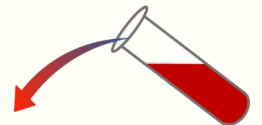


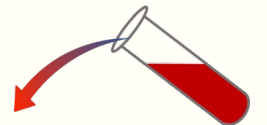
# Cancer Associated Thrombosis: 150 Years Since Trousseau

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**Chief, General Hematology Section**  
**gas199@miami.edu**



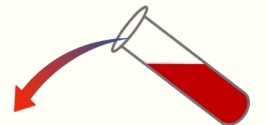
# Disclosures

- Research Support (Past 5 years):
  - Amgen
  - Janssen Scientific Affairs
  - Sobi/Dova Pharmaceuticals
  - Anthos Therapeutics
- Advisory Boards (Past 5 years)
  - Janssen Scientific Affairs
  - Sobi/Dova Pharmaceuticals
  - Luzsana (HengruiUSA) Biotechnology
  - Sanofi



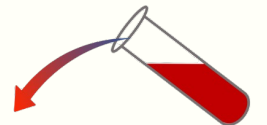
# Topics To Cover

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.

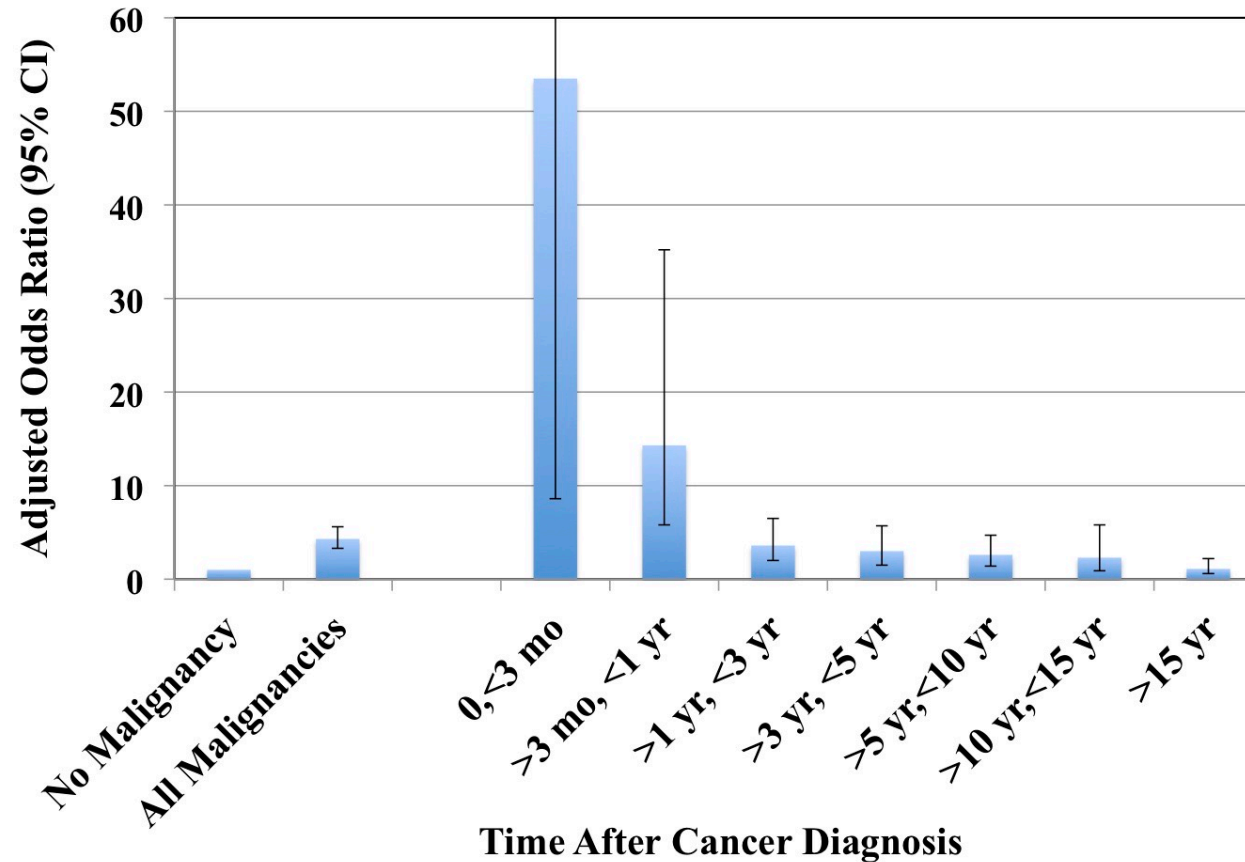


# 1. Scope of The Problem

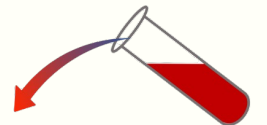
- Venous thromboembolism (VTE), is major source of morbidity and mortality in cancer patients.
- Incidence rates of cancer-associated thrombosis (CAT) vary with cancer type, stage, treatment, and comorbidities, but it is estimated that approximately 15-20 % of cancer patients will develop a venous thromboembolic 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.



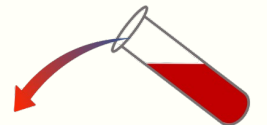
Redrawn from Blom JW, et al. JAMA 2005;293(6):715-722.



# 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)

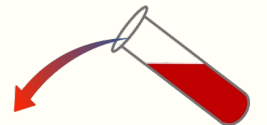
- Patients presenting with a Cancer-Related Venous Thromboembolism have markedly higher risk of mortality than cancer patients in general.
- However, very few of these patients are dying from the VTE. Most are dying from their underlying cancer.
- Cancer Associated Thrombosis is a marker of aggressive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



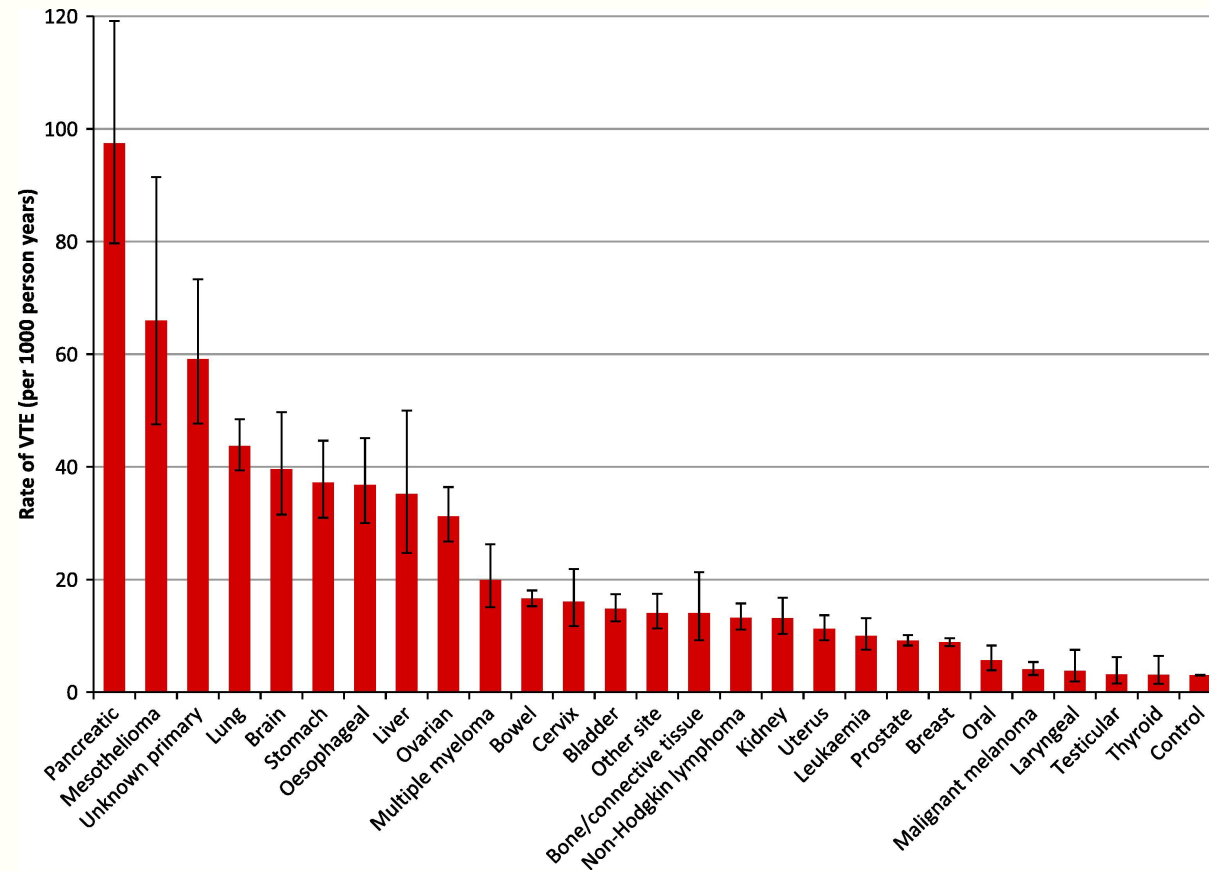
# Cause of Death Over 12-Months Follow-Up After Venous Thromboembolism

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

- 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



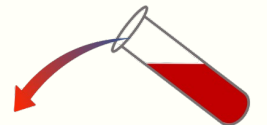
# Rate of Venous Thromboembolism by Cancer Site: Many similar studies



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

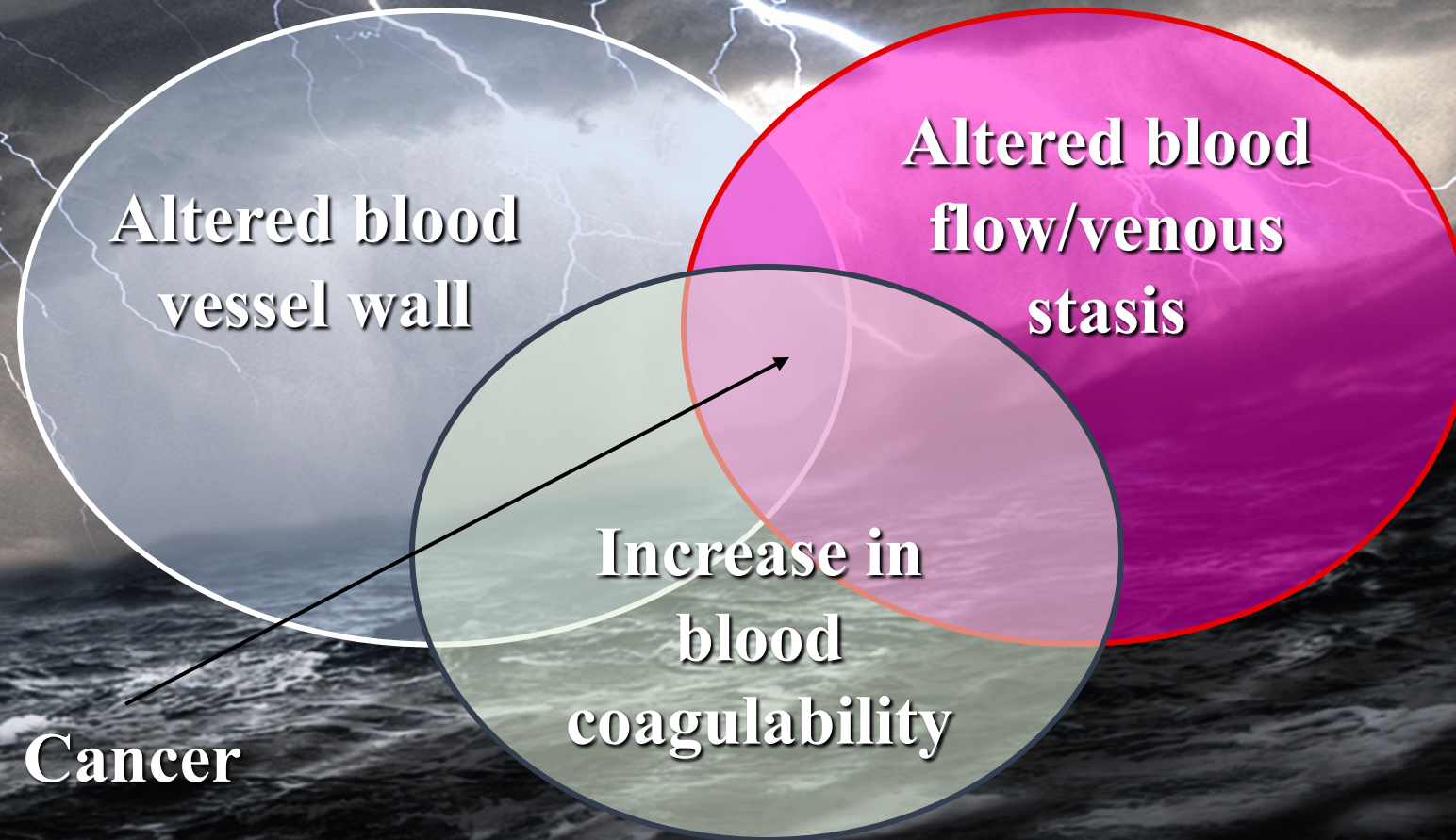
Slide 8

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## 2. Pathophysiology Of Thrombosis: Virchow's Triad



# Coagulation And Vascular Factors Contribute to Cancer Associated Thrombosis

## 1. Tissue Factor and Other Coagulation Changes:

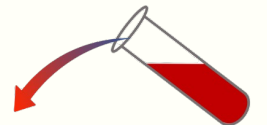
- Tumor cells directly produce and release Tissue Factor.
- Tissue Factor circulates in microparticles and may result in systemic thrombotic risk.
- Neutrophil Extracellular Traps (NET).

## 2. Platelets:

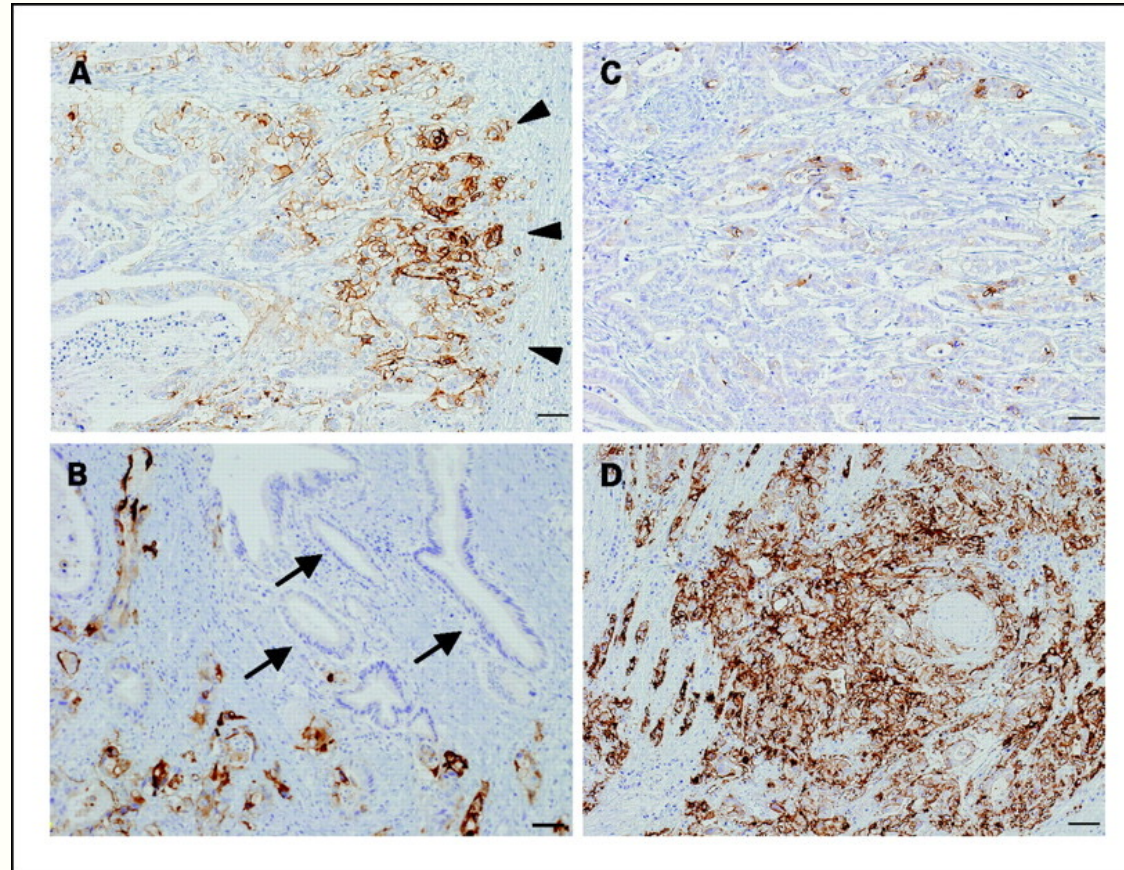
- Elevated platelet count increases thrombosis rates in cancer.
  - Khorana AA & Connolly GC. JCO. 27:4839-4847, 2009.
- P-Selectin. Marker of *in vivo* platelet activation.

## 3. Vascular Abnormalities:

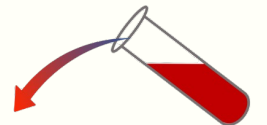
- Abnormal structure of tumor-associated vessels.
- Chemotherapy and Antiangiogenic agents target endothelial cells.



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



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

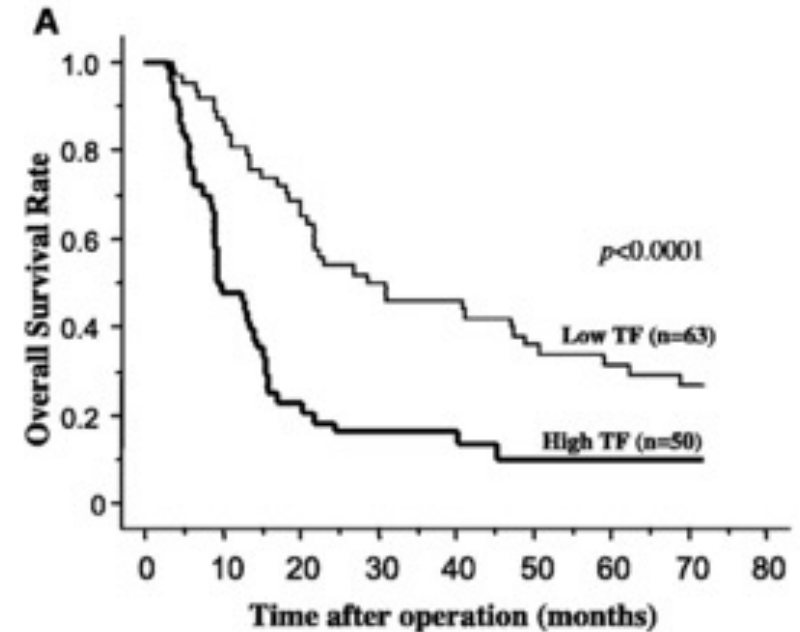


# TF Expression In Pancreatic Cancer and:

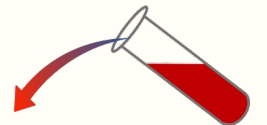
## Thrombosis Rates

- 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

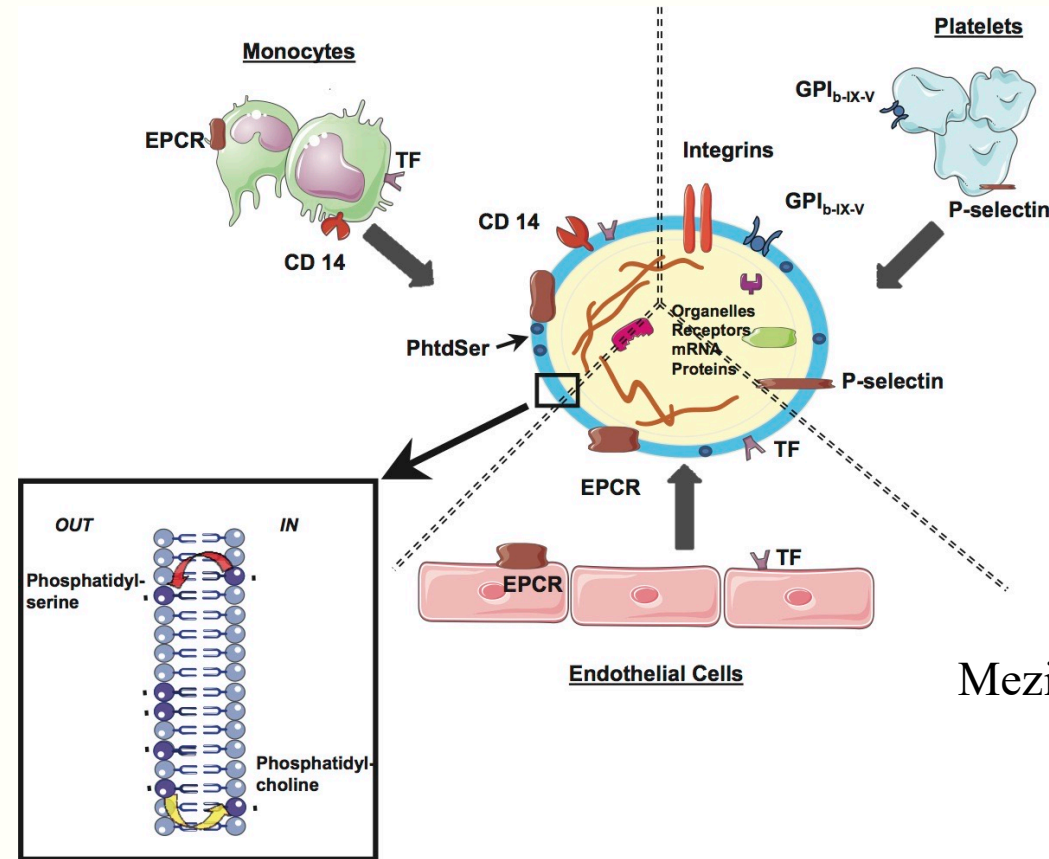
## Overall Survival



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

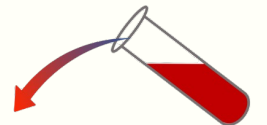


# Tissue Factor Circulates in Cell-Derived Microparticles.



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

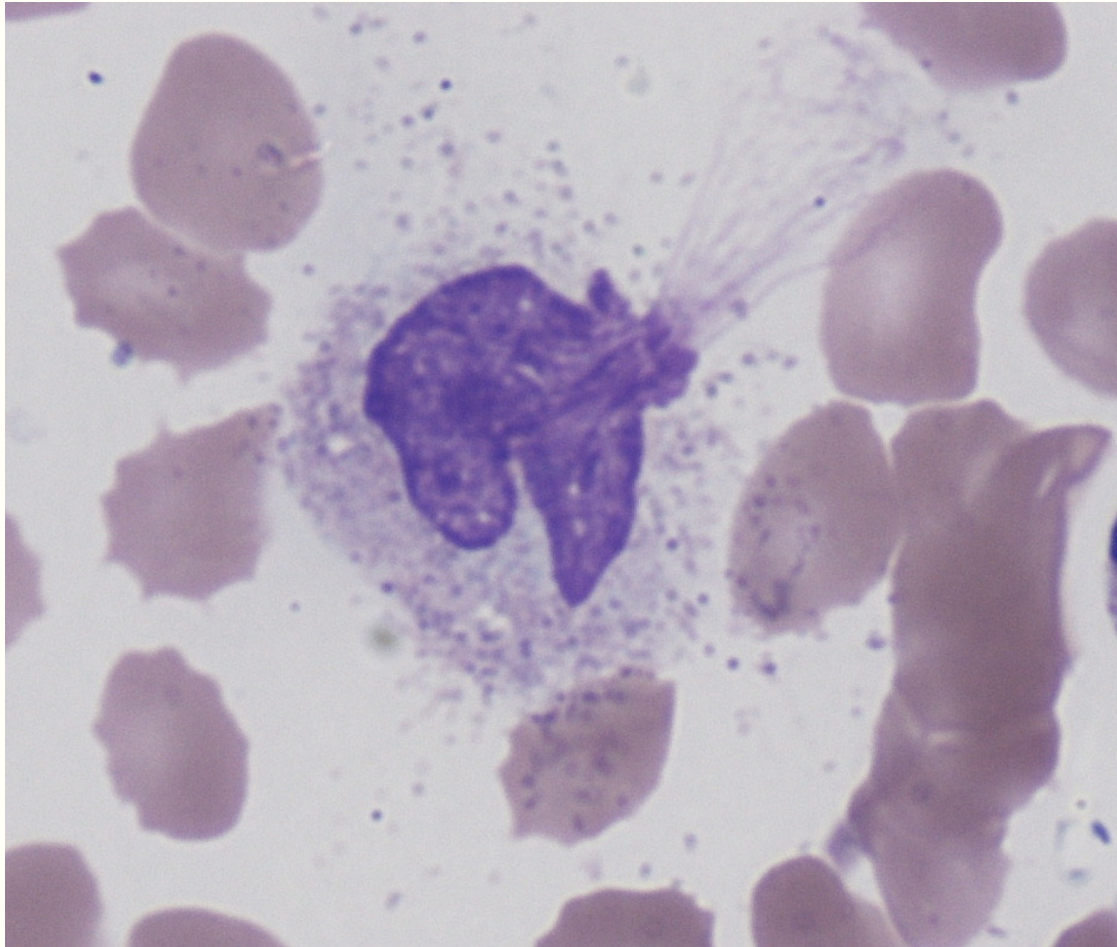
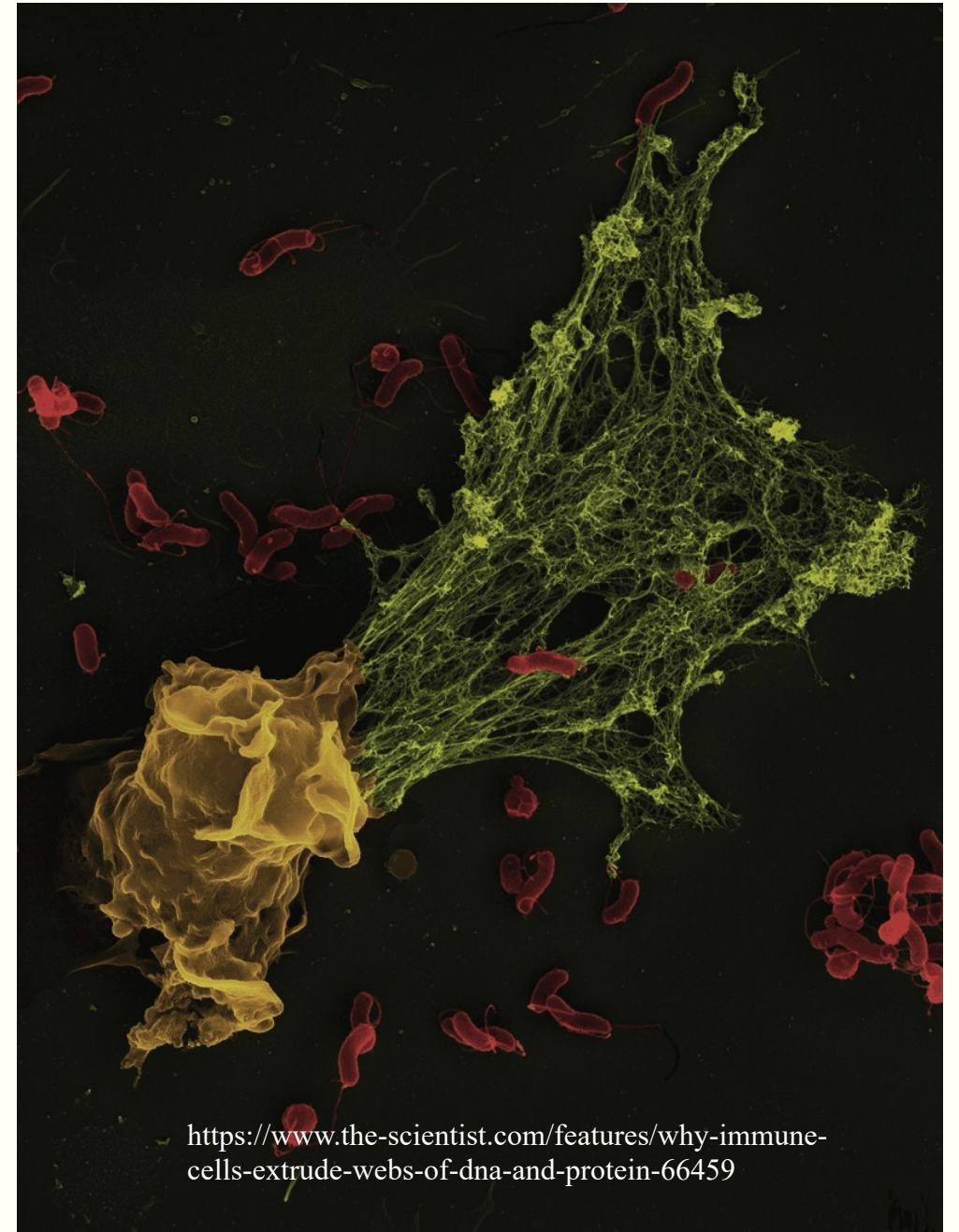


Image by Soff  
**HematologyEducationOnline**

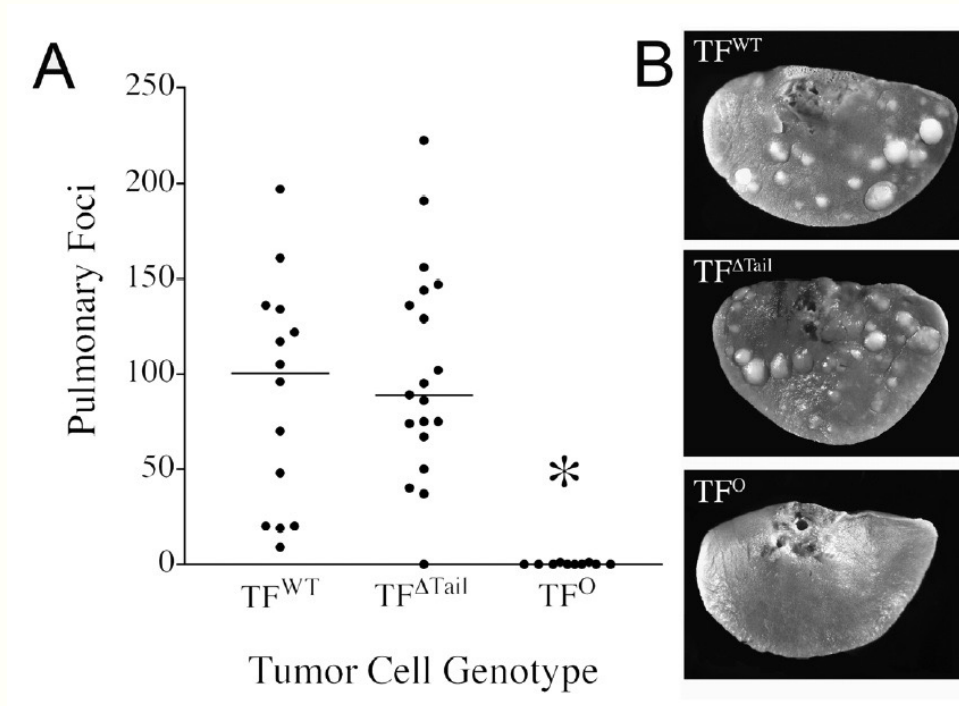
**Slide 14**



<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!

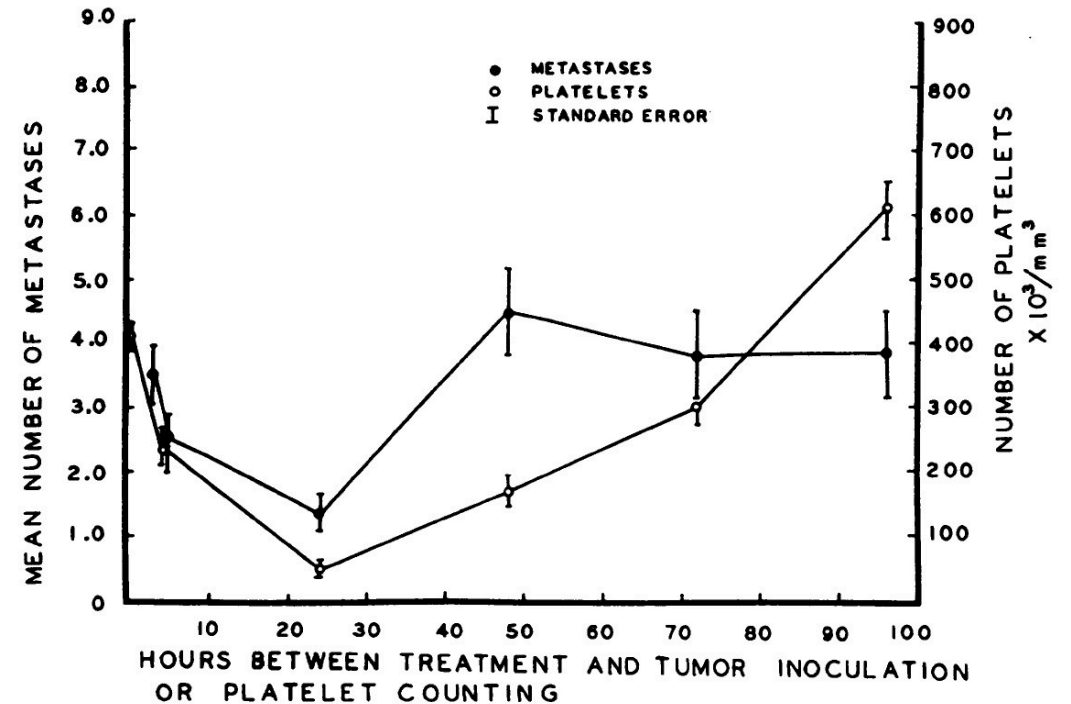
- Tissue Factor Expression in Fibrosarcoma Cells.
- Palumbo, J et al. Blood 2007



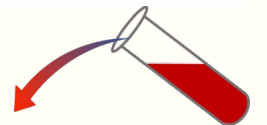
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Slide 15

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



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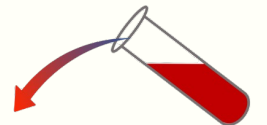


### 3. Screening For Occult Malignancy In Patients With VTE

- 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?



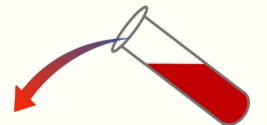
<https://www.needpix.com/photo/100955/inspector-man-detective-male-person-tracing-the-steps-tracing-steps-searching-for-traces-searching>





# Screening For Occult Cancer After Unprovoked Venous Thromboembolism

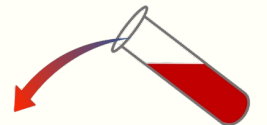
- Randomized clinical trial to assess the efficacy and safety of adding CT of the abdomen and pelvis to a limited screening strategy for occult cancer.
- Limited occult-cancer screening:
  - Basic blood testing,
  - Chest radiography,
  - Screening for breast, cervical, and prostate cancer.
- Carrier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

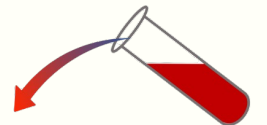


# 4. Management of Thrombosis In Cancer Patients

**DVT & PE**  
**BLOOD**  
**CLOTS:**  
**TREATMENT**  
**OPTIONS**



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

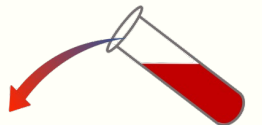


# Difficulty Using Warfarin For Anticoagulation in Cancer Patients

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

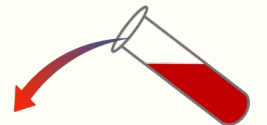
	Cancer	No Cancer	HR
Recurrent Thrombosis	20.7%	6.8%	3.2
Major Bleeding	12.4%	4.9%	2.2

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



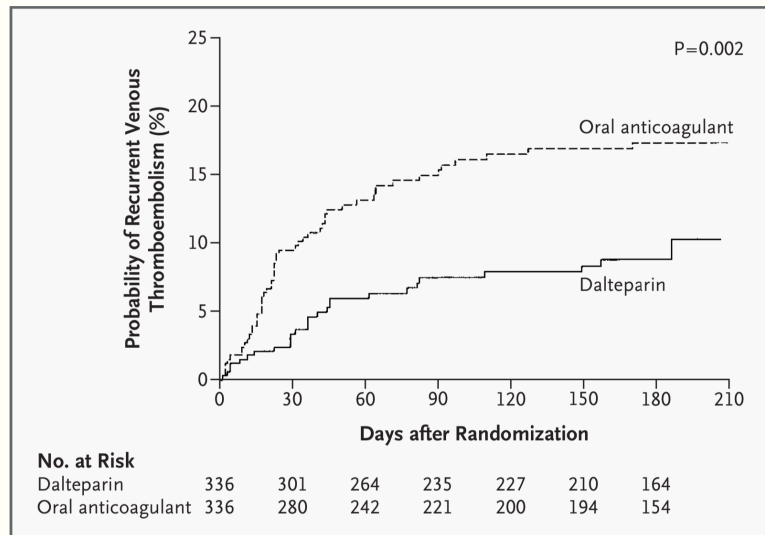
# The CLOT Study

- 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

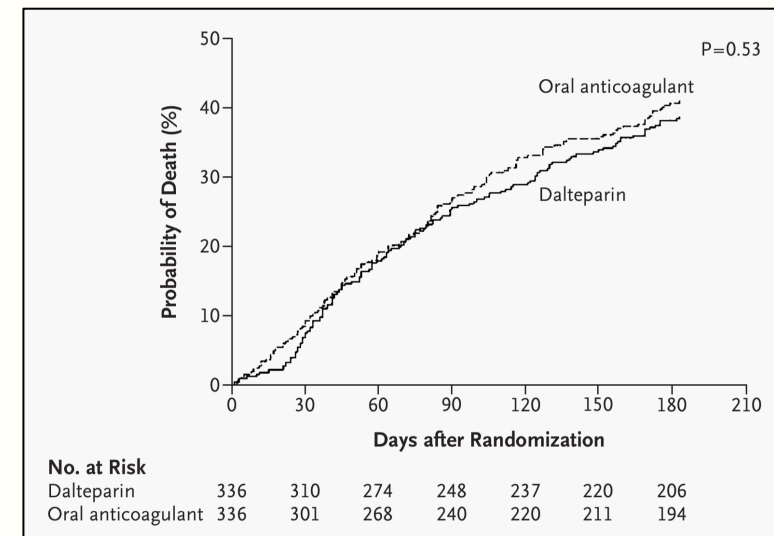


# Dalteparin Resulted in 50% Reduction in Recurrent Thrombosis

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



## Death From All Causes

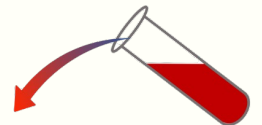


Lee, A. et al. *NEJM* 2003;349:146-153

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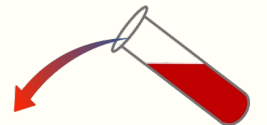
December 1, 2022



# Pooled Analysis of Anticoagulation Trials in Cancer Associated Thrombosis

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

- 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!



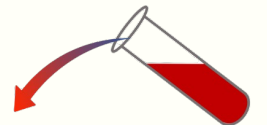
<https://hairyfarmerfamily.files.wordpress.com/2011/05/heparin.jpg>



[https://hannahcrafted.files.wordpress.com/2014/03/img\\_9252.jpg](https://hannahcrafted.files.wordpress.com/2014/03/img_9252.jpg)

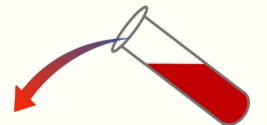
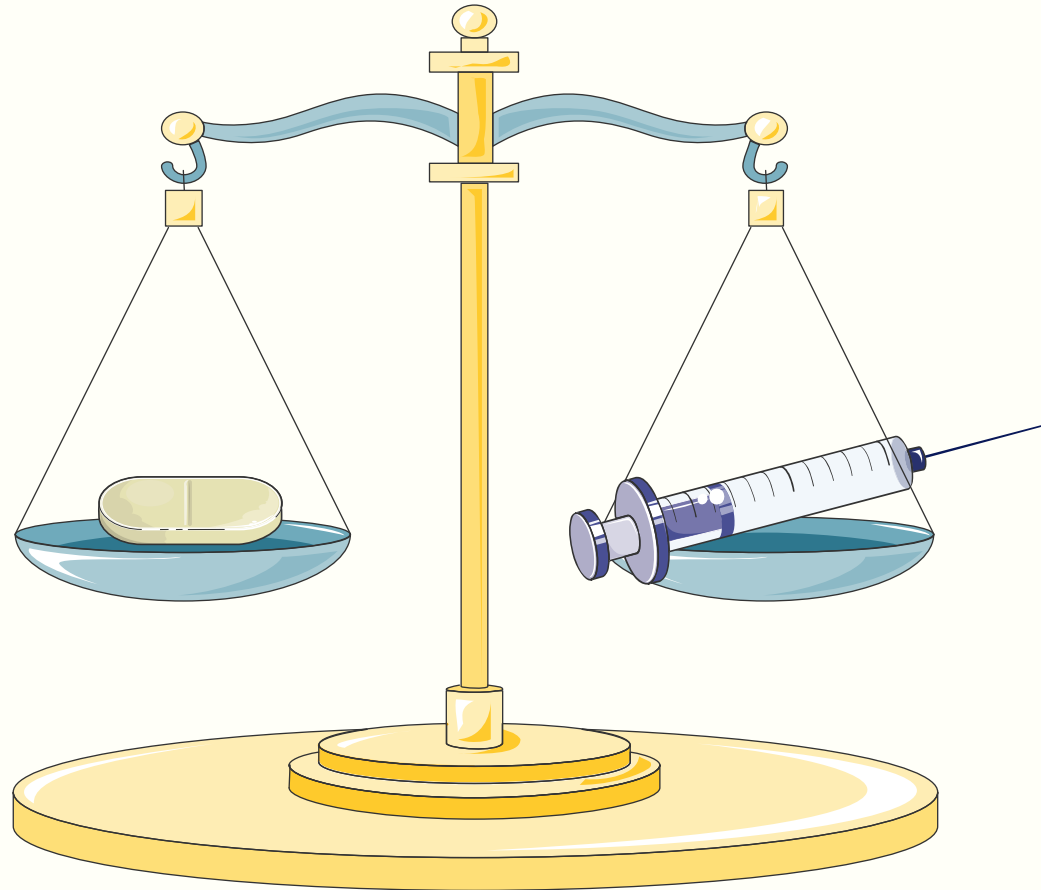


<http://www.bigtrial.net/2015/04/narcs-supervisor-never-read-indictment.html>

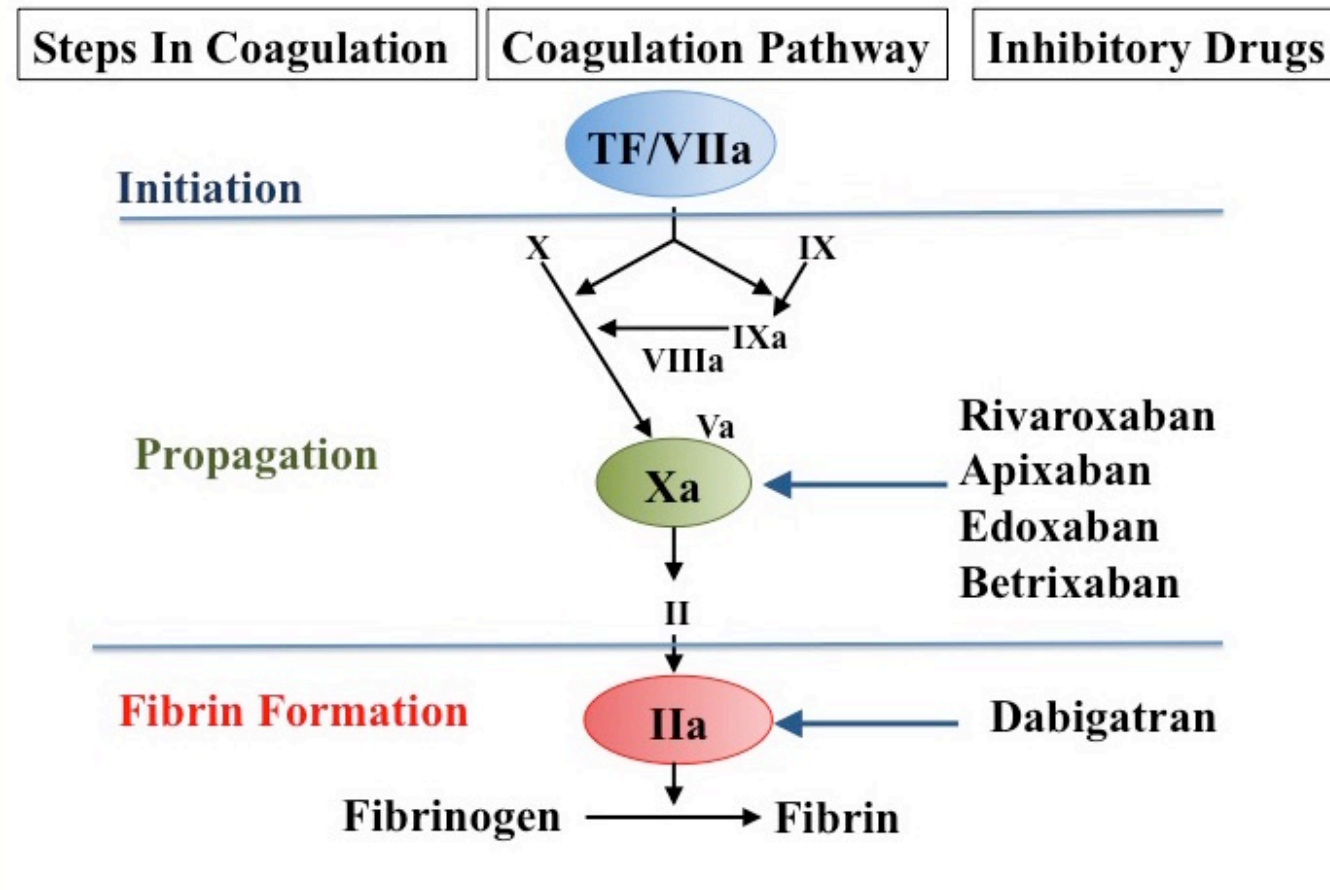




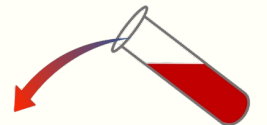
# Isn't There a Pill For That?



# 5. Direct Oral Anticoagulants

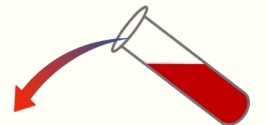


Adapted from Soff, Arteriosclerosis, Thrombosis, and Vascular Biology 2012, 32:569-574.



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

1. LMWH has been standard of care for Treatment of 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).



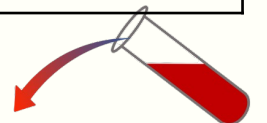
# “Rivaroxaban treatment of cancer-associated venous thromboembolism: MSKCC institutional experience”

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

Mantha et al, JTT, 2017

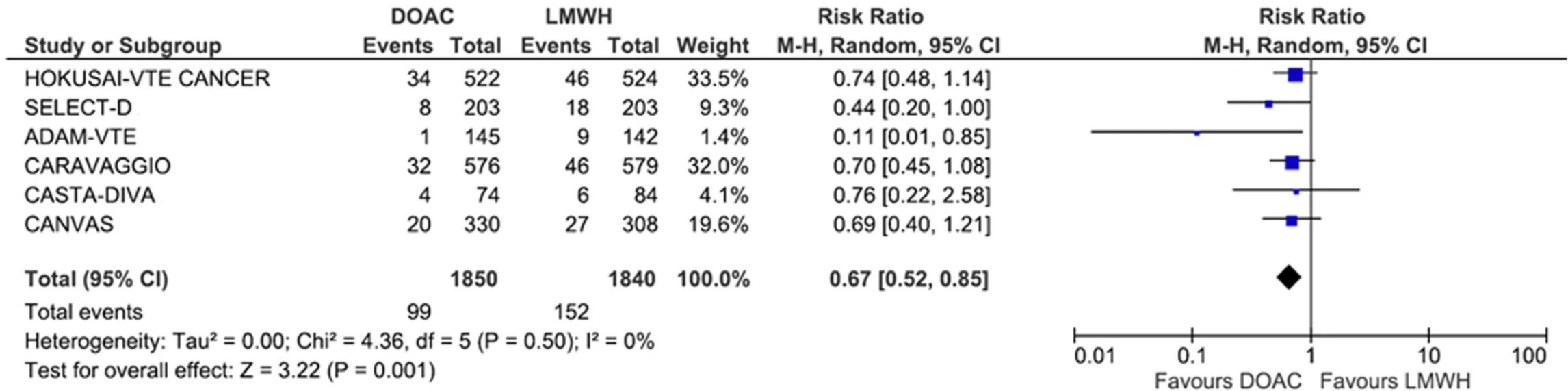
➤ N=1072 Patients with pulmonary embolism or symptomatic DVT. 6 Month Follow-up.

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%)

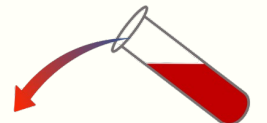


# DOAC vs. LMWH for the treatment of cancer associated thrombosis. Systematic review and meta-analysis of randomized controlled trials

## A. Recurrent venous thromboembolism

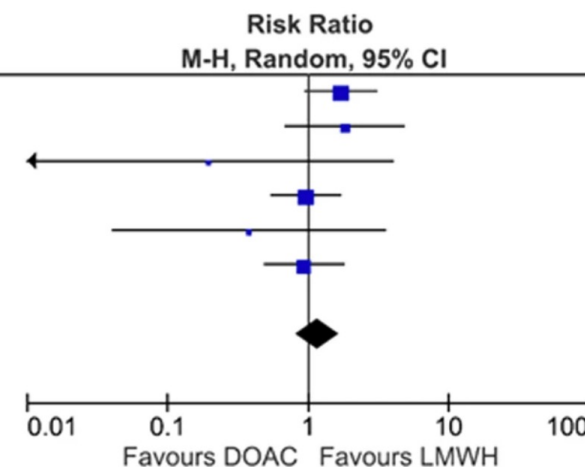


➤ Frere et al. Journal of Hematology & Oncology (2022) 15:69 <https://doi.org/10.1186/s13045-022-01289-1>



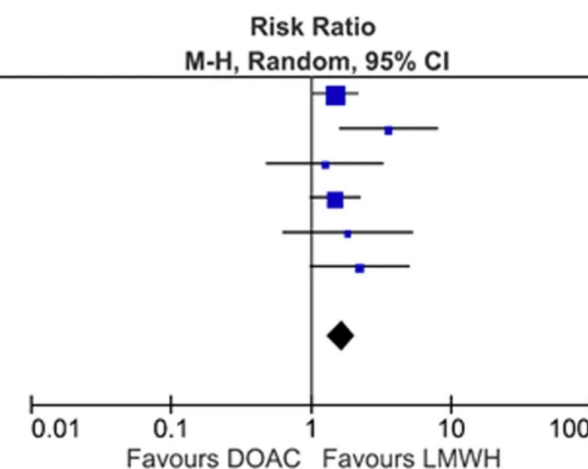
## B. Major bleeding

Study or Subgroup	DOAC		LMWH		Weight	Risk Ratio
	Events	Total	Events	Total		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]
<b>Total (95% CI)</b>		<b>1850</b>		<b>1840</b>	<b>100.0%</b>	<b>1.17 [0.82, 1.67]</b>
Total events	80		68			
Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 5.66, df = 5 (P = 0.34); I <sup>2</sup> = 12%						
Test for overall effect: Z = 0.85 (P = 0.39)						

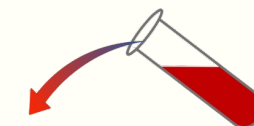


## C. Clinically relevant non major bleeding

Study or Subgroup	DOAC		LMWH		Weight	Risk Ratio
	Events	Total	Events	Total		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]
<b>Total (95% CI)</b>		<b>1850</b>		<b>1840</b>	<b>100.0%</b>	<b>1.66 [1.31, 2.09]</b>
Total events	177		105			
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 4.82, df = 5 (P = 0.44); I <sup>2</sup> = 0%						
Test for overall effect: Z = 4.23 (P < 0.0001)						

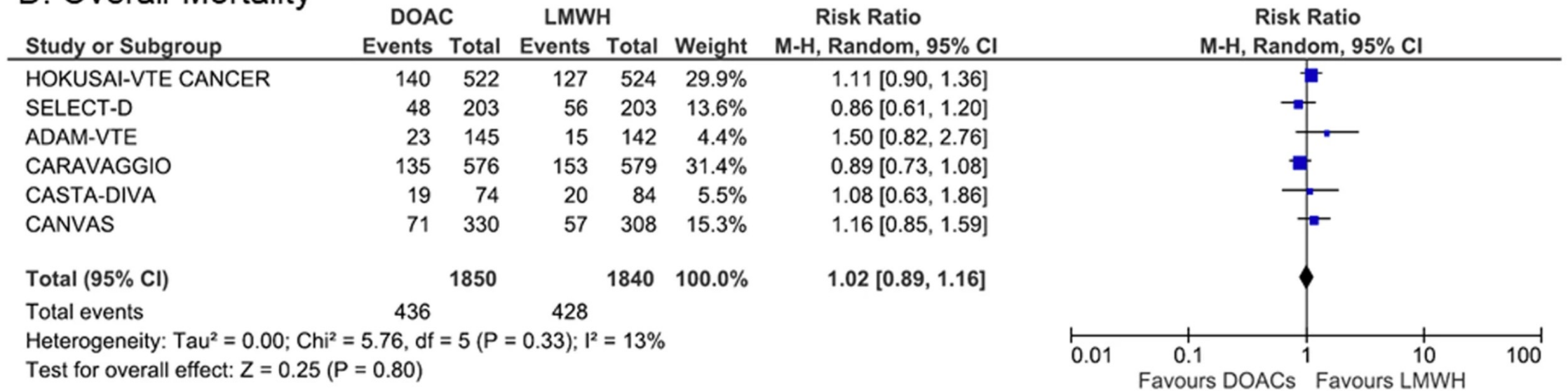


- Frere et al. Journal of Hematology & Oncology (2022) 15:69 <https://doi.org/10.1186/s13045-022-01289-1>

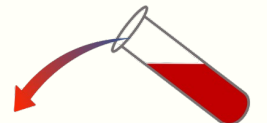


# DOAC vs. LMWH for the treatment of cancer associated thrombosis. Systematic review and meta-analysis of randomized controlled trials

## D. Overall Mortality

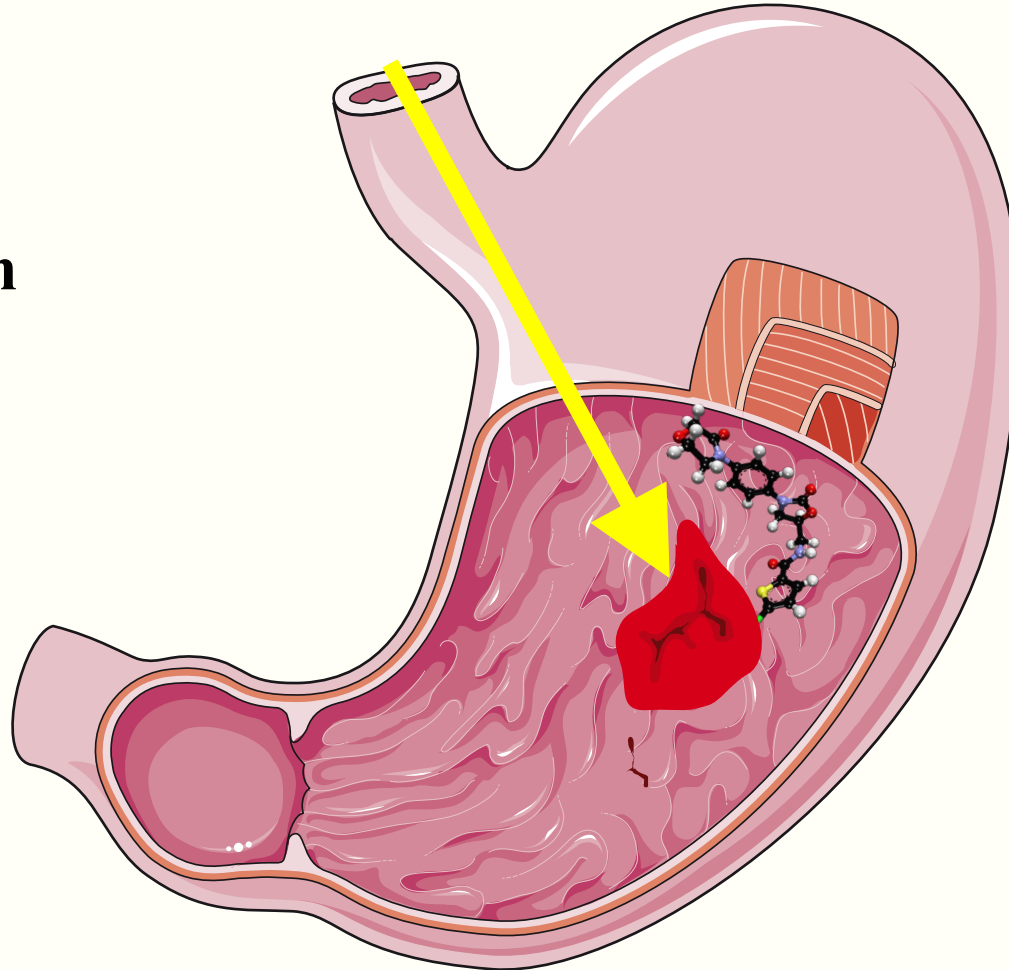


➤ Frere et al. Journal of Hematology & Oncology (2022) 15:69 <https://doi.org/10.1186/s13045-022-01289-1>

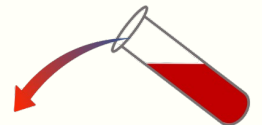


# In Setting of Upper GI Cancer or Pathology, A DOAC Has Increased Risk of Bleeding!

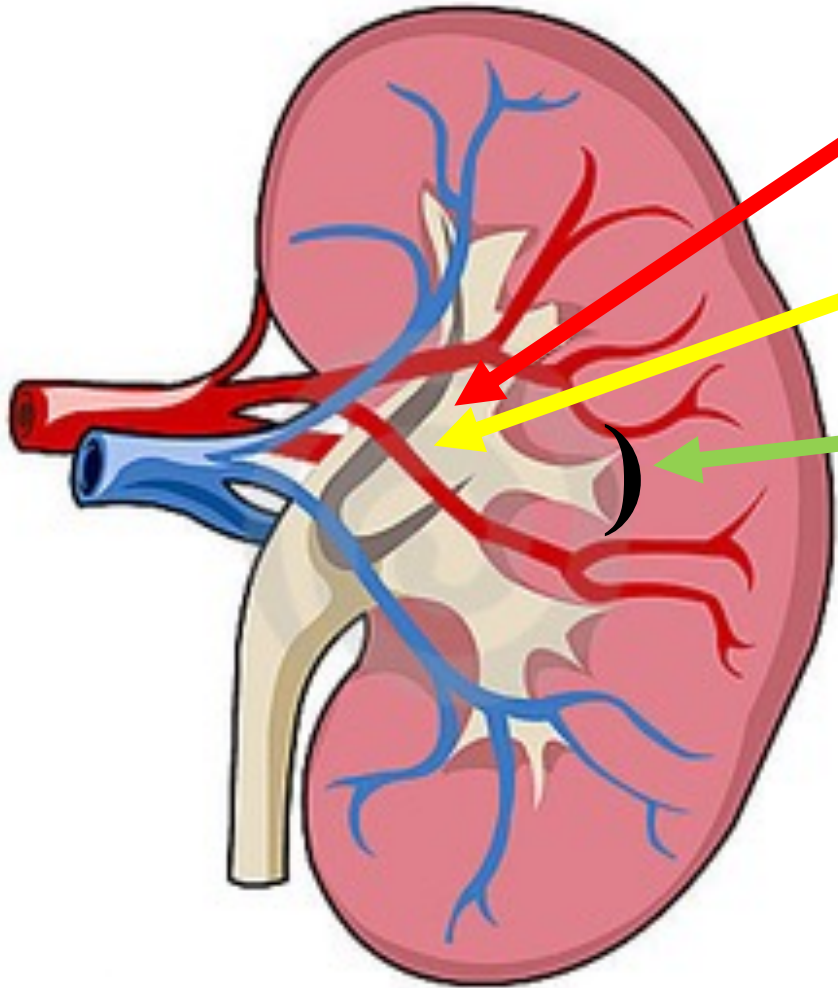
**Rivaroxaban**



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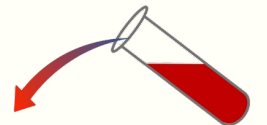


**DOAC (Rivaroxaban, MWt. 436)**

**LMWH (Enoxaparin, MWt. ~4500)**

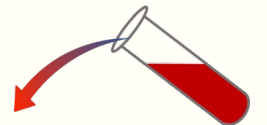
**Antithrombin III (MWt. 58,000)**

- DOACs and LMWH 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.



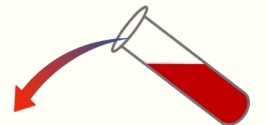
# Recurrent VTE Versus Bleeding

- Both recently reported 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!**



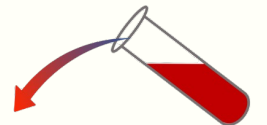
# Recurrent VTE Versus Bleeding

- 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?”

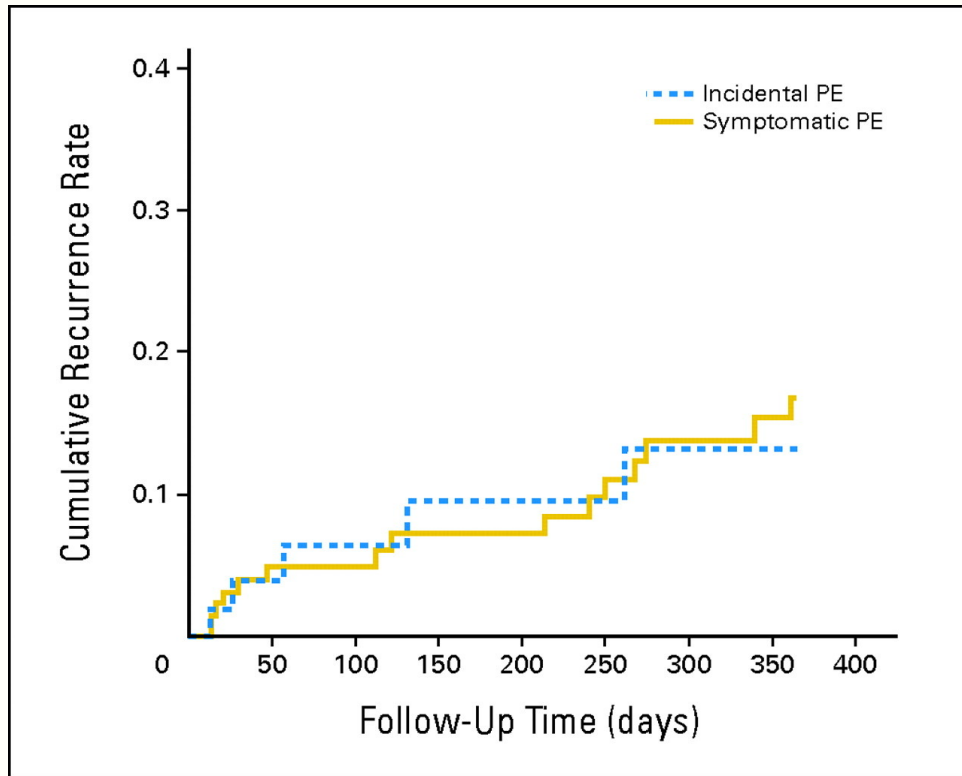


# 6. Incidental Thrombosis/ Pulmonary Embolism

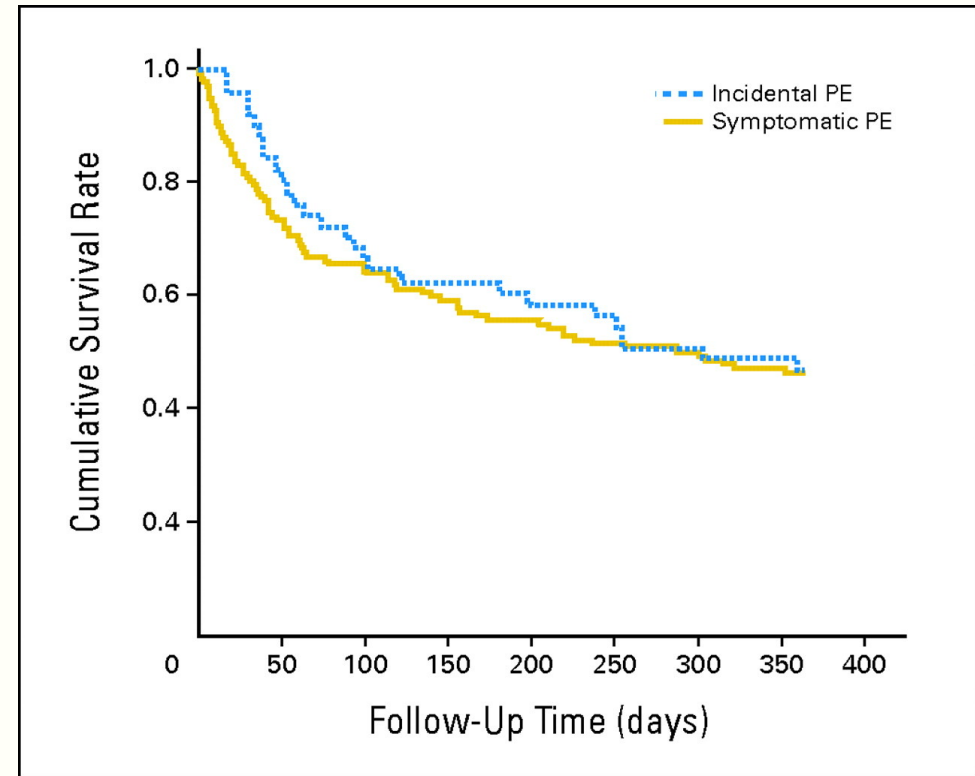
- Clinical relevance?
- Risks of recurrence, need for anticoagulation?
- Retrospective cohort study (2004-2010)
- Incidental Pulmonary Embolism (n=51)
- Symptomatic Pulmonary Embolism (n=144)
- Observed for 1 year
  - Den Exter P L et al. JCO 29:2405-2409, 2011.



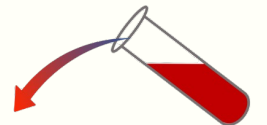
# Cumulative Recurrent VTE



# Cumulative Overall Survival

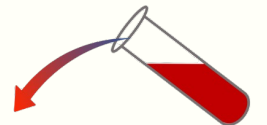


den Exter P L et al. JCO 2011;29:2405-2409



# 7. Primary Thrombosis Prophylaxis

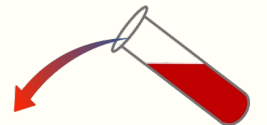
- Is there a role for thrombosis prophylaxis in outpatient, ambulatory cancer patients prior to development of a thrombosis?
- Balance: risk:benefit:cost:convenience



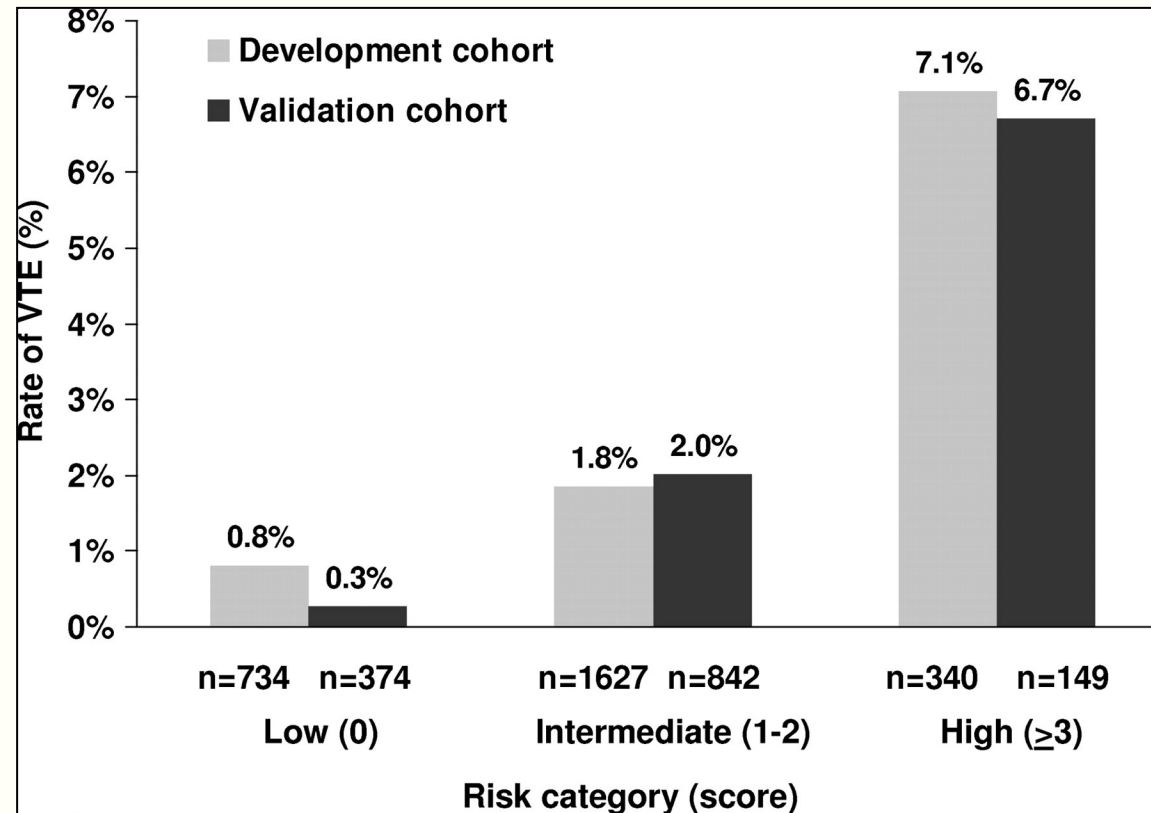
# Predictive Model for Chemotherapy-Associated VTE

Patient Characteristic	Risk Score
<b>Site of Cancer</b>	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testis)	1
Prechemotherapy platelet count $\geq$ 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/m <sup>2</sup> or more	1

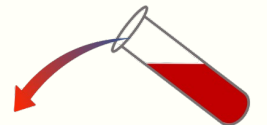
- Khorana AA *et al.* *Blood*. 111:4902-4907, 2008.
- Khorana AA & Connolly GC. *JCO*. 27:4839-4847, 2009



# 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



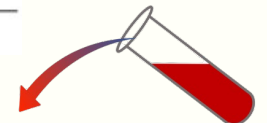


# Risk Prediction Scores for Venous Thromboembolism in Cancer Patients

- 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

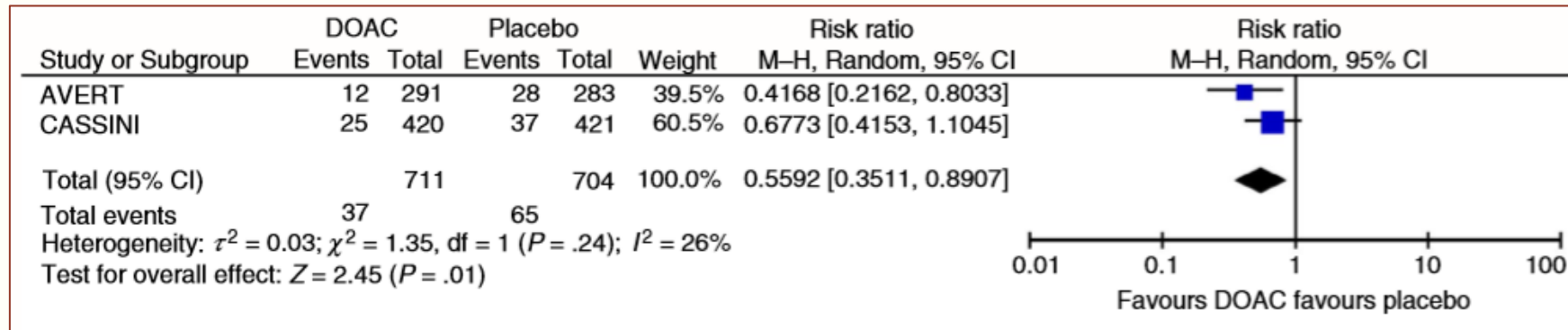
Item	Khorana score (points)	Vienna CATS score (points)	PROTECHT score (points)	CONKO score (points)
Pancreatic or gastric cancer (very high-risk tumors)	+2	+2	+2	+2
Lung, gynecological, lymphoma, bladder, or testicular (high-risk tumors)	+1	+1	+1	+1
Pre-chemotherapy hemoglobin <10 g/dL or use of erythropoietin stimulating agents	+1	+1	+1	+1
Pre-chemotherapy white blood cell count >11 x 10 <sup>9</sup> /L	+1	+1	+1	+1
Pre-chemotherapy platelet count ≥350 x 10 <sup>9</sup> /L	+1	+1	+1	+1
Body Mass Index >35 kg/m <sup>2</sup>	+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.

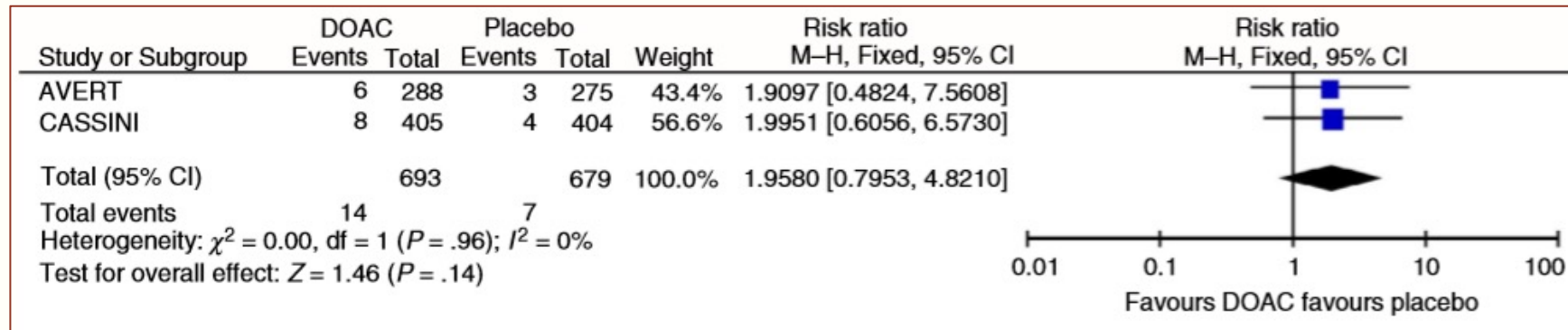


# DOAC for the prevention of thrombosis in ambulatory patients with cancer, with Khorana Score of $\geq 2$

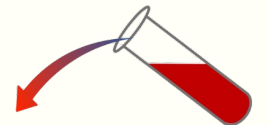
## Venous thromboembolism



## Major Bleeding (on-treatment)

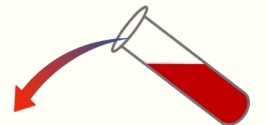


- AVERT: Apixaban. Carrier et al, NEJM, December 2018
- CASSINI: Rivaroxaban. Khorana et al, NEJM 2019
- Li A et al, J Thromb Haemost. 2019;17:2141–2151



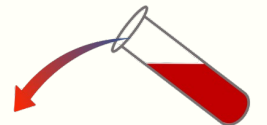
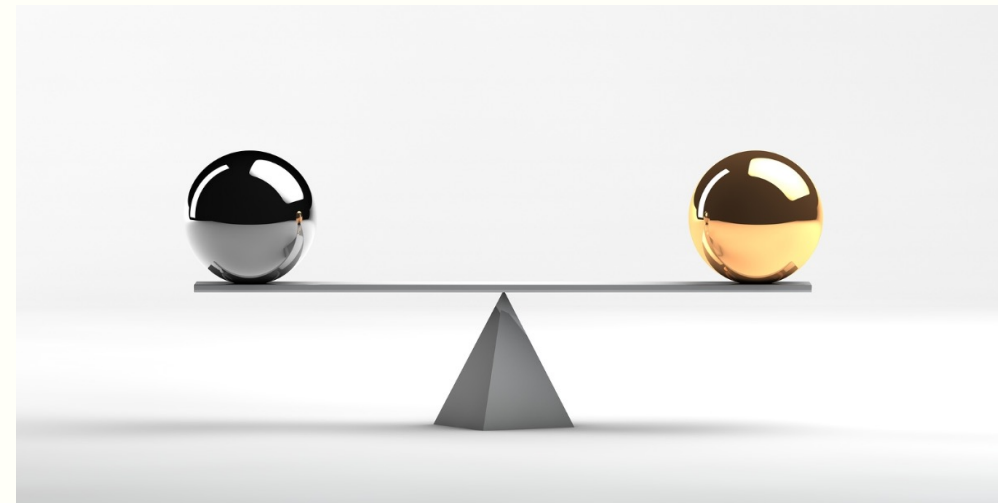
# 8. Anticoagulation and Brain Cancer

- 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.





## 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  $\geq 50,000/\mu\text{L}$ . 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  $50,000/\mu\text{L}$  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  $\geq 50,000/\mu\text{L}$  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 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
$>50,000/\mu\text{L}$	Full-dose enoxaparin	1 mg/kg twice daily	1.5 mg/kg daily
25,000–50,000/ $\mu\text{L}$	Half-dose enoxaparin	0.5 mg/kg twice daily	—
$<25,000/\mu\text{L}$	Temporarily hold enoxaparin		

- Note: NCCN currently does not recommend use of DOACs below a platelet count of  $50,000/\mu\text{L}$  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.

