Cancer- Related Bleeding and Thrombosis

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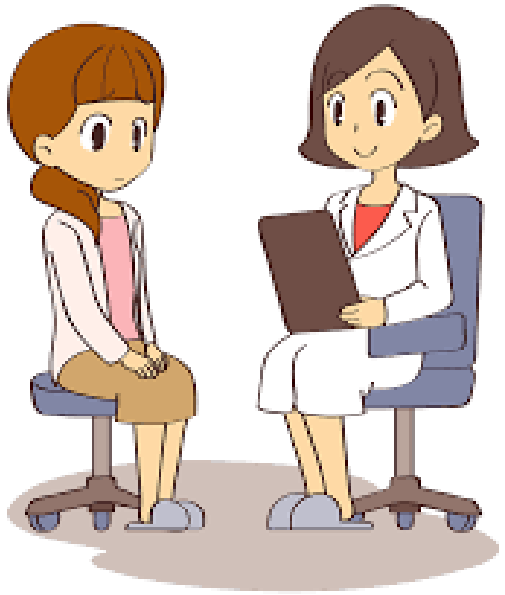


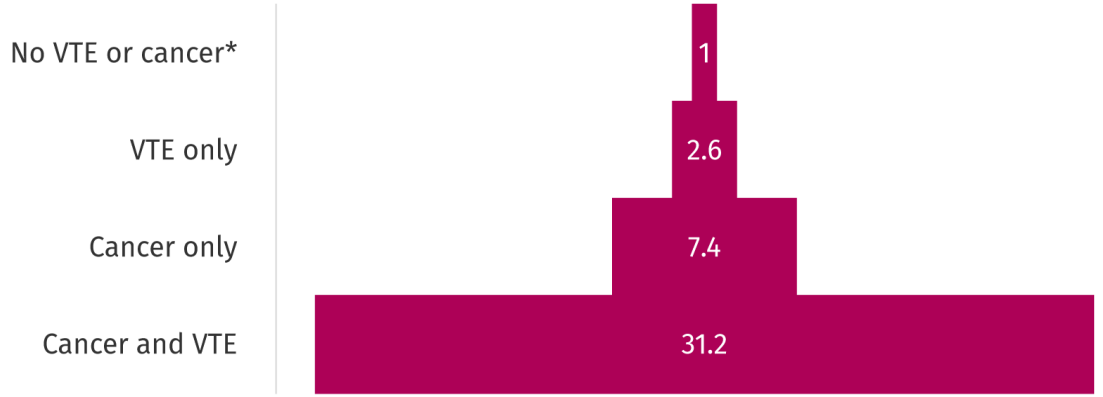
A 55 year old woman presents after recent diagnosis of metastatic lung adenocarinoma. She is concerned as her friend had pancreatic cancer and died from a pulmonary embolism.

She asks what her risk of having a pulmonary embolism and if there is anything that can be done to prevent this?

The Epidemiology of Cancer Associated Thrombosis

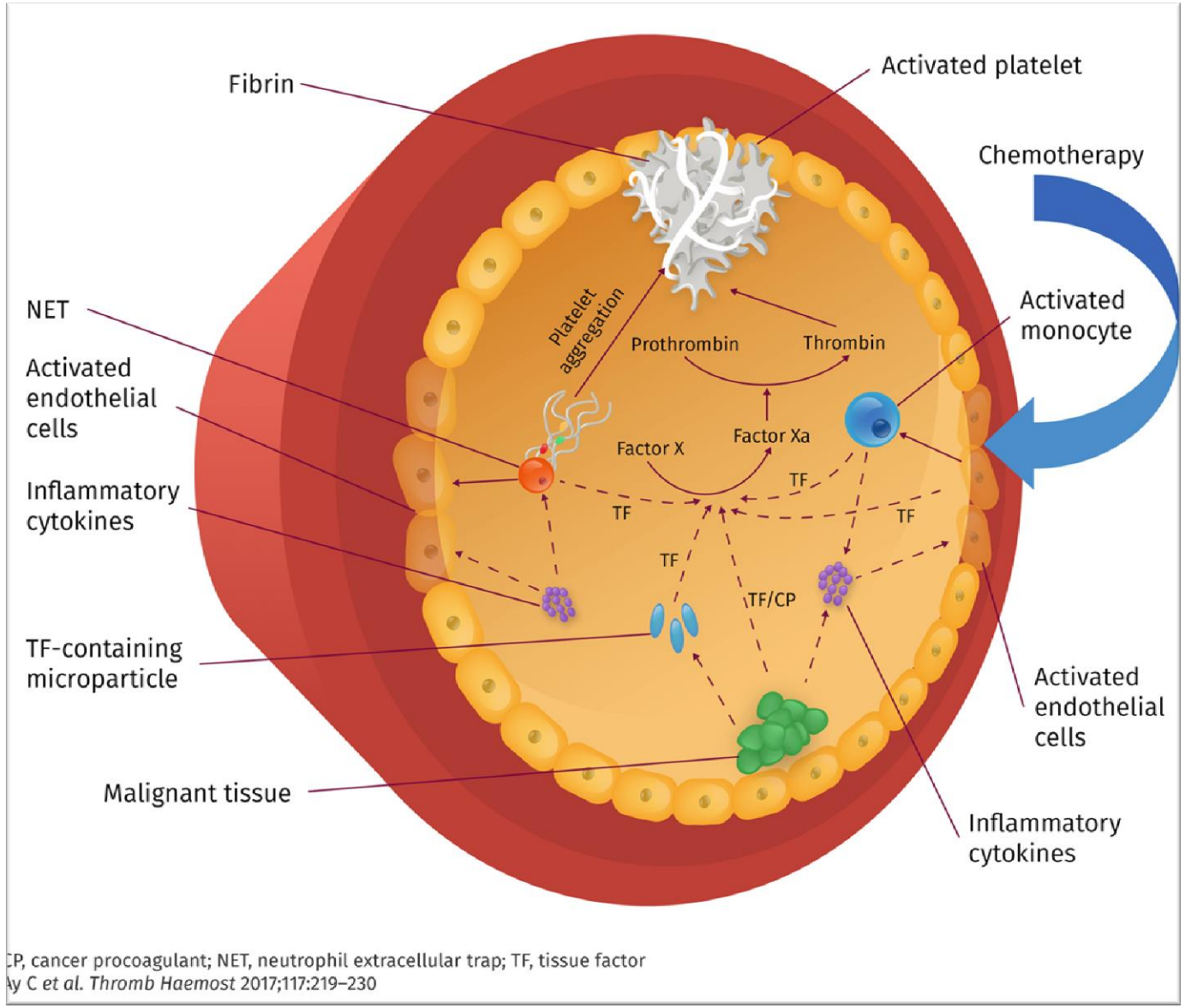
- Cancer accounts for nearly 20% of all VTE cases (1)
- The risk of VTE in cancer patients is is ~5x greater than noncancer controls (2)
- Cancer is a known predictor of mortality in those with VTE (3)

Gender adjusted Hazard ratios of death in participants with and without cancer (The Tromso study 1994-2007)



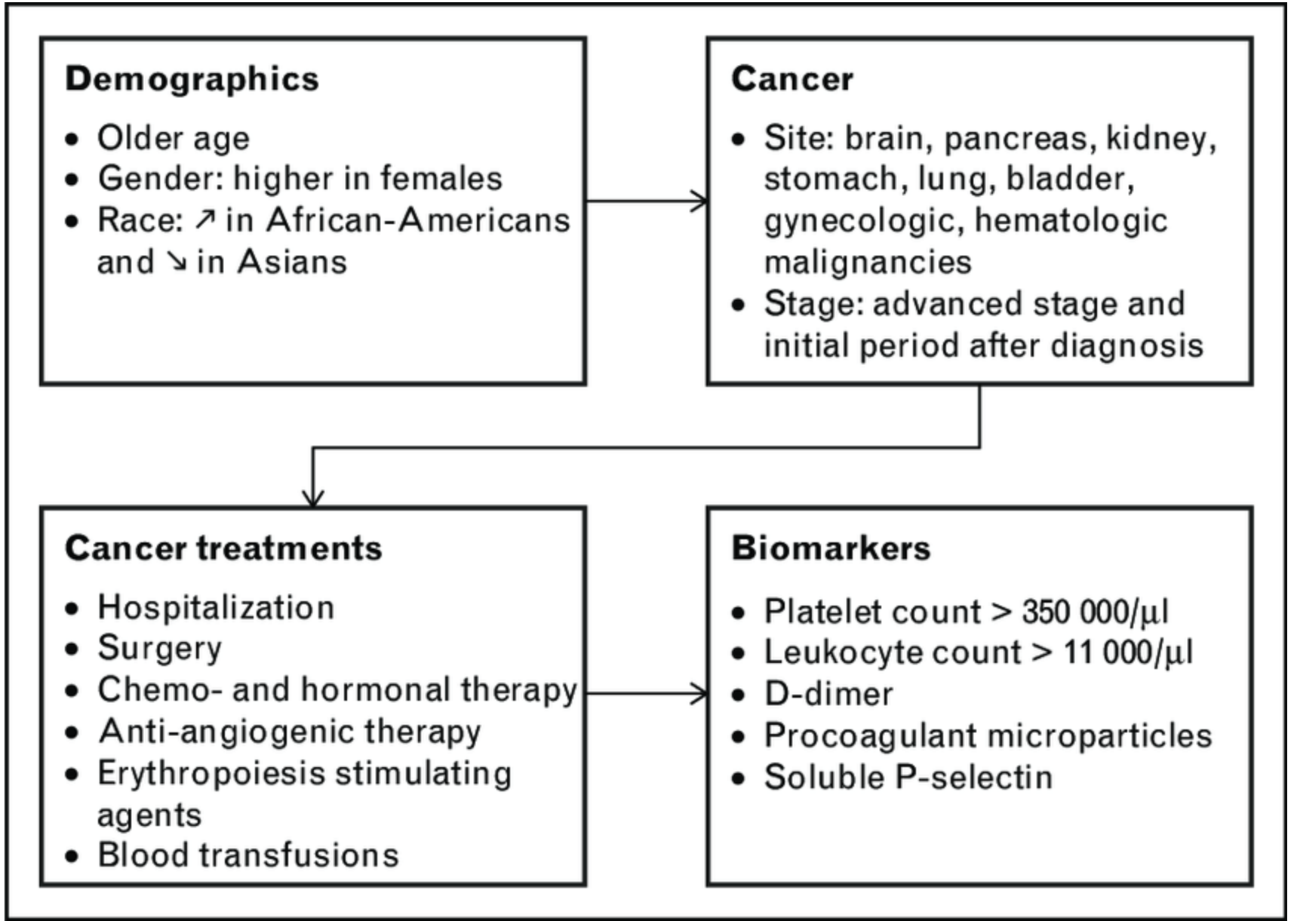
*Reference
VTE, venous thromboembolism
Timp JF *et al. Blood* 2013;122:1712–1723

1. Heit JA, et al. Arch Intern Med 2002; 162: 1245–1248.
2. Cronin-Fenton et al. Br J Cancer 2010, 103 947-953
3. Braeken et al. Am J Empidemiology 2010, 171 (p 11069-1115)

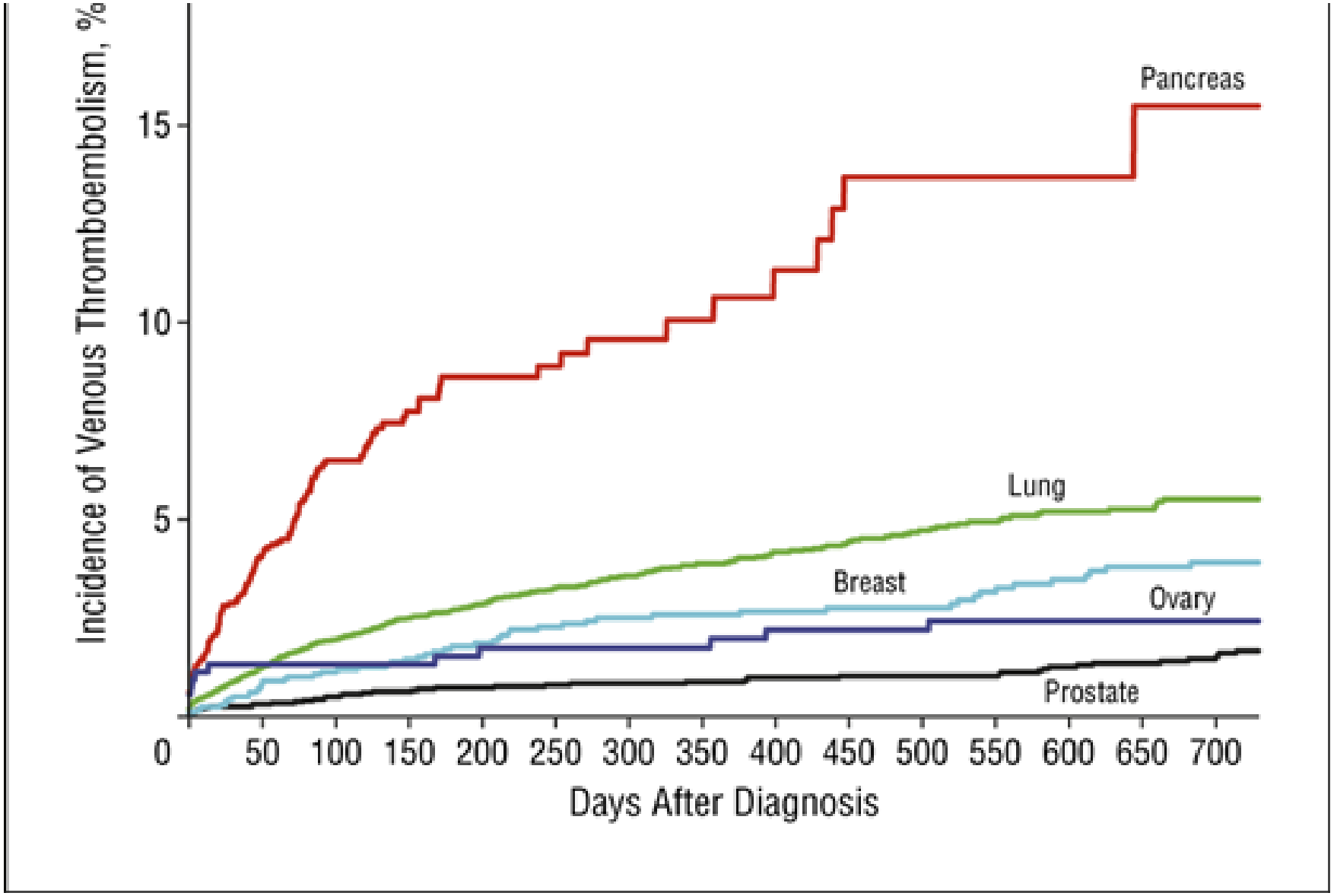


CP, cancer procoagulant; NET, neutrophil extracellular trap; TF, tissue factor
Ay C *et al. Thromb Haemost* 2017;117:219–230

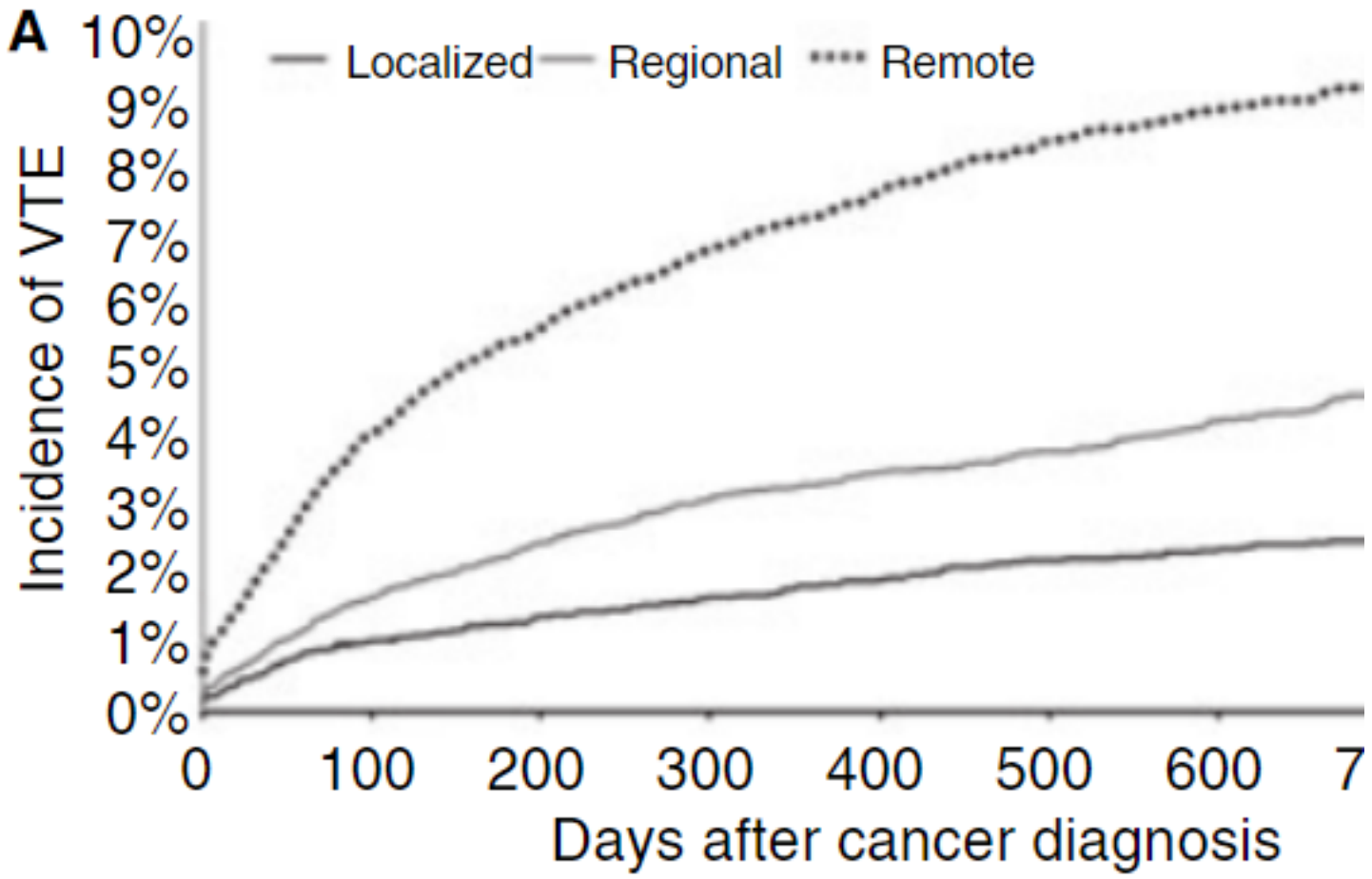
Ay et al. J Thromb and Haemostais, 2017, 117:219-230.



Ay et al. J Thromb and Haemostais, 2017, 117:219-230.



Chew et al. Arch Intern Med, 2006, 166, 458-464



For metastatic lung cancer the 1 year cumulative incidence of VTE is 7%.

Chew et al. J Thromb and Haemostais, 2008, 6:601-608.

Khorana Score

Patient Characteristic	Risk Score
Site of Primary Cancer ➢ Very High Risk (stomach, pancreas) ➢ High Risk (lung, lymphoma, gynecologic, bladder, testicular)	 2 1
Prechemotherapy platelet count ≥ 350 x 10^9/L	1
Hgb < 10 g/dL	1
Prechemotherapy leukocyte count ≥ 11 x 10^9/L	1
BMI 35 kg/m^2	1

Total Score	Risk of Symptomatic VTE
0	Low (0.8-3%)
1-2	Intermediate (1.8-8.4%)
3 or higher	High (7.1-41%)

Khorana et al. Blood. 2008;111(10):4902-7.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Cancer-Associated Venous Thromboembolic Disease

NCCN Guidelines Index
Table of Contents
Discussion

VTE PROPHYLAXIS FOLLOWING DISCHARGE AND FOR AMBULATORY CANCER PATIENTS AT RISK[a]

AT-RISK POPULATION

- Adult medical or surgical patient
- Diagnosis of cancer
- Patient received VTE prophylaxis during hospitalization
- Cancer inpatient intended for discharge
- Outpatients at risk
- Providers are encouraged to discuss VTE risk factors, bleeding risk factors, risks and benefits of VTE prevention, and the importance of patient adherence to care programs

Surgical oncology patient → Out-of-hospital primary VTE prophylaxis is recommended for up to 4 weeks post-operation for high-risk abdominal or pelvic cancer surgery patients[h] → See Prophylactic Anticoagulation Options for Surgical Oncology Outpatients (VTE-C)

Medical oncology patient

- Multiple myeloma patients receiving immunomodulatory drugs (IMiDs) → See VTE Risk Assessment Models and Prophylaxis based on SAVED (VTE-3) and IMPEDE VTE (VTE-4) Scores
- Other cancer patients: VTE risk evaluation based on Khorana score (See VTE-D)
  - Intermediate or high risk for VTE (Khorana score ≥2)
    - Consider oral anticoagulant prophylaxis for up to 6 months[c,i]
      - Apixaban 2.5 mg PO BID
      - Rivaroxaban 10 mg PO QD
  - Low risk for VTE (Khorana score <2)
    - No routine VTE prophylaxis

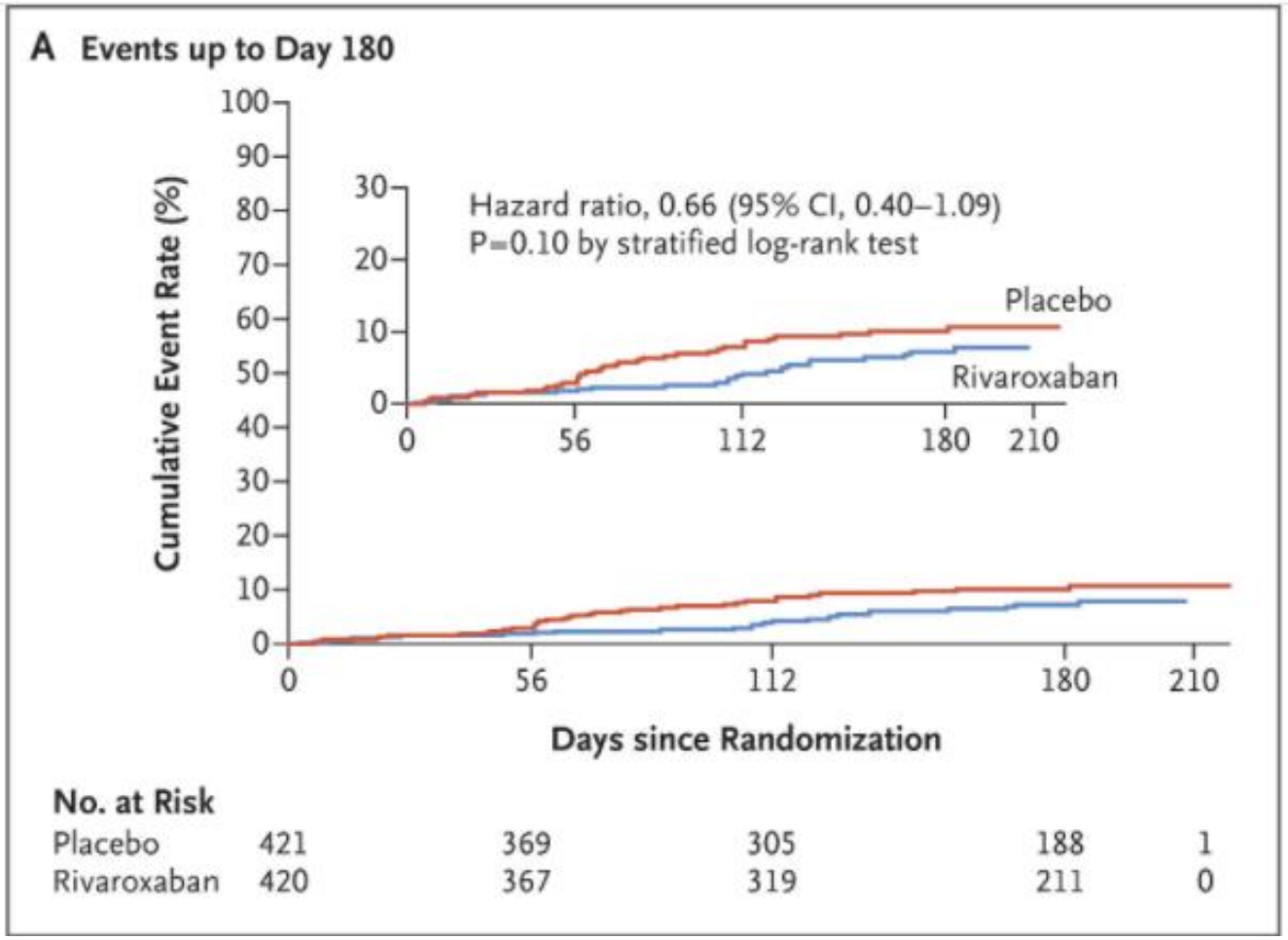
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer

- Double blind randomized trial of high risk ambulatory cancer patients (Khorana score ≥2) assigned to prophylactic rivaroxaban 10mg daily for 180 days
  - **All underwent screening ultrasound prior to enrollment**

- VTE occurred in 6% of rivaroxaban group vs 8.8% placebo group (HR 0.66, 95% CI 0.1-1.09, p=0.10)
- Major bleeding occurred in 2% of rivaroxaban group vs 1% in placebo group (HR 1.96; 95% CI 0.59-6.49)
- VTE prophylaxis with rivaroxaban did not significant lower incidence of VTE or death due to VTE in follow up



Khoranna et al. N Engl J Med 2019; 380:720-7

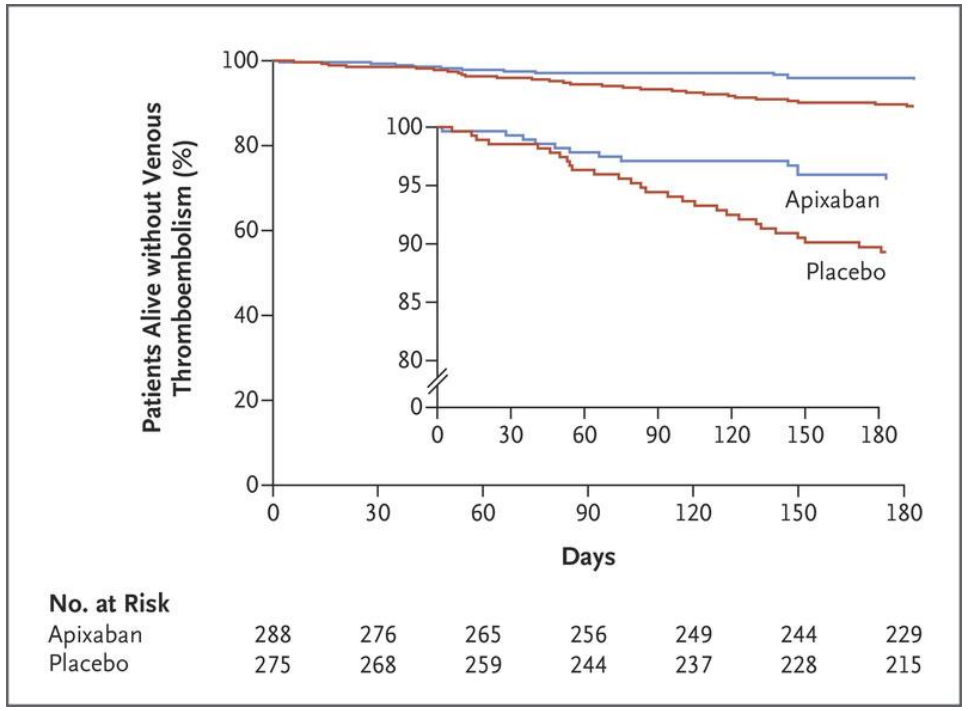
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban to Prevent Venous Thromboembolism in Patients with Cancer

- Randomized, placebo controlled, study of apixaban 2.5mg BID for thromboprophylaxis in ambulatory cancer patients for 180 days
  - Also used Khorana score of ≥2
  - Did not perform baseline ultrasound prior to enrollment to exclude those with VTE
- VTE in 4.2% of those in apixaban group and 10.2% in placebo group (HR 0.41, 95% CI 0.26-0.65, p<0.001)
- Major Bleeding occurred in 3.5% of those in apixaban group vs 1.8% in placebo (HR 2; 95% CI 1.01-3.95; p=0.046)

Carrier et al. N Engl J Med 2019; 380:711-719


Patients Alive without Venous Thromboembolism (%)
100
80
60
40
20
0
0
30
60
90
120
150
180
Days
100
95
90
85
80
0
Apixaban
Placebo
No. at Risk
Apixaban 288 276 265 256 249 244 229
Placebo 275 268 259 244 237 228 215

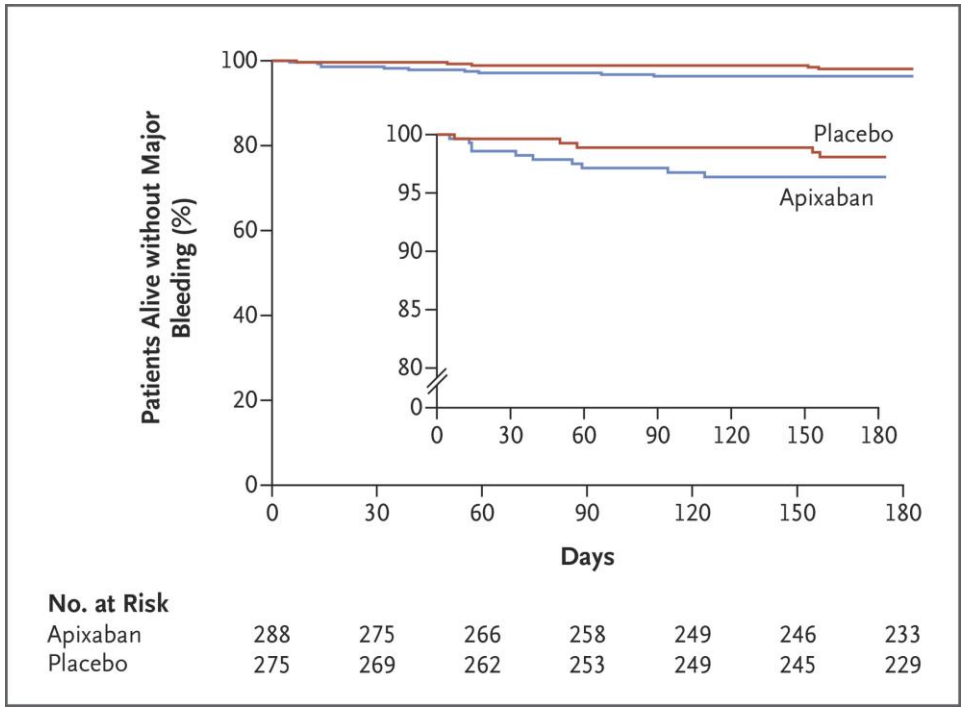

Patients Alive without Major Bleeding (%)
100
80
60
40
20
0
0
30
60
90
120
150
180
Days
100
95
90
85
80
0
Placebo
Apixaban
No. at Risk
Apixaban 288 275 266 258 249 246 233
Placebo 275 269 262 253 249 245 229

Table 1. Cumulative Analysis of the AVERT and CASSINI Trials.*

Outcome	CASSINI Trial		AVERT Trial		Cumulative Values				
	Rivaroxaban	Placebo	Apixaban	Placebo	DOACs	Placebo	Relative Risk (95% CI)	Absolute Difference	No. Needed to Treat or Harm†
			number/total number (percent)					*percentage points*	
Primary efficacy outcome									
ITT analysis	25/420 (6.0)	37/421 (8.8)	12/288 (4.2)	28/275 (10.2)	37/708 (5.2)	65/696 (9.3)	0.56 (0.38–0.83)	−4.1	24
Analysis during treatment period	11/420 (2.6)	27/421 (6.4)	3/288 (1.0)	20/275 (7.3)	14/708 (2.0)	47/696 (6.8)	0.29 (0.16–0.53)	−4.8	21
Symptomatic VTE: ITT analysis	15/420 (3.6)	19/421 (4.5)	9/288 (3.1)	22/275 (8.0)	24/708 (3.4)	41/696 (5.9)	0.58 (0.35–0.94)	−2.5	40
Major bleeding	8/405 (2.0)	4/404 (1.0)	10/288 (3.5)	5/275 (1.8)	18/693 (2.6)	9/679 (1.3)	1.96 (0.88–4.33)	1.3	77
Death from any cause	84/420 (20.0)	100/421 (23.8)	35/288 (12.2)	27/275 (9.8)	119/708 (16.8)	127/696 (18.2)	0.92 (0.73–1.16)	−1.4	71

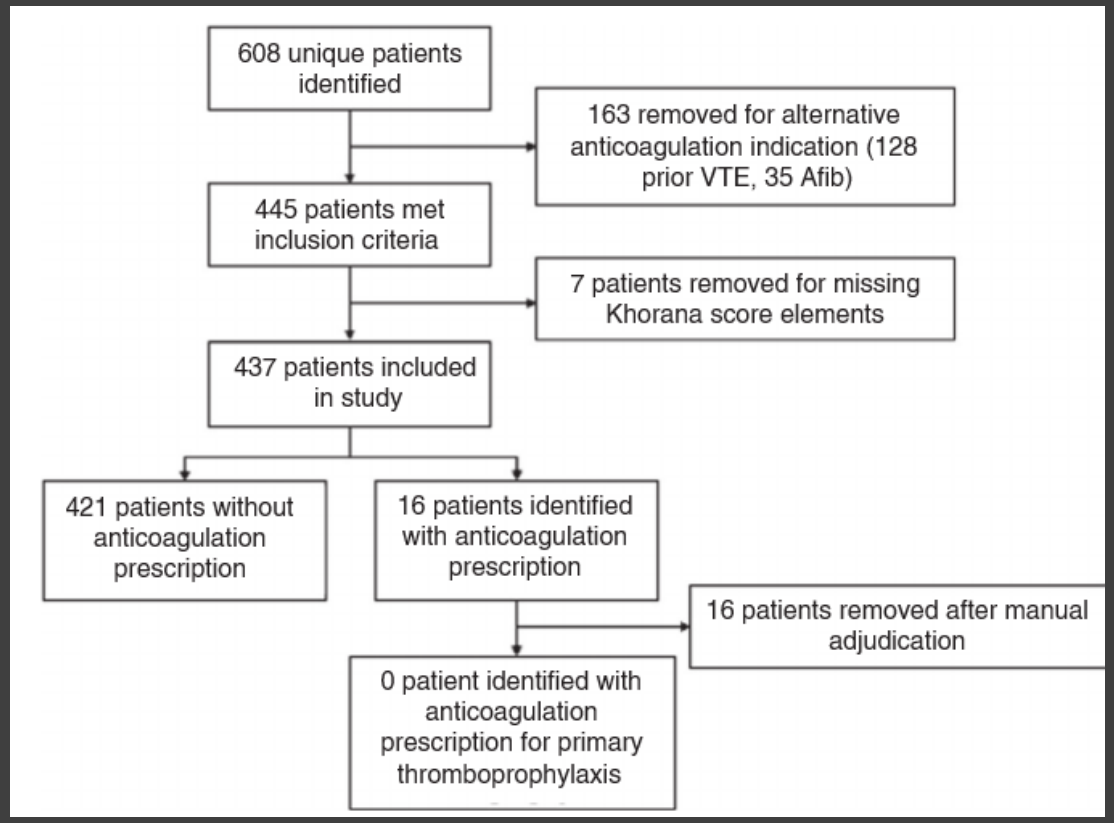
* In the AVERT trial, the modified intention-to-treat analysis was the primary analysis (574 patients underwent randomization). DOACs denotes direct oral anticoagulants, ITT intention to treat, and VTE venous thromboembolism.

† The number needed to treat is shown for all outcomes except major bleeding (number needed to harm).

Criticisms of CASSINI and AVERT

- The most common cancers (colorectal, breast, prostate) were underrepresented
- Khorana score has been shown to perform poorly in some cancers and does not account for chemotherapy regimen
- ***Percentage of patients discontinued trial regimen prematurely was high (up to nearly 50%)***

" For patients with cancer predicted to be a high risk of VTE based on the Khorana score, none were prescribed anticoagulation without another clinical indication, demonstrating primary prophylaxis is virtually never used."

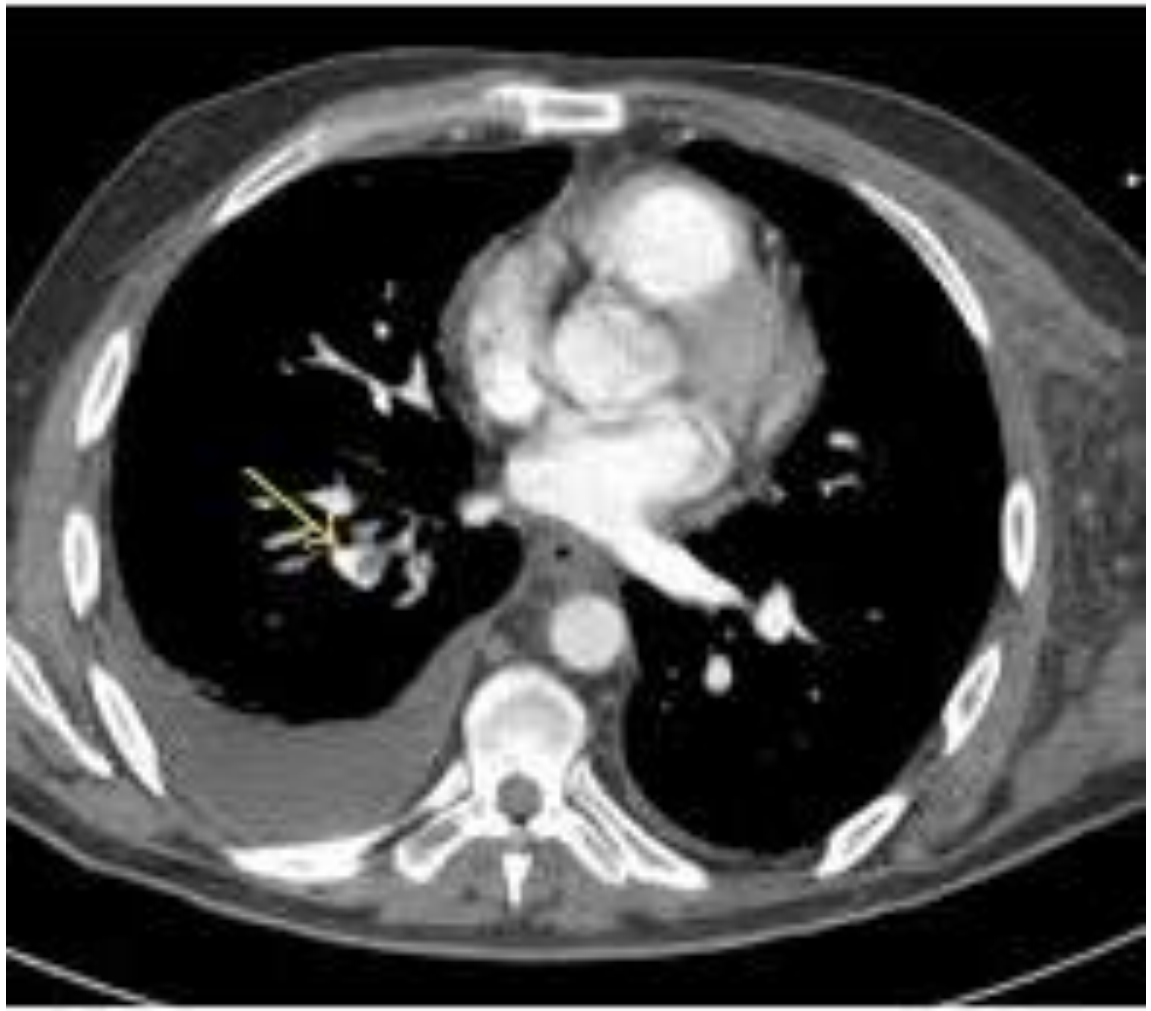


1. How often do you ...	Never	Rarely	Sometimes	Usually	Always
Use risk scores to identify patients at high risk of VTE?	58%	29%	8%	4%	0%
Talk to your patients with cancer about the risk of blood clots?	0%	29%	29%	38%	4%
2. How familiar are you with ...		Not at all	A little bit	Somewhat	Quite a bit
ISTH recommendations for VTE risk assessment and primary prophylaxis?		67%	21%	8%	4%
The Khorana score?		67%	17%	13%	4%

Martin et al. Res. Pract. Thromb. Haemost.. 2020;00:1–5.

The patient develops a new segmental pulmonary embolism while receiving her second cycle of chemotherapy.

She is initially given low molecular weight heparin but hates giving herself injections and would like to know about alternative therapies.



Treatment of CAT- an Evolution or Revolution?

Hokusai : Edoxaban vs. Dalteparin

- Open label, randomized, noninferiority trial comparing LMWH for 5 days followed by edoxaban 60mg daily vs. Dalteparin
  - Excluded patients with CrCl>95 ml/min
- Recurrent VTE 7.9% Edoxaban vs. 11.3% Dalteparin (HR 0.71; 95% CI 0.42-1.06, p=0.09)
- Edoxaban associated with higher absolute rate of major bleeding vs. Dalteparin (6.9% vs. 4.0%, HR .77; 95% CI 1.03-3.04, p=0.04)
- ***Patients with GI malignancy were more likely to have increase in risk of bleeding with edoxaban vs dalteparin (3.8% vs 1.1%, p=0.02)**

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

SELECT- D: Rivaroxaban vs Dalteparin

- Open label, randomized trial rivaroxaban 20mg daily vs. Dalteparin
- 6 month cumulative VTE recurrence 4% rivaroxaban vs. 11% Dalteparin (HR 0.43, 95% CI 0.19-0.99)
- Major bleeding was 6% for rivaroxaban vs. 4% Dalteparin (HR 1.83; 95% CI 0.68-4.96)

***Numerically higher rate of CRNM bleeding in rivaroxaban (13% versus 4%; Most bleeding events – GI bleeds)**

Young et al. J Clin Oncol. 2018 Jul 10; 36(20):2017-2023

CARAVAGGIO: Apixaban vs Dalteparin

- Open label, randomized trial of apixaban 5mg BID daily vs. Dalteparin
- Recurrent VTE rate 5.6% Apixaban vs. 7.9% Dalteparin (HR 0.63; 95% CI 0.37-1.07, p<0.001)
- Major bleeding 3.8% in Apixaban vs. 4% Dalteparin (HR 0.82; 955 CI 0.4-1.69, p=0.60)

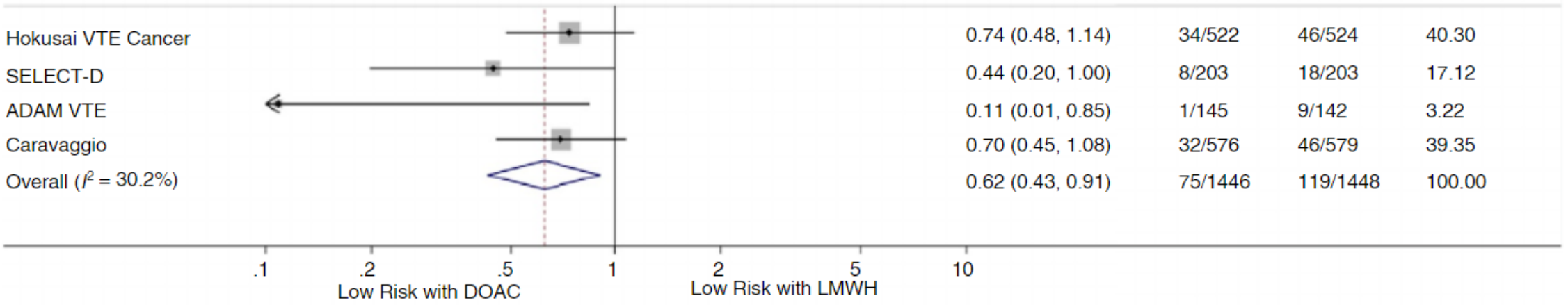
***GIB not studied as primary endpoint (and few pts with UGI and hematologic malignancy)**

***Excluded those with brain malignancy and metastases**

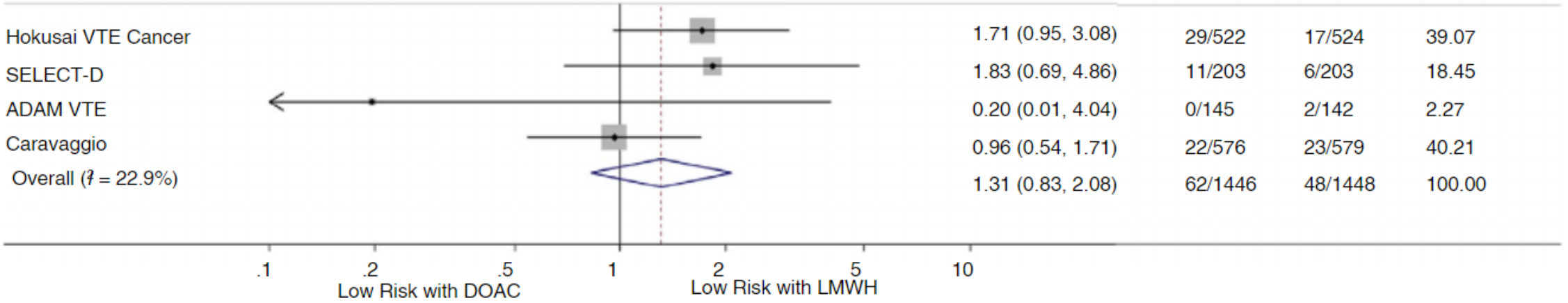
Angnelli et al . N Engl J Med 2020; 382:1599-1607

(A)

Recurrent VTE

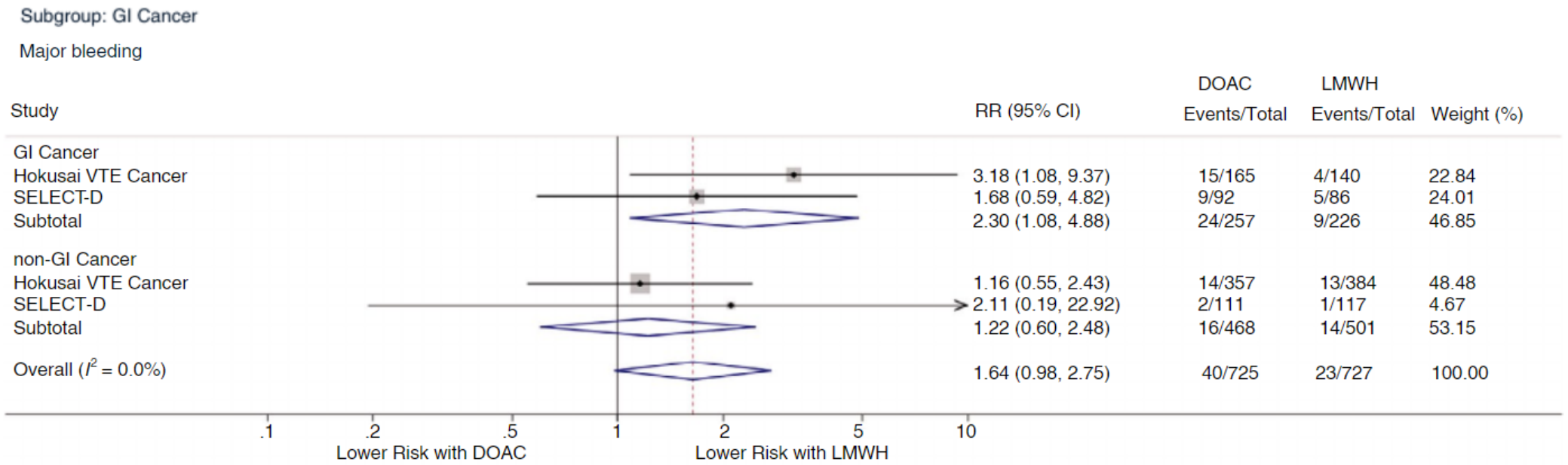


Major Bleeding



Moiik et al. RPTH 2020; 4: 550-561

Risk of major bleeding was significantly elevated in patients with GI cancer treated with DOACs compared to LMWHs (9.3% vs 4.0%; RR, 2.30 [95% CI, 1.08-4.88]; *P* = .031; I^2 = 0.0%).



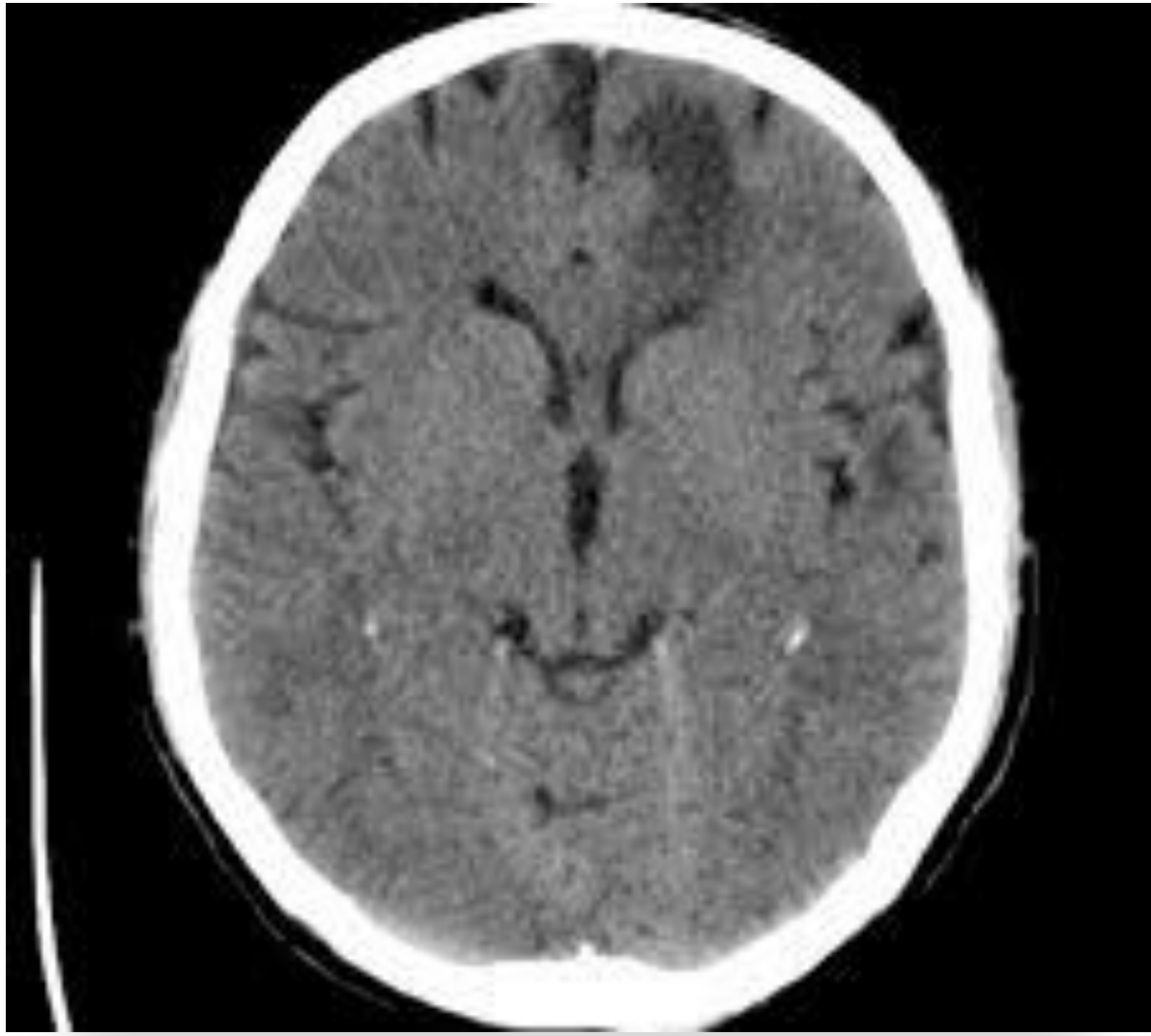
Moiik et al. RPTH 2020; 4: 550-561

Take Home Points

- **DOACs may cause increased GI bleeding in those with upper GI cancer and possible increase in GU bleeding as well**
- Meta-analysis shows possible decrease in recurrent VTE for those treated with DOACs
- General lack of patients with brain malignancy and metastatic brain lesions in these trials
- **Beware of drug interactions**
  - P-glycoprotein or CYP3A4 inhibitors were excluded on trial and few were receiving checkpoint inhibitors

She is treated with Apixaban 5mg BID for 3 months. She then presents with confusion and MRI shows metastatic disease

She is referred for radiation therapy



Limited Data on Anticoagulation with Intracranial Metastases

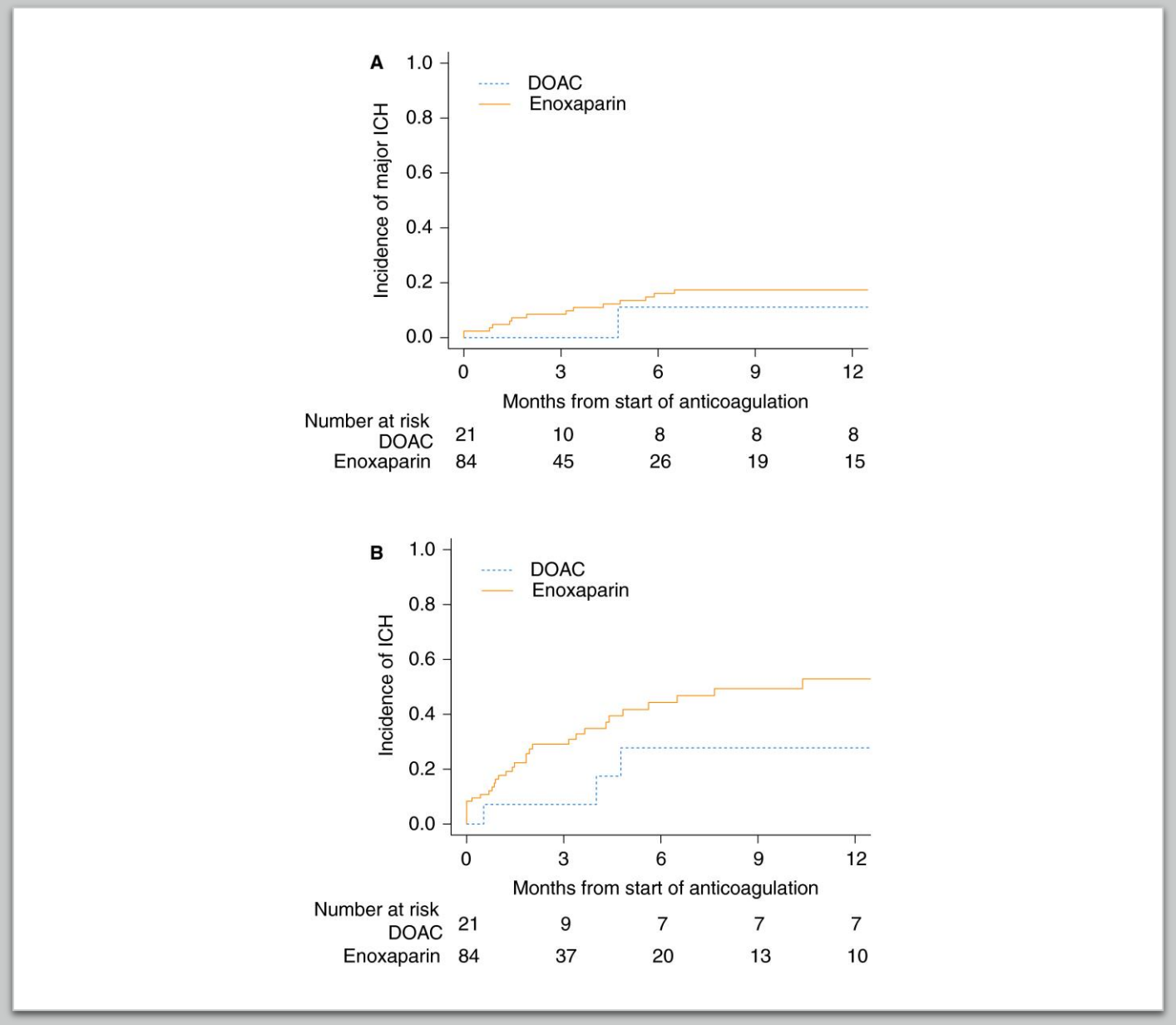
- Matched, retrospective cohort study of 293 cancer patients with brain metastases
- 104 with therapeutic enoxaparin and 189 controls

- 12 month Cumulative incidence of ICH at 1 year in enoxaparin group 19% vs 21% in control group (p=0.97, HR 1.02)

Donato et al. 2015, *Blood*; 126(4):

ICH with DOACs in patients with brain tumors

- Retrospective cohort study including 172 brain tumor patients (primary and brain metastases)
- In the brain metastases cohort the 12 month CI of ICH was 27.8% vs 52.9%, (p=0.15) and major ICH was 11.1% vs 17.8% (p=0.38)
- No deaths of ICH in either cohort



Carney et al. JTH 2018, 17 (72-76)

IN SUMMARY . . ..

- DOACs may be considered in primary prophylaxis in cancer patients
  - Need better predictive models of CAT to assess benefit
  - Longer follow up is also needed
- Use of DOACs in treating CAT has become standard of care
  - Increased risk of GI and GU bleeding in those with upper GI or intraluminal GU malignancy
  - Drug interactions
  - Most data was prior to use of immunotherapy
- More data is needed (including randomized trials) to evaluate use of DOACs in patients with CNS malignancy but preliminary data suggests it is non inferior to LMWH