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Managing Anticoagulation Complications in Cancer Patients

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Financial Disclosure Information

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BMS/*Pfizer Research Grants*

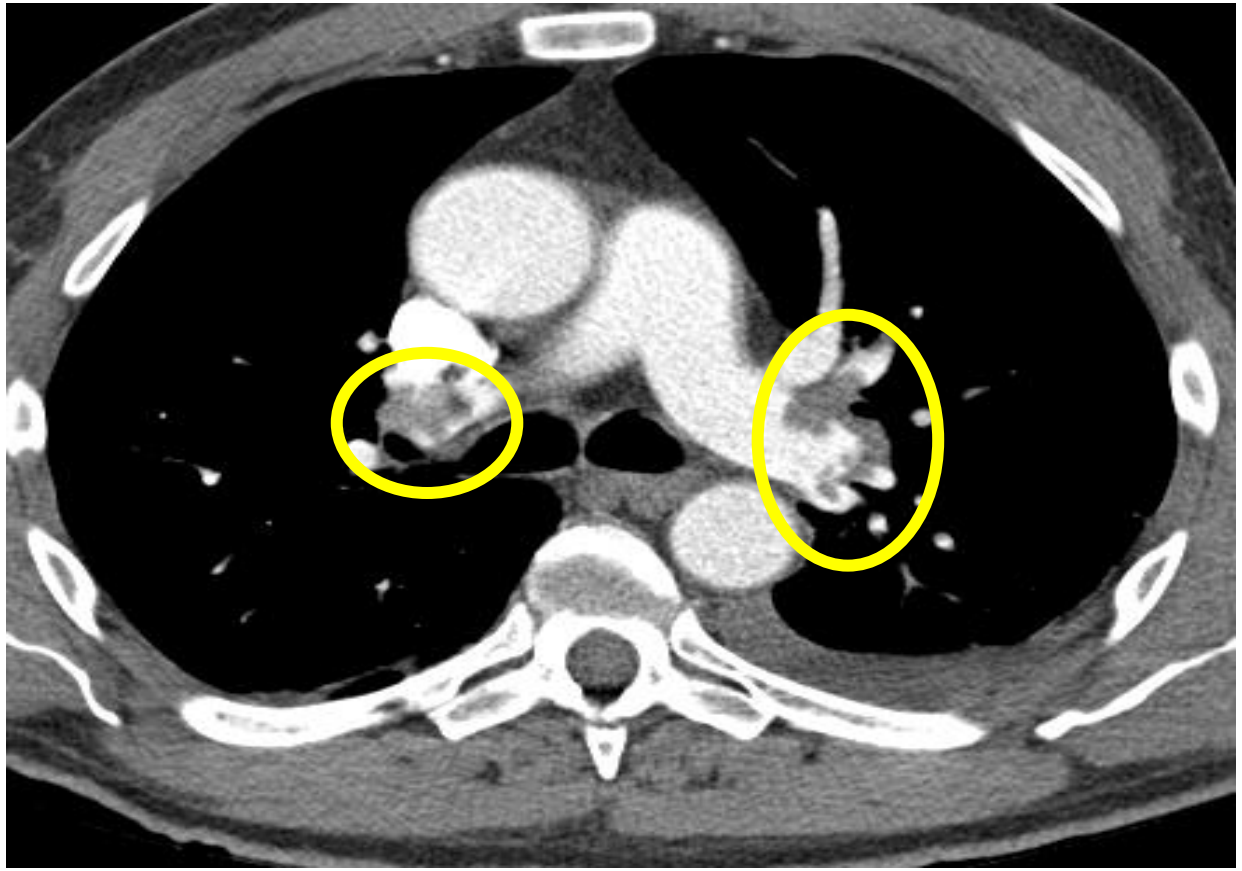
Anticoagulation Complications in Cancer Patients
Learning objectives

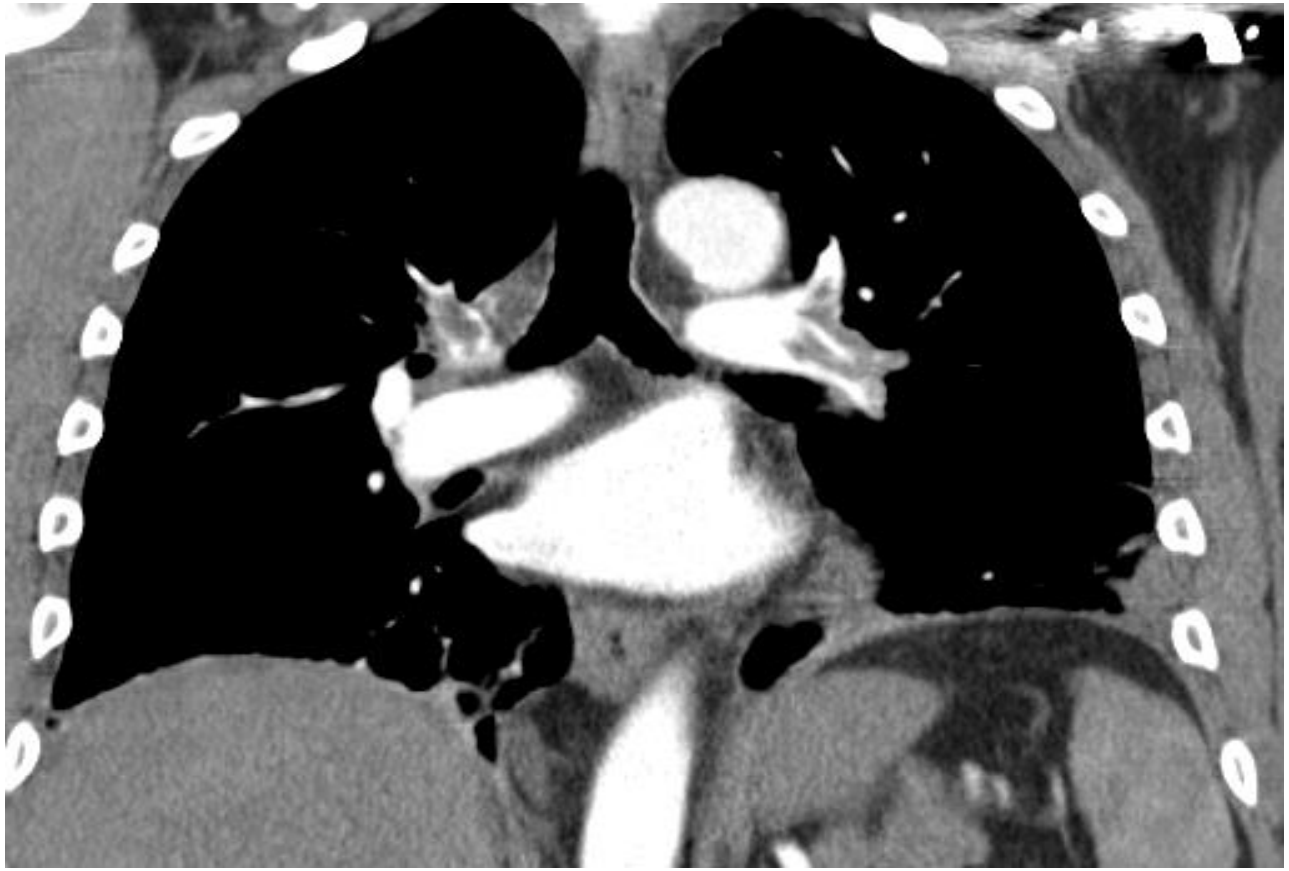
- To understand the nature of the problem
- To define a strategy for working through the evaluation and management of AC failures in Cancer patients.

71 y/o Female

August 16	Localized pancreatic cancer
August 23	Expl laparoscopy “negative”
August 26	Port placed, FOLFIRINOX started
October 22	Develops dyspnea and chest pain

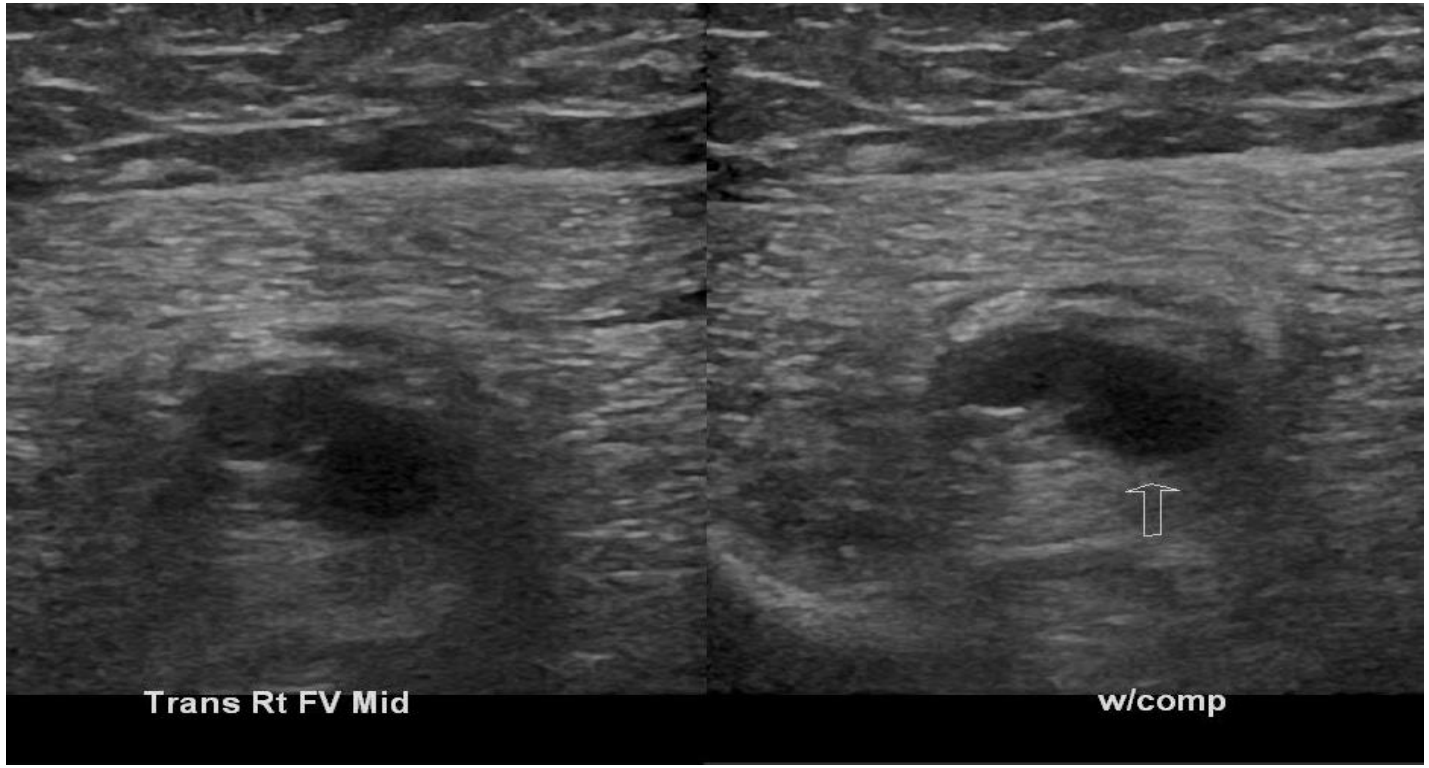
71 y/o Female

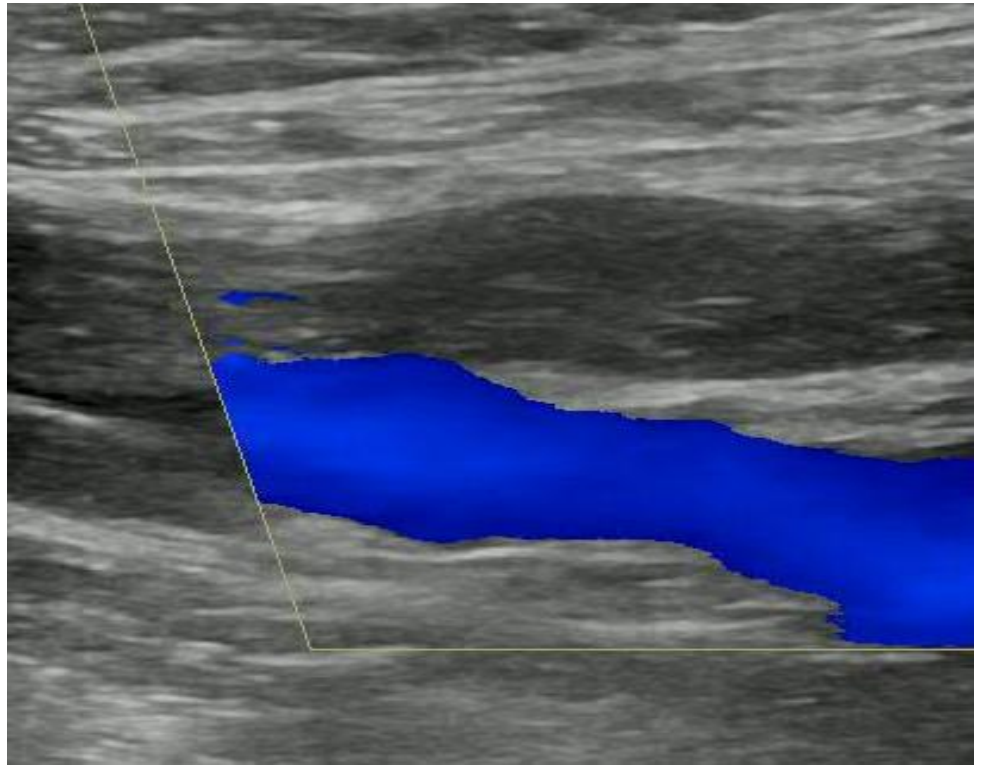




71 y/o Female

- She received enoxaparin 1 mg/kg twice daily for 1 month then 1.5 mg/kg daily. December, she notes painless swelling of her right leg.





What would you recommend now?

1. IVC filter
2. Add aspirin
3. Change to a DOAC
4. Increase LMWH dose by 25%
5. Not clear from what you have presented

Anticoagulant Failure in Cancer: Nature of the Problem

USA

- 1.9 M new cancer diagnoses expected (2022)
  - 609,360 deaths
- > 14 M cancer survivors
- 1 in 5 cancer patients develop thrombosis
- ~ 3 M cancer patients with VTE

What is the risk of developing a new thrombus on anticoagulants (anticoagulation failure) in cancer patients?

Risk of Anticoagulant Failure: Oral Agents

Agent	Trial	Trial Duration (days)	Treatment failures (%)
Edoxaban	Hokusai Cancer VTE	365	7.9%
Rivaroxaban	SELECT D	180	4%
Apixaban	CARAVAGGIO/ADAM	180	0.7 – 5.6%
Warfarin	CLOT	180	16%
	CATCH	127	10.5%

Risk of Anticoagulant Failure: Parenterals

Agent	Trial	Trial Duration (days)	Treatment failures (%)
Dalteparin	Hokusai Cancer VTE	365	13.5%
	SELECT D	180	11%
	CARAVAGGIO	180	7.9%
	ADAM VTE	180	6.3%
	CLOT	180	9%
Tinzaparin	CATCH	160	7.2%

Lots of data: Let's summarize AC Failure rates

- **DOACs:** 4% at 6 months (Riva),
  0.7 – 5.6% at 6 months (Apixa)
  8% at 1 year (Edoxa)
- **Warfarin:** ~ 2.5% failure rate per month
  (CLOT 16% @ 6 mos. CATCH 10.5% @ 4 mos)
- **LMWH:** 10% at 6 months or
  14% at 1 year

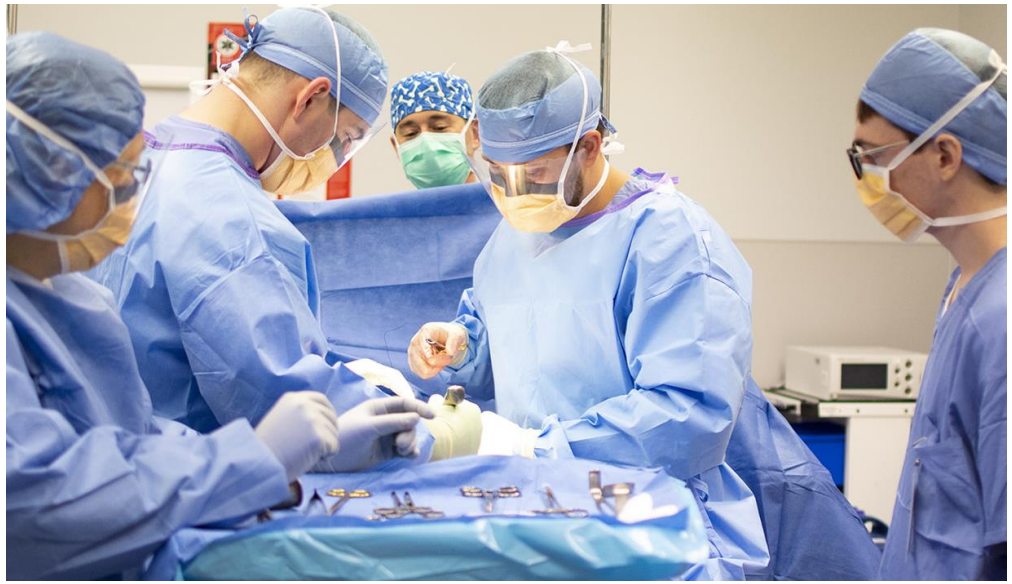
Amounts to nearly 300,000 patients in this category!

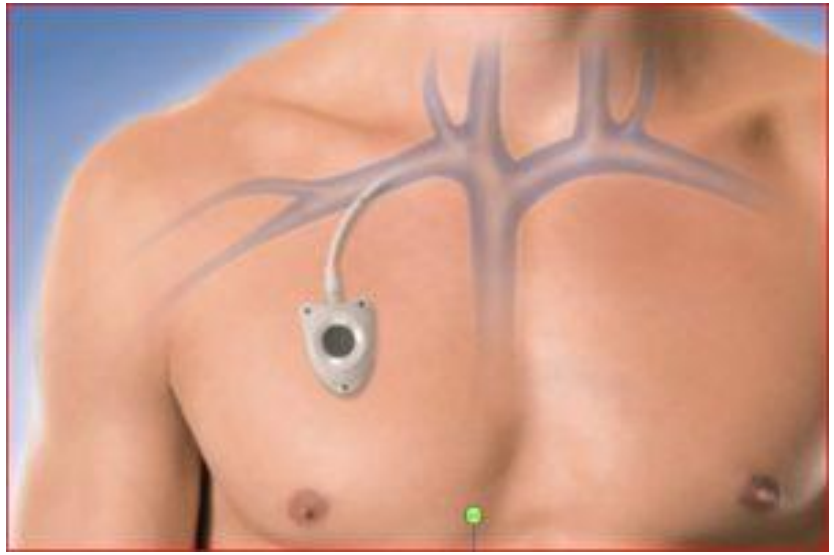
How does this compare to ***no therapy***?

30% annual recurrence
off anticoagulants

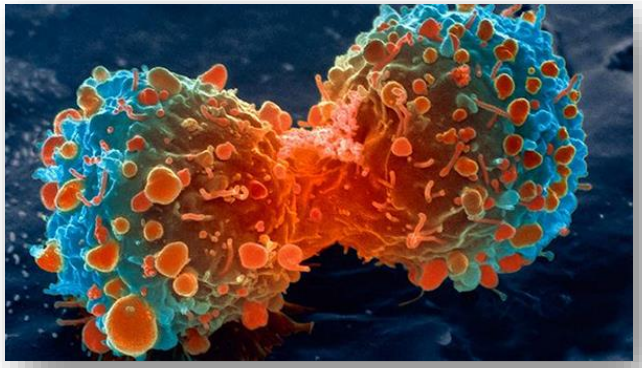
Are there Risk Factors for Anticoagulant Failure in Cancer?

Factors Contributing to Recurrent ***VTE*** in Cancer





Cancer Specific Risk Factors



- ***Stomach*** or ***Pancreas*** vs. Other Cancers

  HR 5.55 (95%CI 1.97 – 15.66)

- ***Lymphoma, Lung, GYN,*** or ***Bladder*** vs. Other Cancers

  HR 2.69 (95%CI 1.11 – 6.53)

- ***Metastatic disease*** vs. Nonmetastatic disease

  HR 2 - 3

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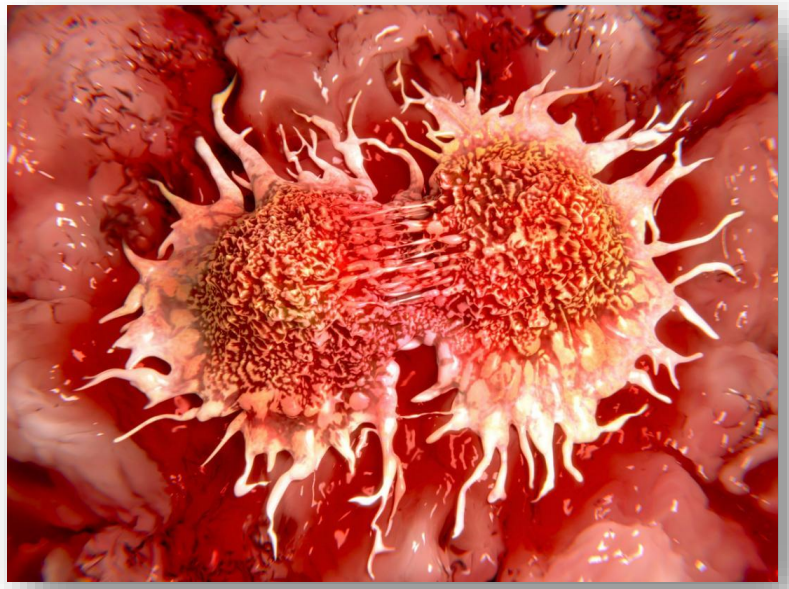
SELECT D Trial. J Clin Oncol 2018
Blood 2017

VTE Specific Risk Factors



- ***Symptomatic*** vs. Incidental PE

  HR 2.78 (95%CI 1.20 – 6.41)

- ***VTE within 3 months of Cancer Diagnosis***

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SELECT D Trial. J Clin Oncol 2018
Blood 2017

Anticoagulant Failures: Bottom Line

- Cancer associated VTE is ***common***
- Anticoagulation ***Failures*** are also ***common***
- These failures are ***Anticoagulant*** specific, ***Cancer*** specific, and VTE ***presentation type*** specific

What are the ***implications*** of Anticoagulant Failure in Cancer?

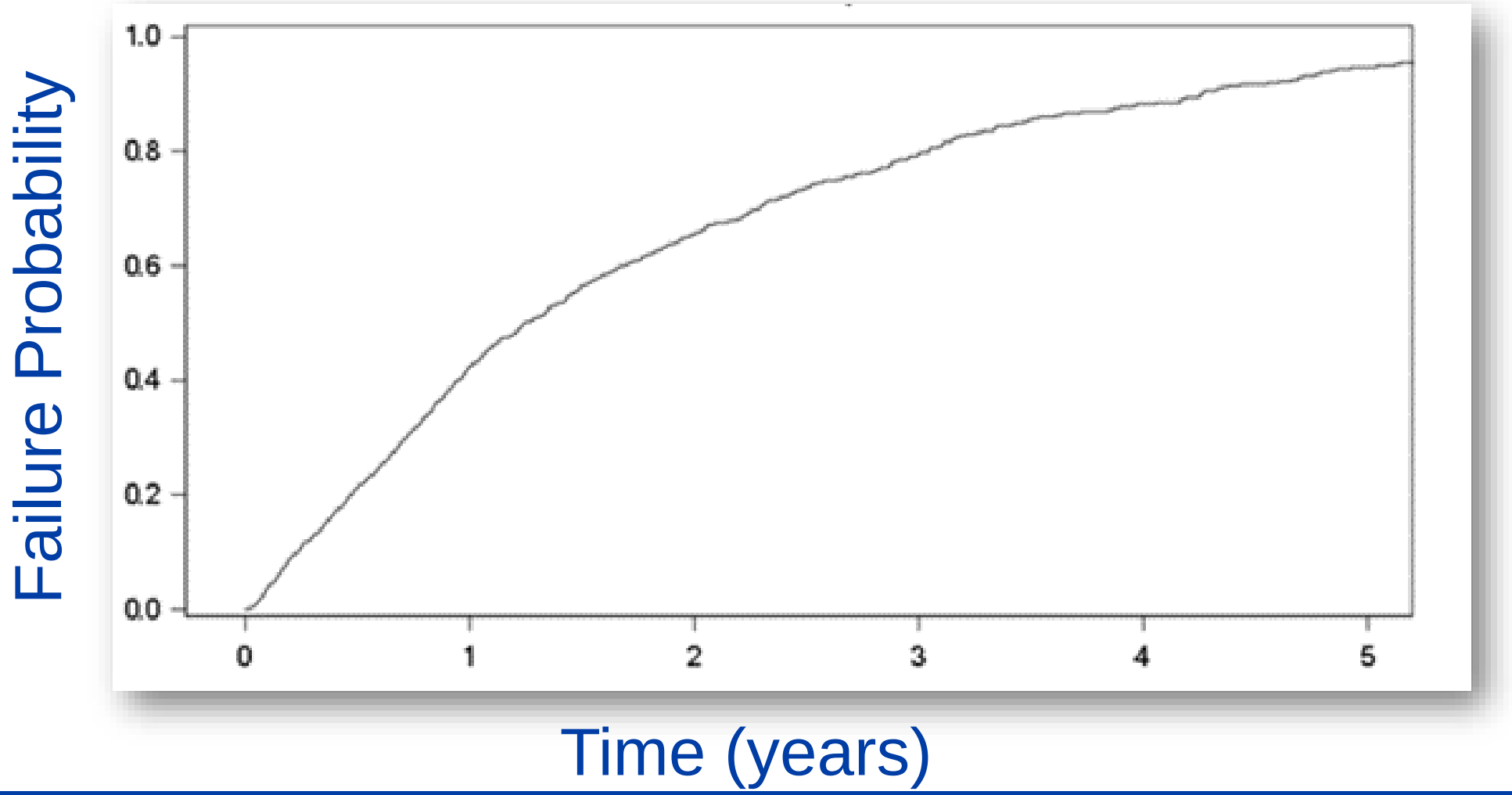
Survival Implications of Thrombus Recurrence

- 1,812 cancer patients with VTE receiving anticoagulation
- 97 patients with VTE recurrence (5.7%)

PE	47%
Leg DVT	33%
Arm DVT	6%
Portal/Renal/Ovarian	9%
Second Recurrence	12%

- Hazard Ratio for ***Mortality 1.52*** (95% CI 1.16 – 2.00) p=0.0028

Events rates ***highest in first year***, curve ***never flattens***



Thromb Haemost 2022 (in Press)

Survival Implications of Thrombus Recurrence

- Hazard Ratio for ***Mortality 1.52*** (95% CI 1.16 – 2.00) p=0.0028
- Incident Leg DVT ***increased risk of VTE recurrence***

  HR 1.78 (1.08 – 2.89) p=0.02
- Pancreatic cancer ***borderline*** increased risk

  HR 1.65 (0.99 – 2.75) p=0.057

- Other factors ***did not*** impact risk: metastatic disease, chemotherapy, age, gender, Ottawa scores, surgery, trauma

What are the steps to decision making?

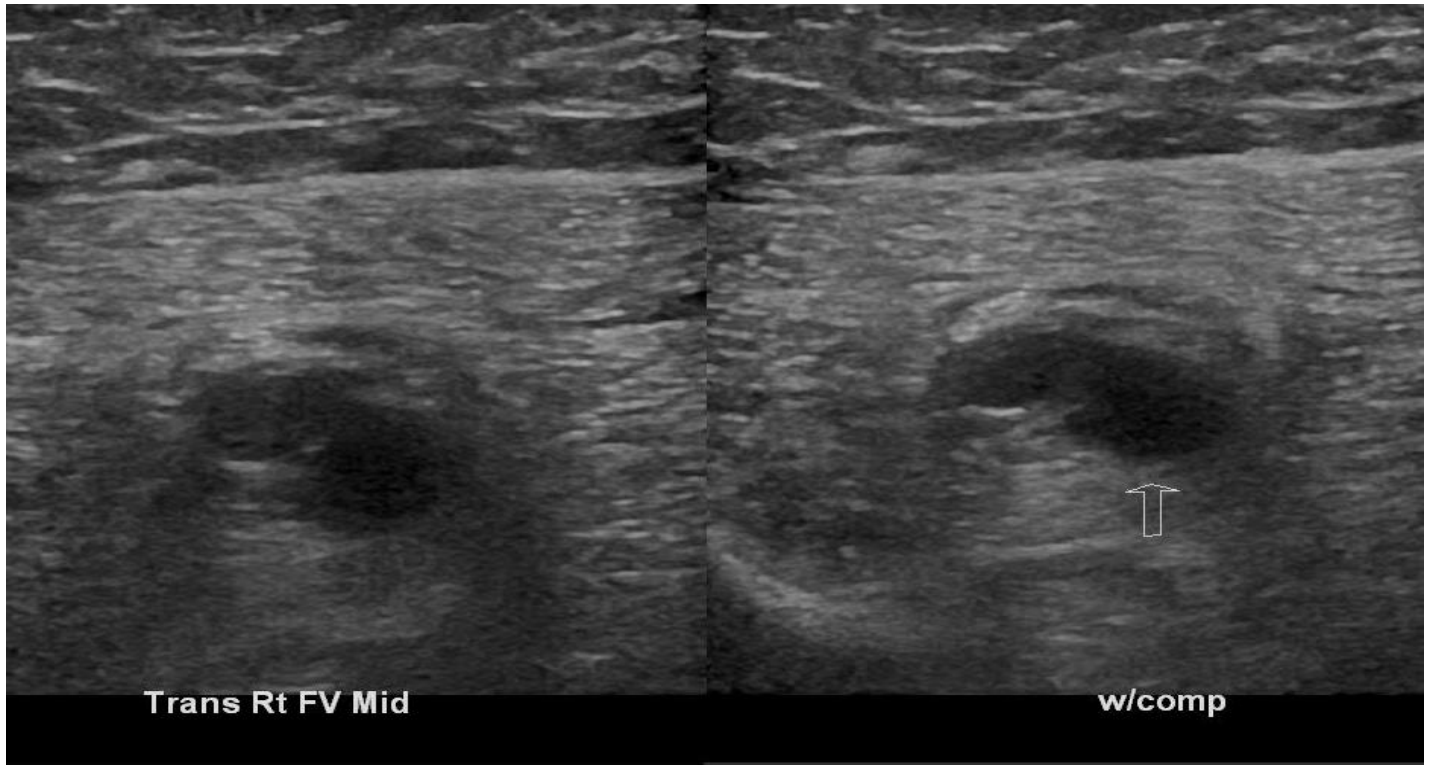
Step-wise approach

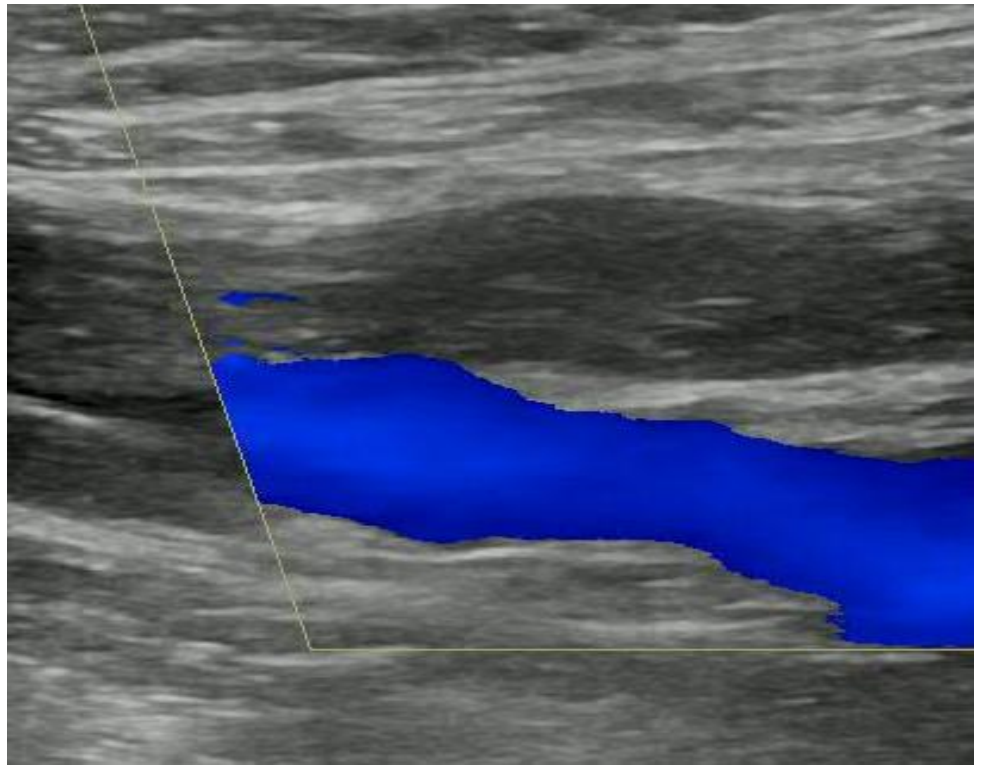
1. Has there truly been an Anticoagulant Failure?

- The original VTE must be reviewed and confirmed (US, venography, CT, or MRI).
- Recurrent VTE must be distinguished from the original by comparing serial imaging.
- To be classified as a recurrent event, there must be new filling defects evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution.

Back to our patient

- Leg imaging was not performed with the original PE…….





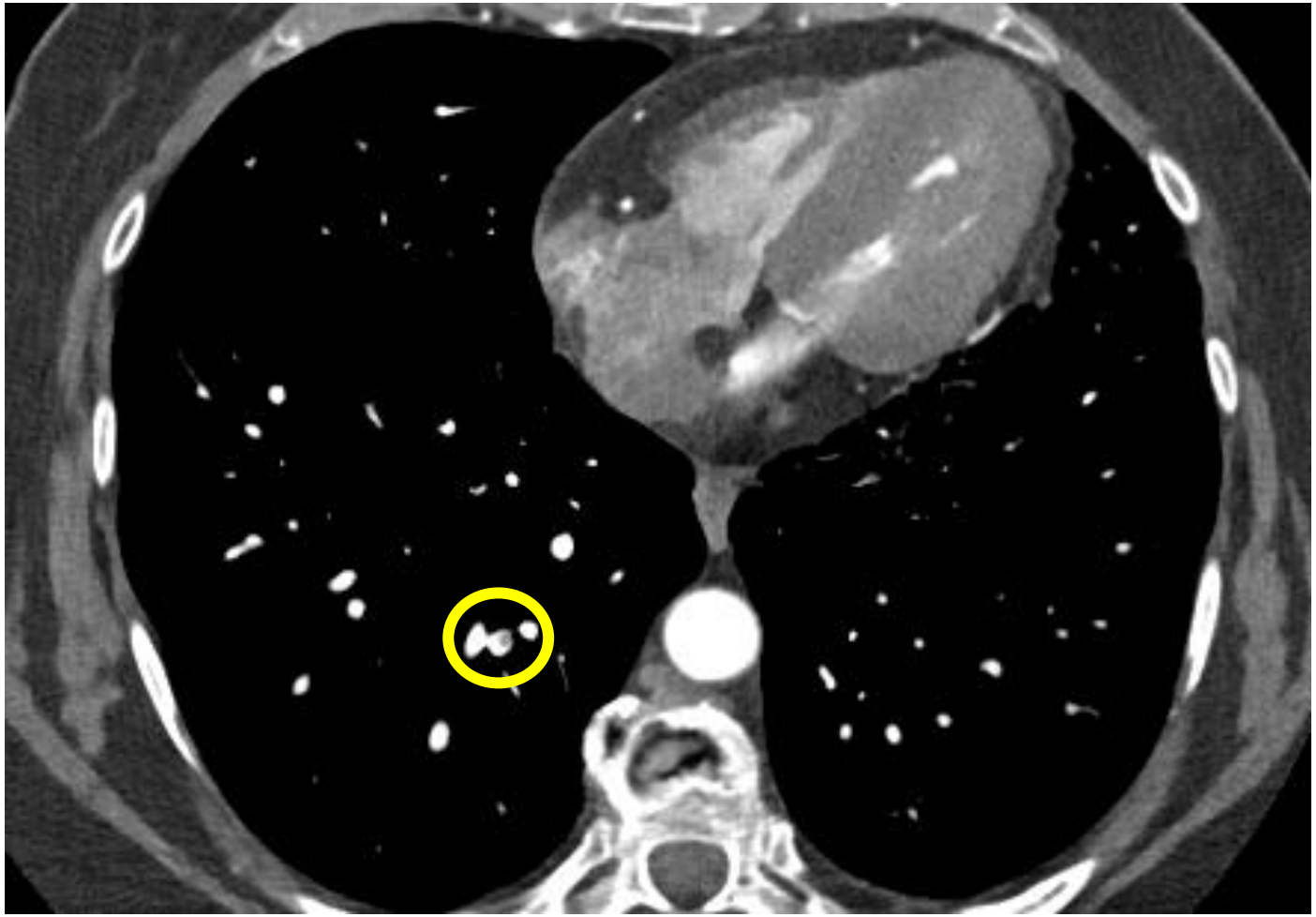
Another patient example

58 y/o Female

Stage IV adenocarcinoma lung

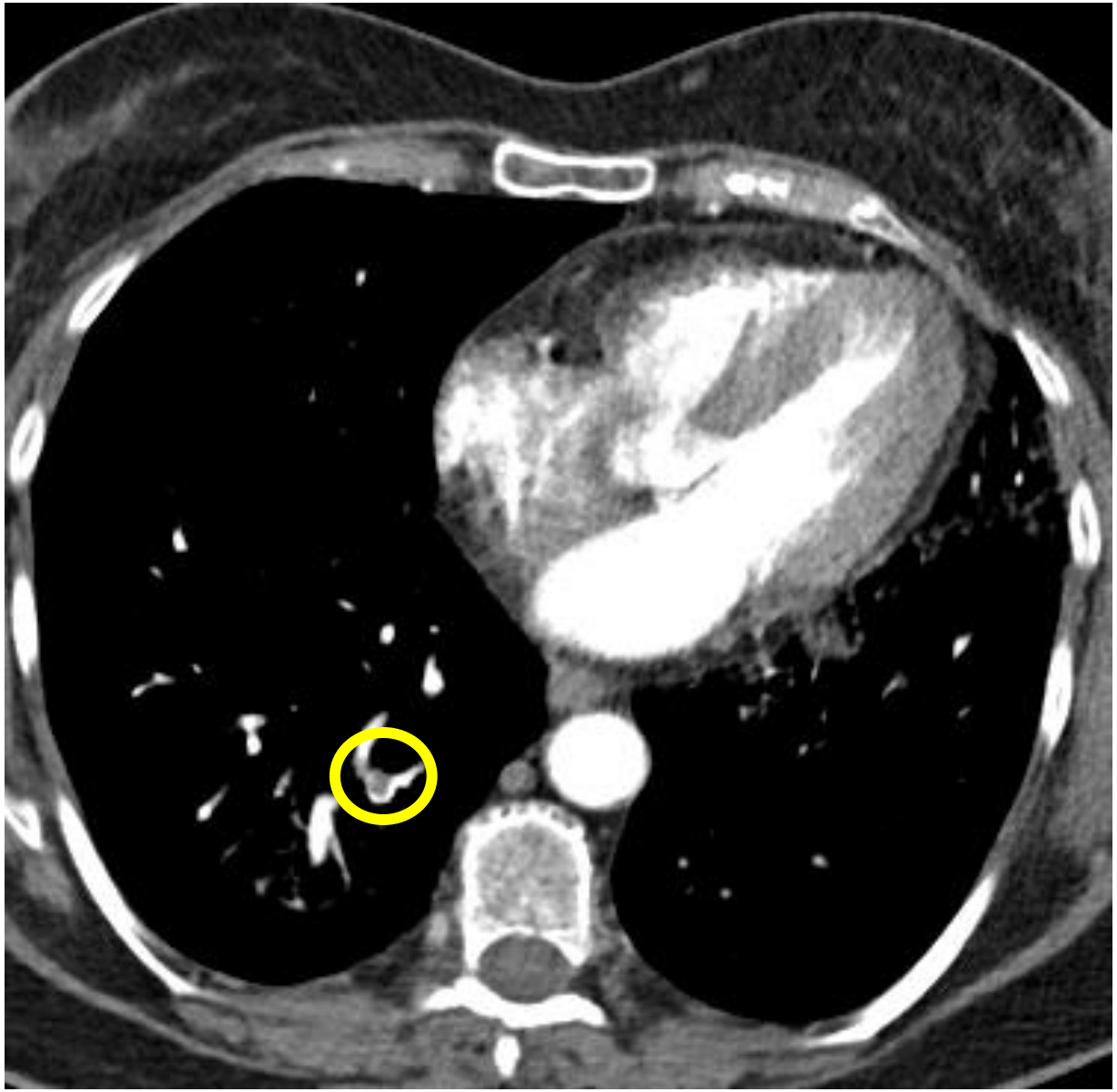
Sept 27	ED evaluation for dyspnea.
	CTA Chest: Bilateral PE
	US leg veins: Negative
	Treated: Xarelto
Nov 2	Recurrent dyspnea
	CTA Chest: New PE

“Positive for Acute Pulmonary Embolism”

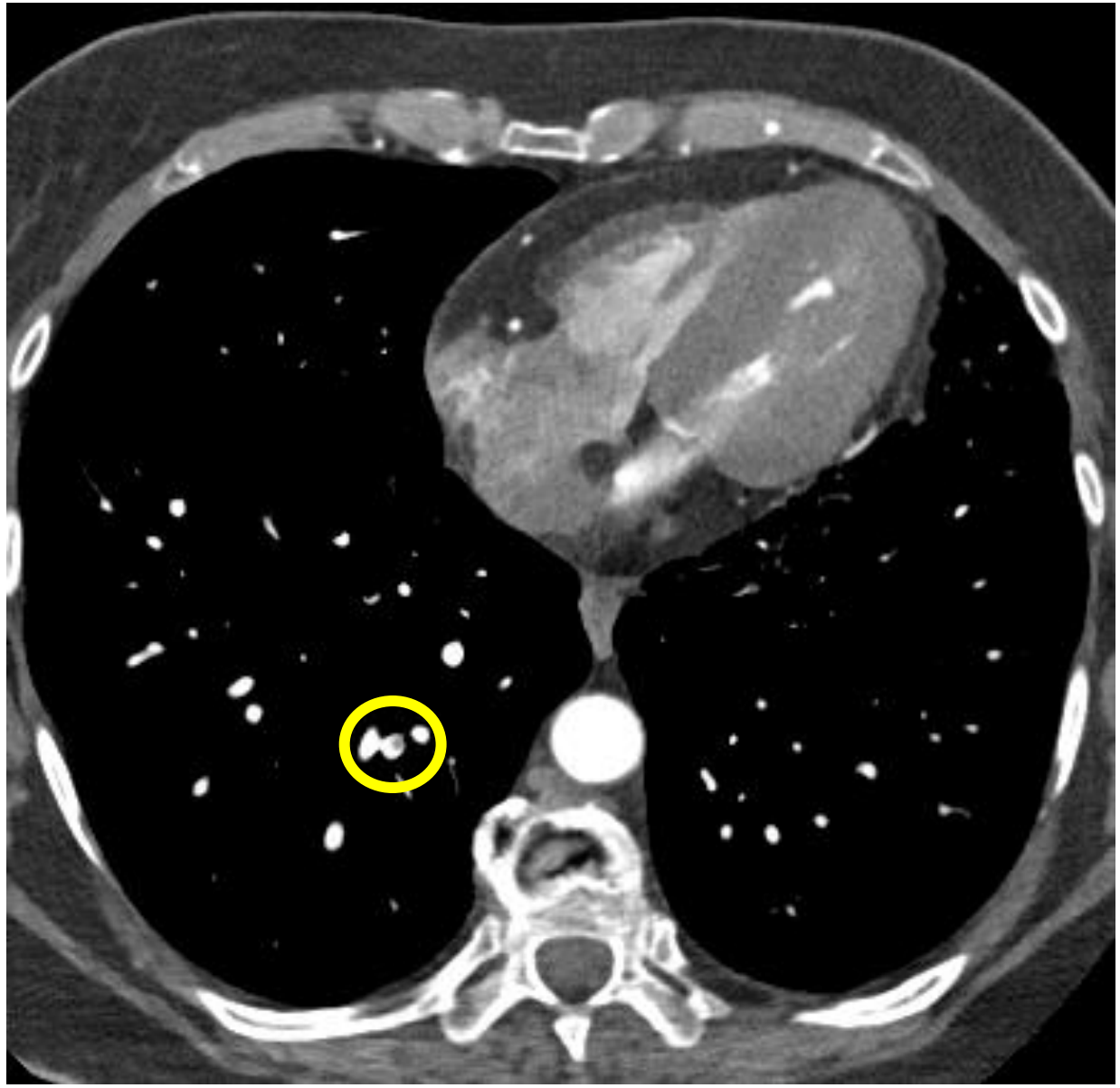


US leg veins are negative. What would you do with this patient.

1. IVC filter
2. Add aspirin
3. Change to another DOAC
4. Change to LMWH
5. Skip the radiology interpretation and Look at the images yourself



September 27



November 2

The intervening CT comparison was a non-contrast study!

US leg veins are negative. What would you do with this patient.

1. IVC filter
2. Add aspirin
3. Change to another DOAC
4. Change to LMWH
5. ***Skip the radiology interpretation and Look at the images yourself***

2. Is drug metabolism normal?

- Is the dose correct?
- Can you check a drug level prior to discontinuing?

Therapeutic Drug Levels*

Drug	Dose	C-min (ng/mL) Trough (pre dose)	C-max (ng/mL) 2 – 4 hours post dose
Apixaban	5 mg twice daily	63 (22-177)	132 (59-302)
Rivaroxaban	20 mg daily	26 (6-87)	270 (189-419)

Even if ***turn around is slow***, this will help for ***future decision making***!

*ACL TOP 700 (HemosIL Liquid Anti-Xa kit) 1-stage chromogenic assay

How am I going to remember these #s????

Therapeutic Drug Levels*

Drug	Dose	C-min (ng/mL) Trough (pre dose)	C-max (ng/mL) 2 – 4 hours post dose
Apixaban	5 mg twice daily	63 (22-177) 50	132 (59-302) 150
Rivaroxaban	20 mg daily	26 (6-87) 30	270 (189-419) 300

*ACL TOP 700 (HemosIL Liquid Anti-Xa kit) 1-stage chromogenic assay

2. Is drug metabolism normal?

- Is the dose correct?
- Can you check a drug level prior to discontinuing?
- Is the patient “hyper-clearing”? (LMHW, dabigatran, edoxaban)
- Are there drug interactions? (CYP 3A4 inducers)
- Is the patient taking the drug appropriately? (Drug absorption, meals, and rivaroxaban)
- Is there altered GI motility? (Gastric bypass or resection)

3. Is the patient compliant?

- Drug levels
- Pill counts
- Pharmacy review
- Recent interruptions for procedures

Patterns of Utilization and Comparative Effectiveness of Treatment Options in Cancer-associated Thrombosis

- OPTUM Labs claims database
- 5100 ***propensity score matched*** Cancer Patients with VTE
  - DOACs 2,512
  - LMWH 1,488
  - Warfarin 1,460
- Cancer types (4 most common)
  - Lung 913
  - Urologic 830
  - Breast 699
  - Colorectal 580

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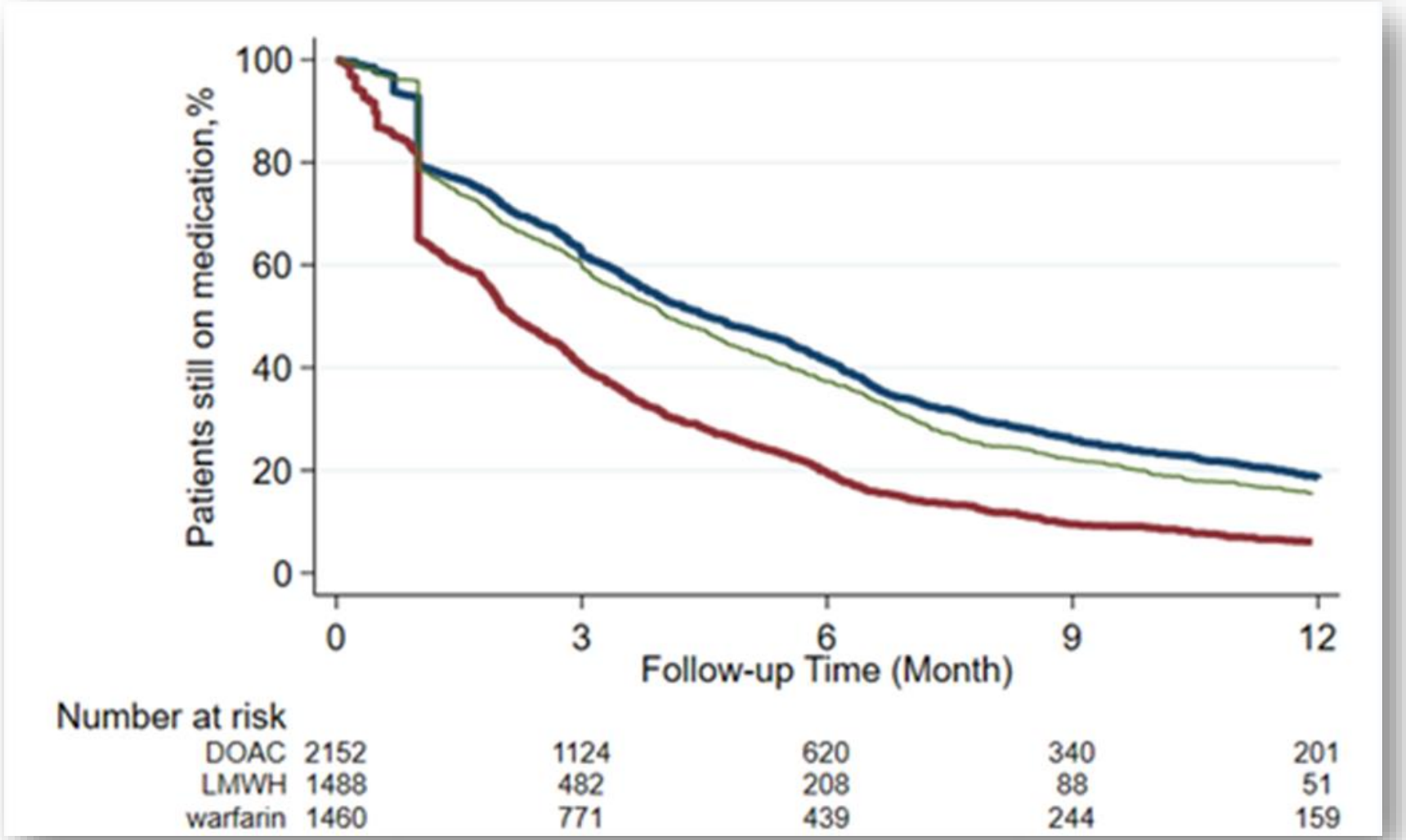
Unpublished data

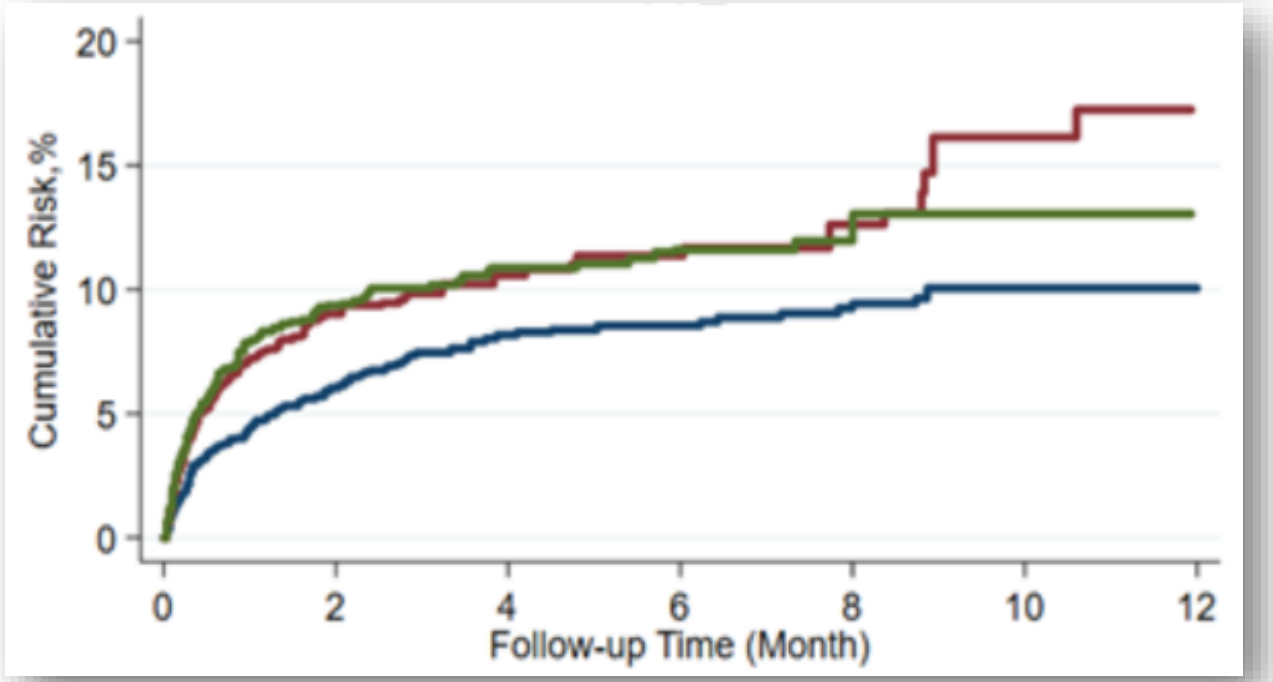
Anticoagulant Adherence over Follow up



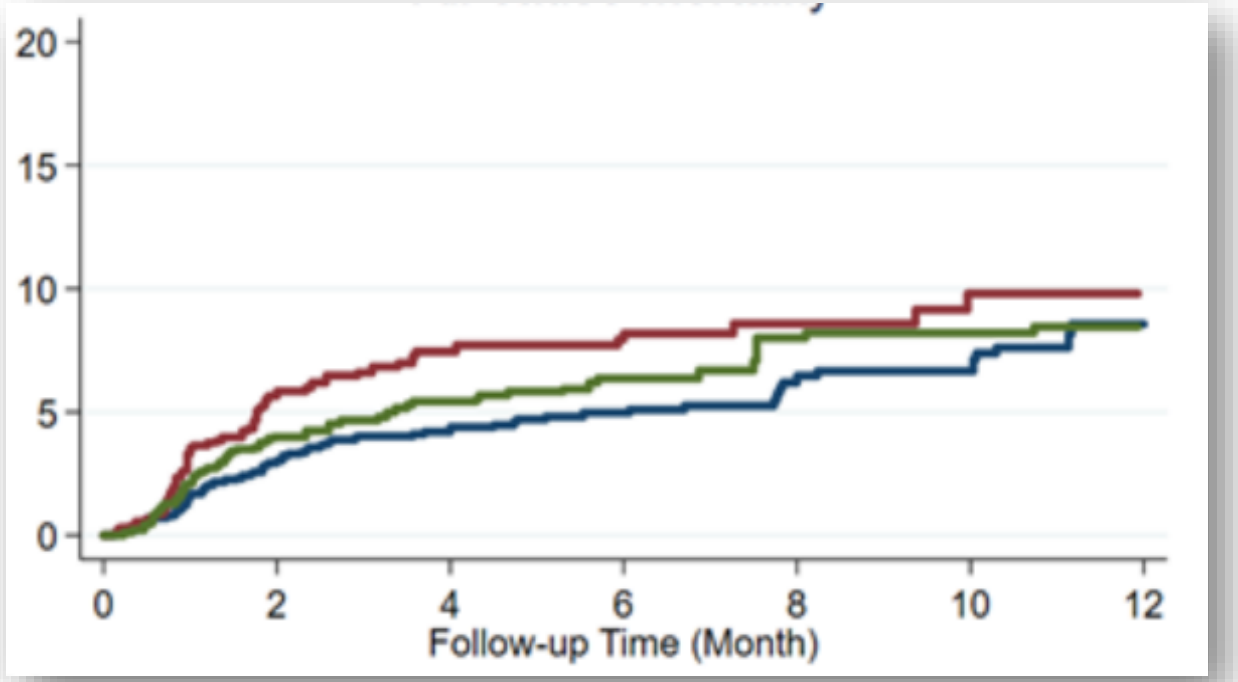
Unpublished data

Efficacy Outcomes in Weighted Cohorts

Venous Thromboembolism Recurrence



All-cause Mortality



Unpublished data

Anticoagulation Satisfaction survey

Cycle (Months)

Cycle*	Fear of bleeding limited participation in vigorous activities	Fear of bleeding limited participation in activities of daily life	Concern for excessive bruising	Limited my diet	Added stress to my life	Was difficult to carry out	Caused me a great deal of worry	Caused me a great deal of irritation	Caused me a great deal of frustration	Was a burden to me	Negatively impacted my quality of life	Confidence that the drug protected me from clots	I am satisfied with my blood thinner
0	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
1	Neutral	Neutral	Favors apixaban	Neutral	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors dalteparin	Favors apixaban
2	Neutral	Neutral	Neutral	Neutral	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Neutral	Neutral	Favors apixaban
3	Neutral	Neutral	Neutral	Neutral	Favors apixaban	Neutral	Favors apixaban	Favors apixaban	Neutral	Favors apixaban	Neutral	Neutral	Favors apixaban
4	Neutral	Neutral	Favors apixaban	Neutral	Neutral	Favors apixaban	Neutral	Favors apixaban	Neutral	Favors apixaban	Neutral	Neutral	Favors apixaban
5	Neutral	Neutral	Favors apixaban	Neutral	Favors apixaban	Favors apixaban	Neutral	Favors apixaban	Neutral	Favors apixaban	Neutral	Neutral	Neutral
6	Neutral	Neutral	Favors apixaban	Neutral	Neutral	Favors apixaban	Neutral	Favors apixaban	Neutral	Favors apixaban	Neutral	Neutral	Neutral

Favors Apix

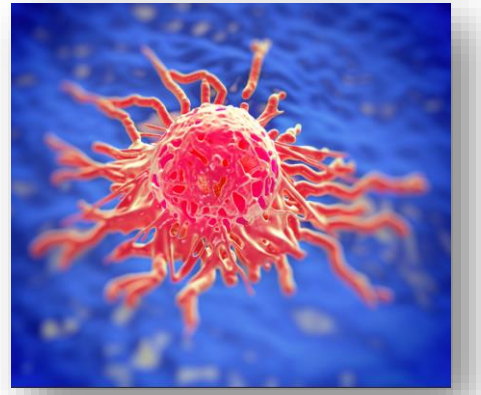
Favors Dalt

Premature discontinuation: Apixaban 6 (4%) vs. Dalteparin 22 (15%), p=0.0012

4. Is there drug specific complications?

- Heparin induced thrombocytopenia
- Antiphospholipid syndrome

Cancer/APS Relationship



Prevalence of APS Abs in Cancer

- 20% have solid or non-solid cancer
- Stomach, colon, prostate, ovary, lung, kidney, liver, breast, lymphoma, leukemia

Prevalence of Cancer in patients with APS Abs

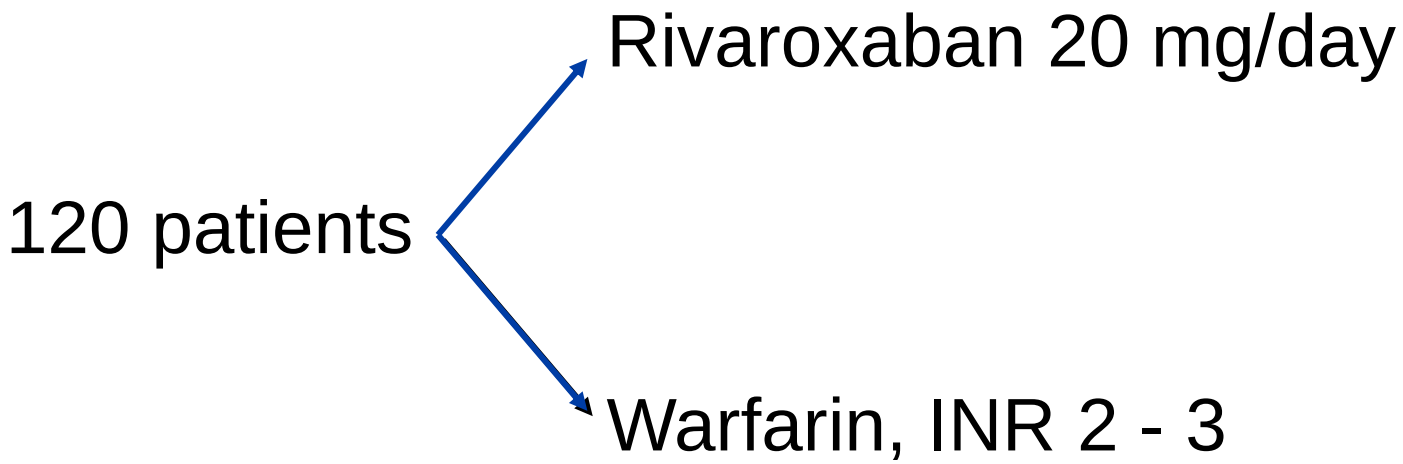
- 20% of APS patients have cancer

Sem Thromb Haemost 2008;282 Br J Cancer 1995;72:447 Haemost 1994;24:175

TRAPS

Rivaroxaban vs. Warfarin in APS

Patients: "***Triple*** positive" APS (ACLA > 40 U, β2GP1 > 40 U, Lupus Anticoagulant)
*(Non-inferiority design, **Sample size 536,** assuming 6% annual event rate)*



1◦ endpoint composite: Thromboembolism, Major bleed, Vascular Death

Blood. 2018;132:1365

Early trial termination!

Outcome, n	"As treated" analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	*P*
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01
Arterial thrombosis	7 (12)	0	—	—
Ischemic stroke	4 (7)	0		
Myocardial infarction	3 (5)	0		
Venous thromboembolism	0	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3
Death	0	0	—	—

Blood. 2018;132:1365

Rivaroxaban vs Warfarin in APS

Spanish Trial

Intension to treat	Rivaroxaban (n=95)	Warfarin (n=95)	P-value
All events	12.6%	6.3%	0.150
Arterial	***11.6%***	***3.2%***	***0.04***
Venous	2.1%	3.2%	0.65
Stroke	10.5%	0%	0.001

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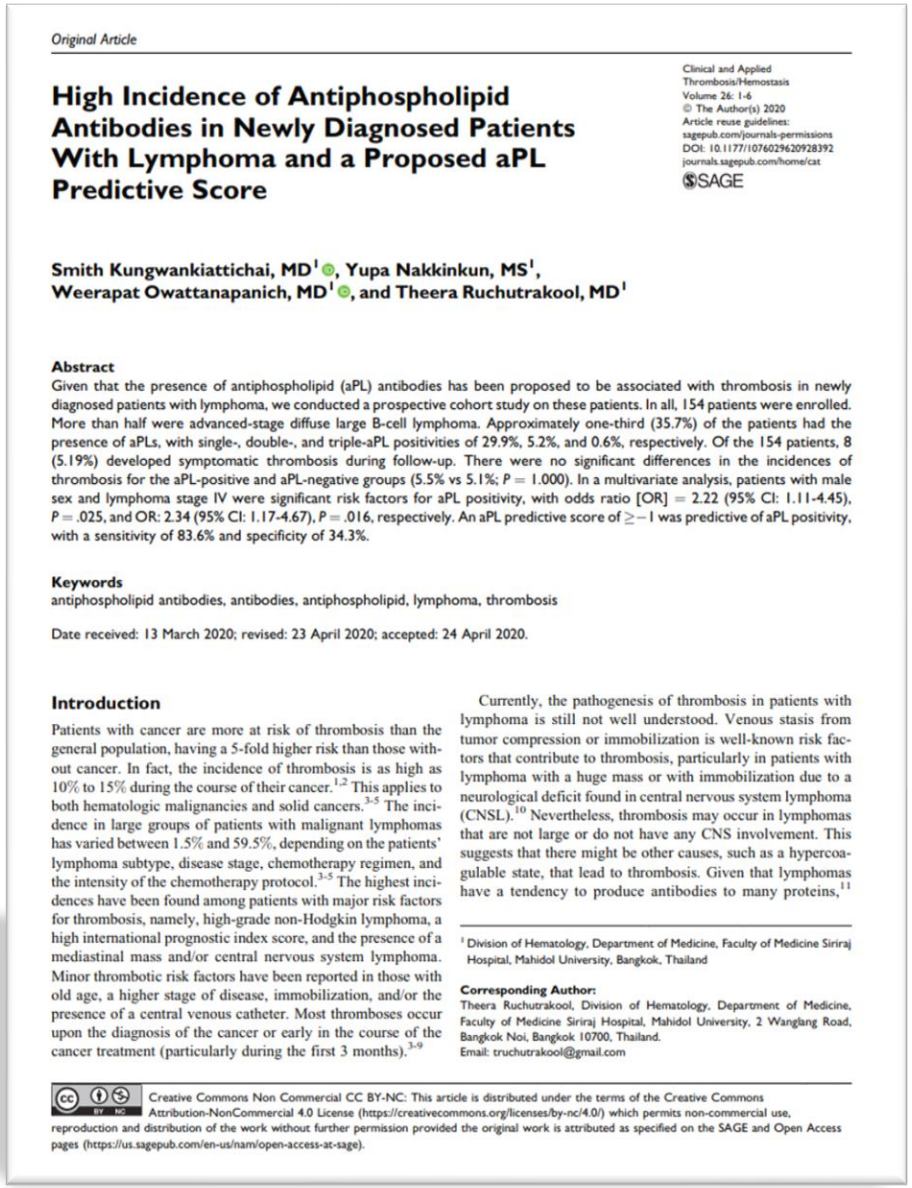
Ann Intern Med 2019; 171:685-694.



Original Article

High Incidence of Antiphospholipid Antibodies in Newly Diagnosed Patients With Lymphoma and a Proposed aPL Predictive Score

Clinical and Applied Thrombosis/Hemostasis
Volume 26: 1-6
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Smith Kungwankiattichai, MD[1], Yupa Nakkinkun, MS[1], Weerapat Owattanapanich, MD[1], and Theera Ruchutrakool, MD[1]

Abstract

Given that the presence of antiphospholipid (aPL) antibodies has been proposed to be associated with thrombosis in newly diagnosed patients with lymphoma, we conducted a prospective cohort study on these patients. In all, 154 patients were enrolled. More than half were advanced-stage diffuse large B-cell lymphoma. Approximately one-third (35.7%) of the patients had the presence of aPLs, with single-, double-, and triple-aPL positivities of 29.9%, 5.2%, and 0.6%, respectively. Of the 154 patients, 8 (5.19%) developed symptomatic thrombosis during follow-up. There were no significant differences in the incidences of thrombosis for the aPL-positive and aPL-negative groups (5.5% vs 5.1%; $P = 1.000$). In a multivariate analysis, patients with male sex and lymphoma stage IV were significant risk factors for aPL positivity, with odds ratio [OR] = 2.22 (95% CI: 1.11-4.45), $P = .025$, and OR: 2.34 (95% CI: 1.17-4.67), $P = .016$, respectively. An aPL predictive score of ≥ -1 was predictive of aPL positivity, with a sensitivity of 83.6% and specificity of 34.3%.

Keywords

antiphospholipid antibodies, antibodies, antiphospholipid, lymphoma, thrombosis

Date received: 13 March 2020; revised: 23 April 2020; accepted: 24 April 2020.

Introduction

Patients with cancer are more at risk of thrombosis than the general population, having a 5-fold higher risk than those without cancer. In fact, the incidence of thrombosis is as high as 10% to 15% during the course of their cancer.[1,2] This applies to both hematologic malignancies and solid cancers.[3-5] The incidence in large groups of patients with malignant lymphomas has varied between 1.5% and 59.5%, depending on the patients' lymphoma subtype, disease stage, chemotherapy regimen, and the intensity of the chemotherapy protocol.[3-5] The highest incidences have been found among patients with major risk factors for thrombosis, namely, high-grade non-Hodgkin lymphoma, a high international prognostic index score, and the presence of a mediastinal mass and/or central nervous system lymphoma. Minor thrombotic risk factors have been reported in those with old age, a higher stage of disease, immobilization, and/or the presence of a central venous catheter. Most thromboses occur upon the diagnosis of the cancer or early in the course of the cancer treatment (particularly during the first 3 months).[3-9]

Currently, the pathogenesis of thrombosis in patients with lymphoma is still not well understood. Venous stasis from tumor compression or immobilization is well-known risk factors that contribute to thrombosis, particularly in patients with lymphoma with a huge mass or with immobilization due to a neurological deficit found in central nervous system lymphoma (CNSL).[10] Nevertheless, thrombosis may occur in lymphomas that are not large or do not have any CNS involvement. This suggests that there might be other causes, such as a hypercoagulable state, that lead to thrombosis. Given that lymphomas have a tendency to produce antibodies to many proteins,[11]

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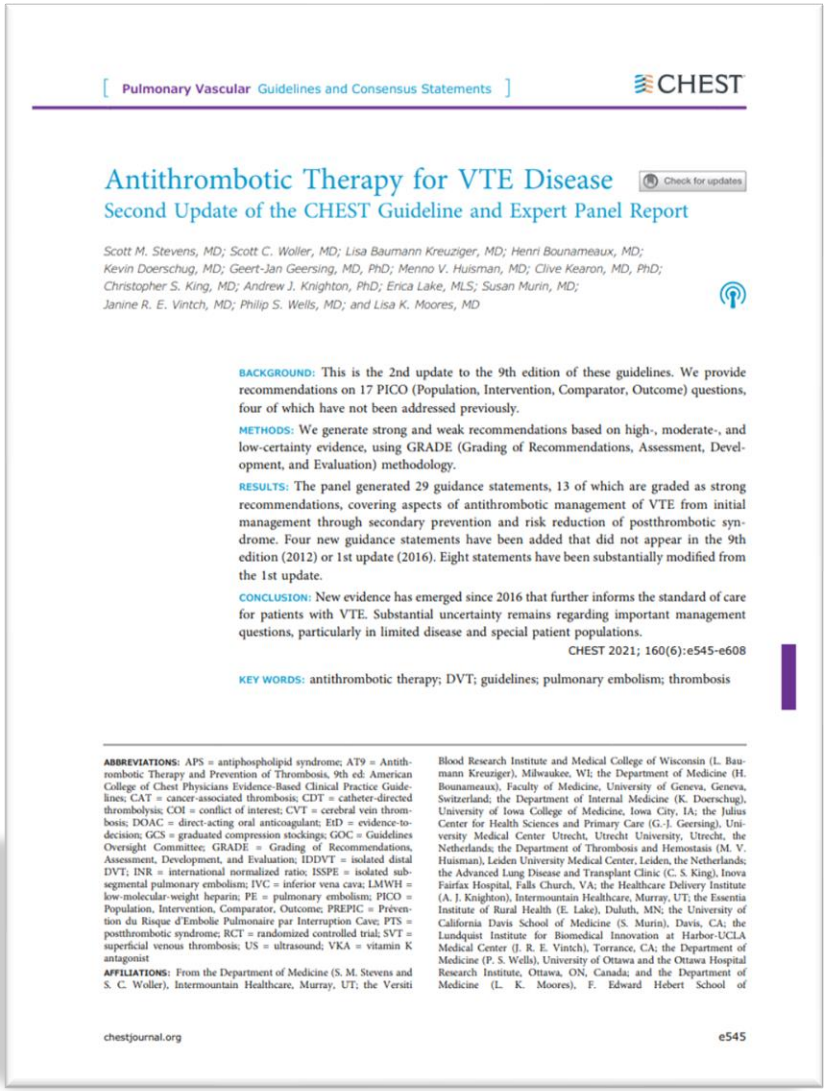
154 Advanced B-cell Lymphoma

35.7% were APS positive

- 29.9% single
- 5.2% double
- 0.6% triple

Thrombosis outcomes

- 5.5% APS positive
- 5.1% APS negative



[Pulmonary Vascular Guidelines and Consensus Statements] CHEST

Antithrombotic Therapy for VTE Disease

Second Update of the CHEST Guideline and Expert Panel Report

Scott M. Stevens, MD; Scott C. Woller, MD; Lisa Baumann Kreuziger, MD; Henri Bounameaux, MD; Kevin Doerschug, MD; Geert-Jan Geersing, MD, PhD; Menno V. Huisman, MD; Clive Kearon, MD, PhD; Christopher S. King, MD; Andrew J. Knighton, PhD; Erica Lake, MLS; Susan Murin, MD; Janine R. E. Vintch, MD; Philip S. Wells, MD; and Lisa K. Moores, MD

BACKGROUND: This is the 2nd update to the 9th edition of these guidelines. We provide recommendations on 17 PICO (Population, Intervention, Comparator, Outcome) questions, four of which have not been addressed previously.

METHODS: We generate strong and weak recommendations based on high-, moderate-, and low-certainty evidence, using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.

RESULTS: The panel generated 29 guidance statements, 13 of which are graded as strong recommendations, covering aspects of antithrombotic management of VTE from initial management through secondary prevention and risk reduction of postthrombotic syndrome. Four new guidance statements have been added that did not appear in the 9th edition (2012) or 1st update (2016). Eight statements have been substantially modified from the 1st update.

CONCLUSION: New evidence has emerged since 2016 that further informs the standard of care for patients with VTE. Substantial uncertainty remains regarding important management questions, particularly in limited disease and special patient populations.

CHEST 2021; 160(6):e545-e608

KEY WORDS: antithrombotic therapy; DVT; guidelines; pulmonary embolism; thrombosis

ABBREVIATIONS: APS = antiphospholipid syndrome; AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; CAT = cancer-associated thrombosis; CDT = catheter-directed thrombolysis; COI = conflict of interest; CVT = cerebral vein thrombosis; DOAC = direct-acting oral anticoagulant; EtD = evidence-to-decision; GCS = graduated compression stockings; GOC = Guidelines Oversight Committee; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; IDDVT = isolated distal DVT; INR = international normalized ratio; ISSPE = isolated subsegmental pulmonary embolism; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PICO = Population, Intervention, Comparator, Outcome; PREPIC = Prévention du Risque d'Embolie Pulmonaire par Interruption Cave; PTS = postthrombotic syndrome; RCT = randomized controlled trial; SVT = superficial venous thrombosis; US = ultrasound; VKA = vitamin K antagonist

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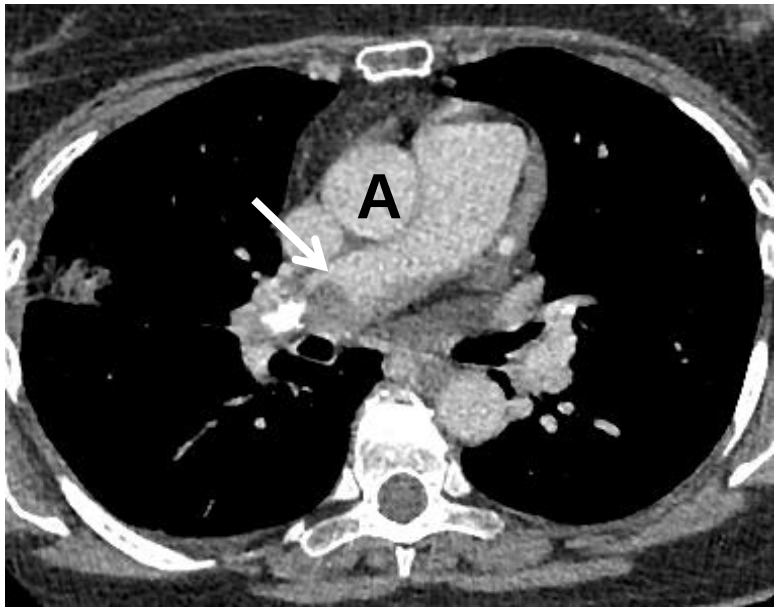
In patients with antiphospholipid syndrome, we suggest ***warfarin*** (Target INR 2.5)

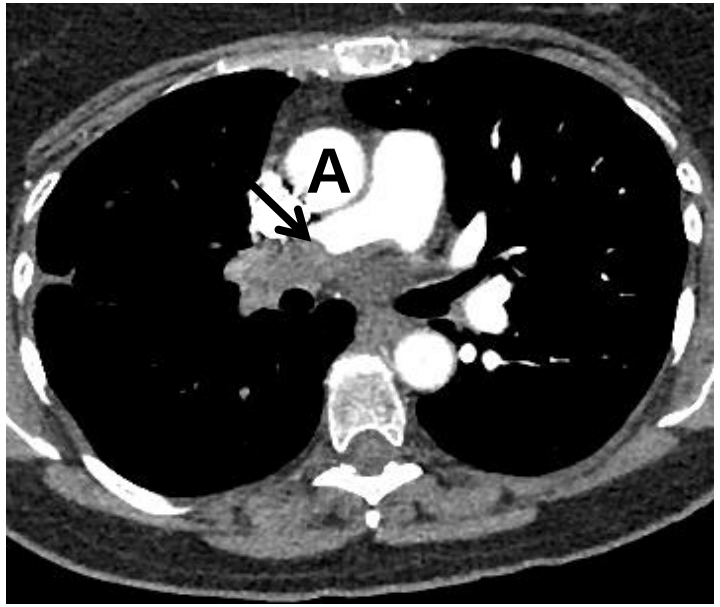
DOACs should be avoided especially if positive for ***lupus anticoagulant***

5. Is the anticoagulant failure due to ***tumor thrombus***?

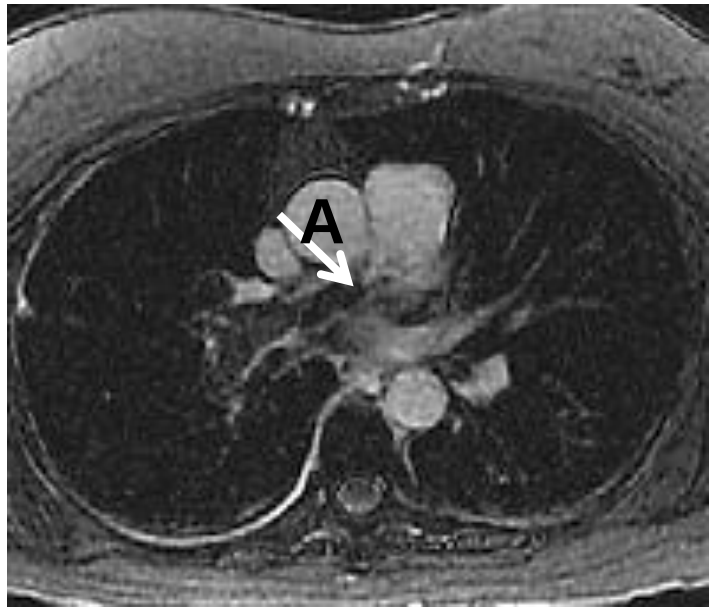
63 year-old female with cough, dyspnea, pleurisy



May
Apixaban



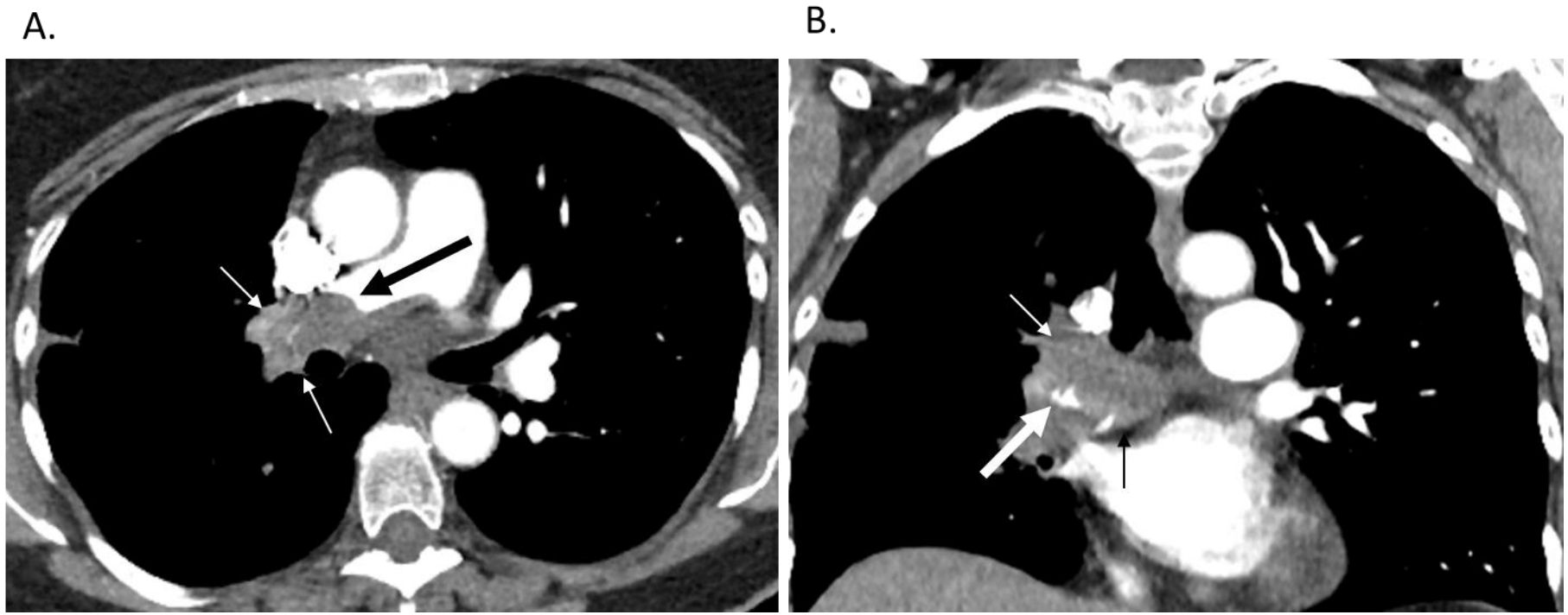
July



August

J Thromb Thrombolysis 2021;52:1129

63 year-old female with cough, dyspnea, pleurisy

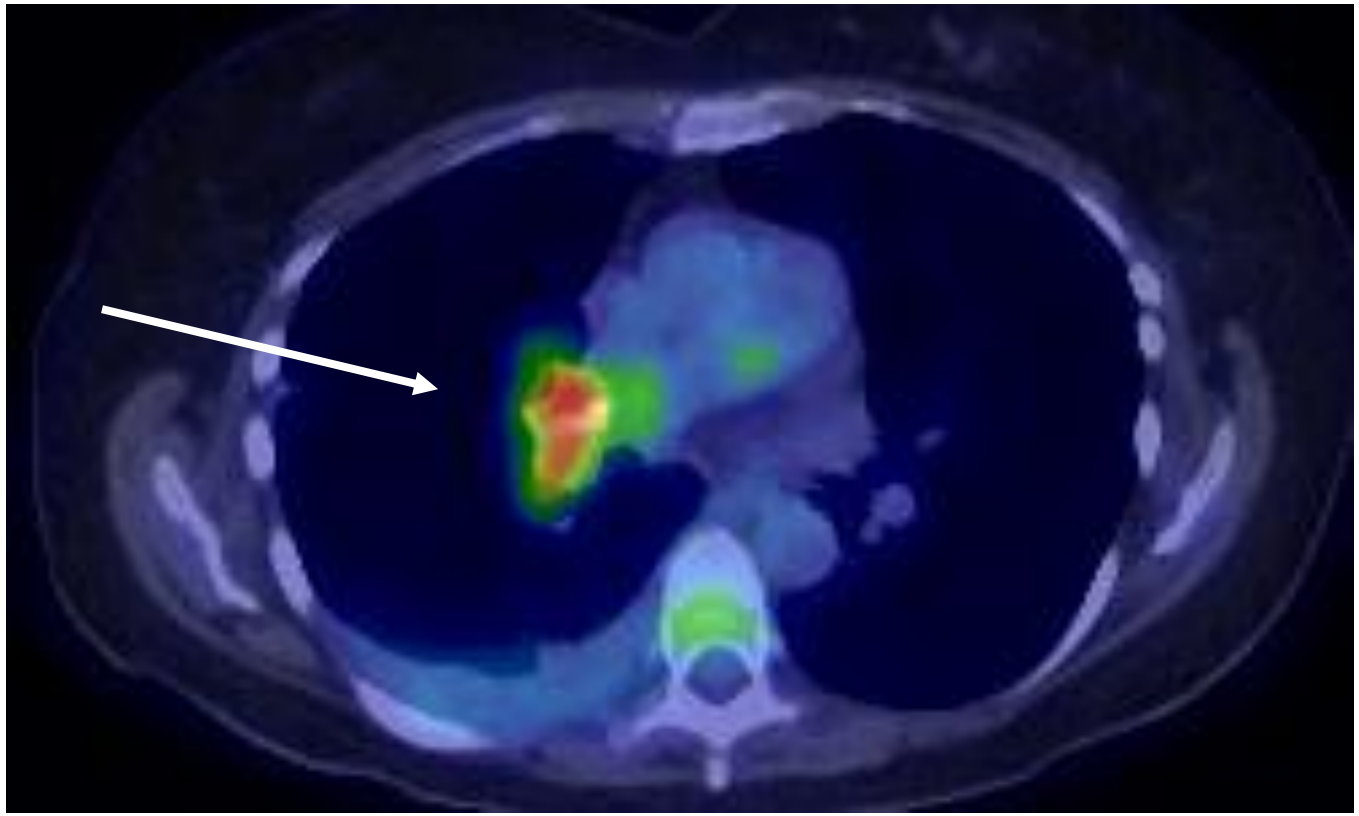


"Wall Eclipsing Sign"

Lesion extends beyond arterial boundary

J Thromb Thrombolysis 2021;52:1129

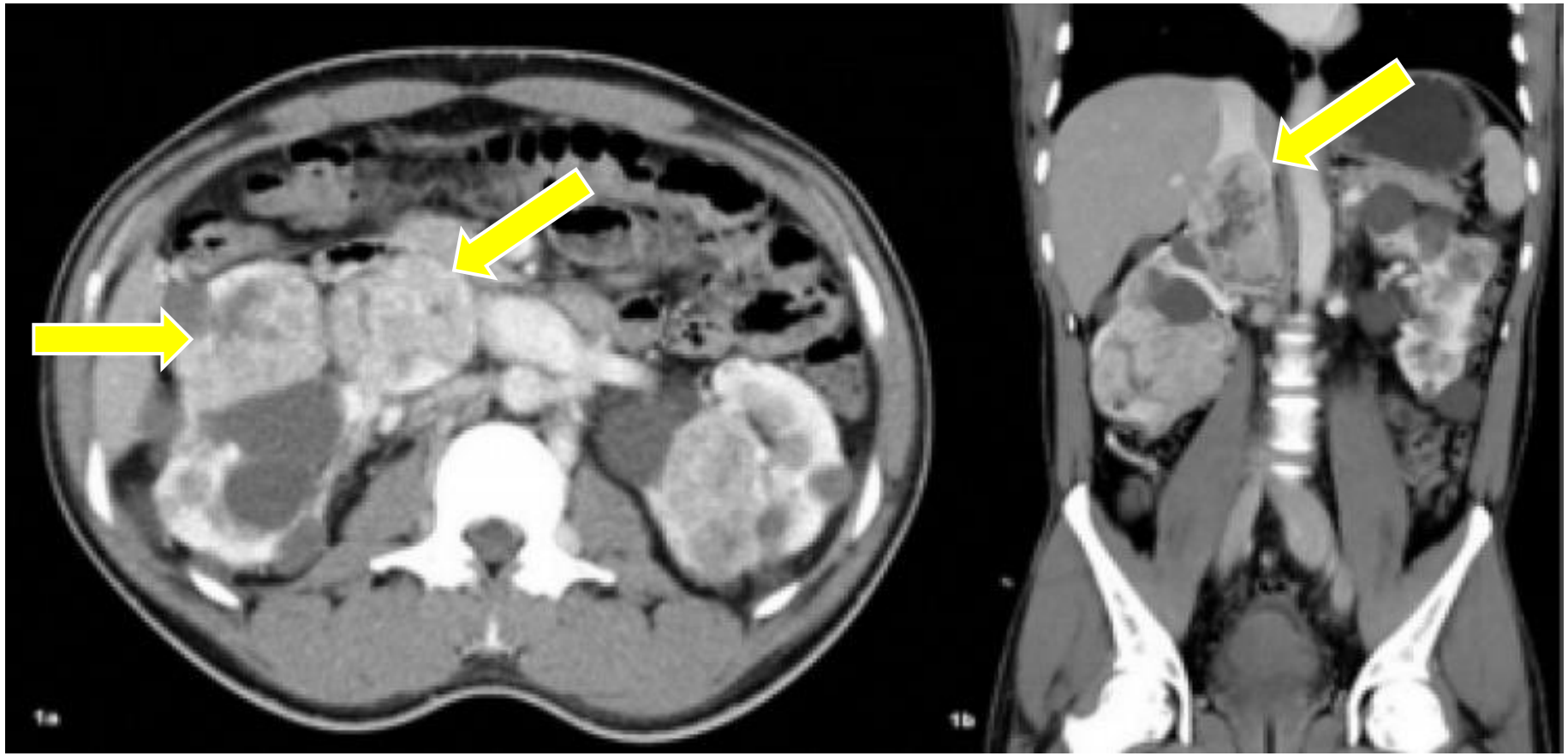
63 year-old female with cough, dyspnea, pleurisy



PET Imaging: ***Pulmonary artery sarcoma***

J Thromb Thrombolysis 2021;52:1129

Renal Cell Carcinoma with "Tumor Thrombus"



TF positive tumor

Int J Urol 2012;9:1-4 Blood 1986 68:394-399

Are there any Risk Prediction Tools of VTE Recurrence among Cancer Patients?

Vascular Medicine

Development of a Clinical Prediction Rule for Risk Stratification of Recurrent Venous Thromboembolism in Patients With Cancer-Associated Venous Thromboembolism

Martha L. Louzada, MD, MSc; Marc Carrier, MD, MSc; Alejandro Lazo-Langner, MD, MSc; Vi Dao, MD; Michael J. Kovacs, MD; Timothy O. Ramsay, PhD; Marc A. Rodger, MD, MSc; Jerry Zhang, BSc; Agnes Y.Y. Lee, MD, MSc; Guy Meyer, MD; Philip S. Wells, MD, MSc

Background—Long-term low-molecular-weight heparin (LMWH) is the current standard for treatment of venous thromboembolism (VTE) in cancer patients. Whether treatment strategies should vary according to individual risk of VTE recurrence remains unknown. We performed a retrospective cohort study and a validation study in patients with cancer-associated VTE to derive a clinical prediction rule that stratifies VTE recurrence risk.

Methods and Results—The cohort study of 543 patients determined the model with the best classification performance included 4 independent predictors (sex, primary tumor site, stage, and prior VTE) with 100% sensitivity, a wide separation of recurrence rates, 98.1% negative predictive value, and a negative likelihood ratio of 0.16. In this model, the score sum ranged between −3 and 3 score points. Patients with a score ≤0 had low risk (≤4.5%) for recurrence and patients with a score >1 had a high risk (≥19%) for VTE recurrence. Subsequently, we applied and validated the rule in an independent set of 819 patients from 2 randomized, controlled trials comparing low-molecular-weight heparin to coumarin treatment in cancer patients.

Conclusions—By identifying VTE recurrence risk in cancer patients with VTE, we may be able to tailor treatment, improving clinical outcomes while minimizing costs. (***Circulation***. **2012;126:448-454.**)

Key Words: cancer ■ clinical prediction rule ■ venous thromboembolism ■ recurrence

For many years, management of venous thromboembolism (VTE) in cancer patients was similar to that for noncancer patients, that is, initial therapy with low-molecular-weight heparin (LMWH) or unfractionated heparin followed by vitamin K antagonists (VKAs) for at least 3 months.[1–4] However, in the early 2000s, Prandoni et al[5] demonstrated a significant increase in VTE recurrence risk in patients with malignancy compared with noncancer patients, with a 1-year cumulative incidence of recurrent VTE of 20.7% for cancer patients and 6.8% for noncancer patients (hazard ratio, 3.2; 95% confidence interval [CI], 1.9–5.4). Therefore, studies were developed that aimed to target a better treatment strategy for this population.[5–8] These data were summarized in a systematic review of randomized, controlled trials (RCTs) that compared VKA versus LMWH for 3 to 6 months to treat cancer-associated venous thrombosis. The study demonstrated a VTE recurrence rate of 13% in patients treated with VKA and 7% in patients treated with LMWH, with similar major bleeding rates of ≈5%.[9] Therefore, the current standard of care for patients with cancer-associated VTE is long-term LMWH.[10–12]

Clinical Perspective on p 454

Nevertheless, the association between VTE recurrence risk and treatment management according to malignancy characteristics is largely unknown. A better understanding of the different malignancy characteristics that may influence the risk of VTE recurrence is needed, so that the practitioner may offer a better tailored treatment approach for the patient with cancer-associated VTE without exposing the patient to an unnecessary risk of bleeding and to the high psychological and financial cost of prolonged use of LMWH. We recently reported a systematic review that suggested that patients of younger age (<65 years old) or with metastatic malignancy or lung malignancies sustain the greatest risk for recurrent

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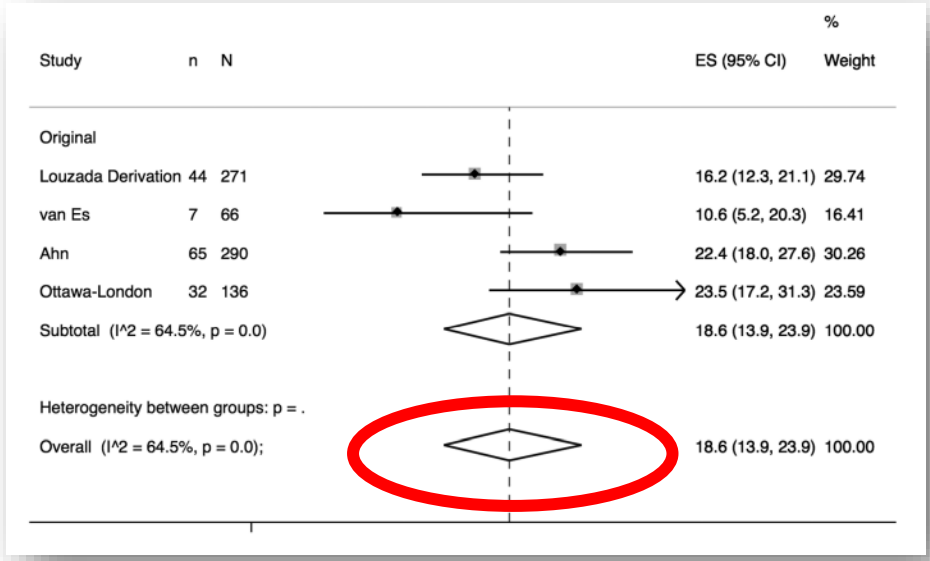
The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.051920/-/DC1.
Correspondence to Martha de Lacerda Louzada, Department of Medicine, Division of Hematology, University of Western Ontario, 800–E3637 Commissioners Rd E, London, ON, Canada, N6A 5W9. E-mail martha.louzada@lhsc.on.ca

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.111.051920**

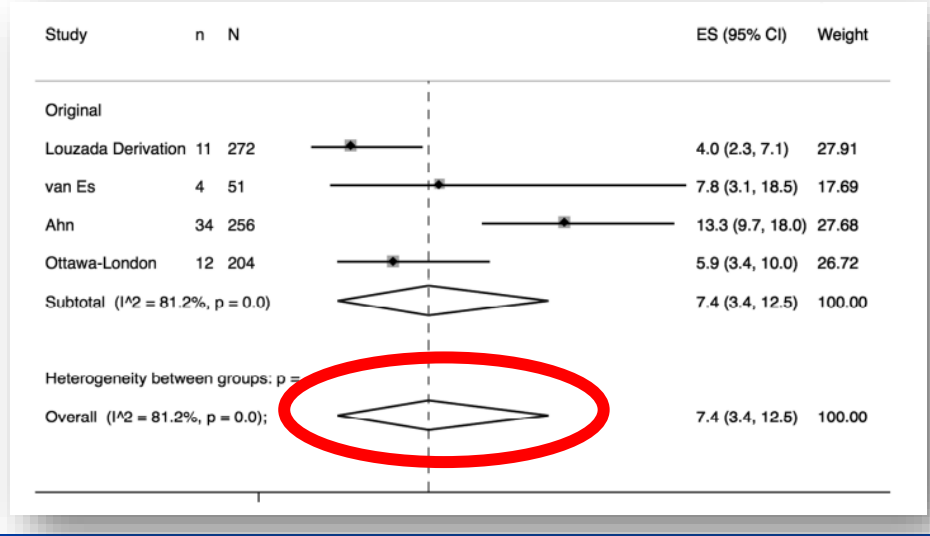
Ottawa Score

Circulation. 2012;126:448

High Risk



Low Risk



Haematol 2020;105:1436

Regular Article

THROMBOSIS AND HEMOSTASIS

Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study

Cheng E. Chee,[1] Aneel A. Ashrani,[2] Randolph S. Marks,[3] Tanya M. Petterson,[4] Kent R. Bailey,[4] L. Joseph Melton III,[5] and John A. Heit[2,5,6]

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Key Points

- VTE recurrence risk in patients with cancer can be stratified by cancer type, stage, stage progression, and presence of leg paresis.
- Patients with cancer at high VTE recurrence risk should be considered for secondary prophylaxis.

Active cancer is the major predictor of venous thromboembolism (VTE) recurrence, but further stratification of recurrence risk is uncertain. In a population-based cohort study of all Olmsted County, Minnesota, residents with active cancer-related incident VTE during the 35-year period from 1966 to 2000 who survived 1 day or longer, we estimated VTE recurrence, bleeding on anticoagulant therapy, and survival and tested cancer and noncancer characteristics and secondary prophylaxis as predictors of VTE recurrence and bleeding, using Cox proportional hazards modeling. Of 477 patients, 139 developed recurrent VTE over the course of 1533 person-years of follow-up. The adjusted 10-year cumulative VTE recurrence rate was 28.6%. The adjusted 90-day cumulative incidence of major bleeding on anticoagulation was 1.9%. Survival was significantly worse for patients with cancer who had recurrent VTE (particularly pulmonary embolism) and with bleeding on anticoagulation. In a multivariable model, brain, lung, and ovarian cancer; myeloproliferative or myelodysplastic disorders; stage IV pancreatic cancer; other stage IV cancer; cancer stage progression; and leg paresis were associated with an increased hazard, and warfarin therapy was associated with a reduced hazard, of recurrent VTE. Recurrence rates were significantly higher for cancer patients with 1 or more vs no predictors of recurrence, suggesting these predictors may be useful for stratifying recurrence risk. (*Blood*. 2014;123(25):3972-3978)

Introduction

Active cancer is associated with a two- to ninefold increased risk for recurrent venous thromboembolism (VTE).[1-8] Moreover, the hazard of death is increased threefold among patients with cancer who have recurrent VTE, suggesting that prevention of VTE recurrence may be important for long-term survival.[9,10] However, patients with cancer also have a high risk for anticoagulant-associated major bleeding,[2,5,11-14] such that secondary prophylaxis for all patients with active cancer and incident VTE may be inappropriate. Independent predictors of VTE recurrence among patients with cancer are uncertain[15]; patient sex; brain cancer among women; lung, gastrointestinal, and genitourinary cancer; myeloproliferative disorders; tumor stage; adenocarcinoma; metastasis; and chemotherapy all have been suggested as predictors of VTE recurrence,[1-5,7,9,15-18] but no studies have comprehensively tested all of these characteristics. To address this important gap in knowledge, we conducted a population-based historical cohort study of patients with active cancer and incident VTE to estimate VTE recurrence, estimate bleeding while receiving anticoagulation therapy, estimate survival after VTE recurrence and bleeding, and test baseline cancer and noncancer characteristics and secondary prophylaxis as potential predictors of VTE recurrence and bleeding.

Methods

Study setting, design, and population

Using the resources of the Rochester Epidemiology Project (see supplemental Appendix, available on the *Blood* Web site),[19] we identified the inception cohort of all Olmsted County, Minnesota, residents with incident deep vein thrombosis (DVT), pulmonary embolism (PE), and/or chronic thromboembolic pulmonary hypertension (CTEPH) during the 35-year period from 1966 to 2000, as previously described.[20,21] This study was confined to residents with active cancer-associated incident VTE during this period, defined as the presence of active cancer (see supplemental Appendix for definition of active cancer) within 92 days before or after the incident VTE event date. We followed each Olmsted County resident with incident VTE and active cancer, conditional on surviving 1 day, forward in time from the onset of incident VTE symptoms or signs to first DVT or PE recurrence (see supplemental Appendix for definition of VTE recurrence), using the patient's complete (inpatient and outpatient) medical record while residing in the community.[8,22] For deceased patients, all autopsy reports and death certificates were reviewed regardless of the location at death. The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. The study was conducted in accordance with the Declaration of Helsinki.

Submitted January 16, 2014; accepted April 22, 2014. Prepublished online as *Blood* First Edition paper, April 29, 2014; DOI 10.1182/blood-2014-01-549733.

The online version of this article contains a data supplement.

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Predicting VTE Recurrence in Cancer Patients

Olmsted County 1966-2000

- 681 incident cases (20% of total)
- DVT 60% PE ± DVT 40%
- 66% had stage III/IV cancer
- 30% mortality within 24 hrs

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Blood 2014;123:3972

Independent predictors of VTE recurrence among patients with active cancer

Characteristic	HR	95% CI
Stage IV Pancreatic	6.38	2.68 – 15.13
Brain	4.57	2.07 – 10.09
Myeloprolif/myelodyspl	3.49	1.59 – 7.68
Ovarian	3.22	1.57 – 6.59
Stage IV cancer	2.85	1.74 – 4.57
Lung	2.73	1.63– 4.55
Cancer stage progression	2.14	1.30 – 3.52

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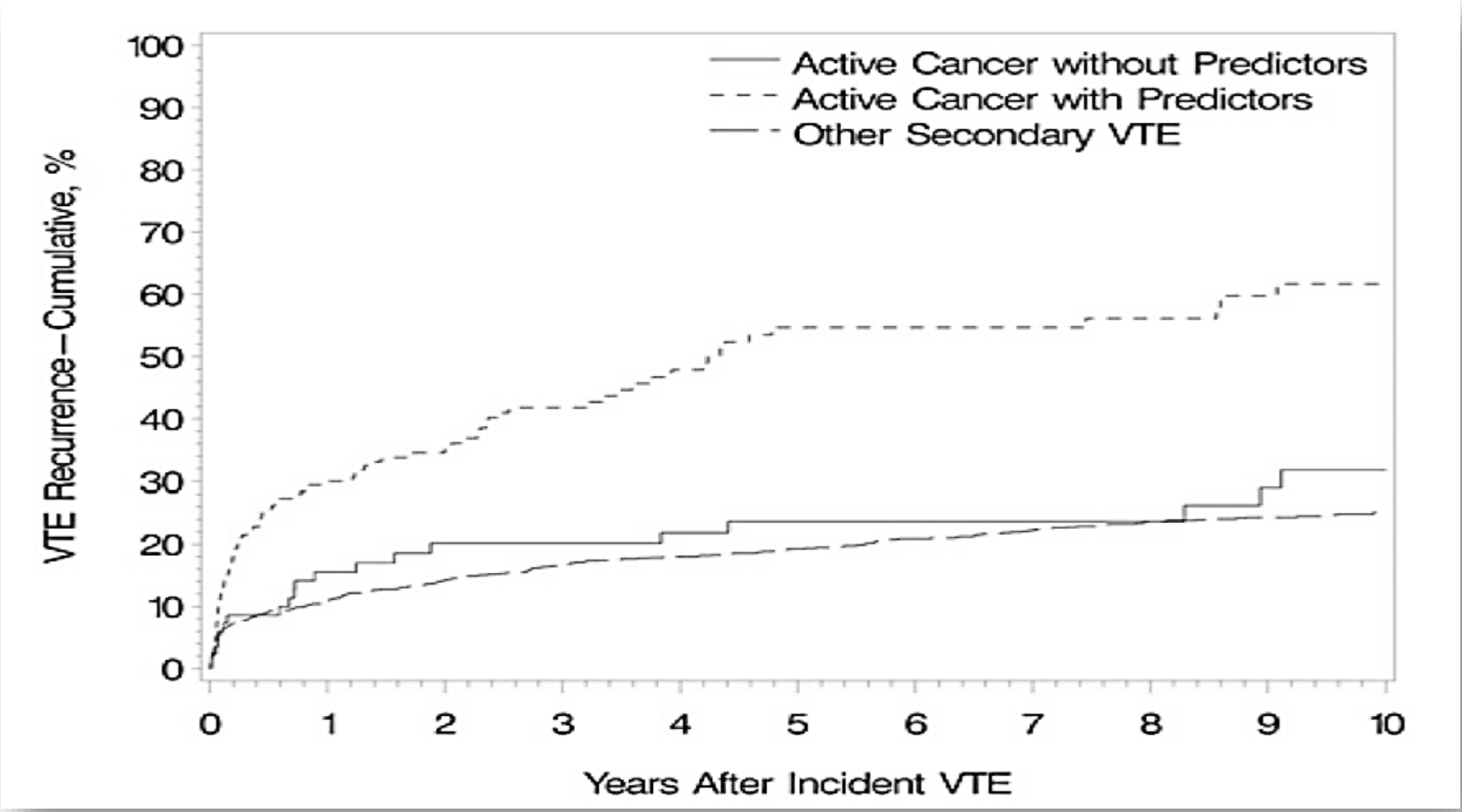
Blood 2014;123:3972

Cumulative incidence of VTE recurrence by VTE predictor status



3-fold increased recurrence rate with any predictor

Blood 2014;123:3972

Treatment Failure: Guidance

- Symptomatic recurrent VTE despite therapeutic anticoagulation (non-LMWH agent) transition to ***therapeutic LMWH***.
- If recurrence on LMWH, ***increase current dose by 25%***.
- ***Avoid IVC filters*** unless anticoagulation is contraindicated (e.g. active bleeding). Then consider retrievable filter.

J Thromb Thrombolysis. 2016;41:81-91

Efficacy: Recurrent VTE

Trial	Outcome	P
HOKUSAI VTE Cancer		0.09
Edoxaban	7.9%	
Dalteparin	11.3%	
SELECT D		<0.05
Rivaroxaban	4.0%	
Dalteparin	11.0%	
ADAM VTE		0.03
Apixaban	0.7%	
Dalteparin	6.3%	
CARAVAGGIO		<0.001 Noninferiority
Apixaban	5.6%	
Dalteparin	7.9%	

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Recurrent VTE despite Anticoagulants

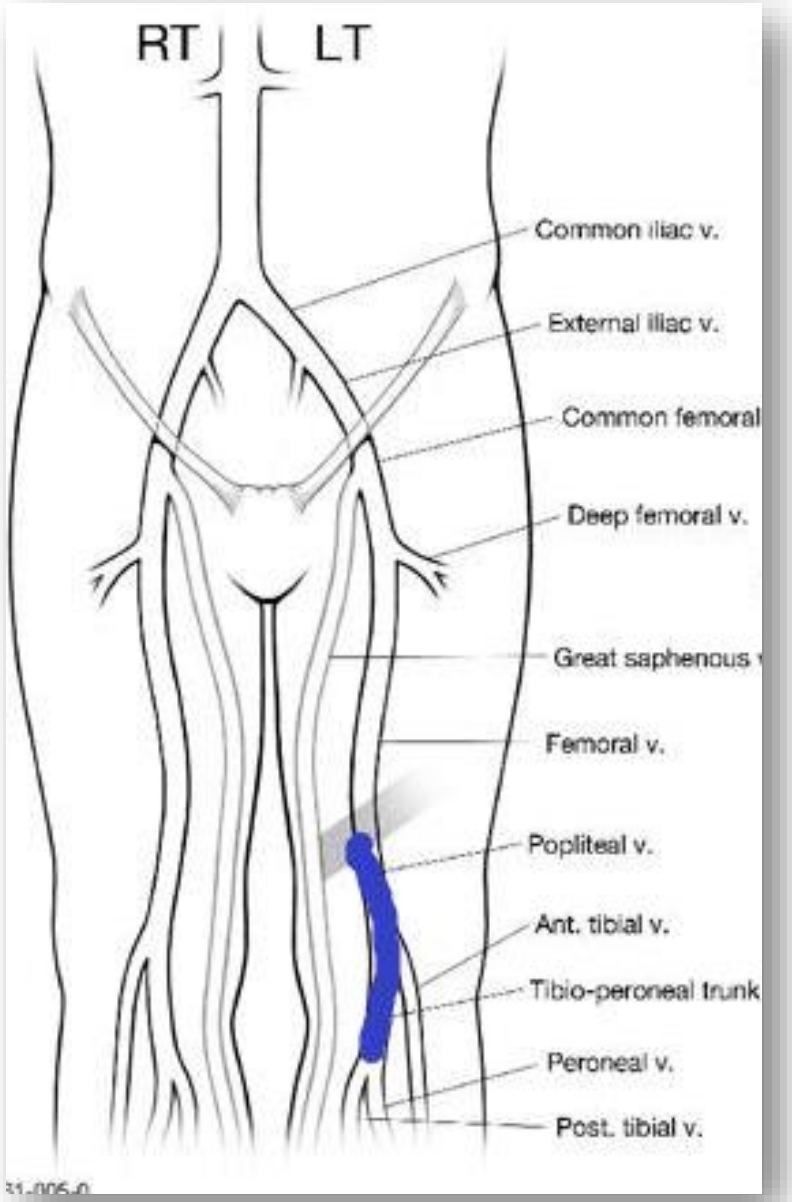
- Follow a ***step-wise approach*** to evaluation
- Change ***antithrombotic strategy*** from what “failed”
- ***Low molecular weight heparin*** is drug of choice
- ……..however ***DOAC data*** may offer an alternative
- Need improved ***risk assessment tools*** for VTE recurrence prediction.

J Thromb Thrombolysis. 2016;41:81-91

49 y/o Male

July	Weight loss and abdominal pain
	EGD: Bulky mass @ GE junction
	Pathology: Poorly differentiated adenocarc
September	Port placed
	FLOT (5 FU, leucovorin, oxaliplatin, docetaxel)
	Develops left leg swelling

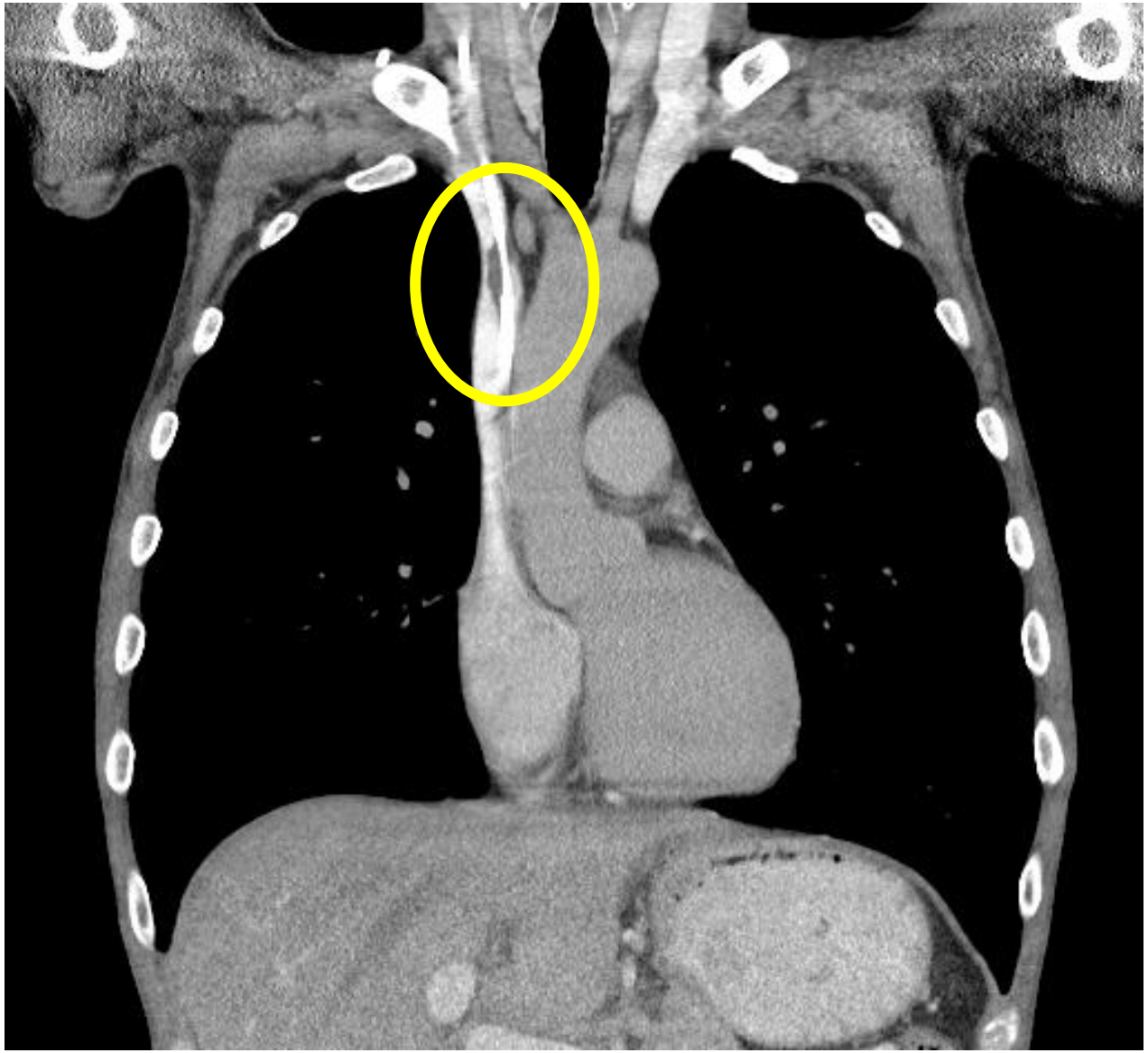
Ultrasound Results



Blue is bad

49 y/o Male

September	Apixaban started
	Recurrent melena: Hgb drop ***10.5 to 6.8***
	Transfusion of 1 unit RBC (x 3)
	“Innumerable iron transfusions”
	Apixaban self discontinued



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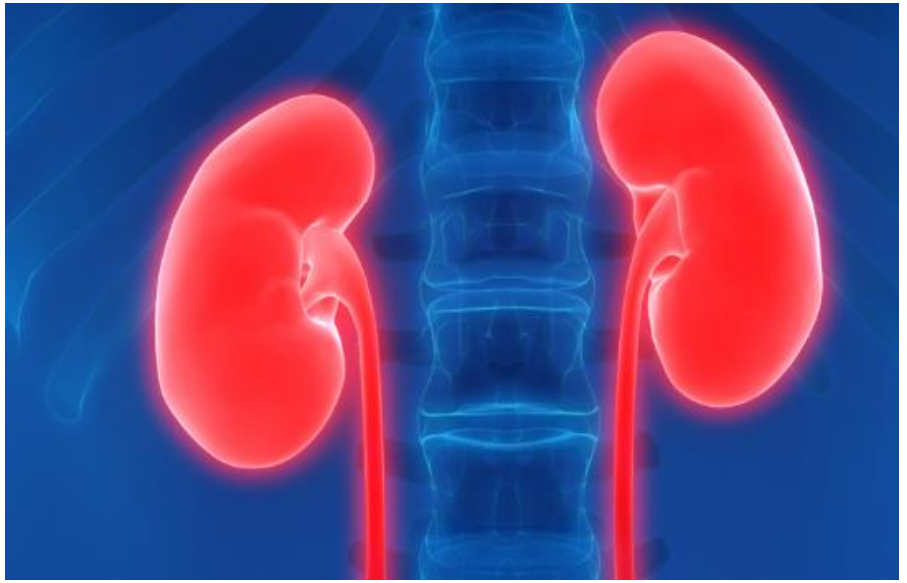
October

49 y/o Male

How would you manage this patient?

1. Restart apixaban
2. Start rivaroxaban
3. Start Enoxaparin
4. IVC filter

Factors Contributing to ***Major Bleeding*** in Cancer



What is the ***risk of major bleeding*** on anticoagulants in cancer patients?

Risk of Major Bleeding: Oral Agents

Agent	Trial	Trial Duration (days)	Major Bleed (%)
Edoxaban	Hokusai Cancer VTE	365	6.9%
Rivaroxaban	SELECT D	180	4%
Apixaban	CARAVAGGIO/ADAM	180	0 – 3.8%
Warfarin	CLOT	180	4%
	CATCH	127	2.4%

Risk of Major Bleed: Parenterals

Agent	Trial	Trial Duration (days)	Major Bleed (%)
Dalteparin	Hokusai Cancer VTE	365	4.0%
	SELECT D	180	6%
	CARAVAGGIO	180	4.0%
	ADAM VTE	180	1.4%
	CLOT	180	6%
Tinzaparin	CATCH	160	2.7%

Let's summarize Major Bleed Rates

- **DOACs:** 4% at 6 months (Riva),
  0 – 4% at 6 months (Apixa)
  7% at 1 year (Edoxa)
- **Warfarin:** ~ 0.6% rate per month
- **LMWH:** 4-6% at 6 - 12 months

What are the

Consequences of major bleeding

in cancer patients?

Survival Implications of Bleeding

- 1,812 cancer patients with VTE receiving anticoagulation
- 98 patients with major bleeding (5.4%)

  Hazard Ratio for ***Mortality 1.82*** (95% CI 1.41 – 2.31) p<0.001

- 104 patients with clinically relevant nonmajor bleeding (5.7%)

  Hazard Ratio for Mortality 1.38 (95% CI 1.05 – 1.81) p<0.019

Thromb Haemost 2022 (in Press)

Survival Implications of Bleeding

- Predictors of Bleeding outcomes:
  - High BMI ***increased major bleeding risk*** (per kg):

    HR 1.01 (1.00 – 1.01)

  - High Ottawa scores ***decreased major bleeding*** risk:

    HR 0.66 (0.46 – 0.96)

  - Apixaban treatment ***decreased major bleeding*** risk:

    HR 0.62 (0.45 – 0.84)

Survival Implications of Bleeding

- Low molecular weight heparin use (n=583) and adverse outcomes:
  - Major bleeding and mortality

    HR 2.00 (1.41 – 2.83) p<0.0001

  - Any bleeding (combined major and CRNMB) and mortality

    HR 1.70 (1.26 – 2.31)

  - Neither CRNMB nor VTE recurrence impacted mortality with LMWH

Where does ***major bleeding occur*** in cancer patients?

Bleeding Location

	Major	Clin Rel Non-Major
Gastrointestinal	***46 (46.9%)***	***32 (30.8%)***
Urologic	***11 (11.2%)***	***27 (26.0%)***
Intramuscular	8 (8.2%)	4 (3.8%)
Ear, nose, throat	2 (2.0%)	21 (20.2%)
Oral	1 (1.0%)	2 (1.9%)
Gynecological	2 (2.0%)	2 (1.9%)
Post procedural	1 (1.0%)	1 (1.0%)
Intracranial	7 (7.1%)	0 (0.0%)
Pulmonary	0 (0.0%)	3 (2.9%)
Cutaneous	0 (0.0%)	3 (2.9%)
Second Bleed	***5 (5.1%)***	***5 (4.8%)***
Fatal Bleed	***5 (5.1%)***	***0 (0.0%)***

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Thromb Haemost 2022 (in Press)

How do ***anticoagulants*** impact ***GI bleeding*** in cancer patients?

GI Bleeding, DOACs and LMWH

	DOAC	Dalteparin
CARAVAGGIO (Apix)		
UGI	**0.9%**	**1.0%**
LGI	**1.0%**	**0.7%**
HOKUSAI (Edox)		
UGI	**3.3%**	**0.6%**
LGI	**0.6%**	**0.6%**
SELECT D (Riva)		
UGI	**2.4%**	**2.0%**
LGI	**0.5%**	**0%**

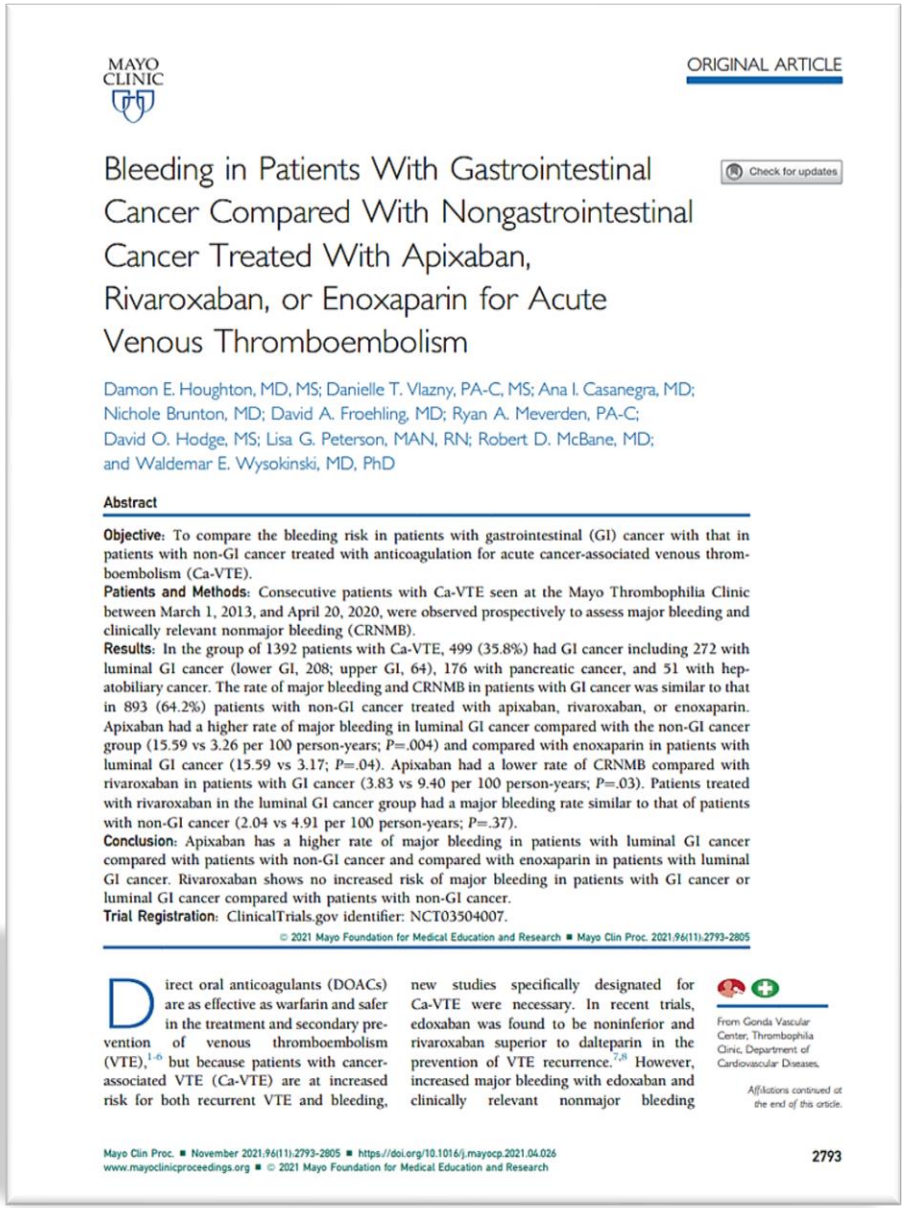
Guideline Statements

- LMWH preferred for ***luminal GI tumors***, GU tumors, or active GI mucosal ulcers, gastritis, esophagitis, or colitis.

ISTH J Thromb Haemost 2018;16:1891

- There is an increase in major bleeding risk with DOACs, particularly observed in ***GI and potentially genitourinary malignancies***. Caution with DOACs is also warranted in other settings with high risk for mucosal bleeding.

ASCO J Clin Oncol 2020;38:496



MAYO CLINIC

ORIGINAL ARTICLE

Bleeding in Patients With Gastrointestinal Cancer Compared With Nongastrointestinal Cancer Treated With Apixaban, Rivaroxaban, or Enoxaparin for Acute Venous Thromboembolism

Check for updates

Damon E. Houghton, MD, MS; Danielle T. Vlazny, PA-C, MS; Ana I. Casanegra, MD; Nichole Brunton, MD; David A. Froehling, MD; Ryan A. Meverden, PA-C; David O. Hodge, MS; Lisa G. Peterson, MAN, RN; Robert D. McBane, MD; and Waldemar E. Wysokinski, MD, PhD

Abstract

Objective: To compare the bleeding risk in patients with gastrointestinal (GI) cancer with that in patients with non-GI cancer treated with anticoagulation for acute cancer-associated venous thromboembolism (Ca-VTE).

Patients and Methods: Consecutive patients with Ca-VTE seen at the Mayo Thrombophilia Clinic between March 1, 2013, and April 20, 2020, were observed prospectively to assess major bleeding and clinically relevant nonmajor bleeding (CRNMB).

Results: In the group of 1392 patients with Ca-VTE, 499 (35.8%) had GI cancer including 272 with luminal GI cancer (lower GI, 208; upper GI, 64), 176 with pancreatic cancer, and 51 with hepatobiliary cancer. The rate of major bleeding and CRNMB in patients with GI cancer was similar to that in 893 (64.2%) patients with non-GI cancer treated with apixaban, rivaroxaban, or enoxaparin. Apixaban had a higher rate of major bleeding in luminal GI cancer compared with the non-GI cancer group (15.59 vs 3.26 per 100 person-years; $P=.004$) and compared with enoxaparin in patients with luminal GI cancer (15.59 vs 3.17; $P=.04$). Apixaban had a lower rate of CRNMB compared with rivaroxaban in patients with GI cancer (3.83 vs 9.40 per 100 person-years; $P=.03$). Patients treated with rivaroxaban in the luminal GI cancer group had a major bleeding rate similar to that of patients with non-GI cancer (2.04 vs 4.91 per 100 person-years; $P=.37$).

Conclusion: Apixaban has a higher rate of major bleeding in patients with luminal GI cancer compared with patients with non-GI cancer and compared with enoxaparin in patients with luminal GI cancer. Rivaroxaban shows no increased risk of major bleeding in patients with GI cancer or luminal GI cancer compared with patients with non-GI cancer.

Trial Registration: ClinicalTrials.gov identifier: NCT03504007.

 ■ Mayo Clin Proc. 2021;96(11):2793-2805

Direct oral anticoagulants (DOACs) are as effective as warfarin and safer in the treatment and secondary prevention of venous thromboembolism (VTE),[1-6] but because patients with cancer-associated VTE (Ca-VTE) are at increased risk for both recurrent VTE and bleeding, new studies specifically designated for Ca-VTE were necessary. In recent trials, edoxaban was found to be noninferior and rivaroxaban superior to dalteparin in the prevention of VTE recurrence.[7,8] However, increased major bleeding with edoxaban and clinically relevant nonmajor bleeding

From Gonda Vascular Center, Thrombophilia Clinic, Department of Cardiovascular Diseases.

Affiliations continued at the end of this article.

Mayo Prospective Registry

- 1392 Cancer patients
  - **Gastrointestinal: 499**
    - Luminal: 272
    - Pancreatic: 176
    - Hepatobiliary: 51
  - **Non-Gastrointestinal: 893**

- **Outcomes assessed @ 3, 6 month**

MAYO CLINIC

Mayo Clin Proc. 2021;96:2793

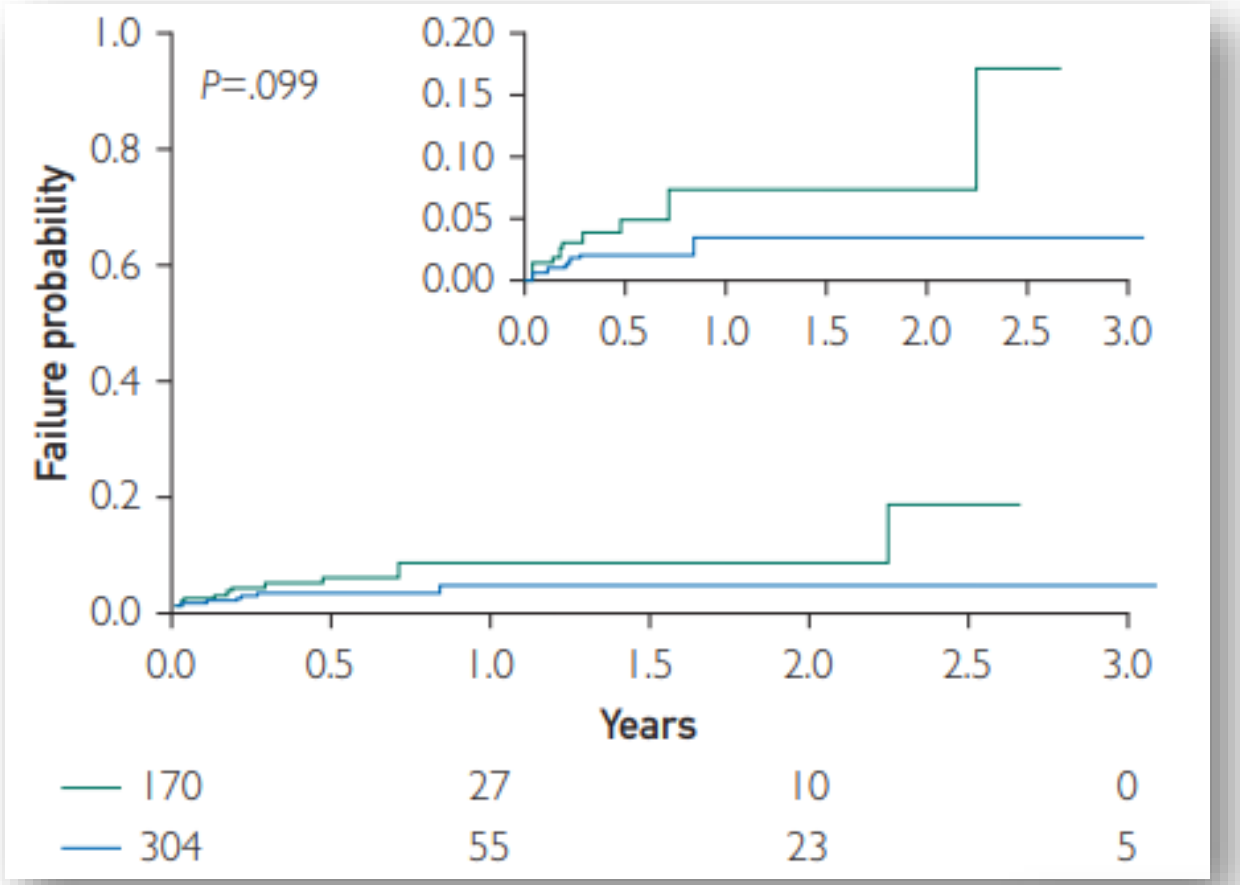
Major Bleeding: GI vs. Non-GI cancers

Events /100 person-yrs	Cancer Site		p - value
	All GI	Non-GI	
Apixaban	9.0	3.3	0.10
Rivaroxaban	5.2	4.9	0.98
Enoxaparin	6.6	9.8	0.27

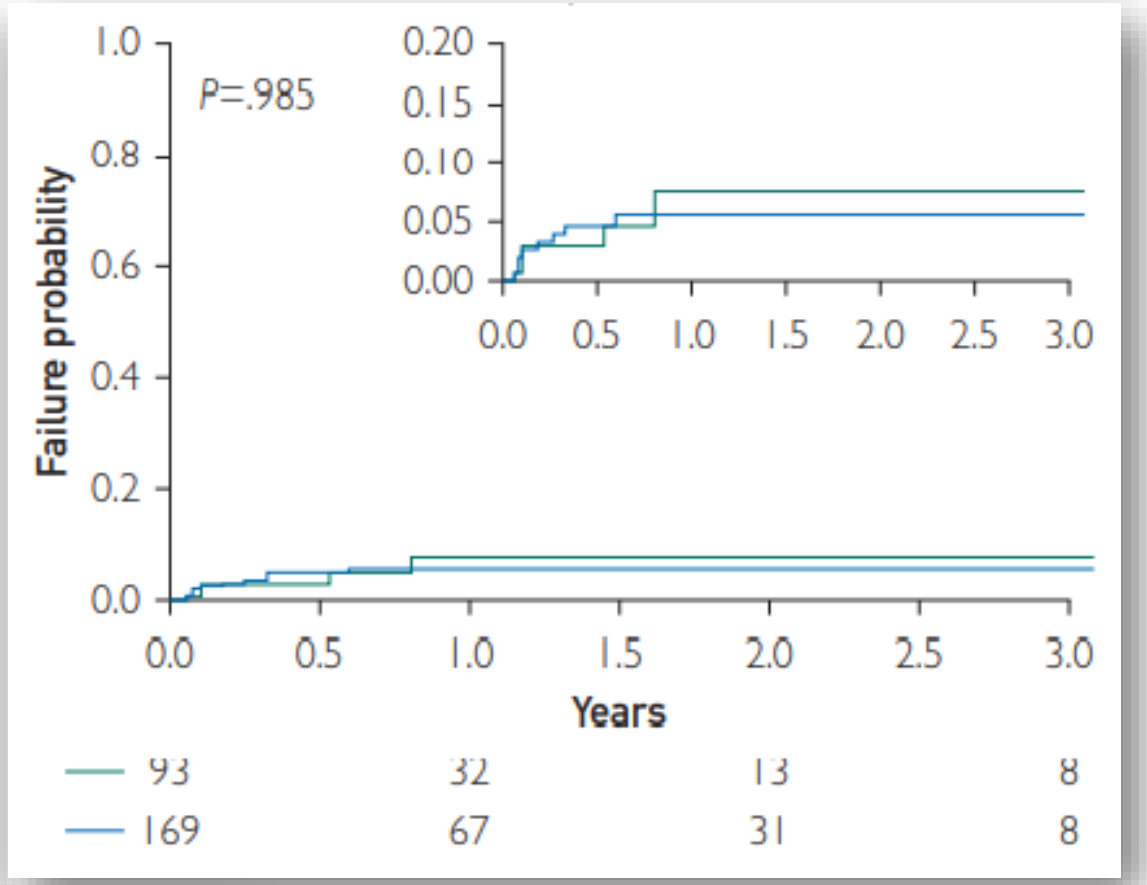
No difference in major bleeding between GI and Non-GI cancer sites

Major Bleeding: GI vs. Non-GI cancers

Apixaban



Rivaroxaban



Gastrointestinal cancer
Non-gastrointestinal cancer

Mayo Clin Proc. 2021;96:2793

Major Bleeding: Luminal GI vs. Non-GI

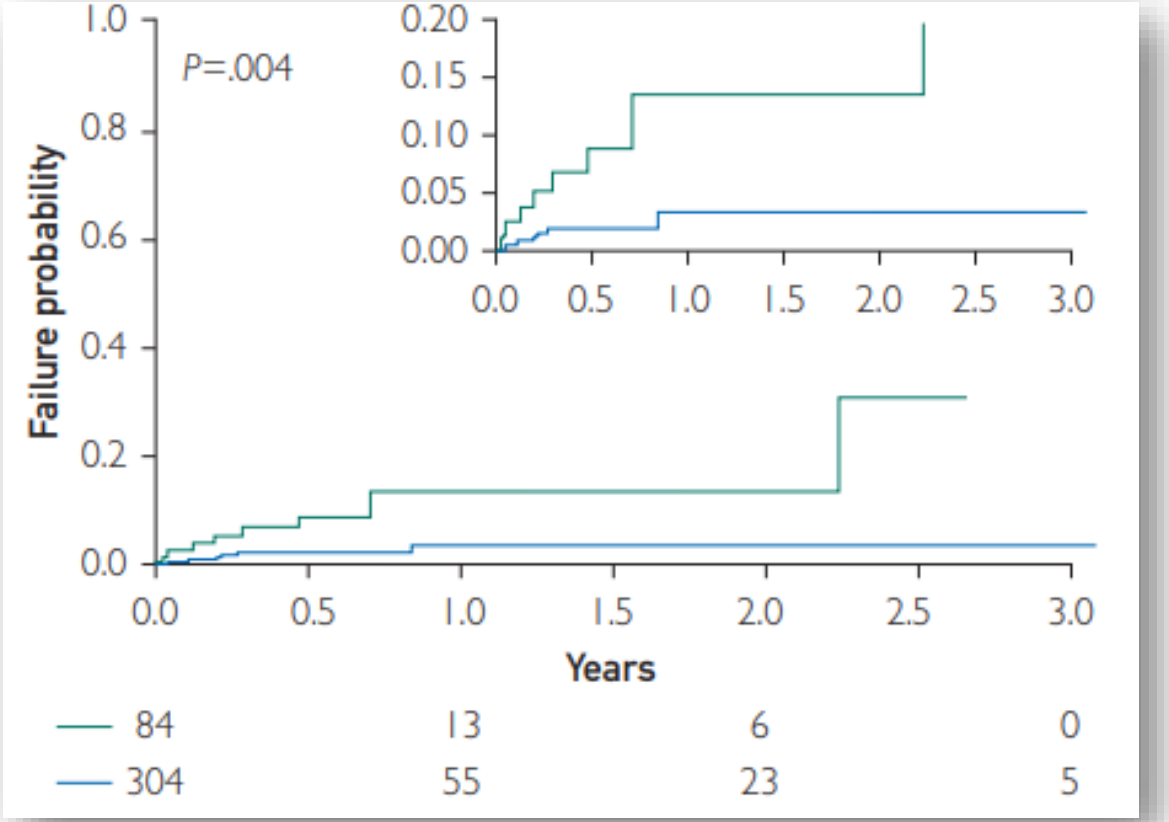
Events /100 person-yrs	Cancer Site		p - value
	Luminal	Non-GI	
Apixaban	**15.6**	**3.3**	**0.004**
Rivaroxaban	2.0	4.9	0.37
Enoxaparin	3.2	9.8	0.08

Luminal tumors experienced significantly greater major bleeding with ***apixaban***.

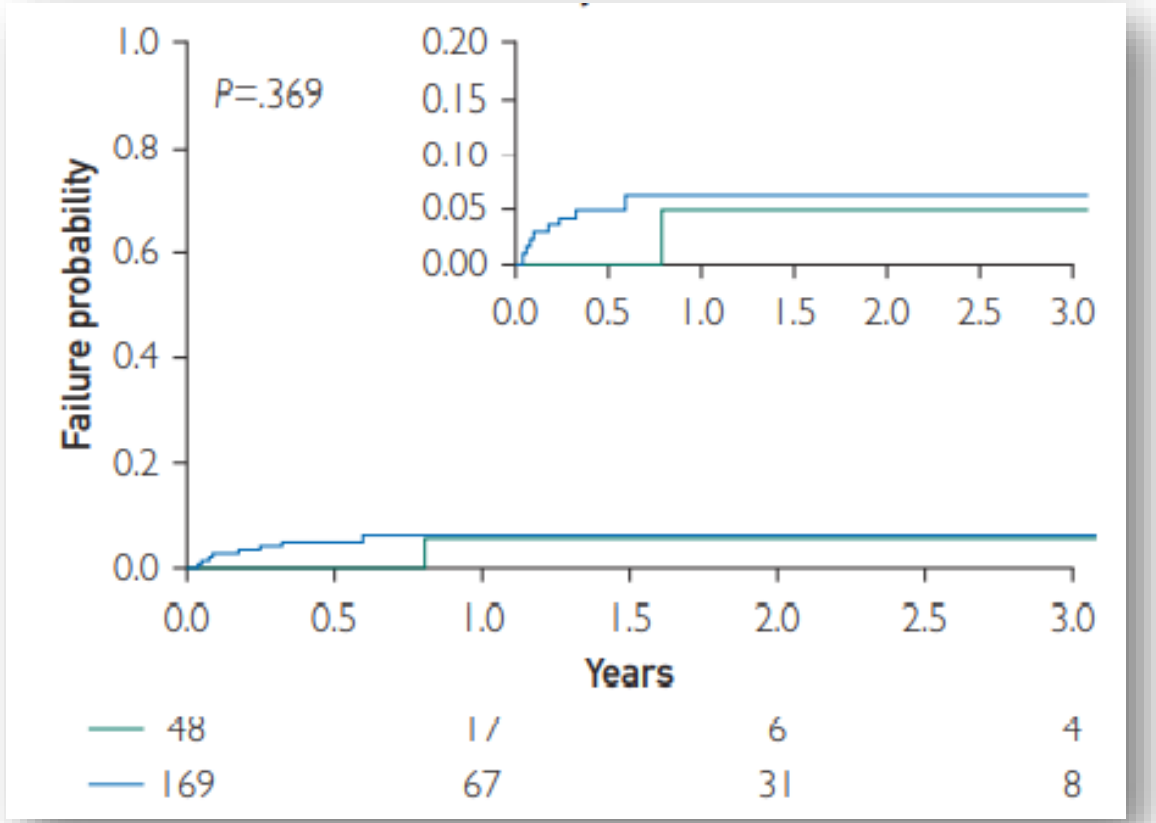
Mayo Clin Proc. 2021;96:2793

Luminal GI vs. Non-GI

Apixaban



Rivaroxaban



Luminal gastrointestinal cancer
Non-gastrointestinal cancer

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Mayo Clin Proc. 2021;96:2793

Major Bleeding Specifics

Apixaban group

170 GI cancers (84 luminal)

- 9 major bleeds
- ***all from GI luminal tumor***
- ***No fatal GI bleeding***

Major Bleeding Specifics

Rivaroxaban group

93 GI cancers (48 luminal tumors)

- 5 major GI bleeds
- ***1 bled from GI luminal tumor***
- ***No fatal GI bleeding***

Major Bleeding Specifics

Enoxaparin group

189 GI cancers (108 luminal tumors)

- ***8 of 11*** major bleeds from ***GI source***
- ***None*** of the patients with ***upper GI luminal tumor*** had a major bleed
- ***3*** major bleeds were from ***lower GI luminal tumor***
- ***No fatal GI bleeding***

Mayo Clin Proc. 2021;96:2793

Go to the Supplement!

Bleeding	apixaban		rivaroxaban		enoxaparin		Total
	GI cancer N=170	non-GI N=304	GI cancer N=93	non-GI N=169	GI cancer N=189	non-GI N=305	N=1230
Major bleeding, n (%)	9 (5.3)	7 (2.3)	5 (5.4)	9 (5.3)	11 (5.8)	23 (7.5)	64 (5.2)
Fatal bleeding, n	0	1	0	1	0	1	3
Location, n							
Gastrointestinal	9	2	5	4	8	4	32
Genitourinary	0	0	0	3	0	4	7
Intramuscular	0	0	0	0	2	6	8
Epistaxis	0	1	0	0	0	0	1
Menorrhagia	0	0	0	0	0	2	2
Surgical site	0	0	0	0	0	1	1
Other	0	4	0	2	1	6	13

25% of patients on antiplatelet therapy
PPI use?

Mayo Clin Proc. 2021;96:2793

Let's Summarize!

- GI bleeding is an issue for ***all anticoagulants*** (including all DOACs).
- GI bleeding is an issue for ***all cancers*** (not just those with luminal tumors).

Let's Summarize!

- Houghton publication provides important ***"real world"*** (but non-randomized) dataset.
- High proportion on ***antiplatelet agents*** (25%; which could be stopped).
- ***PPI therapy*** may improve upper GI bleeding rates.
- GI bleeding outcomes are important but ***non-fatal***.
- Regardless of anticoagulant chosen, it remains important to ***monitor these patients carefully***.

How should we ***Manage*** these patients?

Step-wise approach

Step 1. Has there truly been a major bleed?

- Many causes of anemia in cancer patients apart from bleeding
  - Nutritional
  - Phlebotomy
  - Procedural
  - Bone marrow failure

Bleeding Definitions

Major bleeding

- ***Overt bleeding*** plus drop in hgb ≥ 2 g/dL; transfusion ≥ 2 units or
- ***Bad bleeding:*** intracranial, intraspinal/epidural, intraocular, retroperitoneal, pericardial, intraarticular, intramuscular with compartment syndrome, or fatal bleeding

MAYO CLINIC

J Thromb Haemost. 2010;8:202

Bleeding Definitions

Clinically Relevant Nonmajor bleeding

- ***overt bleeding*** plus
- medical intervention, unscheduled contact with health care team, or temporary anticoagulant cessation

MAYO CLINIC

J Thromb Haemost. 2015;13:2119

STEP 2.

Quick ***Pharmacology*** Inventory

Pharmacology

- What ***DOAC?***
- What ***dose?***
- When was the ***last dose*** taken?
- What is the rate of ***anticipated metabolism?***
- What is the ***drug concentration*** now?

STEP 3.

Promote local hemostasis if possible

Clip it

Suture it

Cauterize it

Compress it

Embolize it

Resect it

Radiate it

STEP 4.

Weigh the ***Risks*** and ***Benefits*** of Restarting!

Did they require *Reversal*?

	Idarucizumab	Andexanet alpha	KCentra
Chemical Structure	Humanized Monocl FAB	Truncated rFXa	Prothrombin Complex Concentrate
Target	Dabigatran	DXi	DXi
Company	Boehringer Ingelheim	Portola	CSL Behring

STEP 5.

Establish ***current thrombus burden*** inventory

STEP 6.

Gentle hemostatic stress test (IV UH.

Determine whether to switch anticoagulant strategies/dosing.

49 y/o Male with esophageal cancer

How did I manage this patient?

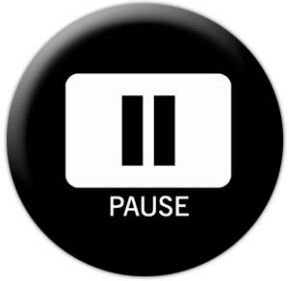
1. ***Restart apixaban but at 2.5 mg twice daily (plans to survey and escalate if possible)***
2. Start rivaroxaban
3. Start Enoxaparin
4. IVC filter

Overall Summary

- ***Bleeding outcomes*** for cancer patients are infrequent but challenging.
- Follow a ***step-wise approach*** to management.
- Promote ***local hemostasis*** when feasible.
- Survey management safety and efficacy and be ***willing to change strategies*** when needed

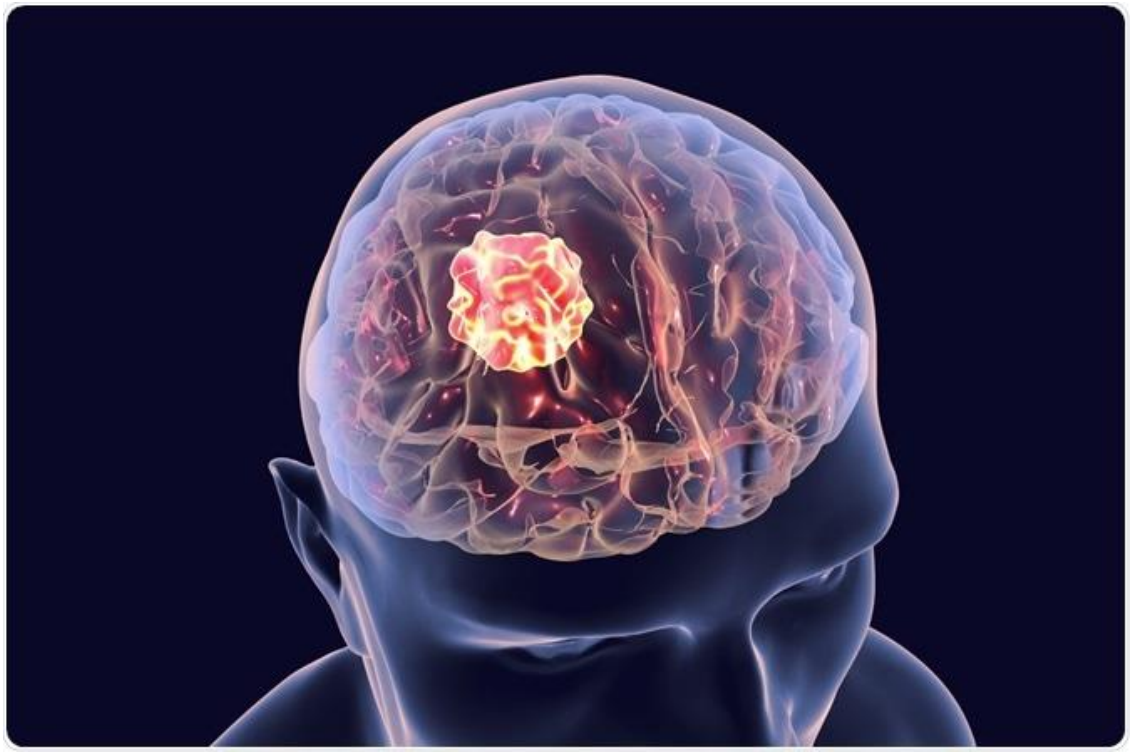
Is there ***anything more*** to learn?

Situations prompting a ***PAUSE***



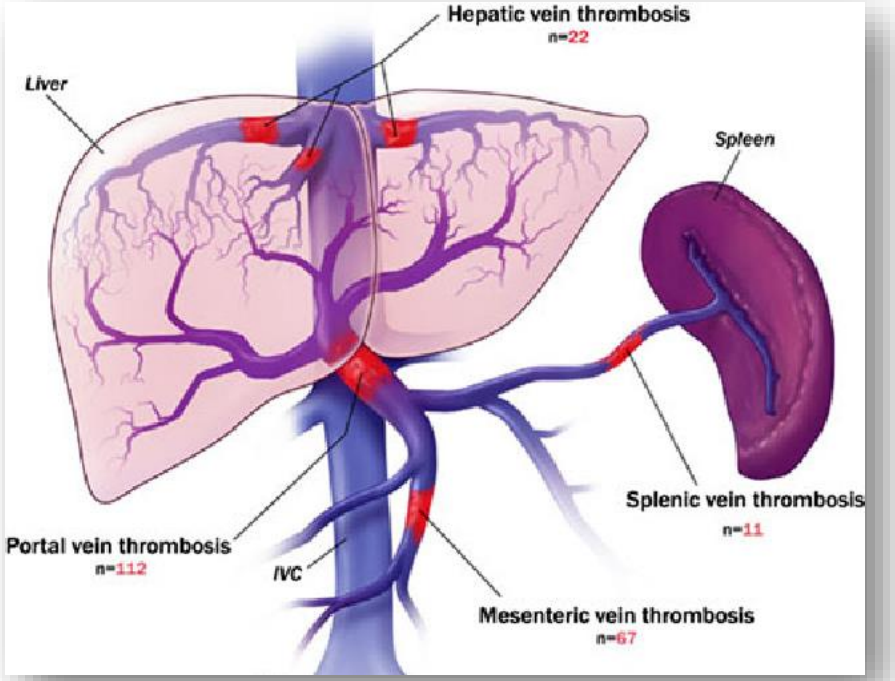
- GI malignancies with luminal tumor (***Edoxaban/Rivaroxaban***)
- Severe ***renal*** impairment (CrCl < 30 mL/min)
- Severe ***liver*** impairment (LFT> 3X upper normal limit)
- Severe ***thrombocytopenia*** (<50-100K)
- Altered ***GI anatomy/absorption***
- Medication interactions (strong ***CYP 3A4 inducer/inhibitors***)

Brain Cancer or Metastasis

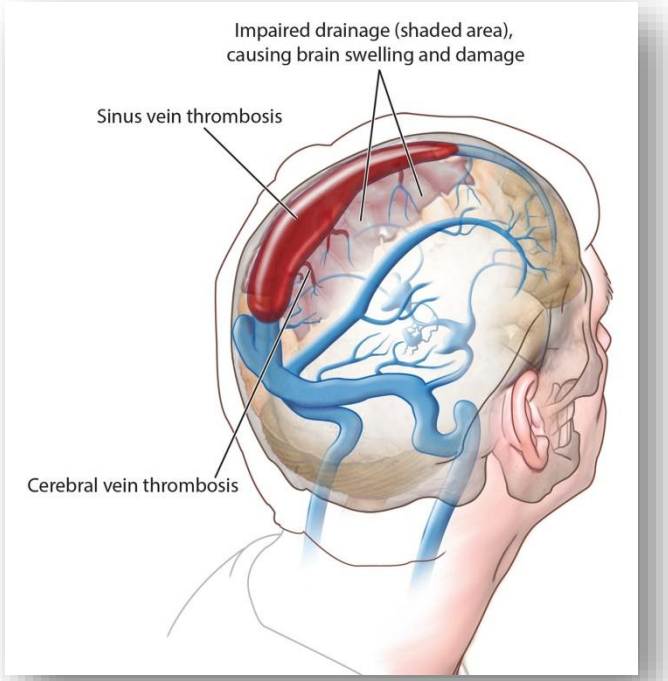


Trial	Total Randomized
HOKUSAI VTE Cancer	74
SELECT D	3
ADAM VTE	8
CARAVAGGIO	Exclusion criteria
Total	85

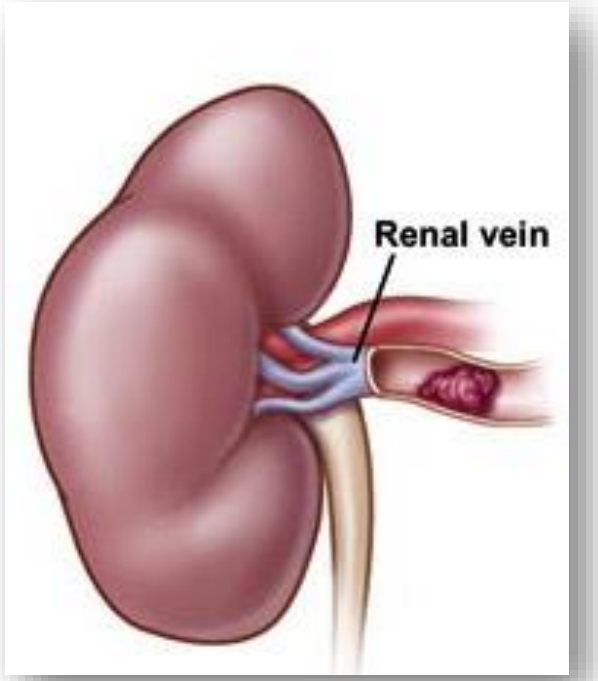
Atypical Thrombus Locations



Splanchnic Veins



Cerebral Veins/Sinuses



Renal Veins

Cancer-Associated VTE: Conclusions

- Cancer associated VTE is ***common*** and adds to ***morbidity*** and ***mortality***.
- DOAC treatment appears to be ***safe*** and ***effective***…..but requires proper ***patient selection***
- ***Lots*** of work remaining in this space!

Questions & Discussion