Cancer Associated Thrombosis

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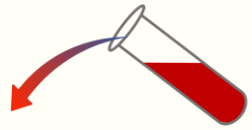
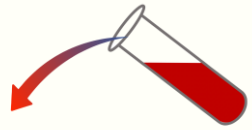
Disclosures

- Research Support (Past 2 years):
  - Amgen
  - Sobi/Dova Pharmaceuticals
  - Anthos Therapeutics
- Data Safety Monitoring Committee
  - Alpine Immune Sciences
- Advisory Boards (Past 2 years)
  - Sanofi
  - Novartis



Topics To Cover

1. Scope of The Problem: Clinical Relevance Of Thrombosis In Cancer.
2. Pathophysiology Of Thrombosis: Virchow's Triad.
3. Screening For Occult Malignancy In Patients With VTE
4. Management of Thrombosis In Cancer Patients
5. Direct Oral Anticoagulants
6. Incidental Thrombosis/ Pulmonary Embolism
7. Primary Thrombosis Prophylaxis
8. Anticoagulation and Brain Cancer
9. Management of Anticoagulation in Setting Of Chemotherapy-Induced Thrombocytopenia.



Trousseau Syndrome

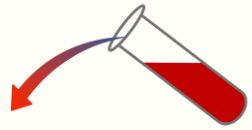
- Armand Trousseau first described association of "migratory superficial thrombophlebitis" and cancer in 1865.
- Recognized in himself.
- Attributed thromboembolism in malignancy to changes in the blood rather than local inflammatory or mechanical forces.
- The first recognized paraneoplastic syndrome.

Armand Trousseau: October 14, 1801- June 23, 1867

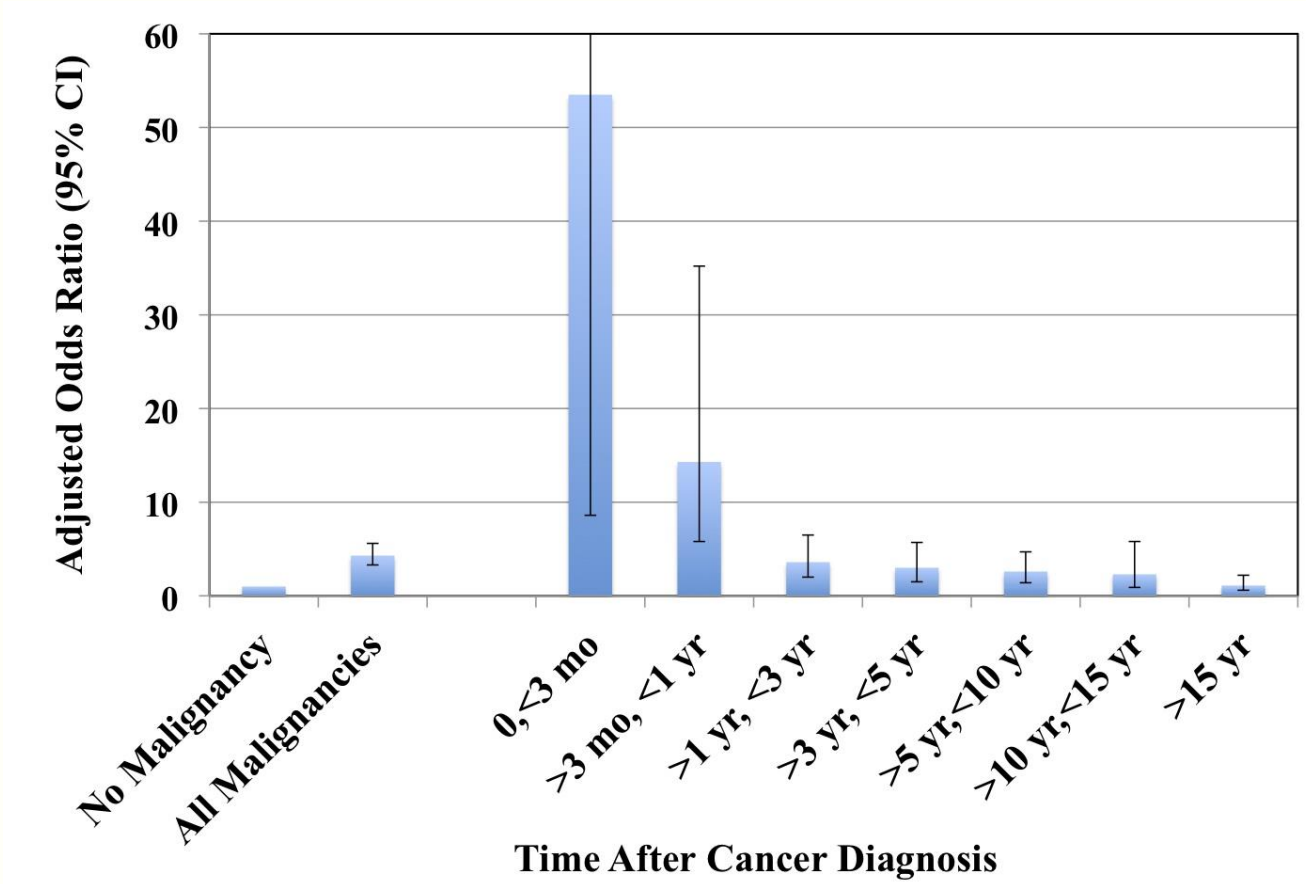
1. Scope of The Problem

- Venous thromboembolism (VTE), is major source of morbidity and mortality in cancer patients.
- Incidence rates of cancer-associated thrombosis (CAT) vary with cancer type, stage, treatment, and comorbidities, but it is estimated that approximately 15-20 % of cancer patients will develop a venous thromboembolic episode at some point during the course of their illness.
- Thrombosis is the second leading cause of death in cancer patients, after cancer itself.

- Ay C, et al. Thromb Haemost. 2017; 117: 219-30. 10.1160/TH16-08-0615.
- Khorana AA, et al. J Thromb Haemost. 2007; 5: 632-4. 10.1111/j.1538-7836.2007.02374.x.
- Weitz JI, et al. J Thromb Thrombolysis. 2020;50(2):267-77.
- Deitcher SR. Semin Thromb Hemost. 2003; 29: 247-58. 10.1055/s-2003-40963.
- Prandoni P. Blood. 2005; 106: 4027-33. 10.1182/blood-2005-04-1508.



Relationship of Initial Thrombosis With Time From Cancer Diagnosis: Thrombosis in cancer typically presents early in the course of disease.



Redrawn from Blom JW, et al. JAMA 2005;293(6):715-722.

Mortality Rates In Cancer as Function of VTE

Exposure	HR (95% CI)
None	**1.0 (reference)**
VTE only	**2.6 (2.0-3.3)**
Cancer only	**7.4 (6.8-8.2)**
Cancer-Related VTE	**31.2 (24.6-39.6)**

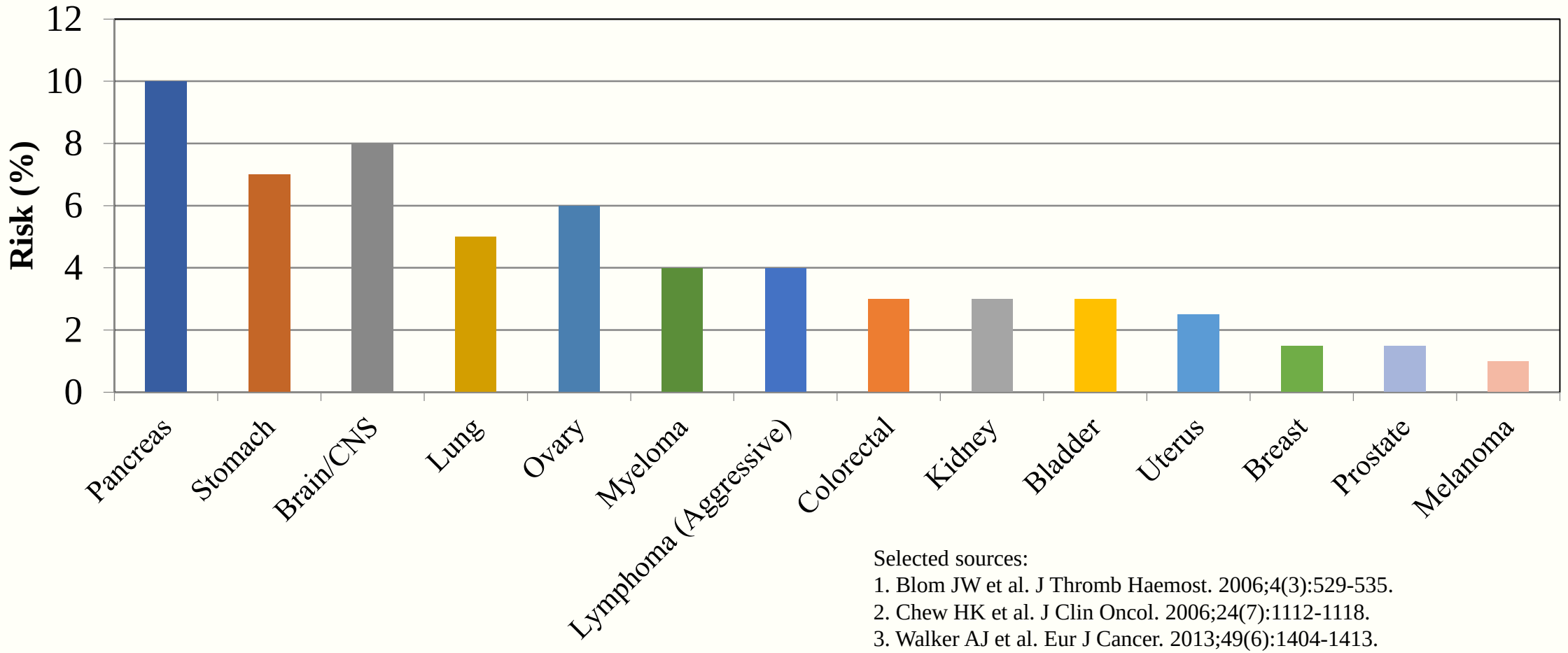
- Patients presenting with a Cancer-Related Venous Thromboembolism have markedly higher risk of mortality than cancer patients in general.
- Age And Gender-Adjusted HR.
- However, very few of these patients are dying from the VTE. Most are dying from their underlying cancer.
- **Cancer Associated Thrombosis is a marker of aggressive cancer!**
- VTE were at time of presentation.
  - Timp JF et al. Blood 2013;122:1712-1723

Cause of Death Over 12-Months Follow-Up After Venous Thromboembolism

Active Cancer (N=372)	History of Cancer (N=79)
Cancer (83.3)	**Cancer (77.5)**
VTE (3.2)	**VTE (5.6)**
Bleed (1.4)	**Cardiac (4.2)**
Stroke (1.2)	**Bleed (2.8)**
Cardiac (1.2)	**Stroke (0.0)**
Other (9.8)	**Other (9.9)**

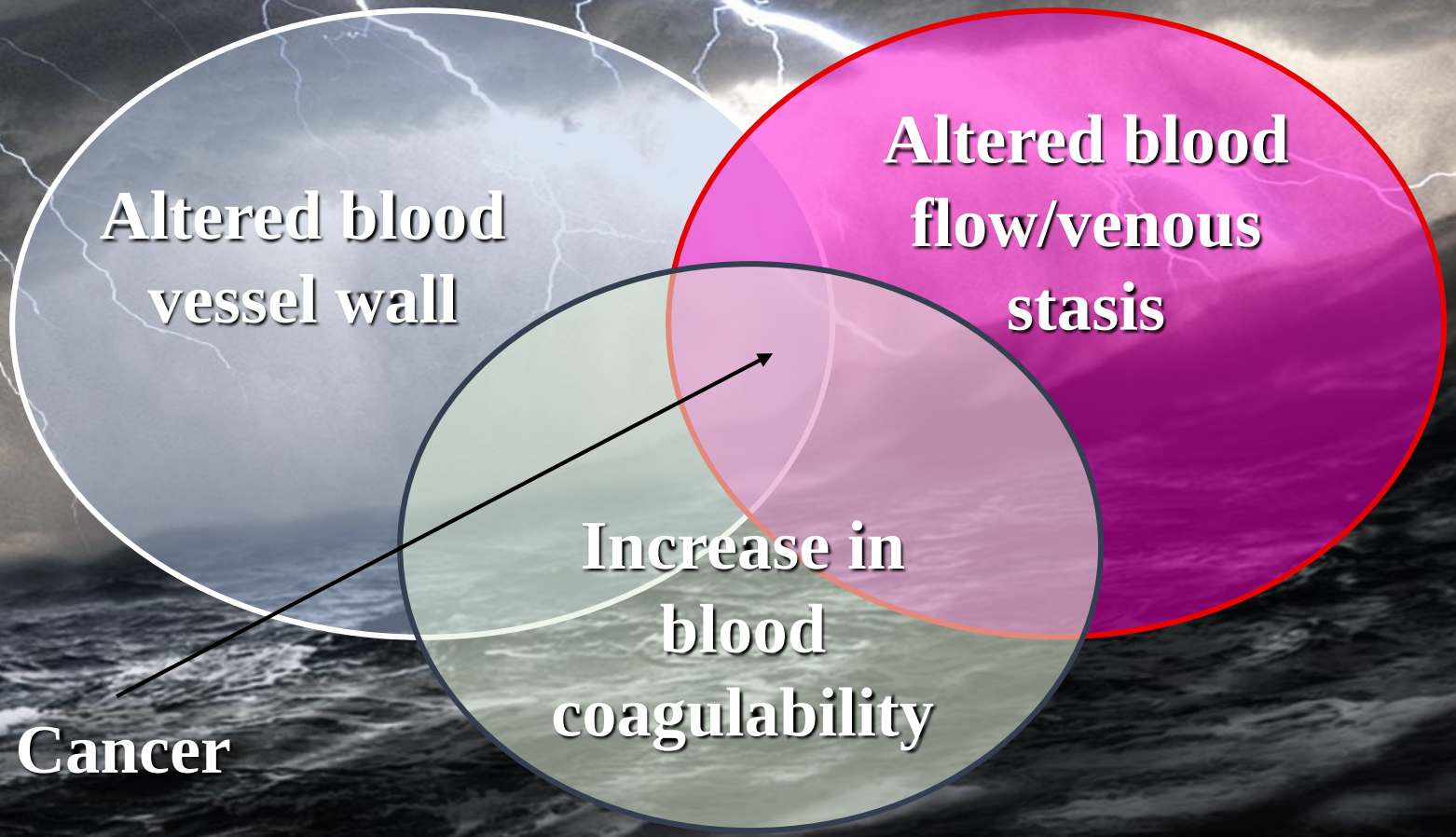
- The Global Anticoagulant Registry in the FIELD (GARFIELD)–VTE (ClinicalTrials.gov: NCT02155491)
- Prospective, observational study of 10,684 patients with objectively diagnosed VTE from 415 sites in 28 countries.
- 1075 patients with active cancer, 674 patients with a history of cancer, and 8935 patients without cancer.
- Weitz et al. Journal of Thrombosis and Thrombolysis 50:267–277, 2020.

12-Month VTE Risk by Individual Cancer Sites



Selected sources:
1. Blom JW et al. J Thromb Haemost. 2006;4(3):529-535.
2. Chew HK et al. J Clin Oncol. 2006;24(7):1112-1118.
3. Walker AJ et al. Eur J Cancer. 2013;49(6):1404-1413.
4. Horsted F et al. BMJ. 2012;345:e5556.
5. Cronin-Fenton DP et al. J Thromb Haemost. 2010;8(5):953-960.
6. Mulder FI et al. Blood. 2021;137(16):2203-2214.

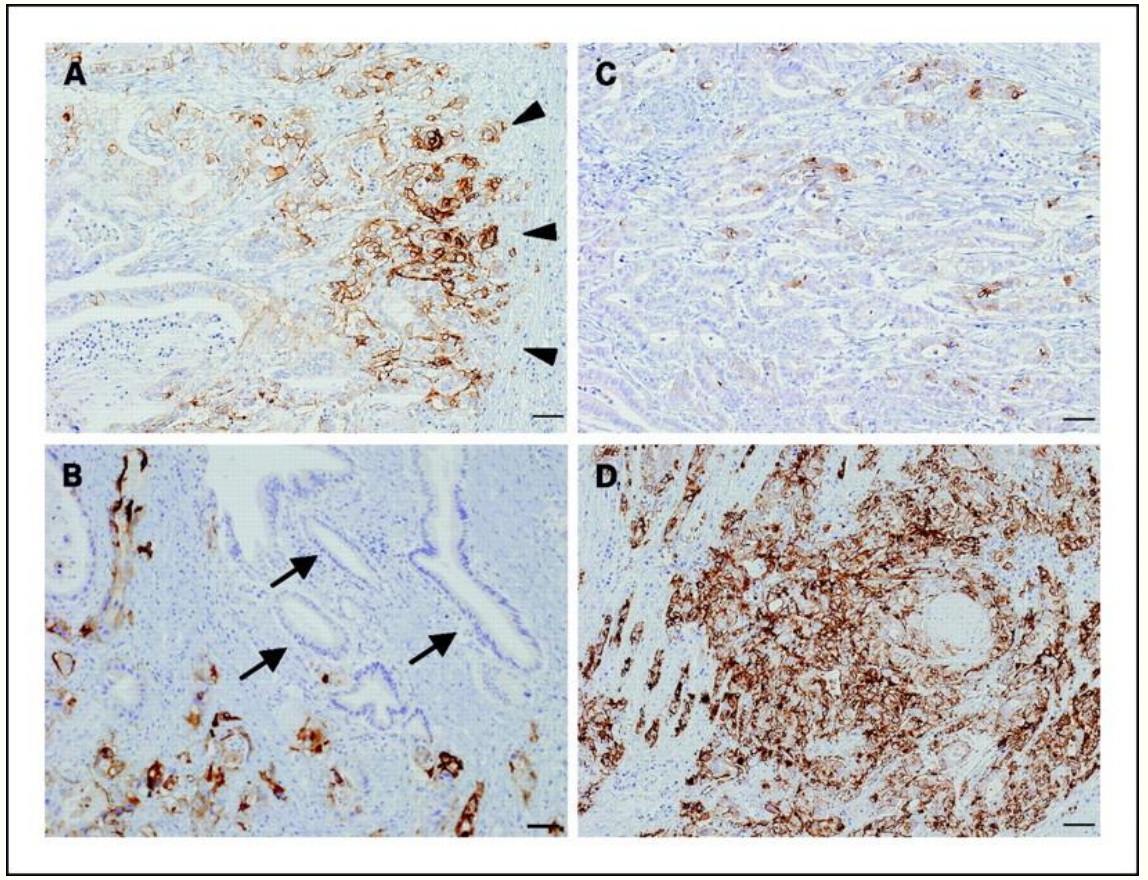
2. Pathophysiology Of Thrombosis: Virchow's Triad



Coagulation And Vascular Factors Contribute to Thrombosis

1. Tissue Factor and Other Coagulation Changes:
   - Tumor cells directly produce and release Tissue Factor.
   - Tissue Factor circulates in microparticles and may result in systemic thrombotic risk.
2. Platelets:
   - Cancer cell express Podoplanin (PDPN) and other direct platelet activators.
     - Hisada Y. et al Blood. 2017 Sep 28;130(13):1499-1506. doi: 10.1182/blood-2017-03-743211. Epub 2017 Aug 14. PMID: 28807983; PMCID: PMC5620413.
   - Elevated platelet count increases thrombosis rates in cancer.
     - Khorana AA & Connolly GC. JCO. 27:4839-4847, 2009.
   - P-Selectin. Marker of *in vivo* platelet activation.
3. Vascular Abnormalities:
   - Abnormal structure of tumor-associated vessels.
   - Chemotherapy and Antiangiogenic agents target endothelial cells.
4. Neutrophil Activation and NETosis
   - NETs act as a scaffold for FXII activation, platelet adhesion, and fibrin deposition.

TF Expression is Markedly Increased in Pancreatic Cancer, Compared With Normal Pancreatic Epithelium.



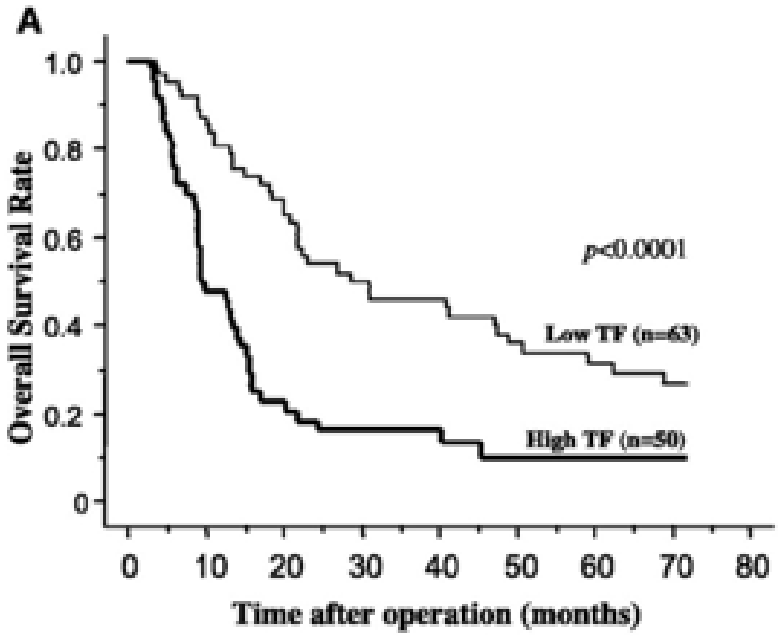
- Nitori N. et al. *Clin. Canc. Res*. 11, 2531-2539, 2005

TF Expression In Pancreatic Cancer and:

Thrombosis Rates

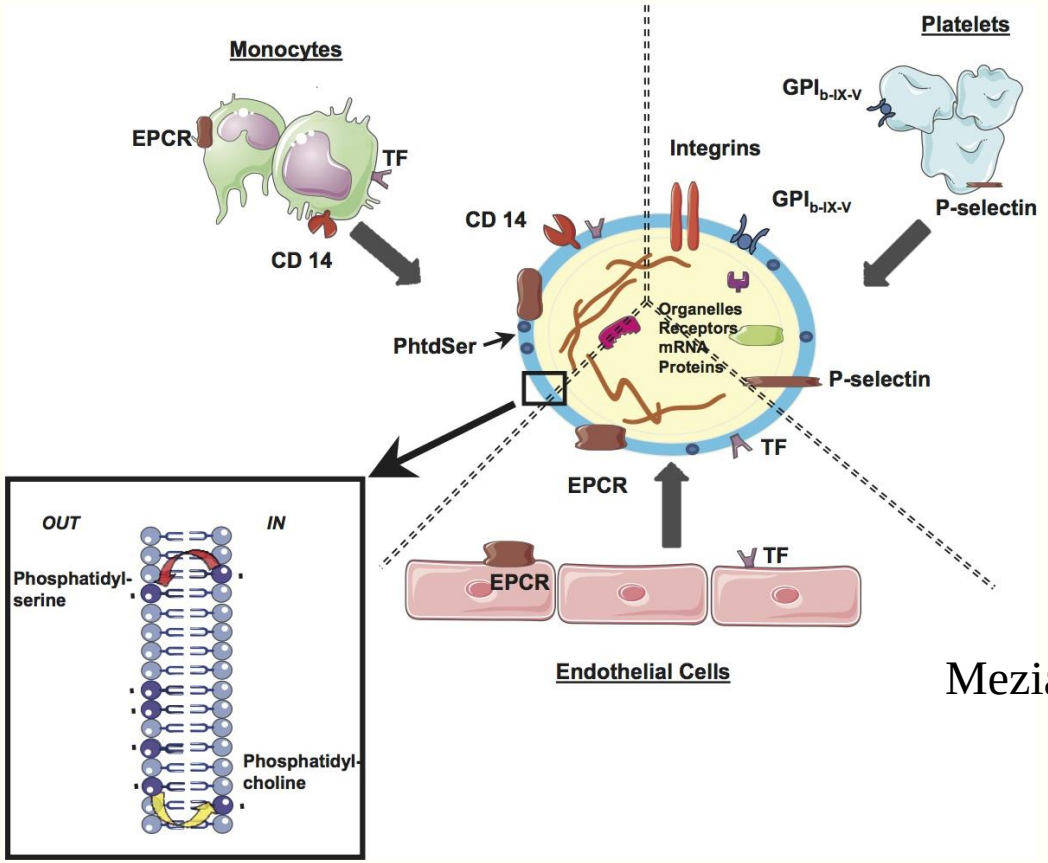
- High TF, VTE Rate: 26.3%
- Low TF, VTE Rate: 4.5%
- ~ 6-fold Risk Ratio, (P = 0.04).
  - Khorana AA. et al, *Clin. Canc. Res*. 13, 2870-2875, 2007

Overall Survival



- Nitori N. et al. *Clin. Canc. Res*. 11, 2531-2539, 2005

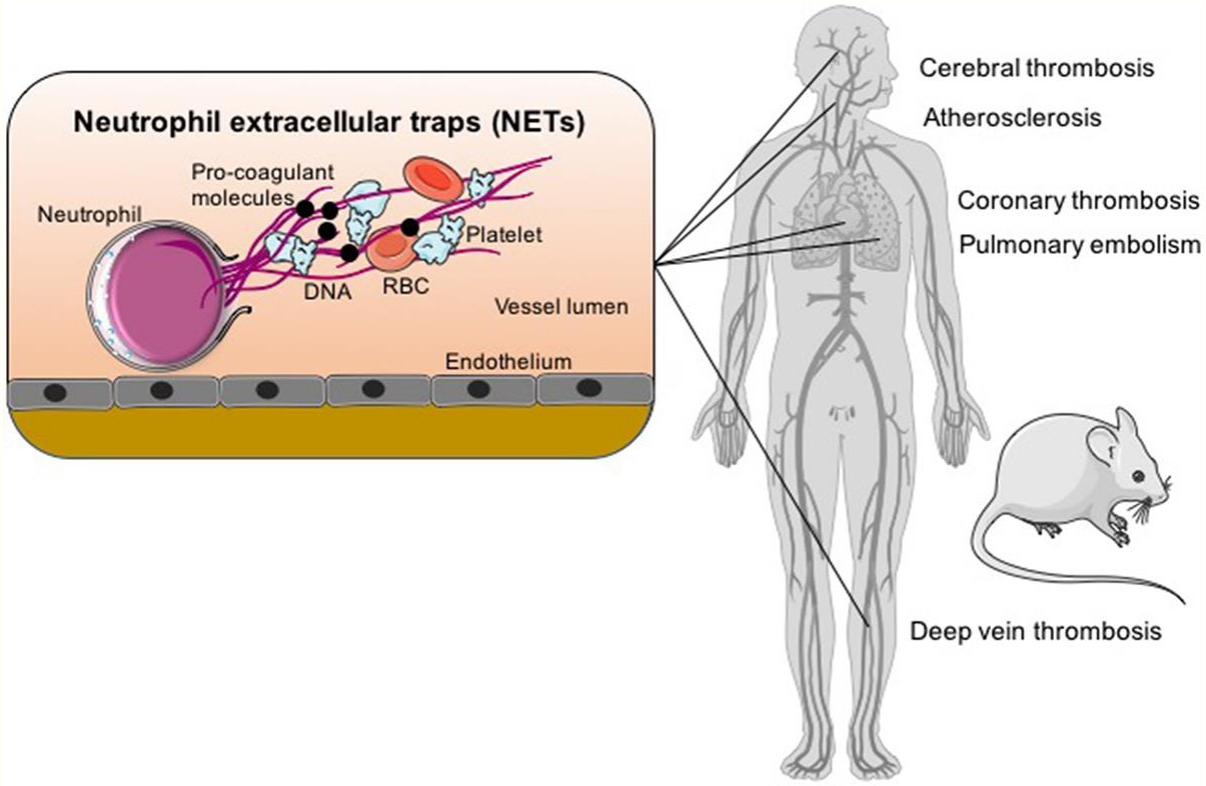
Tissue Factor Circulates in Cell-Derived Microparticles.



Meziani *et al. Critical Care* 2010 14:236

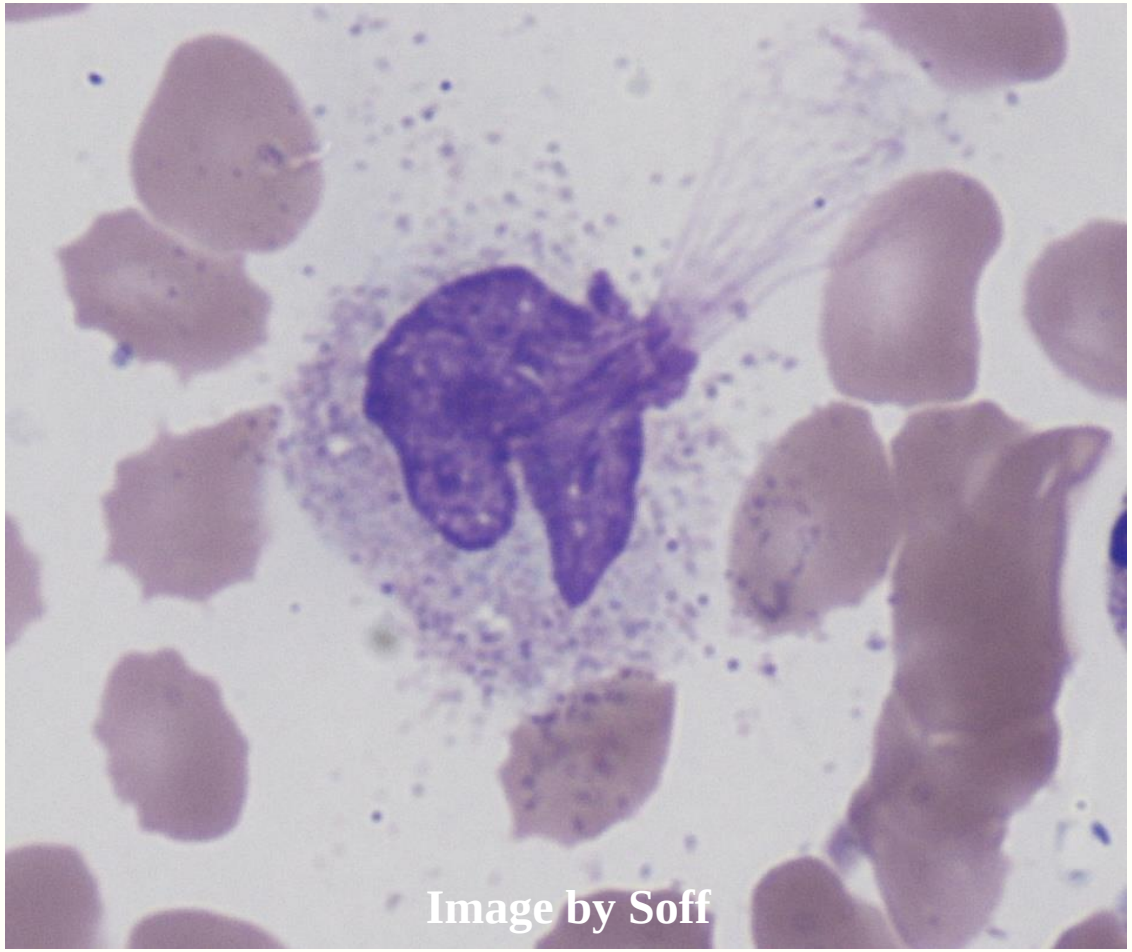
- TF Microparticle levels are increased in cancer, as well as other inflammatory states.
  - Sepsis, Sickle Cell Disease, Cancer, others
- No consensus on methodology for analysis.
- Has not entered routine research/clinical use.

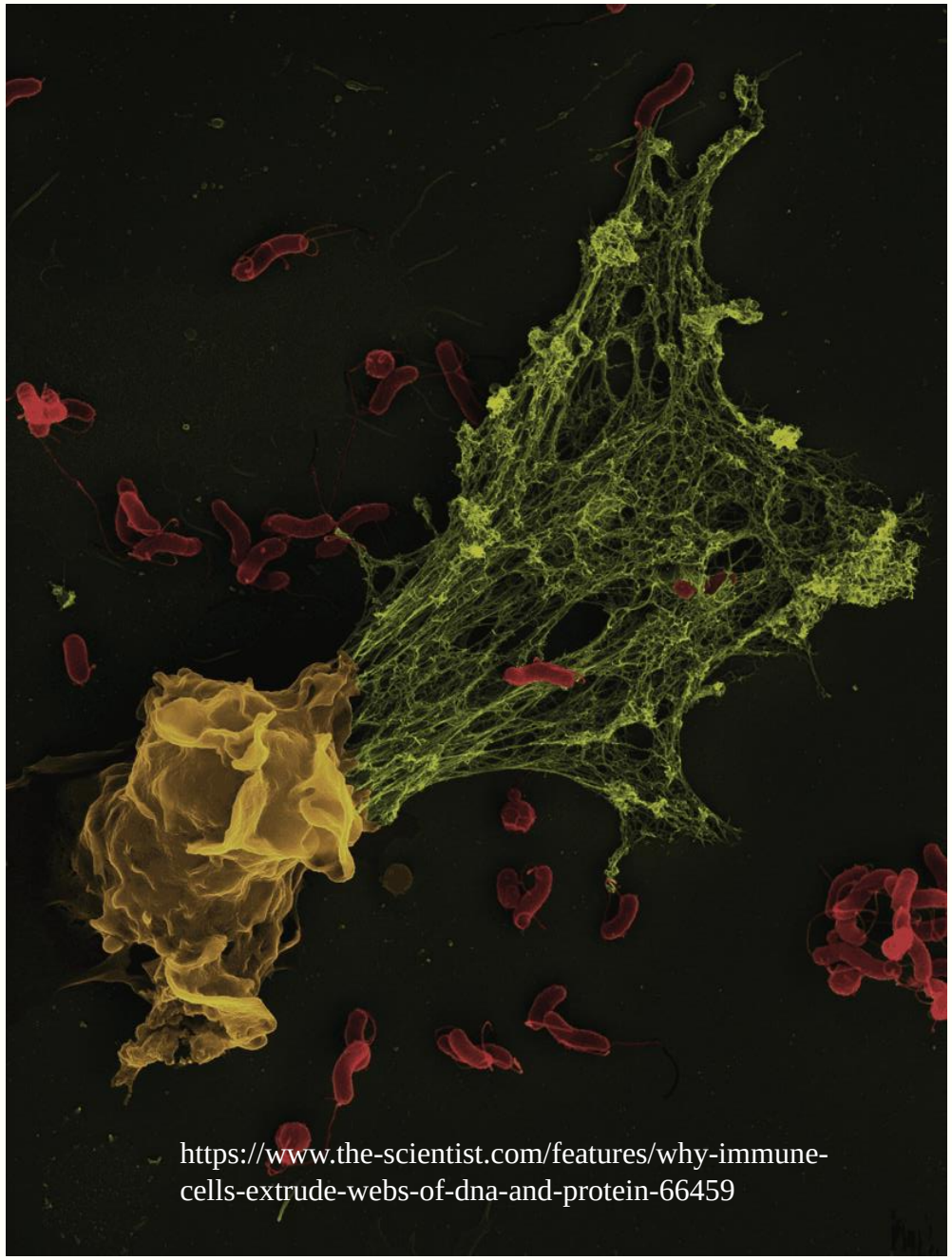
Neutrophil Extracellular Traps



- Provides a scaffold for platelets, red blood cells, extracellular vesicles, and procoagulant molecules.
- Enhance coagulation by both activating the intrinsic pathway and degrading Tissue Factor Pathway Inhibitor).
- Proposed to contribute to thrombus formation and propagation in arterial, venous, and cancer-associated thrombosis".
  - Thålin, C., et al (2019). Neutrophil Extracellular Traps. Arteriosclerosis, Thrombosis, and Vascular Biology, 39(9), 1724-1738. https://doi.org/10.1161/ATVBAHA.119.312463

Neutrophil Extracellular Traps

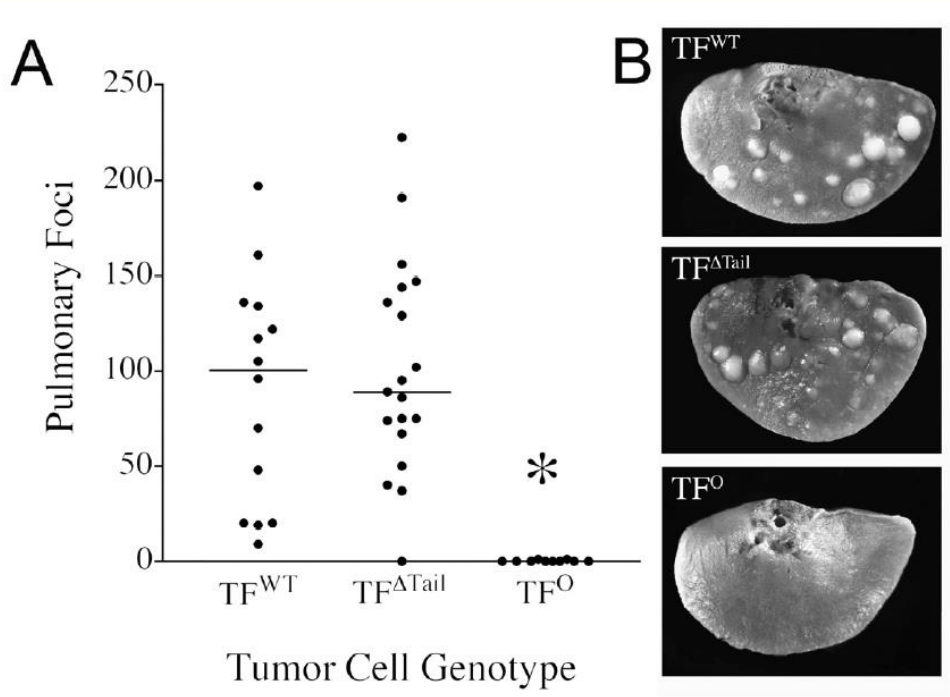




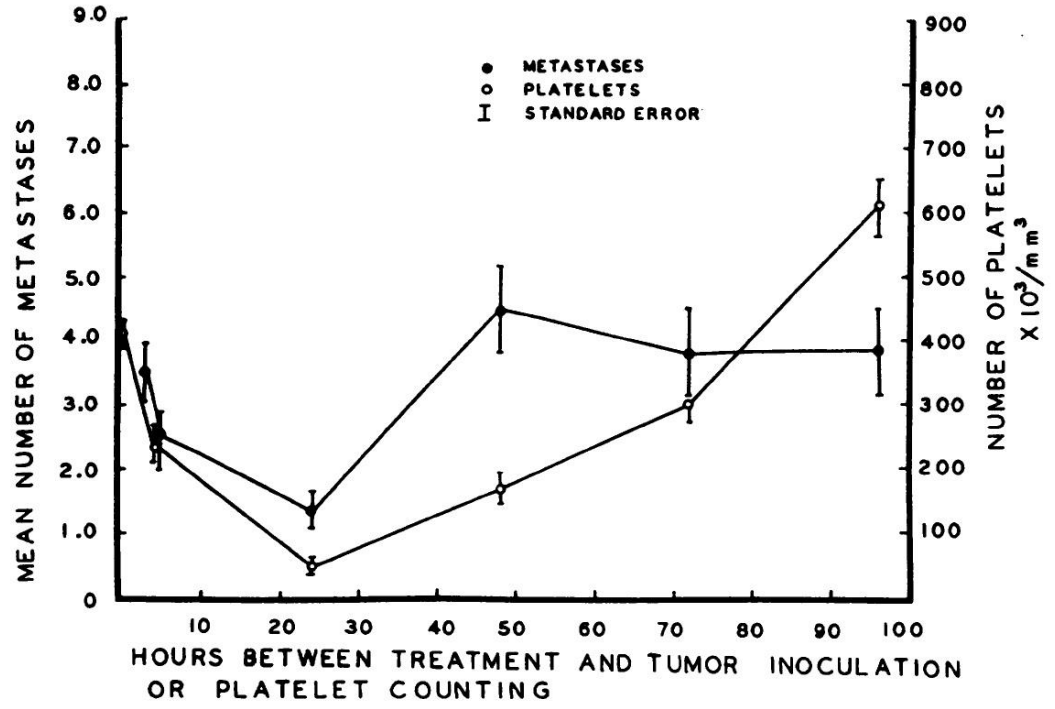
https://www.the-scientist.com/features/why-immune-cells-extrude-webs-of-dna-and-protein-66459

The Coagulation System Plays Key Role in Tumor Growth in Mice, But The Mechanism is Not Known!

- Tissue Factor Expression in Fibrosarcoma Cells.
- Palumbo, J et al. Blood 2007



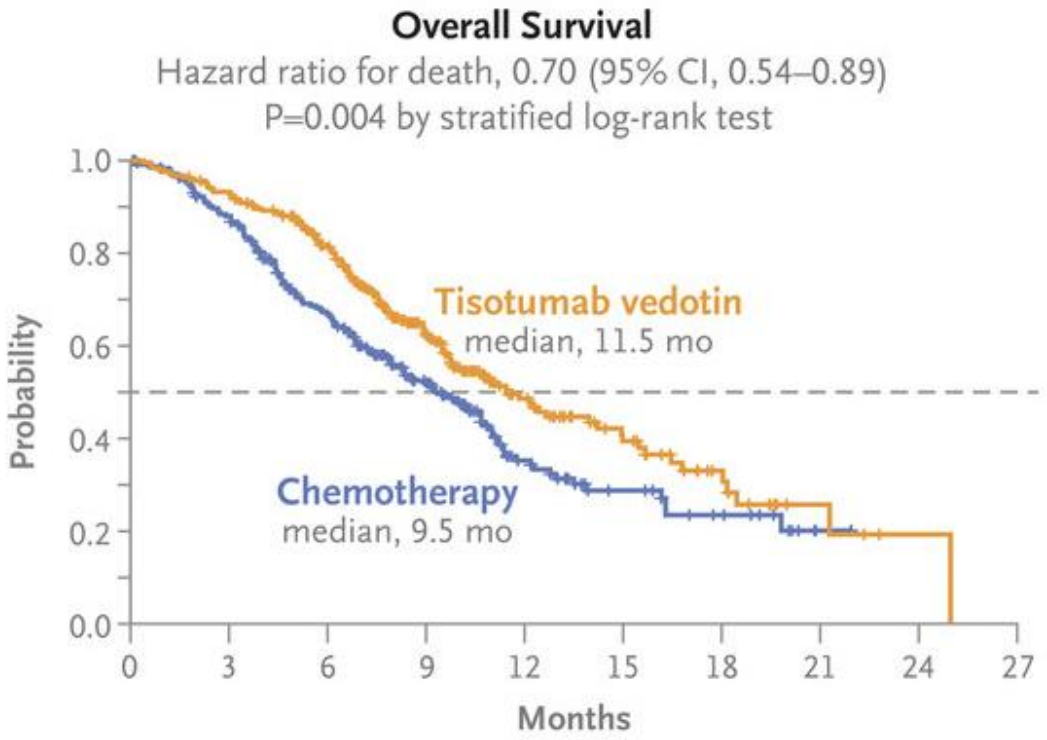
- Platelets and Metastasis
- Gasic GJ, et al, PNAS, 1968.

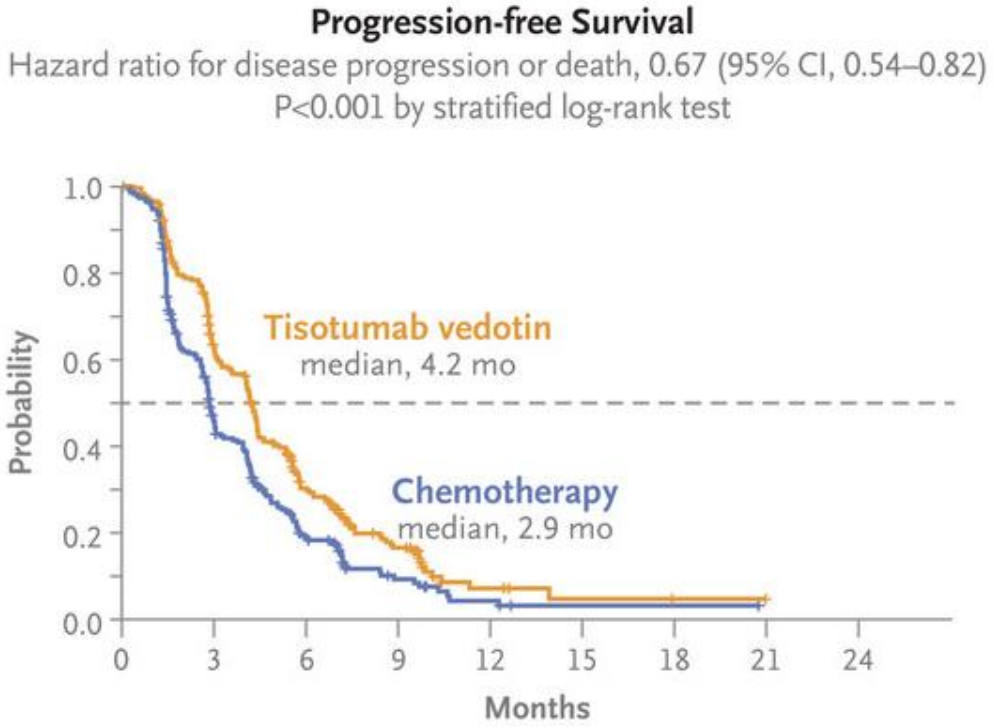


Tissue Factor As Target For Anti-Cancer Therapy

- **Tisotumab Vedotin:**
  - A tissue factor-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy."

- **Tisotumab Vedotin as Second- or Third-Line Therapy for Recurrent Cervical Cancer**
  - Vergote, I. et al. N Engl J Med 2024;391:44-55, 2024. DOI: 10.1056/NEJMoa2313811
  - A phase 3, open-label trial of tisotumab vedotin as second- or third-line therapy in patients with recurrent or metastatic cervical cancer.
  - Patients were randomly assigned, in a 1:1 ratio, to receive tisotumab vedotin monotherapy (2.0 mg per kilogram of body weight every 3 weeks) or the investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed).
  - The primary end point was overall survival.





Vergote, I. et al. N Engl J Med 2024;391:44-55, 2024. DOI: 10.1056/NEJMoa2313811

3. Screening For Occult Malignancy In Patients With VTE

- Since VTE often is related to an underlying occult malignancy, should one aggressively look for cancer in patients presenting with an unprovoked thrombosis?
- Will identification of occult cancer impact outcome?
- Is the occult cancer already metastatic?

https://www.needpix.com/photo/100955/inspector-man-detective-male-person-tracing-the-steps-tracing-steps-searching-for-traces-searching

Screening For Occult Cancer After Unprovoked Venous Thromboembolism

- Randomized clinical trial to assess the efficacy and safety of adding CT of the abdomen and pelvis to a limited screening strategy for occult cancer.
- Limited occult-cancer screening:
  - Basic blood testing,
  - Chest radiography,
  - Screening for breast, cervical, and prostate cancer.

- Carrier M et al. N Engl J Med 2015; 373:697-704

Screening For Occult Cancer After Unprovoked Venous Thromboembolism

Cohort	New Cancer	Missed Cancers	Mean Time to Cancer Diagnosis	Cancer Mortality
Limited-screening (N=431)	14 (3.2%)	4 (29%)	4.2 months	1.40%
Limited-screening plus-CT (N=423)	19 (4.5%)	5 (26%)	4.0 months	0.90%
	P=0.28	P=1.0	P=0.88	P=0.75

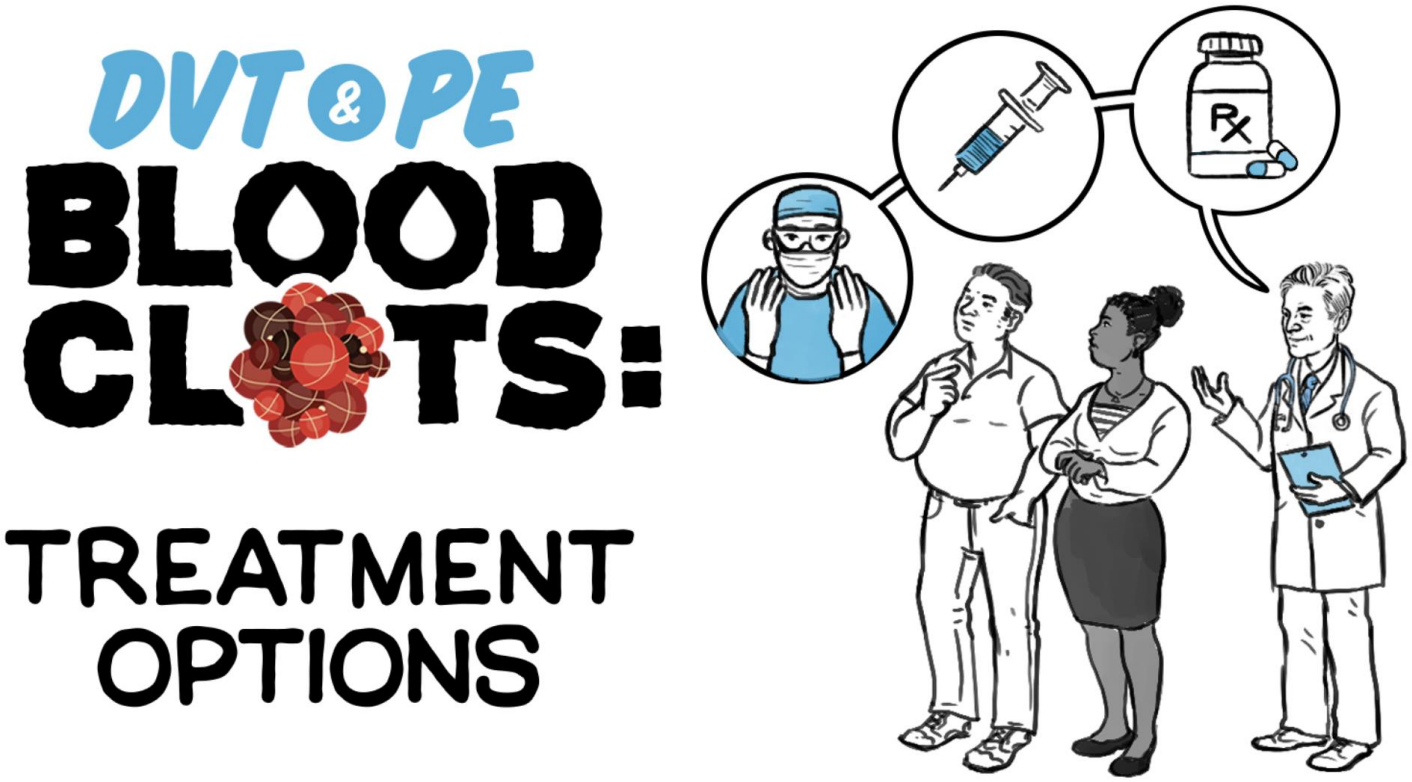
Carrier M et al. N Engl J Med 2015;373:697-704.

Screening for Occult Cancer after Unprovoked Venous Thromboembolism; Assessing the Current Literature and Future Directions.

Patel SS, et al. Eur J Haematol. 2023 Jan;110(1):24-31. doi: 10.1111/ejh.13874.

- "… extensive screening for cancer using PET/CT, endoscopy, and additional laboratory testing do not provide patients with unprovoked VTE any survival advantage even if they are diagnosed with a cancer."
- "A few studies have shown an earlier time to diagnosis among the unprovoked VTE population."
- "**In accordance with current guidelines proposed by the ISTH, we recommend against extensive screening of asymptomatic patients with unprovoked VTE beyond age and gender-specific cancer screening, unless otherwise guided by history and physical examination. The proposed recommendation will save patients and clinicians time, money, and undue stress and will provides a more universal approach to managing patients with unprovoked VTE.**"

4. Management of Thrombosis In Cancer Patients

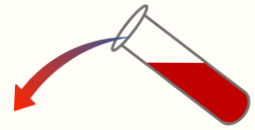


https://www.clotwise.com/DVTPE/

Framework For Anticoagulation: Four Questions.

1. Is anticoagulation indicated (reflecting a balance of indications and contraindications)?
2. Which anticoagulant should be used?
3. What dose of anticoagulant should be used?
4. What duration of anticoagulation should be planned?

- Soff GA. J Clin Oncol 42, 494-499(2024), Volume 42, Number 5, DOI: 10.1200/JCO.23.01905

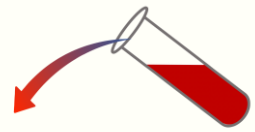


Difficulty Using Warfarin For Anticoagulation in Cancer Patients

- Unpredictable levels of anticoagulation
  - Drug interactions
  - Malnutrition/anorexia
  - Vomiting
  - Liver dysfunction.
- Need for interruption of therapy
  - Invasive procedures
  - Chemotherapy-induced thrombocytopenia

	Cancer	No Cancer	HR
Recurrent Thrombosis	**20.7%**	**6.8%**	**3.2**
Major Bleeding	**12.4%**	**4.9%**	**2.2**

Prandoni, P. et al *Blood* 100:3484-3488, 2002



The CLOT Study

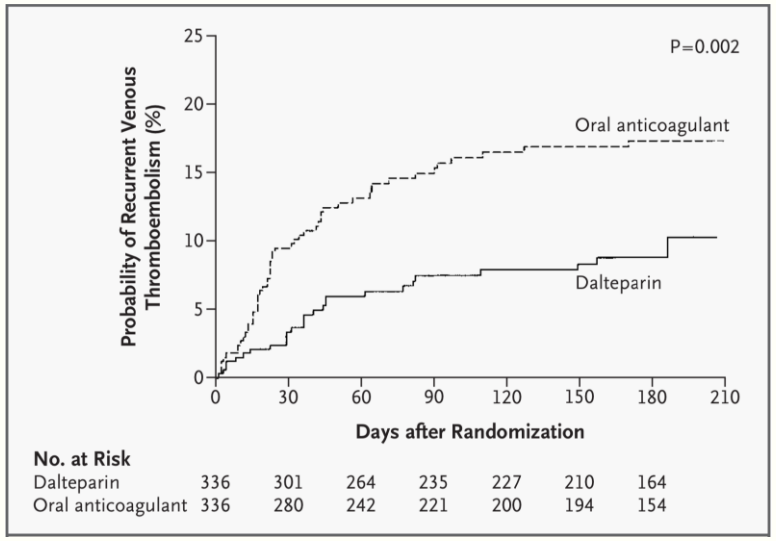
- Patients with cancer and DVT &/or PE.
- All received LMWH (Dalteparin 200 IU/kg, SQ, daily for 5-7 days, then randomized to:
  - 6 months of Warfarin (INR target 2.5) or
  - 6 months of Dalteparin:
    - 200 IU/kg, SQ, daily for 1 month, then 150 IU/kg for 5 months.

  - Lee et al. NEJM 349:146-53, 2003

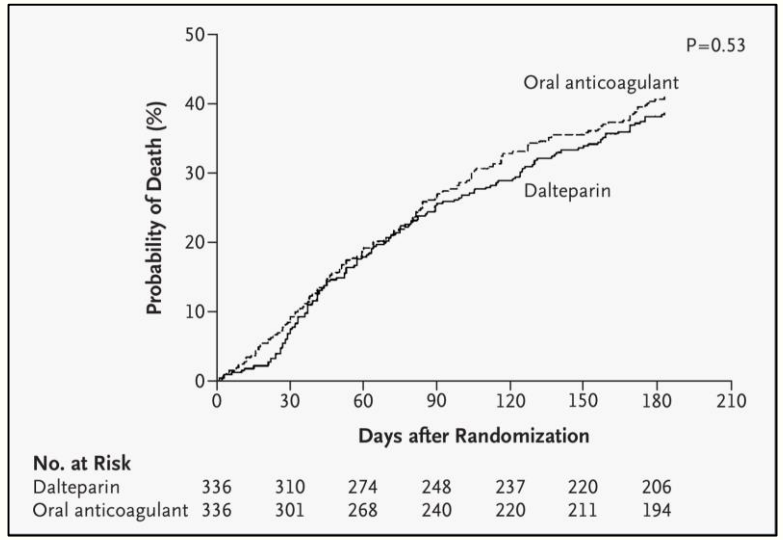
Dalteparin Resulted in 50% Reduction in Recurrent Thrombosis

6 Month	VTE Recurrence	Major Bleed	All Bleed
Dalteparin	**9%**	**6%**	**14%**
Warfarin	**17%**	**4%**	**19%**
	HR 0.48, P=0.002	**NS**	**NS**

Recurrent VTE



Death From All Causes



Lee, A. et al. *NEJM* 2003;349:146-153

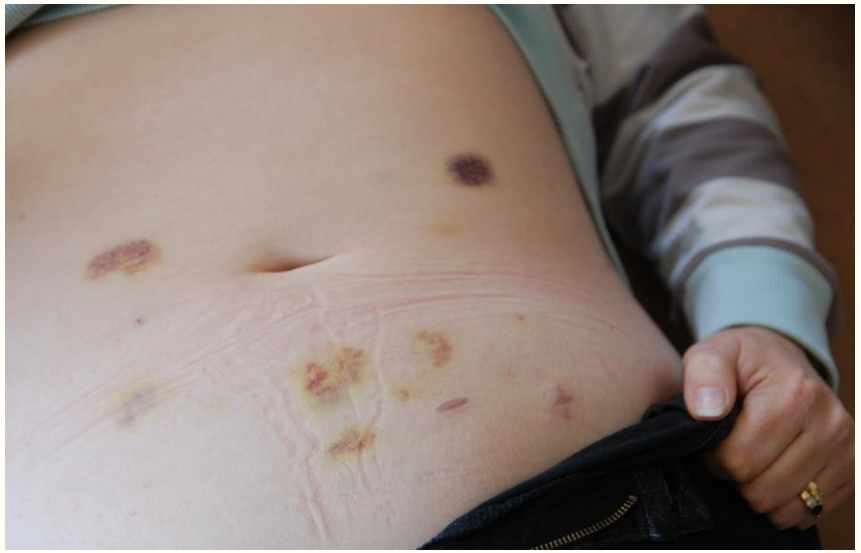
Pooled Analysis of LMWH vs. Warfarin Anticoagulation Trials in Cancer Associated Thrombosis

	Recurrent VTE (Events/At Risk)	Major Bleeding (Events/At Risk)
LMWH	**7.3% (62/846)**	**4.5% (42/925)**
Warfarin	**12.4% (101/817)**	**4.0% (36/895)**

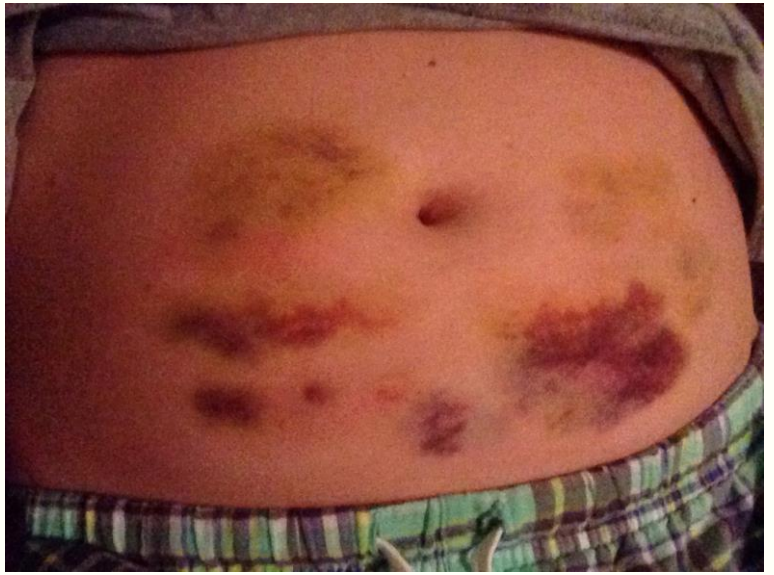
- LMWH: Dalteparin, Enoxaparin, Tinzaparin.
  - Lee AY, et al. N Engl J Med 2003; 349(2):146–153
  - Deitcher SR, et al. Clin Appl Thromb Hemost 2006;12(4):389–396
  - Lee et al, JAMA. 2015;314(7):677-686.

LMWH For Cancer-Associated Thrombosis: Was the preferred anticoagulant from 2003 - ~2014

- Recurrent VTE: ~7-8%/6 months
- Major Bleeding: ~4-6%/6 months
- Hurts! Poor compliance.

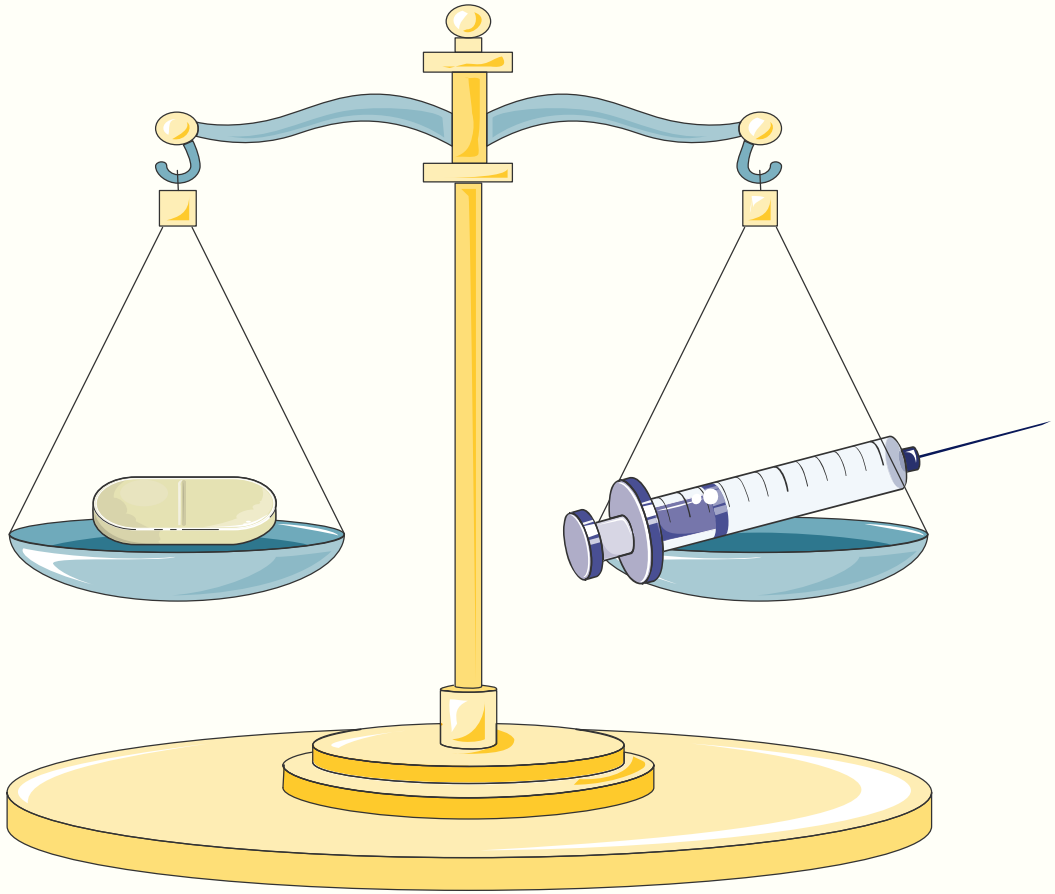


https://hairyfarmerfamily.files.wordpress.com/2011/05/heparin.jpg

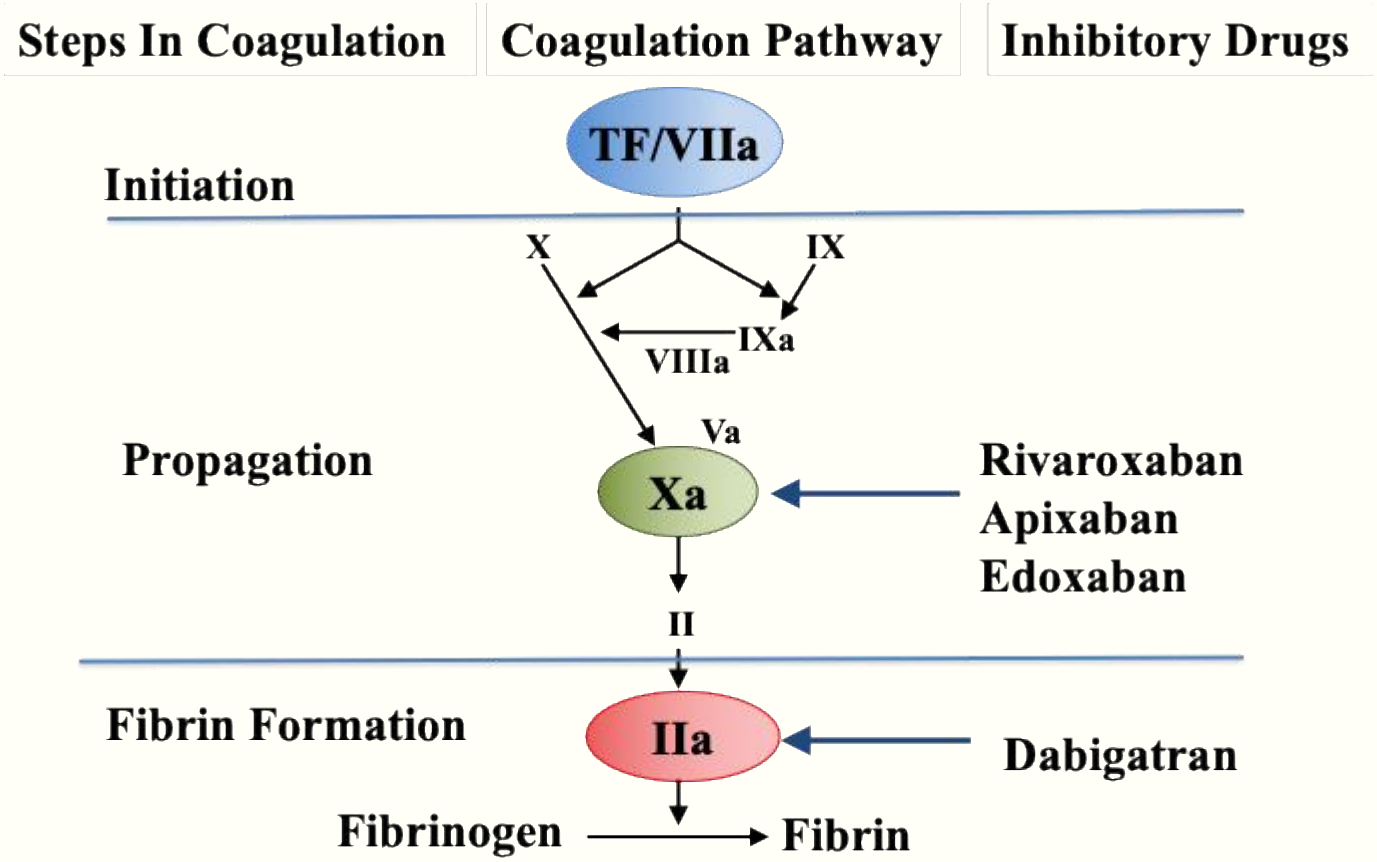


https://hannahcrafted.files.wordpress.com/2014/03/img_9252.jpg

Isn’t There a Pill For That?



5. Direct Oral Anticoagulants



FDA Approval for treatment of VTE:

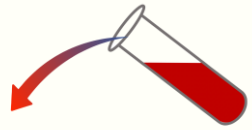
- Rivaroxaban: November 2012
- Apixaban: August 2014

- FDA approval did not explicitly address cancer associated VTE. (i.e. on label, even though no specific trials for CAT, comparing with LMWH).

Adapted from Soff, Arteriosclerosis, Thrombosis, and Vascular Biology 2012, 32:569-574.

Rivaroxaban for Cancer-Associated Thrombosis: (Quality Assurance Program, 2014-2016)

1. LMWH had been the standard of care for Treatment of CAT.
2. EINSTEIN:
   - Rivaroxaban noninferior to warfarin in a general population.
   - Einstein-DVT: 6.8% with active cancer (NEJM 2010)
   - Einstein-PE: 4.7% with active cancer (NEJM 2012)
3. Knowledge Gap
   - No studies comparing rivaroxaban with LMWH in CAT.
   - However, in 2012 rivaroxaban was FDA approved for VTE treatment, without specifically addressing CAT.



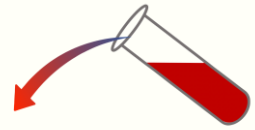
"Rivaroxaban treatment of cancer-associated venous thromboembolism: MSKCC institutional experience"

Soff et al. Research and Progress in Thrombosis & Haemostasis, 2019
Mantha et al, JTT, 2017

- N=1072 Patients with pulmonary embolism or symptomatic DVT. 6 Month Follow-up.

Event	N=1072 Cohort	< 75 yo. (N=890)	≥ 75 yo.* (N=182)
Recurrent VTE	**4.2%** (95% CI=2.7%-5.6%)	**4.1%** (2.5%-5.8%)	**4.5%** (0.6%-8.3%)
Major Bleeding	**2.2%** (95% CI=1.1-3.2%)	**2.2%** (1.0%-3.4%)	**1.8%** (<1-4.2%)
CRNMB	**5.5%** (95% CI=3.7-7.1%)	**5.5%** (3.6%-7.3%)	**5.5%** (1.1%-9.7%)
All-Cause Mortality	**22.2%** (95% CI=19.4-24.9%)	**21.3%** (18.3%-24.2%)	**26.7%** (19.2%-33.6%)

- **Used reduced dose in elderly. Rivaroxaban 10 mg bid X 21 days, then 15 mg daily.**
  - **NOT per FDA approved guidelines.**
- **Did not use in patients with active GI or GU luminal pathology.**



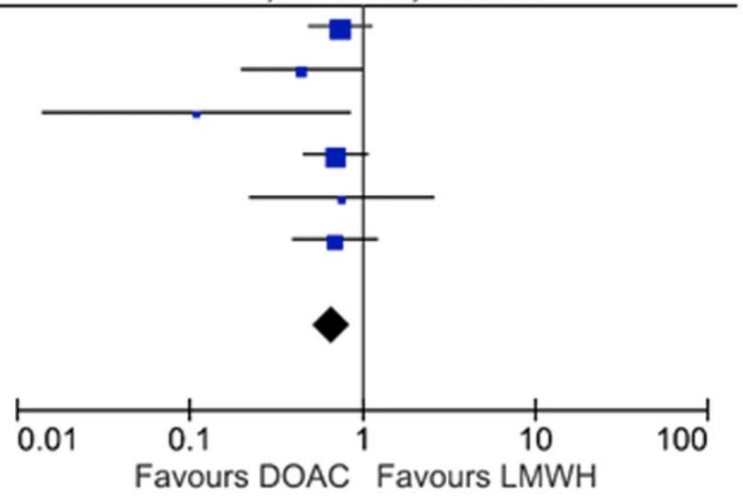
DOAC vs. LMWH for the treatment of cancer associated thrombosis. Systematic review and meta-analysis of randomized controlled trials

A. Recurrent venous thromboembolism

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	34	522	46	524	33.5%	0.74 [0.48, 1.14]
SELECT-D	8	203	18	203	9.3%	0.44 [0.20, 1.00]
ADAM-VTE	1	145	9	142	1.4%	0.11 [0.01, 0.85]
CARAVAGGIO	32	576	46	579	32.0%	0.70 [0.45, 1.08]
CASTA-DIVA	4	74	6	84	4.1%	0.76 [0.22, 2.58]
CANVAS	20	330	27	308	19.6%	0.69 [0.40, 1.21]
Total (95% CI)		**1850**		**1840**	**100.0%**	**0.67 [0.52, 0.85]**
Total events	99		152			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.36$, df = 5 (P = 0.50); $I^2 = 0\%$

Test for overall effect: Z = 3.22 (P = 0.001)



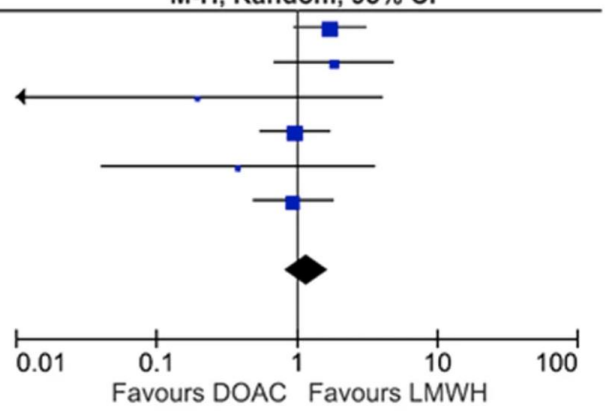
- Frere et al. Journal of Hematology & Oncology (2022) 15:69 https://doi.org/10.1186/s13045-022-01289-1

B. Major bleeding

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	29	522	17	524	29.2%	1.71 [0.95, 3.08]
SELECT-D	11	203	6	203	12.2%	1.83 [0.69, 4.86]
ADAM-VTE	0	145	2	142	1.4%	0.20 [0.01, 4.04]
CARAVAGGIO	22	576	23	579	30.3%	0.96 [0.54, 1.71]
CASTA-DIVA	1	74	3	84	2.5%	0.38 [0.04, 3.56]
CANVAS	17	330	17	308	24.5%	0.93 [0.49, 1.80]
Total (95% CI)		**1850**		**1840**	**100.0%**	**1.17 [0.82, 1.67]**
Total events	80		68			

Heterogeneity: Tau² = 0.02; Chi² = 5.66, df = 5 (P = 0.34); I² = 12%

Test for overall effect: Z = 0.85 (P = 0.39)

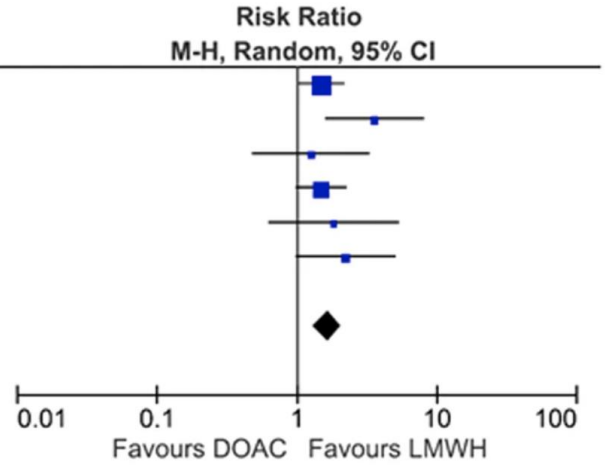


C. Clinically relevant non major bleeding

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	64	522	43	524	40.6%	1.49 [1.04, 2.16]
SELECT-D	25	203	7	203	8.2%	3.57 [1.58, 8.07]
ADAM-VTE	9	145	7	142	5.9%	1.26 [0.48, 3.29]
CARAVAGGIO	52	576	35	579	32.1%	1.49 [0.99, 2.26]
CASTA-DIVA	8	74	5	84	4.8%	1.82 [0.62, 5.31]
CANVAS	19	330	8	308	8.3%	2.22 [0.98, 4.99]
Total (95% CI)		**1850**		**1840**	**100.0%**	**1.66 [1.31, 2.09]**
Total events	177		105			

Heterogeneity: Tau² = 0.00; Chi² = 4.82, df = 5 (P = 0.44); I² = 0%

Test for overall effect: Z = 4.23 (P < 0.0001)



- Frere et al. Journal of Hematology & Oncology (2022) 15:69 https://doi.org/10.1186/s13045-022-01289-1

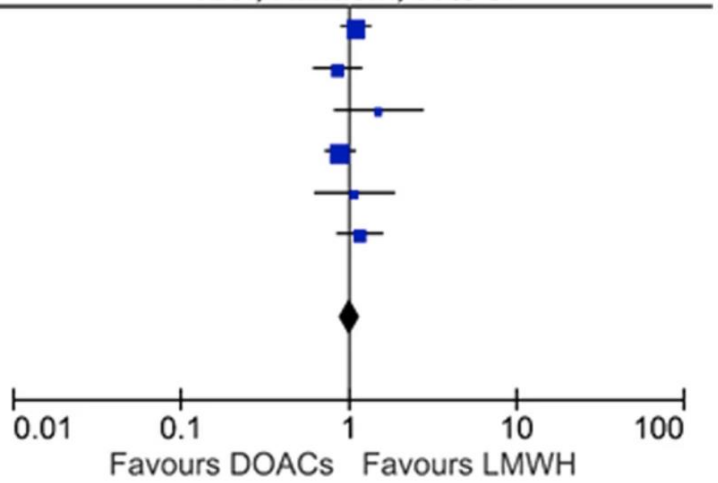
DOAC vs. LMWH for the treatment of cancer associated thrombosis. Systematic review and meta-analysis of randomized controlled trials

D. Overall Mortality

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	140	522	127	524	29.9%	1.11 [0.90, 1.36]
SELECT-D	48	203	56	203	13.6%	0.86 [0.61, 1.20]
ADAM-VTE	23	145	15	142	4.4%	1.50 [0.82, 2.76]
CARAVAGGIO	135	576	153	579	31.4%	0.89 [0.73, 1.08]
CASTA-DIVA	19	74	20	84	5.5%	1.08 [0.63, 1.86]
CANVAS	71	330	57	308	15.3%	1.16 [0.85, 1.59]
Total (95% CI)		**1850**		**1840**	**100.0%**	**1.02 [0.89, 1.16]**
Total events	436		428			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.76$, df = 5 (P = 0.33); $I^2 = 13\%$

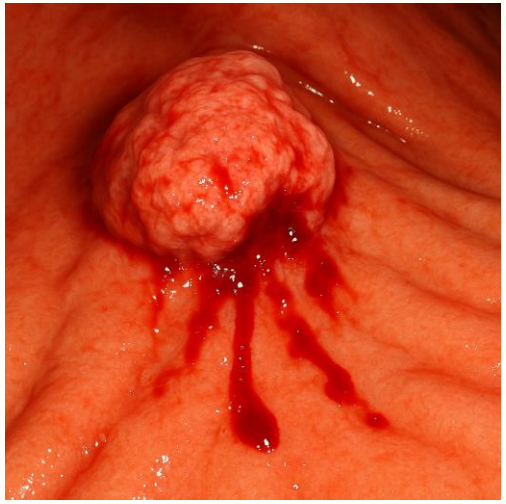
Test for overall effect: Z = 0.25 (P = 0.80)

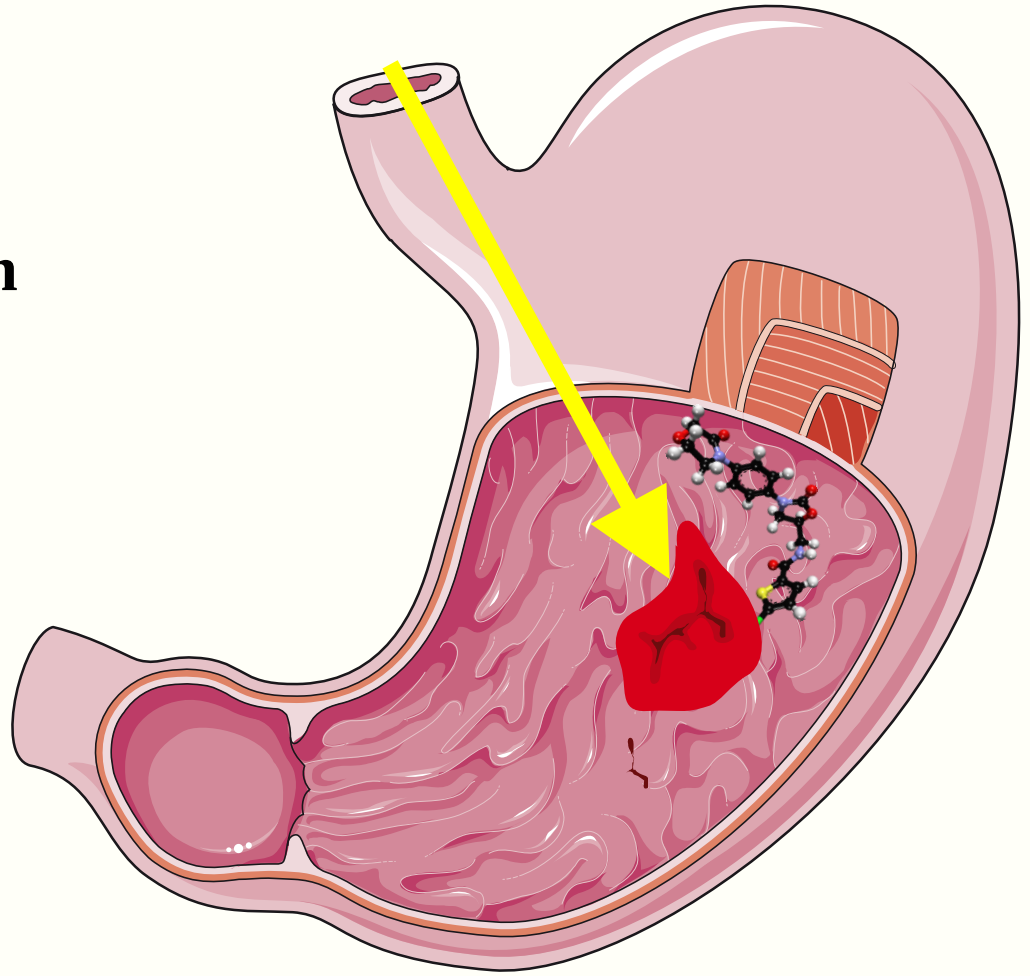


- Frere et al. Journal of Hematology & Oncology (2022) 15:69 https://doi.org/10.1186/s13045-022-01289-1

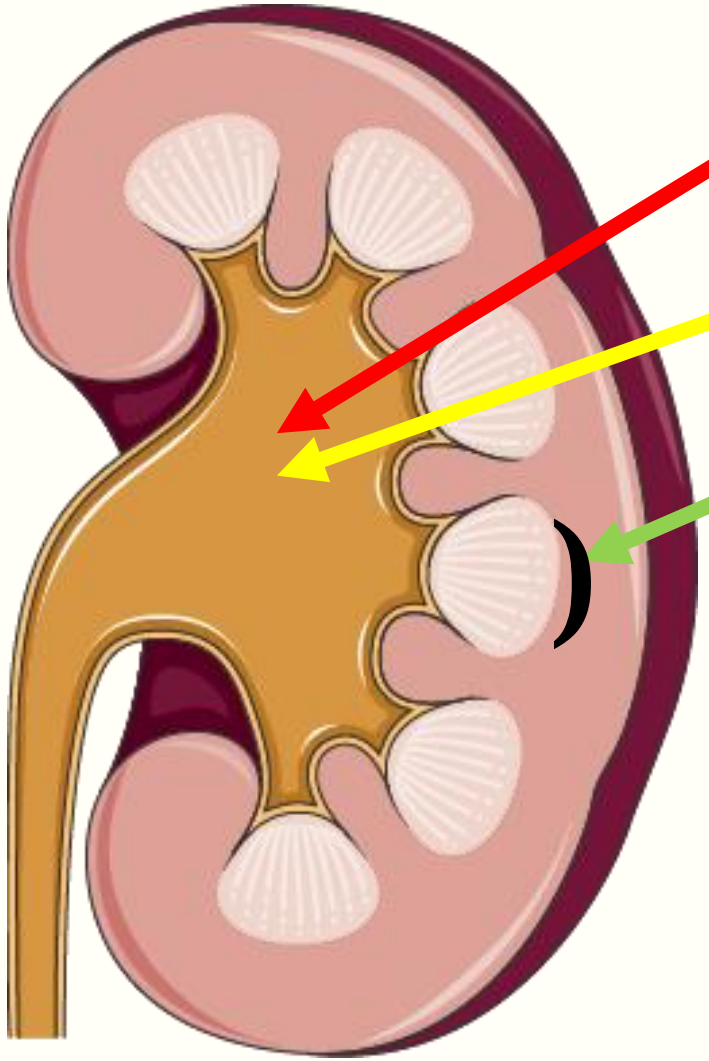
In Setting of Upper GI Cancer or Pathology, A DOAC Has Increased Risk of Bleeding!

Rivaroxaban





SERVIER
moved by you



DOAC (Rivaroxaban, MWt. 436)

LMWH (Enoxaparin, MWt. ~4500)

Antithrombin III (MWt. 58,000)

- **DOACs and LWMH are both cleared, in part, in the urinary tract.**
- **However, DOACs are “direct” and will have anticoagulant activity, while LMWH are “indirect” and will not have activity, in the absence of ATIII.**
- **Under normal circumstances, ATIII is not cleared in the urine.**

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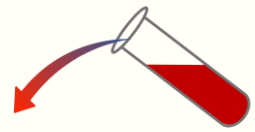
Increased Major Bleeding Was In Mostly Limited to Patients With GI/GU Cancer

	Edoxaban	Dalteparin	
GI Cancer at Randomization			**p-value**
Yes	**13.2% (18/136)**	**2.4% (3/125)**	**0.0169**
No	**4.7% (18/386)**	**4.5% (18/399)**	
Urothelial Cancer at Randomization			
Yes	**13.2% (5/38)**	**0.0% (0/31)**	
No	**6.4% (31/484)**	**4.3% (21/493)**	

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

Bleeding in GI/GU Cancers

- "All guidelines recommend caution in using DOACs in patients with GI cancers because of the higher reported risk of bleeding complications."
  - Lyman GH, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021 Feb 23;5(4):927-974.
- "Caution with direct factor Xa inhibitors is warranted in GI and genitourinary malignancies and other settings with high risk for mucosal bleeding."
  - Key NS et al. ASCO Guideline Update. J Clin Oncol 41, 3063-3071(2023) Volume 41, Number 16

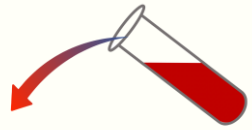


Recurrent VTE Versus Bleeding

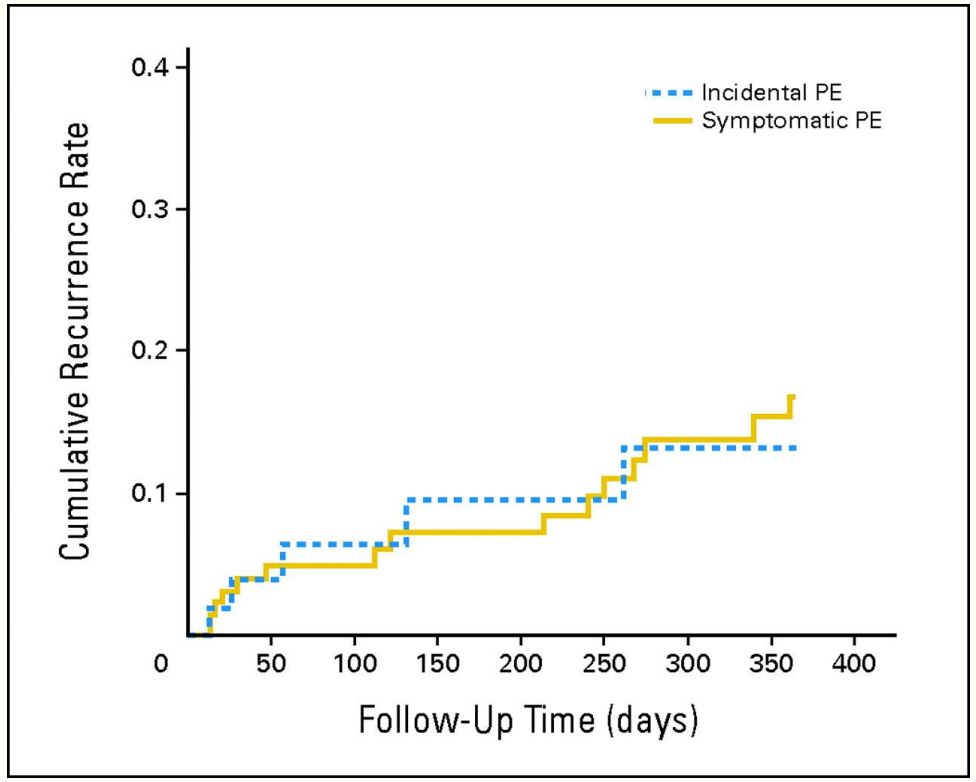
- The appropriate question is not which anticoagulant is better (i.e. a DOAC versus low molecular weight heparin).
- Bleeding appears to be in “improperly” selected patients.
- GI/GU Bleeding not increased in patients without anatomic risk.
- DO NOT USE DOACS IN PATIENTS WITH ACTIVE GI OR GU LESIONS OF INSTRUMENTATION!
- The appropriate question, “In a given patient which anticoagulant is appropriate?”

6. Incidental Thrombosis/ Pulmonary Embolism

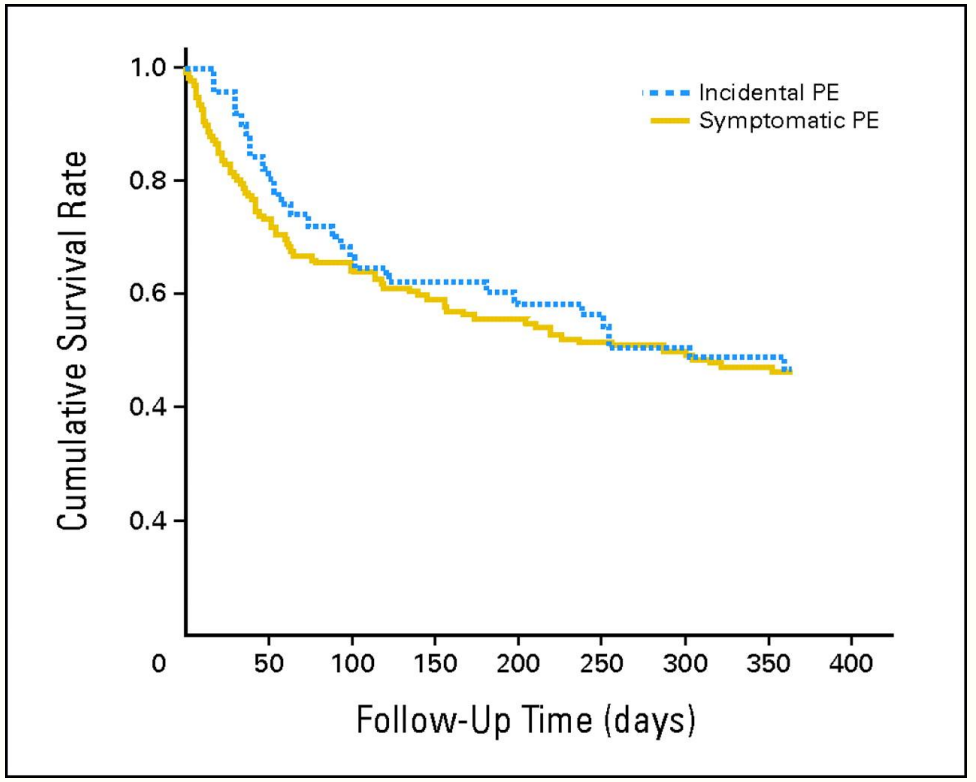
- Clinical relevance?
- Risks of recurrence, need for anticoagulation?
- Retrospective cohort study (2004-2010)
- Incidental Pulmonary Embolism (n=51)
- Symptomatic Pulmonary Embolism (n=144)
- Observed for 1 year
  - Den Exter P L et al. JCO 29:2405-2409, 2011.



Cumulative Recurrent VTE



Cumulative Overall Survival



den Exter P L et al. JCO 2011;29:2405-2409

7. Primary Thrombosis Prophylaxis

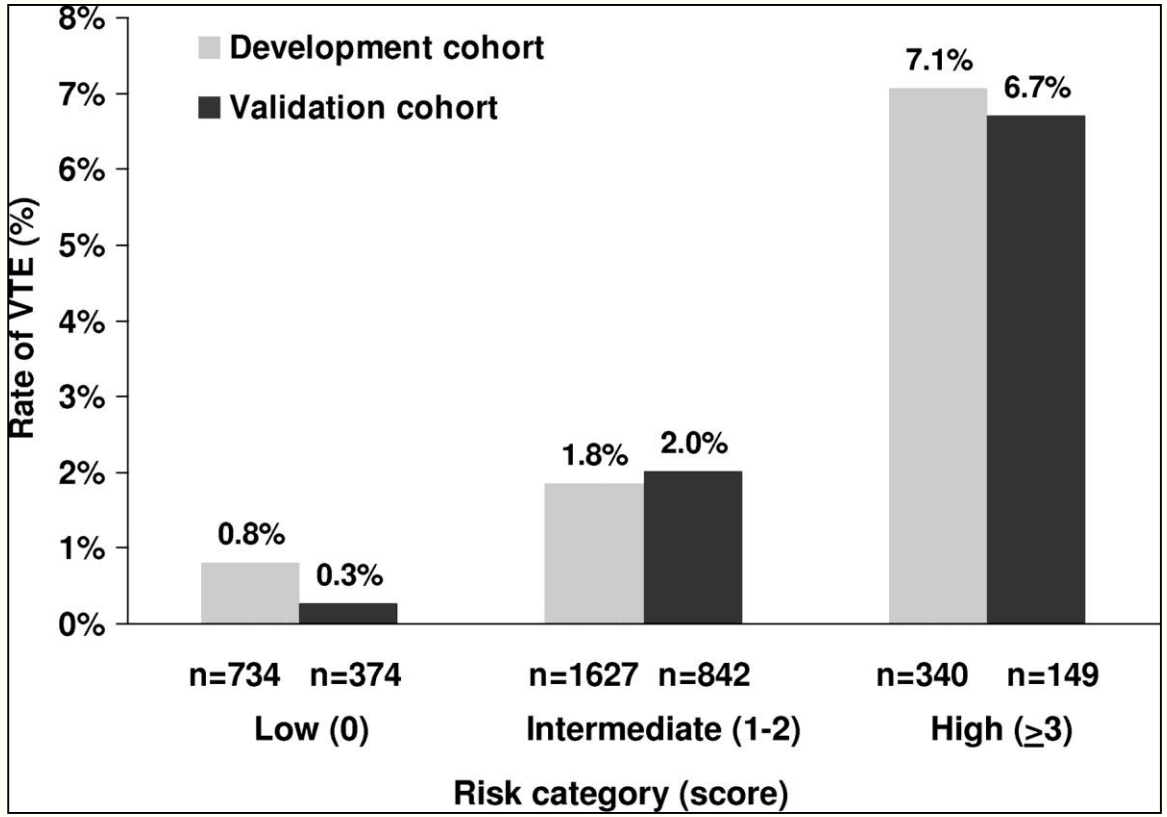
- Is there a role for thrombosis prophylaxis in outpatient, ambulatory cancer patients prior to development of a thrombosis?
- Balance: risk:benefit:cost:convenience

Predictive Model for Chemotherapy-Associated VTE

Patient Characteristic	Risk Score
Site of Cancer	
Very high risk (stomach, pancreas)	**2**
High risk (lung, lymphoma, gynecologic, bladder, testis)	**1**
Prechemotherapy platelet count ≥ 350K/mcL	**1**
Hemoglobin < 10 g/dL or use of red cell growth factors	**1**
Prechemotherapy leukocyte count more than 11K/mcL	**1**
BMI 35 kg/m2 or more	**1**

- Khorana AA *et al. Blood*. 111:4902-4907, 2008.
- Khorana AA & Connolly GC. JCO. 27:4839-4847, 2009

Rates of VTE According To Scores From The Risk Model In The Derivation And Validation Cohorts



- Possible role in identifying population where primary anticoagulation prophylaxis is appropriate.
- Khorana, A. A. et al. Blood 2008;111:4902-4907

Risk Prediction Scores for Venous Thromboembolism in Cancer Patients

- Some incorporate biomarkers or molecular profiles that may improve prediction capability, but at trade-off that the additional information will not be routinely available.
- The goal is to identify high-risk patients for whom prophylactic anticoagulation may be warranted.
  - Van Es et al, Haematologica. 2017 Sep; 102(9): 1494–1501., doi: 10.3324/haematol.2017.169060

Item	Khorana score (points)	Vienna CATS score (points)	PROTECHT score (points)	CONKO score (points)
Pancreatic or gastric cancer (very high-risk tumors)	+2	+2	+2	+2
Lung, gynecological, lymphoma, bladder, or testicular (high-risk tumors)	+1	+1	+1	+1
Pre-chemotherapy hemoglobin <10 g/dL or use of erythropoietin stimulating agents	+1	+1	+1	+1
Pre-chemotherapy white blood cell count >11 x 10^9/L	+1	+1	+1	+1
Pre-chemotherapy platelet count ≥350 x 10^9/L	+1	+1	+1	+1
Body Mass Index >35 kg/m^2	+1	+1	+1	–
D-dimer >1.44 µg/L	–	+1	–	–
Soluble P-selectin >53.1 ng/L	–	+1	–	–
Gemcitabine chemotherapy	–	–	+1	–
Platinum-based chemotherapy	–	–	+1	–
WHO performance status ≥2	–	–	–	+1

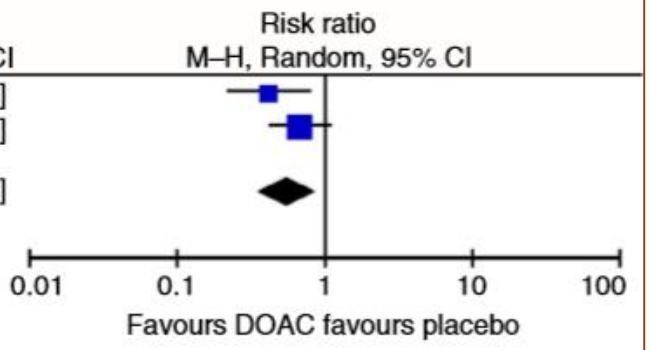
WHO: World Health Organization.

DOAC for the prevention of thrombosis in ambulatory patients with cancer, with Khorana Score of ≥ 2

Venous Thromboembolism

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk ratio M–H, Random, 95% CI
AVERT	12	291	28	283	39.5%	0.4168 [0.2162, 0.8033]
CASSINI	25	420	37	421	60.5%	0.6773 [0.4153, 1.1045]
Total (95% CI)		711		704	100.0%	0.5592 [0.3511, 0.8907]
Total events	37		65			

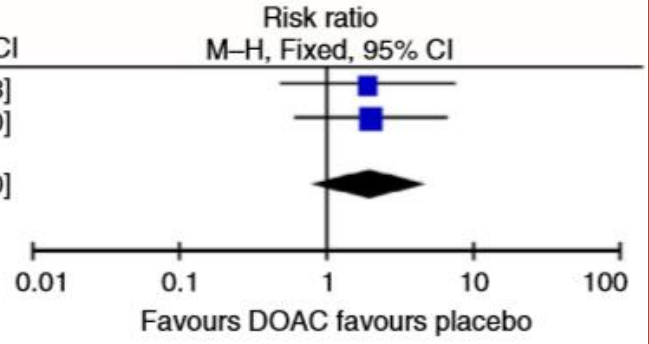
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 1.35$, df = 1 ($P = .24$); $I^2 = 26\%$
Test for overall effect: $Z = 2.45$ ($P = .01$)



Major Bleeding (on-treatment)

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk ratio M–H, Fixed, 95% CI
AVERT	6	288	3	275	43.4%	1.9097 [0.4824, 7.5608]
CASSINI	8	405	4	404	56.6%	1.9951 [0.6056, 6.5730]
Total (95% CI)		693		679	100.0%	1.9580 [0.7953, 4.8210]
Total events	14		7			

Heterogeneity: $\chi^2 = 0.00$, df = 1 ($P = .96$); $I^2 = 0\%$
Test for overall effect: $Z = 1.46$ ($P = .14$)

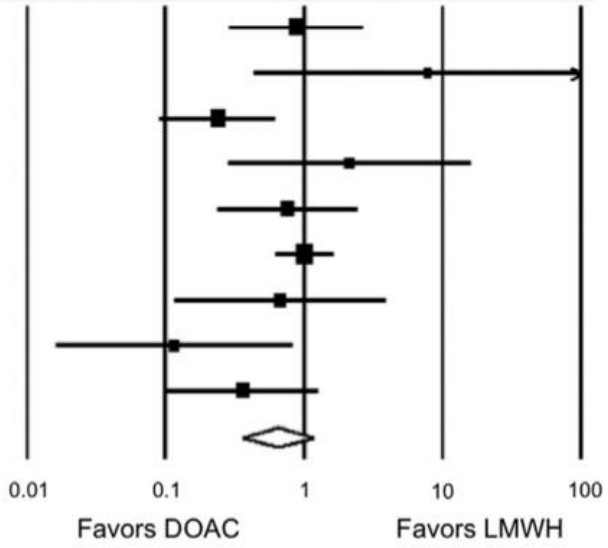


- AVERT: Apixaban. Carrier et al, NEJM, December 2018
- CASSINI: Rivaroxaban. Khorana et al, NEJM 2019
- Li A et al, J Thromb Haemost. 2019;17:2141–2151

8. Anticoagulation and Brain Cancer: Risk of Intracranial Hemorrhage (ICH)

- Studied the safety and efficacy of direct-acting oral anticoagulants (DOACs) for therapeutic anticoagulation in the setting of primary or metastatic brain cancer.
- Meta-analysis and systematic review of studies that compared the risk of intracranial hemorrhage (ICH) in patients with brain cancer treated with DOACs vs low-molecular-weight heparin (LMWH).
  - Iyengar V., et al. Journal of Thrombosis and Haemostasis, 22, 423-429, (2024), ISSN 1538-7836.

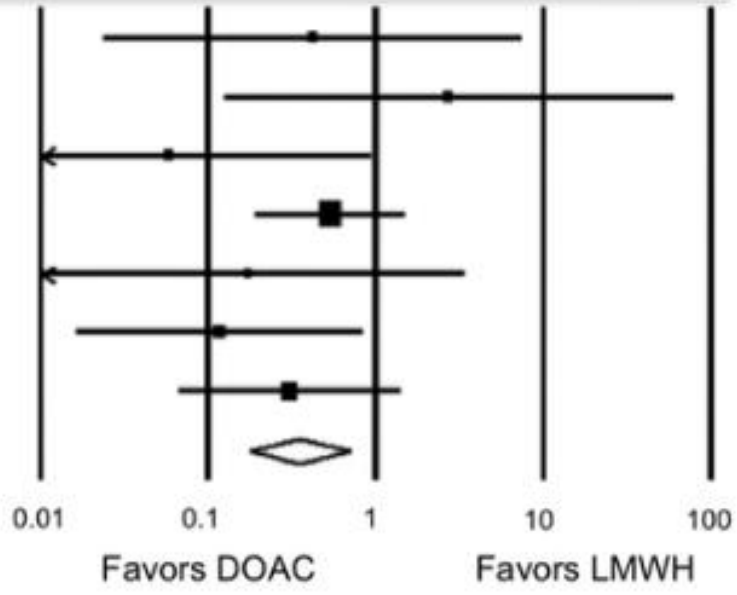
		DOAC		LMWH		
Study	**Cancer type**	**Events**	**Total**	**Events**	**Total**	**M-H Risk Ratio (95% CI)**
Abraham et al. (2018)	Both	4	45	9	90	0.889 (0.289 – 2.730)
Burth et al. (2001)	Both	3	15	0	17	7.875 (0.440 – 141.082)
Carney et al. (2019)	Both	4	41	53	131	0.241 (0.093 – 0.626)
Kewan et al. (2019)	Metastatic	1	7	5	75	2.143 (0.289 – 15.872)
Leader et al. (2020)	Metastatic	4	41	7	55	0.767 (0.240 – 2.445)
Leader et al. (2023)	Both	25	264	45	484	1.019 (0.640 – 1.622)
Lee et al. (2021)	Both	2	55	3	56	0.679 (0.118– 3.906)
Reed-guy et al. (2022)	Primary	1	32	20	75	0.117 (0.016 – 0.836)
Swartz et al. (2021)	Both	3	52	9	57	0.365 (0.105 - 1.277)
Total						**0.648 (0.360 – 1.167)**



Primary Brain Cancer

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)**

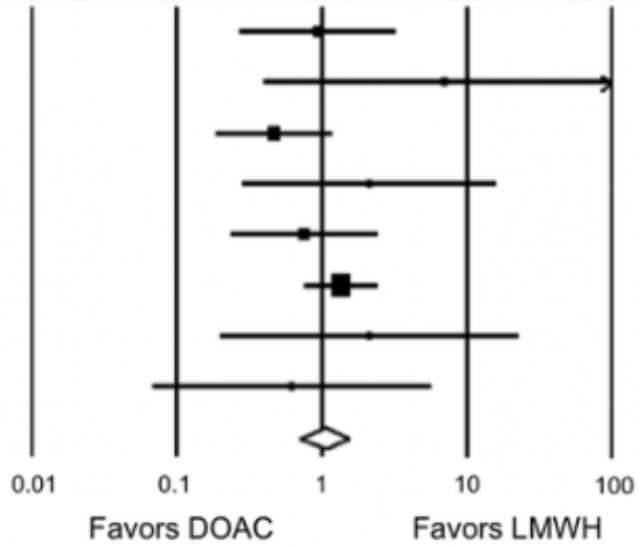


Iyengar V, et al. Journal of Thrombosis and Haemostasis, 22, 423-429, 2024, ISSN 1538-7836.

Metastatic Brain Cancer

B

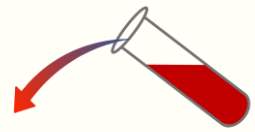
Study	DOAC Events	DOAC Total	LMWH Events	LMWH Total	M-H Risk Ratio (95% CI)
Abraham et al. (2018)	4	32	5	38	0.950 (0.278 – 3.243)
Burth et al. (2001)	2	6	0	9	7.143 (0.402 – 127.072)
Carney et al. (2019)	4	21	34	84	0.471 (0.188 – 1.180)
Kewan et al. (2019)	1	7	5	75	2.143 (0.289 – 15.872)
Leader et al. (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)**



Iyengar V, et al. Journal of Thrombosis and Haemostasis, 22, 423-429, 2024, ISSN 1538-7836.

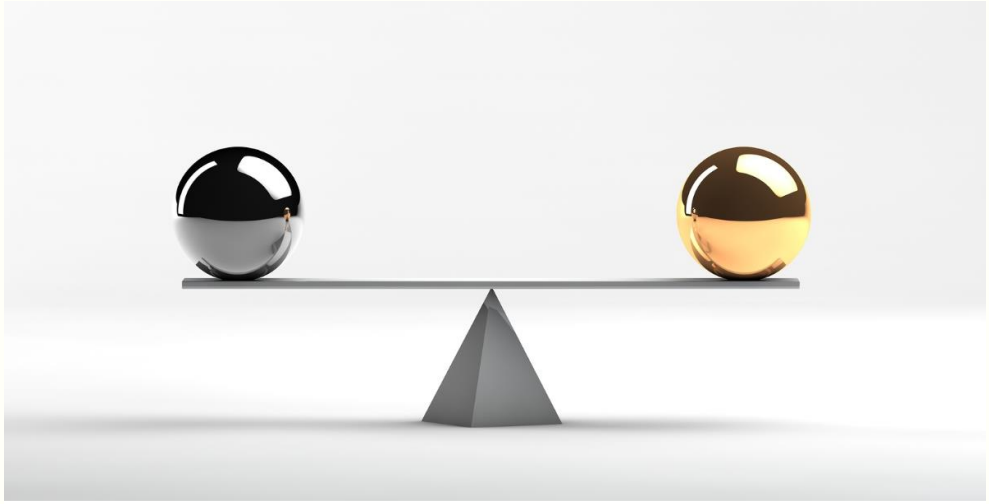
- “Our findings demonstrate that type of cancer (primary vs metastatic) meaningfully influences this risk, as patients with primary brain tumors treated with DOACs had an approximately 65% reduction in the relative risk of ICH relative to those treated with LMWH.
- In contrast, there was no difference in outcomes seen in patients with brain metastasis based on type of anticoagulant.”

  - Iyengar, V.et al. Journal of Thrombosis and Haemostasis, 22, 423-429, 2024, ISSN 1538-7836.



9. Management of Anticoagulation in Setting Of Chemotherapy-Induced Thrombocytopenia.

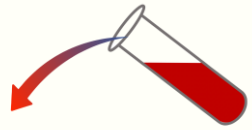
- In cancer patients, need for therapeutic anticoagulation often is concurrent with thrombocytopenia from chemotherapy, or other reasons.
- Anticoagulation and Thrombocytopenia are both risk factors for bleeding.



Guidelines Implemented In 2010

Platelet Count	MSKCC Guidelines
>50,000/mcL	Full Therapeutic Dose
25,000/mcL – 50,000/mcL	Half Dose
<25,000/mcL	Hold Temporarily

- Guidelines disseminated by education and posting on institutional intranet.
- A number of institutions follow a similar strategy.
  - "There is little literature on the management of these difficult patients."
    - Lee, A., *JCO*, 2009.
- "Platelet transfusions may be used to facilitate ongoing anticoagulation."
- Impractical support due to very short duration of improvement.



Quality Assessment/Quality Improvement Initiative

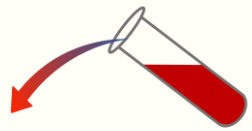
- How are we doing?
- Are we adhering to the Guidelines?
- Are the Guidelines working?
  - Safety?
  - Efficacy?
  - Need for improvement?

- Mantha, S. et al. Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. J Thromb Thrombolysis 43, 514–518 (2017). https://doi.org/10.1007/s11239-017-1478-0

Causes for Thrombocytopenia.

Causes of Thrombocytopenia	Cases (N)	%
Chemotherapy	113	79.0
Mixed Causes	13	9.0
Infection	11	7.6
Myelophthisis	4	2.8
Graft Versus Host Disease	1	0.7
Liver Disease	1	0.7

- 99 Patients/143 episodes of thrombocytopenia (<50,000/mcL), lasting at least 7 days.
  - Mantha, S. et al. Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. J Thromb Thrombolysis 43, 514–518 (2017). https://doi.org/10.1007/s11239-017-1478-0



Clinical Outcomes

During Anticoagulant Modification per Guidelines:

- No Recurrent VTE Episodes (<1%)
- No Major Bleeds (<1%)

- 1 Major Bleed *Before* Dose Reduction of LMWH
  - Trauma-Associated Retroperitoneal Hemorrhage
  - Occurred on the 3rd Day of Thrombocytopenia
  - Platelet Count at the Time: 28,000/mcL

- CRNMB Occurrence: 13 of 140 episodes.
  - Ecchymosis, Epistaxis, or Gingival Bleeding
- 10 Deaths During the Thrombocytopenic Episodes.

- Mantha, S. et al. Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. J Thromb Thrombolysis 43, 514–518 (2017). https://doi.org/10.1007/s11239-017-1478-0

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MANAGEMENT OF ANTICOAGULATION FOR VTE IN PATIENTS WITH CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA

- Thrombocytopenia is a common occurrence in patients with cancer who are receiving therapeutic anticoagulation for cancer-associated thrombosis. Generally, anticoagulation is considered safe with platelet counts ≥50,000/µL. The risk of bleeding is thought to increase as platelet counts decline below this threshold. Traditionally, physicians have transfused platelet concentrations to maintain platelet counts above 50,000/µL in patients with thrombocytopenia on therapeutic anticoagulation, but this is not always feasible depending upon the duration and severity of thrombocytopenia and availability of blood products.

- When managing cancer-associated thrombosis with thrombocytopenia the provider should consider:
  - The patient's risk for recurrent thromboembolism, and
  - The patient's risk of bleeding including the anticipated depth and duration of thrombocytopenia

- For patients at high risk of recurrent thromboembolism (includes recent proximal DVT or PE [within 1 month of anticoagulation treatment], recurrent thromboembolism) management options include:
  - Continuation of therapeutic dose anticoagulation while maintaining platelet count ≥50,000/µL with platelet transfusions
  - Placement of a retrievable IVC filter and discontinuation of anticoagulation until platelet recovery

- For patients at lower risk for recurrent thromboembolism (includes DVT/PE occurring after more than 1 month of anticoagulation treatment, central venous catheter-associated DVT, upper extremity DVT, acute distal DVT) management options include:
  - Use of lower dose anticoagulation as outlined below in the table
  - Removal of central venous catheter in patients with central venous catheter-associated DVT
  - Monitoring of distal DVT with serial US surveillance while patient is off anticoagulation (if clot extends to proximal venous system, then manage as acute high risk)

Enoxaparin Dose Modification in the Setting of Thrombocytopenia

Platelet Count	Dose Adjustment	Suggested Dose of Enoxaparin	Alternative Once-Daily Dosing Regimen
>50,000/µL	Full-dose enoxaparin	1 mg/kg twice daily	1.5 mg/kg daily
25,000–50,000/µL	Half-dose enoxaparin	0.5 mg/kg twice daily	—
<25,000/µL	Temporarily hold enoxaparin		

- Note: NCCN currently does not recommend use of DOACs below a platelet count of 50,000/µL as there is limited published experience using DOACs in this situation.

Note: All recommendations are category 2A unless otherwise indicated.

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Cancer-Associated Venous Thromboembolic Disease Version 3.2025 – November 6, 2025

- MANAGEMENT OF ANTICOAGULATION FOR VTE IN PATIENTS WITH CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA

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