

· ONCOLOGY GRAND ROUNDS ·

CANCER-ASSOCIATED VTE

# Balancing Risk and Reward with Modern Anticoagulation

· ceCONCOLOGY  ·



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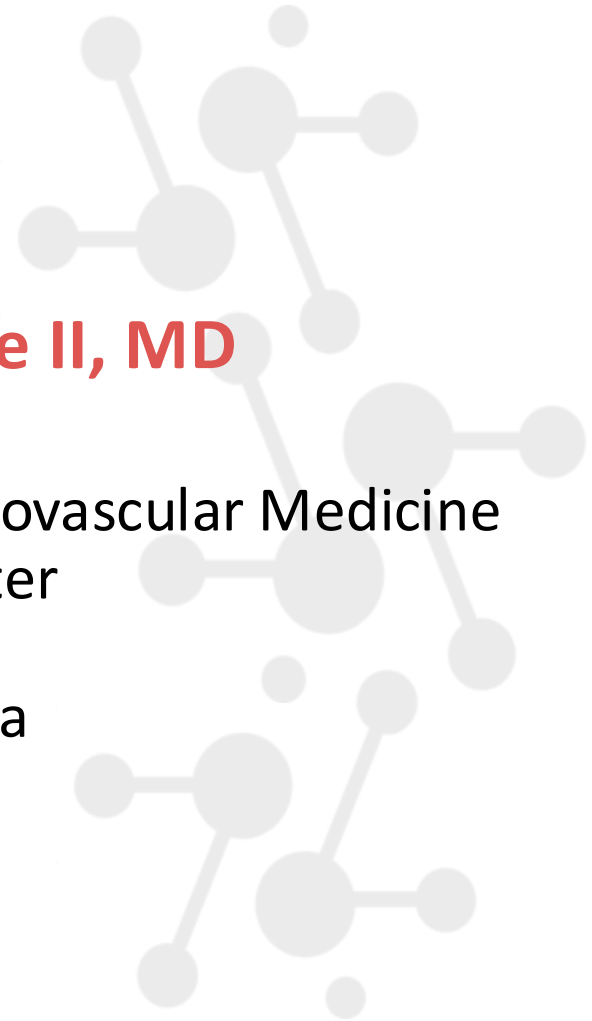
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# Disclosures



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# Learning Objectives

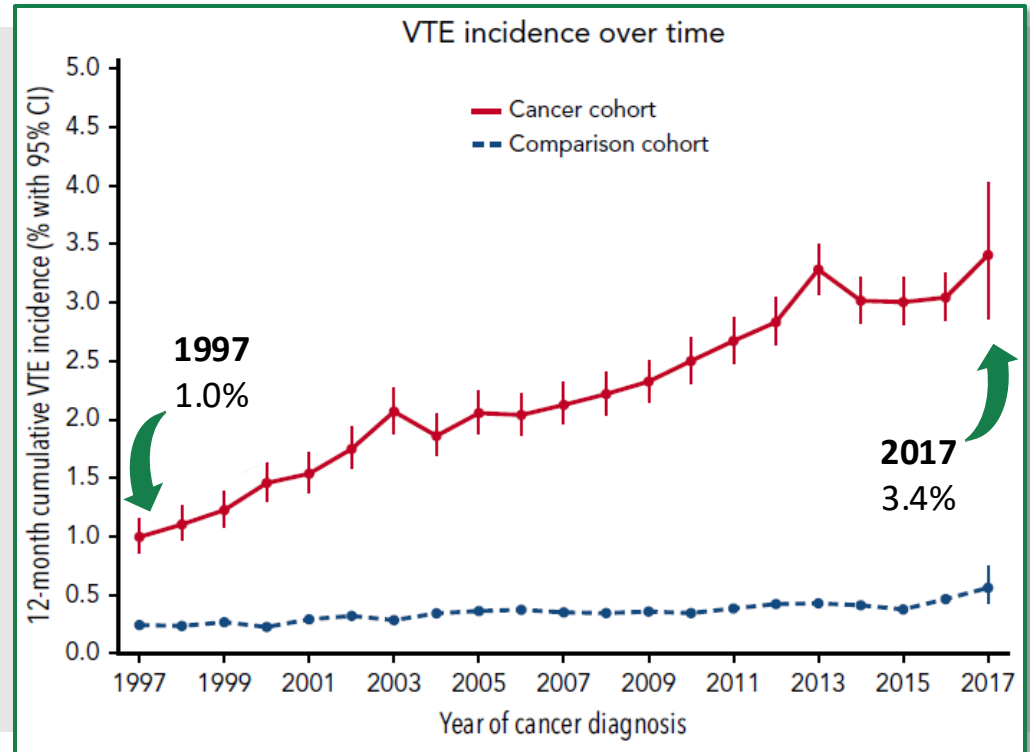


1. Identify disease-, treatment-, and patient-related factors that increase the risk for cancer-associated venous thromboembolism (CA-VTE) in patients with cancer
2. Integrate available anticoagulant treatment strategies into practice that also factor in treatment duration
3. Incorporate CA-VTE management strategies aligned to the most current guidelines and evidence in patients with cancer
4. Develop strategies to coordinate care among members of the CA-VTE team, including patients, caregivers, and other health care providers (HCPs), to achieve optimal adherence and CA-VTE outcomes

# Cumulative Incidence of Cancer-associated Thrombosis Is Increasing over Time



- 12-month cumulative VTE incidence increasing by 3-fold for cancer patients, and even 6-fold for those receiving chemotherapy or targeted therapy
- This increase was paralleled by improved 12-month survival and increased use of CT scans



# Individual VTE Risk Factors



Patient-related factors

Age, sex, prior VTE, or other co-morbidity

Cancer-related factors

Tumor site, stage

Treatment-related factors

CVC, chemotherapy, hospitalization

Biomarker factors

CBC parameters, D-dimer, tissue factor, P-selectin, etc.

**Individual risk factors do not reliably identify patients with cancer at high risk of VTE. In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool.**



# VTE Risk Stratification in Ambulatory Cancer Patients Receiving Chemotherapy

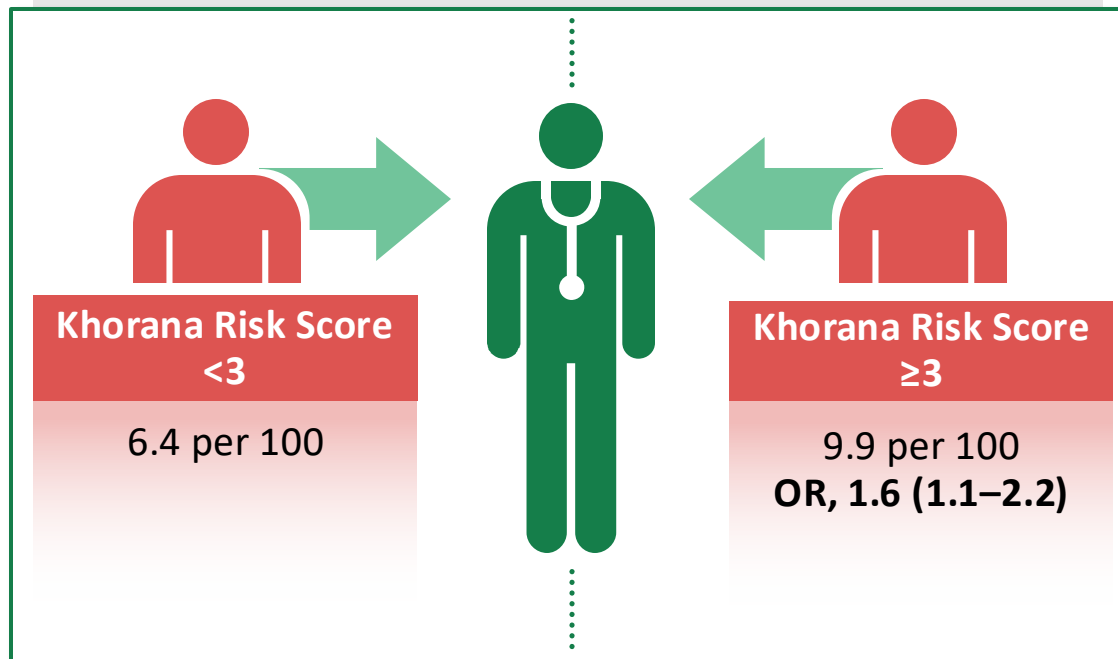


Khorana Risk Score Factor	Points
<b>Site of primary tumor</b>	
• Very high risk (stomach, pancreas)	2
• High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
• All other sites	0
<b>Pre-chemotherapy platelet count <math>\geq 350,000/\mu\text{L}</math></b>	1
<b>Hemoglobin level <math>&lt; 100</math> g/L or use of ESAs</b>	1
<b>Pre-chemotherapy WBC <math>&gt; 11,000/\mu\text{L}</math></b>	1
<b>BMI <math>\geq 35</math> kg/m<sup>2</sup></b>	1

Khorana Score	Risk of VTE at 6 months
Low risk (0)	1.5%
Intermediate risk (1–2)	3.8% 9.6%
High risk ( $\geq 3$ )	17.7%



# Prognostic Performance of the Khorana Score



- Individual patient level meta-analysis (N=3,293)
- The 6-month cumulative VTE incidence
  - 4.1% among low-risk patients (95% CI, 1.9–8.4)
  - 6.8% among intermediate-risk patients (95% CI, 4.5–10)
  - 10% among the high-risk patients (95% CI, 6.7–15)
- The dichotomous Khorana Risk Score performed differently in specific cancer types
  - Lung cancer patients (OR, 1.1; 95% CI, 0.72–1.7)
  - Other cancer types (OR, 3.2; 95% CI, 1.8–5.6)

# Patient Case



A 57-year-old male was recently diagnosed with metastatic pancreatic cancer.



His medical history includes:

- Intermittent abdominal pain for 5 months, with increasing frequency
- Laboratory studies find a WBC of 112 k/ $\mu$ L, hemoglobin of 10.7 g/dL, and platelets were 67k
- His history is positive for hypertension, controlled on lisinopril



**What is his risk of VTE?**



# Patient Case



Khorana Risk Score Factor	Points			Khorana Score
<b>Site of primary tumor</b>				
• Very high risk (stomach, pancreas)	2	Pancreas	+2	Low risk 0
• High risk (lung, lymphoma, gynecologic, bladder, testicular)	1			
• All other sites	0			
<b>Pre-chemotherapy platelet count</b> ≥350,000/μL	1	Low platelets	+0	Intermediate risk 1–2
<b>Hemoglobin level &lt;100 g/L or use of ESAs</b>	1	Normal hemoglobin	+0	
<b>Pre-chemotherapy WBC &gt;11,000/μL</b>	1	High WBC	+1	High risk ≥3
<b>BMI ≥35 kg/m<sup>2</sup></b>	1	No obesity	+0	

# Summary of Primary Prophylaxis



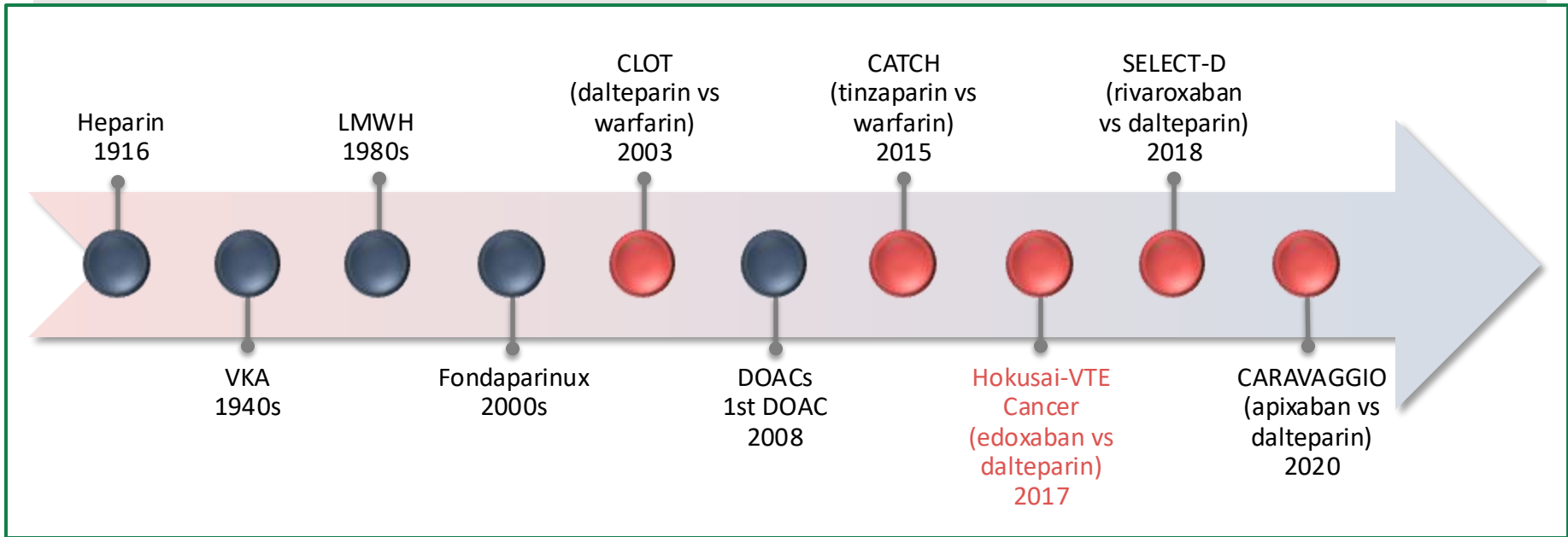
- VTE is a common complication among ambulatory cancer patients receiving systemic therapy and its cumulative incidence is increasing over time
- Risk stratification scores (Khorana score) can help clinicians identify patients at higher risk of VTE
- Primary thromboprophylaxis using LMWH or DOACs provides a favorable risk benefit ratio



## Ambulatory patients with cancer receiving systemic therapy:

- Routine pharmacologic thromboprophylaxis should **not** be offered to all outpatients with cancer
- High-risk outpatients with cancer (Khorana score  $\geq 2$ ) **may be** offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH provided there are no significant risk factors for bleeding and no drug interactions
  - Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting
- Patients receiving medications associated with higher risk of VTE/PE (e.g., thalidomide or lenalidomide) should be offered LMWH to prevent blood clots

# Evolution of Anticoagulant Therapy



# Considerations for Selecting an Anticoagulant



Efficacy

Safety

Tumor Type

Intracranial  
Disease

Drug  
Interactions

Comorbidities

Patient  
Preferences

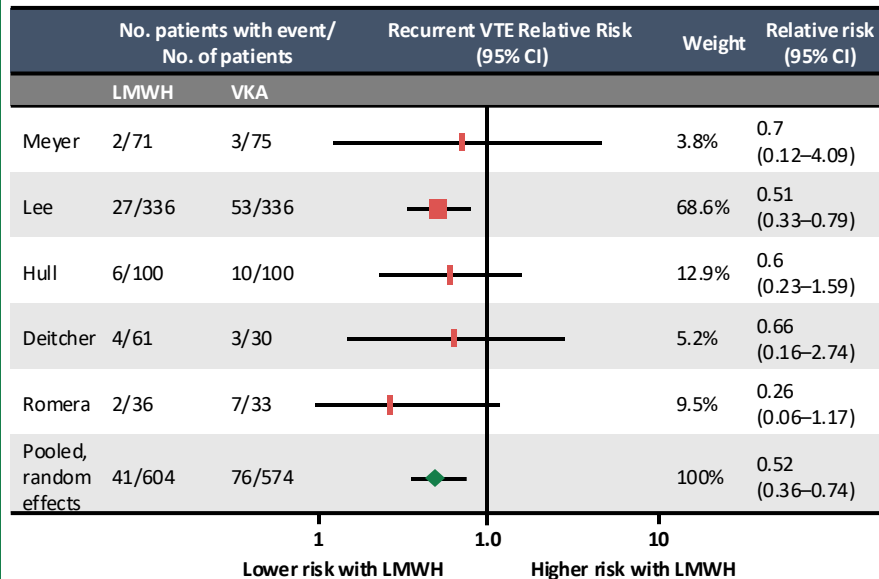


# LMWH vs VKA

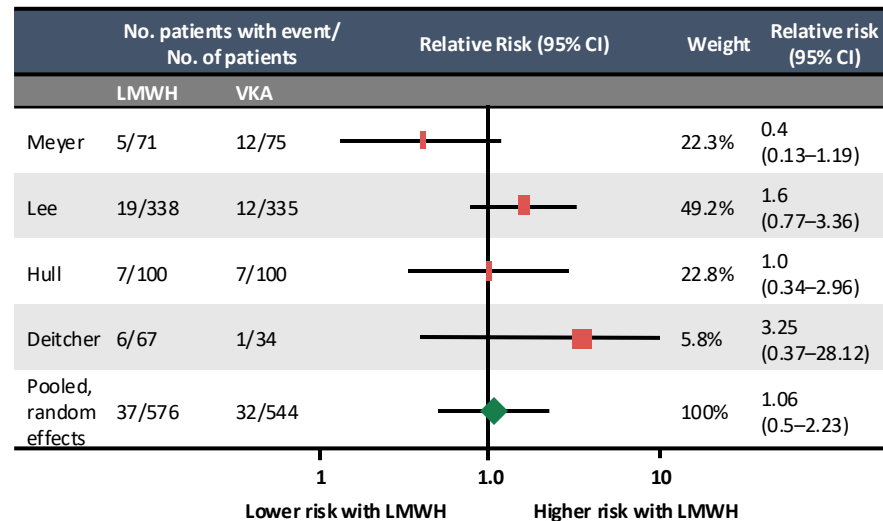
## Better Efficacy, Similar Safety



### Recurrent VTE



### Major Bleeding



# ADAM VTE Trial

## Key Eligibility Criteria

- Patients had active cancer
- Qualifying thrombosis (acute lower extremity or upper extremity DVT, PE, splanchnic, or cerebral vein thrombosis)

## Stratification

- Cancer status
- VTE risk using Khorana score

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### Apixaban (n=145)

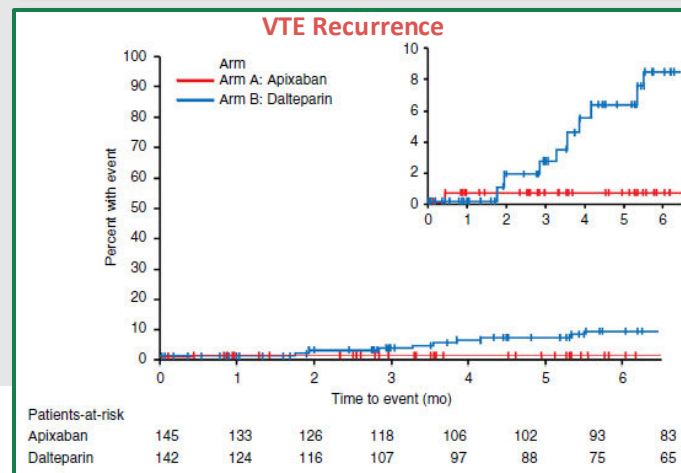
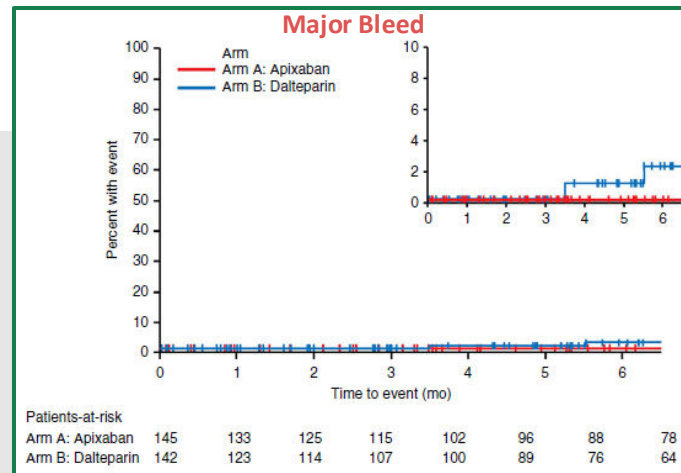
10 mg twice daily for 7 days  
5 mg twice daily thereafter

### Dalteparin (n=142)

Weight-based SC therapy at 200 IU/kg once daily  
for the first month, followed by 150 IU/kg  
for months 2–6

**Primary endpoints:** Major bleeding (overt bleeding + Hgb decrease  $\geq 2$  g/dL; transfusion  $\geq 2$  units RBC; CNS bleeding)

**Secondary endpoints:** Recurrent DVT (PE, fatal PE, or ATE)



ATE, arterial thromboembolism; CNS, central nervous system; DVT, deep vein thrombosis; PE, pulmonary embolism; RBC, red blood cells; SC, subcutaneous.

# DOAC vs LMWH Randomized Trials



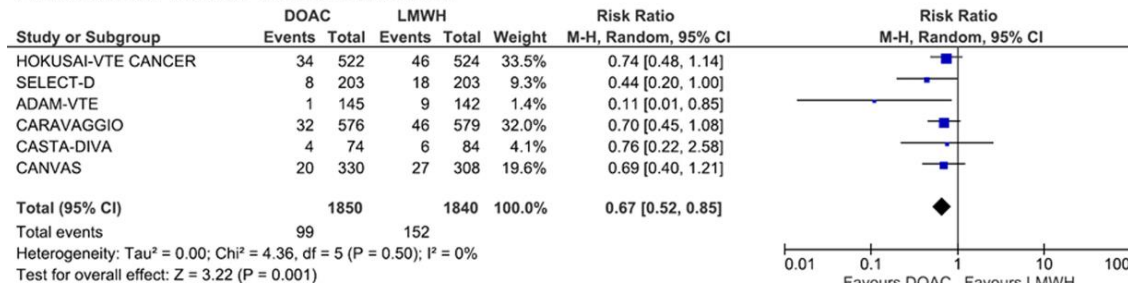
Trial Characteristics	HOKUSAI-VTE Cancer	SELECT-D	CARAVAGGIO	ADAM VTE
<b>Design and sample size</b>	Non-inferiority Phase 3 (N=1,046)	Pilot (N=406)	Non-inferiority Phase 3 (N=1,155)	Superiority Phase 3 (N=287)
<b>DOAC</b>	LMWH × 5 days then edoxaban 60 mg PO daily	Rivaroxaban 15 mg BID × 21 days then 20 mg daily	Apixaban 10 mg BID × 7 days then 5 mg BID	10 mg twice daily 7 d 5 mg twice daily thereafter
<b>LMWH</b>	Dalteparin 200 U/kg daily × 1 month then 150 U/kg daily	Dalteparin 200 U/kg daily × 1 month then 150 U/kg daily	Dalteparin 200 U/kg daily × 1 month then 150 U/kg daily	Dalteparin 200 U/kg daily × 1 month then 150 U/kg daily
<b>DOAC dose reduction</b>	<60 kg; CrCl: 30–50 cc/min; drug-to-drug interactions	—	—	—
<b>Primary outcome</b>	Recurrent VTE or major bleeding	Recurrent VTE	Recurrent VTE	Major bleeding
<b>Duration of treatment</b>	12 months	6 months	6 months	6 months

Raskob GE, et al. *N Engl J Med.* 2018;378(7):615–624. Young AM, et al. *J Clin Oncol.* 2018;36(20):2017–2023. Agnelli G, et al. *N Engl J Med.* 2020;382:1599–1607. McBane RD II, et al. *J Thromb Haem.* 2020;18(2):411–421.

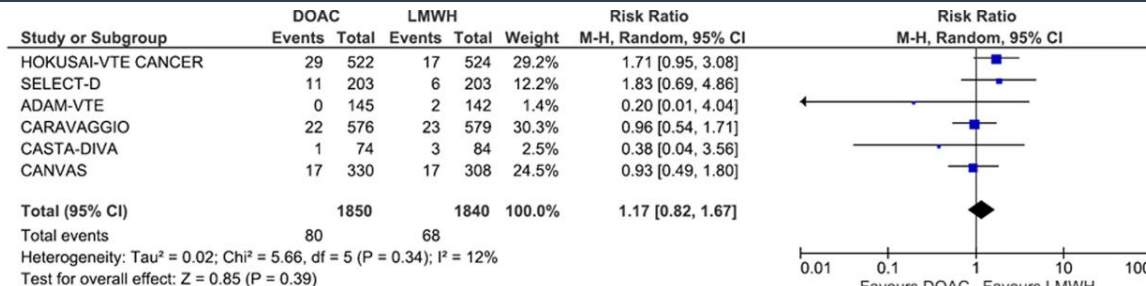
BID, twice daily; CrCl, creatinine clearance; PO, by mouth.

# Recurrent VTE and Major Bleeding

## Recurrent VTE: LMWH 8.3% vs DOAC 5.4%



## Major Bleeding: LMWH 3.7% vs DOAC 4.3%



# Clinically Relevant Non-major Bleeding



## CRNMB: LMWH 5.7% vs DOAC 9.6%

Study or Subgroup	DOAC		LMWH		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	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			

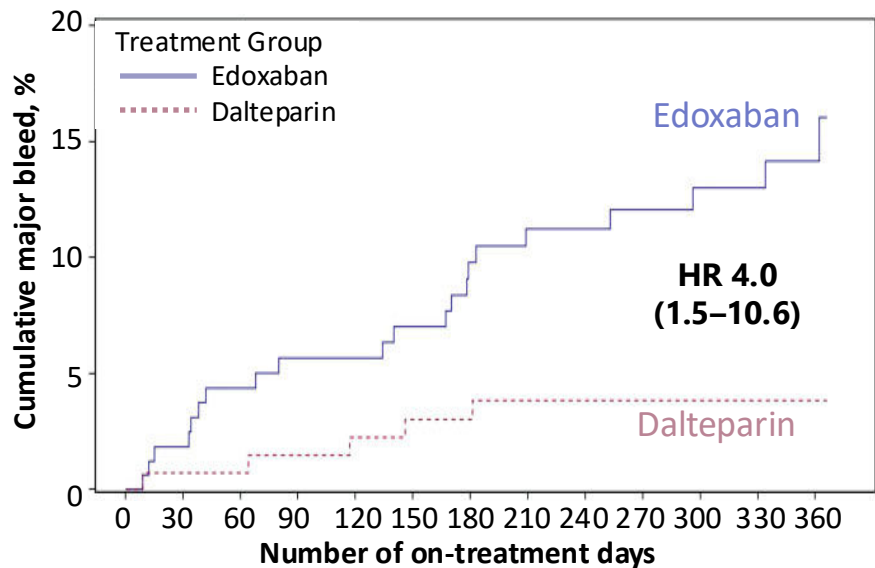
Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 4.82, df = 5 (P = 0.44); I<sup>2</sup> = 0%  
Test for overall effect: Z = 4.23 (P < 0.0001)

- Clinically relevant non-major bleeding (CRNMB): any sign or symptom of hemorrhage that does not fit criteria for major bleeding but meets at least one of the following
  - Requires medical intervention by a healthcare professional
  - Leads to hospitalization or increased level of care
  - Prompts a face-to-face evaluation

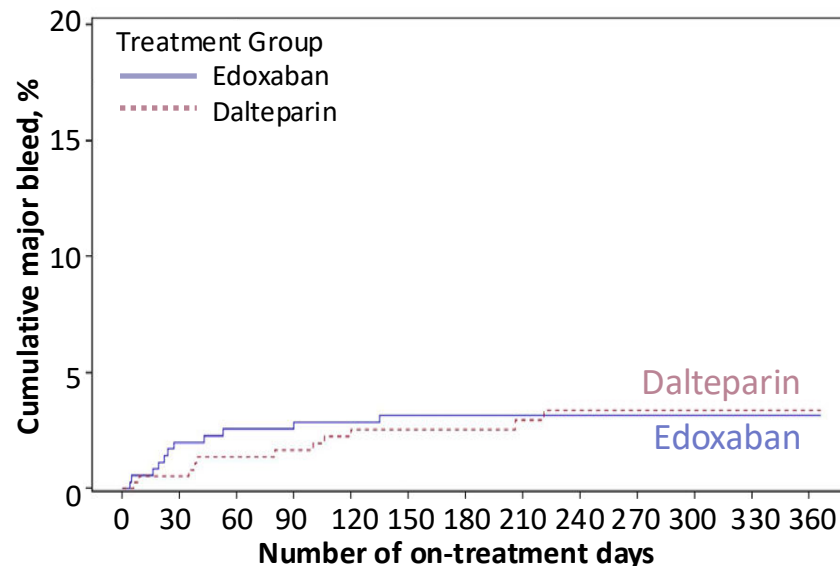
# Major Bleeding by Tumor Type



## GI Cancers

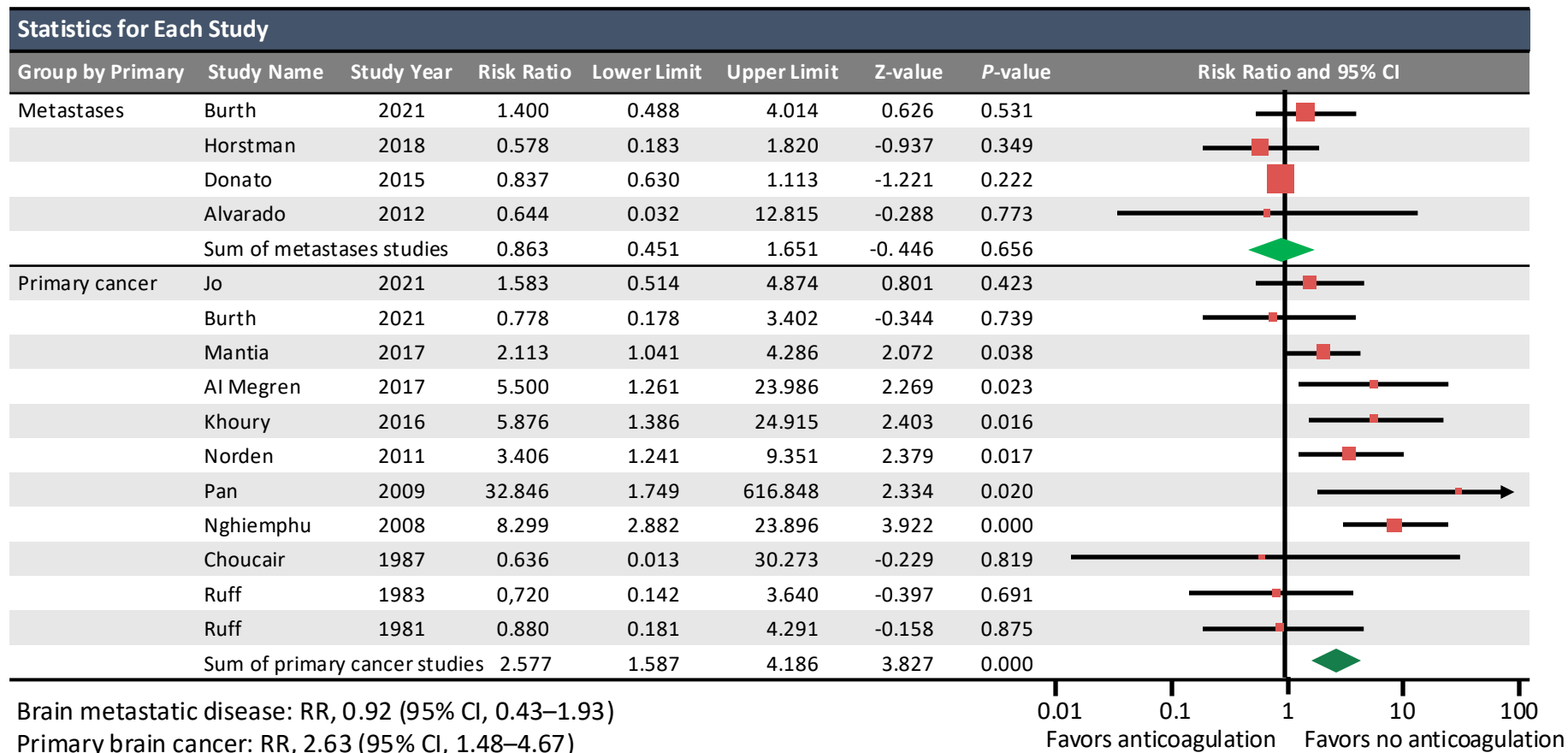


## Non-GI Cancers



- No fatal bleeds in edoxaban group
- 2 fatal bleeds in dalteparin group

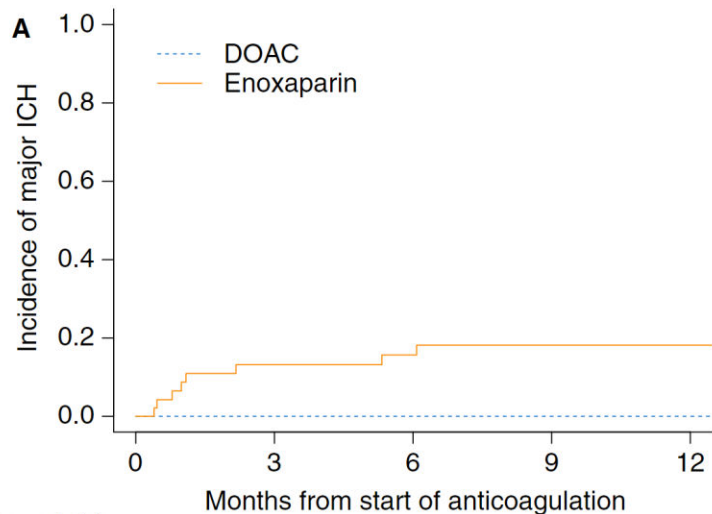
# Intracranial Disease



# Intracranial Disease

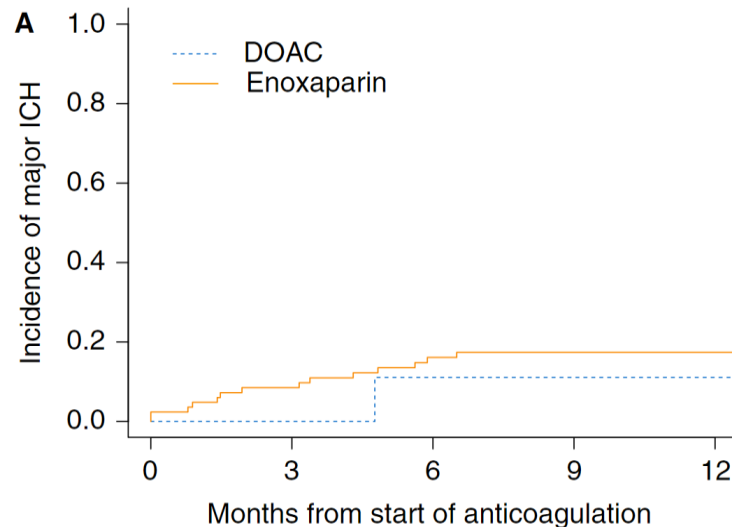


## Primary CNS Tumors



Number at risk	0	3	6	9	12
DOAC	20	18	17	16	15
Enoxaparin	47	32	18	14	11

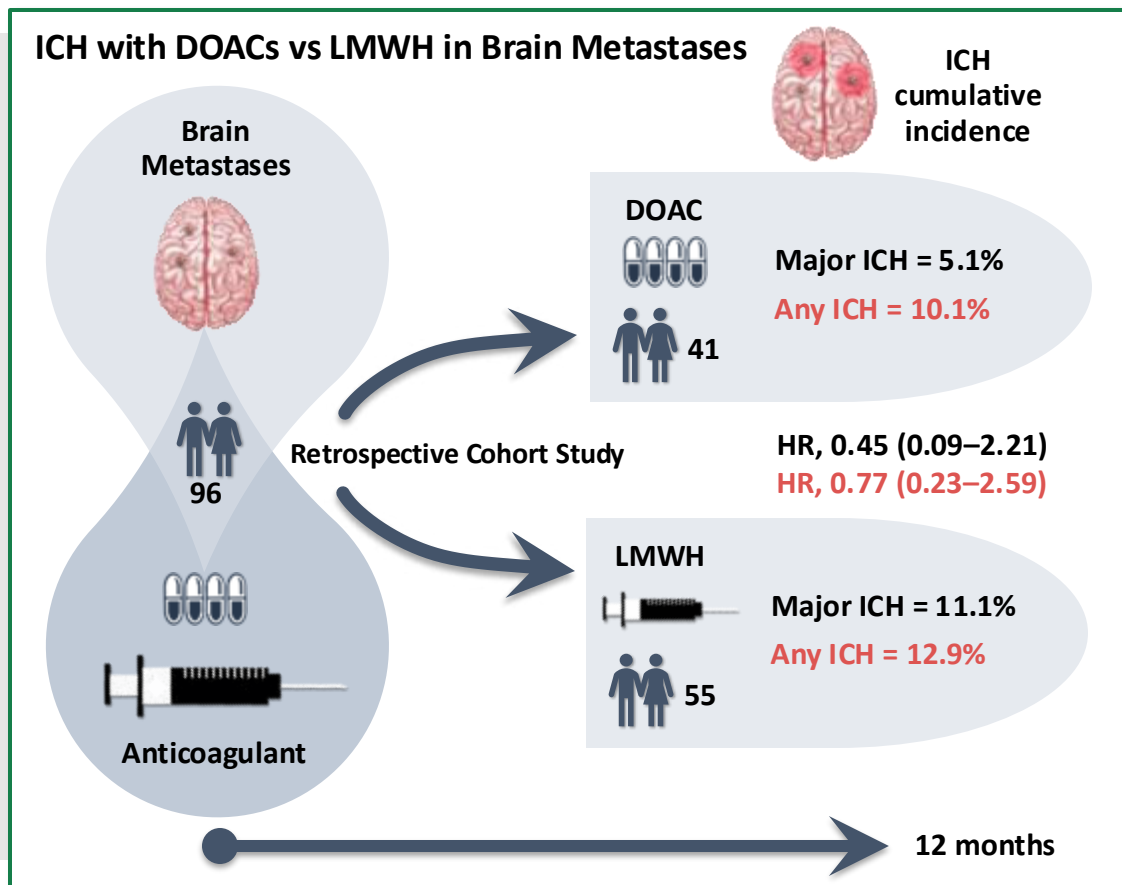
## Brain Metastases



Number at risk	0	3	6	9	12
DOAC	21	10	8	8	8
Enoxaparin	84	45	26	19	15



# Brain Metastases



DOACs are associated with a lower risk of major bleeding than LMWH in patients with primary or metastatic brain cancer

Major ICH was defined as spontaneous,  $\geq 10$  mL in volume, symptomatic, or requiring surgical intervention.

# Clinically Relevant Drug Interactions



## Apixaban/Rivaroxaban

**Strong inhibitors  
of CYP3A4**

(e.g., clarithromycin,  
ketoconazole)

(e.g., phenytoin,  
rifampicin)

**Strong inducers of  
CYP3A4**

Avoid DOACs with  
strong inhibitors  
or strong inducers

## All DOACs

**Strong inhibitors  
of P-gp**

(e.g., ketoconazole,  
ritonavir)

(e.g., carbamazepine,  
rifampin)

**Strong inducers of  
P-gp**

# Drug-Drug Interactions for Patients with Cancer

- TacDOAC: 202 patients on DOAC and targeted anticancer therapy
  - High rate of bleeding complication in patients receiving BTK inhibitors
- Retrospective cohort study of 86 patients on LMWH/DOAC and VEGFR TKI
  - High risk of bleeding in patients on LMWH
  - Inadequate sample size to assess bleeding rate of patients on DOAC
- Post-hoc analysis of the Caravaggio study
  - Concomitant anticancer agents had no effect on the risk of recurrent VTE or bleeding (apixaban or dalteparin)

# Drug-Drug Interactions



- Risk of hospitalization with hemorrhage among patients taking clarithromycin or azithromycin and DOACs

30-day Rate of Hemorrhage with Clarithromycin vs Azithromycin among Patients Taking DOACs				
Characteristic	No. of Events	Cumulative Incidence, %	HR (95% CI)	
			Unadjusted	Adjusted
<b>Major hemorrhage</b>				
Clarithromycin	51/6,592	0.77	1.81 (1.27–2.57)	1.71 (1.20–2.45)
Azithromycin	79/18,351	0.43		
<b>Any hemorrhage or receipt of pRBC transfusion</b>				
Clarithromycin	109/6,592	1.65	1.53 (1.21–1.93)	1.53 (1.21–1.94)
Azithromycin	199/18,351	1.08		

- Drug-drug interactions were associated with a small but statistically significantly greater 30-day risk of hospital admission with major hemorrhage

# Drug-Drug Interactions



## Rates of Hemorrhage Comparing Use of Tamoxifen and Aromatase Inhibitors in Patients Receiving Concurrent DOACs

Characteristic	No./Total No.	Cumulative Incidence, %	Rate per 1,000 Person-years (95% CI)	Weighted HR (95% CI)
<b>Major hemorrhage</b>				
Tamoxifen	29/1,179	2.5	23.4 (16.3–33.7)	0.68 (0.44–1.06)
Aromatase inhibitors	119/3,574	3.3	31.1 (26.0–37.2)	
<b>Any hemorrhage</b>				
Tamoxifen	58/1,179	4.9	47.7 (36.9–61.8)	1.04 (0.75–1.43)
Aromatase inhibitors	165/3,574	4.6	43.7 (37.5–50.9)	

## Summary of Additional Analyses

Additional Analyses	Outcome, Weighted HR (95% CI)	
	Major Hemorrhage	Any Hemorrhage
Restricted to those with eGFR measures and added as a covariate	0.67 (0.39–1.16)	1.09 (0.74–1.61)
Limit follow-up to 90 days	0.83 (0.41–1.68)	1.07 (0.62–1.86)
New DOAC users	0.73 (0.42–1.29)	1.09 (0.71–1.66)
Prevalent DOAC	0.63 (0.31–1.29)	1.00 (0.61–1.66)
Duration from cancer diagnosis added as a covariate	0.68 (0.44–1.05)	1.03 (0.75–1.43)
Death as competing risk	0.68 (0.37–1.25)	1.04 (0.66–1.65)

Risk of hospitalization or ER visits with major bleeding among patients taking tamoxifen or an aromatase inhibitor and DOACs (N=4,753)



# GI Disease or Surgery

## Absorption



**Edoxaban<sup>1</sup>**: tablets disintegrate in the stomach (dependent on an acidic environment), absorption primarily in the proximal small intestine



**Rivaroxaban<sup>2</sup>**: significantly absorbed through the stomach, reduced absorptive surface area may decrease bioavailability



**Apixaban<sup>3</sup>**: absorbed throughout GI tract including significant (>50%) absorption in the distal small bowel or ascending colon

<sup>1</sup>FDA-approved drug: edoxaban. Revised August 2019. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/206316s015lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206316s015lbl.pdf).

<sup>2</sup>FDA-approved drug: rivaroxaban. Revised December 2021. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/215859s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215859s000lbl.pdf).

<sup>3</sup>FDA-approved drug: apixaban. Revised June 2019. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/202155s021lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202155s021lbl.pdf).

# Liver Disease Clearance



**Edoxaban: hepatic clearance 50%**



**Rivaroxaban: hepatic clearance 65%**



**Apixaban: hepatic clearance 75%**

- Patients with active liver disease were excluded from clinical trials
- Body clearance, plasma protein binding, cytochrome P450 metabolism, biliary clearance affected by liver disease
- Use DOACs with caution in setting of hepatic impairment



## Patient Priorities in Choosing Anticoagulation

**1**

No interference with cancer treatment

**2**

Efficacy and safety

**3**

Route of administration





## Recommendation 20

- For patients with cancer and VTE, the ASH guideline panel *suggests* DOAC (apixaban or rivaroxaban) or LMWH be used for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

## Recommendation 23

- For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH (conditional recommendation, low certainty in the evidence of effects ⊕⊕○○).

# NCCN 2023 Guidelines



- Apixaban, edoxaban, or rivaroxaban preferred for patients without gastric or gastroesophageal lesions
- LMWH preferred for patients with gastric or gastroesophageal lesions

**Access a digital HCP point-of-care resource with information about common risk factors, links to the most recent guidelines, and information about how to discuss VTE with patients**

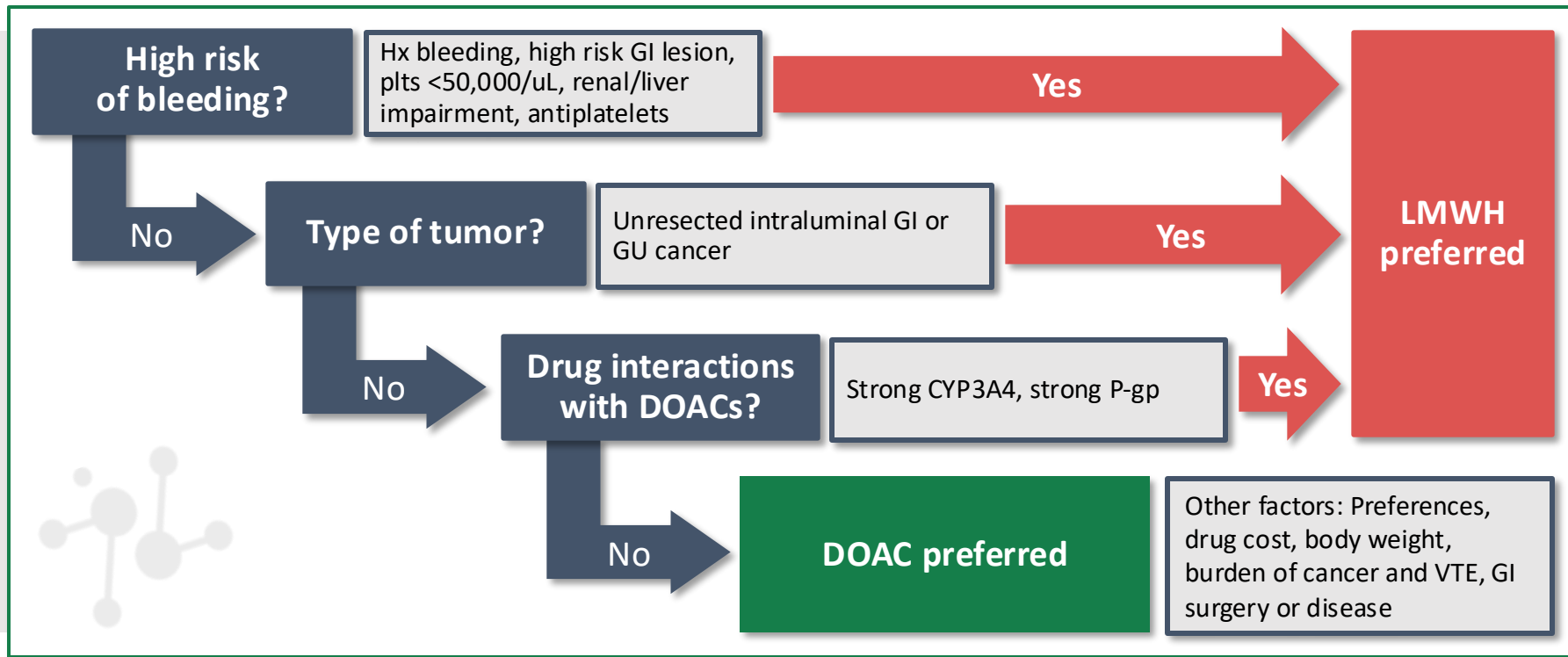


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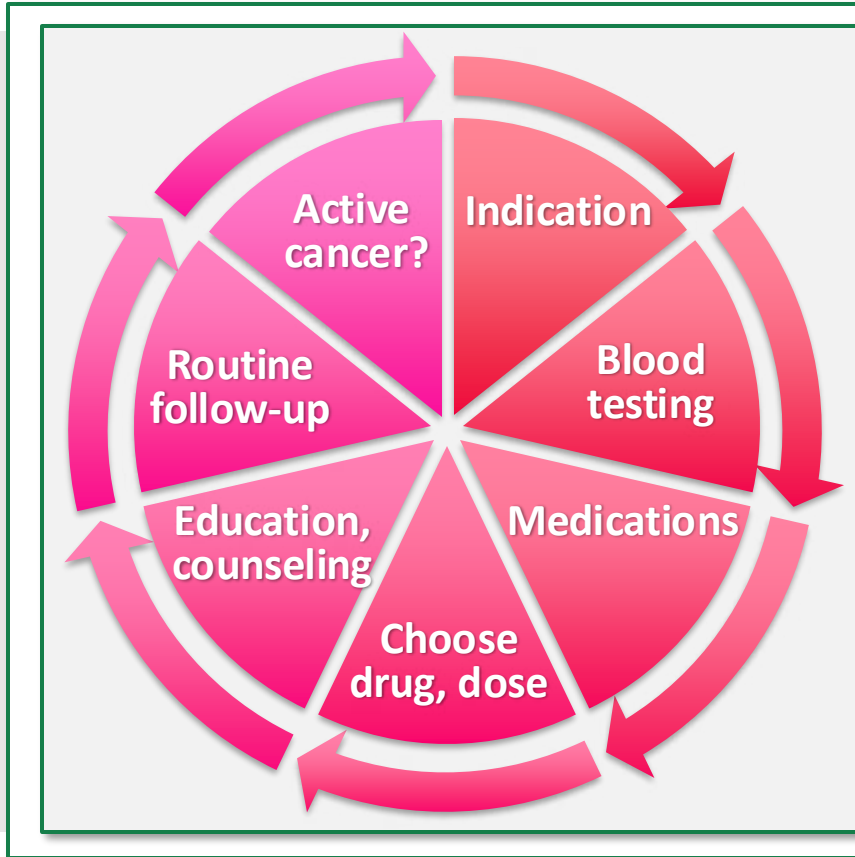
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# Choosing DOAC or LMWH

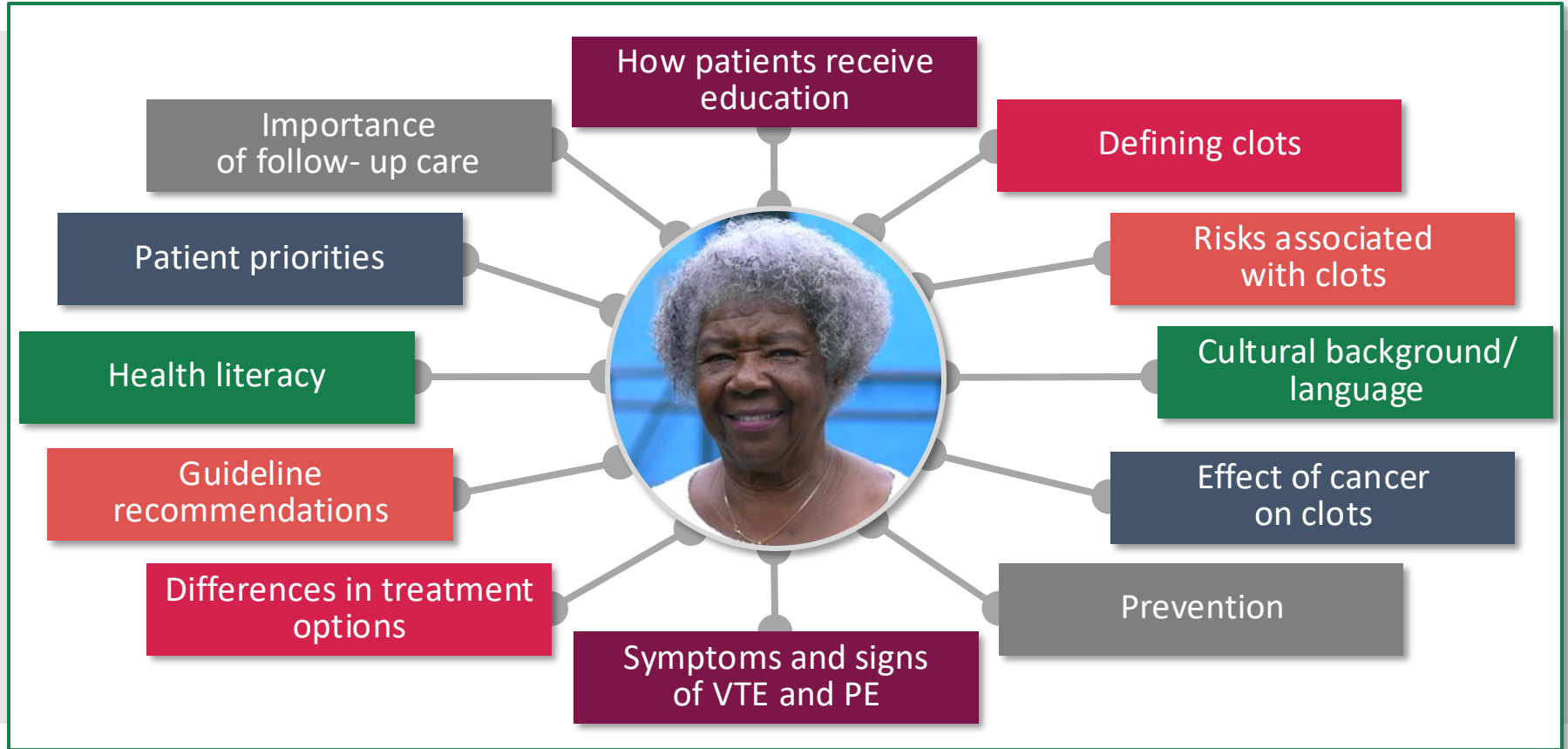


# Approach to Anticoagulant Management



Evaluate and address modifiable bleeding risk factors

# Involving Patients in Clot Prevention



# Patient Case



**Mark is a 57-year-old male who was recently diagnosed with metastatic pancreatic cancer.**



His medical history includes:

- Khorana score = 3 (high risk for VTE)
- No history of bleeding
- Cancer treatment plan: FOLFIRINOX (standard chemotherapy for pancreatic cancer)



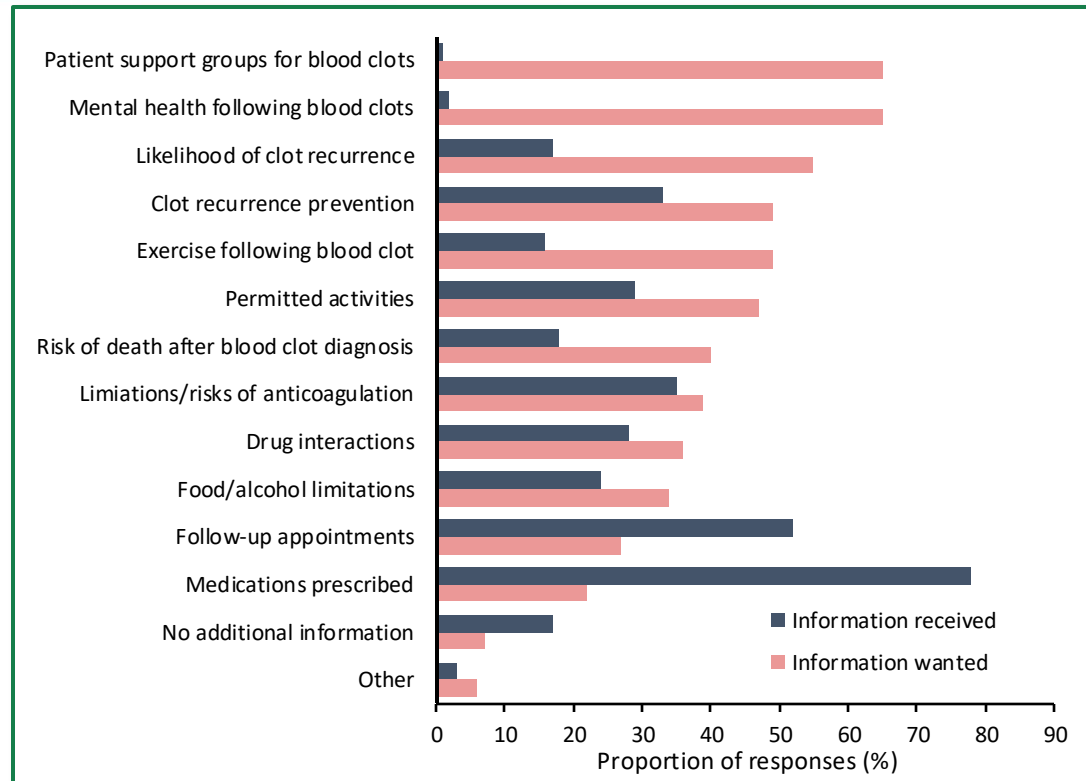
VTE prophylaxis plan: apixaban (2.5 mg BID)



# Patient Reported Gaps in Blood Clot Education and Support from Clinicians



- 1,050 patients responded to the online survey
- 50% had at  $\geq 3$  health care visits before they were correctly diagnosed
- 55% felt their diagnosis was explained to their satisfaction
- 16% of respondents received printed or electronic information on blood clots at the time of diagnosis
- 97% were treated with anticoagulation, but only 48% recall being provided with specific information about the medication, including risks and benefits



# Patient Resources



Access a digital patient education resource that includes information about risk factors, signs and symptoms, and the importance of adherence to care



Click here

or scan the QR code

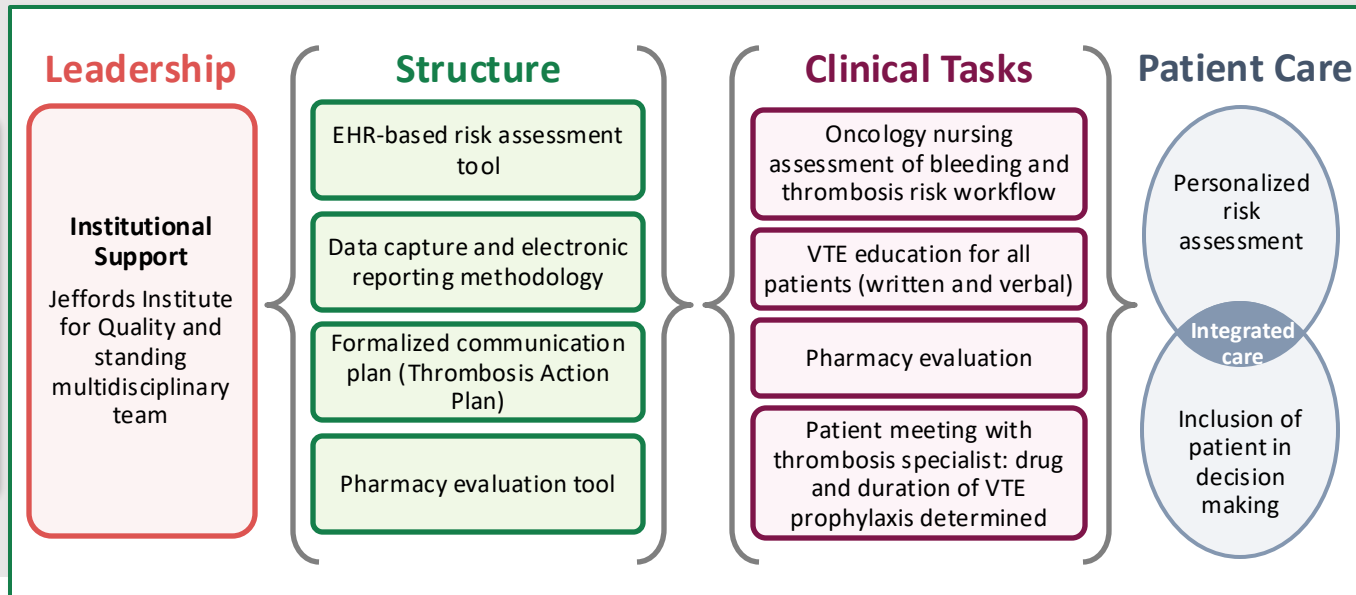




# VTE Prevention in the Ambulatory Cancer Clinic



High-risk patients are identified using the Khorana and PROTECHT scores via an EHR-based risk assessment tool



Multidisciplinary program implemented by nurses, oncologists, pharmacists, hematologists, and advanced practice providers

Patients with a predicted high risk of VTE during treatment were offered a hematology consultation to consider VTE prophylaxis

# Summary of CA-VTE Treatment



- DOACs reduce recurrence of VTE compared to LMWH
  - Are equivalent to LMWH in reducing major bleeding
  - Increase risk of clinically-relevant, non-major bleeding compared to LMWH
- DOACs are associated with a lower risk of major bleeding than LMWH in patients with primary or metastatic brain cancer
- Avoid apixaban and rivaroxiban with strong inducers or inhibitors of CYP3A4 and all DOACs with strong inhibitors or strong inducers of Pgp
- DOACs display differing mechanisms of absorption and elimination; must consider patient-specific needs
- An implementation strategy using a multidisciplinary approach can help increase VTE education to patients and optimize the use of primary thromboprophylaxis

# SMART Goals

*Specific, Measurable, Attainable, Relevant, Timely*



**Put information into action!** Consider the following goals; then *set a time frame* that fits with your work environment and *a reasonable improvement target* that aligns with your patient population.

- Increase the percentage of patients with cancer who are assessed for VTE using a VTE or bleeding risk assessment tool, as documented by inclusion of assessment results in electronic health record (EHR) patient charts.
- Ensure that patients are compliant with prescribed VTE prophylaxis or treatment, as documented by patient-reported behavior and medication receipt in EHR patient charts.
- Increase the percentage of patients with cancer who participate in their therapy decision using shared decision making, as documented by increased delivery of patient education in EHR patient charts.

**Resources for this program can be accessed on CEConcepts.com, or by clicking the button or scanning the QR code below.**

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- Complete the post-test and activity evaluation at the link provided
- Over the next 3 months, actively work to incorporate improvements from this presentation into your clinical practice
- In approximately 3 months, complete the follow-up survey from Creative Educational Concepts



**CEC will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity.**

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# Balancing Risk and Reward with Modern Anticoagulation

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