Cancer Associated Thrombosis: 150 Years Since Trousseau

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Disclosures

- Research Support (Past 5 years):
  - Amgen
  - Janssen Scientific Affairs
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  - Anthos Therapeutics
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  - Janssen Scientific Affairs
  - Sobi/Dova Pharmaceuticals
  - Sanofi
  - Novartis
  - Agios Pharmaceuticals.

Topics To Cover

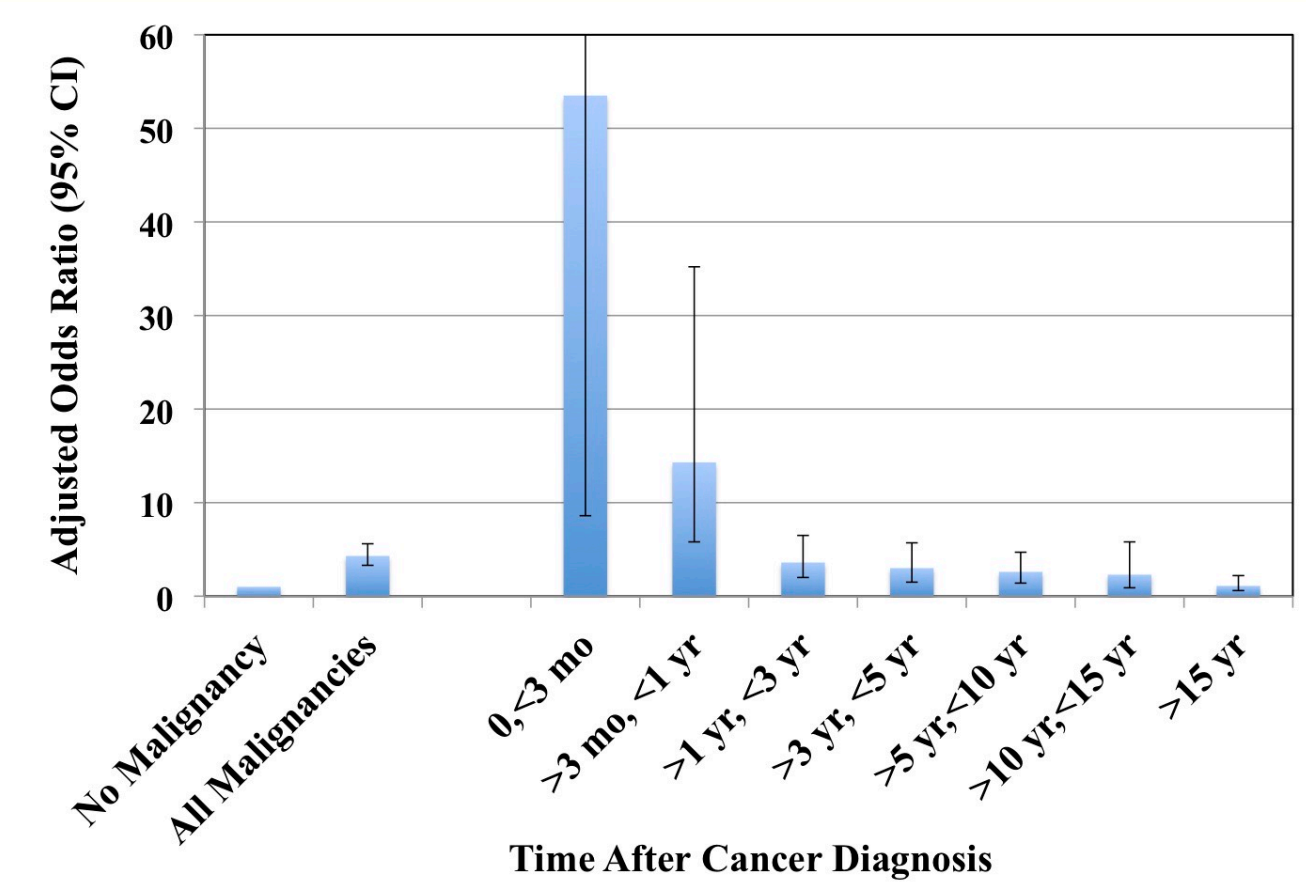
1. Scope of The Problem: Clinical Relevance Of Thrombosis In Cancer.
2. Pathophysiology Of Thrombosis: Virchow's Triad.
3. Screening For Occult Malignancy In Patients With VTE
4. Management of Thrombosis In Cancer Patients
5. Direct Oral Anticoagulants
6. Incidental Thrombosis/ Pulmonary Embolism
7.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

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)**

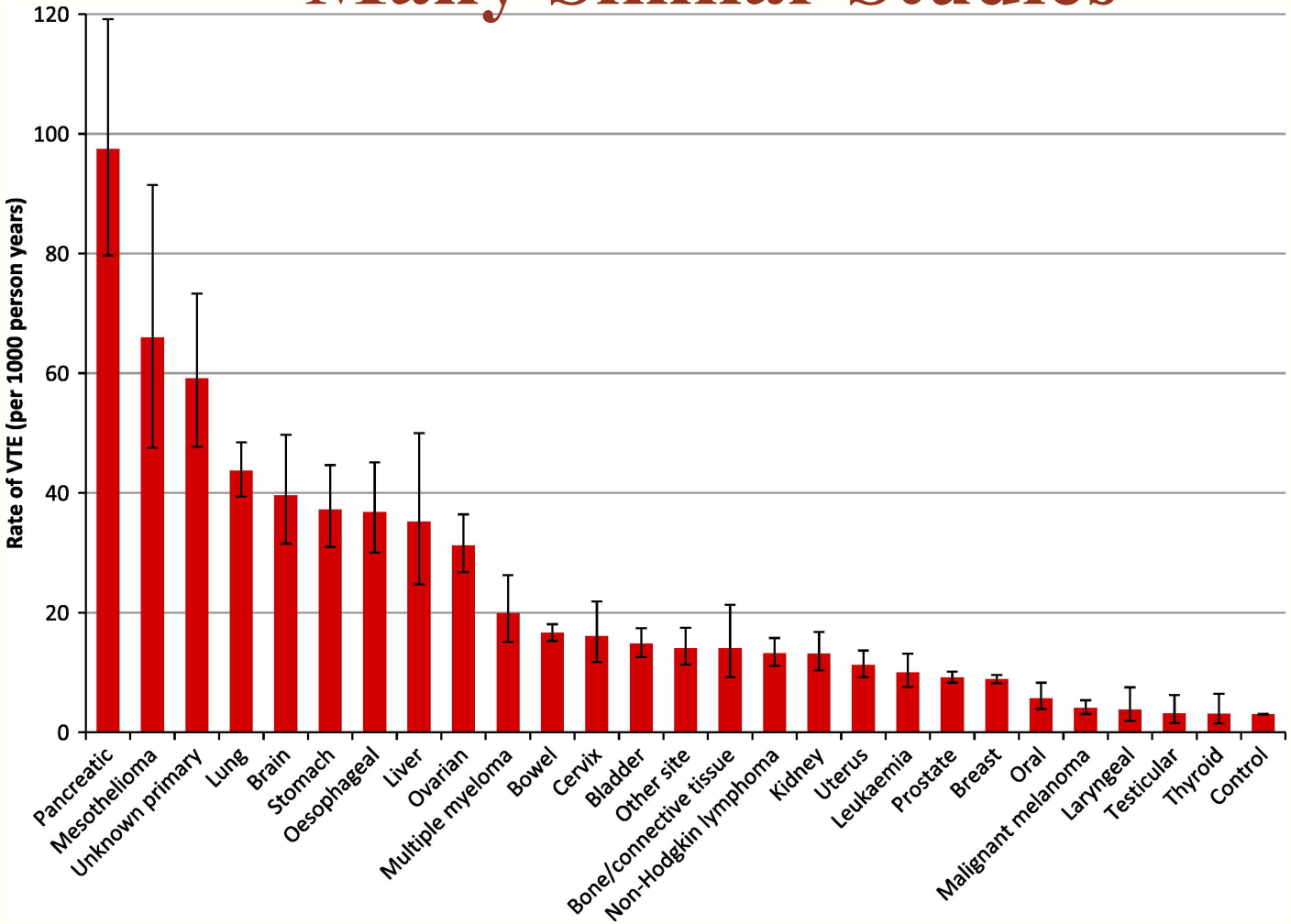
- Patients presenting with a Cancer-Related Venous Thromboembolism have markedly higher risk of mortality than cancer patients in general.
- However, very few of these patients are dying from the VTE. Most are dying from their underlying cancer.
- Cancer Associated Thrombosis is a marker of aggressive cancer!
- Age And Gender-Adjusted HR.
- 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)**

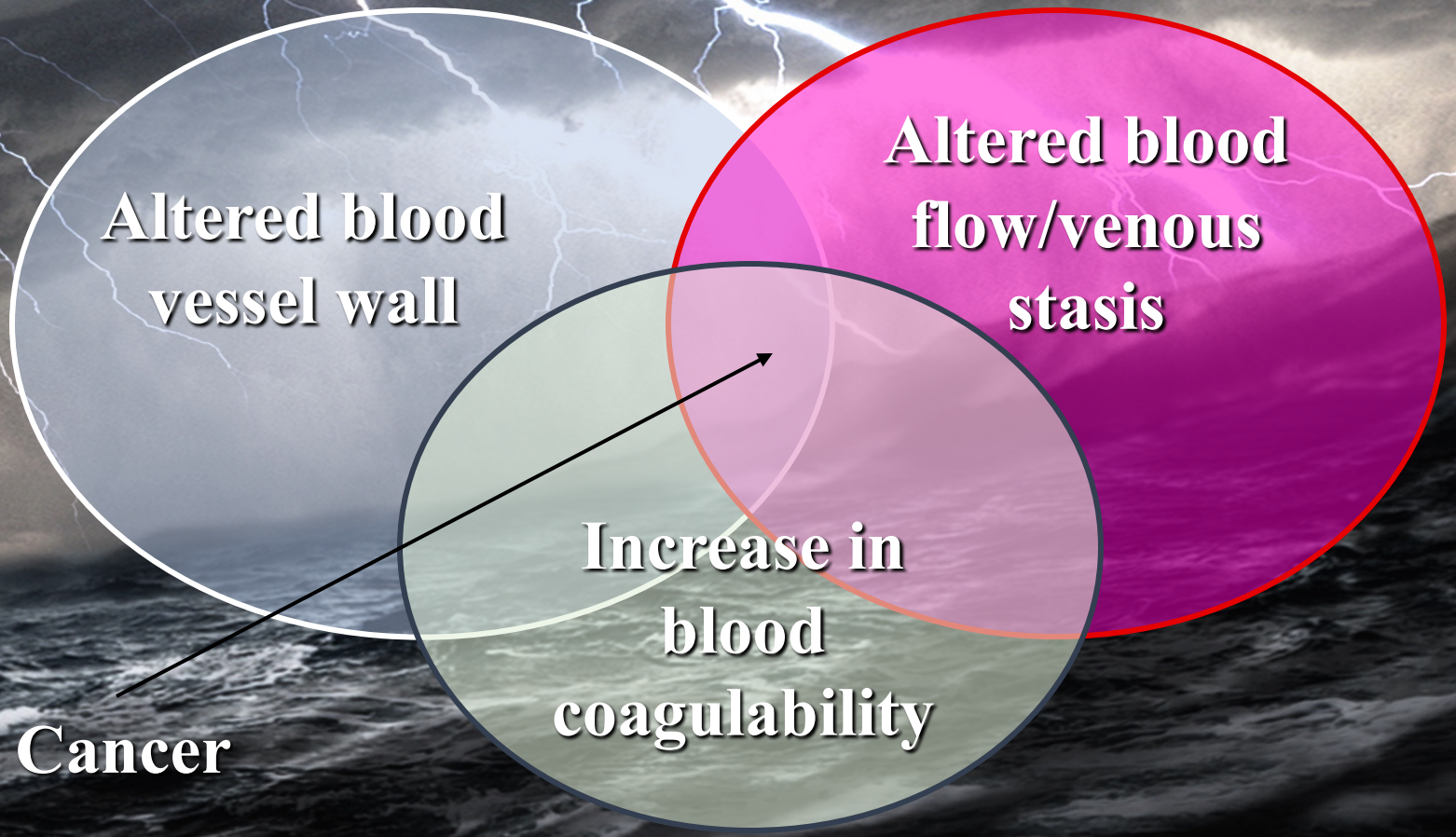
- The Global Anticoagulant Registry in the FIELD (GARFIELD)–VTE (ClinicalTrials.gov: NCT02155491)
- Prospective, observational study of 10,684 patients with objectively diagnosed VTE from 415 sites in 28 countries.
- 1075 patients with active cancer, 674 patients with a history of cancer, and 8935 patients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

Rate of Venous Thromboembolism by Cancer Site: Many Similar Studies



- A.J. Walker et al. / European Journal of Cancer 49 (2013) 1404–1413

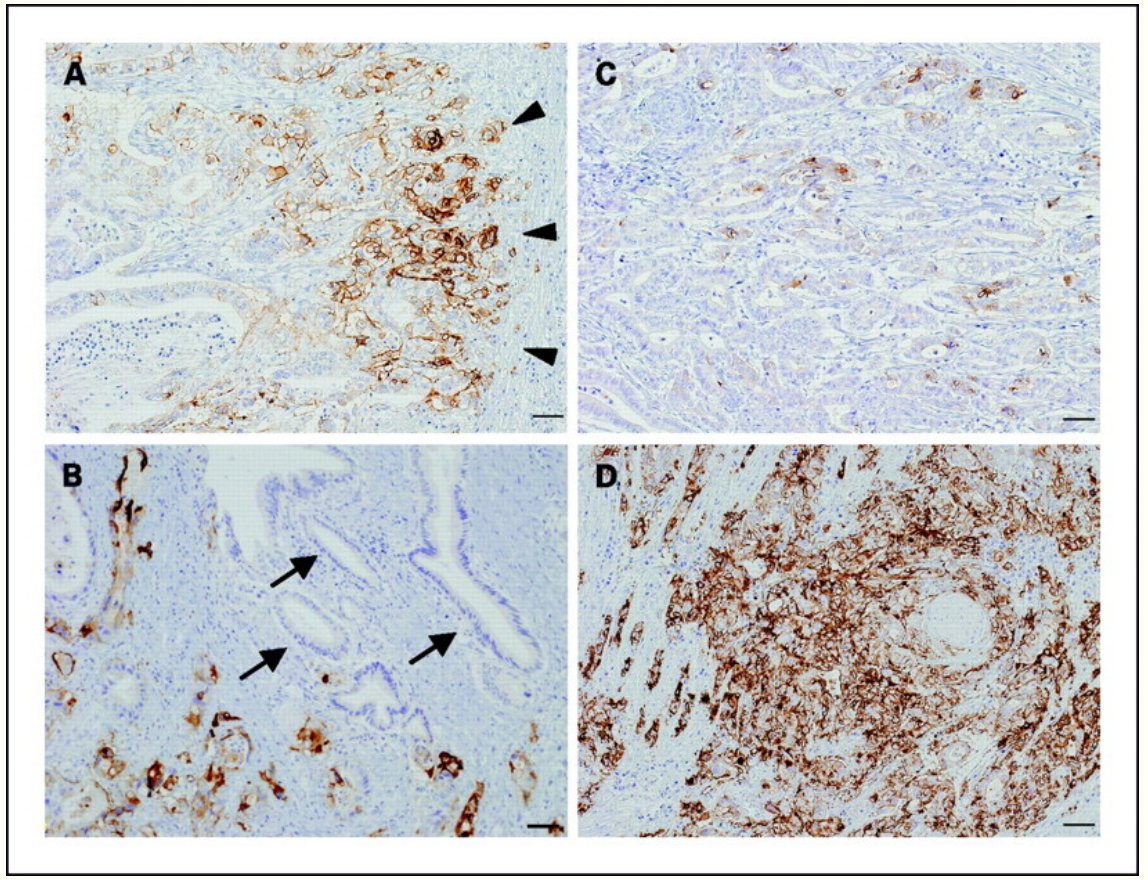
2. Pathophysiology Of Thrombosis: Virchow's Triad



Coagulation And Vascular Factors Contribute to Cancer Associated 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.
   - Neutrophil Extracellular Traps (NET).
2. Platelets:
   - 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.

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



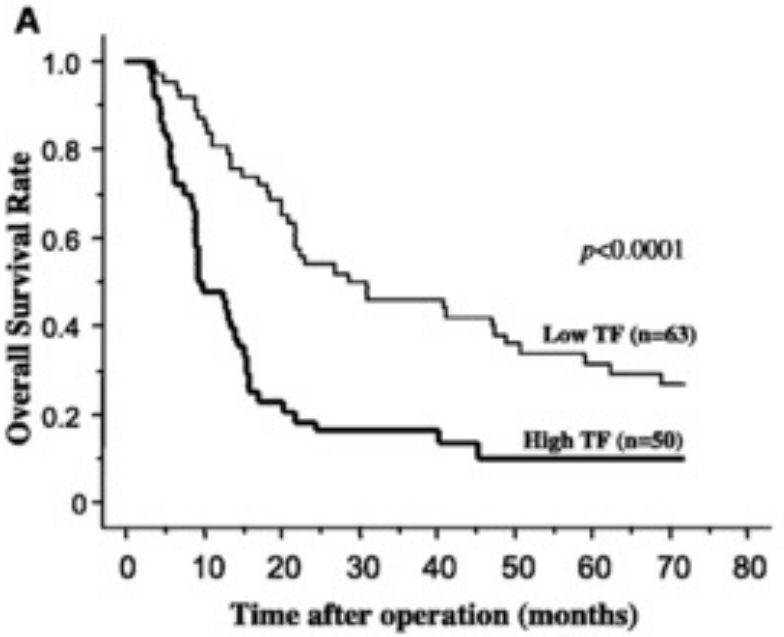
- Nitori N. et al. *Clin. Canc. Res*. 11, 2531-2539, 2005

TF Expression In Pancreatic Cancer and:

Thrombosis Rates

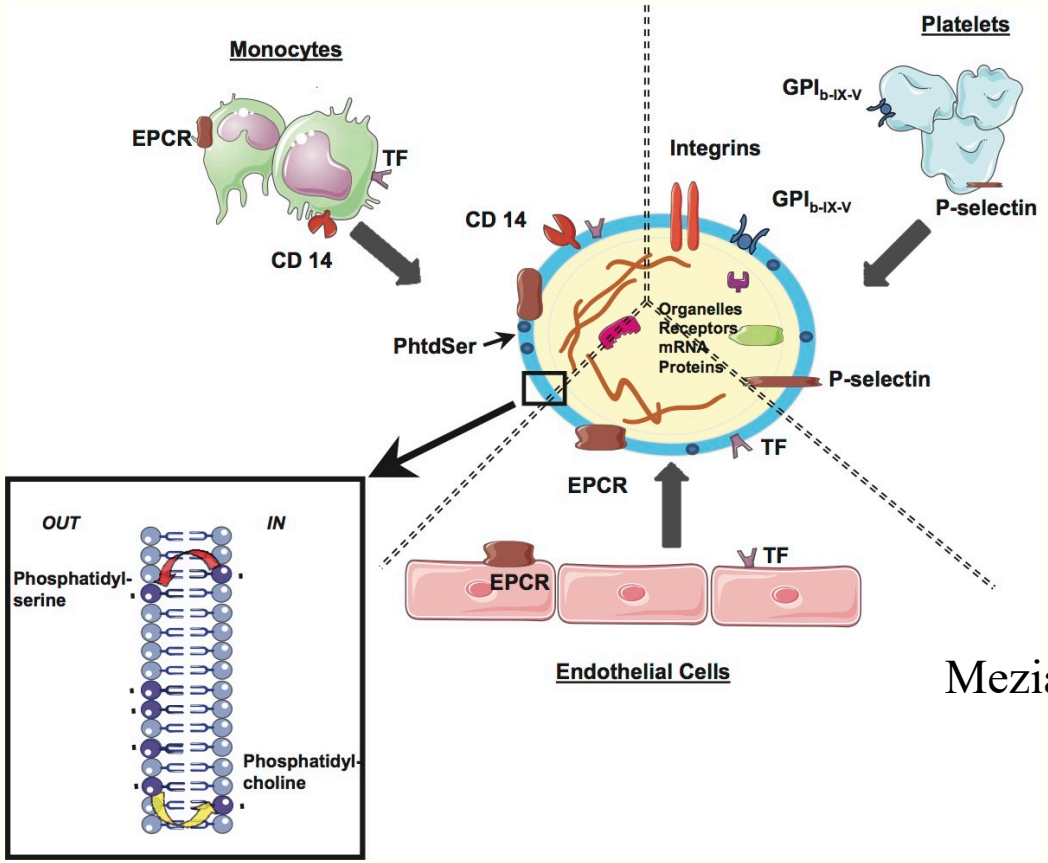
- High TF, VTE Rate: 26.3%
- Low TF, VTE Rate: 4.5%
- ~ 6-fold Risk Ratio, (P = 0.04).
  - Khorana AA. et al, *Clin. Canc. Res*. 13, 2870-2875, 2007

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

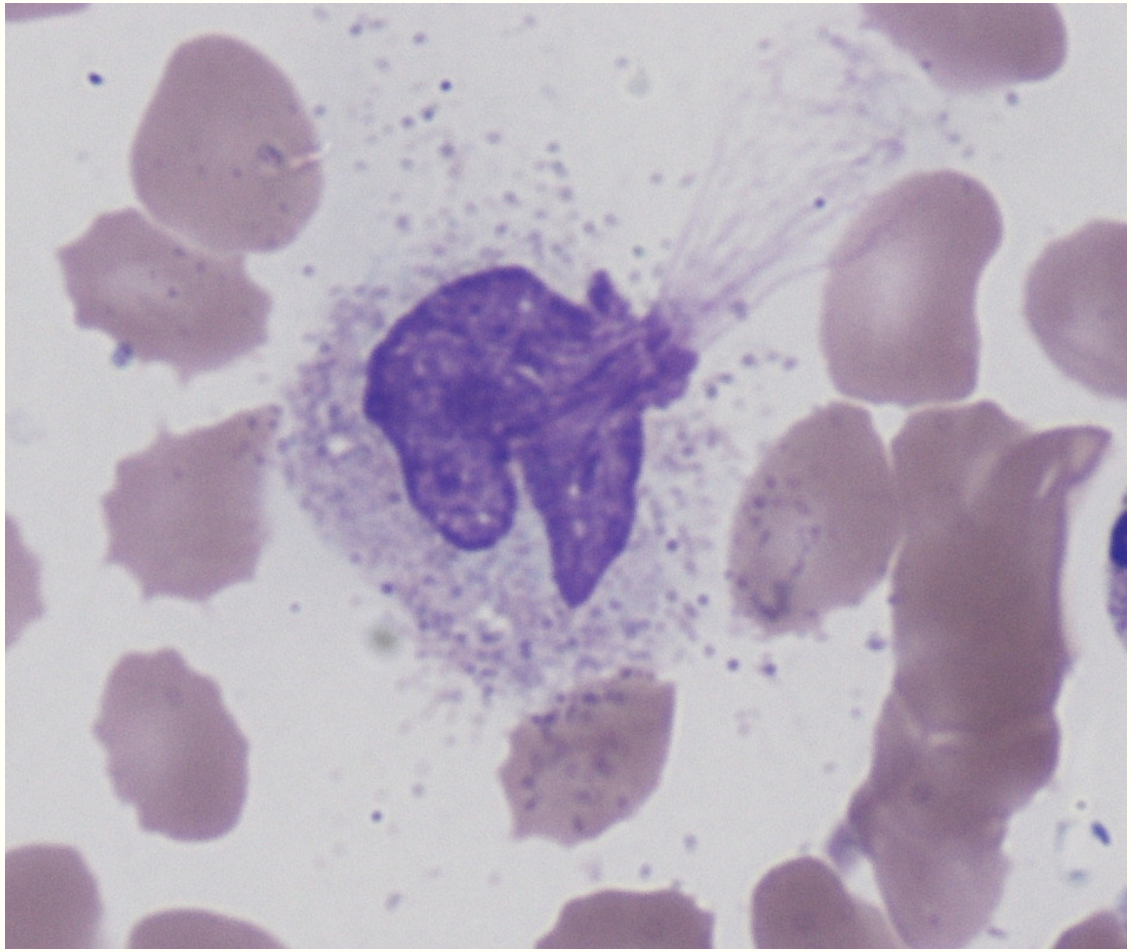
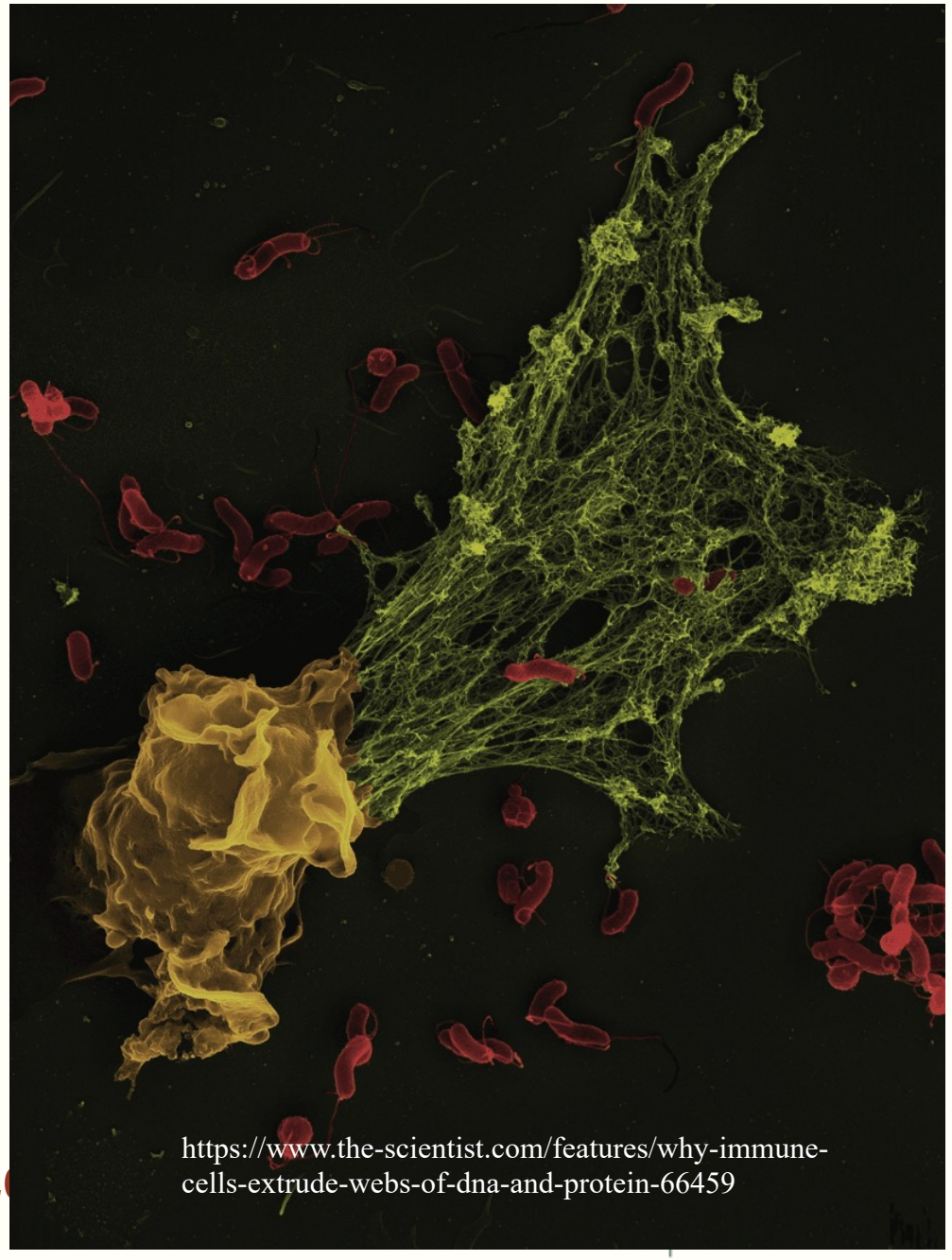


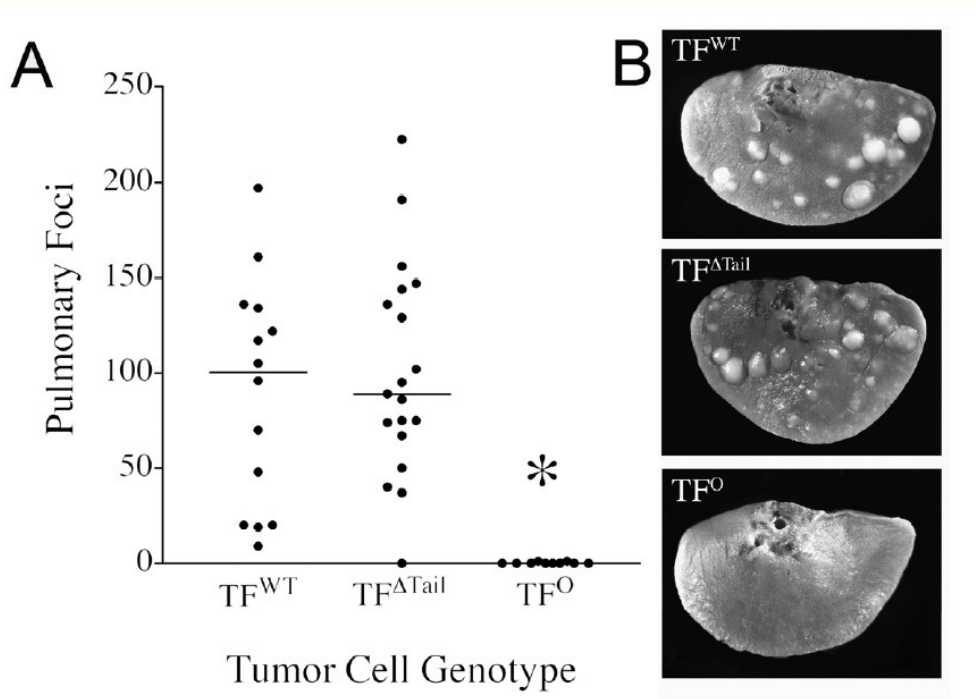
Image by Soff



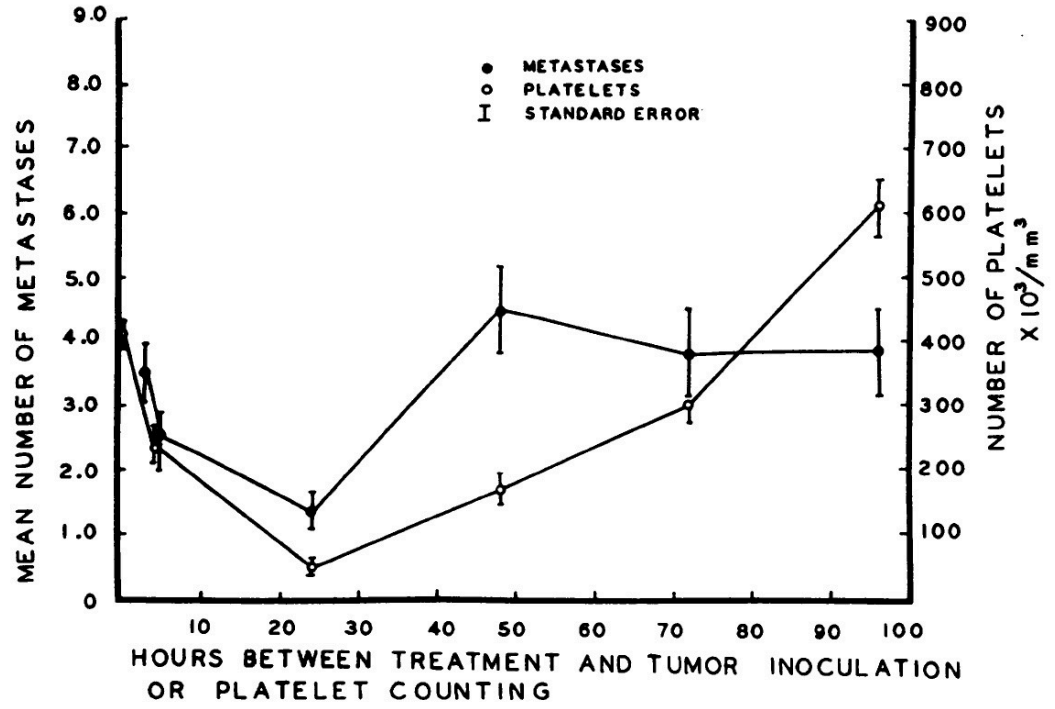
https://www.the-scientist.com/features/why-immune-cells-extrude-webs-of-dna-and-protein-66459

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.



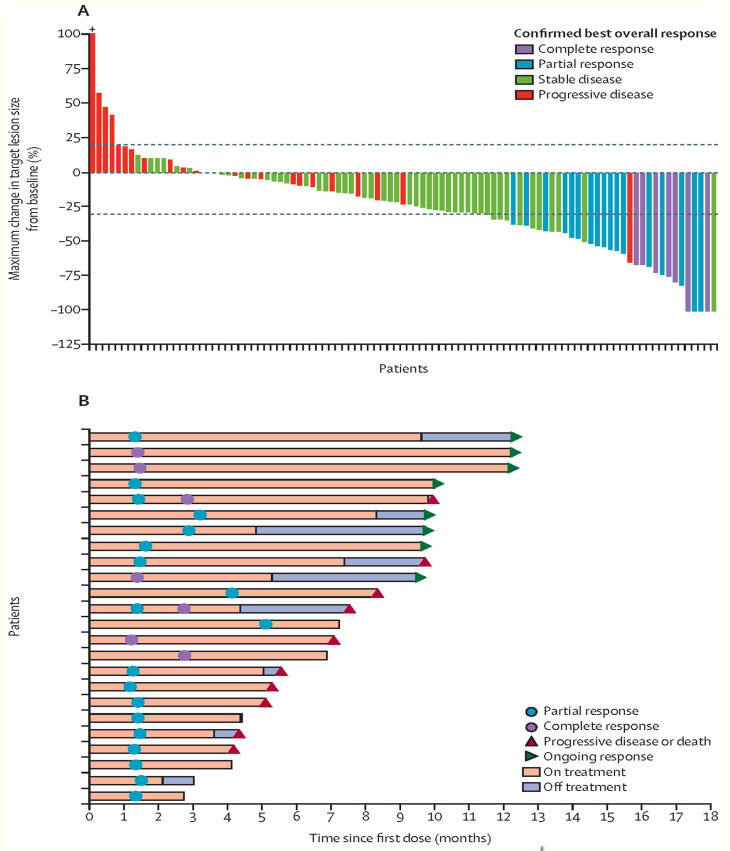
Tissue Factor As Target For Anti-Cancer Therapy

➢ Tisotumab Vedotin

- "TIVDAK (Tisotumab Vedotin) is 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."

- The confirmed objective response rate was 24% (95% CI 16–33), with seven (7%) complete responses and 17 (17%) partial responses.
- 3% Grade 2 and 3% Grade 3 bleeding.
  - Coleman RL et al. Previously treated recurrent or metastatic cervical cancer: a multicentre, open-label, single-arm, phase 2 study. The Lancet Oncology 2021 22609-619DOI: (10.1016/S1470-2045(21)00056-5)

"Previously treated recurrent or metastatic cervical cancer: a multicentre, open-label, single-arm, phase 2 study."



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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.

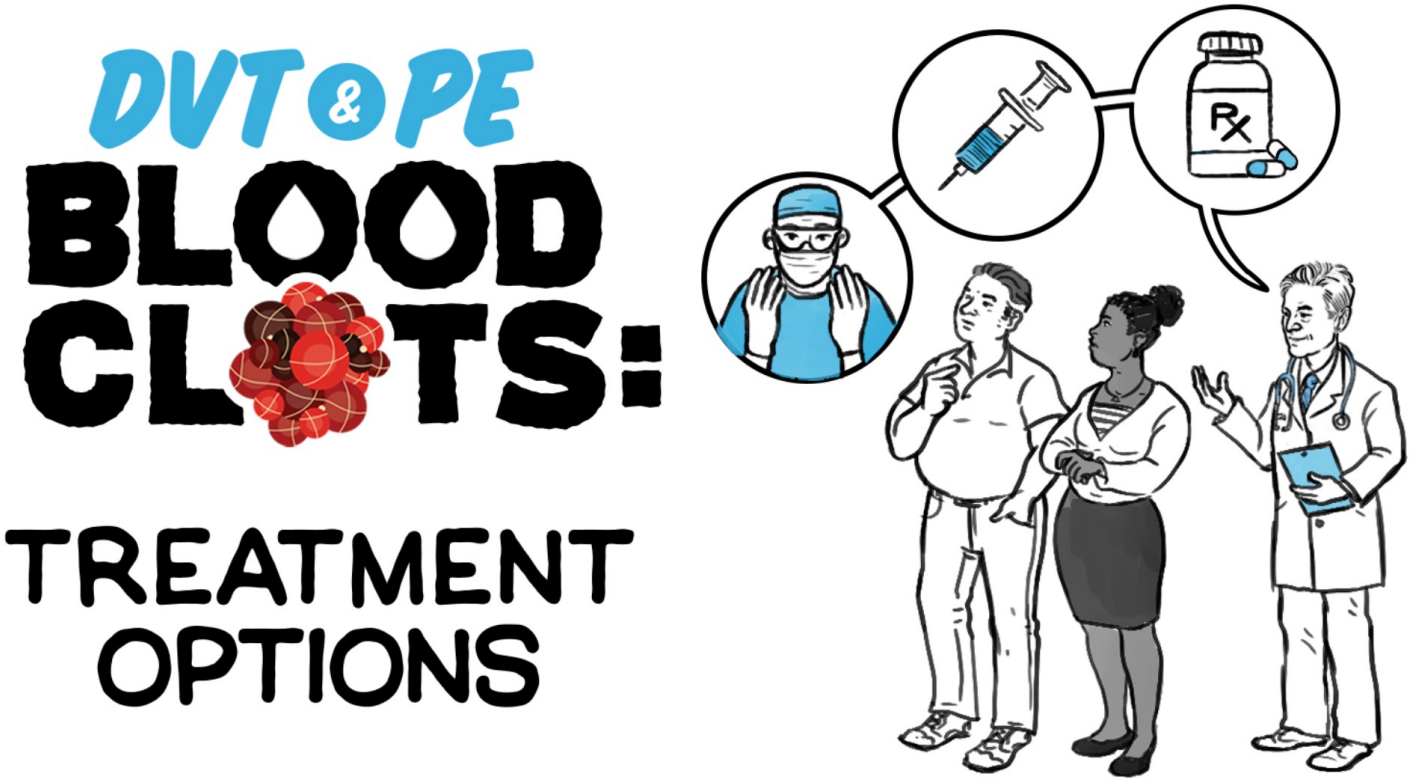
  - Carrier M et al. N Engl J Med 2015; 373:697-704

Screening For Occult Malignancy In Patients With VTE

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.

4. Management of Thrombosis In Cancer Patients



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

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 et al *Blood* 100:3484-3488, 2002

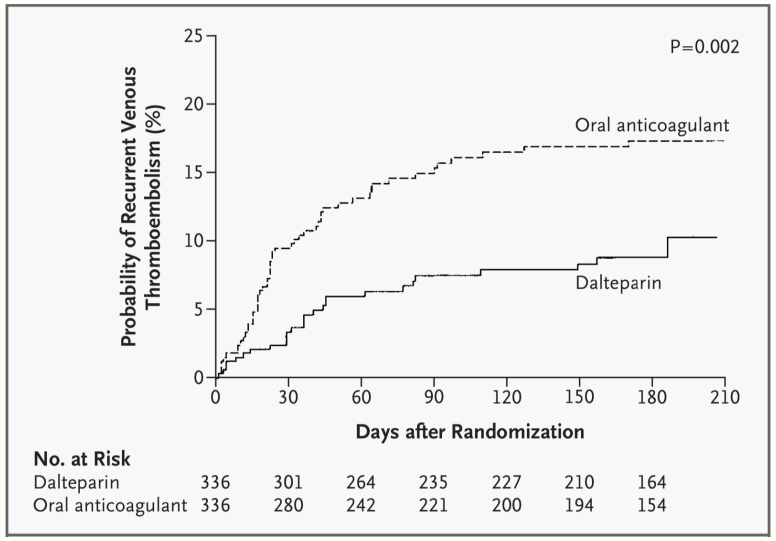
The CLOT Study

- 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.

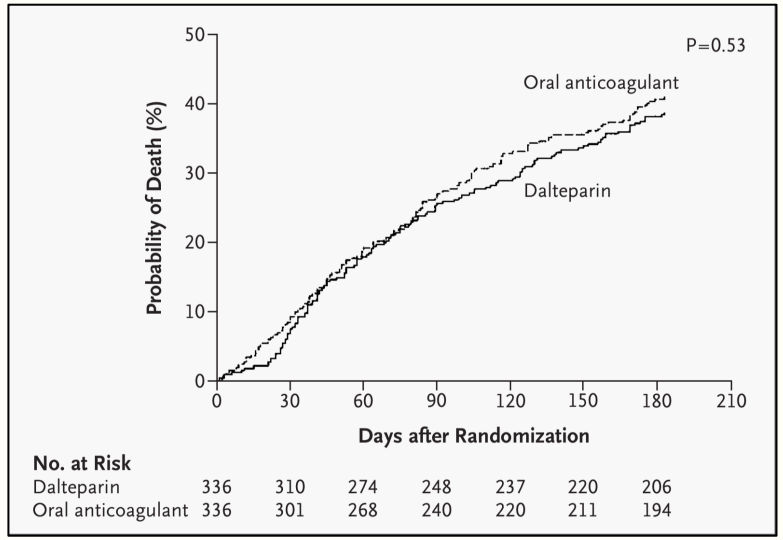
  - Lee et al. NEJM 349:146-53, 2003

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**



Death From All Causes



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

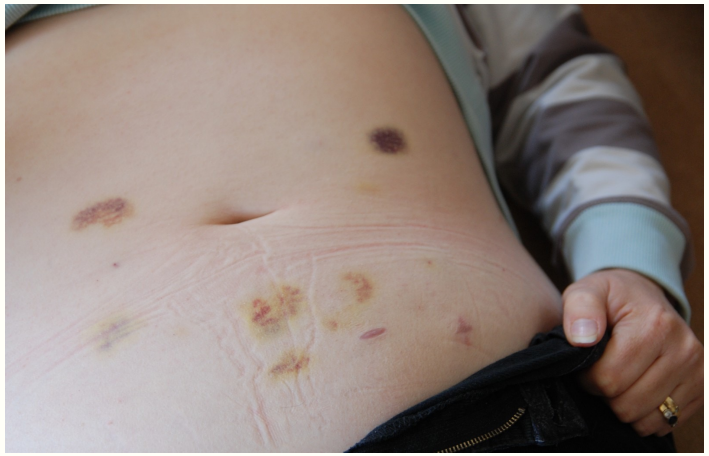
Pooled Analysis of Anticoagulation Trials in Cancer Associated Thrombosis

	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)**

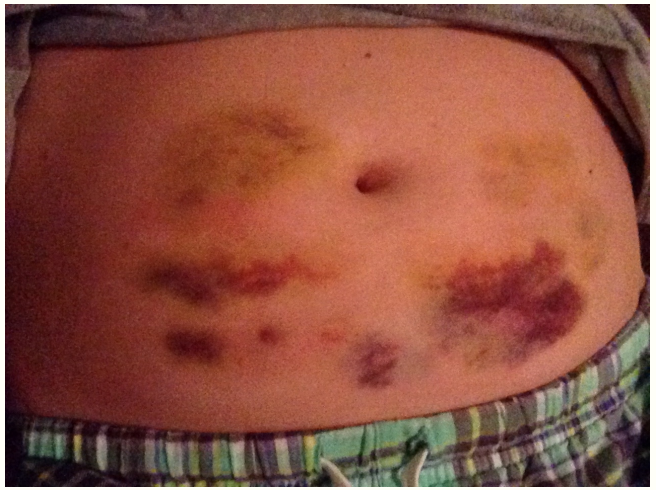
- LMWH: Dalteparin, Enoxaparin, Tinzaparin.
  - Lee AY, et al. N Engl J Med 2003; 349(2):146–153
  - Deitcher SR, et al. Clin Appl Thromb Hemost 2006;12(4):389–396
  - Lee et al, JAMA. 2015;314(7):677-686.

LMWH For Cancer-Associated Thrombosis

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



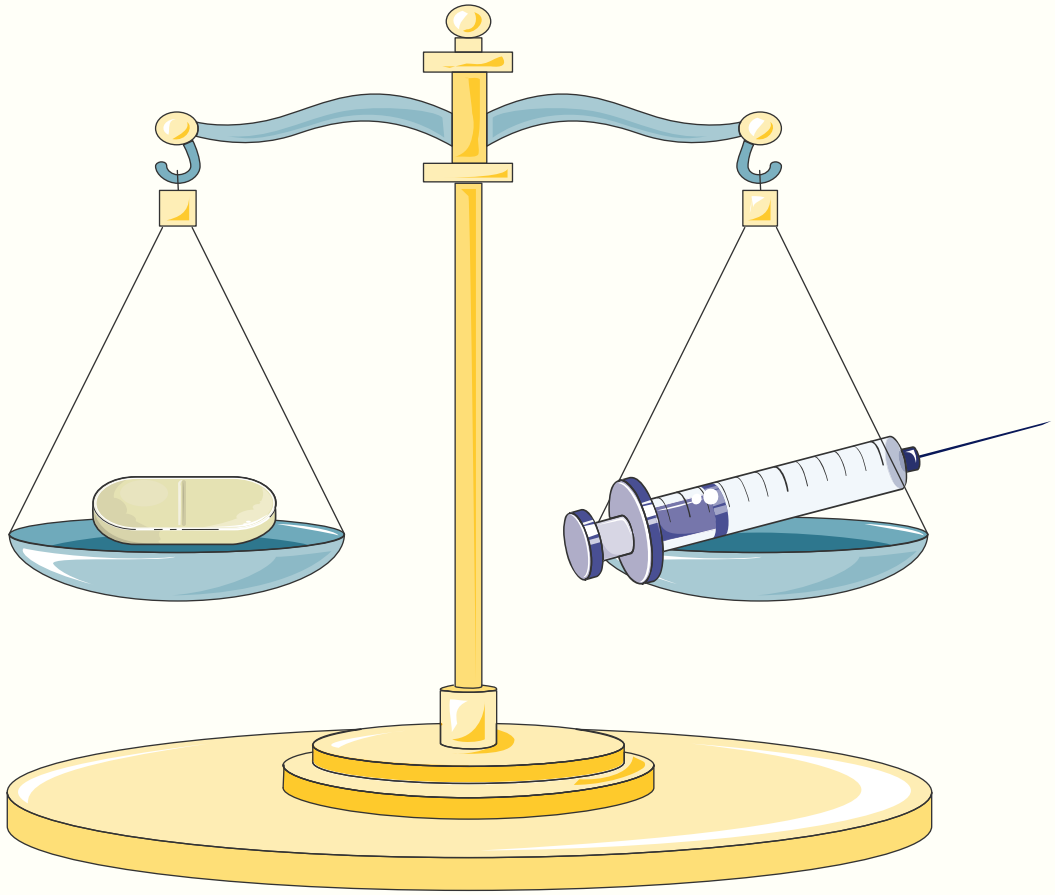
https://hairyfarmerfamily.files.wordpress.com/2011/05/heparin.jpg



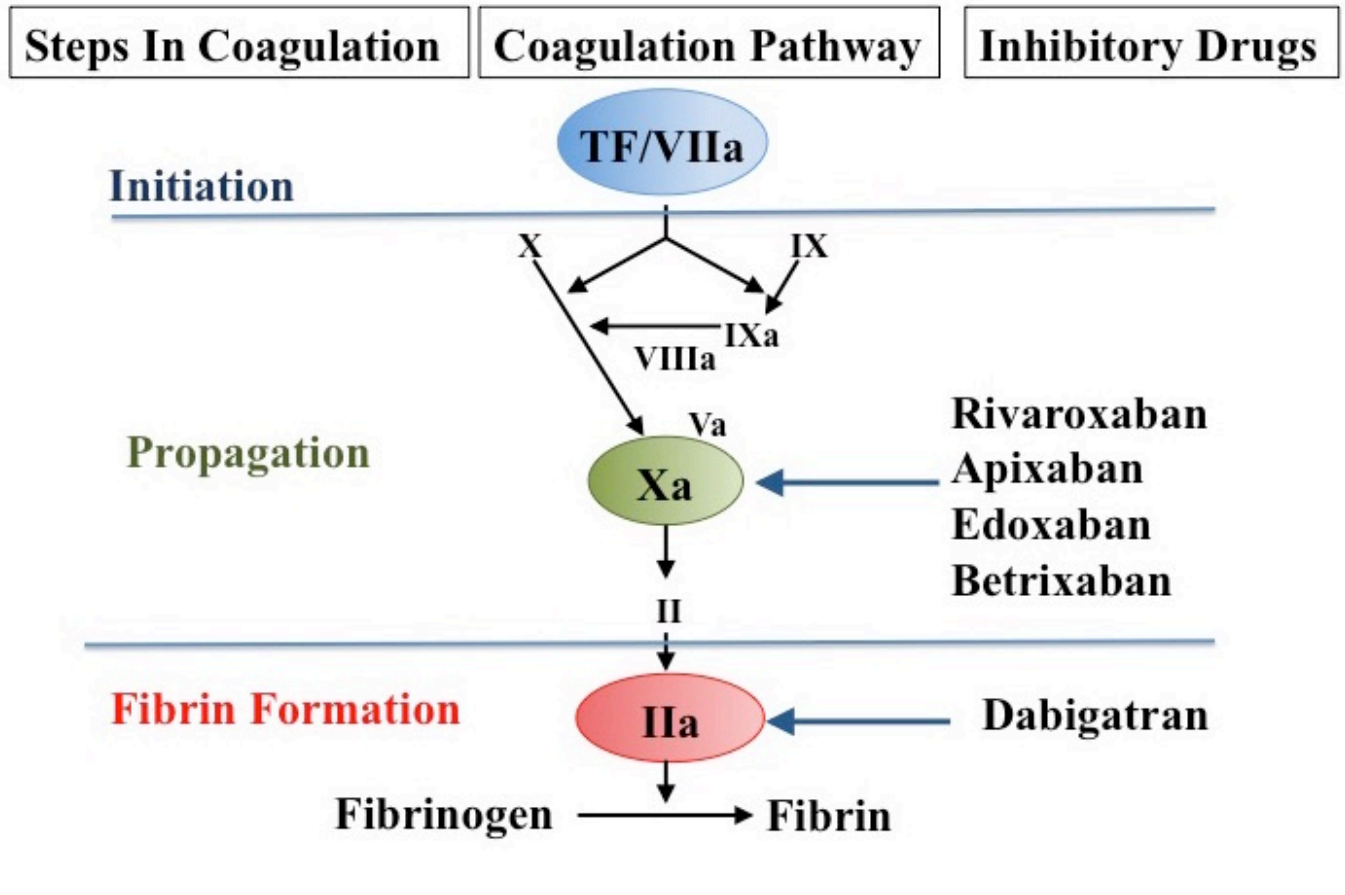
https://hannahcrafted.files.wordpress.com/2014/03/img_9252.jpg

http://www.bigtrial.net/2015/04/narcs-supervisor-never-read-indictment.html

Isn’t There a Pill For That?



5. Direct Oral Anticoagulants



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

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

1. LMWH has been standard of care for Treatment if Cancer-Associated Thrombosis (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.
   - But rivaroxaban was FDA approved for VTE treatment. (2012).

"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%)**

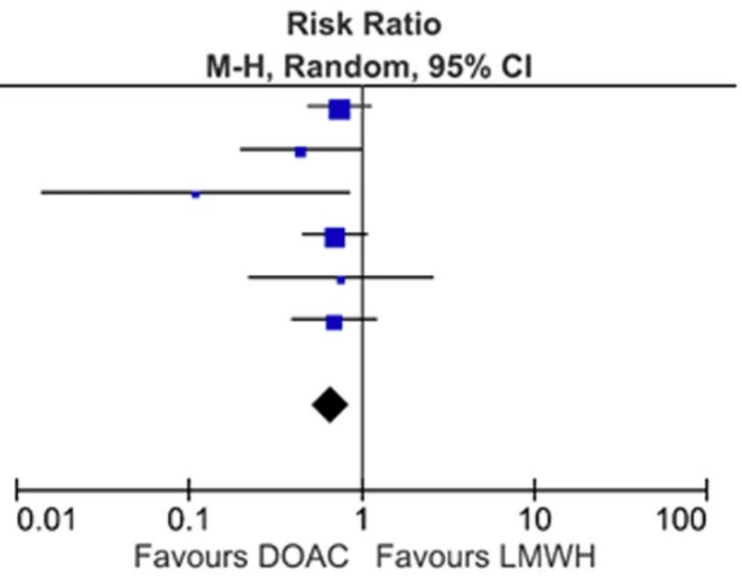
DOAC vs. LMWH for the treatment of cancer associated thrombosis. Systematic review and meta-analysis of randomized controlled trials

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)

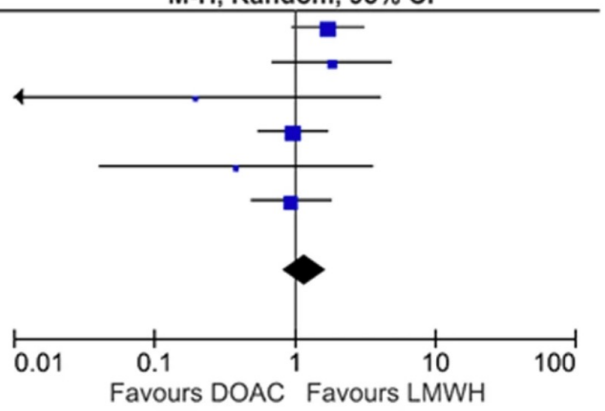


- Frere et al. Journal of Hematology & Oncology (2022) 15:69 https://doi.org/10.1186/s13045-022-01289-1

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			

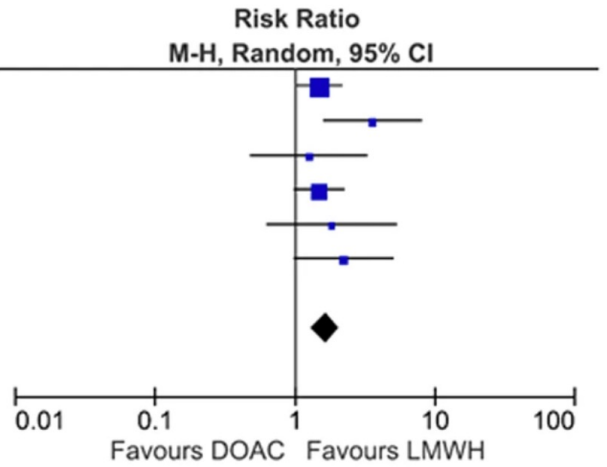
Heterogeneity: Tau² = 0.02; Chi² = 5.66, df = 5 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.85 (P = 0.39)



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)



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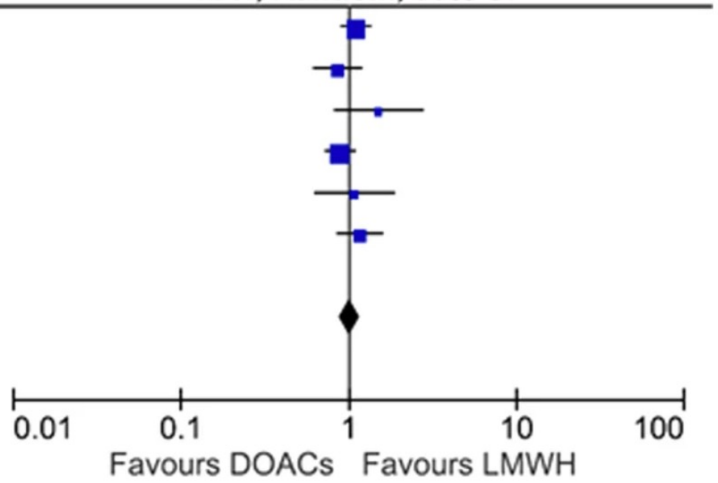
DOAC vs. LMWH for the treatment of cancer associated thrombosis. Systematic review and meta-analysis of randomized controlled trials

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: Tau² = 0.00; Chi² = 5.76, df = 5 (P = 0.33); I² = 13%

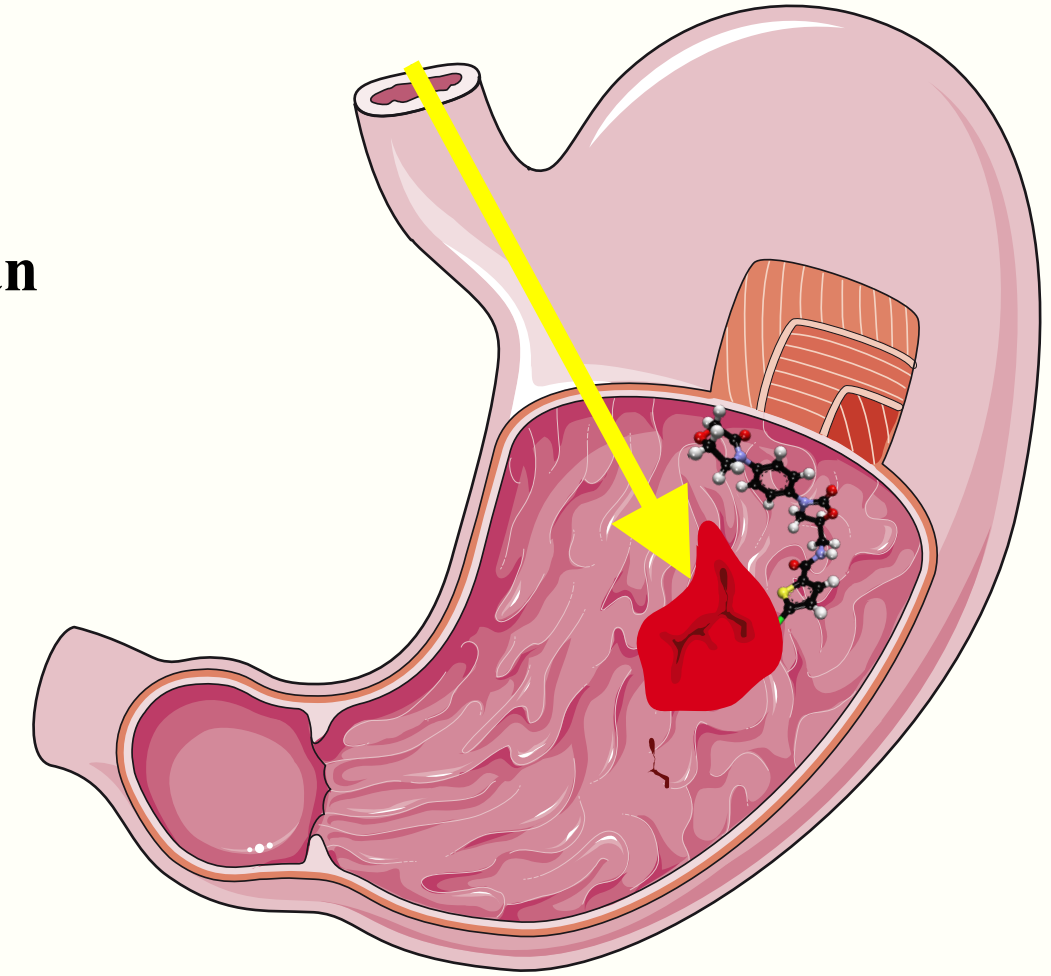
Test for overall effect: Z = 0.25 (P = 0.80)

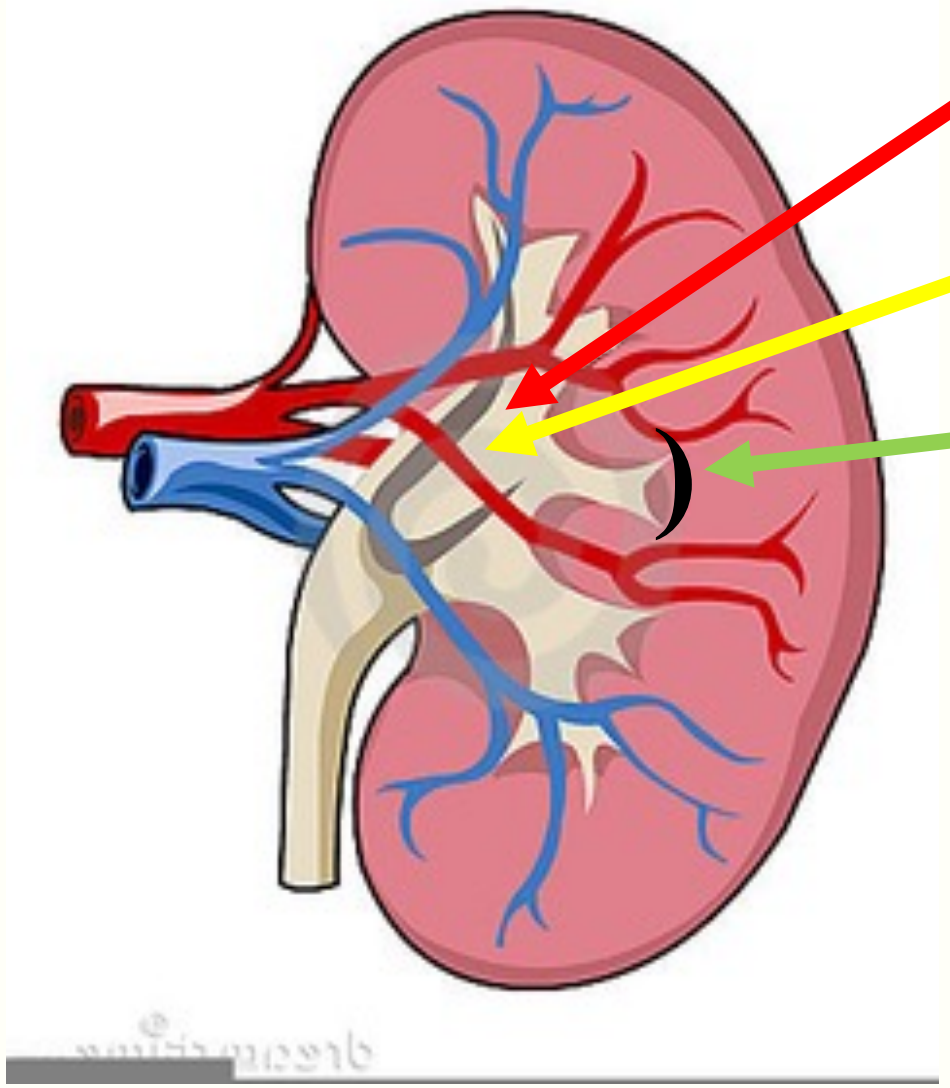


- Frere et al. Journal of Hematology & Oncology (2022) 15:69 https://doi.org/10.1186/s13045-022-01289-1

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

Rivaroxaban





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.**

http://www.clker.com/cliparts/8/2/e/8/15167234661784776136human-kidney-clipart.med.png

Recurrent VTE Versus Bleeding

- Pooled analysis of studies of DOAC versus LMWH showed preserved efficacy (trend towards lower), at price of increased bleeding.
- 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!

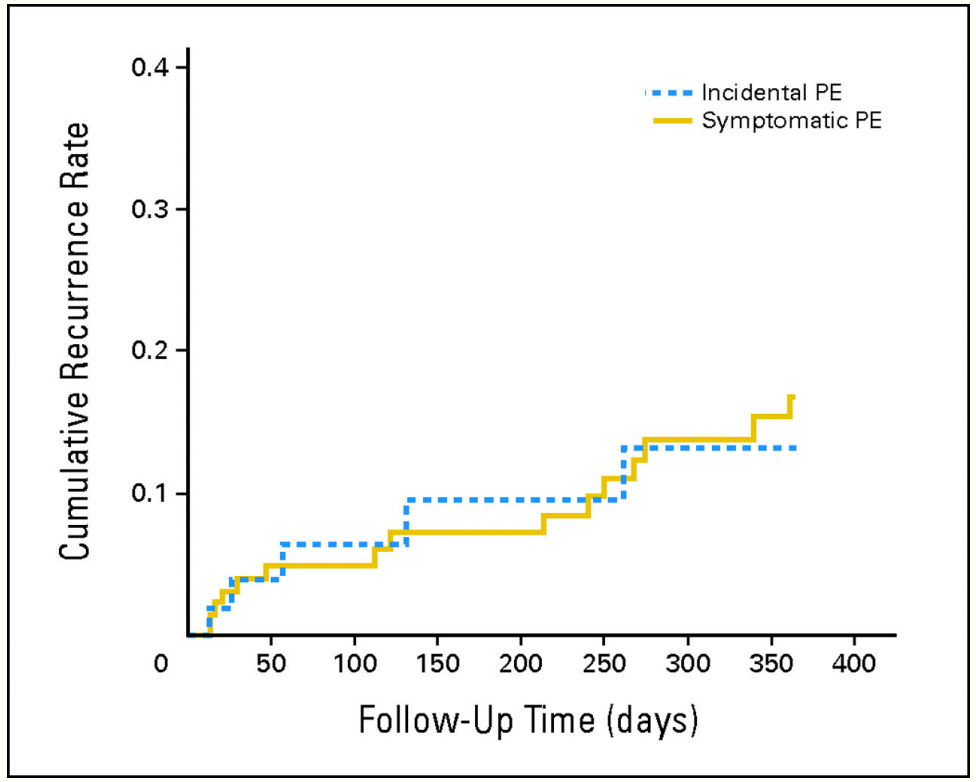
Recurrent VTE Versus Bleeding

- The appropriate question is not which anticoagulant is better (i.e. a DOAC versus low molecular weight heparin).
- The appropriate question, “In a given patient which anticoagulant is appropriate?”

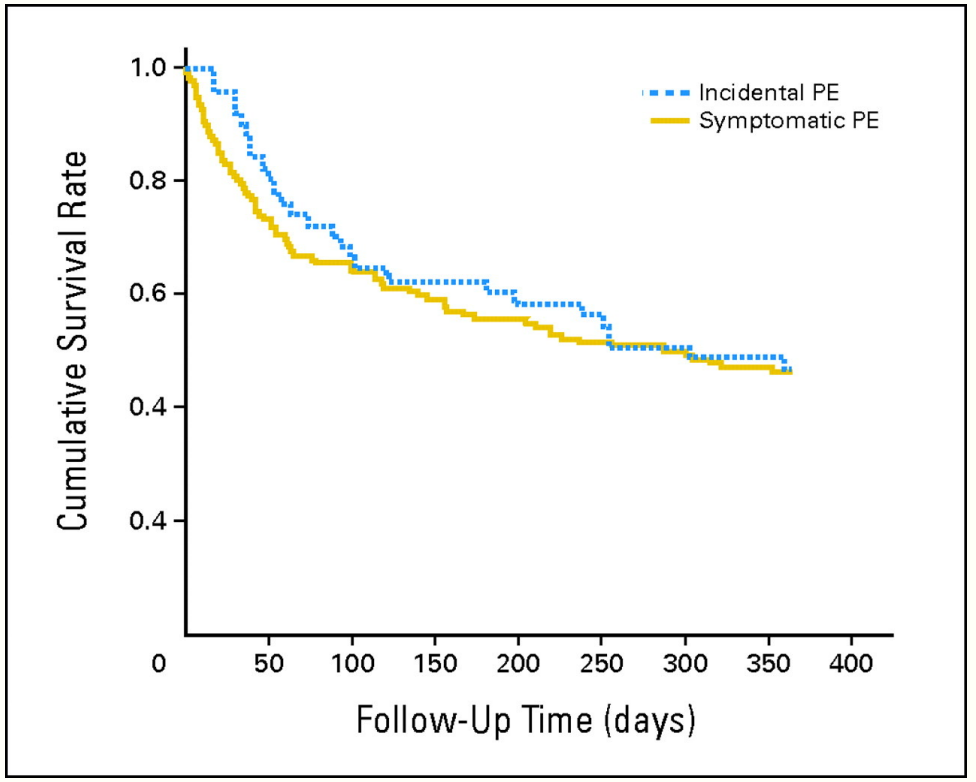
6. Incidental Thrombosis/ Pulmonary Embolism

- 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

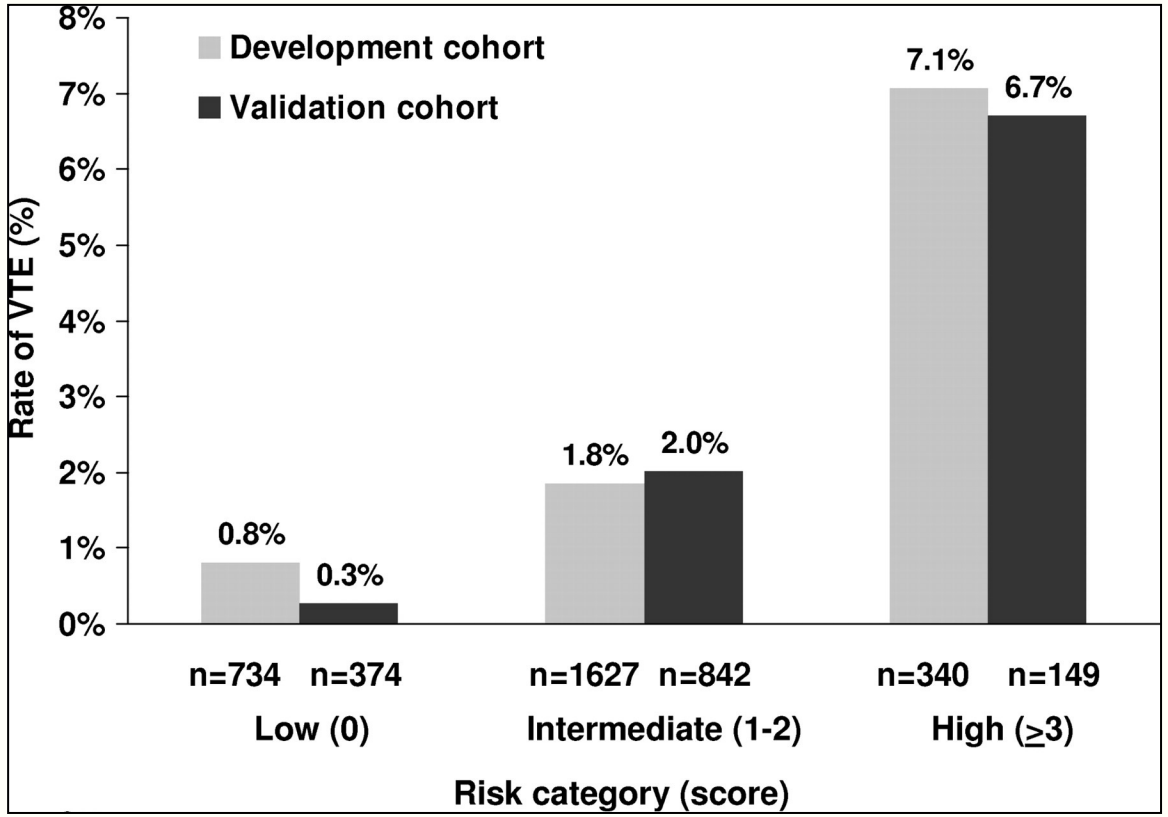
- Is there a role for thrombosis prophylaxis in outpatient, ambulatory cancer patients prior to development of a thrombosis?
- Balance: risk:benefit:cost:convenience

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

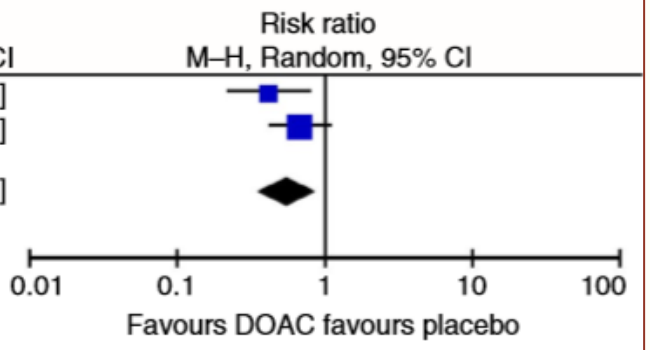
WHO: World Health Organization.

DOAC for the prevention of thrombosis in ambulatory patients with cancer, with Khorana Score of $\geq$ 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			

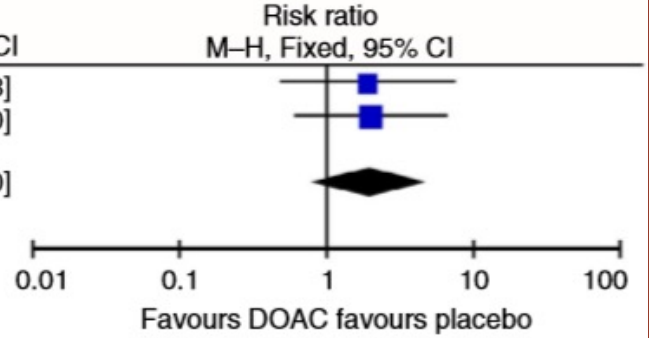
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 1.35$, df = 1 ($P = .24$); $I^2 = 26\%$
Test for overall effect: $Z = 2.45$ ($P = .01$)



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

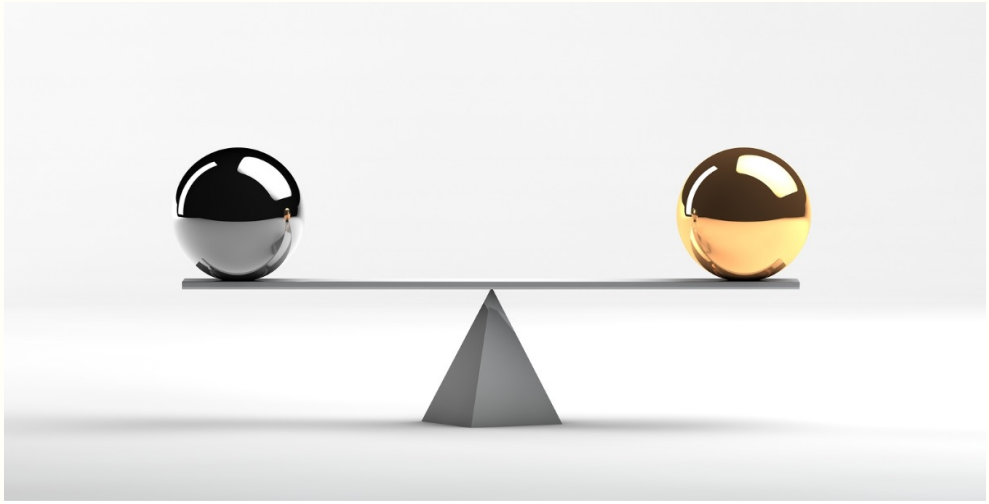
- Brain metastases: The risk for intracranial hemorrhage was fourfold higher in patients with melanoma or renal cell carcinoma than lung cancer, but the risk was not influenced by the administration of enoxaparin.
  - Donato J, et al Blood. 2015;126(4):494-9.

- High-grade glioma: The cohort that received enoxaparin was 3 times more likely to develop a major ICH than those not treated with anticoagulation.
  - Mantia C, et al Blood. 2017;129(25):3379-85.

- DOAC versus LMWH: In patients with brain metastases or primary brain tumors DOACs did not increase the risk of any ICH relative to enoxaparin.
  - Carney BJ, et al. J Thromb Haemost. 2019;17(1):72-6.

8. 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.
- No validated approach to management.



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.

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Cancer-Associated Venous Thromboembolic Disease

NCCN Guidelines Index
Table of Contents
Discussion

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 a patient with 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 occuring after more than 1 month of anticoagulation treatment, central venous catheter-associated DVT, upper extremity DVT, acute distal DVT) management options include:
  - Use lower dose anticoagulation as outlined below in table
  - Remove central venous catheter in patients with central venous catheter-associated DVT
  - Monitor distal DVT with serial US surveillance while patient is off anticoagulation (if clot extends to proximal venous system, then manage as acute high-risk patient)

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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.