Thrombosis and Clot Management

Lymphoma Tumor Board

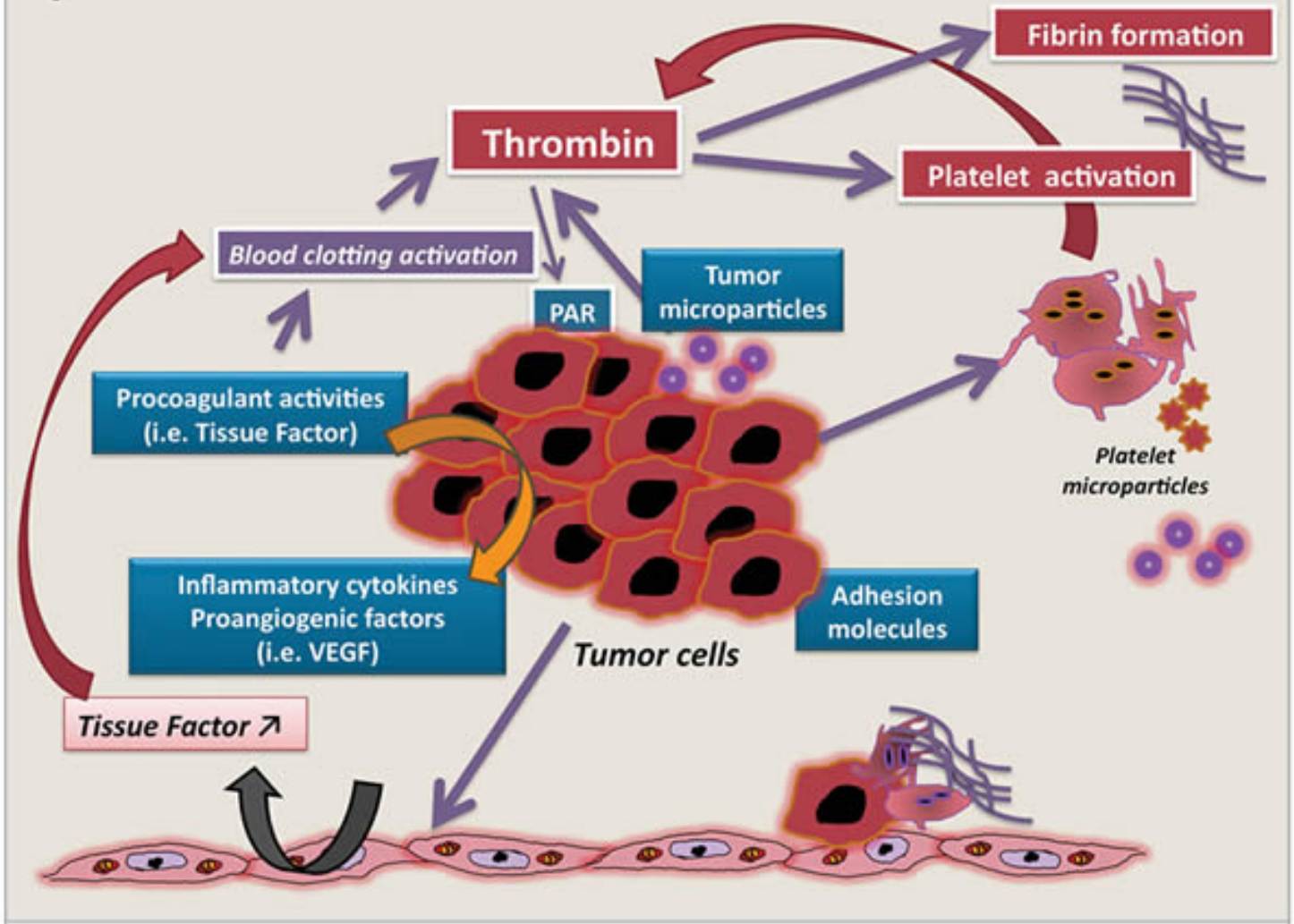
October 13, 2017

Venous thromboembolism (VTE)

- Venous thromboembolism (VTE) is a leading cause of death in patients with cancer, regardless of cancer stage.
- Cancer is associated with a hypercoagulable state and a four-fold increase in thrombosis risk
- Types of thromboembolism include:
  - Deep vein thrombosis (DVT) – most common
  - Pulmonary embolism (PE)
  - Splanchnic veins and upper extremity venous system – less common
  - Catheter-related thrombosis – less common
- Advances in the management of VTE since the induction of low-molecular-weight-heparin (LMWH) have been modest
- Used for long-term therapy
- High risk for bleeding in cancer patients can limit therapeutic options
- "TF of tumor origin is a key molecule that initiates blood clotting and also supports tumor growth and metastasis by coagulation-independent mechanisms, such as up-regulation of VEGF and activation of PAR-2."

Anna Falanga, MD (2011). The Cancer-Thrombosis Connection. Blood, July-August 2011, Volume 8, Issue 4

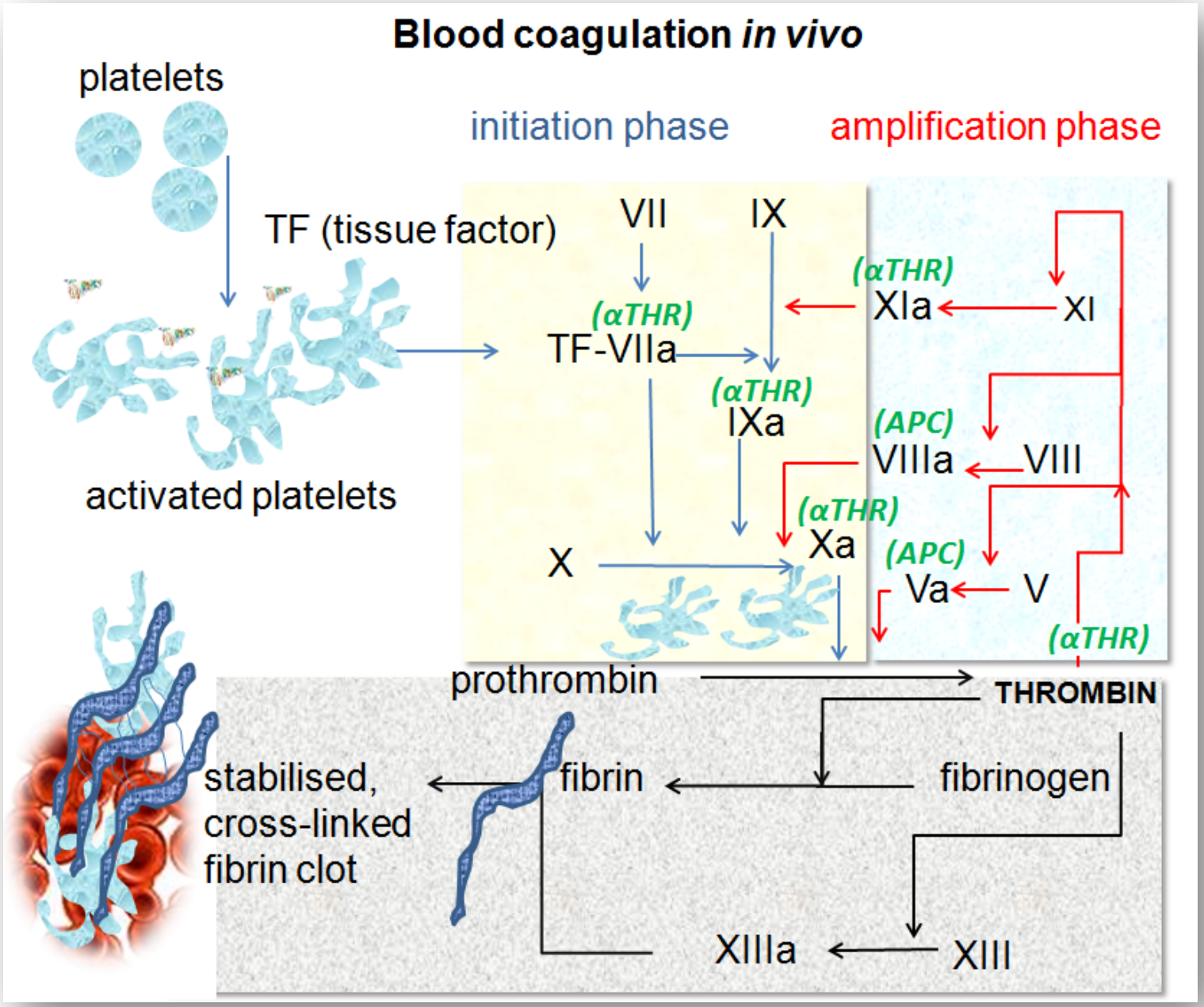
Figure



Mechanisms of hemostatic system activation by tumor cells involves different hemostatic pathways. Tumor cells produce procoagulant, fibrinolytic, and platelet-aggregating activities and release proinflammatory and proangiogenic cytokines and procoagulant microparticles. Tumor cells interact with host vascular and blood cells (i.e., platelets, leukocytes, and endothelial cells) by means of direct adhesion, which activates the prothrombotic properties of these cells. Tumor cell-derived TF plays a central role in the generation of thrombin, but TF can also contribute to tumor growth and metastasis by coagulation-independent mechanisms, including influencing the expression of VEGF by the malignant cells and vascular cells and activating the PAR-2 signaling.

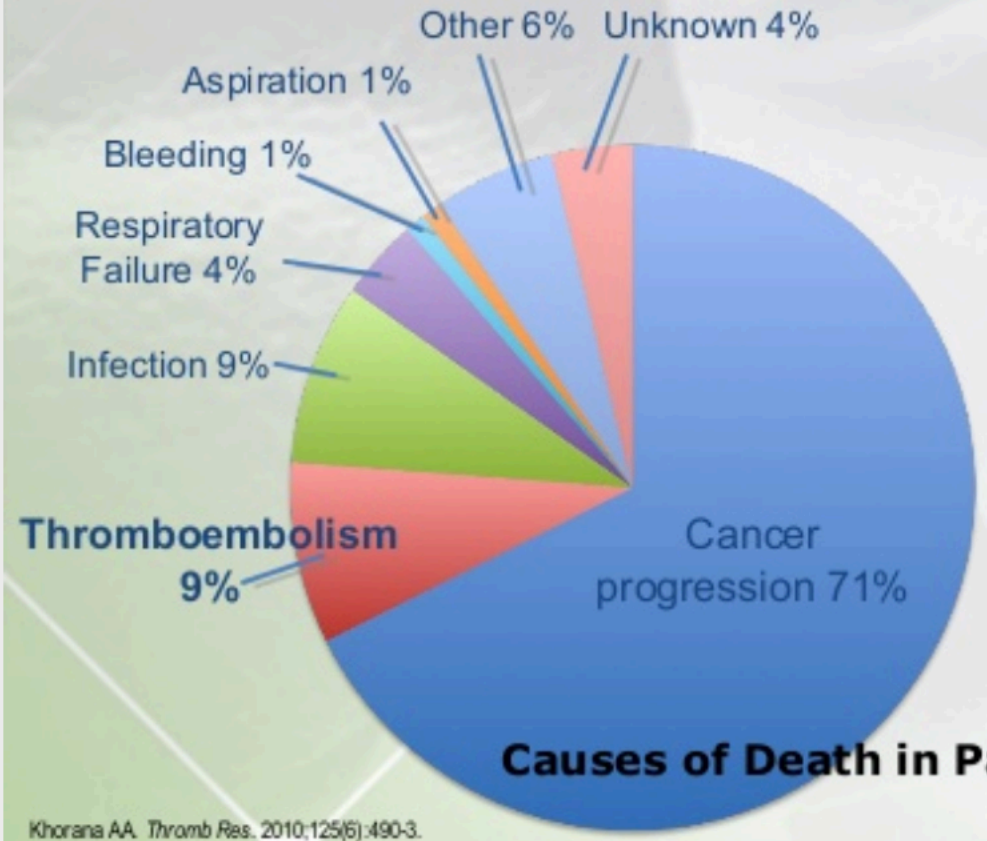
The generation of activated coagulation proteases (FVIIa, FXa, thrombin) and the formation of fibrin represent coagulation-dependent mechanisms of tumor progression, as they promote neo-angiogenesis and tumor proliferation. Fibrin coats also protect circulating cancer cells from attack by the host immune system.

Coagulation System



Why should we care?

- 47-fold increased risk of mortality from VTE
- 2nd leading cause of death in cancer patients



Causes of Death in Patients with Cancer

- VTE associated with early mortality during chemotherapy (HR=6.98)

Khorana AA. *Thromb Res*. 2010;125(6):490-3.

VTE Oncology Simplified

Risk Factors for Cancer-Associated VTE

Patient-related factors

- Increased age
- Ethnicity (risk increased in African Americans)
- Co-morbidities (infection, renal and pulmonary disease, arterial thromboembolism, VTE history, inherited prothrombotic mutations)
- Obesity
- Performance status

Treatment-related factors

- Chemotherapy, antiangiogenesis agents, hormonal therapy
- Radiation therapy
- Surgery ≥60 mins
- ESAs, transfusions
- Indwelling venous access

Cancer-related factors

- Primary site of cancer
- Stage (risk increases with higher stage)
- Histology
- Time since diagnosis (risk increases during first 3-6 months)

Biomarkers

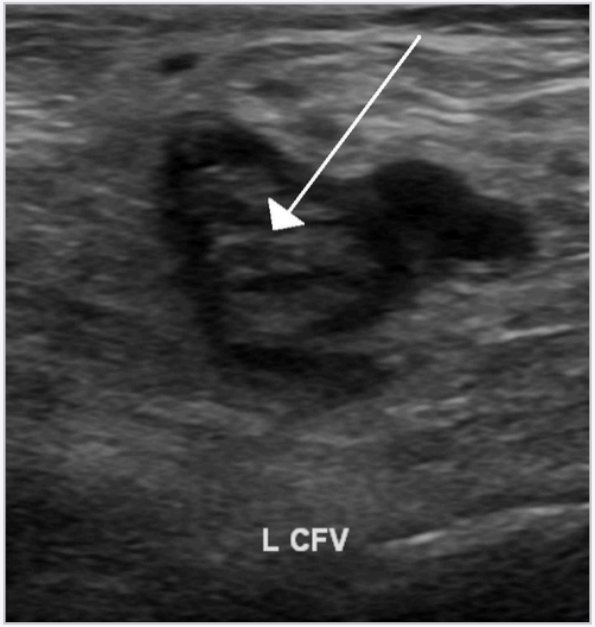
- Platelet count ≥ 350 x 10^9/L
- Leukocyte count >11 x 10^9/L
- Hemoglobin < 100g/L

Lyman GH, *et al. ASCO Update. J Clin Oncol.* 2013; accessed online ahead of Print.

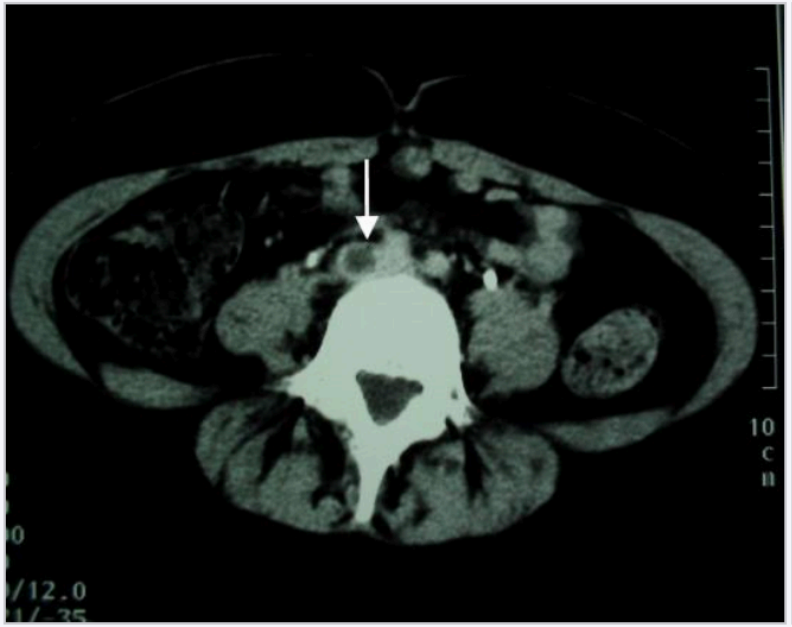
Probability of DVT

- Clinical prediction rule called the Wells Score is used in suspected cases of DVT in patients.
- **Wells score criteria**: (possible score −2 to 9)
  - Active cancer (treatment within last 6 months or palliative): +1 point
  - Calf swelling ≥ 3 cm compared to asymptomatic calf (measured 10 cm below tibial tuberosity): +1 point
  - Swollen unilateral superficial veins (non-varicose, in symptomatic leg): +1 point
  - Unilateral pitting edema (in symptomatic leg): +1 point
  - Previous documented DVT: +1 point
  - Swelling of entire leg: +1 point
  - Localized tenderness along the deep venous system: +1 point
  - Paralysis, paresis, or recent cast immobilization of lower extremities: +1 point
  - Recently bedridden ≥ 3 days, or major surgery requiring regional or general anesthetic in the past 12 weeks: +1 point
  - Alternative diagnosis at least as likely: −2 points
  - **Those with Wells scores of +2 or more have a 28% chance of having DVT, those with a lower score have 6% odds**

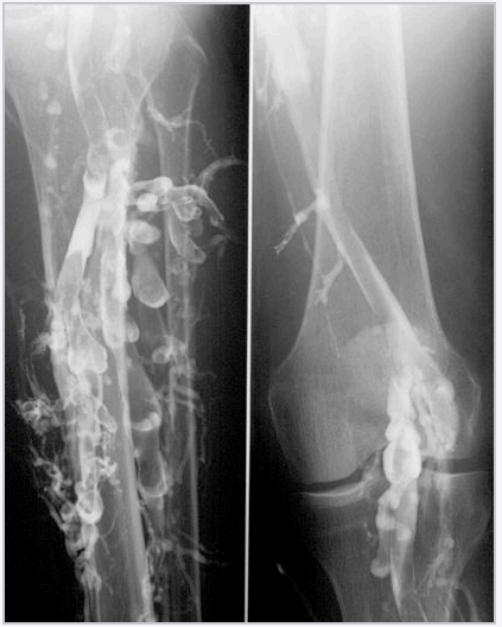
Imaging of VTE



An ultrasound with a blood clot visible in the left common femoral vein

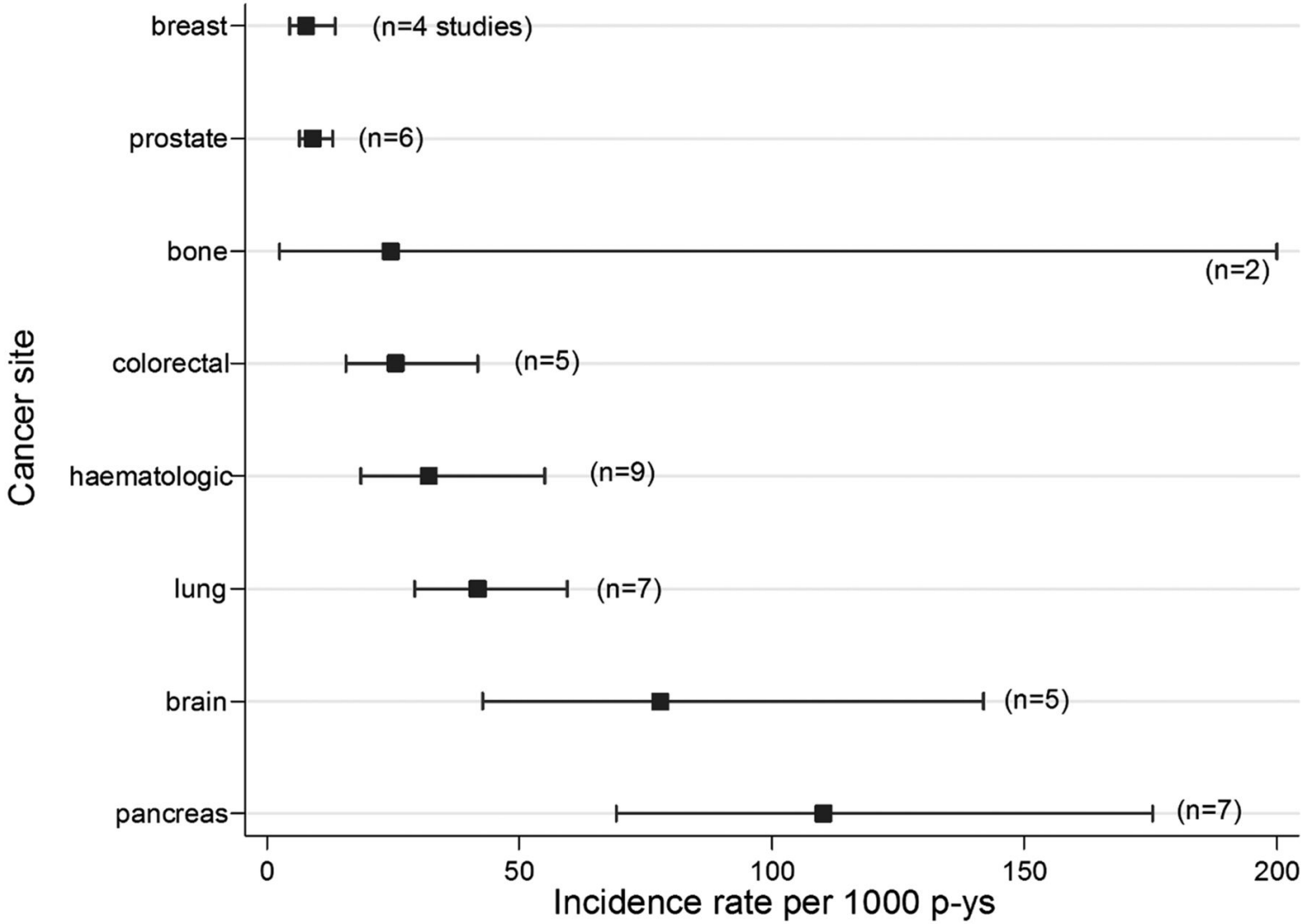


An abdominal CT scan with a clot in the right common iliac vein



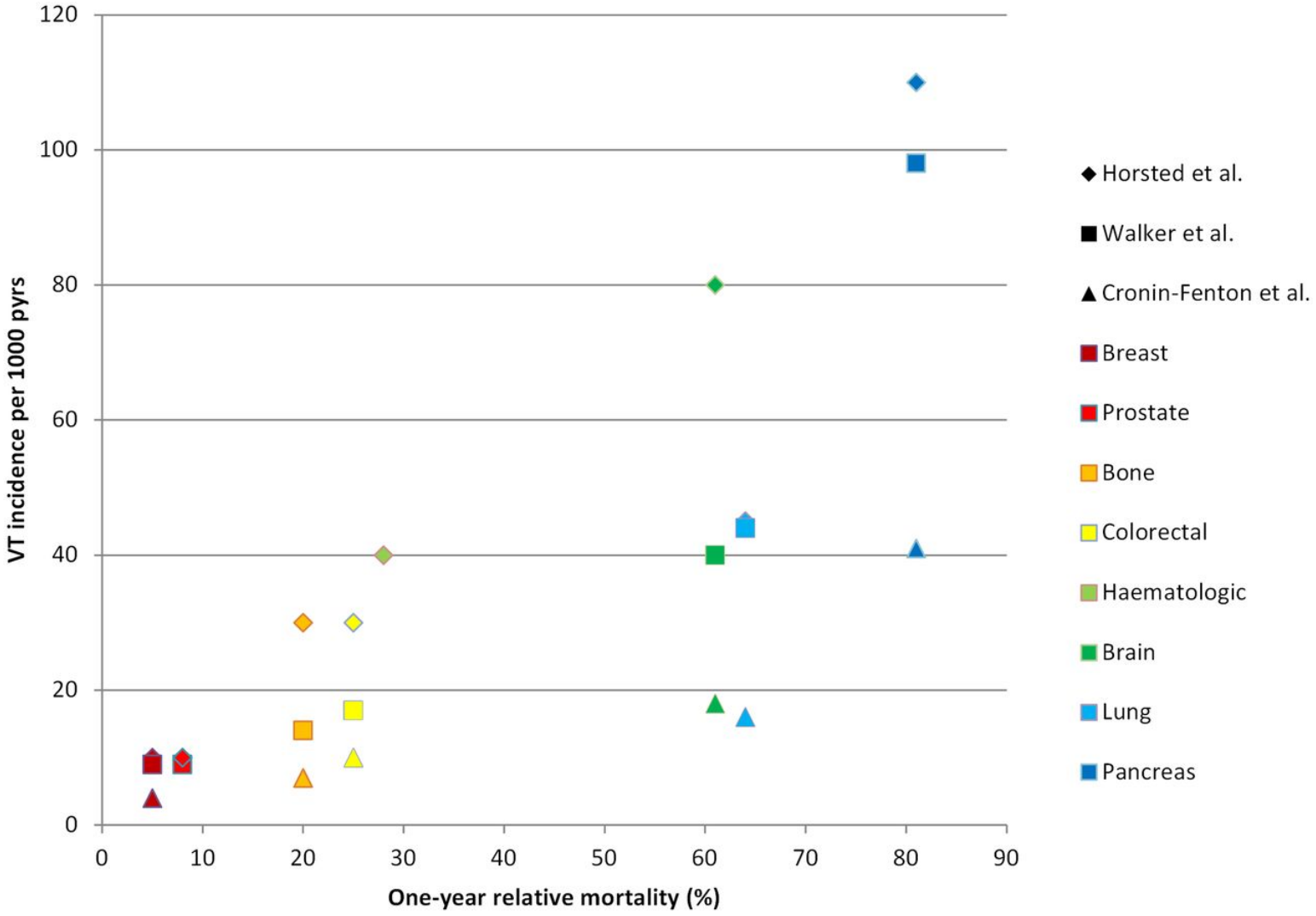
Venograms of DVT

Pooled incidence rates (per 1000 person-years) of venous thrombosis per type of cancer



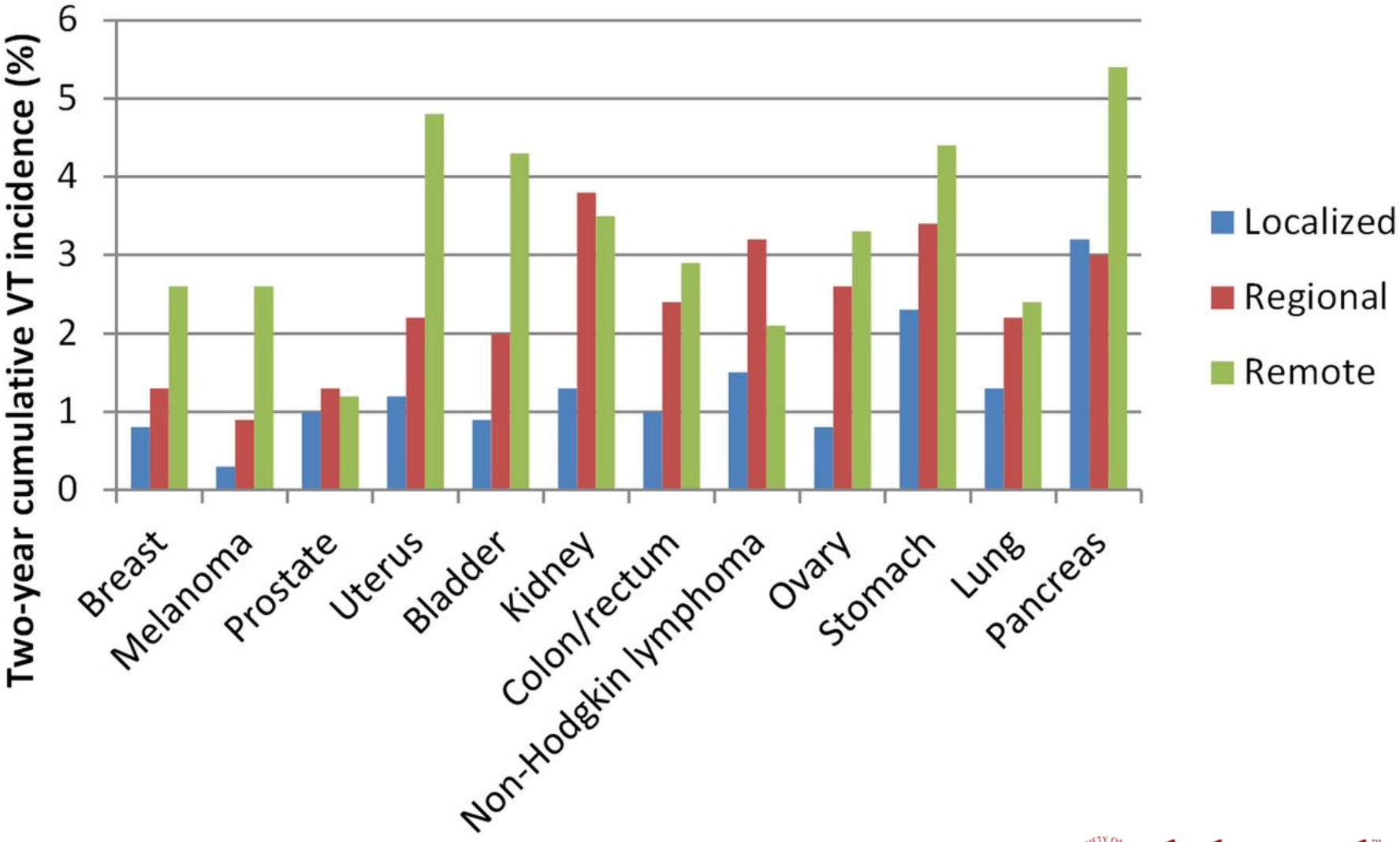
Jasmijn F. Timp et al. Blood 2013; 122:1712-1723

Incidence rates of venous thrombosis (VT) per type of cancer plotted against the 1-year relative mortality for each cancer type



Jasmijn F. Timp et al. Blood 2013; 122:1712-1723

Two-year cumulative incidence (%) of venous thrombosis per type and stage of cancer



Jasmijn F. Timp et al. Blood 2013; 122:1712-1723

Guidelines for management of VTE in cancer patients

Table 2. Guidelines for Managing VTE in Cancer Patients

Recommendation	NCCN (2014)	ASCO (2015)	ACCP (2015)
Initial therapy	LMWH preferred	LMWH recommended	LMWH recommended
Chronic therapy	LMWH preferred over warfarin for 1st 6 mo	LMWH preferred for ≥6 mo	LMWH preferred Extended therapy >3 mo recommended. In patients not treated with LMWH, VKA suggested over rivaroxaban or dabigatran
Chronic outpatient treatment	Novel oral anticoagulants not currently recommended for VTE thromboprophylaxis or treatment owing to insufficient clinical data in cancer patients	Novel oral anticoagulants not currently recommended for patients with cancer and VTE owing to limited data in cancer patients	LMHW and VKA recommended over rivaroxaban or dabigatran

ACCP: American College of Chest Physicians; ASCO: American Society of Clinical Oncology; LMWH: low-molecular-weight heparin; NCCN: National Cancer Comprehensive Network; VKA: vitamin K antagonist; VTE: venous thromboembolism.
Source: References 15, 19, 20.

Anticoagulants for VTE

Table 3. Pharmacokinetics of Oral Anticoagulants					
Factor	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Bioavailability	~100%	3%-7%	10-mg dose: 80%-100% 20-mg dose: 66% (fasting)	50%; prolonged absorption	62%
Time to max concentration	4 h (peak anti-coagulant effect delayed 72-96 h)	1-2 h	2-4 h	3-4 h	1-2 h
Protein binding	35%	92%-95%	87%	99%	55%
Metabolism	CYP2C9, 2C19, 2C8, 2C18, 1A2, 3A4	Conjugation, prodrug is Pgp substrate	CYP3A4/5, CYP2J2, hydrolysis, Pgp substrate	CYP3A4 (major), CYP1A2, 2C8, 2C19, 2J2 (all minor), Pgp substrate	Conjugation, hydro-lysis, CYP3A4 (all minor), Pgp substrate
Elimination	Hepatic metabolism	Renal (80%)	Renal (66%; 36% unchanged)	Renal (27%), fecal	Renal (50%), metabolism and biliary/intestinal excretion (50%)
Half-life	~40 h	12-17 h	5-9 h; longer in elderly	12 h	10-14 h

max: maximum; Pgp: P-glycoprotein.
Source: References 27-31.

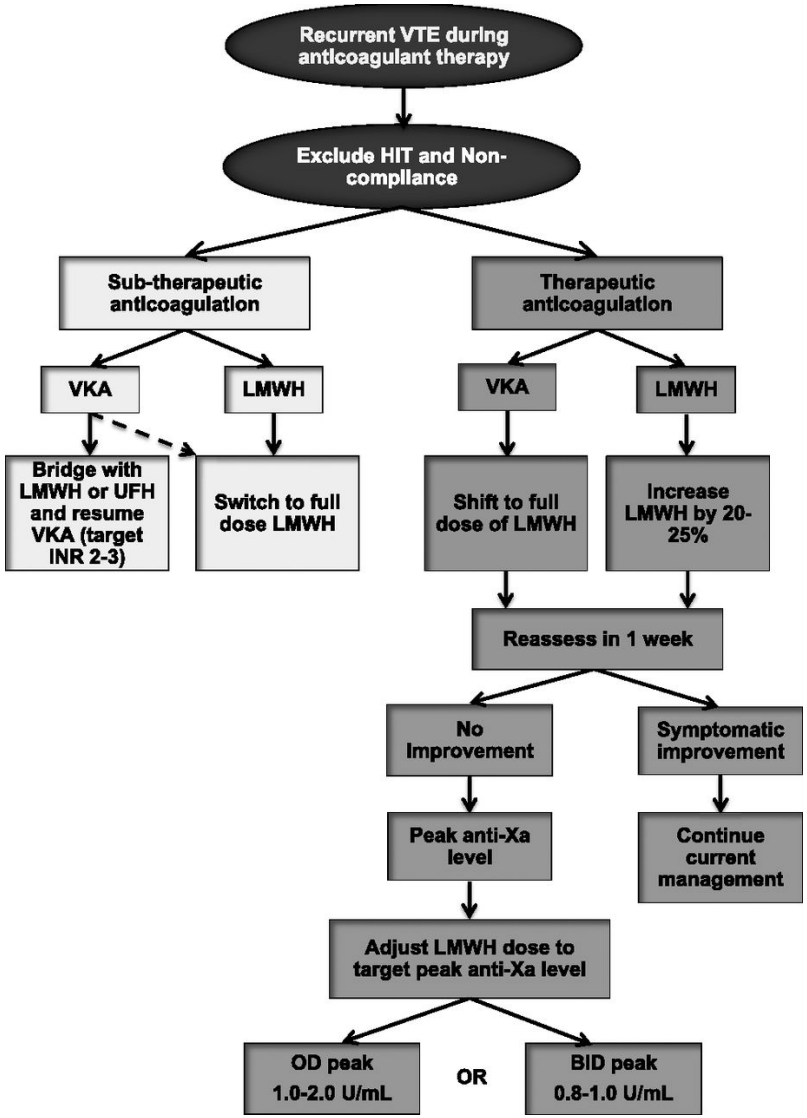
Treatment for VTE

Table 4. Common Agents for the Treatment of VTE

Agent	Usual Dosage	Dosage Adjustment	Food Considerations
Enoxaparin	1 mg/kg SC q12h or 1.5 mg/kg SC once daily	CrCl <30 mL/min: 1 mg/kg once daily. Not approved for use in dialysis patients	None
Dalteparin[a]	Initial: 200 U/kg SC once daily × 30 days (max 18,000 U) Maintenance: ~150 U/kg once daily (max 18,000 U)	Caution in renal impairment. If CrCl <30 mL/min, manufacturer recommends monitoring anti-Xa levels	None
Warfarin	Dosage adjusted to maintain INR 2-3	Based on INR results	Vitamin K–containing foods may decrease effectiveness
Dabigatran	5-10 days with parenteral agent, then 150 mg po bid	CrCl <30 mL/min: no manufacturer recommendation	None
Rivaroxaban	15 mg po bid × 21 days, then 20 mg po once daily	CrCl <30 mL/min: avoid use	Take doses >10 mg/day with food to increase bioavailability
Apixaban	10 mg po bid × 7 days, then 5 mg po bid. After ≥6 mo, 2.5 mg bid	No adjustment necessary, but in Hokusai VTE trial, patients excluded if CrCl <30 mL/min	None
Edoxaban	5-10 days with parenteral agent, then 60 mg po once daily	CrCl 15-50 mL/min: 30 mg once daily; CrCl <15 mL/min: avoid use. Moderate-to-severe hepatic impairment (Child-Pugh B-C): avoid use. Weight ≤60 kg: 30 mg once daily	None

[a] Dalteparin is FDA-approved only for VTE treatment in cancer patients; it is used off-label in VTE patients without cancer.
CrCl: creatinine clearance; INR: international normalized ratio; max: maximum; VTE: venous thromboembolism.
Source: References 33-38.

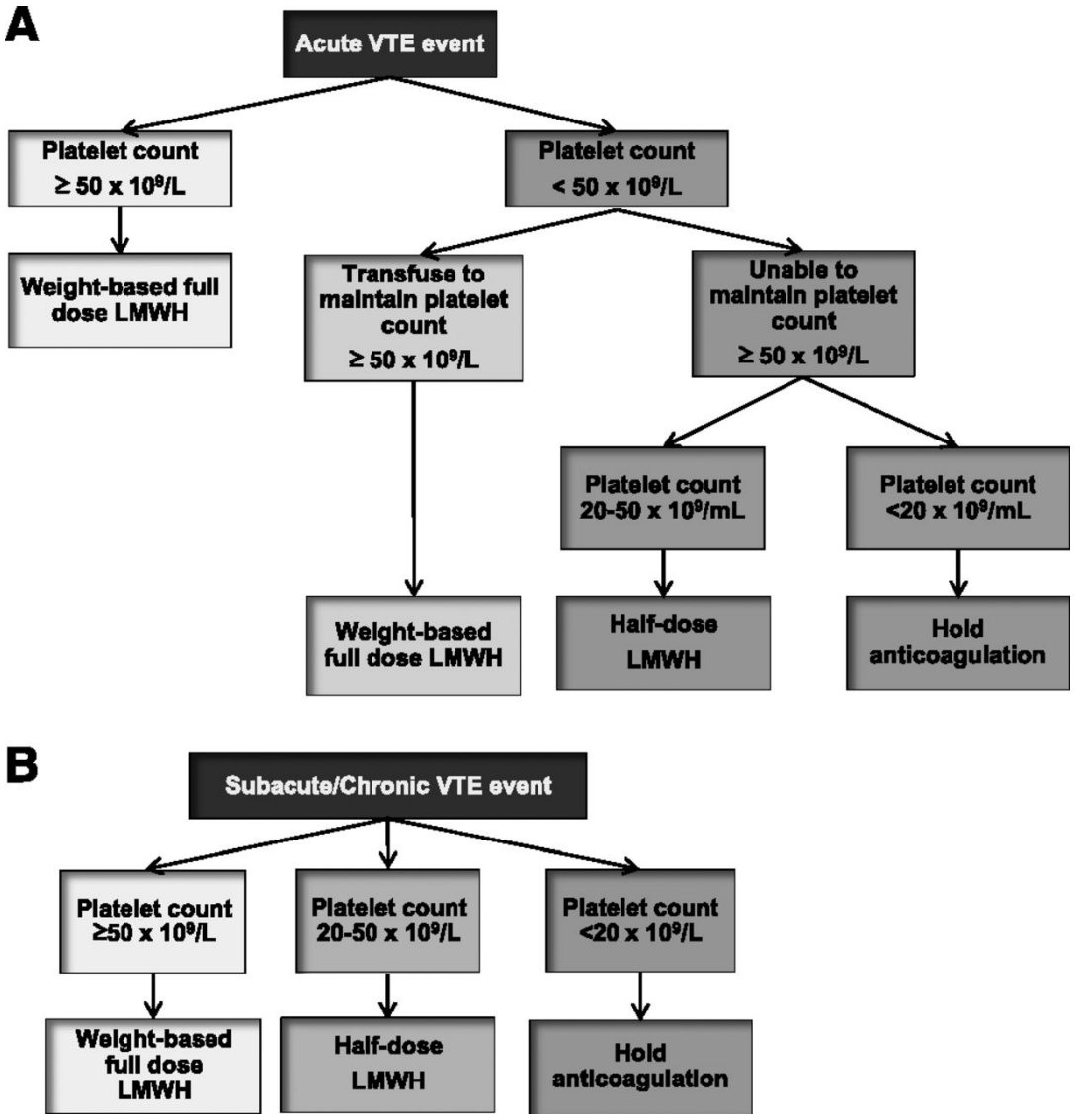
Management algorithm of recurrent VTE in patients with cancer



Agnes Y. Y. Lee, and Erica A. Peterson Blood 2013; 122:2310-2317

blood

Management algorithm of VTE in patients with cancer and thrombocytopenia



Agnes Y. Y. Lee, and Erica A. Peterson Blood 2013; 122:2310-2317

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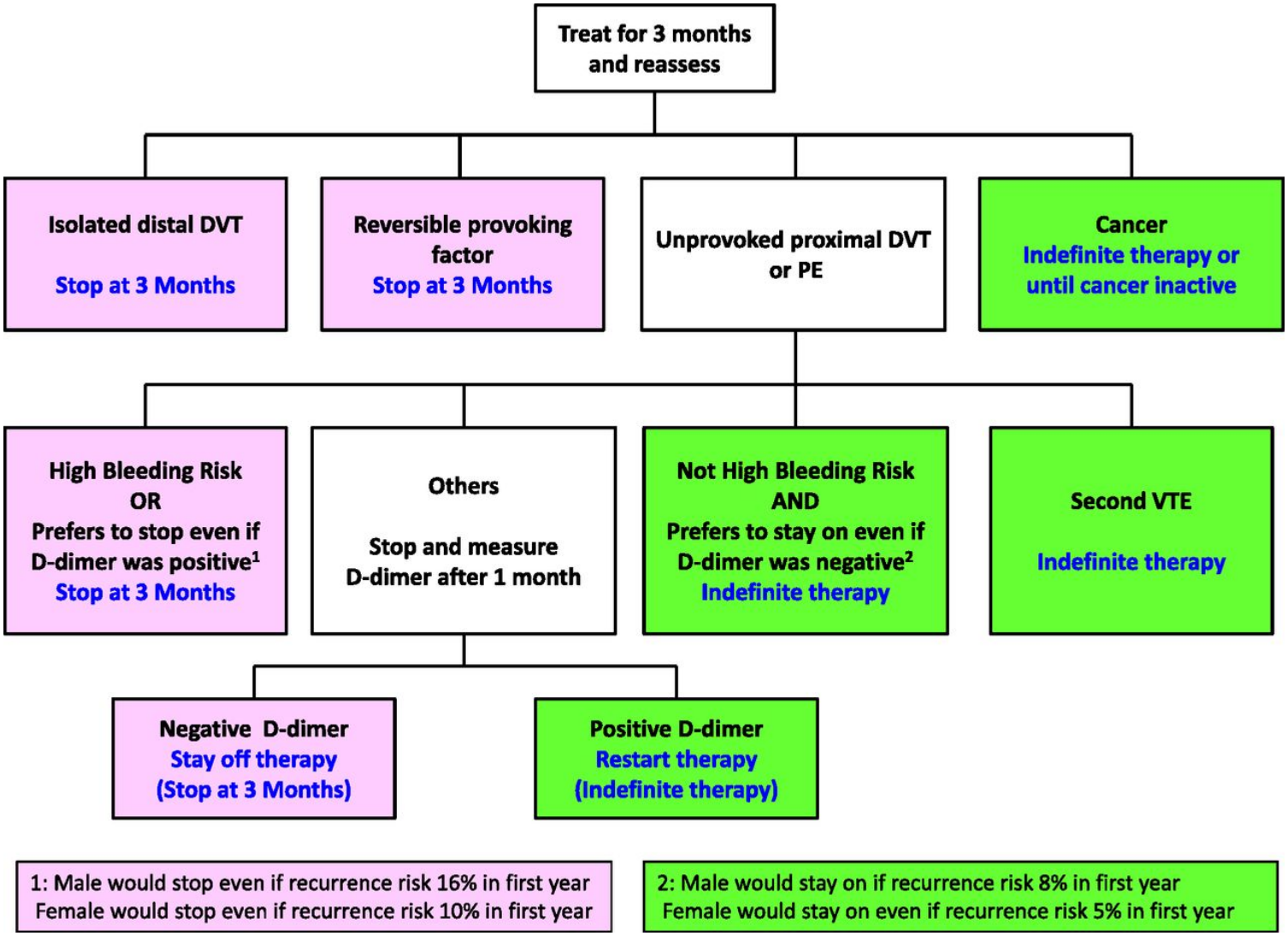
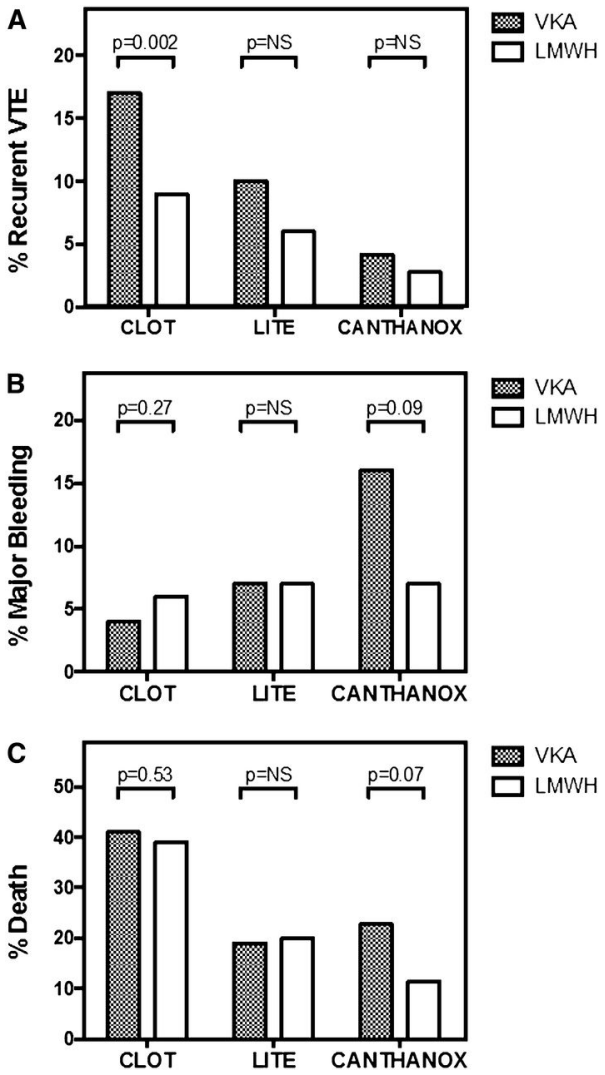
Patients with VTE who should be treated for 3 months and who should be treated indefinitely



Clive Kearon, and Elie A. Akl Blood 2014; 123:1794-1801

blood

Comparison of randomized controlled trials of different preparations of LMWH vs VKA for the long-term management of cancer-associated thrombosis



Agnes Y. Y. Lee, and Erica A. Peterson Blood 2013; 122:2310-2317

Risks of recurrent VTE after stopping anticoagulant therapy

Table 1

Risks of recurrent VTE after stopping anticoagulant therapy which justify strong or weak recommendations to either stop anticoagulants at 3 months or to treat indefinitely

Effect of 5 y of anticoagulation on mortality*	Recommendation	Risk of recurrent VTE without anticoagulation† (%)			
		Low bleeding risk‡		Intermediate bleeding risk§	
		5 y	First y	5 y	First y
Any increase	Strong for 3 mo	<9	<3	<18	<6
0%–0.5% decrease	Weak for 3 mo	9–24	3–8	18–33	6–11
0.5%–1% decrease	Weak for indefinite	24–39	8–13	33–48	11–16
>1% decrease	Strong for indefinite	>39	>13	>48	>16

Assumptions as described in text and in the ACCP guidelines[1] for: case fatality of recurrent VTE (3.6%) and major bleeding (11.3%); proportion of major bleeds attributable to anticoagulation (62%); risk reduction for VTE with anticoagulation (88%).

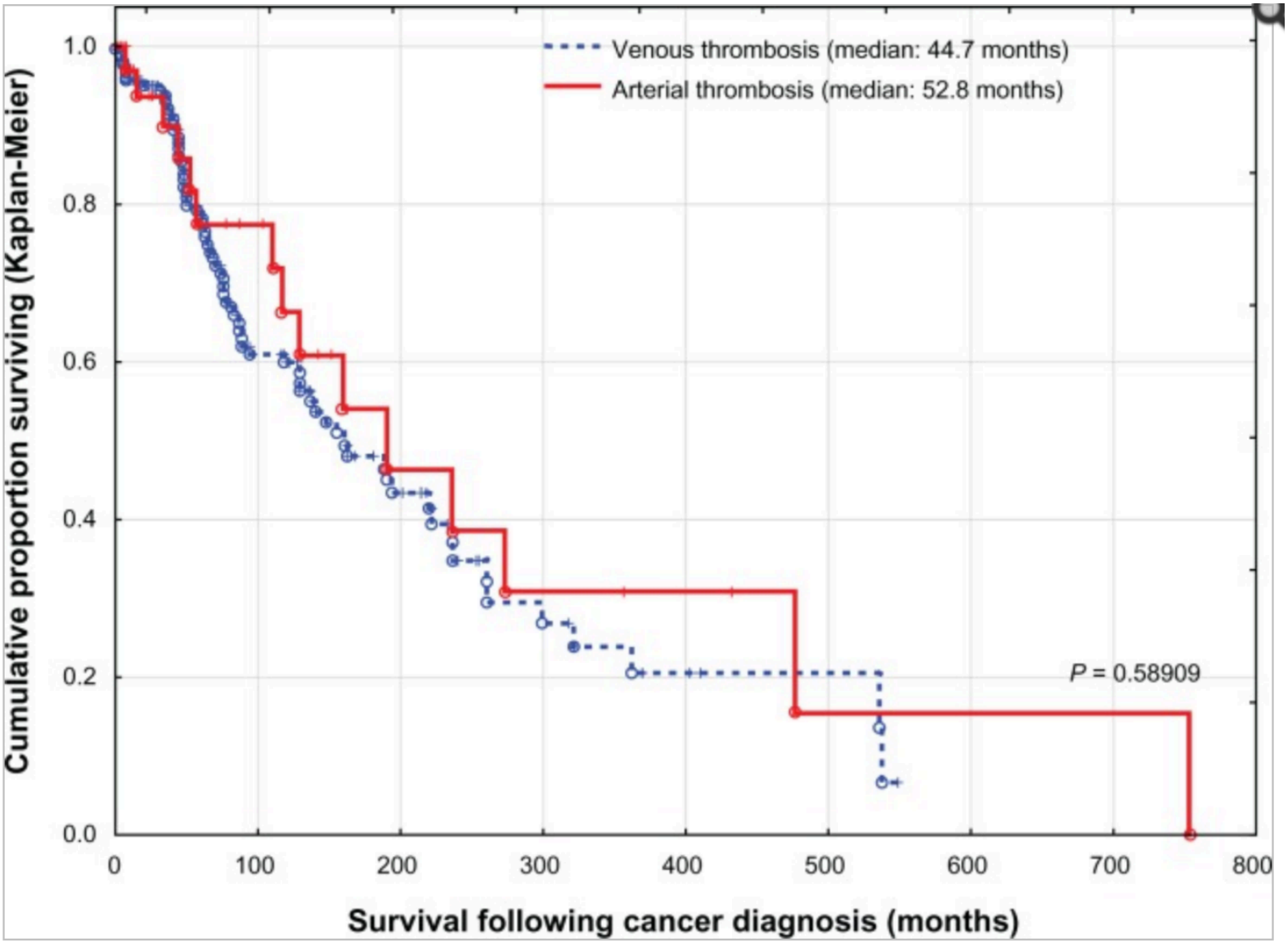
↵* Net effect of decrease in recurrent VTE and increase in bleeding.

↵† Calculations based on a 5-year period, with one-third of recurrences in the first year and two-thirds in the next 4 years.

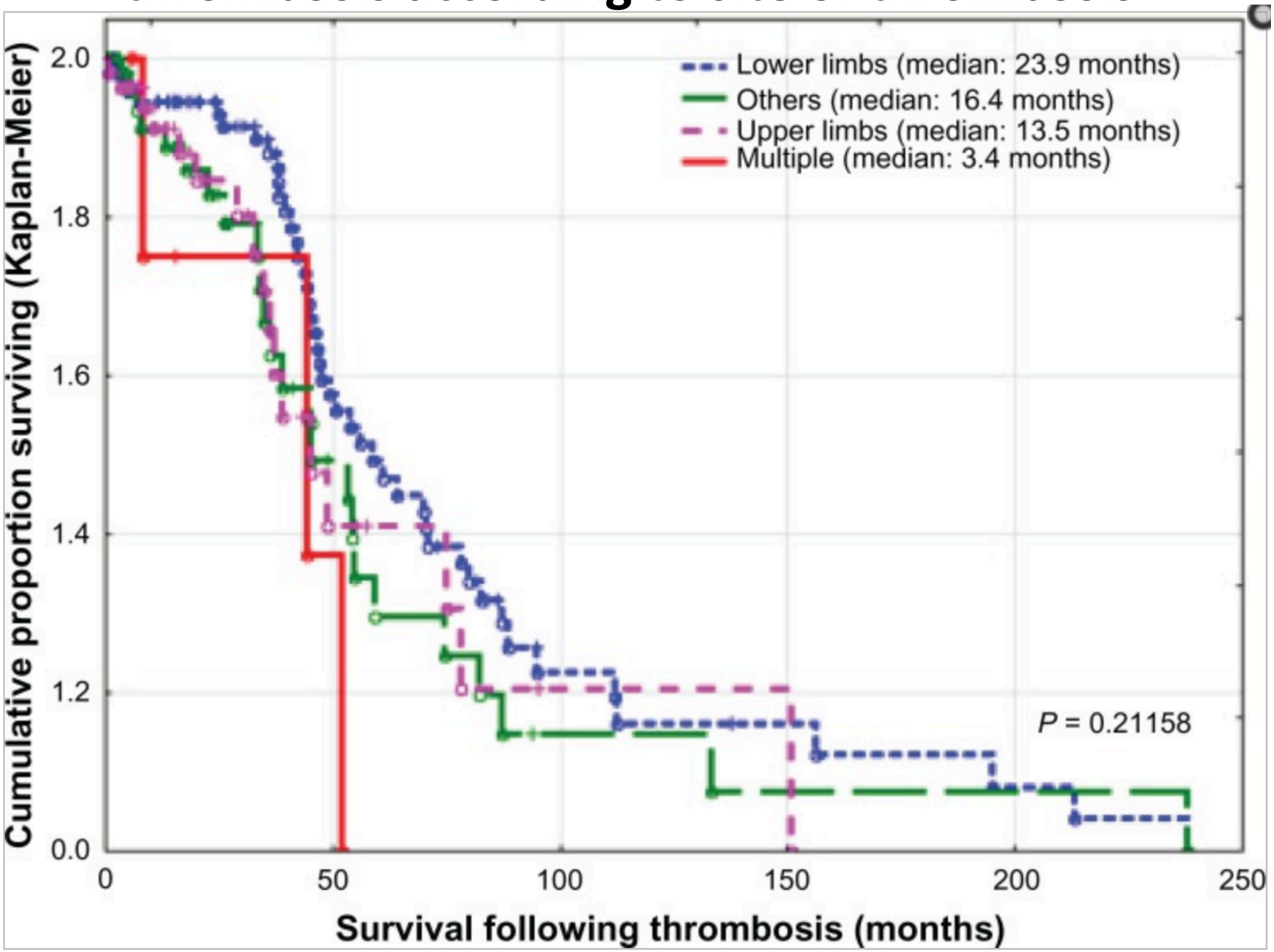
↵‡ Risk of major bleeding of 0.8% for each of the 5 years.

↵§ Risk of major bleeding of 1.6% for each of the 5 years.

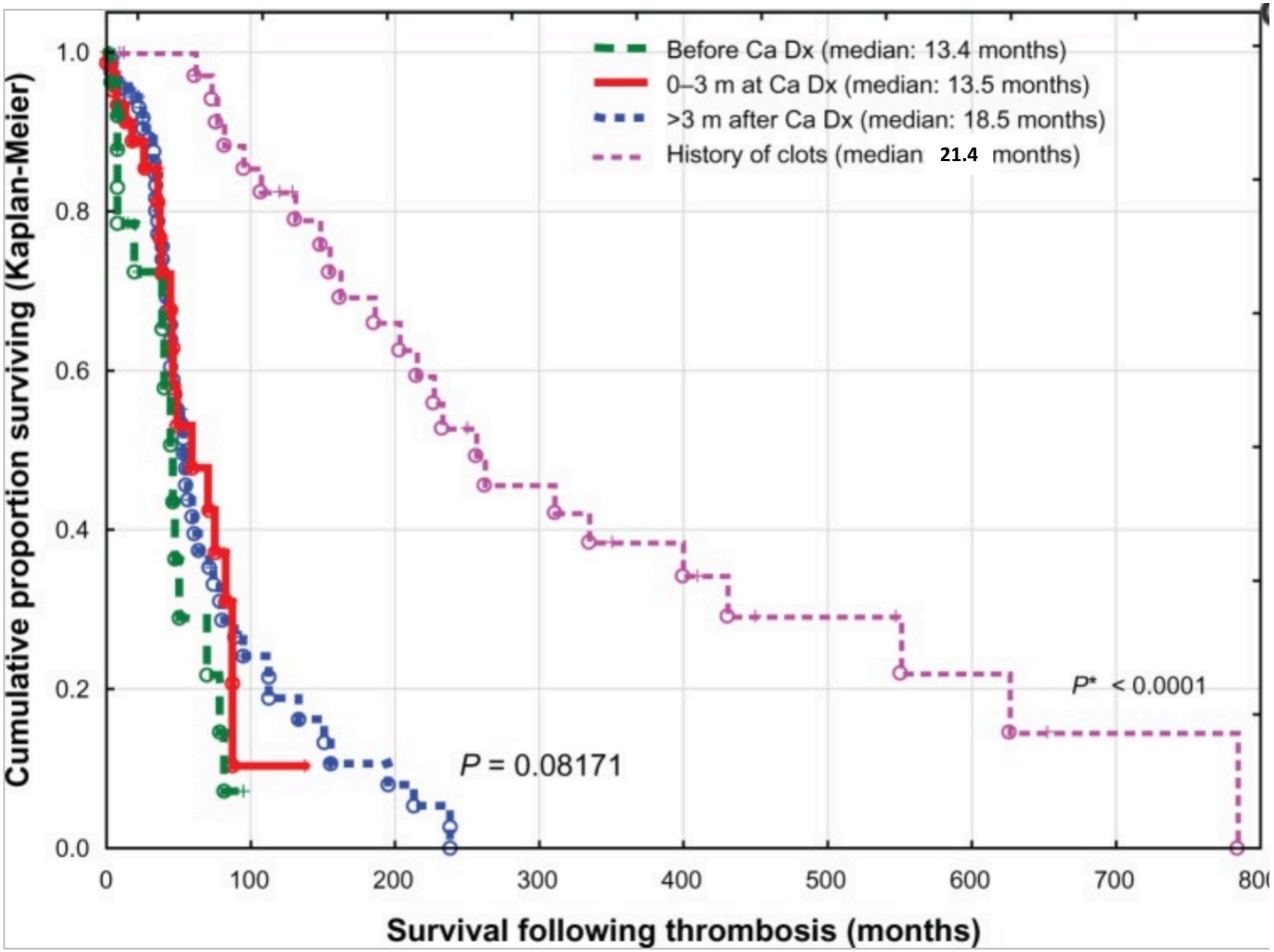
Survival of patients with cancer-related thrombosis following initial diagnosis of cancer



Survival of patients with cancer-related thrombosis according to site of thrombosis



Time elapsed from diagnosis of cancer to onset of thrombosis and impact on survival



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