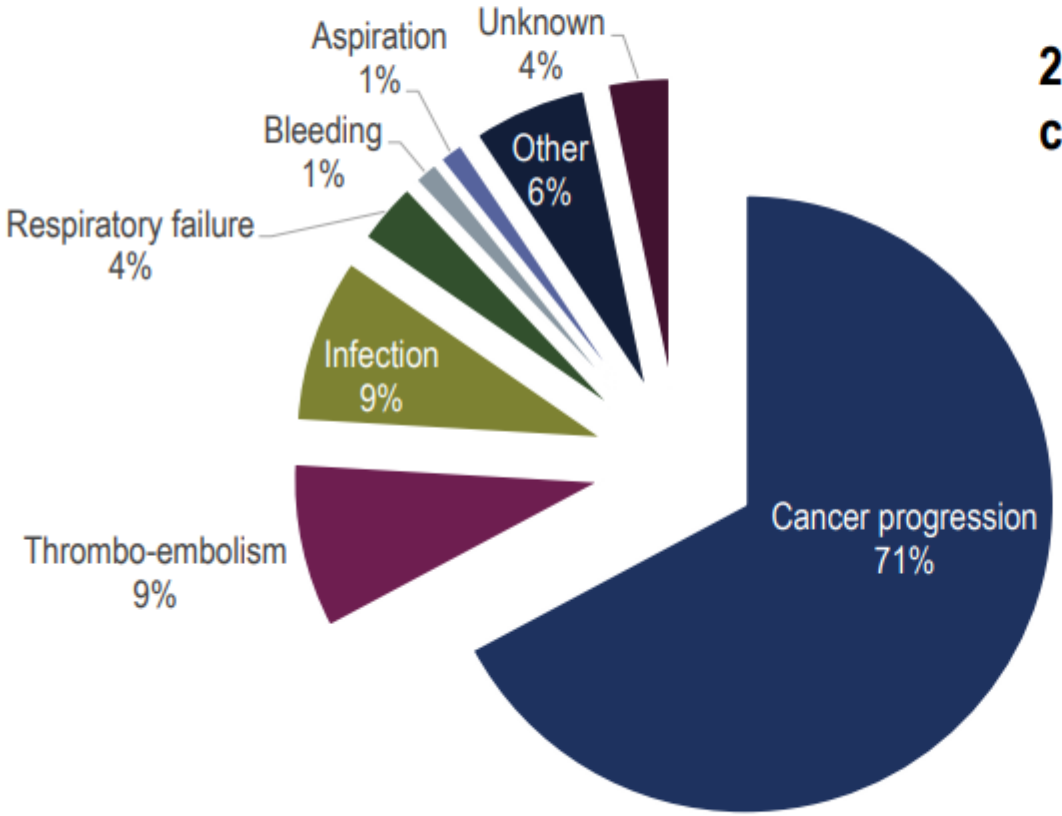
What is the influence in patient's prognosis?

A blood clot in the pulmonary artery

Image: Medical Images RM / STEVE OH, MS CMI

WHY YOU SHOULD CARE

VTE and mortality



2nd leading cause of death in cancer patients

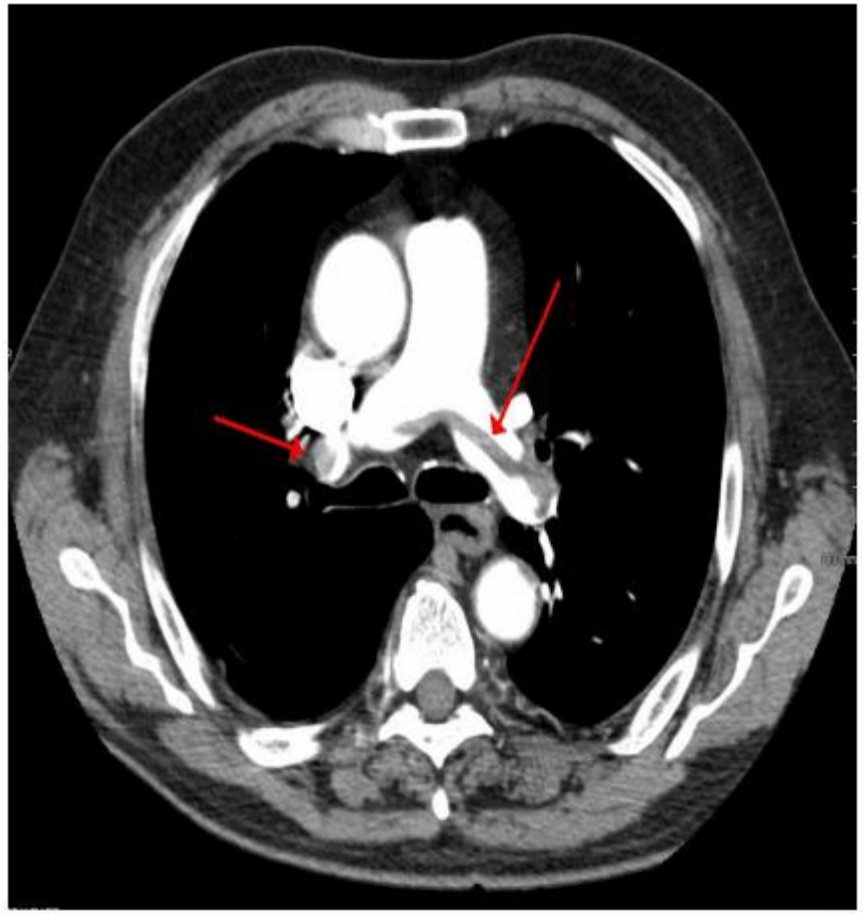
- Accounts for 9% of deaths[1]
- Associated with early mortality during chemotherapy (HR=6.98)[2]
- 47-fold increased risk of mortality from VTE[1]

1. Khorana AA, et al. J Thromb Haemost 2007;5(3):632–4; 2. Kuderer NM, et al. Oncologist 2016.

THROMBOSIS AND CANCER

Question 3

What is the optimal management of this patient?



AIMS OF VTE TREATMENT

Prevention of acute and chronic complications:

- Fatal PE
- Thrombus extension and embolisation
- Early and late recurrences of VTE

Anticoagulation is the cornerstone of VTE treatments!

Cancer-Associated VTE

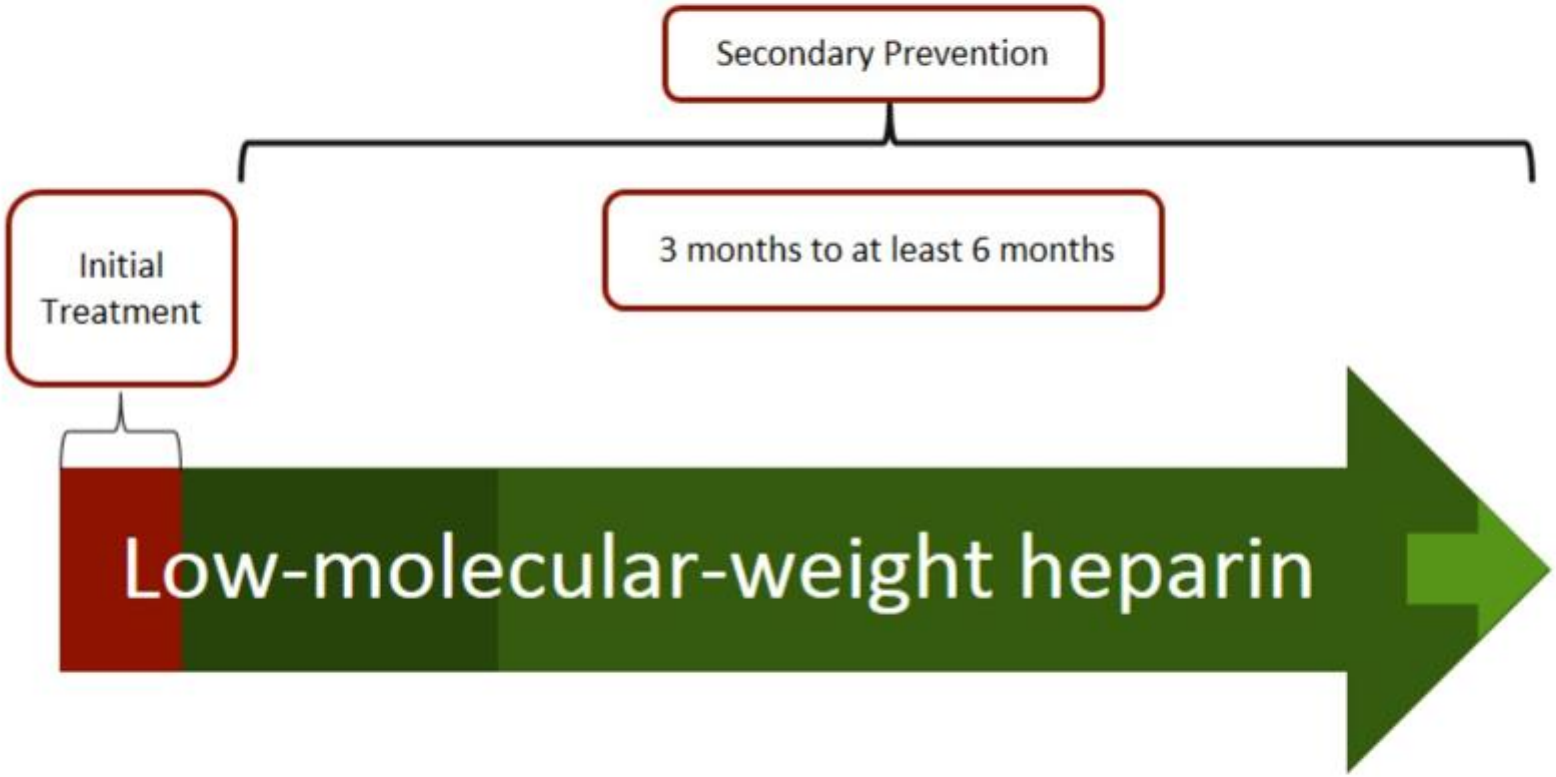
Elyamany G, et al. *Clin Med Insights Oncol*. 2014;8:129-137.

Initial Treatment of Cancer-Associated VTE

- LMWH is recommended for the initial 5 to 10 days of treatment of established DVT and PE

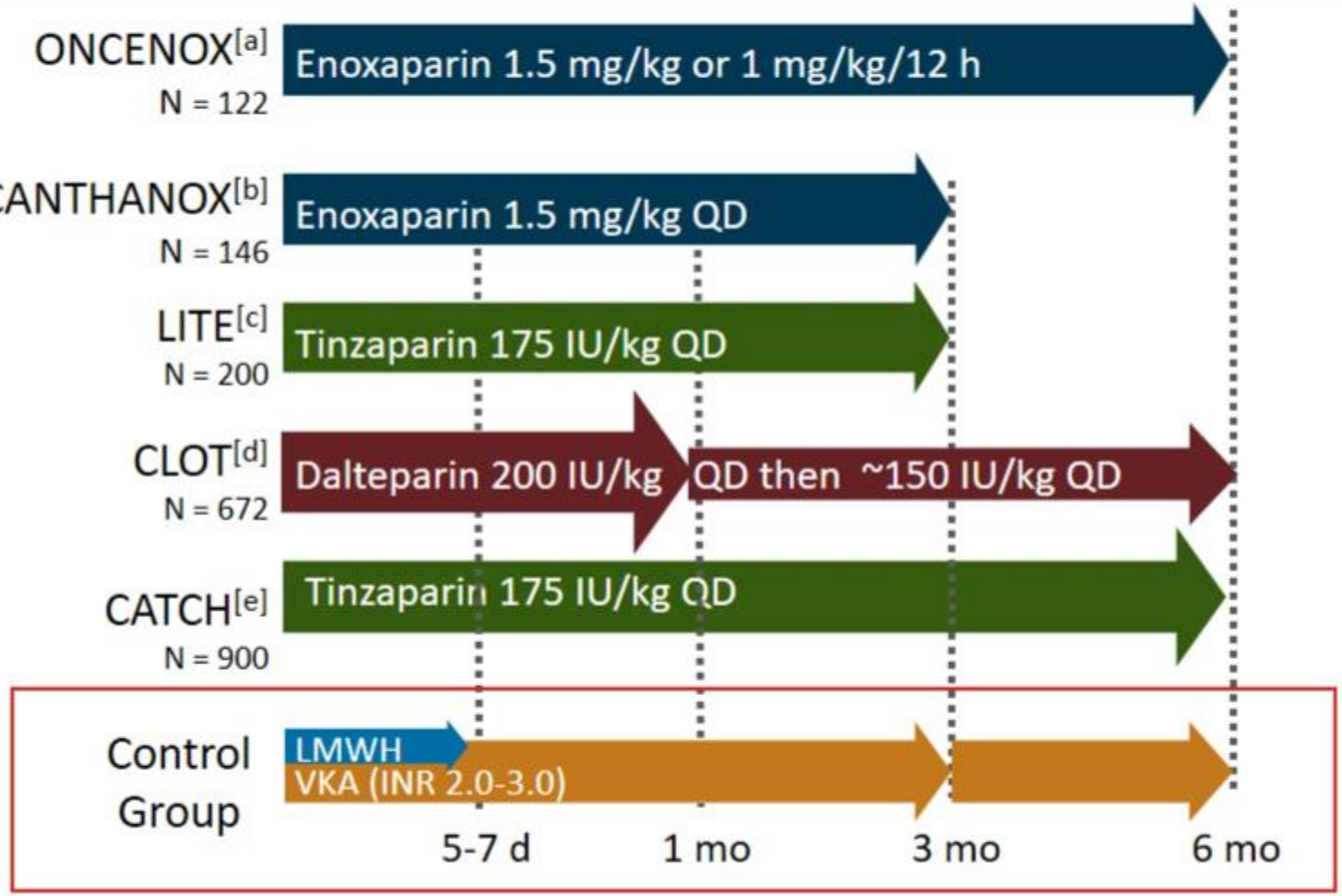
a. Mandala M, et al. *Ann Oncol*. 2011;22(suppl 6):vi85-92.
b. Lyman GH, et al. *J Clin Oncol*. 2015;33:654-656.
c. NCCN website. 2018.
d. Kearon C, et al. *Chest*. 2016;149:315-352.

Guideline Recommendations
Cancer-Associated VTE Treatment



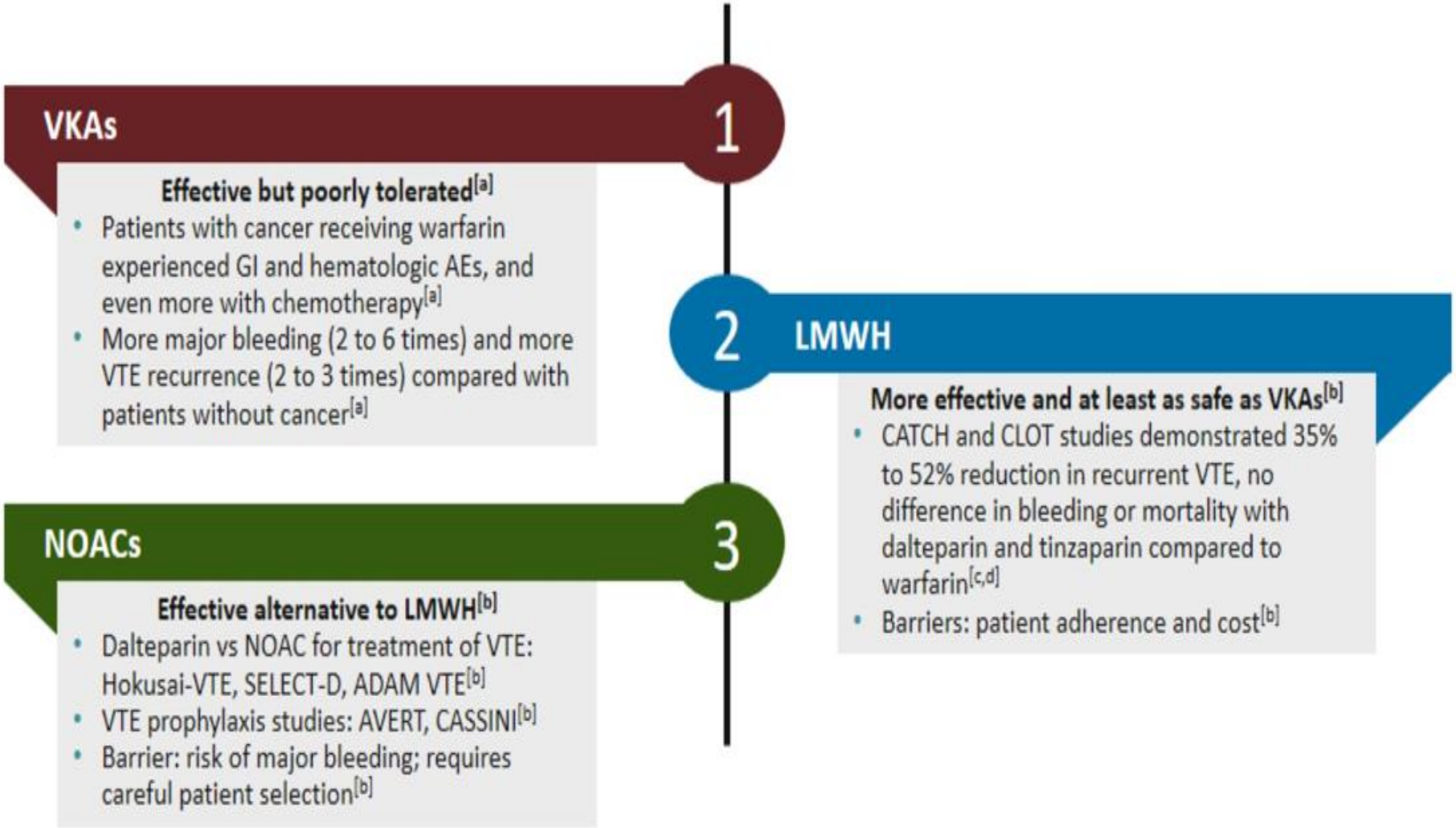
Kearon C, et al. *Chest*. 2012;141(2 suppl):e419S-e496S; Kearon C, et al. *Chest*. 2016;149:315-352; Lyman GH, et al. *J Oncol Pract*. 2015;11:e442-e444.

Treatment of VTE in Cancer



a. Deitcher SR, et al. *Clin Appl Thromb Hemost*. 2006;12:389-396; b. Meyer G, et al. *Arch Intern Med*. 2002;162:1729-1735; c. Hull R, et al. *Am J Med*. 2006;119:1062-1072; d. Lee AY, et al. *N Engl J Med*. 2003;349:146-153; e. Lee AY et al. *JAMA*. 2015;314:677-686.

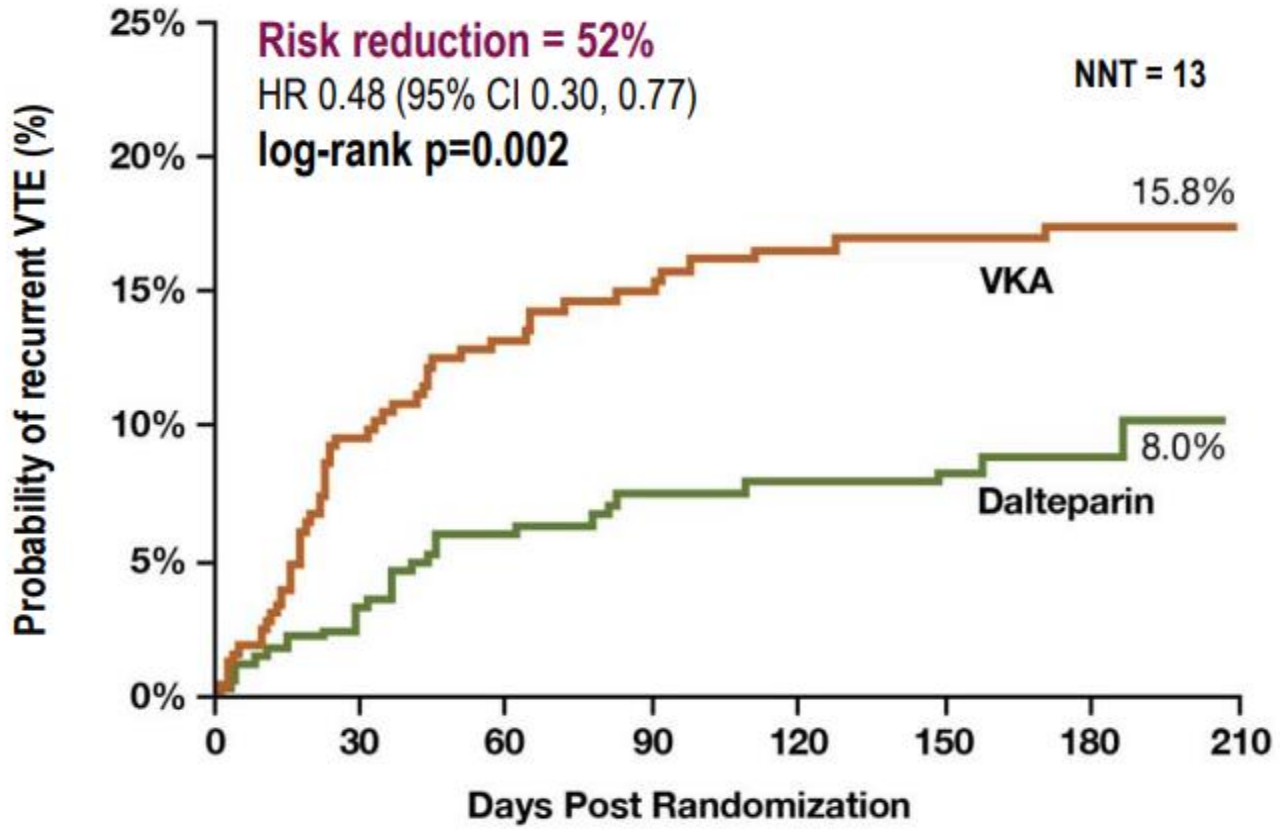
Evolution of Therapeutic Interventions in CAT



a. Brose KM, et al. *Curr Oncol*. 2008;15:S58-S67; b. Farge D, Frere C. *F1000Res*. 2019;8:974; c. Lee AY, et al. *JAMA*. 2015;314:677-686; d. Lee AY, et al. *N Engl J Med*. 2003;349:146-153.

THE CLOT TRIAL

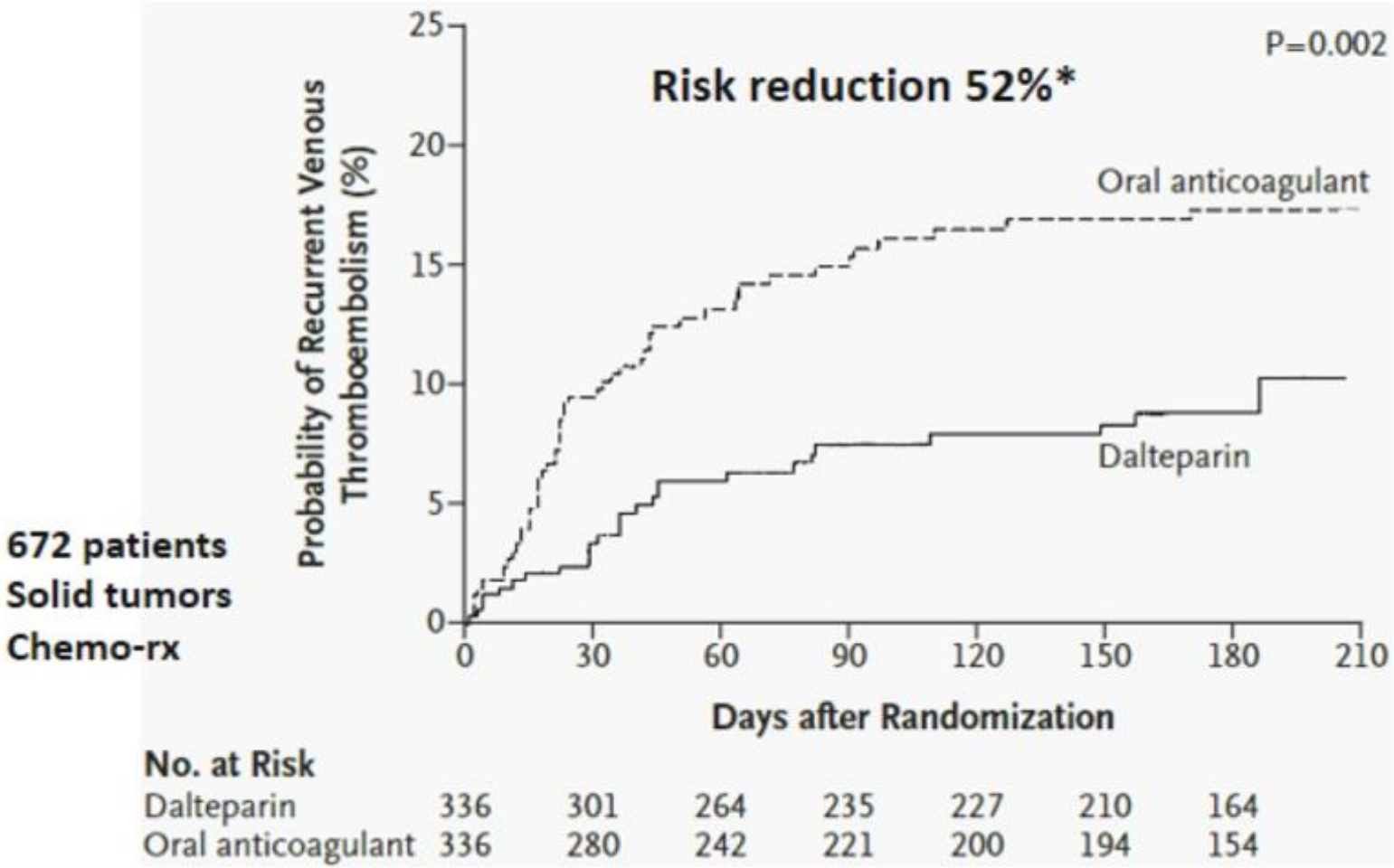
Primary outcome: VTE recurrence



NNT, number needed to treaat; VKA, vitamin K antagonist

From N Engl J Med, Lee AY, *et al.*, Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer, 349, 146–53. Copyright © 2003 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

CLOT Trial



672 patients
Solid tumors
Chemo-rx

38% recurrent VTE in VKA occurred with INR<2.0

Most recurrences in 1st month

Dalteparin: FDA and EMA approved

Lee AYY, et al. *N Engl J Med*. 2003;349:2.

THE CLOT TRIAL

Results: Bleeding

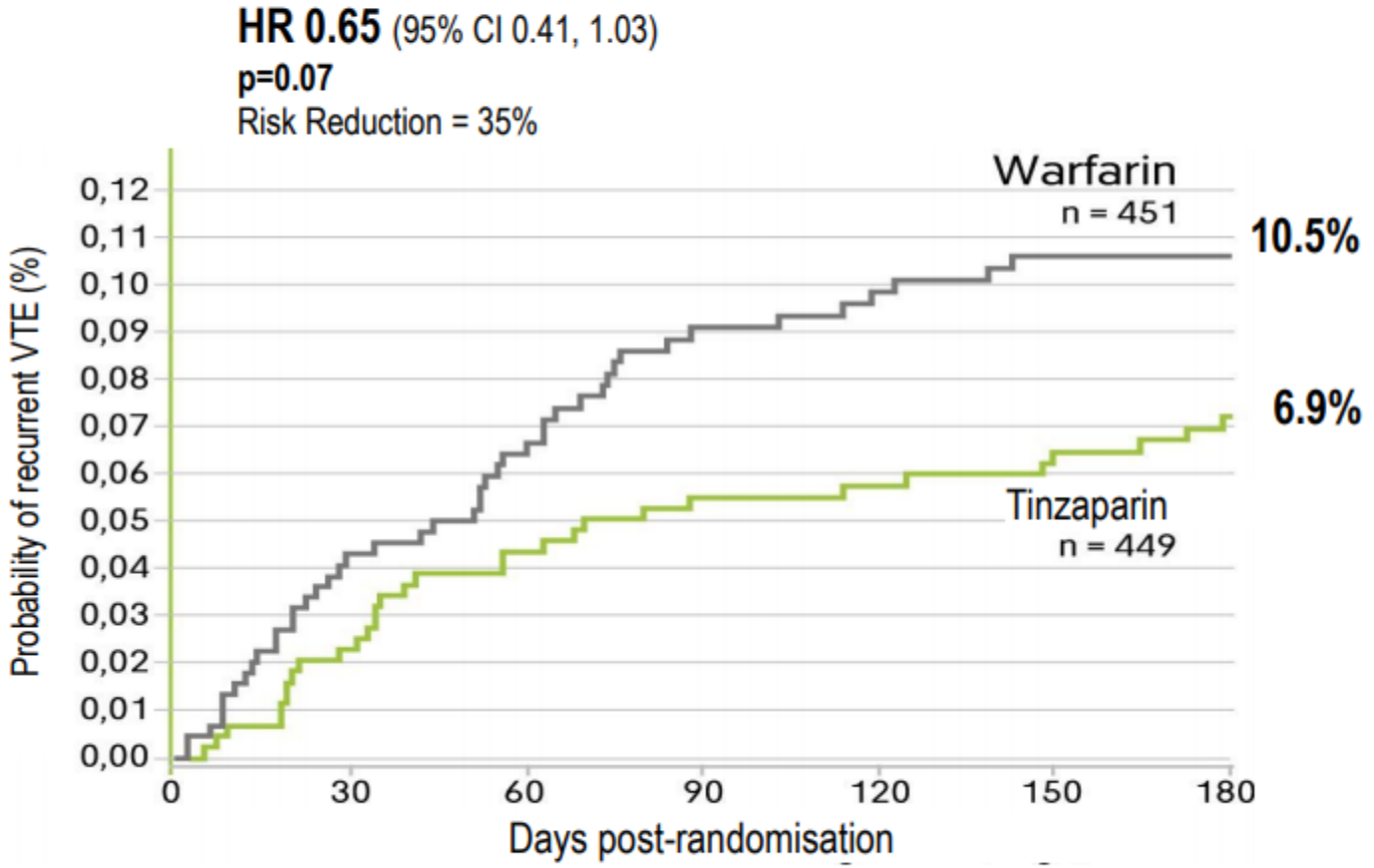
	Dalteparin N=338	VKA N=335	p-value
Major bleed	19 (5.6%)	12 (3.6%)	0.27
Associated with death	1	0	
Critical site*	4	3	
Transfusion of ≥2 units of RBC or drop in Hb ≥2 g/dL	14	9	
Any bleed	46 (13.6%)	62 (18.5%)	0.09

*Intracranial, intraspinal, pericardial, retroperitoneal, intra-ocular, intra-articular

Lee AY, *et al.*, N Engl J Med 2003;349(2):146–53.

CATCH STUDY

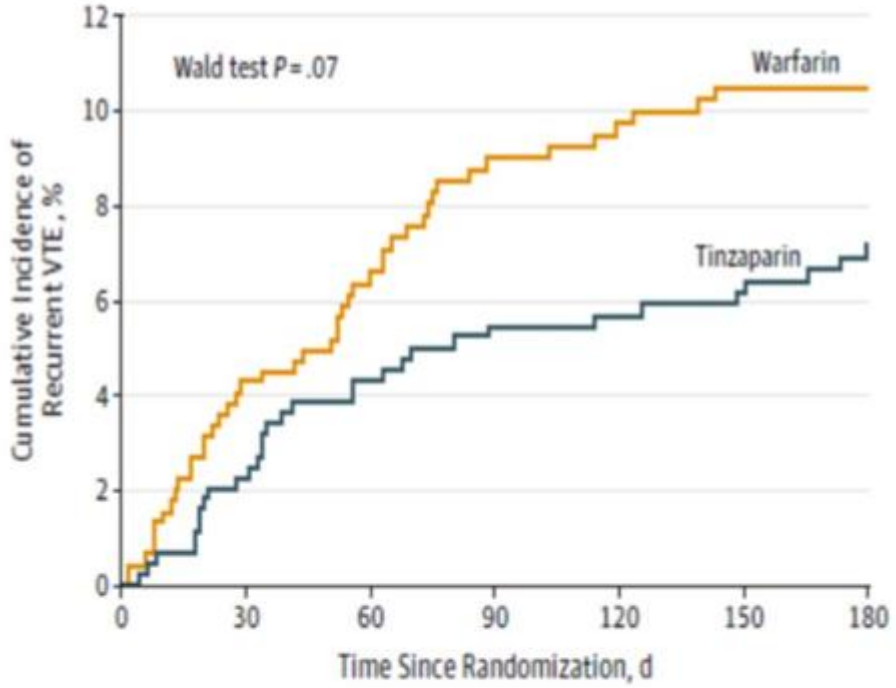
Results: Incidence of VTE recurrence



CATCH Study

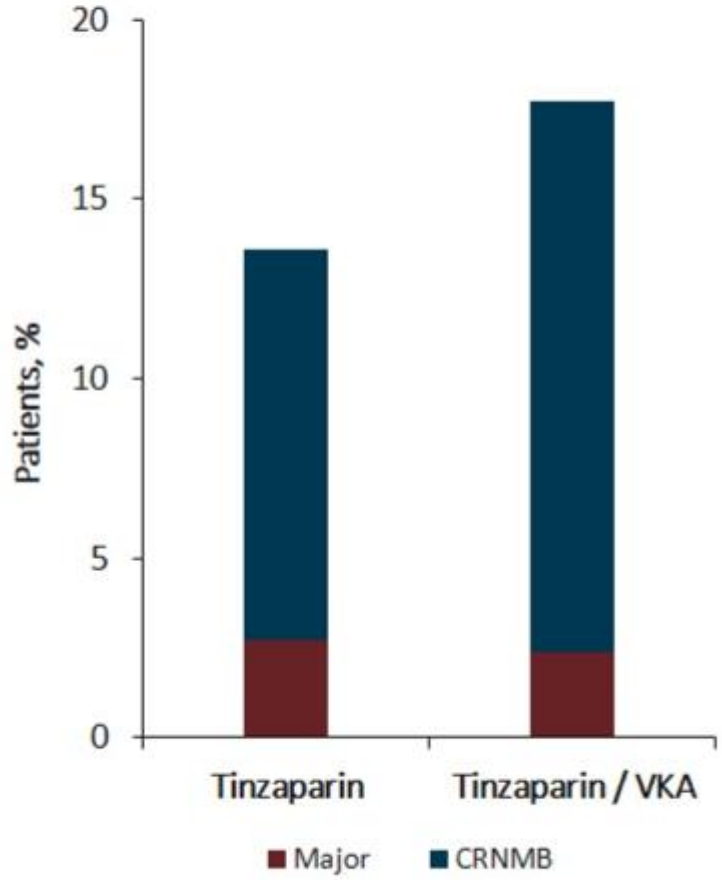
Tinzaparin vs Warfarin in Cancer Patients With VTE

Recurrent VTE



No. at risk				
Tinzaparin	449	357	294	254
Warfarin	451	347	279	249

Major and Nonmajor Bleeding

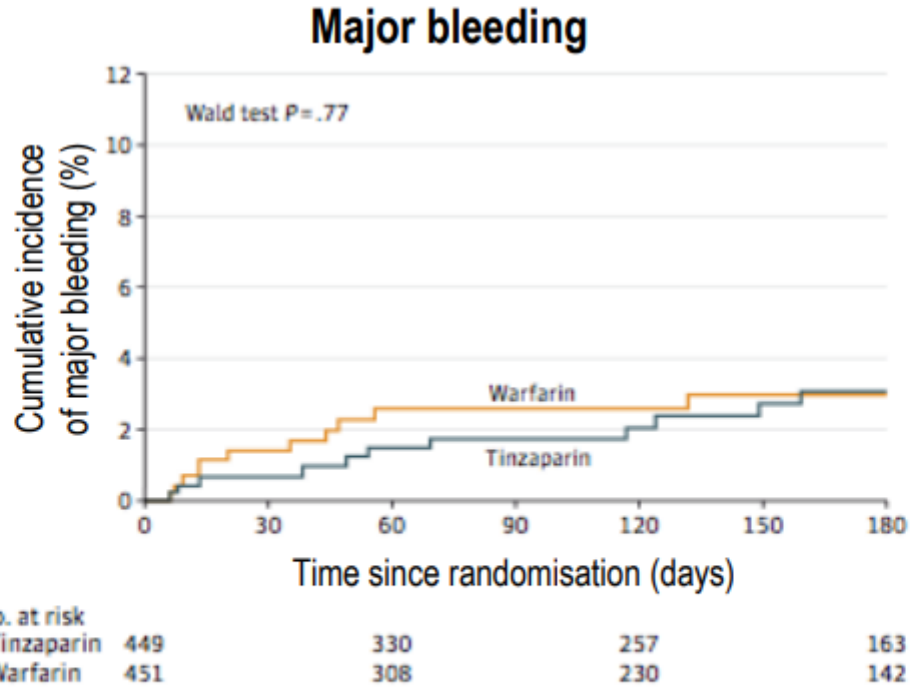


Lee AYY, et al. *JAMA*. 2015;314:677-686.

CATCH STUDY

Bleedings

Bleeding event	Tinzaparin	Warfarin	
Major bleeding	2.9%	2.7%	No difference
Non-major bleeding	11.1%	16.2%	p = 0.03



META-ANALYSIS

LMWH better than VKA for the long term treatment

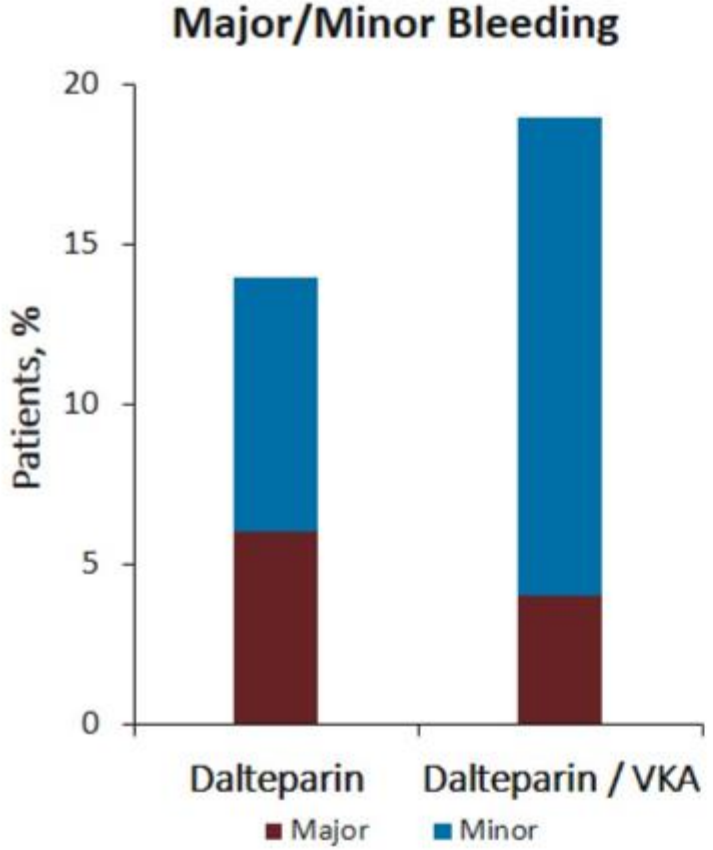
8 randomised control trials

- **Statistically significant reduction in VTE (HR = 0.47;** 95% CI 0.32, 0.71)
- No difference in bleeding (RR = **0.91**; 95% CI 0.64, 1.31)
- No survival benefit (HR = 0.96; 95% CI 0.81, 1.14)

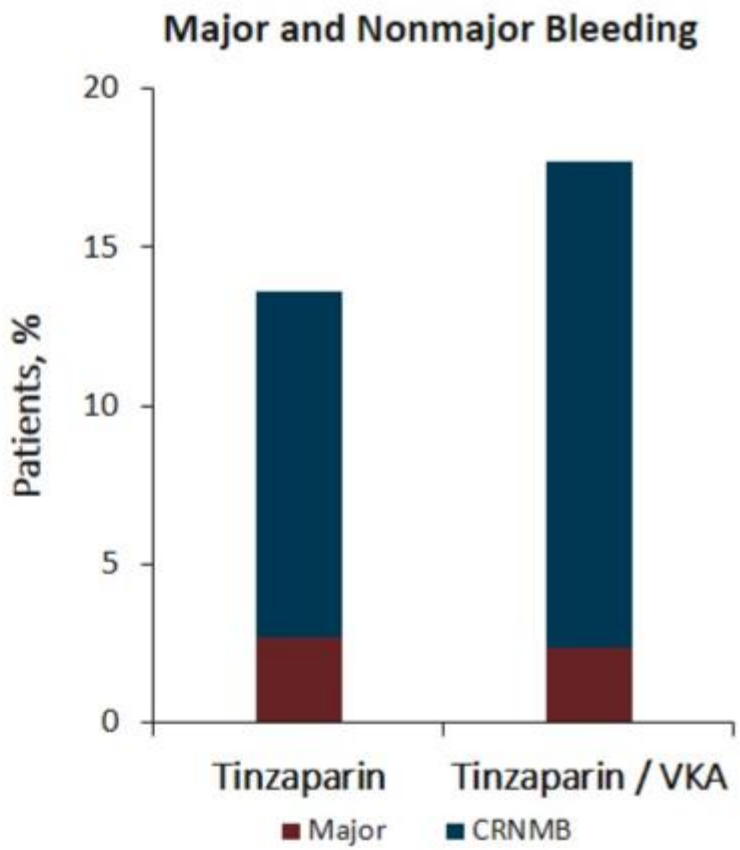
Aki EA, *et al.*, Cochrane Database Syst Rev 2008;(2):CD006650

Comparing Bleeding Rates: LMWH vs VKA

CLOT: *Dalteparin vs Warfarin in Cancer Patients With VTE*



CATCH: *Tinzaparin vs Warfarin in Cancer Patients With VTE*



Lee AY, et al. *N Engl J Med*. 2003;349:146; Lee AYY, et al. *JAMA*. 2015;314:677-686.

THERAPEUTIC ANTICOAGULATION TREATMENT FOR VTE

- Chronic management:
  - LMWH is preferred for the first six months as monotherapy without warfarin in patients with proximal DVT or PE and prevention of recurrent VTE in patients with recurrent or metastatic cancer

- Duration of anticoagulation:
  - Minimum time of 3 months
  - For non-catheter-associated DVT or PE recommended indefinite anticoagulation while cancer is active, under treatment or if risk factors for recurrence persist.

NCCN Guidelines Version 1.2017. Cancer-Associated Venous thromboembolic Disease. Available at: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf. Accessed February 2018

GUIDANCE FOR MANAGING PATIENTS BEYOND 6 MONTHS

Indefinite anticoagulation while cancer is active, under treatment, or if risk factors for recurrence persist

	Favours Continuing Anticoagulation	Favours Stopping Anticoagulation
Patient preference	Primary concern is recurrence	Primary concern is hemorrhage
Malignancy specific	Active malignancy	No evidence of disease
	Ongoing chemotherapy or ESA	Lower-risk diagnosis (eg, breast cancer)
	High-risk diagnosis (e.g., lung cancer)	
Previous history of VTE†	Yes	No
Nature of initial VTE	Life-threatening PE	Non–life-threatening PE
	DVT with severe postphlebitic syndrome	No residual symptoms
Increased risk for hemorrhage	No	Yes
Additional risk factors	Obesity Sex Poor performance status Central venous catheter	Risk factors other than malignancy present when VTE diagnosed (eg, recent surgery)

*Extrapolated in part from unprovoked non–cancer-related VTE; †Before development of cancer-associated VTE.

Zwicker JI, *et al.*, J Clin Oncol 2014;32:3596–9.

MANAGEMENT OF RECURRENCE

For patients already on anticoagulation

- If the patient is on sub-therapeutic dose of warfarin, change the dose to achieve a target INR of 2–3. If INR is therapeutic, switch from warfarin to LMWH
- If the patient is on LMWH, check anti-factor Xa level at 4 hours since last dose
- If the peak anti-factor Xa level is sub-therapeutic (<0.5 units), adjust dose of LMWH to achieve a peak anti-factor Xa level of 0.5–1.5 units
- If the peak anti-factor Xa level is therapeutic, then increase the dose of LMWH by 20%
- If the anti-factor Xa level is therapeutic and the patient is symptomatic from VTE, then consider IVC filter

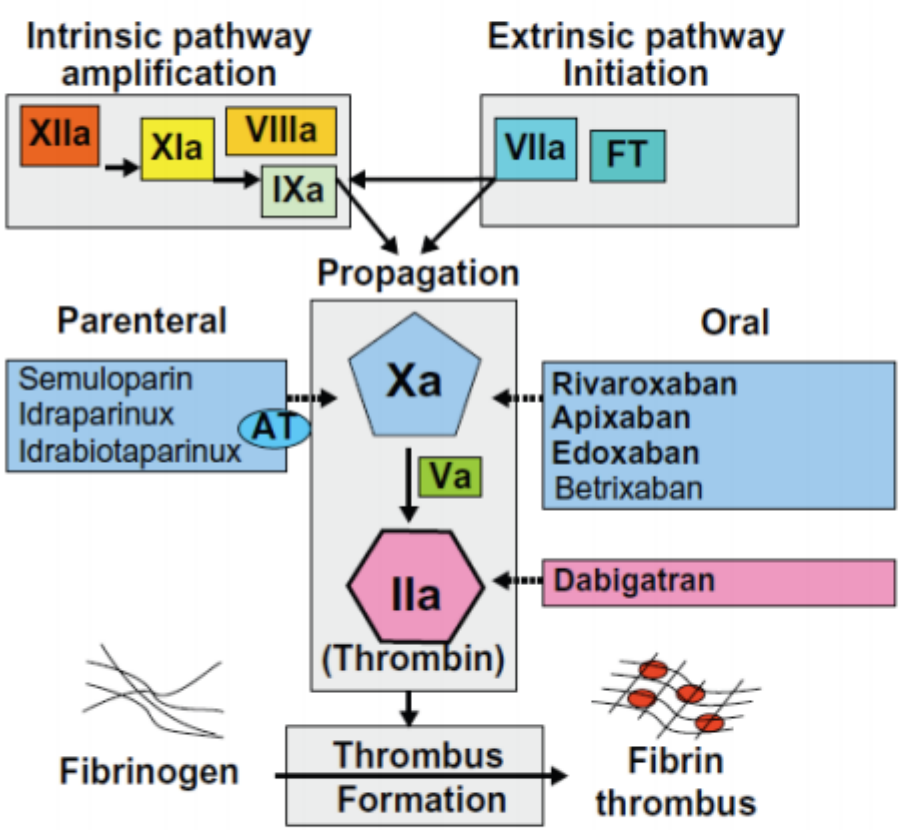
ESMO Handbook of Oncological Emergencies 2016

DOACs

S.H.MIRPOUR;MD

MEDICAL ONCOLOGIST/GUMS/HESHMATHOSPITAL/1401

DO DIRECT FACTOR XA OR IIA INHIBITORS HAVE A ROLE IN CANCER-ASSOCIATED VTE?

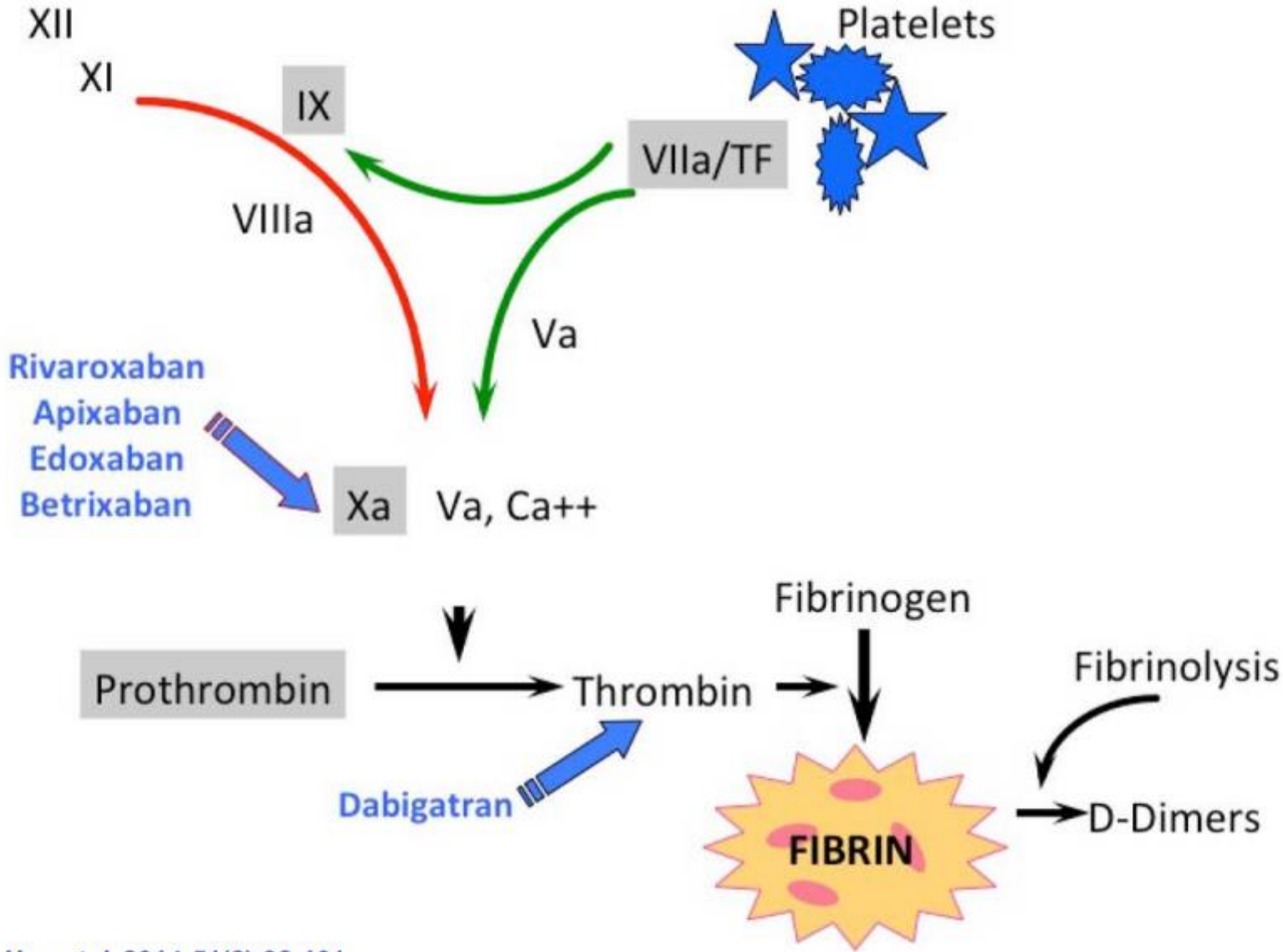


Apixaban, **rivaroxaban**, and **dabigatran** approved for

- the prevention of VTE during major orthopedic surgery
- the prevention of stroke in atrial fibrillation

Rivaroxaban for the treatment of VTE

Site of Action of DOACs



Tsakiris DA, et al. *Semin Hematol.* 2014;51(2):98-101.

General Characteristics of DOACs

Characteristics	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target	IIa	Xa	Xa	Xa	Xa
Pro-drug	Yes	No	No	No	No
Half Life (hrs.)	14-17	7-11	8-14	5-11	37
Route Elimination %	Urine ~ 80 Feces ~ 20	Urine ~ 66 Feces ~ 26	Urine ~ 25 Feces ~ 50	Urine ~ 35 Feces ~ 60	Urine ~ 13 Feces ~ 80
Bioavailability	pH dependent 6-7%	Food dependent 66%	Food dependent 50%	Food dependent 62%	34%
Dosing	Twice/day	Once/day	Twice /day	Once/day	Once/day
Liver CP3A4	No < 2%	Yes 57%	Minor 25%	Minor 35%	No < 1%
Impact P-glycoprotein	Yes	Yes	Yes	Yes	Yes

Schaefer JK, et al. *Ann Hematol.* 2016;95(3):437-449.

Suggested laboratory measurements of DOACs

Clinical objective			
Drug	**Clinically relevant drug levels**	**Estimate drug levels on therapy**	**Excessive drug level**
Dabigatran	TT: normal levels likely excludes relevant drug levels	Dilute TT, ECA, ECT	Normal aPTT, excludes excess drug Diluted TT, ECA, ECT can quantitate
Anti-Xa inhibitors: Rivaroxaban Apixaban Edoxaban Betrixaban	Anti-Xa: normal likely excludes relevant drug levels	Anti-Xa	Anti-Xa and PT Normal PT likely excludes excess drug levels Anti-Xa suitable for quantitation

- Assays should be calibrated for specific drugs based on anti-xa assay
- Dabigatran: based on dilute thrombin time

DOACs Eligibility

Good Candidates

- VTE not requiring thrombolysis
- Adequate liver Function: Childs-Pugh A-B
- No significant drug interactions
- In cancer-associated VTE if refuse LMWH

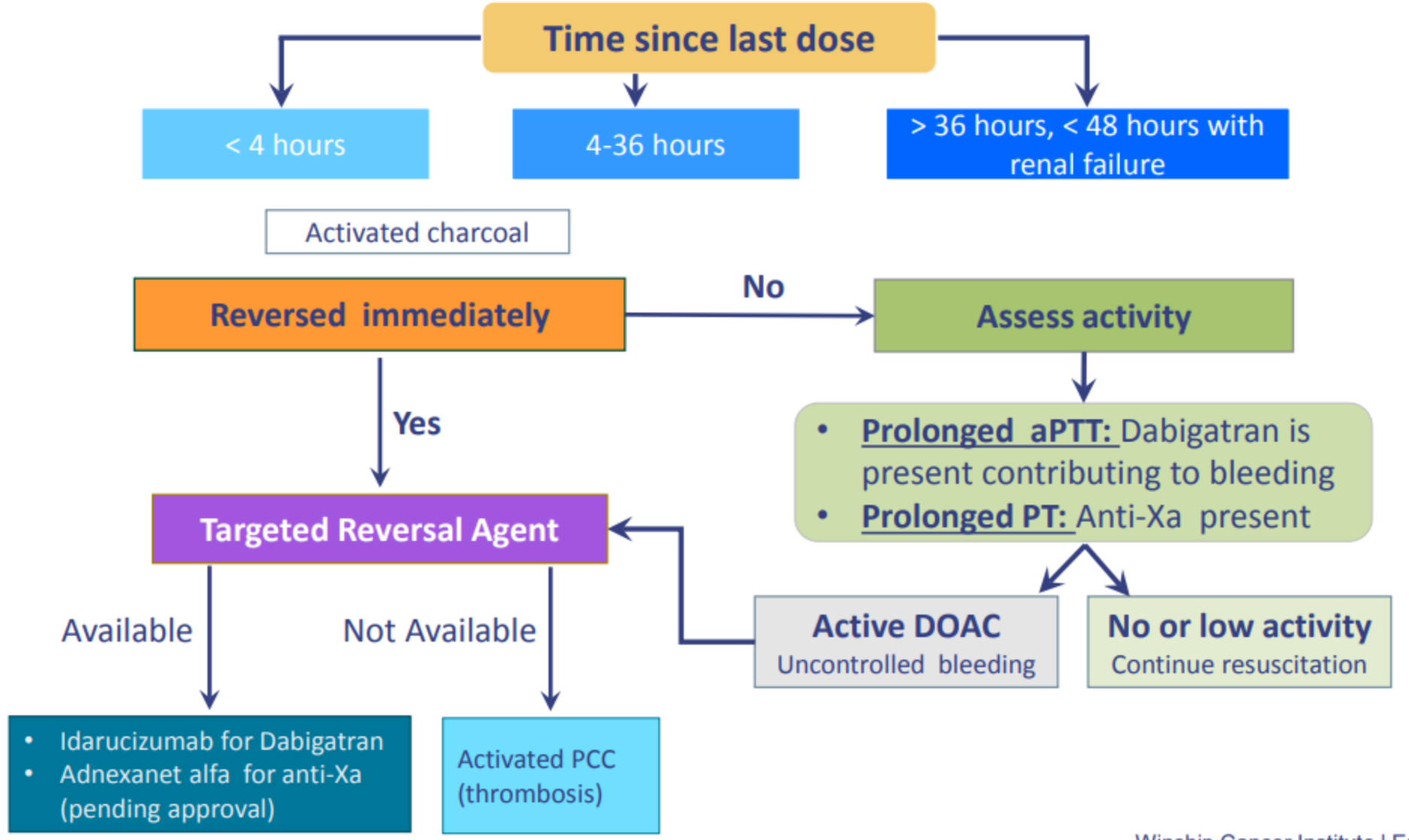
Caution	Agents to use
GI bleed	Apixaban-Edoxaban
CKD	Apixaban-Betrixaban
Elderly	Anti-Xa
Poor compliance	Rivaroxaban-Edoxaban-Betrixaban
CYP3A4 interaction	Dabigatran

Invasive Procedures

Cessation in hours (doses to held)					Resumption	
ClCr mL/min	Dabigatran		Apixaban/Rivaroxaban /Edoxaban			
	Low Bleeding Risk	High Bleeding Risk	Low Bleeding Risk	High Bleeding Risk	Low Bleeding Risk	High Bleeding Risk
> 80	~ 24 (2)	~ 48 (4)	~ 12-24 (1-2)	~ 48 (2-4)	~ 24 hours post-op	~ 48-72 hours post-op
50-80	~ 36 (3)	~ 72 (6)	~ 12-24 (1-2)	~ 48 (2-4)		
30-50	~ 72 (6)	~ 96 (8)	~ 24-36 (1-4)	~ 48 (2-4)		
15-30	Not indicated		~ 38-48 (2-4)	~ 72 (3-6)		

Burnett AE, et al. *J Thromb Thrombolysis.* 2016;41(1):206-232.

DOACs and Bleeding Management



NOVEL ANTICOAGULANTS (NOACs) TRIALS: OUTCOMES IN CANCER PATIENTS

Prespecified subgroup analyses

NOAC Trial	Patients with active cancer	Recurrent VTE	Clinically
EINSTEIN-DVT	Rivaroxaban = 6.8% VKA = 5.2%	Rivaroxaban = 3.4% VKA = 5.6%	Rivaroxaban = 14.4% VKA = 15.9%
EINSTEIN-PE	Rivaroxaban = 4.7% VKA = 4.5%	Rivaroxaban = 1.8% VKA = 2.8%	Rivaroxaban = 12.3% VKA = 9.3%
EINSTEIN-EXT	Rivaroxaban = 4.5% VKA = 4.4%	Not reported	NR
AMPLIFY	Apixaban = 2.5% VKA = 2.8%	reported	NR
AMPLIFY-EXT	Apixa mg = 1.8% Apixaban 5 mg = 1.1%	Not reported	NR
RE-COVER	Dabigatran = 5.0% VKA = 4.5%	Dabigatran = 3.1% VKA = 5.3%	NR
RE-MEDY	Dabigatran = 4.2% VKA = 4.1%	Dabigatran = 3.3% VKA = 1.7%	NR
HOKUSAI-VTE	Edoxaban = 2.6% VKA = 2.4%	Edoxaban = 3.7% VKA = 7.1%	Edoxaban = 18.3% VKA = 25.3%

Patients with cancer <7%

Bauersachs R, *et al.*, NEJM 2010;363:2499–510; Büller HR, *et al.*, NEJM 2012;366:1287–97; Agnelli G, *et al.*, NEJM 2013;369:799–808; Agnelli G, *et al.*, NEJM 2013;368:699–708; Schulman S, *et al.*, NEJM 2009;361:2342–52; Schulman S, *et al.*, NEJM 2013;368:709–71; Hokusai-VTE Investigatprs NEJM 2013;369:1406–15; Raskob GE, *et al.*, Blood 2013;122: Abstract 211

DOACs INTERACTIONS WITH ANTICANCER THERAPIES

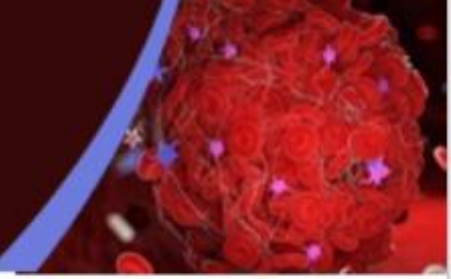
Interaction effect*	Dabigatran P-glycoprotein	Rivaroxaban P-glycoprotein CYP3A4	Apixaban P-glycoprotein CYP3A4
Increases DOAC plasma levels†	Cyclosporine	Cyclosporine	Cyclosporine
	Tacrolimus	Tacrolimus	Tacrolimus
	Tamoxifen	Tamoxifen	Tamoxifen
	Lapatinib	Lapatinib	Lapatinib
	Nilotinib	Nilotinib	Nilotinib
	Sunitinib	Sunitinib	Sunitinib
		Imatinib	Imatinib
		Taxol	
Reduces DOAC plasma levels§	Dexamethasone	Dexamethasone	Dexamethasone
	Doxorubicin	Doxorubicin	Doxorubicin
	Vinblastine	Vinblastine	Vinblastine

†Inhibitors of pgp transport and CYP3A4 pathway; §Inducers-lower DOAC levels.

INJECTABLE ANTICOAGULANTS DIFFERENTIATION

Molecule	Average molecular weight (Daltons)	Manufacturing process	Mode of action/ activity	Anti-Xa activity neutralised (%)	Dosing	Use in renal insufficiency	CAT long term treatment indication
Dalteparin	6.000	Chemical cleavage - nitrous acid	FXa>FIIa 1000/384 IUs	74	Prophylaxis: OD Treatment: OD	Dose adjustment	Yes
Tinzaparin	6.500	Enzymatic cleavage - heparinase	FXa>FIIa 1000/500 IUs	86	Prophylaxis: OD Treatment: OD	CrCl >30 ml/min No accumulation >20 ml/min can be used	Yes
Enoxaparin	4.500	Chemical cleavage - alkaline	FXa>FIIa 1000/233 IUs	54	Prophylaxis: OD Treatment: BID	CrCl <30 ml/min Dose adjustment CrCl 30-80 ml/min Clinical surveillance	No (Only initial treatment -10 days SmPC)
Fondaparinux	1.700	Synthetic	FXa only	-	Prophylaxis: OD Treatment: OD	CrCl 20-50 ml/min Dose reduction by 50%	No

DOAC
Cancer VTE Trials Through Jan 2020



3 RCTs of a DOAC vs dalteparin

Hokusai VTE Cancer[a]
- Edoxaban
- 1046 patients
- Primary outcome composite of recurrent VTE and major bleeding

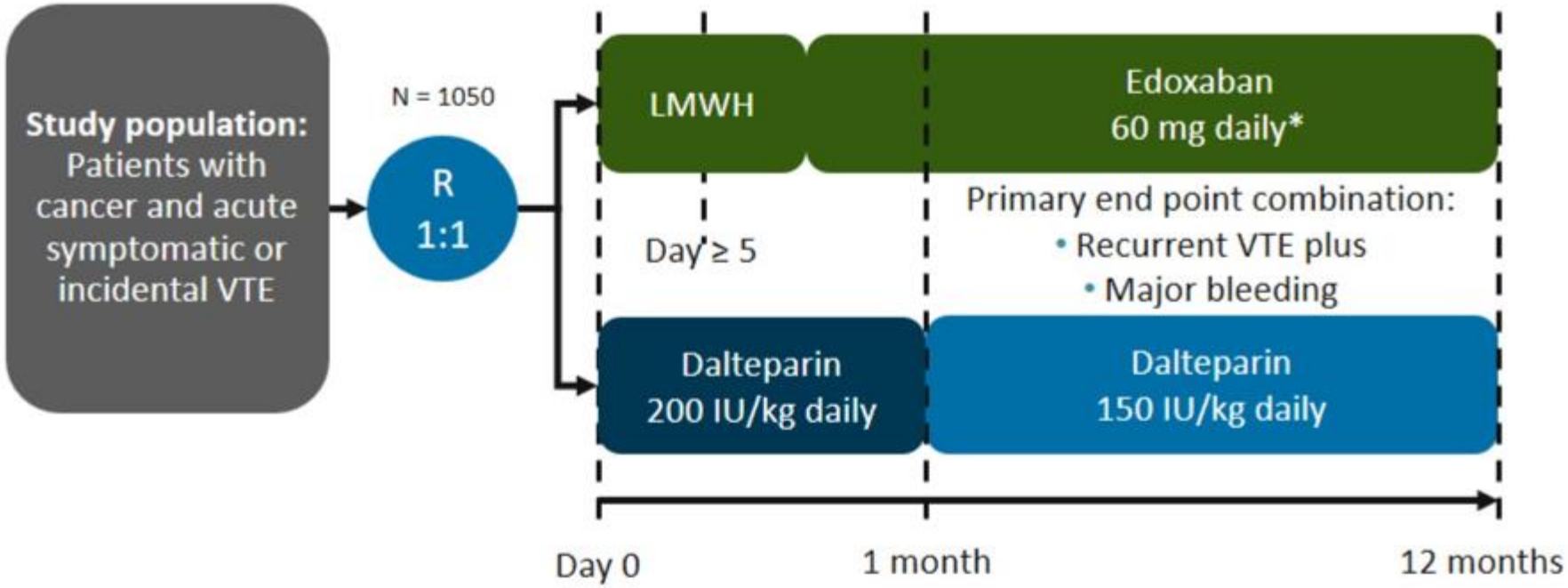
Select-D[b]
- Rivaroxaban
- 406 patients
- Primary outcome recurrent VTE

ADAM[c]
- Apixaban
- 300 patients
- Primary outcome major bleeding

a. Raskob GE, et al. *N Engl J Med*. 2018;378:615-624; b. Young A, et al. *J Clin Oncol*. 2018;36:2017-2023; c. McBane RD, et al. *J Thromb Haemost*. 2020;18:411-421.

Hokusai VTE Cancer: Study Design

Multinational, prospective, randomized, open-label, blinded end point (PROBE), noninferiority trial

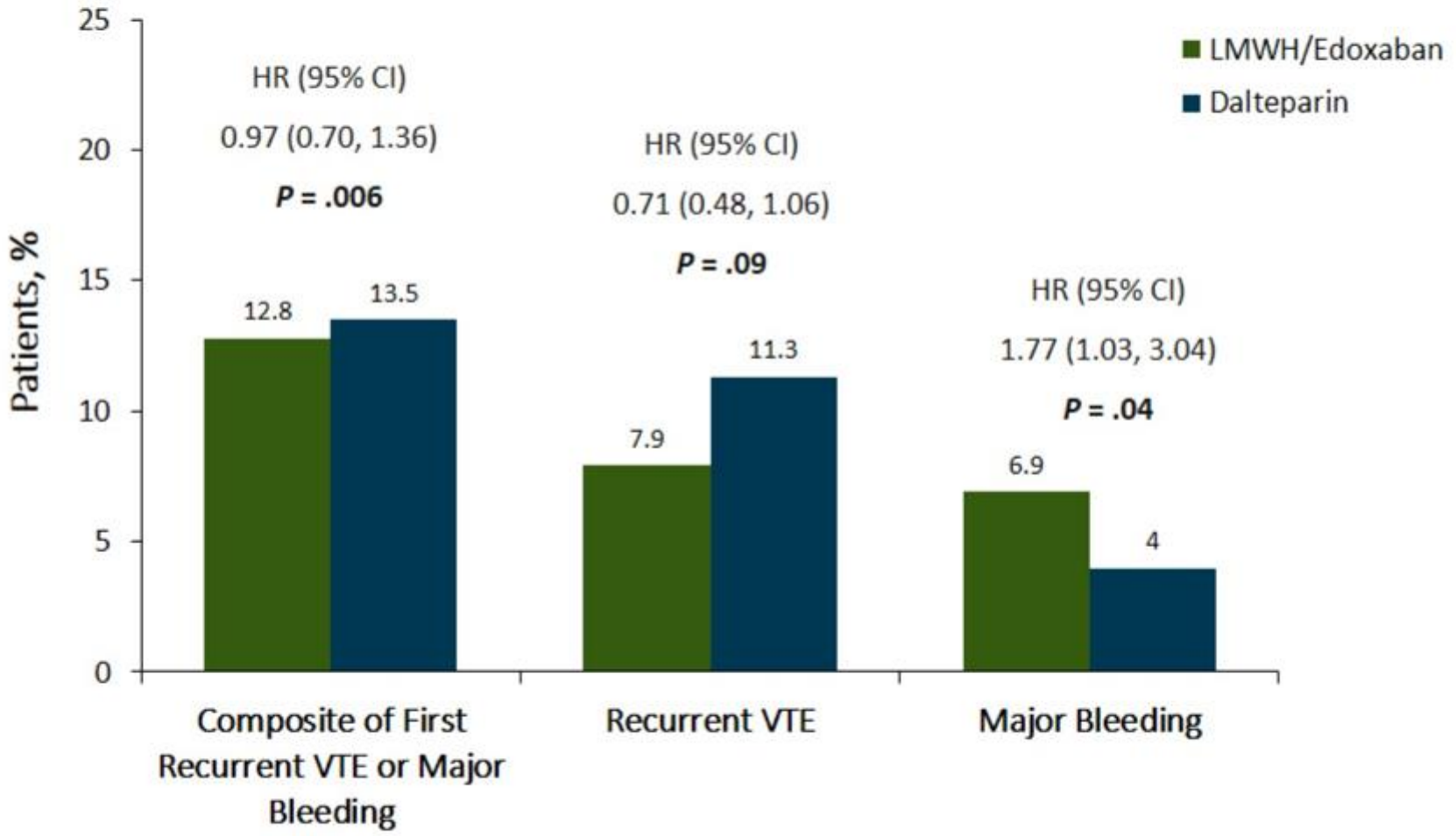


- Efficacy outcome: composite of recurrent VTE through 12 months
- Safety outcome: major bleeding

*Dose adjustment to 30 mg daily in patients with a body weight ≤ 60 kg or CrCl 30-50 mL/min, or concomitant use of P-gp inhibitors.

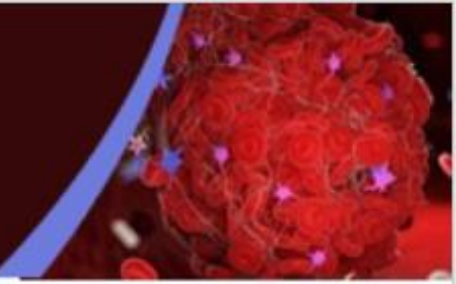
Van Es N, et al. *Thromb Haemost*. 2015;114:1268-1276.

Hokusai VTE Cancer
Primary and Secondary Outcomes



Modified Intention-to-treat population for 12 months (N = 1046).
Raskob GE, et al. *N Engl J Med.* 2018;378:615-624.

Hokusai VTE Cancer



1,046 patients randomized to edoxaban or dalteparin for 12 months

- 98% defined as having active cancer, 53% with metastatic disease
- Patients on edoxaban had 10% greater duration of adherence to study drug (211 vs 184 d)

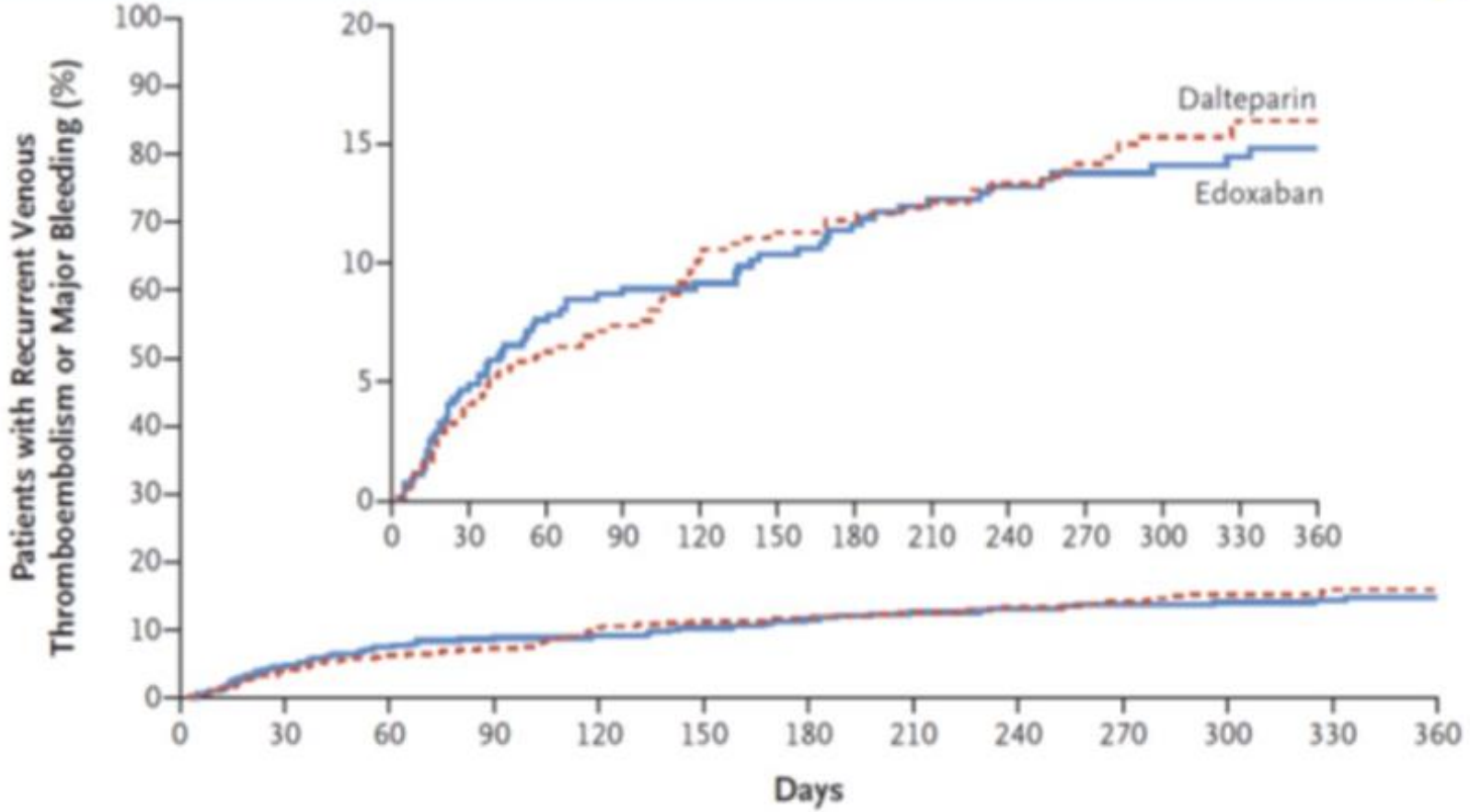
- Edoxaban non-inferior to dalteparin for composite endpoint of recurrent VTE or major bleeding (HR 0.97; 95% CI: 0.70, 1.36; *P* = 0.006)

- Approximately 13% events each arm at 1 yr
  - Fewer recurrent VTE with edoxaban (6.5% v. 10.3%)
  - Increased major bleeding (6.3% v 3.2%)
  - Increased upper GI bleeds primarily with GI malignancies

Raskob GE, et al. *N Engl J Med*. 2018;378:615-624.

Hokusai VTE Cancer

Kaplan-Meier Cumulative Event Rates for the Primary Outcome

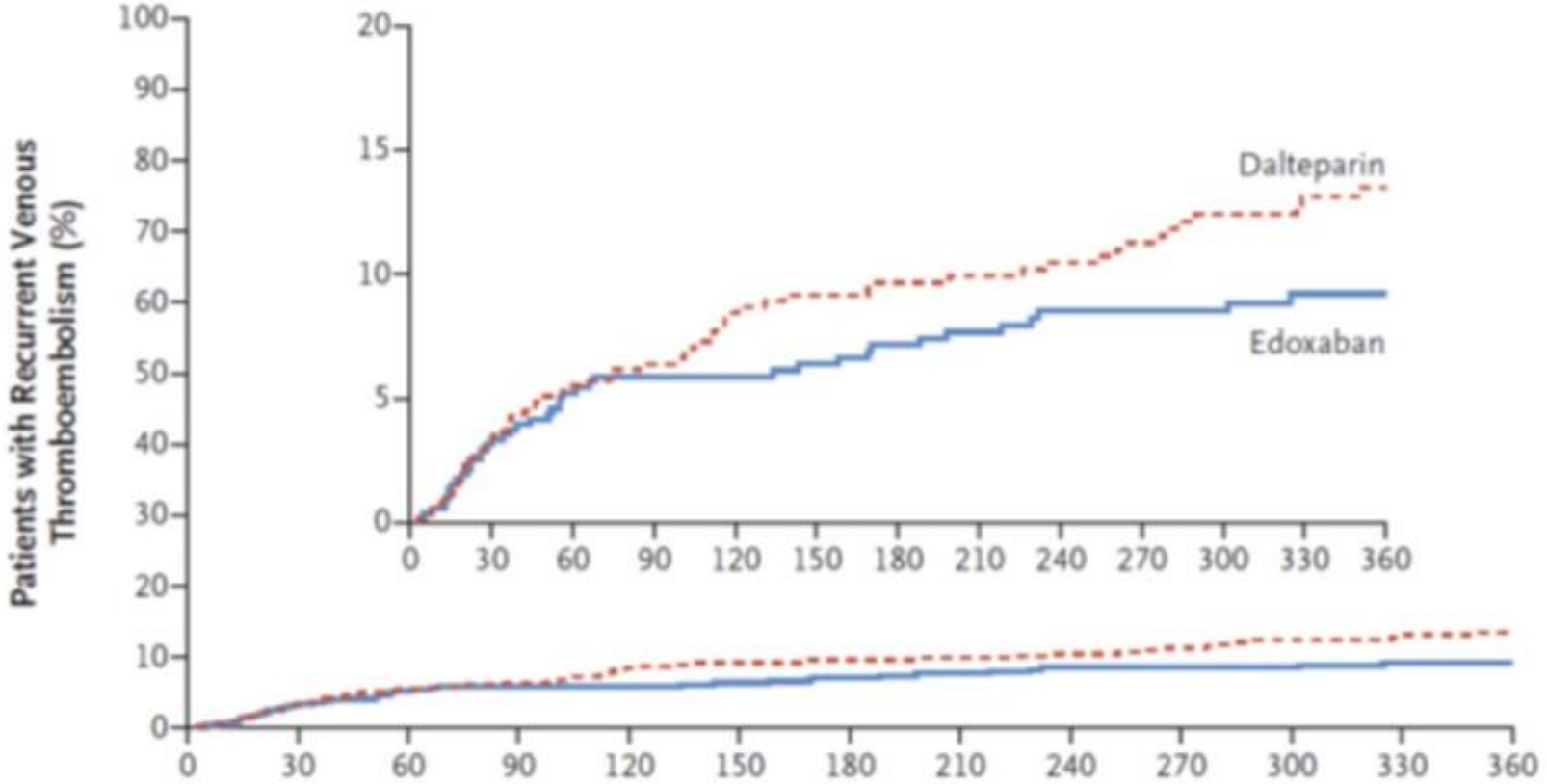


No. at Risk													
Edoxaban	522	472	429	407	388	360	345	328	310	295	270	237	161
Dalteparin	524	485	449	420	385	364	352	340	324	313	276	241	171

Raskob GE, et al. *N Engl J Med*. 2018;378:615-624.

Hokusai VTE Cancer

Kaplan-Meier Cumulative Event Rates for Secondary Outcomes

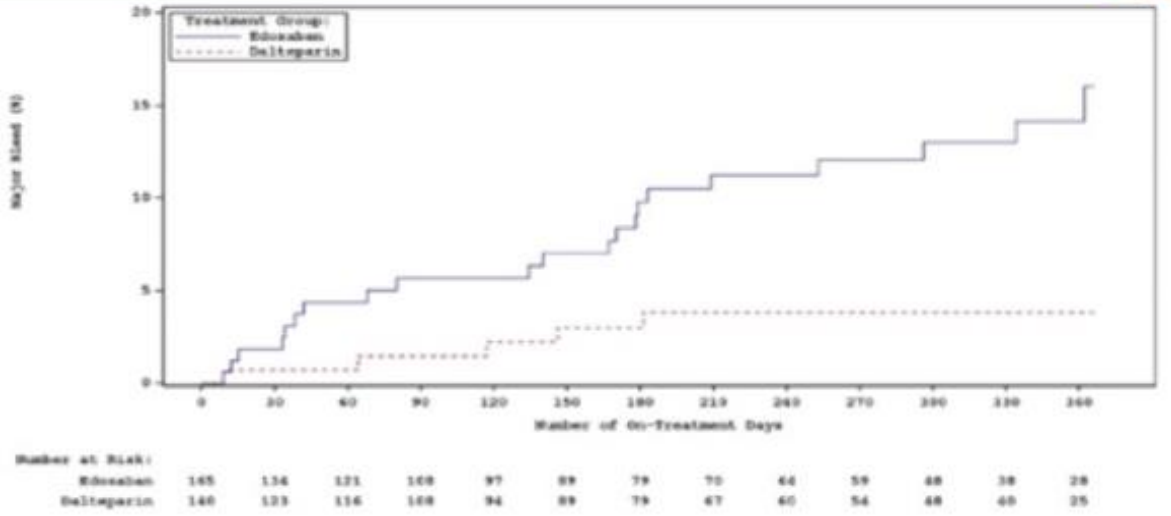


No. at Risk													
Edoxaban	522	480	437	415	395	370	356	340	320	307	281	245	168
Dalteparin	524	488	452	423	389	370	358	348	333	321	282	246	174

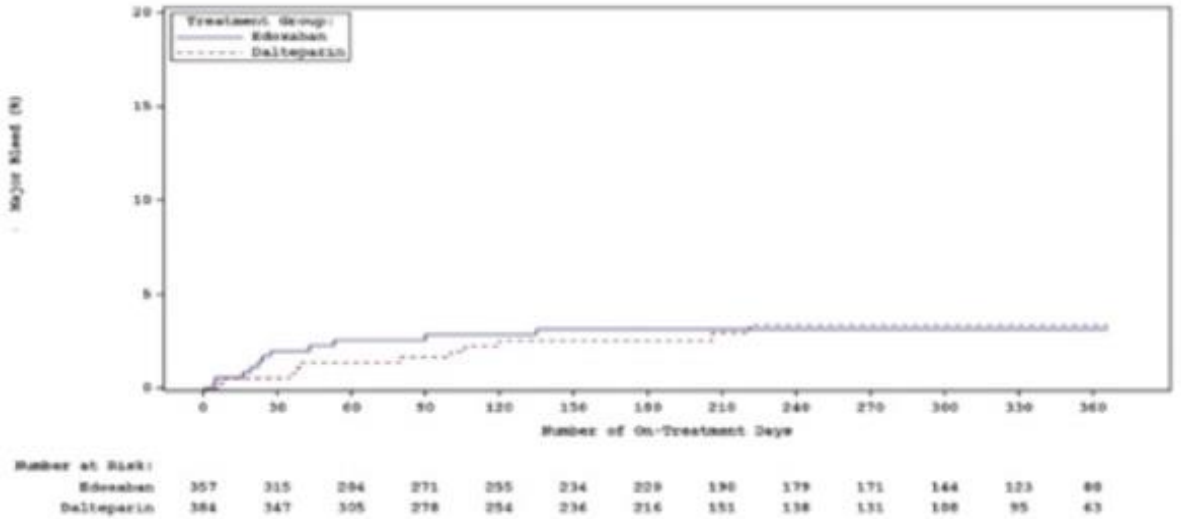
Raskob GE, et al. *N Engl J Med*. 2018;378:615-624.

DOAC for Cancer-Associated VTE
Bleeding

GI bleeds occurred in patients with GI cancers



GI cancers

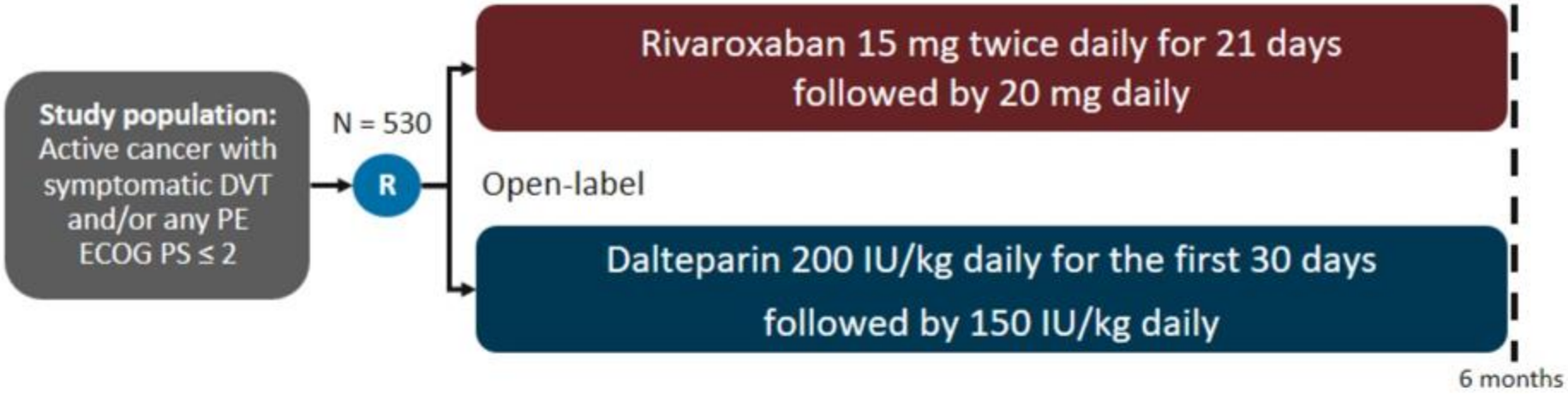


Non-GI cancers

Kraaijpoel N, et al. *Thromb Haemost*. 2018;118:1439-1449.

SELECT-D: Rivaroxaban vs Dalteparin for Treatment of CAT

Study design: prospective, randomized, open-label, multicenter pilot phase 3 study

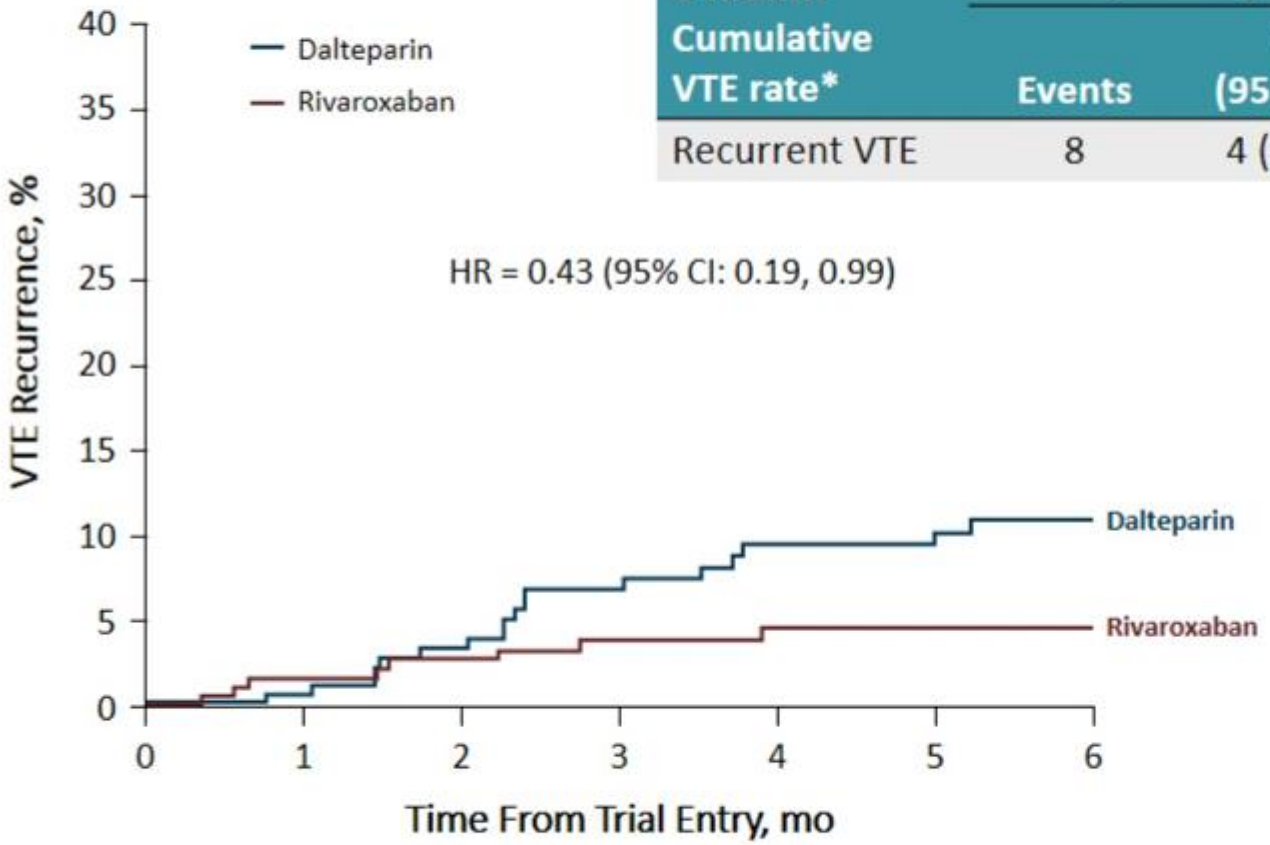


- Efficacy outcome: VTE recurrence at 6 months
- Safety outcome: major bleeding and CRNMB

Young A, et al. *Thromb Res.* 2016;140:S172-S173.

SELECT-D: Primary Outcome

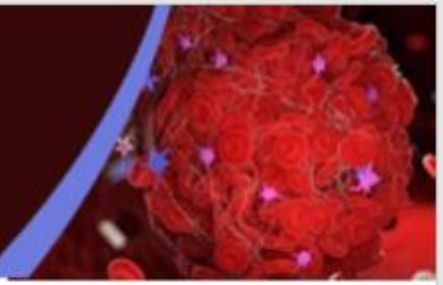
6-month Cumulative VTE rate*	Rivaroxaban (n = 203)		Dalteparin (n = 203)	
	Events	% (95% CI)	Events	% (95% CI)
Recurrent VTE	8	4 (2, 9)	18	11 (7, 16)



*Total 26 patients with recurrent VTE: 2 patients with symptomatic PE and 6 patients with incidental PE receiving dalteparin compared with 2 patients with symptomatic PE and 1 patient with incidental PE receiving rivaroxaban. There was 1 fatal PE in each arm.

Young AM, et al. *J Clin Oncol.* 2018:36:2017-2023.

Select-D Trial
Rivaroxaban vs Dalteparin for Cancer VTE



- 406 patients randomized to rivaroxaban or dalteparin
  - for 6 months
  - planned 2nd randomization to rivaroxaban or placebo for those with PE or residual leg vein thrombosis

- At 3 years
  - closed the 2nd randomization due to low accrual
  - Excluded patients with esophageal or gastric cancer per DSMB for imbalance in bleeding events

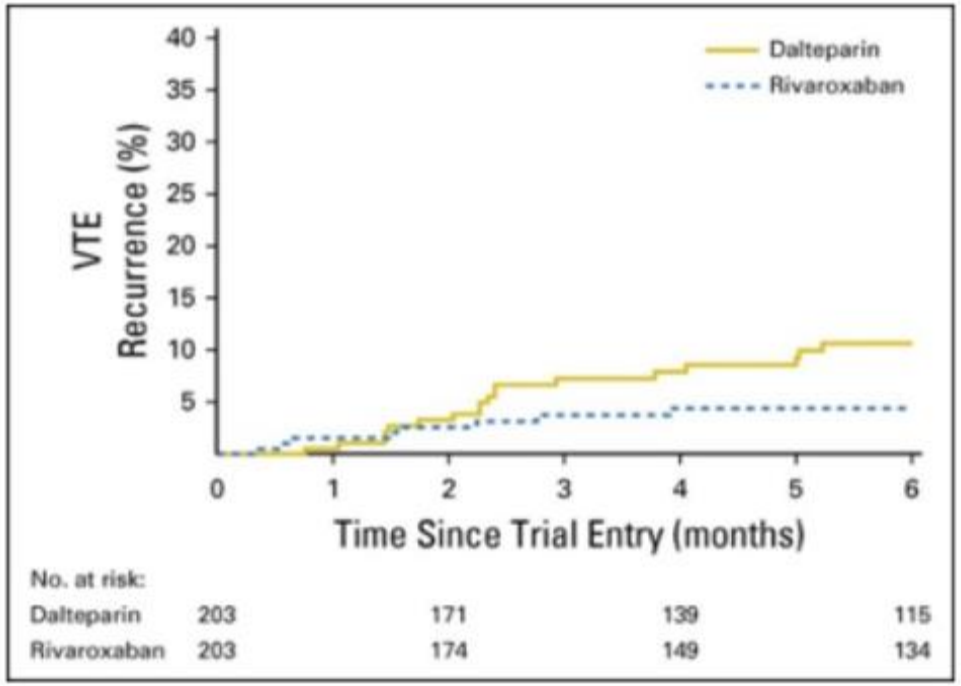
Young A, et al. *J Clin Oncol*. 2018;36:2017-2023.

Select-D Trial
Rivaroxaban vs Dalteparin for Cancer VTE (cont)

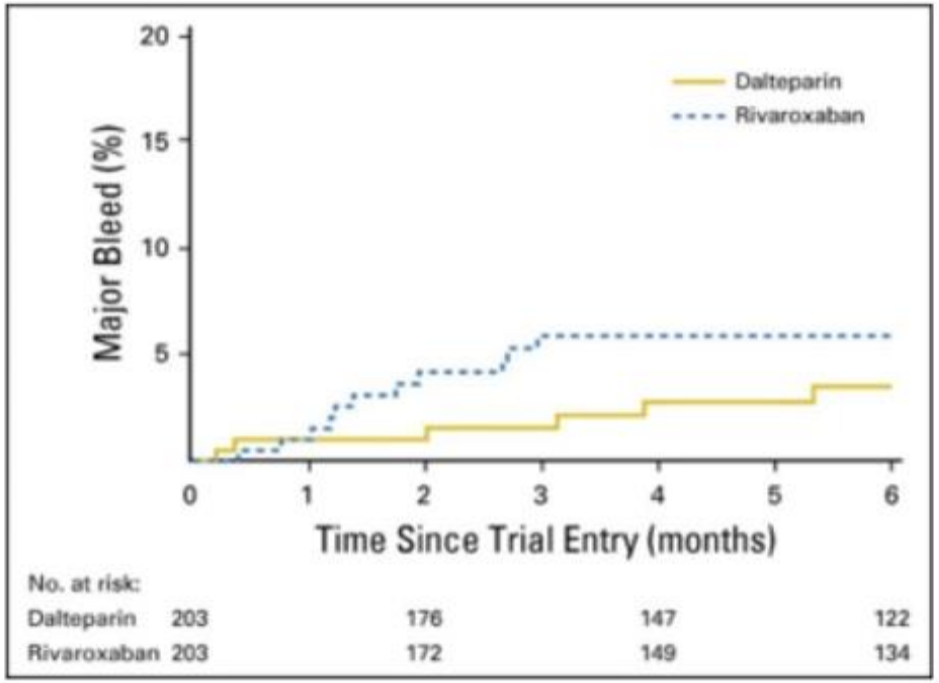
406 patients

58% metastatic disease
69% active treatment

DSMB excluded patients with esophageal and gastric cancers due to imbalance in bleeding



Recurrence: 4% vs 11%
HR 0.43; 95% CI: 0.19, 0.99



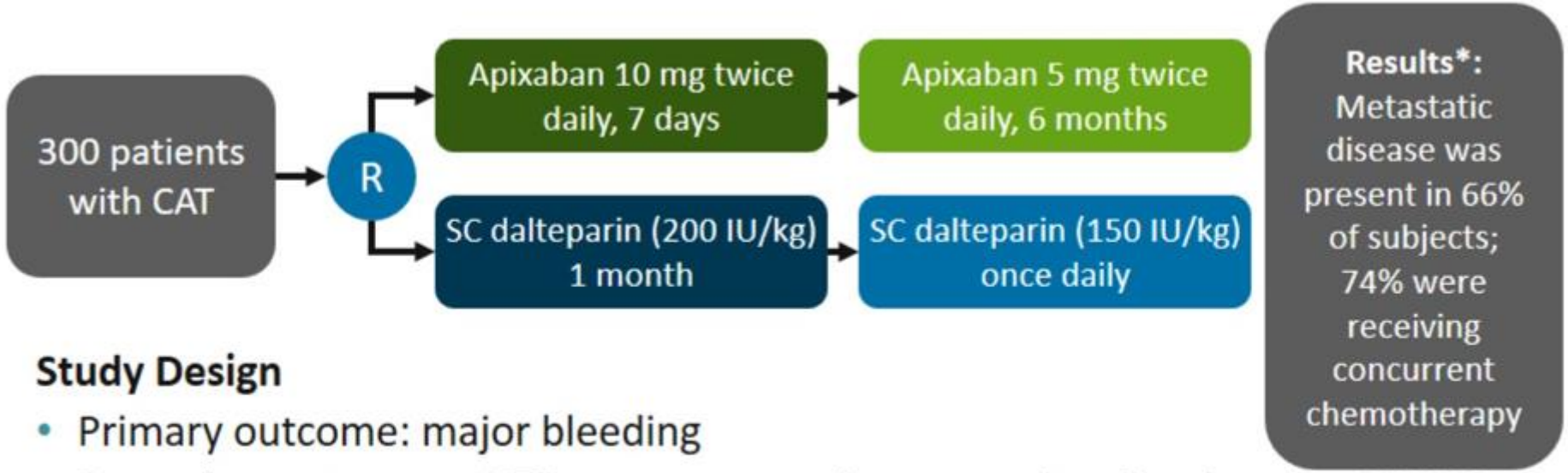
Major bleed: 6% vs 4%
HR, 1.83; 95% CI: 0.68, 4.96

CRNMB 13% vs 4%
HR, 3.76; 95% CI: 1.63, 8.69

Young A, et al. *J Clin Oncol*. 2018;36:2017-2023.

ADAM VTE Study

	Apixaban (n = 145)	Dalteparin (n = 142)	HR (95% CI)	*P* Value
Major bleeding	0%	1.4%	NR	
Major bleeding or CRNMB	6%	6%	NR	
Recurrent VTE	0.7%	6.3%	0.099 (0.013, 0.78)	.0281



Study Design

- Primary outcome: major bleeding
- Secondary outcomes: VTE recurrence and a composite of major plus CRNMB

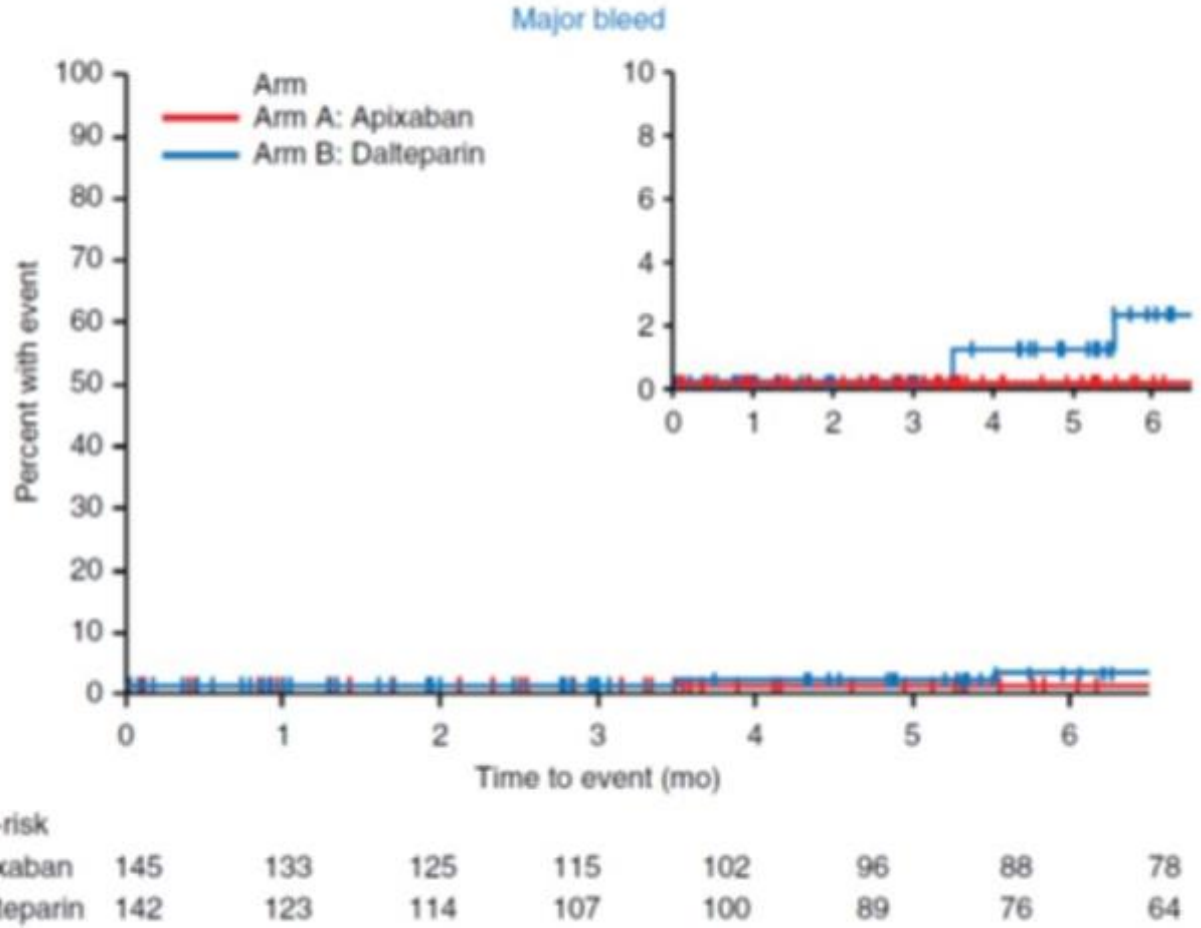
*287 were included in the primary analysis.

McBane RD, et al. *J Thromb Haemost*. 2019.

ADAM VTE
Primary Outcome

300 patients

- RCT: apixaban vs dalteparin
- Primary outcome: major bleeding
- Secondary: recurrent VTE
- QOL assessment
- Qualifying VTE varied



MAJOR BLEEDS

0% of 145 apixaban

1.4% of 142 dalteparin

McBane RD, et al. *J Thromb Haemost*. 2020;18:411-421.

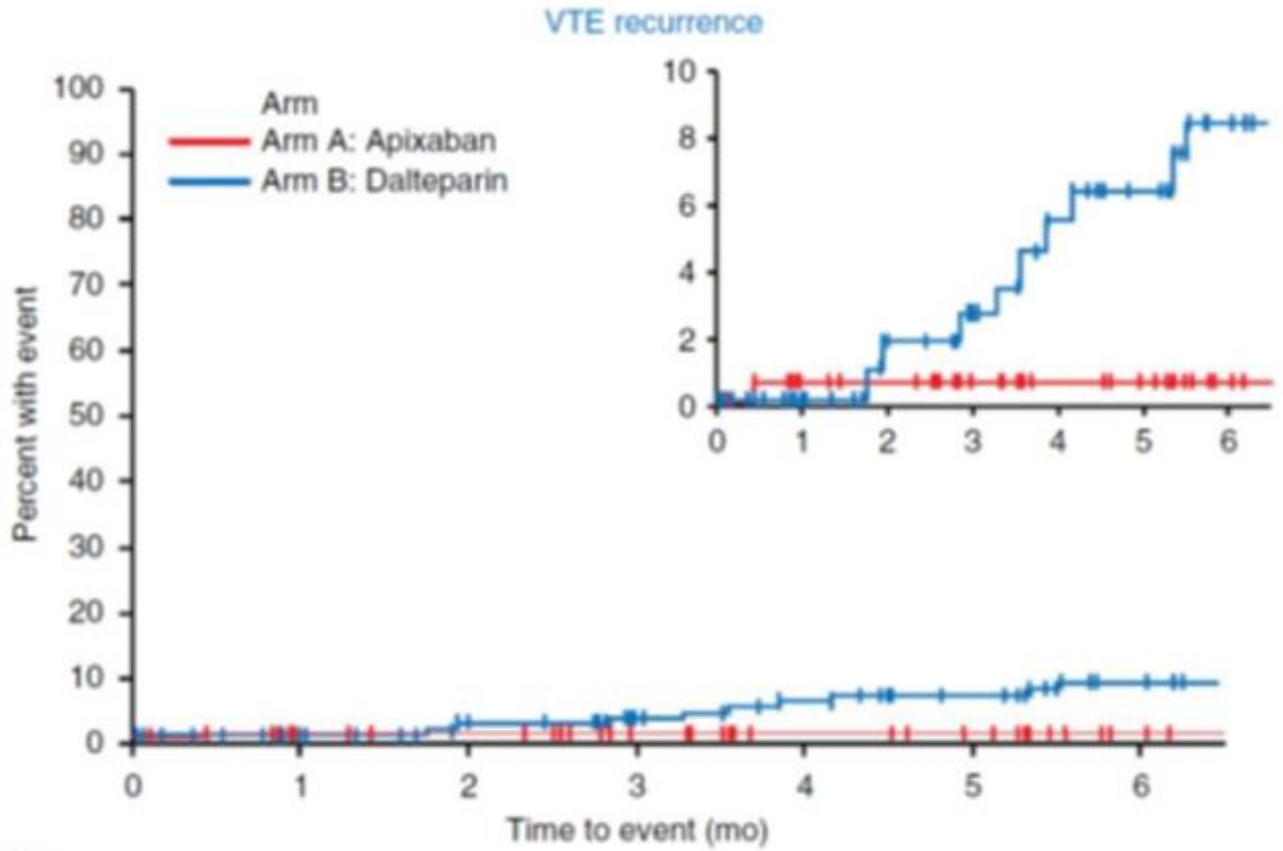
ADAM VTE
Secondary Outcome

VTE recurrence

- 0.7% apixaban
- 6.3% dalteparin

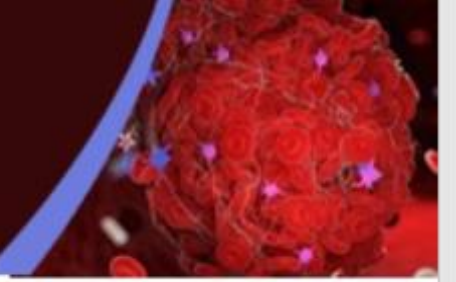
QOL

- Favored apixaban



McBane RD, et al. *J Thromb Haemost*. 2020;18:411-421.

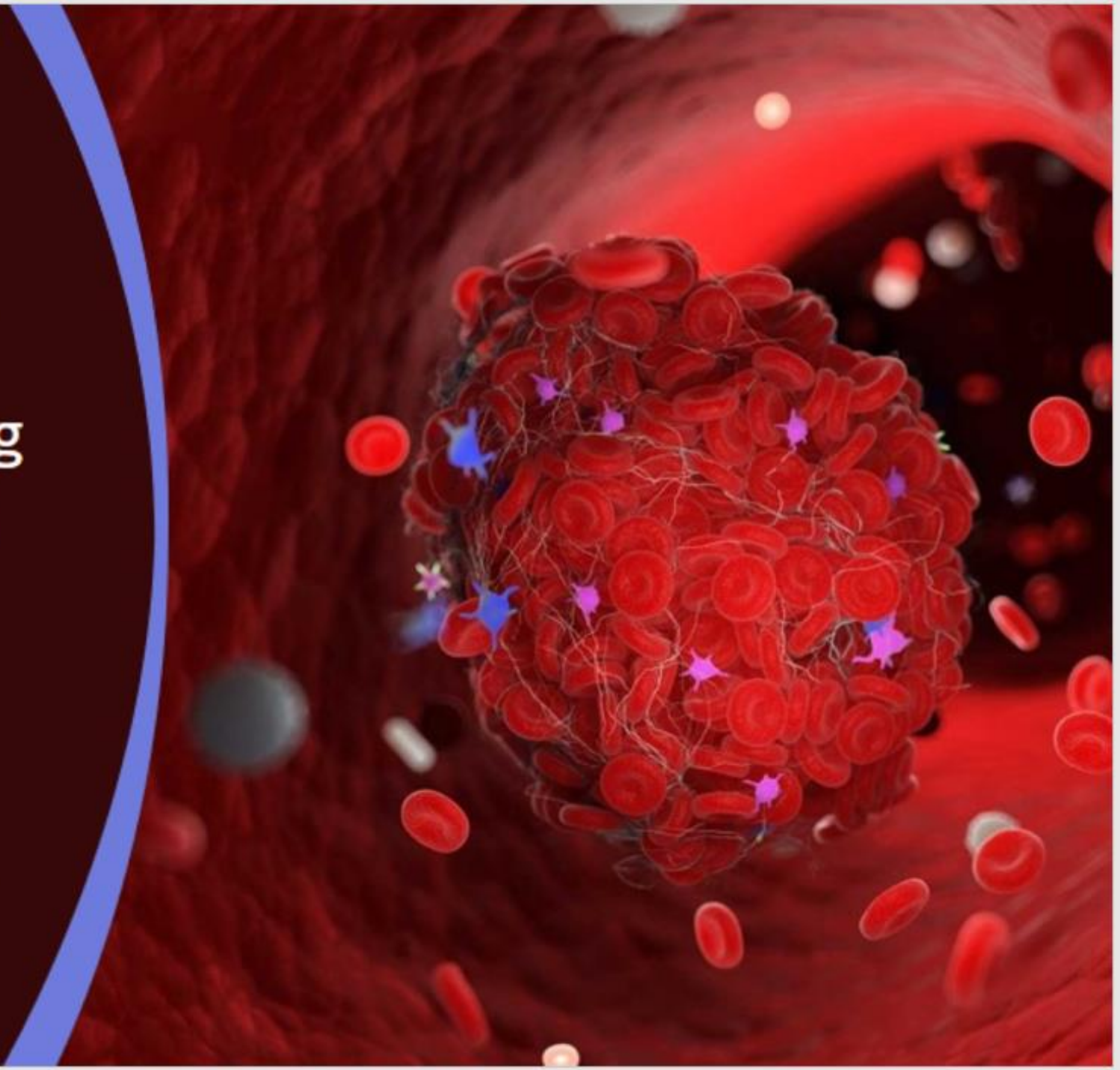
Acute Management of Cancer-Associated VTE



- Edoxaban and rivaroxaban non-inferior to dalteparin in preventing recurrent VTE in patients with cancer
- Increased major bleeding seen with both, especially GI bleeding in patients with GI malignancy
- No safety signal seen with apixaban in ADAM VTE
- Careful consideration and selection of patients is required to use edoxaban or rivaroxaban to treat cancer-associated VTE

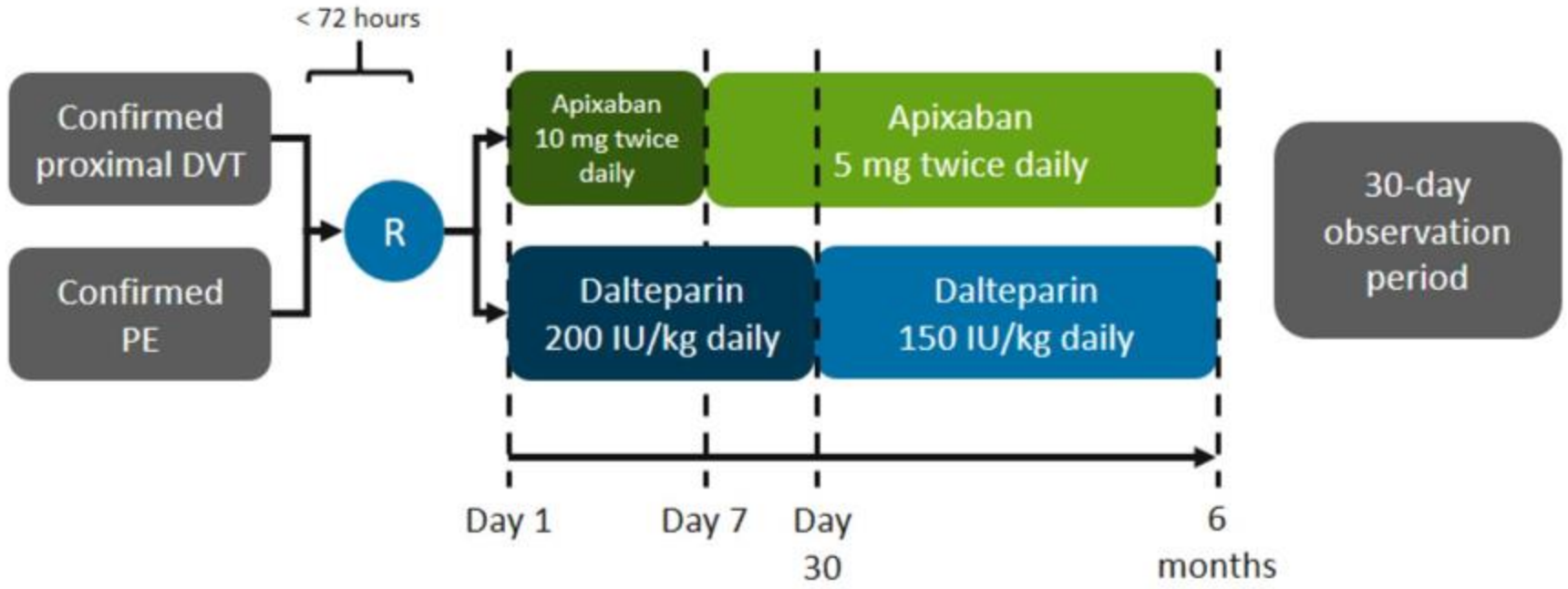
A Medscape LIVE! EVENT

What Do The Latest Trial Data Add When Assessing DOACs in Cancer-Related Thromboembolism?



Giancarlo Agnelli, MD
Dean
School of Medicine and Surgery of the University of Perugia, Italy
Professor of Internal Medicine
Director, Department of Internal Vascular Emergency Medicine and Stroke Unit
University Hospital
Perugia, Italy

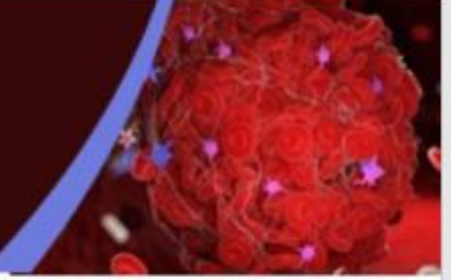
Caravaggio Study



- Primary outcome: recurrent VTE
- Safety outcome: major bleeding (ISTH)
- Results expected early 2020

Agnelli G, et al. *Thromb Haemost*. 2018;118:1668-1678.

CARAVAGGIO
Study Background



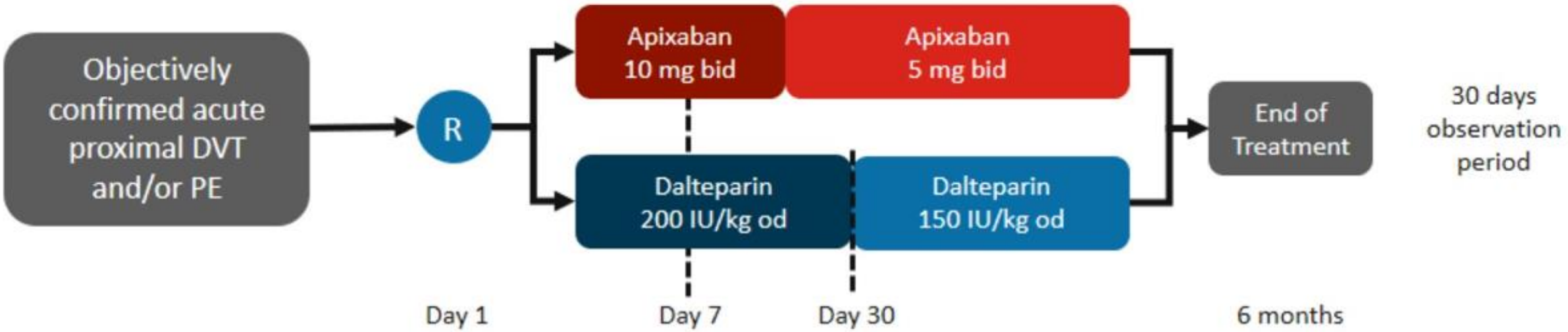
- The high risk of recurrent venous thromboembolism and bleeding in patients with cancer requires specific studies on anticoagulant treatment
- Major guidelines recommend low-molecular-weight heparin and have recently added edoxaban and rivaroxaban
- The clinical benefit of these oral agents is limited by the high risk of bleeding, mainly occurring at gastrointestinal sites

Agnelli G, et al. *N Engl J Med.* 2020;382:1599-1607.

The Caravaggio Study

Aim: To assess whether oral apixaban was non-inferior to subcutaneous dalteparin for the treatment of proximal DVT and/or PE in patients with cancer

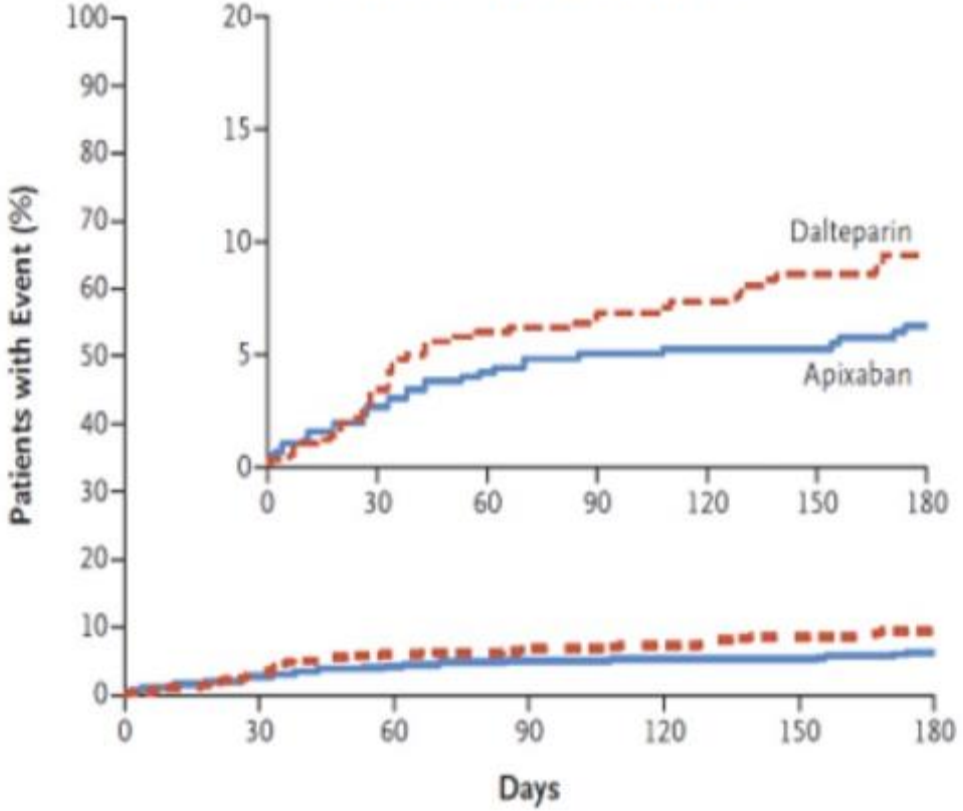
Design: Randomized, open-label, PROBE, non-inferiority study



Agnelli G, et al. *N Engl J Med*. 2020;382:1599-1607.

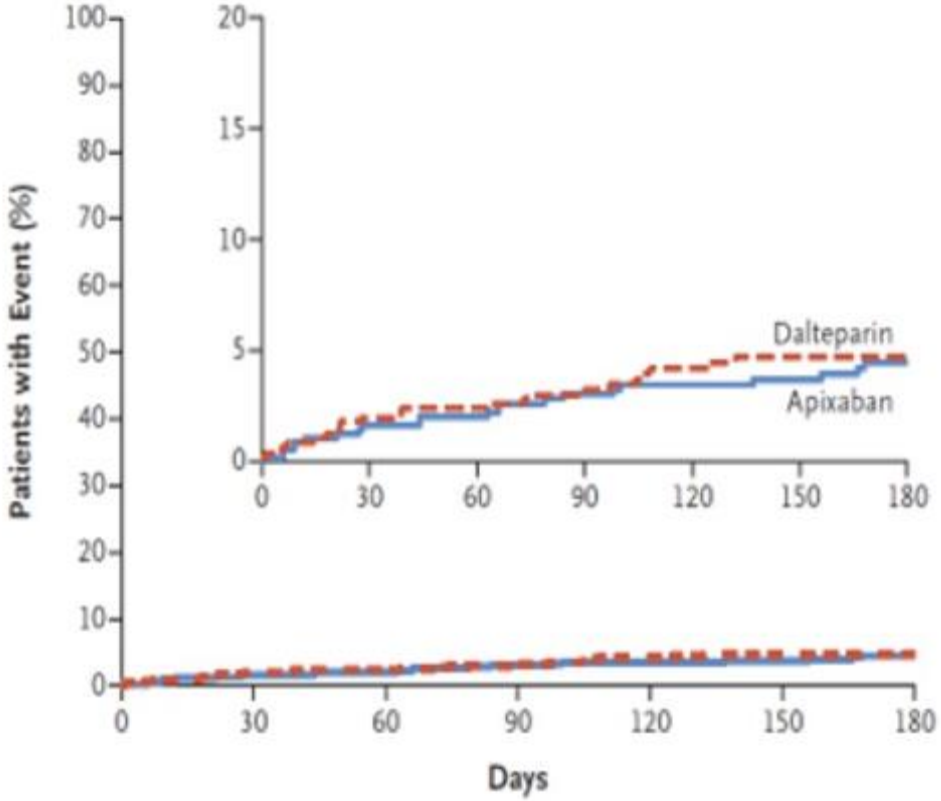
Cumulative Event Rate of VTE Recurrences and Major Bleeding

Recurrent VTE



No. at Risk							
Dalteparin	579	507	462	417	383	352	217
Apixaban	575	522	481	453	424	399	241

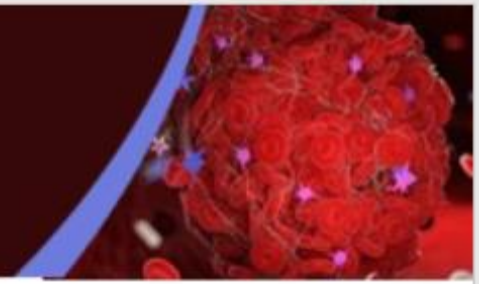
Major Bleeding



No. at Risk							
Dalteparin	579	510	473	430	387	355	222
Apixaban	575	527	490	458	427	402	238

Agnelli G, et al. *N Engl J Med.* 2020;382:1599-1607.

Conclusions

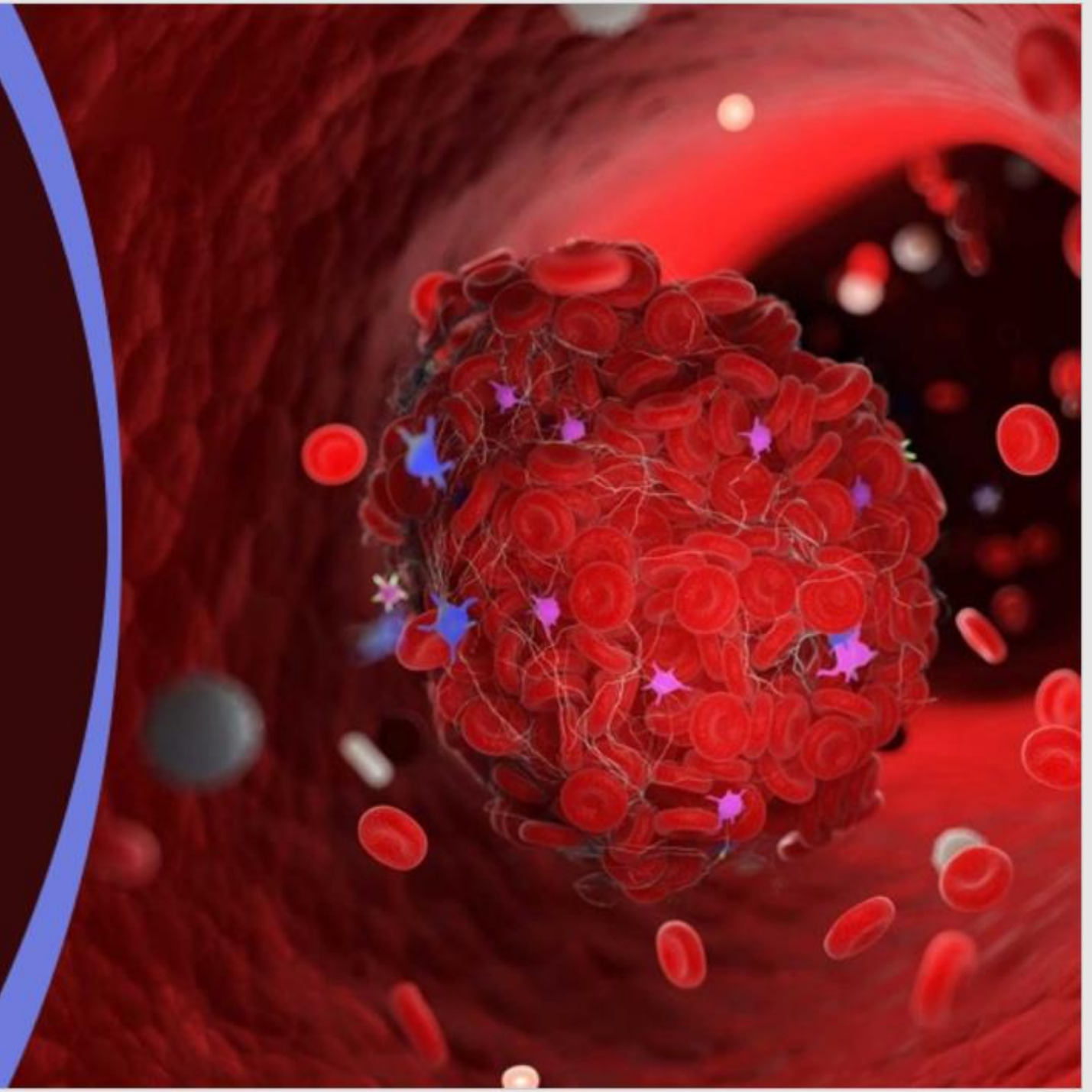


- Oral apixaban was noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism
- No increase in the risk of major bleeding was observed in particular at the gastrointestinal sites
- Findings of Caravaggio expand the proportion of patients with cancer-associated thrombosis who are eligible for treatment with oral direct anticoagulants, including patients with gastrointestinal cancer

Agnelli G, et al. *N Engl J Med*. 2020;382:1599-1607.

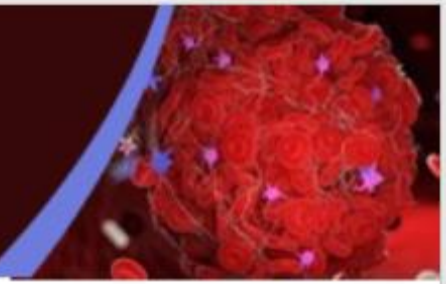
A Medscape LIVE! EVENT

Should DOACs Be Used in Patients With GI Cancer-Associated VTE?



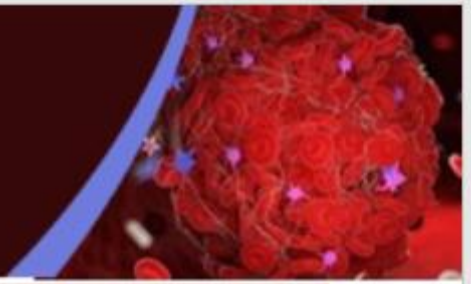
Lord Ajay K. Kakkar, MD, PhD, FRCP, FRCS
Professor of Surgery
University College London
Chairman of University College London
Partners Academic Health Science Partnership
Director of the Thrombosis Research Institute
London, United Kingdom

My Talk Today



- ✓ The Burden of GI cancer and bleeding
- ✓ DOACs in CAT management: GI cancer
- ✓ Clinical considerations

First VTE in Patients With Active Cancer
20% Are GI Cancers



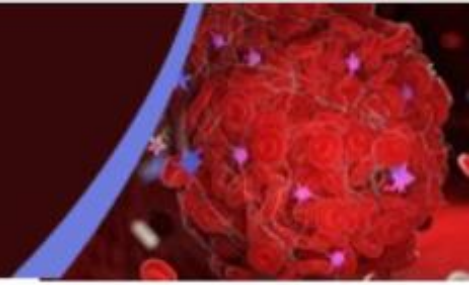
Common cancer types,* n (%)	DVT (n = 3055)	PE (n = 3537)	Total (N = 6592)
Prostate (males)	278 (19.1)	287 (16.1)	565 (17.5)
Breast (females)	225 (14.0)	281 (16.0)	506 (15.1)
Lung	315 (10.3)	603 (17.0)	918 (13.9)
Colon	384 (12.6)	443 (12.5)	827 (12.5)
Hematological	360 (11.8)	309 (8.7)	669 (10.1)
Ovarian (females)	136 (8.5)	182 (10.3)	318 (9.5)
Bladder	186 (6.1)	133 (3.8)	319 (4.8)
Uterus (females)	83 (5.2)	58 (3.3)	141 (4.2)
Pancreas	129 (4.2)	131 (3.7)	260 (3.9)
Stomach	104 (3.4)	133 (3.8)	237 (3.6)
Brain	79 (2.6)	87 (2.5)	166 (2.5)

Patients with active cancer and a first VTE (N=6592). Active cancer was defined as a primary diagnosis of cancer (excluding non-melanoma skin cancer) as a hospital discharge diagnosis or treatment with radiation, chemotherapy, or bone marrow transplantation during hospitalization.

*Patients allocated to different cancer types when ≥2 were recorded on the same day. For some, no cancer type was specified.

Cohen AT, et al. *Thromb Haemost.* 2017;117:57-65.

Burden of GI Bleeding



- Upper GI bleeding results in 61 hospital admissions per 100,000 population annually in the United States[a]
- Tumor-related bleeding is thought to account for 1 to 5% of all episodes of upper GI bleeds[b-d] and 12 to 15% of acute GI hemorrhage[e,f]
- GI bleeding has been shown to occur in 30-40% of patients with GI stromal tumors[g-i]

a. Laine L, et al. *Am J Gastroenterol.* 2012;107:1190-1195; b. Laine L, et al. *West J Med*. 1991. 15:274-5. c. Loftus et al. *Mayo Clin Proc* 1994. 69:736-40 d. Savides et al. *Endoscopy*. 1996. 28:244-8. e. Lightdale et al. *JAMA*. 1973 226(2);139-41 f. Shivshanker et al. *Gastrointest Endosc*. 1983 29(4):273-5 g. Liu et al. *Biomed Res Int.* 2017. 7152406. h. Nilsson et al. *Cancer*. 2005. 103(4):821-9 i. Rammohan et al. *World J Gastrointest Oncol*. 2013. 15;5(6)

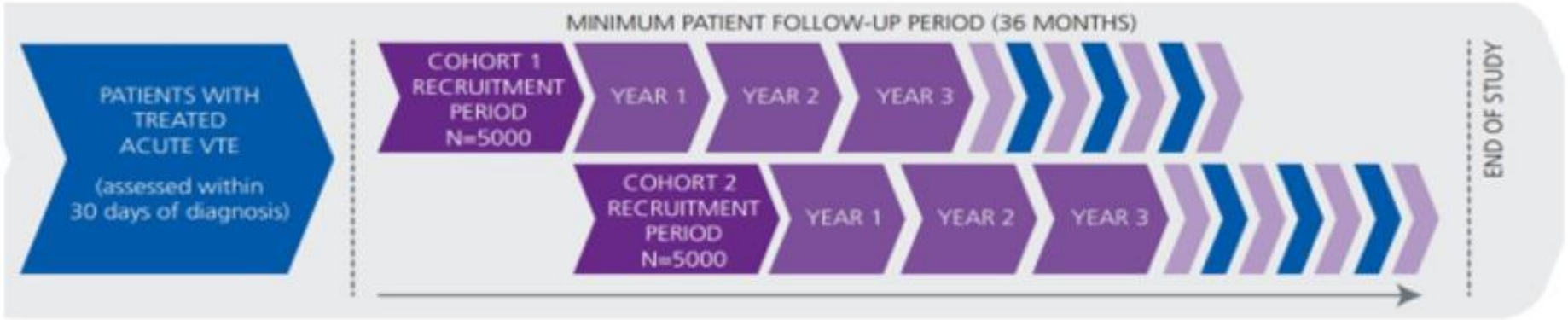
GARFIELD-VTE: A Global Disease Registry

Design

- Independent academic research initiative
- 10,000 newly diagnosed VTE patients in 28 countries
- Randomised selection of sites representative of national VTE care settings
- Unselected prospective patients enrolled consecutively
- Long-term follow-up (minimum of 3 yrs)
- Two sequential cohorts of 5000 pateints

Audit requirements

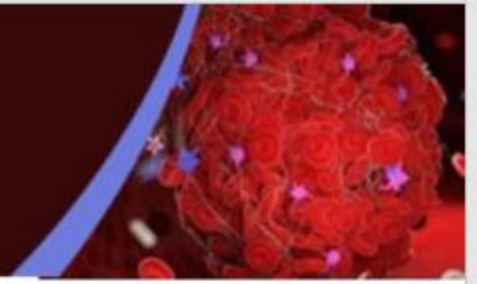
- 10% of all CRFs monitored against source documentation
- Electronic audit trail for all data modifications
- Critical variables subjected to additional audit
- Compliant with Declaration of Helsinki



N.B. Striped area indicates possible follow-up for up to 2 years after the initial 36-month follow-up period
ClinicalTrials.gov identifier: NCT02155491

Weitz J et al, *Thromb Haemost.* 2016;116(6):1172-1179.

Garfield VTE
Outcomes in GI and Non-GI Cancer

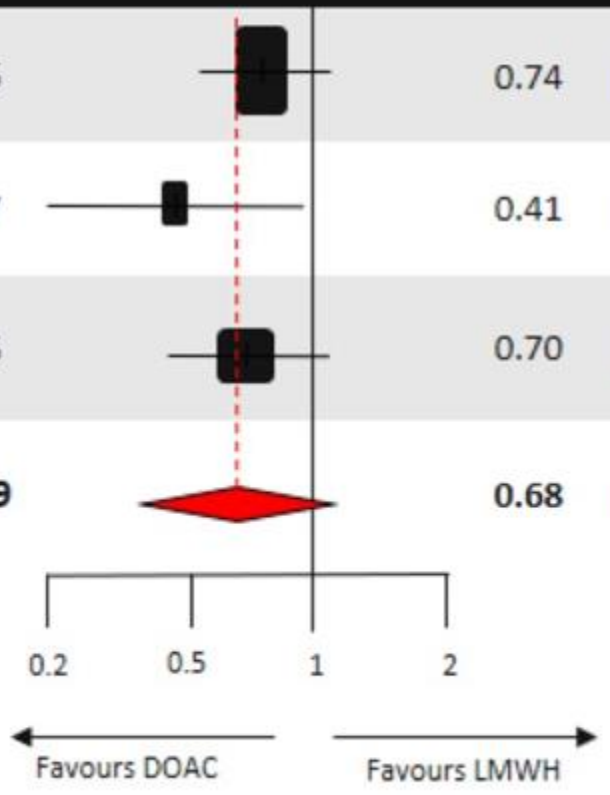


	Recurrent VTE		Major bleeding	
	GI Cancer (n = 53)	Non-GI Cancer (n = 917)	GI Cancer (n = 53)	Non-GI Cancer (n = 917)
3 months	18.8 (4.7-75.3)	17.6 (12.7-24.3)	69.0 (32.9-144.8)	19.5 (14.3-26.5)
6 months	15.4 (5.0-47.6)	12.6 (9.4-12.7)	49.1 (25.5-94.3)	49.1 (25.5-94.3)
12 months	11.7 (4.4-31.3)	8.9 (6.9-11.6)	32.0 (17.2-59.4)	32.0 (17.2-59.4)
24 months	7.8 (2.9-20.9)	7.2 (5.8-9.0)	6.3 (5.0-8.0)	21.3 (11.4-39.5)

Event rates are shown per 100 person-years (95% confidence interval)
Unpublished data

Recurrent VTE in CAT
DOAC vs. LMWH

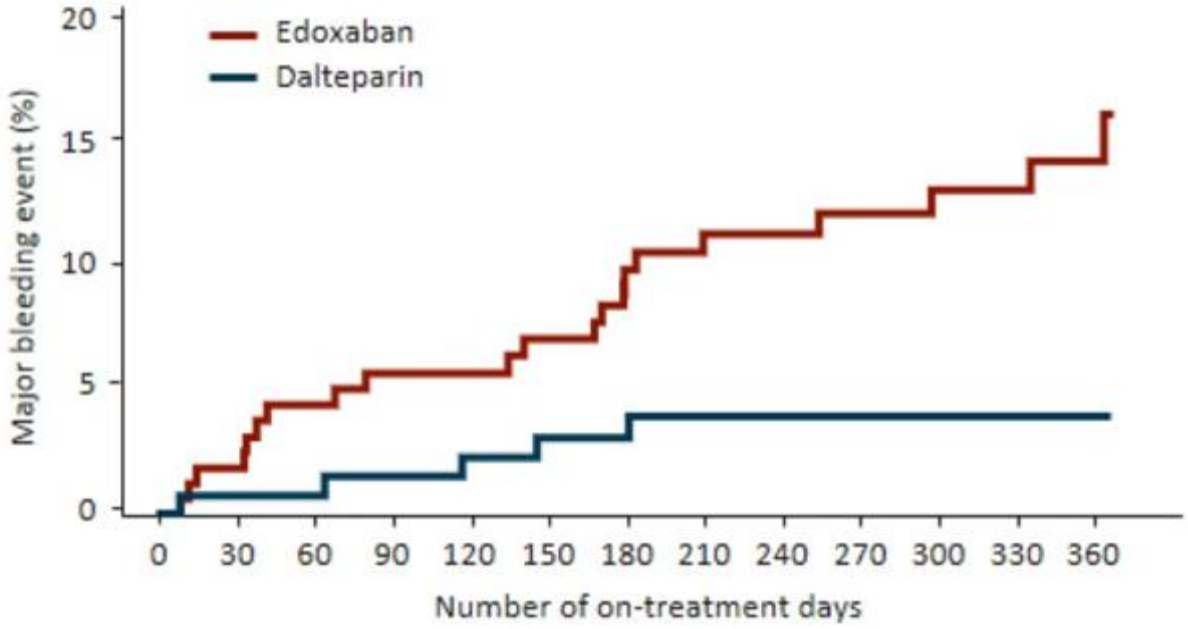
Study	DOAC agent	DOAC		LMWH		Risk Ratio	RR	95% CI	Weight
		Patients	Event	Patients	Event				
Hokusai VTE Cancer	Edoxaban	522	34	524	46		0.74	[0.48; 1.14]	45.4%
SELECT-D	Rivaroxaban	203	7	203	17		0.41	[0.17; 0.97]	11.2%
Caravaggio	Apixaban	576	32	579	46		0.70	[0.45; 1.08]	43.4%
Random effects model **Heterogeneity: I^2 = 0%, t^2< 0.0001, p = .48**		**1301**	**73**	**1306**	**109**		**0.68**	**[0.39; 1.17]**	**100.0%**



Mulder et al. *Blood*. 2020 May 12;blood.2020005819.

Hokusai-VTE-Cancer
Major Bleeding Events in GI Cancer

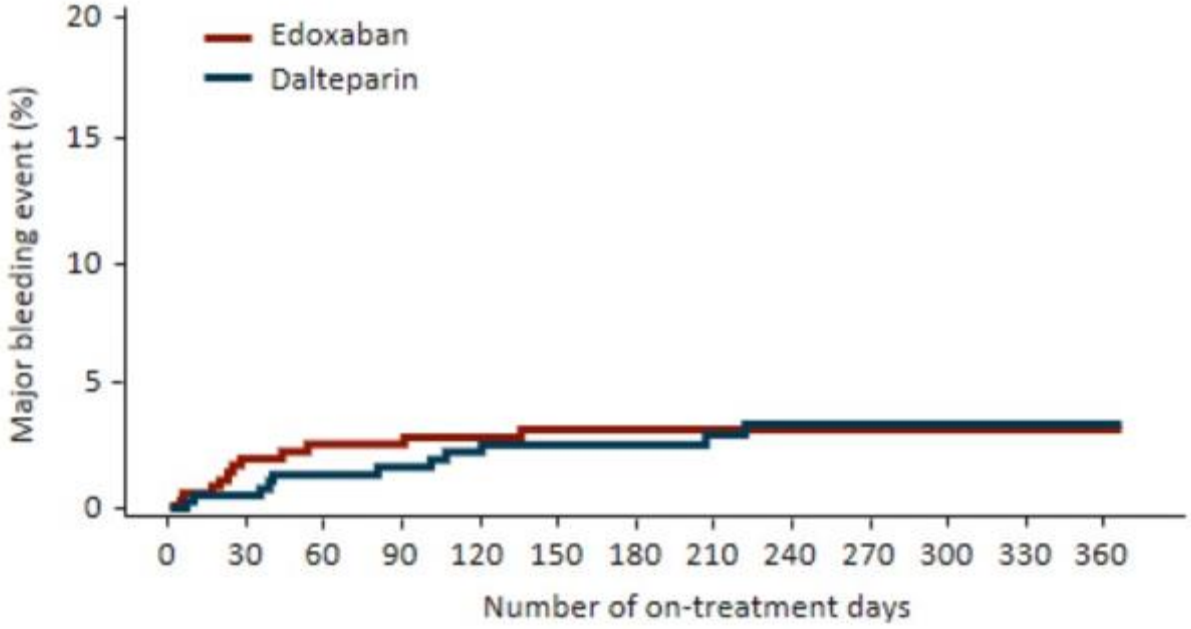
Patients With GI Cancer



Number at risk

Edoxaban	165	134	121	108	97	89	79	70	64	59	48	38	28
Dalteparin	140	123	116	108	94	89	79	67	60	54	48	40	25

Patients With Non-GI Cancer



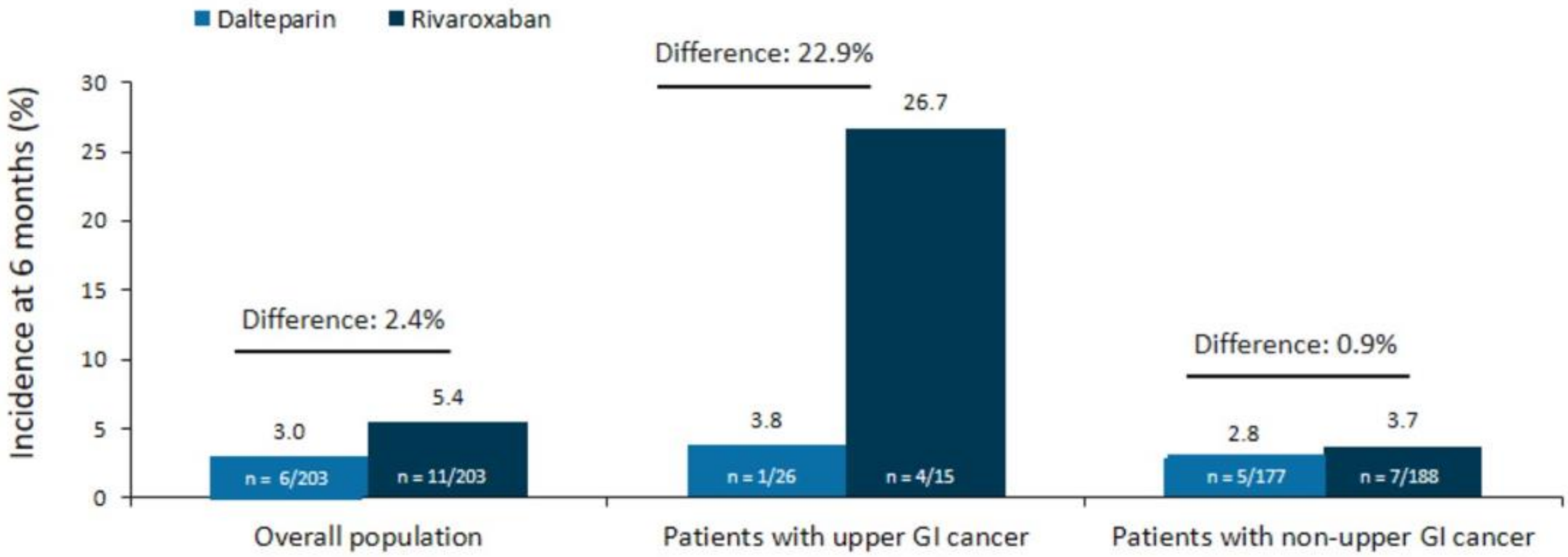
Number at risk

Edoxaban	357	315	284	271	255	234	220	190	179	171	144	123	88
Dalteparin	384	347	305	278	254	236	216	151	138	131	108	95	63

Kraaijpoel N, et al. *Thromb Haemost.* 2018;118:1439-1449.

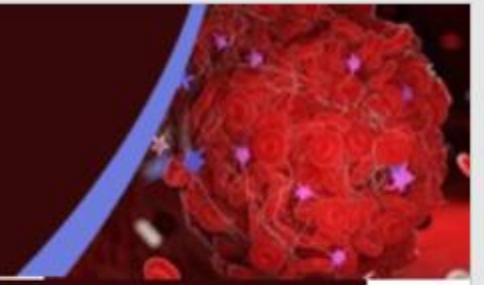
SELECT-D
Major Bleeding Events in Upper GI Cancer

Incidence of major bleeding events in SELECT-D



Equivalent results for CARAVAGGIO are currently unavailable but publication expected.
Results show percentage of patients with an event in the 'at risk' population. Upper GI cancer included esophageal, gastroesophageal, and gastric primary tumor types.
Young AM, et al. *J Clin Oncol.* 2018:36:2017-2023.

Major Bleeding Events in DOAC vs. LMWH Studies



	SELECT-D (6 months)[a]		CARAVAGGIO (6 months)[b]		Hokusai-VTE-Cancer (12 months)*[c]	
	Rivaroxaban (n = 203)	Dalteparin (n = 203)	Apixaban (n = 576)	Dalteparin (n = 579)	Edoxaban (n = 522)	Dalteparin (n = 524)
Overall (n of patients)	11 (5.4)	6 (3.0)	22 (3.8)	23 (4.0)	33 (6.3)	17 (3.2)
Fatal	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.3)	0	2 (0.4)
Site (n of events)						
Intracranial	0	0	0 (0.0)	2 (0.3)	2 (0.4)	4 (0.8)
Genitourinary	1 (0.5)	0	4 (0.7)	1 (0.2)	5 (1.0)	0
Lung	0	0	1 (0.2)	1 (0.2)	NR	NR
Upper airways	0	0	1 (0.2)	2 (0.3)	NR	NR
Gastrointestinal	8 (3.9)	4 (2.0)	11 (1.9)	10 (1.7)	20 (3.8)	6 (1.1)
Upper	5 (2.5)	4 (2.0)	5 (0.9)	6 (1.0)	17 (3.3)	3 (0.6)
Lower	1 (0.5)	0	6 (1.0)	4 (0.7)	3 (0.6)	3 (0.6)
Unknown	2 (1.0)	0	0	0	0	0
Unknown	0	0	2 (0.3)	2 (0.3)	0	0
Other	2 (1.0)	2 (1.0)	3 (0.5)	6 (1.0)	6 (1.1)	7 (1.3)

Data are n (%). *Type of outcome contributing to the primary outcome of first recurrent VTE or major bleeding during the 12-month study period.

a. Young AM, et al. *J Clin Oncol.* 2018;36:2017-2023; b. Agnelli G ,et al. *N Engl J Med.* 2020;382:1599-1607; c. Raskob GE, et al. *N Engl J Med.* 2018;378:615-624.

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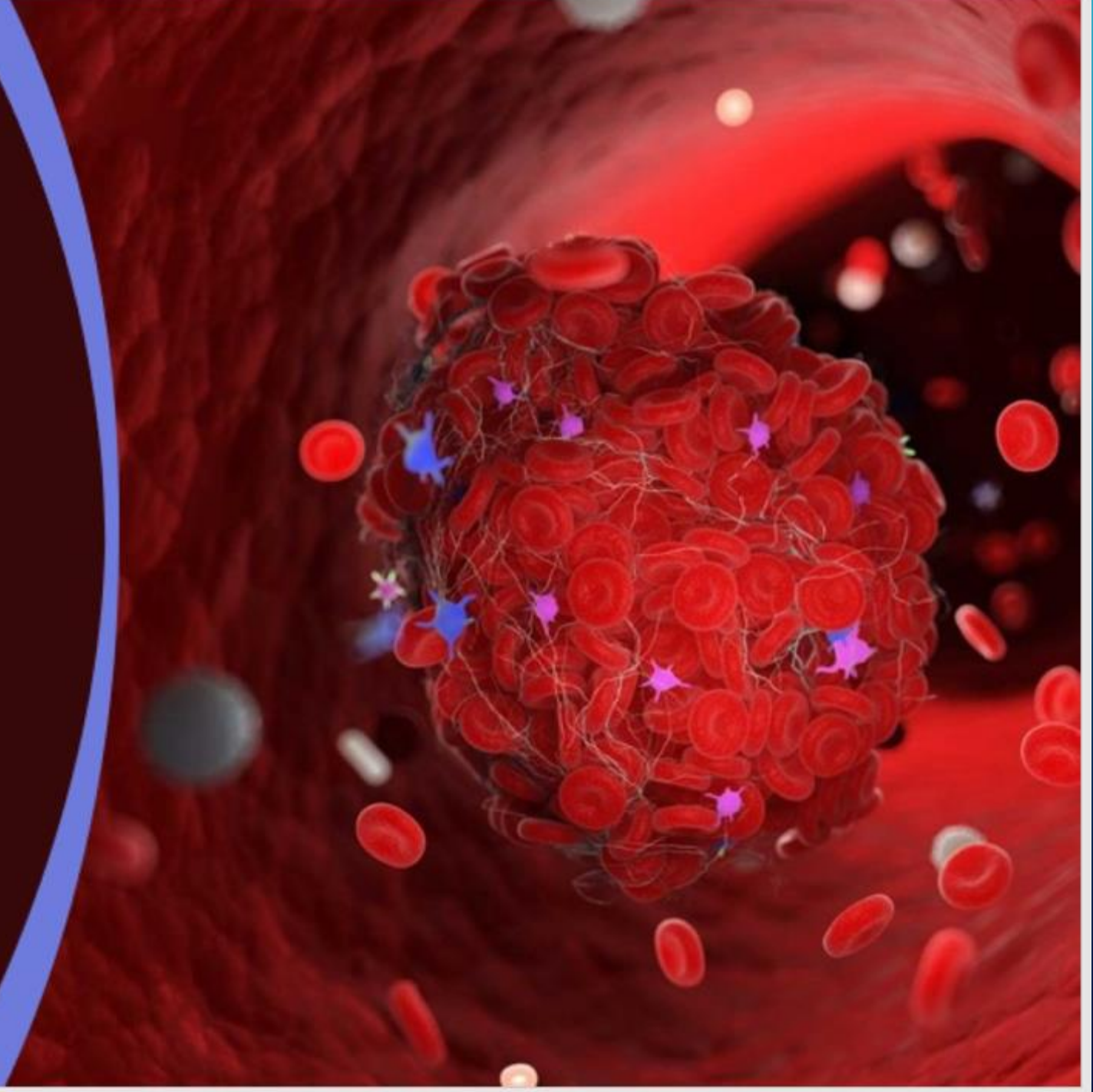
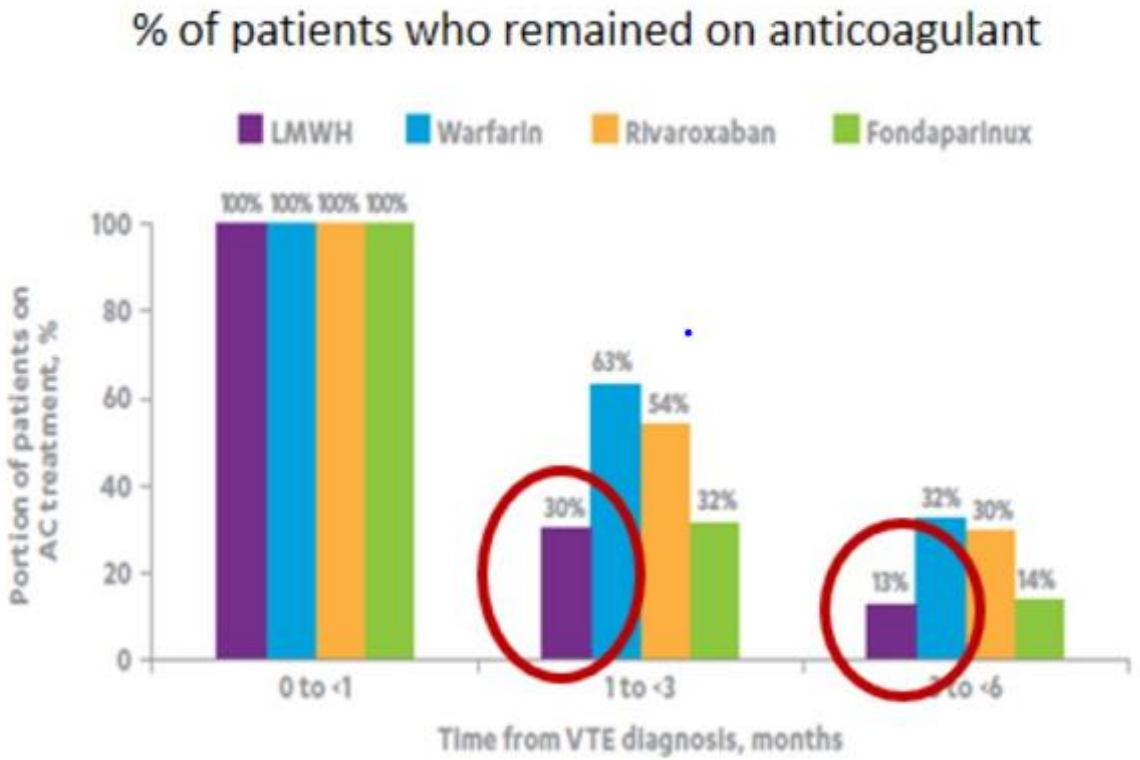
What Can We Expect From Revised Treatment Guidelines?



Alok A. Khorana, MD, FACP, FASCO
Sondra and Stephen Hardis Chair in Oncology Research
Professor of Medicine
Cleveland Clinic Lerner College of Medicine
Taussig Cancer Institute and Case Comprehensive Cancer Center
Cleveland, Ohio, United States

Real World Anticoagulant Use
Duration



N = 52,911 US cancer patients with VTE, 2009-2014

? Cost: "Financial toxicity"

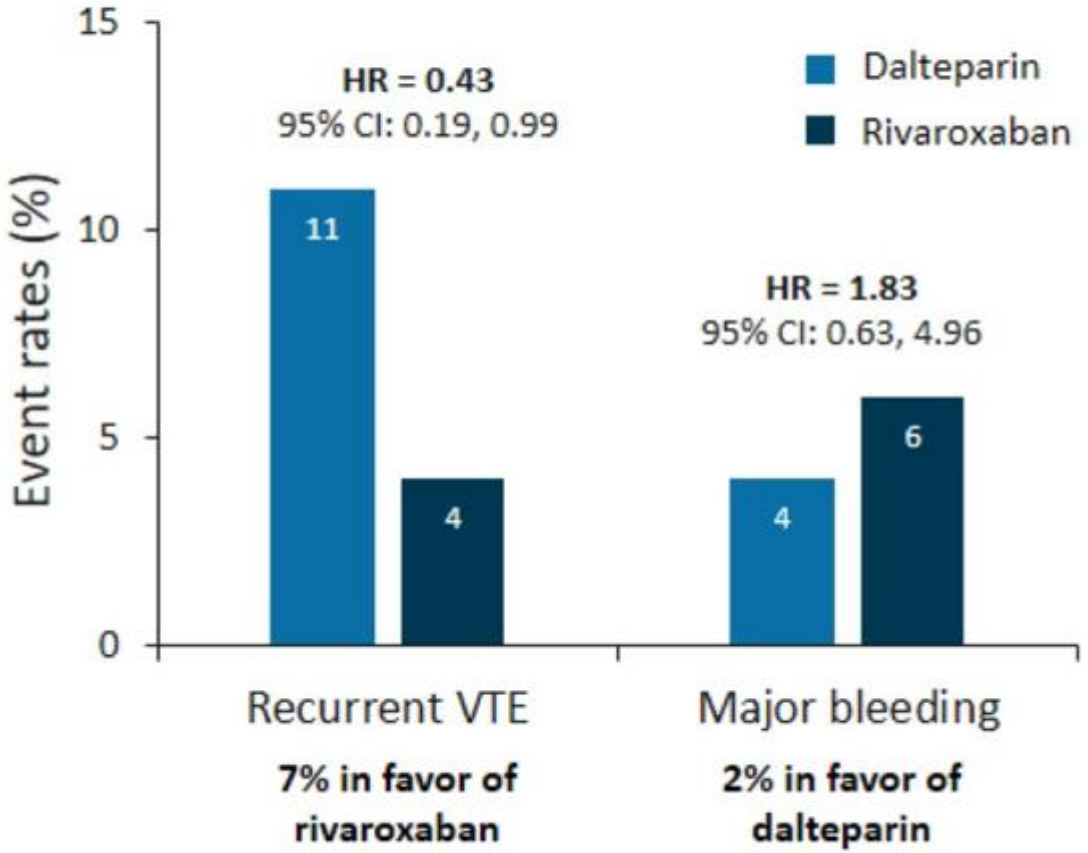
- Cleveland Clinic Pharmacy Ohio AWP
- Enoxaparin $1000 to 1200/month
- DOACs ~$460/month
- Co-payments for injectables often higher or even unaffordable

? Quality of life, convenience (daily self-injections)

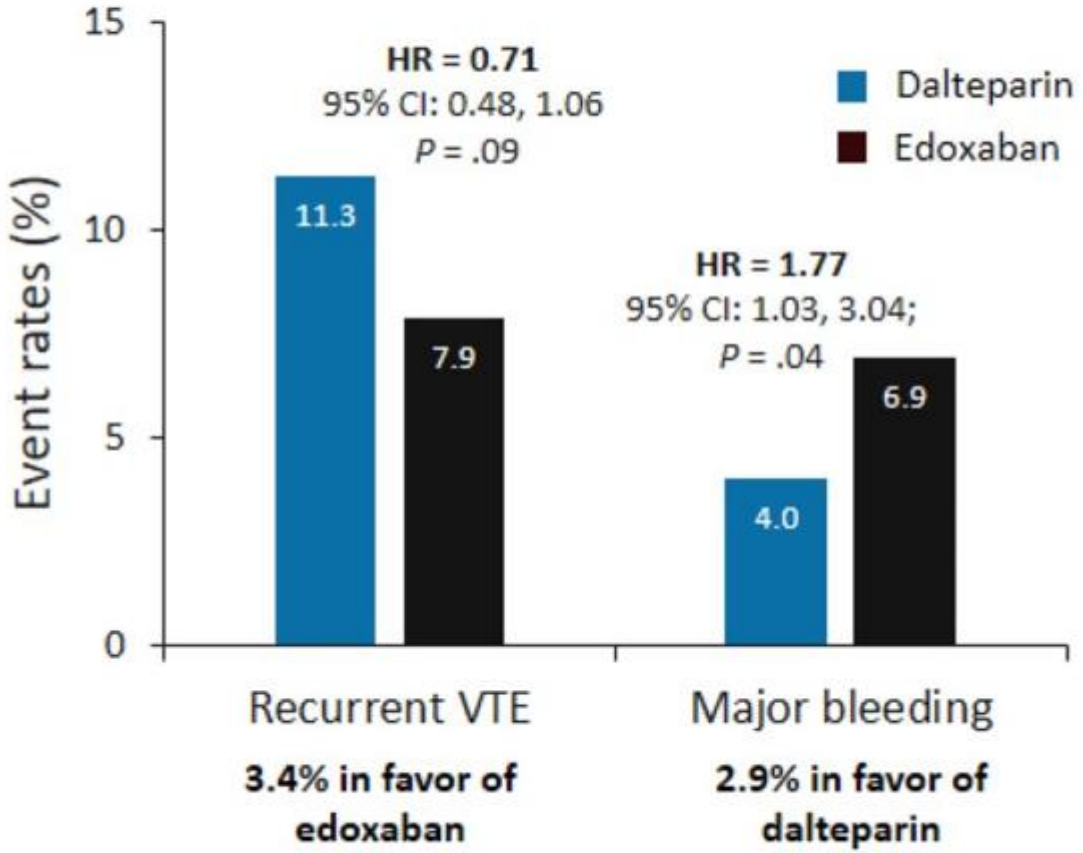
Khorana AA, et al. *Throm Res.* 2016;145:51-53.; goodrx.com

DOACs for Treatment of CAT
SELECT-D and Hokusai VTE Cancer

SELECT-D*[a]



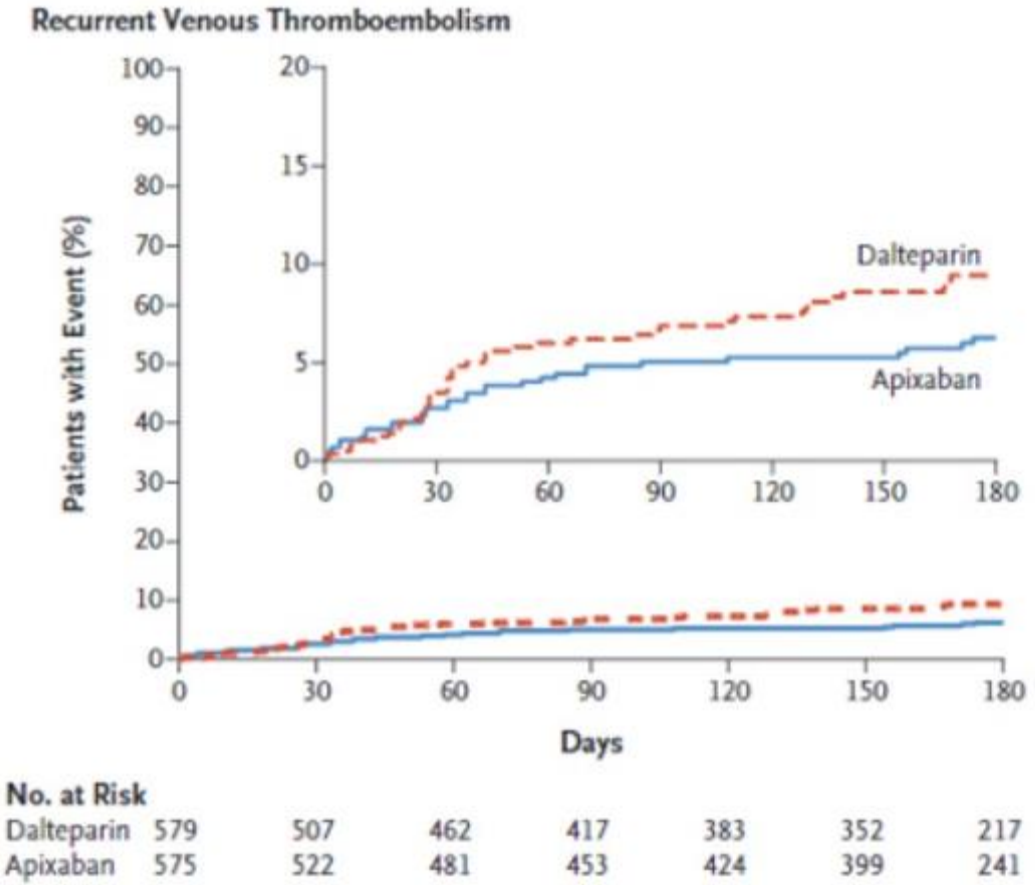
Hokusai VTE Cancer†[b]

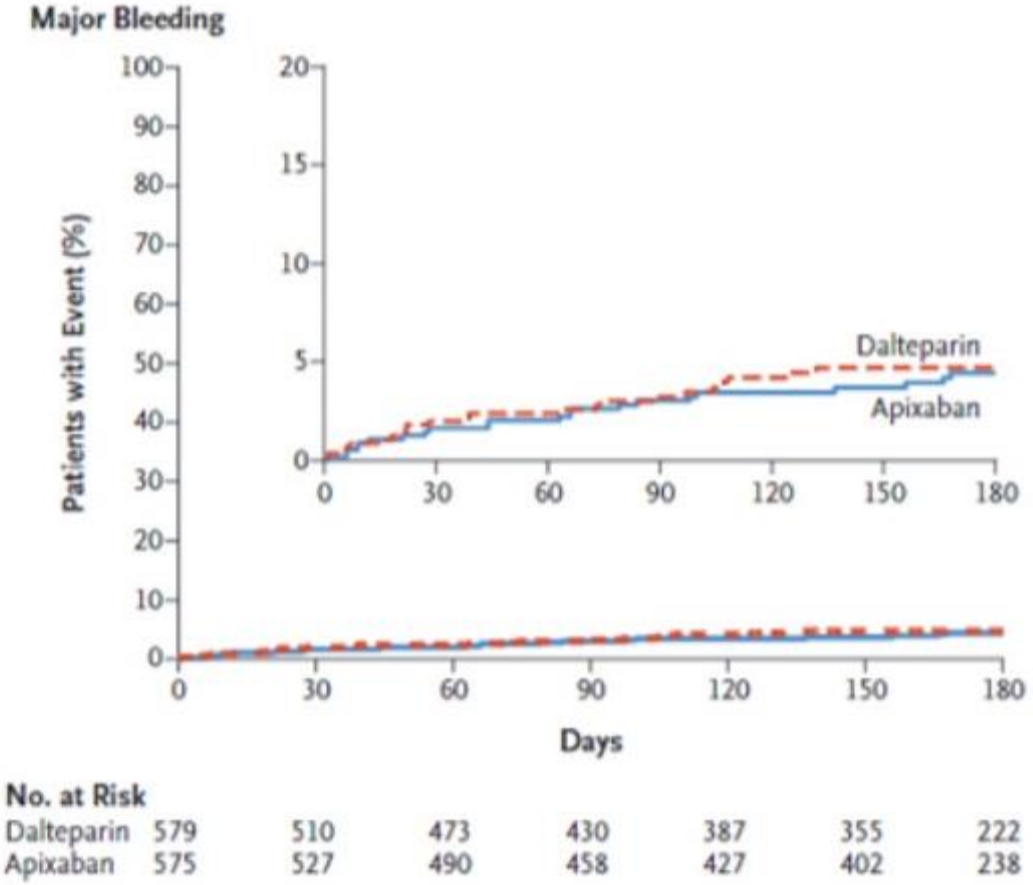


*Results reported are 6-month cumulative event rates; †Results reported are number and percentage of events at 12 months.

a. Young A, et al. *J Clin Oncol*. 2018;36:2017-2023; b. Raskob GE, et al. *N Engl J Med*. 2018;378:615-624.

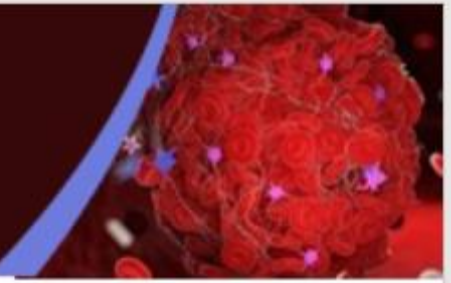
DOACs for Treatment of CAT
CARAVAGGIO





Agnelli G, et al. *N Engl J Med.* 2020;382:1599-1607.

What Can We Expect From Revised Guidelines?



Guideline			
ISTH	**ASCO©**	**ITAC**	**NCCN**
Low risk for bleeding, no DDI: edoxaban or rivaroxaban (LMWH acceptable alternative) High-risk for bleeding or DDI: LMWH (DOACs acceptable alternative)	Initial: LMWH, fondaparinux, rivaroxaban Long-term: LMWH, edoxaban, rivaroxaban Caution: GI, GU cancers	LMWH or DOAC (rivaroxaban/ edoxaban), caution with GI cancers	DOACs (apixaban, edoxaban, rivaroxaban) preferred if no GE/gastric cancer LMWH preferred if GE/gastric cancer

THROMBOSIS AND CANCER

Question 4

Should this patient be managed differently if this were an incidental finding?

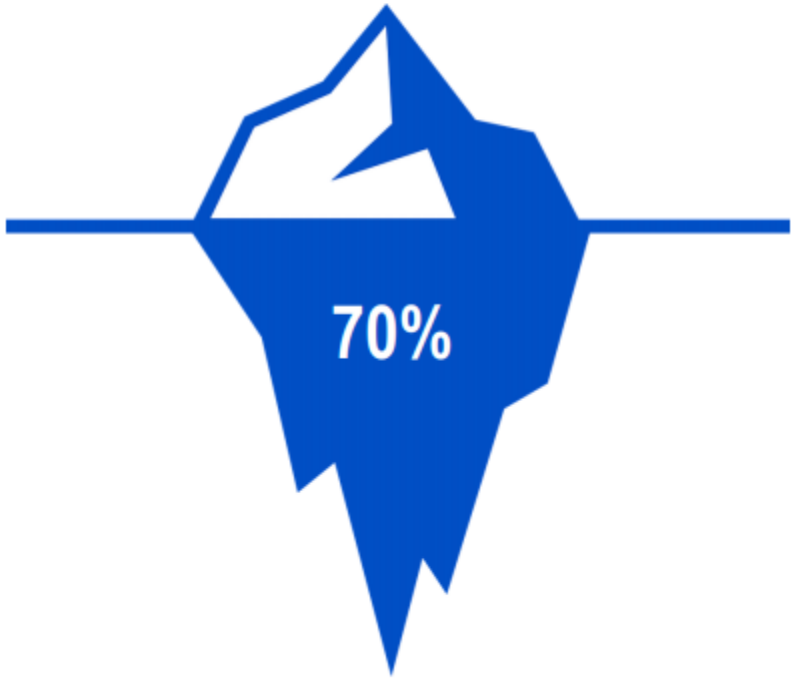
A blood clot in the pulmonary artery

Image: Medical Images RM / STEVE OH, MS CMI

WHAT IS THE TRUE BURDEN OF VTE IN MEDICAL ONCOLOGY

Medical oncology *versus* other settings

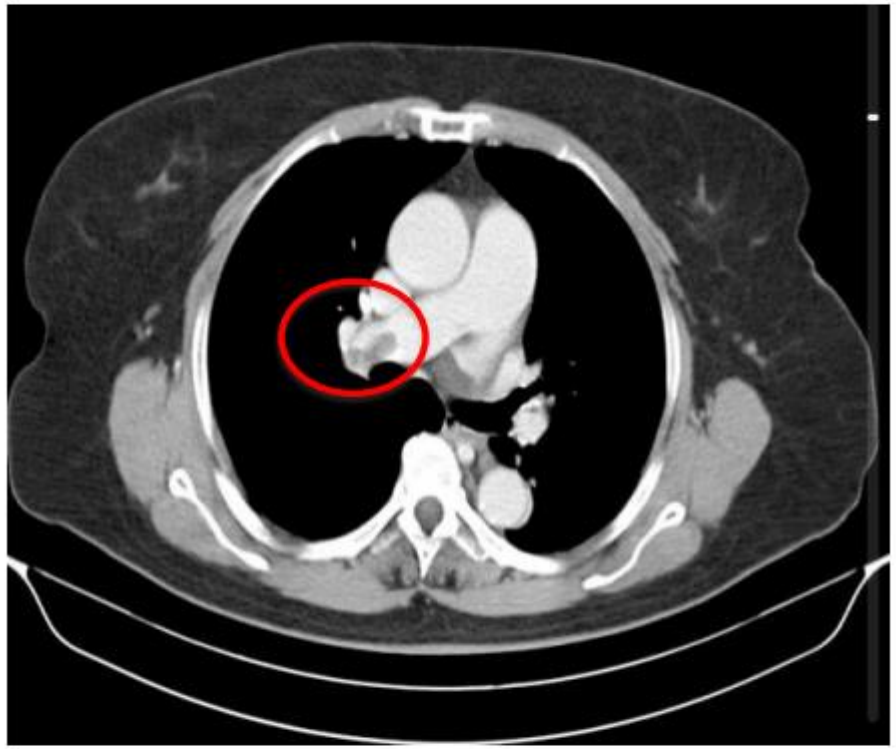
60–70% of fatal PE detected post-mortem are not suspected or diagnosed[1,2]

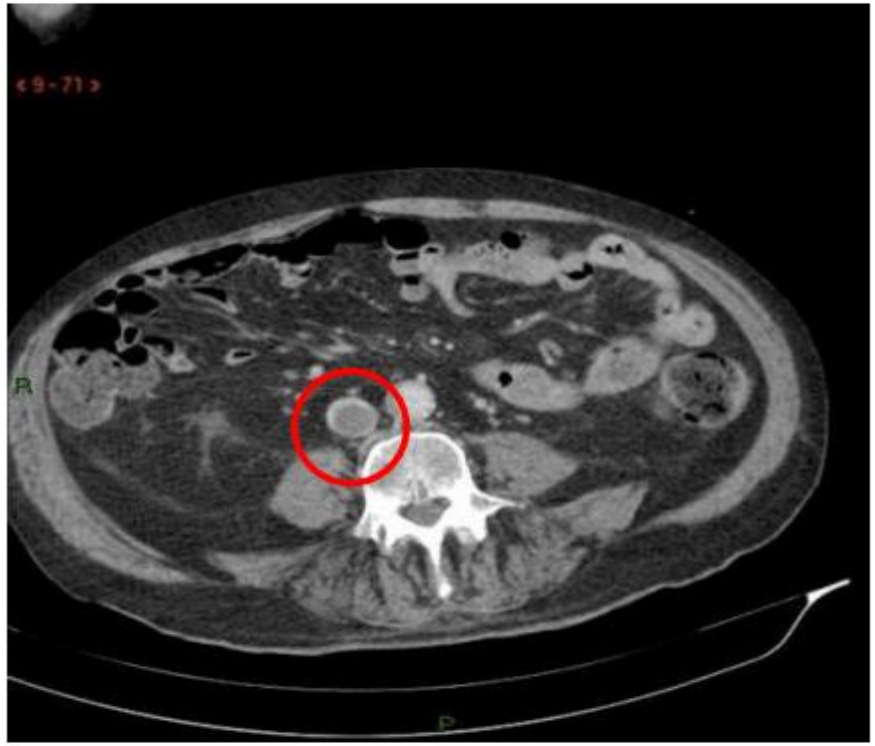


Fatal PE is the leading cause of sudden death among hospitalised patients and contributes to up to 10% of in-hospital deaths[3]

1. Stein PD, *et al.*, Chest 1995;110:978–81; 2. Sander DA, *et al.*, J R Soc Med 1969;82:203–5; 3. Nicolaides AN, *et al.*, Int Angiology 2006;25:101–61

INCIDENTAL VTE





VTE that was diagnosed on a CT scan performed for **another reason than the clinical suspicion of VTE,** usually for tumour staging or to assess the response to chemotherapy.

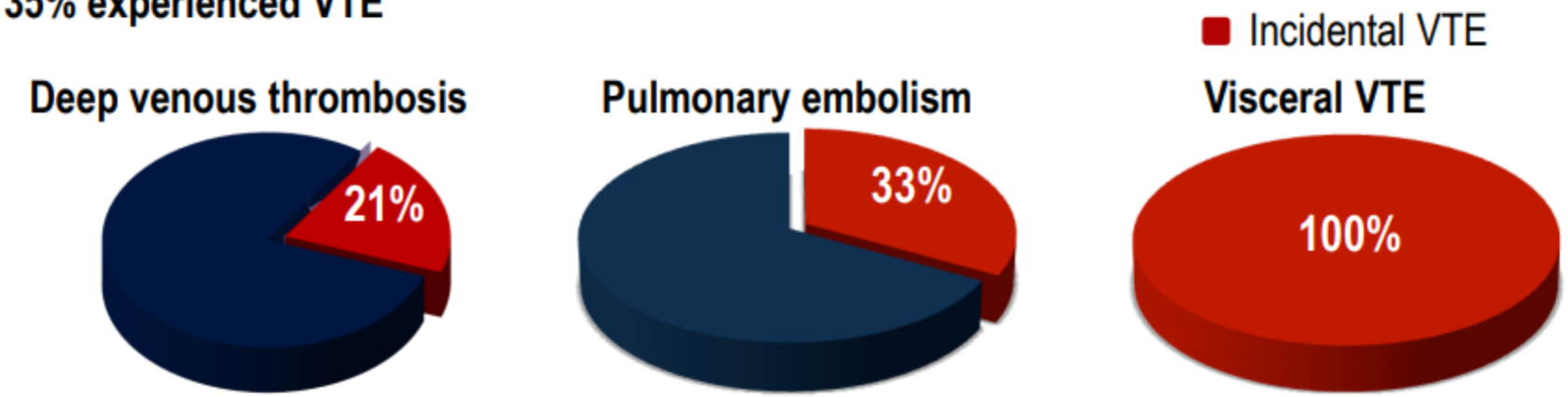
Recommendations: Treat incidental VTE as symptomatic VTE

Di Nisio M, *et al.*, for the Subcommittee on Haemostasis and Malignancy, Diagnosis and treatment of incidental venous thromboembolism in cancer patients: Guidance from the SSC of the ISTH. J Thromb Haemost 2015;13:880–3

WHETHER SYMPTOMATIC OR INCIDENTAL, VTE IS STRONGLY ASSOCIATED WITH WORSENED MORTALITY

135 pancreatic cancer patients / 1,151 radiologic exams

35% experienced VTE

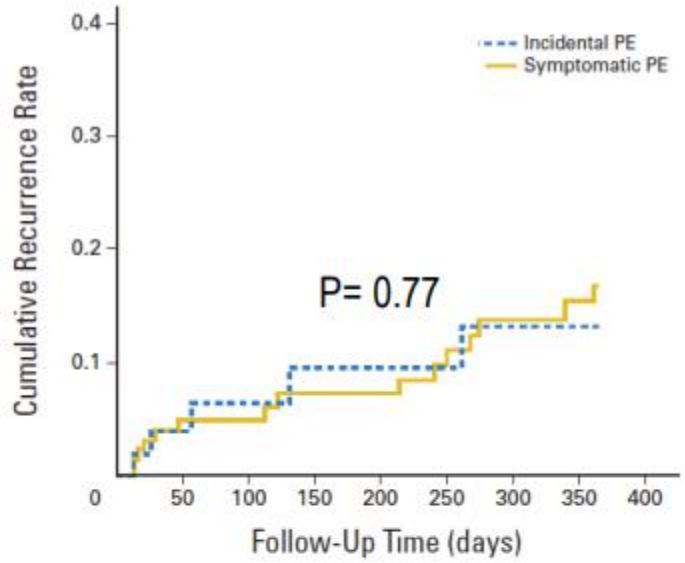


Multivariate analysis / all associated with mortality		
DVT	HR 25; 95% CI 10, 63	p<0.0001
PE	HR 8.9; 95% CI 2.5, 31.7	p=0.007
Incidental visceral events	HR 2.6; 95% CI 1.6, 4.2	p=0.0001

Menapace LA, *et al.*, Thromb Haemost 2011;106(2):371–8.

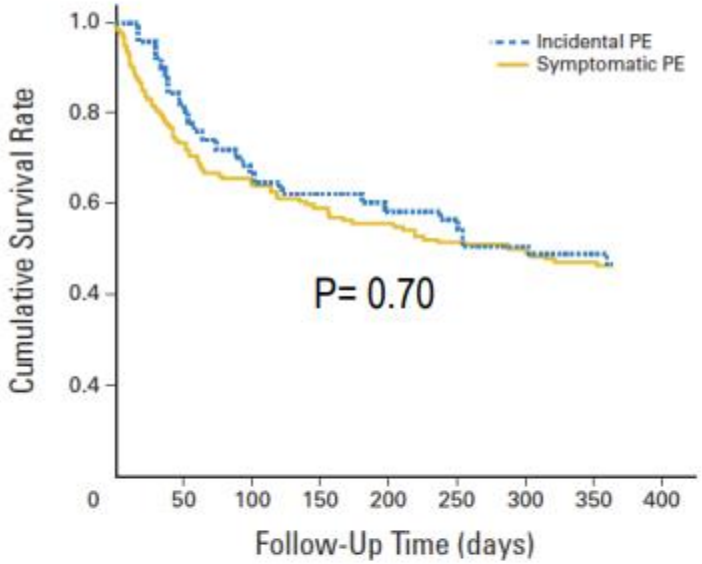
CLINICAL OUTCOME OF PATIENTS WHO WERE INCIDENTALLY DIAGNOSED WITH AND TREATED FOR PE

Cumulative risk of recurrent PE



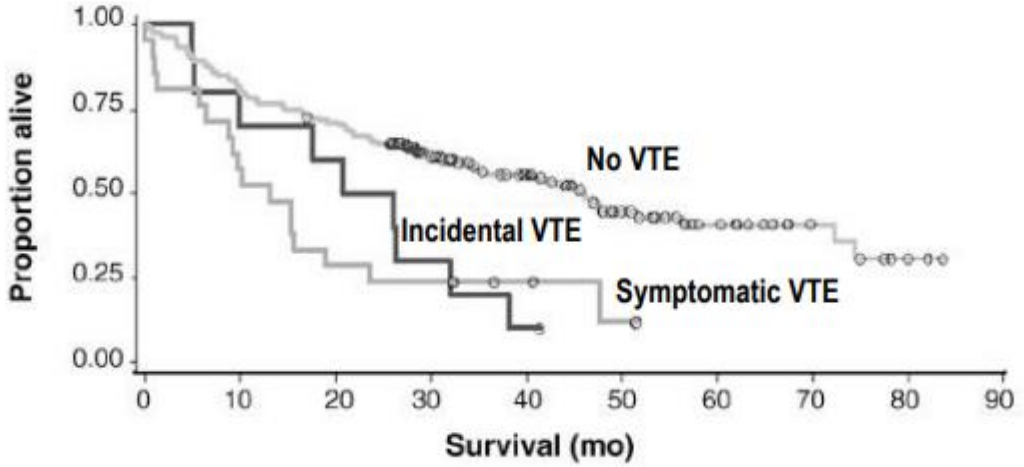
12-month: **13.3%** in the incidental PE group and **16.9%** in the symptomatic

Kaplan-Meier cumulative survival curve



12-month mortality **rate** 52.9 ***vs.*** 53.3%

EFFECT OF INCIDENTAL AND SYMPTOMATIC VTE ON OVERALL SURVIVAL



	Number at risk in each group over time									
Group	Baseline	10	20	30	40	50	60	70	80	90
No VTE	176	140	123	82	55	29	16	7	2	0
Suspected VTE	21	11	5	4	2	0	0	0	0	0
Incidental VTE	10	7	6	3	1	0	0	0	0	0

- Incidental VTE *vs*. no VTE (23.4 months *vs*. 45.8 months; HR, 2.4; 95% CI, 1.2-4.9; P=0.01)
- Incidental VTE *vs*. symptomatic VTE (HR, 1.2; 95% CI, 0.4-2.0; P=0.7)

Reprinted from Clinic Lung Cancer 14(6), Connolly GC, *et al.*, Prevalence and clinical significance of incidental and clinically suspected venous thromboembolism in lung cancer patients, 713–8. Copyright 2013, with permission from Elsevier

THROMBOSIS AND CANCER

Question 5

Could this have been prevented?

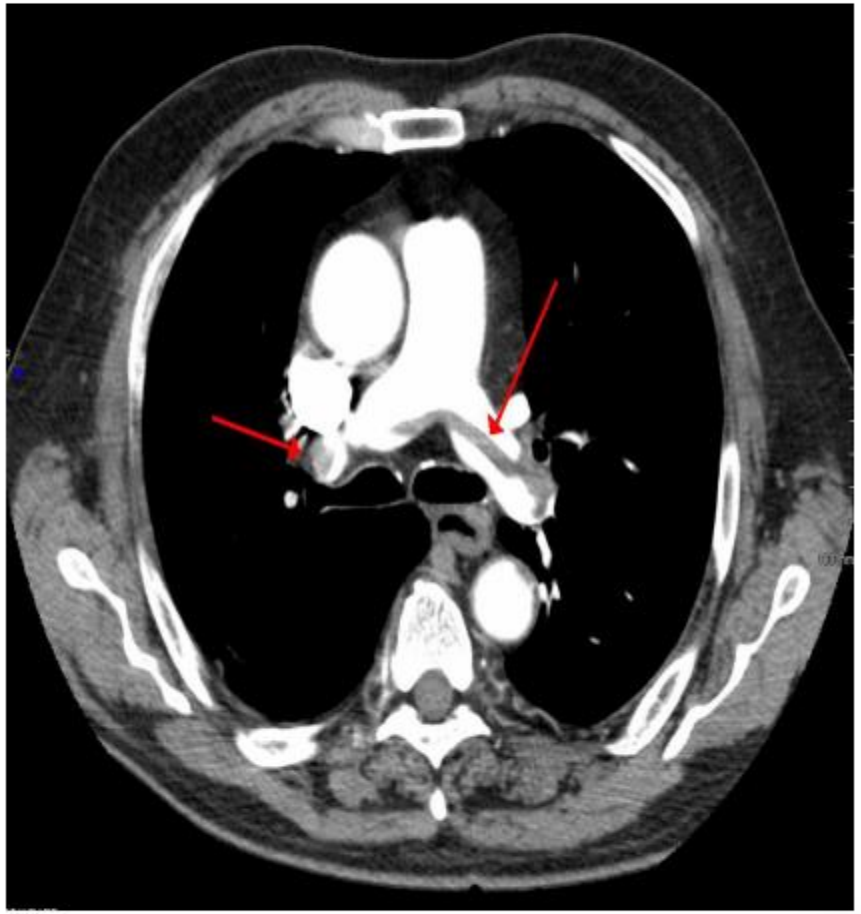


Image by James Heilman, MD (Own work) [CC BY-SA
(https://creativecommons.org/licenses/by-sa/3.0) via Wikimedia C

INCIDENCE AND PREDICTORS OF VTE

Among ambulatory high-risk cancer patients undergoing chemotherapy in the United States

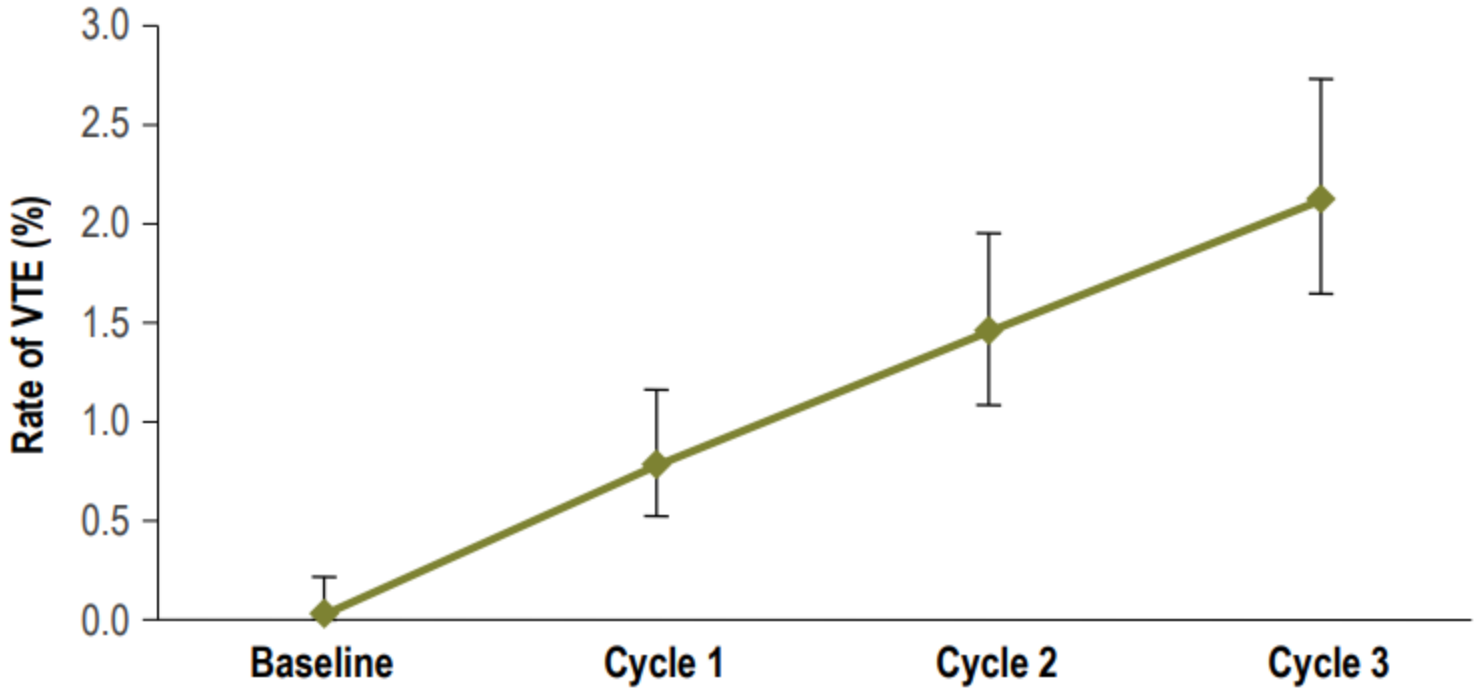
A large, contemporary, real-world analysis

N=17,284 and an age/sex-matched, non cancer control cohort were evaluated
Cancers: bladder, colorectal, lung, ovary, pancreas, or gastric cancers

	Cancer cohort n=2170	Controls n=237	
VTE over 12 months after the initiation of chemotherapy	12.6%	1.4%	P<0.0001
Incidence range: from 8.2% for bladder cancer to 19.2% for pancreatic cancer			

Khorana AA, *et al.*, Cancer. 2013;119(3):648–55.

INCIDENCE OF VTE IN AMBULATORY CANCER PATIENTS UNDERGOING CHEMOTHERAPY



VTE / 2.4 months	VTE/month	VTE /cycle	Cumulative rate (95% CI)
1.93%	0.8%	0.7%	2.2% (1.7, 2.8)

Khorana AA, Cancer 2005;104(12):2822–9.

CHEMOTHERAPY INDUCED THROMBOSIS

Regimen	Contribution to the risk	VTE events rate or RR/Incidence
Cisplatin/platinum based	• Elevated von Willebrand factor (vWF) levels • Release of procoagulant endothelial microparticles	↑ Events 18.1%
L-asparaginase (lymphoblastic leukaemia)	• Depletion of key proteins in the regulation of the coagulation pathway • Synthesis of plasminogen and antithrombin (AT) is markedly impaired with asparaginase-based therapy	↑ Incidence 4.2%
5-Fluorouracil (5FU)	• Depletion of protein C and increased thrombin activity • Endothelial cell damage with the potential to promote thrombus formation	↑ Incidence (15%) – if combined with hematopoietic G-SFE (29%)
Tamoxifen and Aromatase Inhibitors		↑ Risk 2.8% – if Tamo+chemo RR 15.5

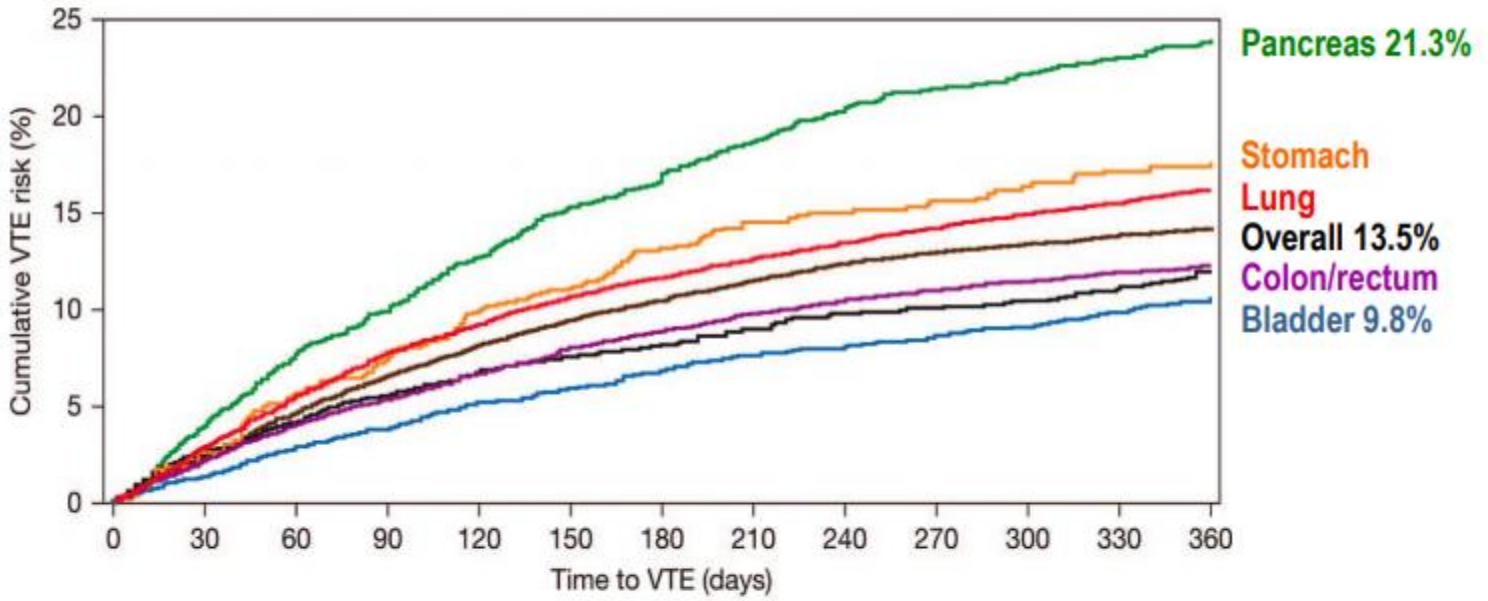
Oppelt P, et al., Vasc Med 2015;20(2):153–61.

OBSERVATIONAL STUDY

Greater rates of VTE than reported in clinical trials

The United States IMPACT health care claims database

27479 patients on chemotherapy



The risk of VTE increases progressively

No plateau or reduction in VTE within 12 months of starting chemotherapy

VTE PROPHYLAXIS FOR AMBULATORY CANCER PATIENTS

- Surgical oncology patient:

  - Out of hospital primary VTE prophylaxis is recommended for up to 4 weeks post operation for high risk abdominal or pelvic cancer surgery patients.

- Medical oncology patient:

  - Multiple myeloma patients (high and low risk)

  - Other patients, no routine VTE prophylaxis recommended outside of a clinical trial setting (consider patient conversation about risks and benefits of VTE prophylaxis in the Khorana score ≥3 patient population).

NCCN Guidelines Version 1.2017. Cancer-Associated Venous thromboembolic Disease. Available at: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf. Accessed February 2018

Predictive Model for Cancer-Associated VTE: Khorana Risk Score

Risk Score Based on Pretreatment Risk Factors

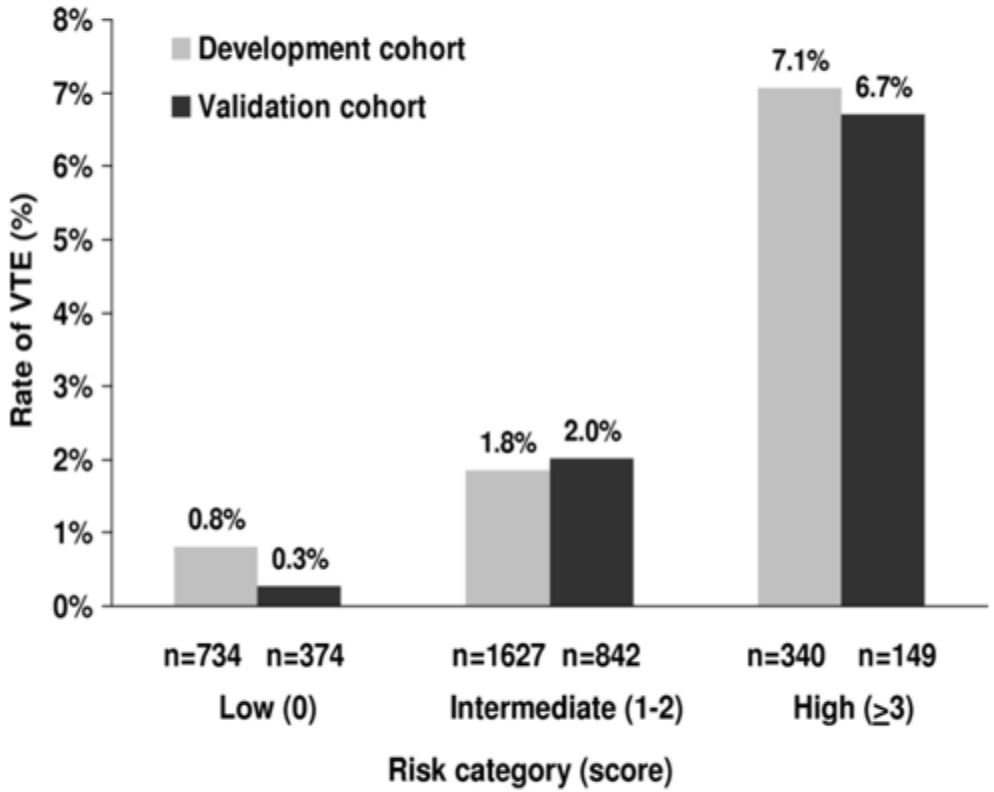
Risk Factors	Risk Score
1. Site of cancer	
a) Very high risk cancer (stomach, pancreas)	2
b) High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
2. Platelet count ≥ 350,000/mm³	1
3. Hemoglobin level < 10 g/dL or use of red cell growth factors	1
4. Leukocyte count > 11,000/mm³	1
5. BMI ≥ 35 kg/m²	1

Low risk: score 0
Intermediate risk: score 1-2
High risk: score ≥ 3

Khorana AA, et al. *Blood*. 2008;111:4902-4907.

Khorana Risk Score

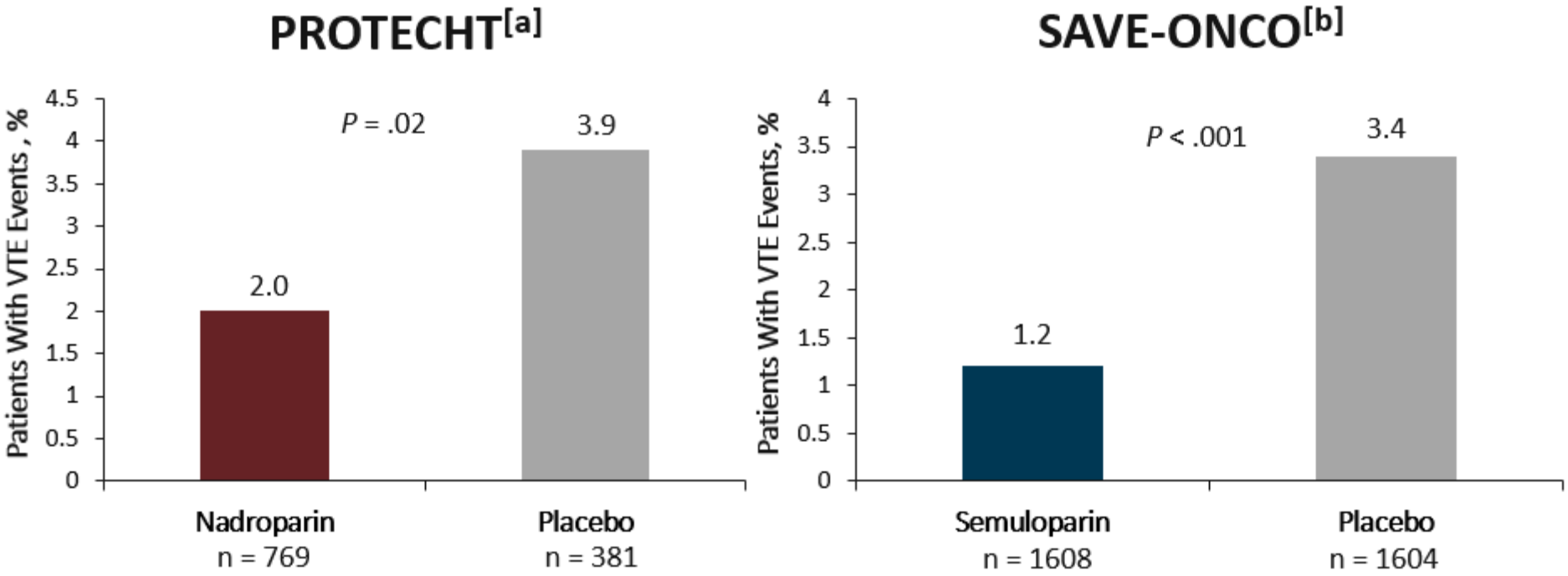
Characteristic	Score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Platelet Count	
≥ 350,000/mm^3	1
Hemoglobin Level	
< 10g/dL or use of ESA	1
Leukocyte Count	
> 11,000/mm^3	1
Body Mass Index	
≥ 35 kg/m^2	1



Khorana AA, et al. *Blood*. 2008;111:4902-4907.

PROTECHT and SAVE-ONCO

Efficacy of LMWH in VTE Prevention

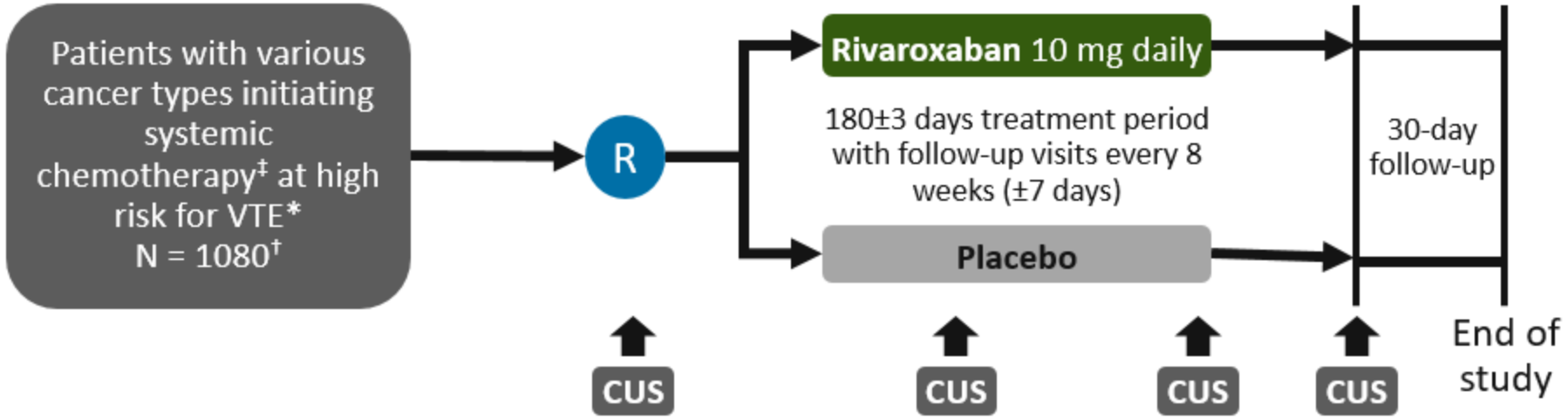


Incidence of thromboembolic events in ambulatory patients with metastatic or locally advanced cancer receiving chemotherapy can be reduced with LMWH thromoboprophylaxis

a. Agnelli G, et al. *Lancet Oncol*. 2009;10:943-949; b. Agnelli G, et al. *N Engl J Med*. 2012;366:601-609.

CASSINI
Study Design

Assessed the efficacy and safety of rivaroxaban vs placebo for VTE prophylaxis in ambulatory patients with cancer initiating systemic cancer therapy and at high risk for VTE



Short design: Multinational, multicenter, randomized, double-blind, placebo-controlled phase 3b superiority study

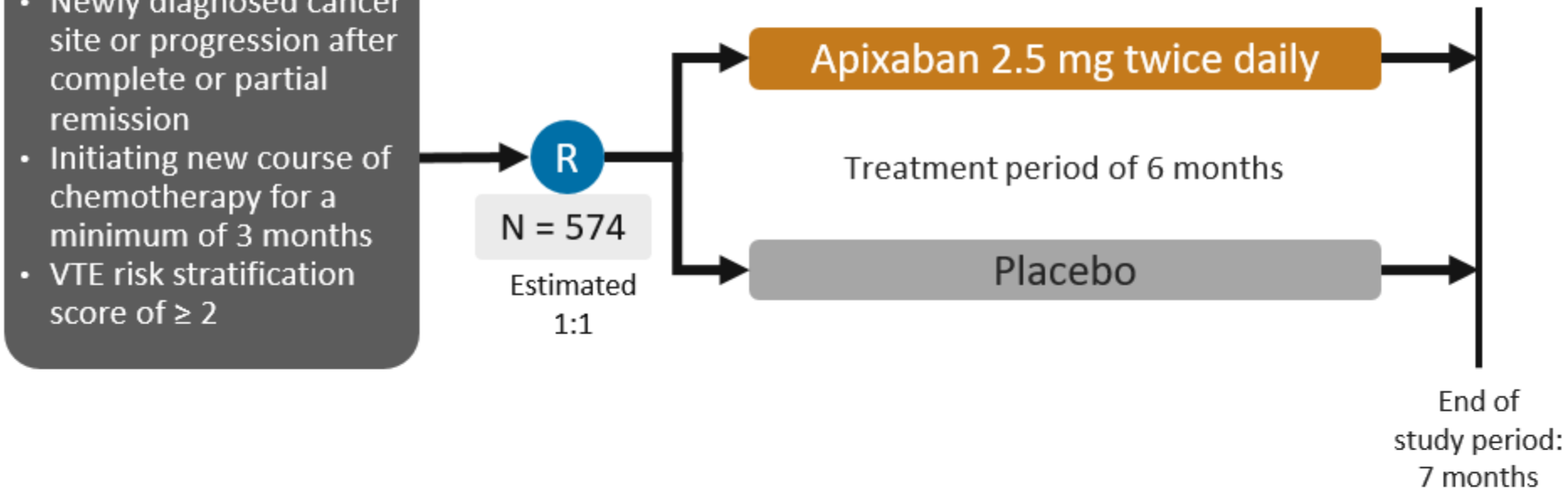
*As indicated by a Khorana risk score ≥ 2; †Patients were stratified at randomization by tumor type (pancreatic or other; up to ~25% of the patients randomly assigned were expected to have advanced pancreatic cancer); ‡Systemic cancer therapy was initiated within 72 hours of the first dose of study drug when at all possible, or within ±1 week of receiving the first dose of study drug with the intention of continuing systemic cancer therapy during the double-blind treatment period. CUS at screening and follow-up visits.

Khorana AA, et al. *Thromb Haemost*. 2017;117:2135-2145. Khorana AA, et al. *N Engl J Med*. 2019; 380:720-728

AVERT
Study Design

Assessed the efficacy and safety of apixaban vs placebo for VTE prophylaxis in ambulatory patients with cancer receiving chemotherapy and at high risk for VTE

- Newly diagnosed cancer site or progression after complete or partial remission
- Initiating new course of chemotherapy for a minimum of 3 months
- VTE risk stratification score of ≥ 2



- Primary outcome: first episode of objectively documented, symptomatic or asymptomatic VTE

Kimpton M, et al. *Thromb Res*. 2018;164:S124-S129; Carrier M, et al. *N Engl J Med*. 2019;380:711-719.

CASSINI vs AVERT

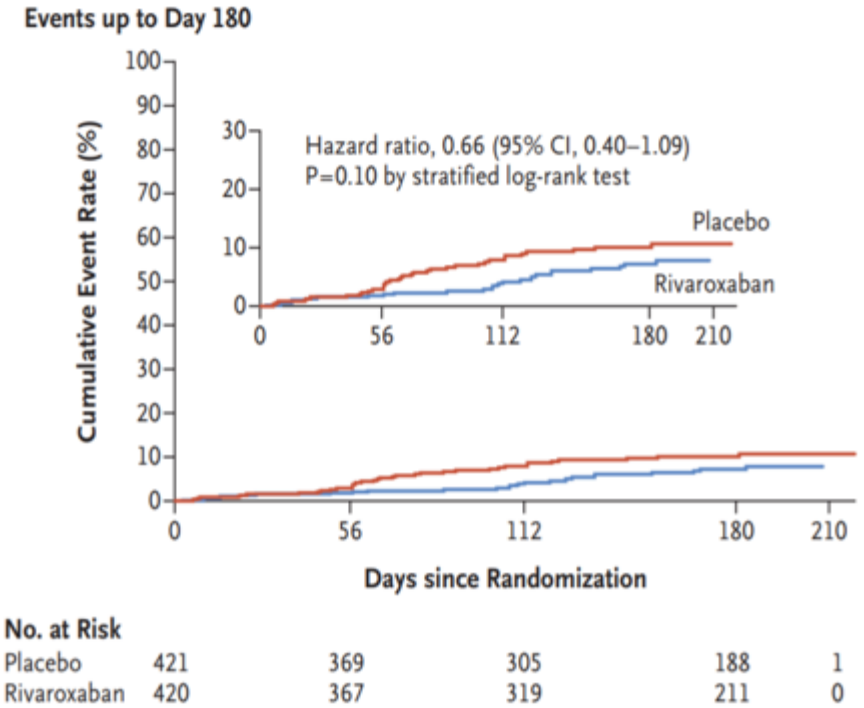
Similarities/Differences in Study Design

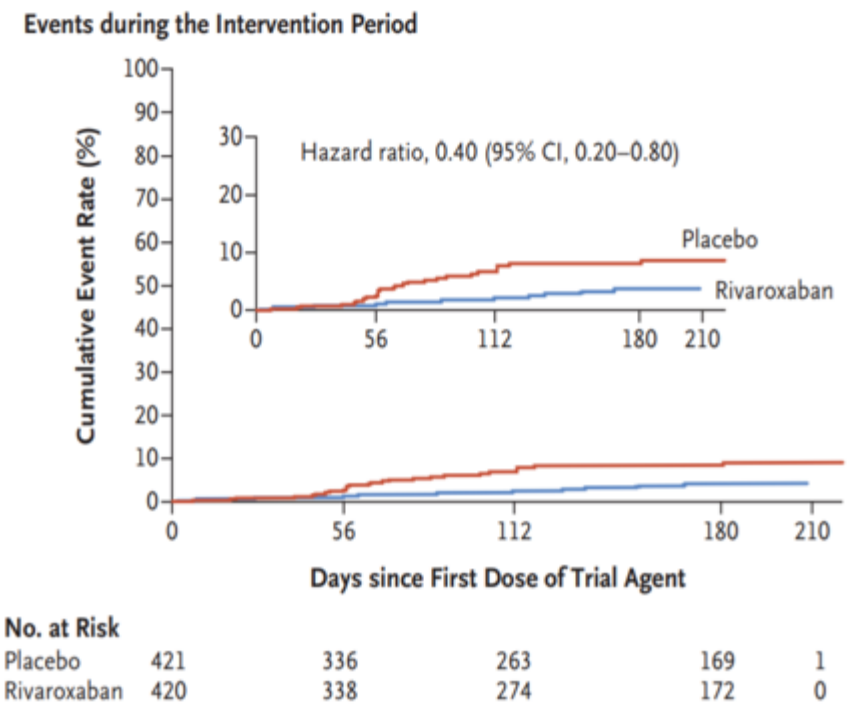
	CASSINI[a]	AVERT[b]
Patient population	Ambulatory patients with solid tumors at high risk of VTE (Khorana score of ≥ 2)	
Entry criterion	Thrombosis free by CUS	CUS not performed
Treatment duration	180 days	
Primary efficacy	Time to first occurrence of objectively confirmed VTE*	
Primary analysis	ITT	mITT
Supportive analysis	On-treatment period	

*Includes symptomatic or asymptomatic VTE and VTE-related death.

a. Khorana AA, et al. *Thromb Haemost*. 2017;117:2135-2145.
b. Kimpton M, et al. *Thromb Res*. 2018;164:S124-S129.

CASSINI
Efficacy/Safety Outcome



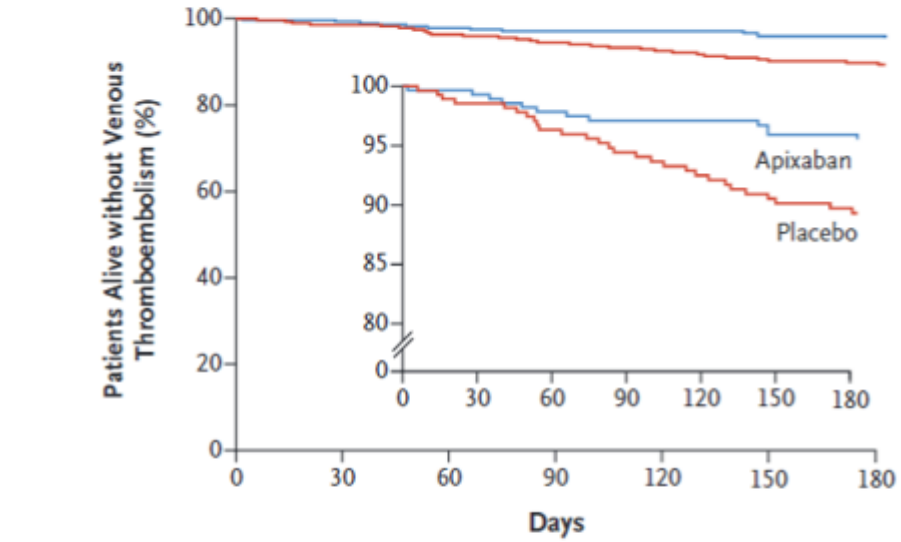


Cumulative Incidence	Rivaroxaban	Placebo	HR (95% CI)	*P* Value
VTE, n, % (ITT)	25/420, 6.0	37/421, 8.8	0.66 (0.40, 1.09)	.10
VTE, n, % (during treatment)	11/420, 2.6	27/421, 6.4	0.40 (0.20, 0.80)	-
Major bleeding (ITT), n, %	8/405, 2.0	4/404, 1.0	1.96 (0.59, 6.49)	.26

From *N Engl J Med*, Khorana AA, et al., Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer, 380, 720-728, Copyright © 2019. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

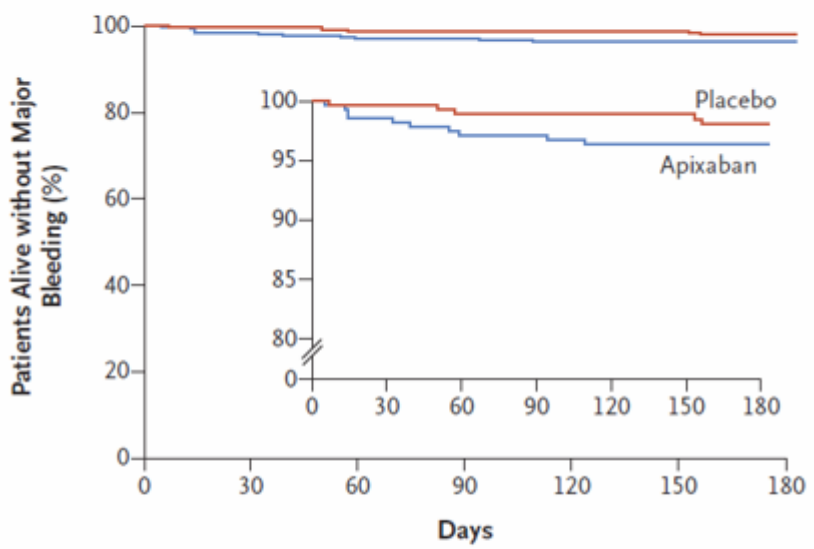
AVERT

Efficacy/Safety Outcome



No. at Risk

Apixaban	288	276	265	256	249	244	229
Placebo	275	268	259	244	237	228	215



No. at Risk

Apixaban	288	275	266	258	249	246	233
Placebo	275	269	262	253	249	245	229

Cumulative Incidence	Apixaban	Placebo	HR (95% CI)	*P* Value	NNT/NNH
VTE (mITT), %	4.2	10.2	0.41 (0.26, 0.65)	< .001	NNT =17
Major bleeding (mITT), %	3.5	1.8	2.00 (1.01, 3.95)	.046	NNH = 59
Major bleeding (on treatment), %	2.1	1.1	1.89 (0.39, 9.24)	NS	NNH = 100

Carrier M, et al. *N Engl J Med*. 2019;380:711-719.

Guidelines Recommendation for Treatment of CAT

NCCN[a]

- LMWH as monotherapy preferred for first 6 months
- Alternatives include rivaroxaban, apixaban, LMWH/warfarin, LMWH/edoxaban, LMWH/dabigatran
- Minimum duration of 3 months is recommended
- Indefinite duration recommended with active cancer or persistent risk factors for VTE recurrence

ASCO®[b]

- LMWH as monotherapy for 6 months
- Warfarin is a suggested alternative
- NOACs not recommended
- Indefinite duration should be considered with active cancer or persistent risk factors for VTE recurrence

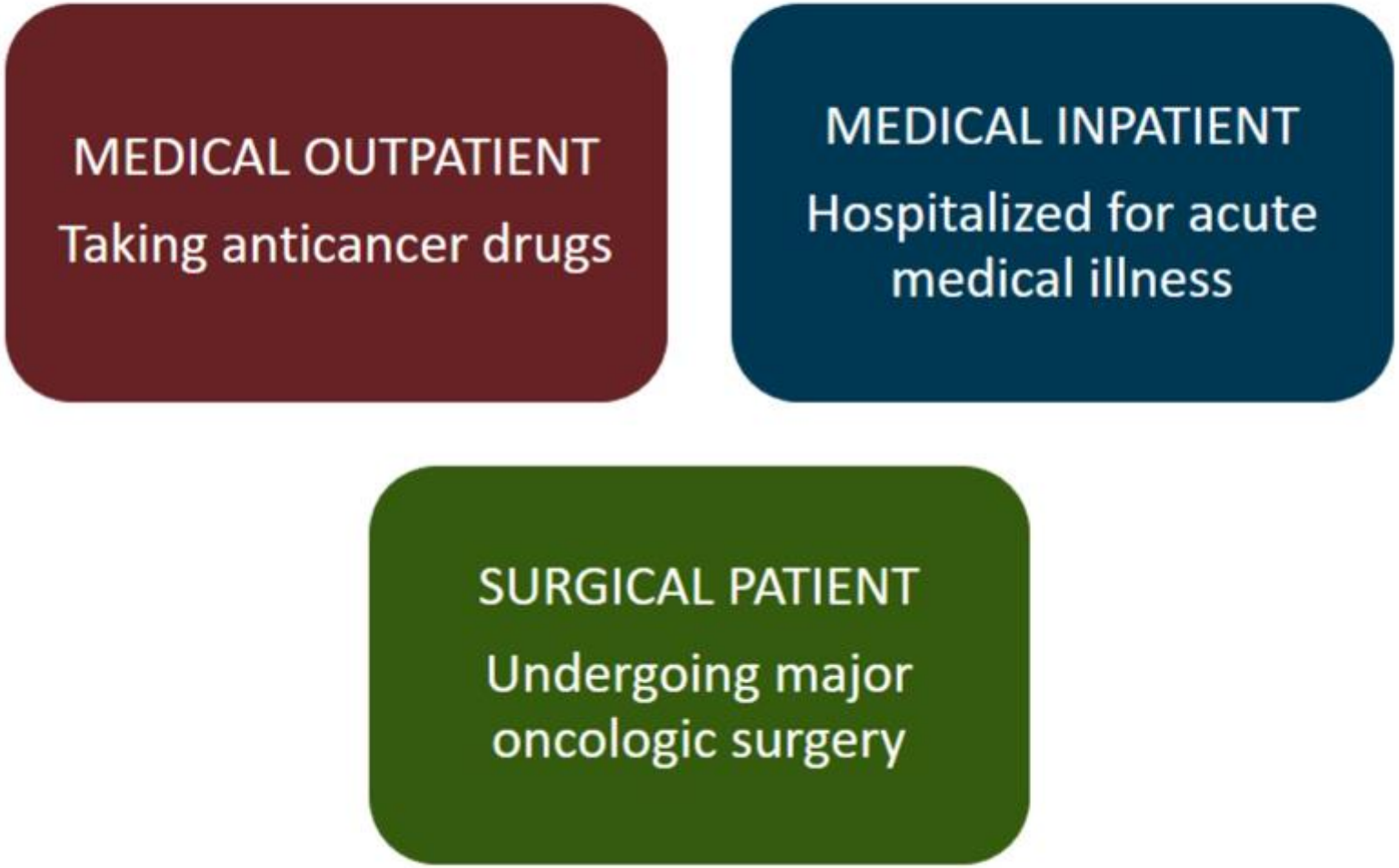
a. NCCN Clinical Practice Guidelines in Oncology®. Version 2.2018.
b. Lyman GH, et al. *J Clin Oncol*. 2015;33:654-656.

ESC Guidelines

PE in Cancer	
Edoxaban or rivaroxaban should be considered as an alternative to LMWH, with the exception of patients with gastrointestinal cancer.	IIa

Konstantinides SV, et al. *Eur Heart J.* 2019. [Epub ahead of print]

Multiple Clinical Scenarios in Patients With Cancer



Ay C, et al. *ESMO Open*. 2017;2:e000188.

VTE Prevention in Medical Outpatients With Cancer

- Routine thromboprophylaxis for VTE in ambulatory medical outpatients is not recommended [a,b]
  - May be considered in high-risk ambulatory patients with cancer
    - Consideration of such therapy should be accompanied by a discussion with the patient about the uncertainty concerning benefits and harms, as well as dose and duration of prophylaxis in this setting
- Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients[b,c]

a. Mandala M, et al. *Ann Oncol*. 2011;22(suppl 6):vi85-92.
b. Lyman GH, et al. *J Clin Oncol*. 2015;33:654-656.
c. Khorana AA, et al. *J Thromb Haemost*. 2014;12:1928-1931.

VTE Prevention in Medical Outpatients With Cancer (cont)

- The identification of ambulatory patients with cancer who might benefit from primary thromboprophylaxis is still one of the most challenging areas
  - Continued risk assessment is important[a-c]

a. Mandala M, et al. *Ann Oncol*. 2011;22(Suppl 6):vi85-92.
b. Lyman GH, et al. *J Clin Oncol*. 2015;33:654-656.
c. Khorana AA. *J Thromb Thrombolysis*. 2016;41:81-91.

VTE Prevention in Medical Inpatients With Cancer

- Most hospitalized patients with active cancer require thromboprophylaxis throughout hospitalization[a-d]
  - In most patients, LMWH is preferred over VKA
    - Recommended doses of LMWH in hospitalized medical patients[a,b]
      - Dalteparin: 5000 units once daily
      - Enoxaparin: 40 mg once daily
      - Fondaparinux: 2.5 mg once daily
  - Use of DOACs is not currently recommended for patients with malignancy and VTE[b]

a. Mandala M, et al. *Ann Oncol*. 2011;22(suppl 6):vi85-92.
b. Lyman GH, et al. *J Clin Oncol*. 2015;33:654-656.
c. NCCN website. Cancer-associated venous thromboembolic disease. 2018.
d. Kearon C, et al. *Chest*. 2016;149:315-352.

Secondary Prevention of Cancer-Associated VTE

- LMWH is recommended for long-term secondary prophylaxis for at least 6 months

a. Mandala M, et al. *Ann Oncol*. 2011;22(Suppl 6):vi85-92.
b. Lyman GH, et al. *J Clin Oncol*. 2015;33:654-656.
c. NCCN website. Cancer-associated venous thromboembolic disease. 2018.
d. Kearon C, et al. *Chest*. 2016;149:315-352.

Secondary Prevention of Cancer-Associated VTE: Beyond 6 Months

- Anticoagulation with LMWH or VKA beyond the initial 6 months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy

Lyman GH, et al. *J Clin Oncol*. 2015;33:654-656.

PROPHYLAXIS IN DIFFERENT CLINICAL SETTINGS

Thromboprophylaxis	Decrease in the incidence of all VTEs	Prophylaxis	NNT
Postoperative VTE[1]	5.6% → 2.6%	Extended *vs.* conventional	40
Hospitalised patients[2]	5.0% → 2.8%	LMWH *vs.* no	45
Outpatients on therapy[3]	3.9% → 2.0%	LMWH *vs.* no	50–60
Outpatients on therapy at high risk (Khorana ≥3)[4]	21% → 12%	LMWH *vs.* no	12–15

1. Fagarasanu A, *et al.*, Ann Surg Oncol 2016;23:1422–30; 2. Agnelli G, *et al.*, Lancet Oncol 2009;10(10):943–9;
3. Verso M, *et al.*, Int Emerg Med 2012;7:291–2; Khorana AA, *et al.*, Blood 2015 126:427. 57th ASH Annual Meeting 2015, abstract 427

OUTPATIENT PROPHYLAXIS ON CHEMOTHERAPY

Patient population	ASCO[1]	ESMO[2]
All outpatients	Routine prophylaxis not recommended	Routine prophylaxis not recommended
Myeloma, receiving IMiD-based regimens	Aspirin or LMWH for low-risk and LMWH for high-risk patients is recommended	Consider LMWH, aspirin, or adjusted-dose warfarin (INR≈1.5)
High-risk outpatients	**Consider LMWH prophylaxis on a case-by-case basis in highly selected** outpatients with solid tumours on chemotherapy ***Discussion with the patient*** about the uncertainty concerning benefits and harms and about dose and duration of prophylaxis in this setting	**Consider in high-risk** ambulatory cancer patients. **Predictive model** may be used to identify patients clinically at high risk for VTE

1. Lyman GH, et al., J Clin Oncol 2015;33:654–6
2. Mandala M, et al., Ann Oncol 2011;22 (Supplement 6):vi85–vi92

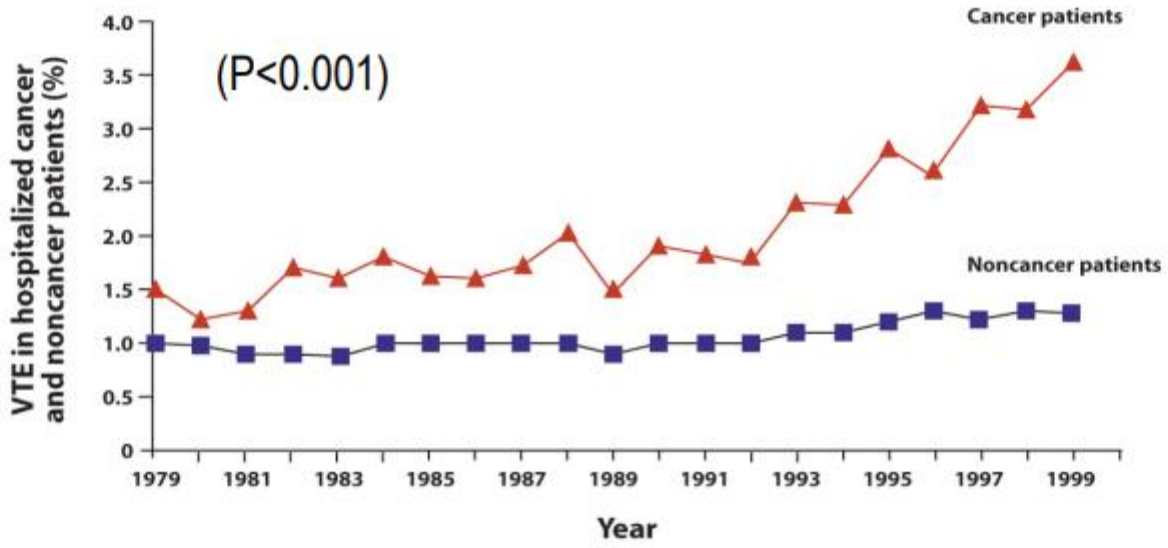
VENOUS THROMBOEMBOLISM PROPHYLAXIS AND TREATMENT IN PATIENTS WITH CANCER

- Routine thromboprophylaxis is not recommended in cancer outpatients
- Based on limited RCT data, clinicians may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumours receiving chemotherapy
- Consideration of such therapy should be accompanied by a discussion with the patient about the uncertainty concerning benefits and harms as well as dose and duration of prophylaxis in this setting
- Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients

Lyman GH, et al., J Oncol Pract. 2015;11(3):e442-4. American Society of Clinical Oncology Clinical Practice Guideline Update

SHOULD PATIENTS WITH CANCER RECEIVE ANTICOAGULATION FOR VTE PROPHYLAXIS WHILE HOSPITALISED?

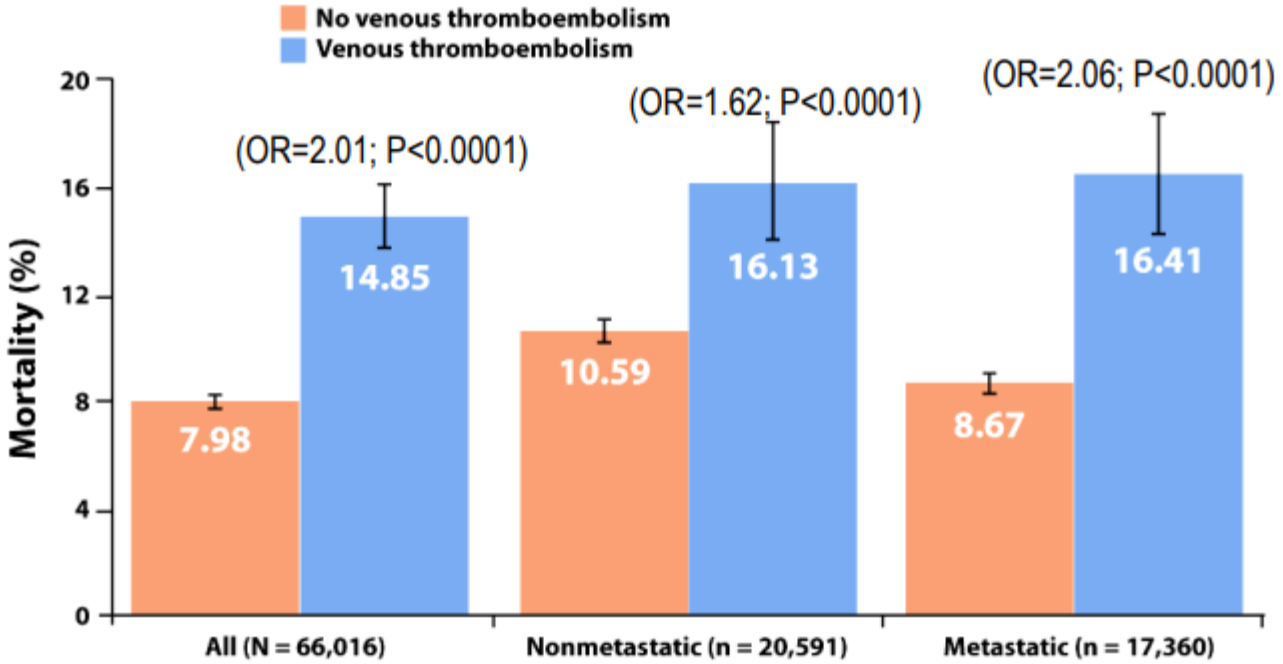
Data from the National Hospital Discharge Survey (US)



Change in incidence of VTE over time in hospitalised cancer and non-cancer patients

VTE IS ASSOCIATED WITH NEARLY A DOUBLING IN THE RISK FOR DEATH AMONG CANCER PATIENTS

Retrospective cohort study conducted using data from over 66,000 adult neutropenic cancer patients (88,000 hospitalisations)



3% to 12% depending on the type of malignancy **experienced VTE during their first hospitalisation**

Khorana AA, *et al.*, J Clin Oncol 2006;24:484–90. Reprinted with permission. © 2011 American Society of Clinical Oncology. All rights reserved

META-ANALYSIS OF VENOUS THROMBOEMBOLISM PROPHYLAXIS

In medically ill patients

12,391 patients (8,357 in placebo-controlled trials) from 9 studies

- Prophylaxis with LMWH, UFH, fondaparinux, and placebo
- **DVT rates**
  - lower with LMWH/fondaparinux compared with placebo (OR 0.60; 95% CI 0.47, 0.75)
  - similar between LMWH and UFH (OR 0.92; 95% CI 0.56, 1.52)
- No differences in the **rate of death or PE** between LMWH/fondaparinux, UFH, or placebo
- **Major bleeding rates similar** across all treatment arms considered
- **Minor bleeding rates similar** with LMWH and UFH and greater than in placebo-treated patients
- Cancer-specific rates were not provided for either VTE or bleeding

Kanaan AO, *et al.*, Clin Ther 2007;29(11):2395x–405.

VENOUS THROMBOEMBOLISM PROPHYLAXIS AND TREATMENT IN PATIENTS WITH CANCER

- **Hospitalised** patients with **active malignancy with acute medical illness or reduced mobility should receive thromboprophylaxis** in the absence of bleeding or other contraindications
- **Hospitalised** patients with **active malignancy without additional risk factors may be considered** for pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications
- Data **inadequate to support or oppose** thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion

Lyman GH, *et al.*, J Oncol Pract. 2015;11(3):e442-4. American Society of Clinical Oncology Clinical Practice Guideline Update

INCIDENCE OF VTE IN SURGICAL PATIENTS

- Cancer patients have **2-fold risk** of post-operative DVT/PE and
- **>3-fold risk** of fatal PE despite prophylaxis
- **33% to 53%** of VTE episodes occurring **after hospital discharge**

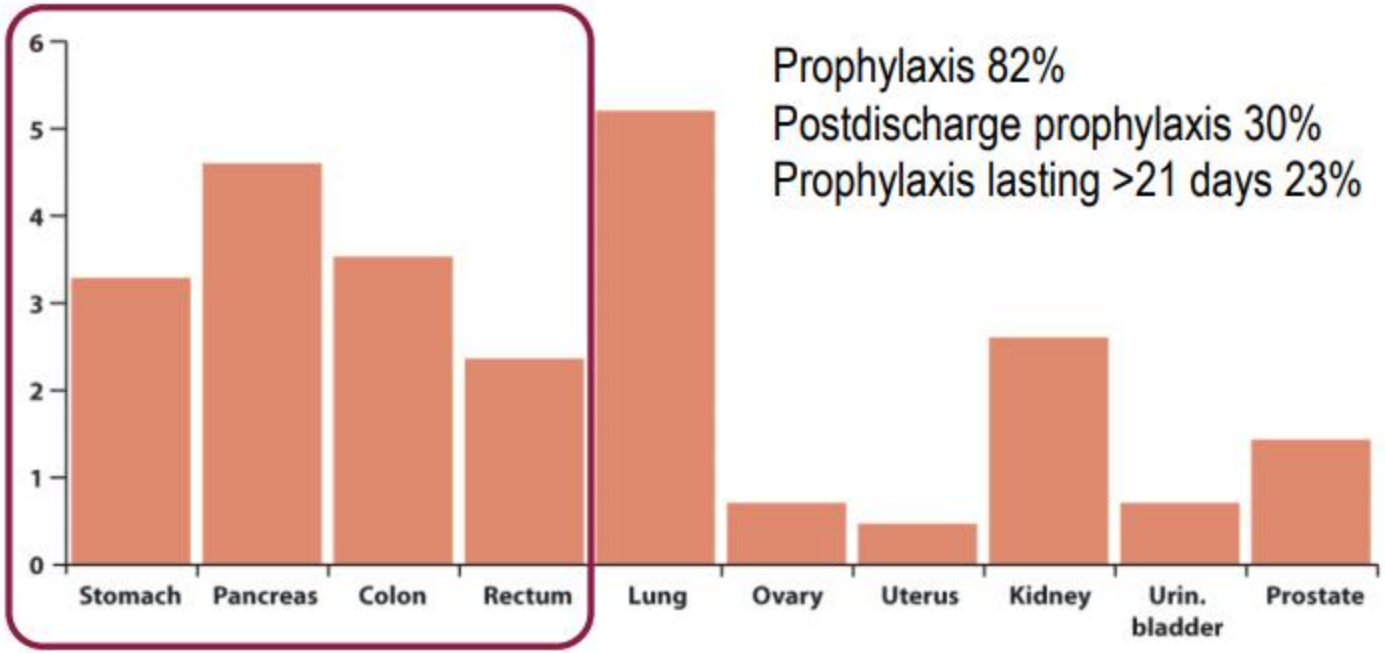
	No Cancer N=16,954	Cancer N=6,124	P-value
Post-op VTE	0.61%	1.26%	<0.0001
Non-fatal PE	0.27%	0.54%	<0.0003
Autopsy PE	0.11%	0.41%	<0.0001
Death	0.71%	3.14%	<0.0001

Kakkar AK, *et al.*, Thromb Haemost 2001;86 (suppl 1):OC1732.

POSTOPERATIVE VTE IN PATIENTS WITH CANCER

@RISTOS was a prospective observational study

2373 patients who underwent surgery for cancer



Prophylaxis 82%
Postdischarge prophylaxis 30%
Prophylaxis lasting >21 days 23%

The risk of VTE varies by site of the **primary tumour**

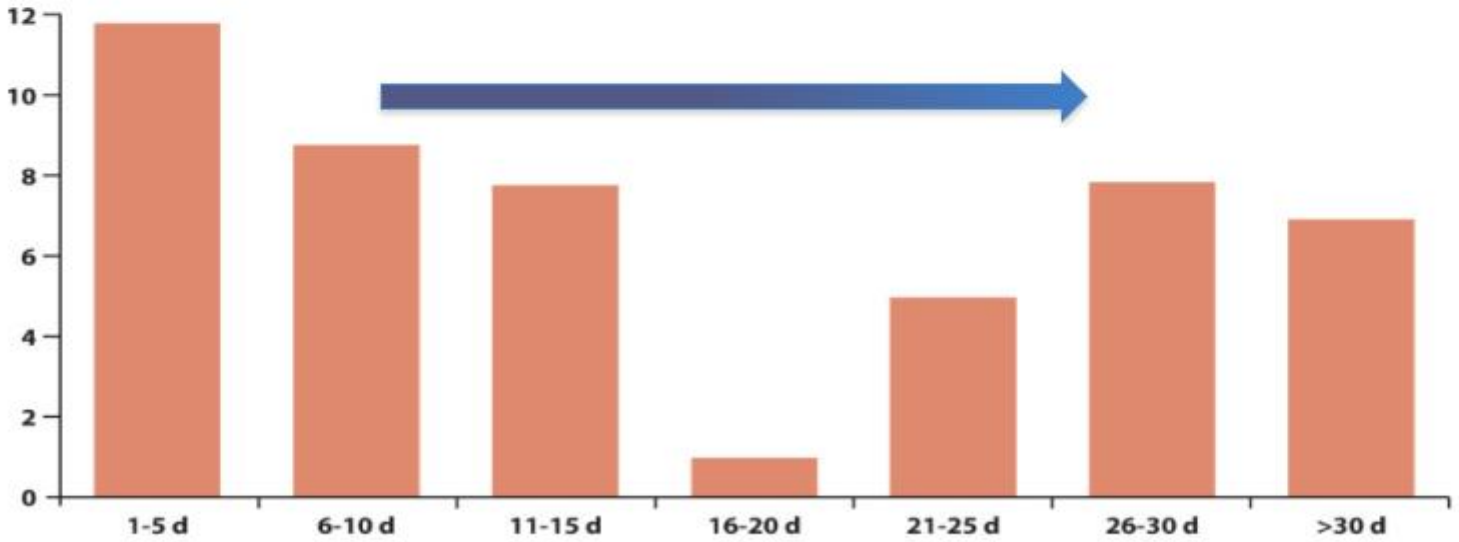
Agnelli G, et al., A Clinical Outcome-Based Prospective Study on Venous Thromboembolism After Cancer Surgery: The @RISTOS ProjectAnn Surg 2006;243(1):89–95.
https://insights.ovid.com/pubmed?pmid=16371741

POSTOPERATIVE VTE IN PATIENTS WITH CANCER

Duration of thromboprophylaxis – @RISTOS study

2373 patients who underwent surgery for cancer

- **40%** of all VTE occurs in the **outpatient setting** (>21 days of surgery)
- **PE** is the most common single cause of death **(46%) at 30 days** after surgery



Agnelli G, et al., A Clinical Outcome-Based Prospective Study on Venous Thromboembolism After Cancer Surgery: The @RISTOS ProjectAnn Surg 2006;243(1):89–95.
https://insights.ovid.com/pubmed?pmid=16371741

4 TRIALS META-ANALYSIS

Prolonged thromboprophylaxis with LMWH for abdominal or pelvic surgery

	Control group	Out-of-hospital LMWH	
Overall VTE	14.3% (95% CI 11.2%, 17.8%)	6.1% (95% CI 4.0%, 8.7%)	P<0.0005
Bleeding	3.7% (95% CI 2.4%, 5.5%)	4.1% (95% CI 2.7%, 6.0%)	P=0.73

Cochrane Database Syst Rev 2009;1:CD004318.

VENOUS THROMBOEMBOLISM PROPHYLAXIS AND TREATMENT IN PATIENTS WITH CANCER

- All patients with malignant disease undergoing major surgical intervention should be considered for pharmacologic thromboprophylaxis with either UFH or LMWH

- Extended prophylaxis with LMWH for up to 4 weeks postoperatively should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features

Lyman GH, *et al.*, J Oncol Pract. 2015;11(3):e442-4. American Society of Clinical Oncology Clinical Practice Guideline Update

THROMBOSIS AND CANCER

Answers!

Why did this occur? **CANCER-THROMBOSIS**

What is the influence in patient's prognosis? **POOR PROGNOSIS**

What is the optimal management of this patient? **LMWH**

Should this patient be managed differently if this were an incidental finding? **NO**

Could this have been prevented? **MAYBE**

CONCLUSIONS

- **Thrombosis in cancer patients** is a common, costly and potentially fatal complication
- **Patients at highest risk** are those with advanced disease receiving systemic chemotherapy and other additional risk factors
- **Primary prophylaxis** is not routinely indicated but could be discussed with patients at high risk
- Selected cancer patients benefit from **extended prophylaxis** up to 4 weeks after surgery
- **Prophylaxis in hospitalised patients** is a safety priority
- **LMWH is the "best" category** available for patients with established VTE and PE, for long-term (**6 months**) secondary prophylaxis

THANK YOU!