CANCER AND THROMBOSIS

ANTICOAGULATION IN ONCOLOGY. WHAT TO DO?

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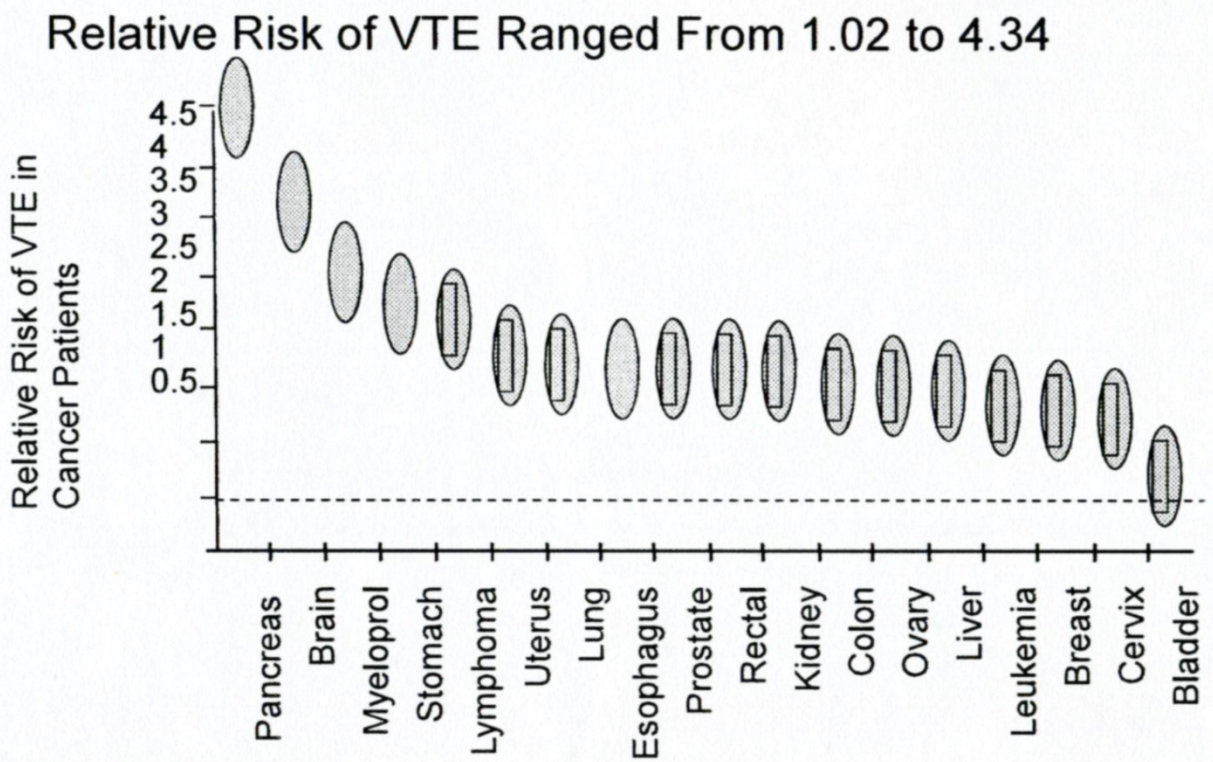
RISK FACTORS FOR HYPERCOAGULABILITY IN CANCER PATIENTS

1) Cell type of cancer
2) Stage of disease progression
3) Frequent surgery
4) Medical comorbidity
5) Too brief period of VTE prophylaxis
6) Longer survival of patients with active cancer
7) Use of ESAS, transfusions, many anti-tumor agents
8) Us, namely overconcern of bleeding, e.g. thrombocytopenia

PATHOGENESIS OF VTE IN CANCER PATIENTS

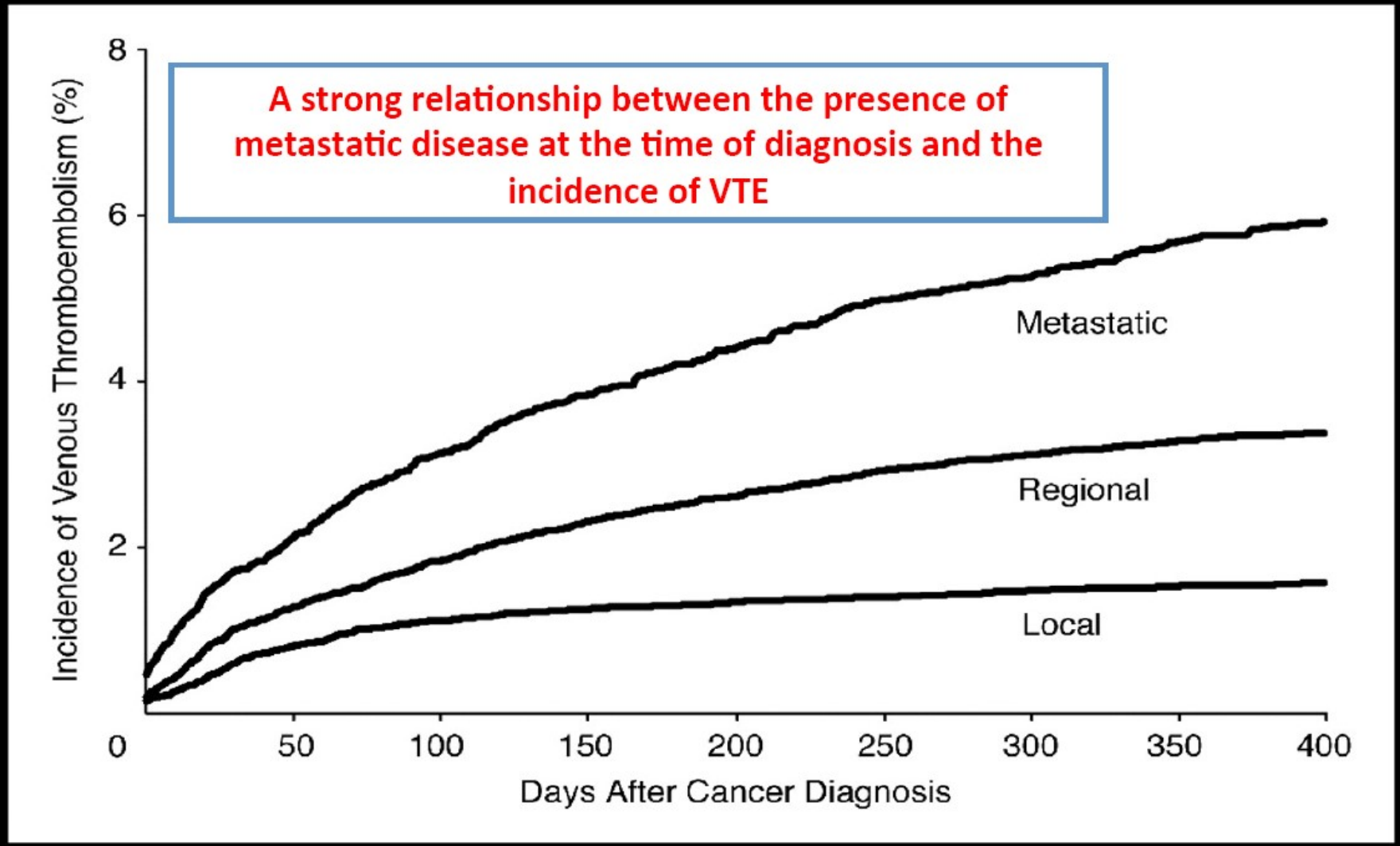
1) Virchow's Triad: stasis, vascular injury, hypercoagulability
2) Tumors and hypercoagulability procoagulants
   - Tissue factor
   - Mucinous secretions
   - Reduced endothelial secretion of tPA
   - Enhanced thrombin generation
3) Cancer and inflammation
   - Increased WBCs
   - Increased cytokines, e.g. TNFα
4) Cancer and thrombocytosis
   - Platelet microparticles
   - Platelet secretions (e.g. P-selectin)

VTE Risk and Cancer Type: "Solid and Liquid"



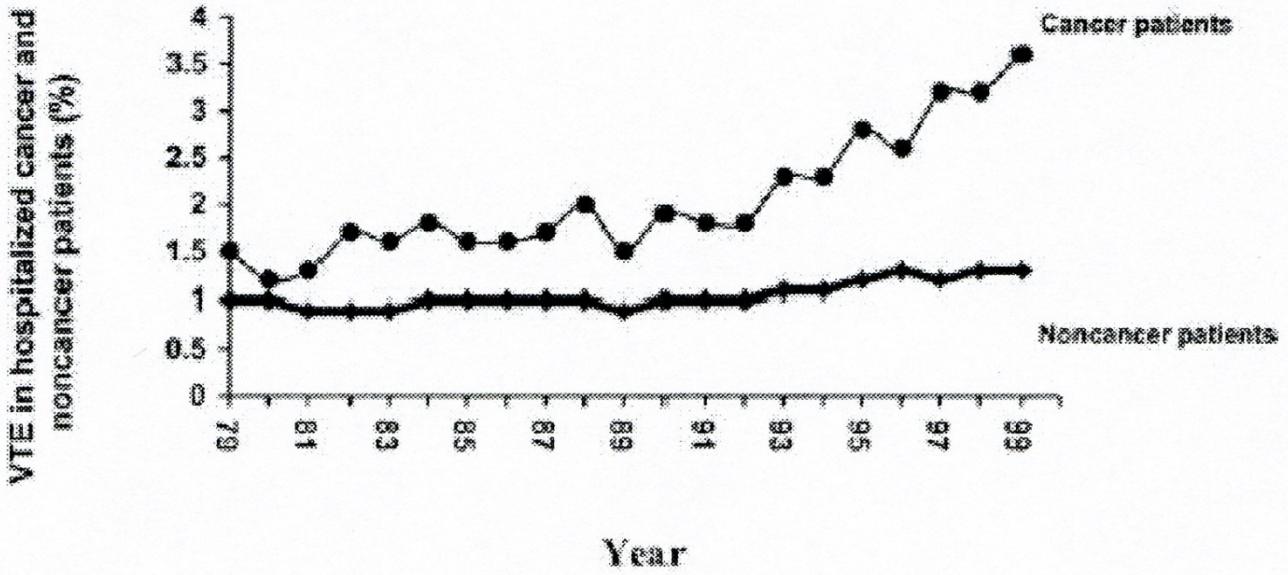
Stein PD, et al. Am J Med 2006; 119: 60-68

Kaplan-Meier plot of the incidence of VTE after colorectal cancer diagnosis stratified by stage



Alcalay A et al. JCO. 2006;24:1112

As Number of Cancer Survivors Increase, VTE Rates Increase



Stein PD, et al. Am J Med 2006; 119: 60-68

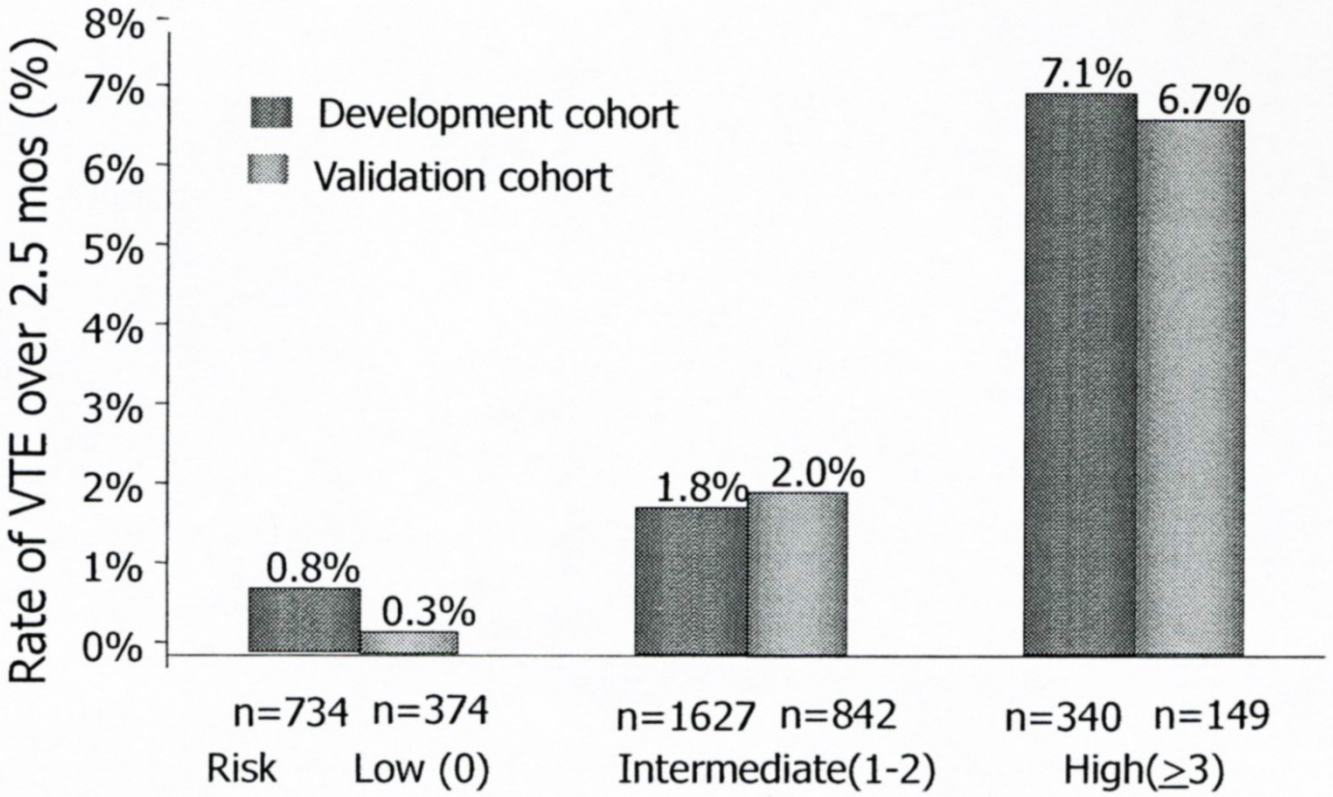
TABLE 23-3 Predictive Model for Chemotherapy-Associated Venous Thromboembolism

Patient Characteristic	Points
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count of ≥350,000/μL	1
Prechemotherapy hemoglobin level of <10 g/dL and/or planned use of erythropoiesis-stimulating agents	1
Prechemotherapy leukocyte count of >11,000/μL	1
Body mass index (BMI) of ≥35 kg/m^2	1

From Khorana AA, Kuderer NM, Culakova E, et al: Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood *111:4902-4907, 2008.*

High-risk score = ≥3; intermediate-risk score = 1 or 2; low-risk score = 0.

Risk Model Validation
in Ambulatory Cancer Patients



Khorana AA et al. *Blood* 2008

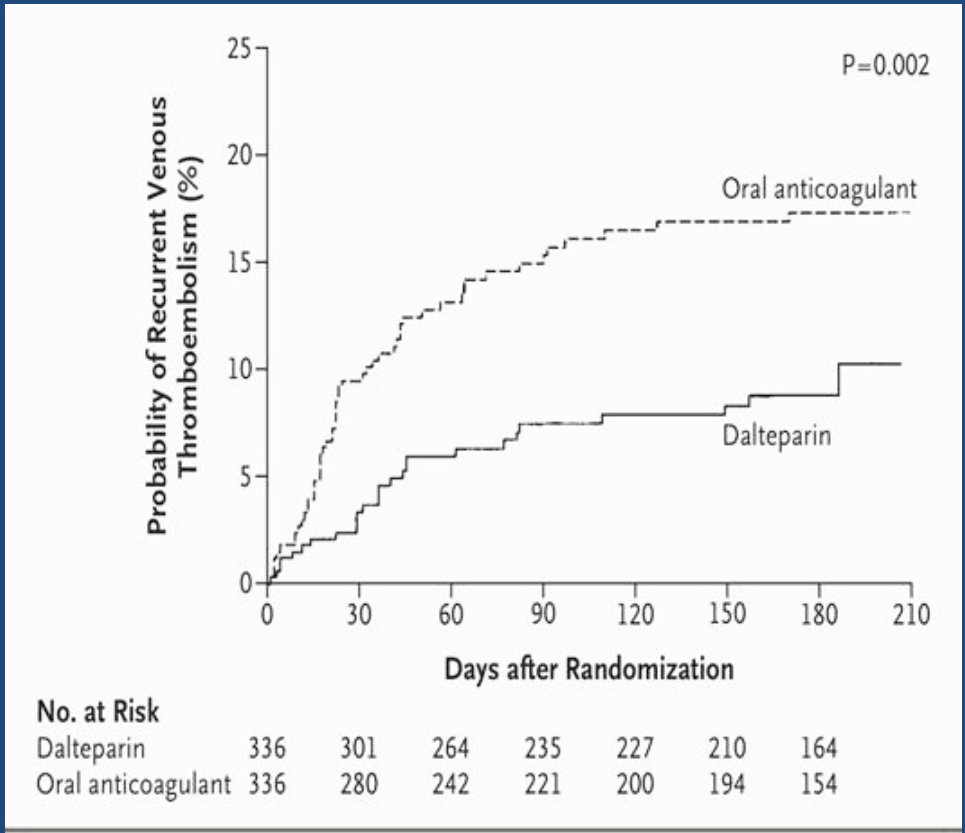


Figure 1. Kaplan–Meier Estimates of the Probability of Symptomatic Recurrent Venous Thromboembolism among Patients with Cancer, According to Whether They Received Secondary Prophylaxis with Dalteparin or Oral Anticoagulant Therapy for Acute Venous Thromboembolism.

An event was defined as an objectively verified, symptomatic episode of recurrent deep-vein thrombosis, pulmonary embolism, or both during the six-month study period. The hazard ratio for recurrent thromboembolism in the dalteparin group as compared with the oral-anticoagulant group was 0.48 (95 percent confidence interval, 0.30 to 0.77; P=0.002 by the log-rank test).

Lee AYY et al. N Engl J Med 2003; 349:146-153.

TABLE 37.7 Comparative Pharmacokinetics and Pharmacodynamics of Direct Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target(s)	IIa	Xa	Xa	Xa	Xa
Prodrug	Yes	No	No	No	No
Bioavailability (%)	6.5 (pH dependent)	80	50	62	34
Peak effect	1.5–3 h	2–4 h	1–3 h	1–2 h	3–4 h
Half-life[a]	12–17 h	5–9 h	9–14 h	10–14 h	19–27 h
Renal elimination (unchanged drug)	80%	33%	25%	50%	6%–13%
Protein binding (%)	35	90	87	55	60
Dialyzable	Yes	No	No	Possible	No
Drug interactions	P-gp	CYP 3A4, P-gp	CYP 3A4, P-gp	CYP 3A4 (minimal), P-gp	P-gp
Monitoring	No	No	No	No	No
Dosing	Twice daily	Once daily	Twice daily	Once daily	Once daily
Antidote	Idarucizumab	Andexanet alfa Ciraparantag (in development)	Andexanet alfa Ciraparantag (in development	Andexanet alfa Ciraparantag (in development	?
Lab measure	PTT TT, ECT	PT Anti-Xa	Anti-Xa	Anti-Xa	Anti-Xa

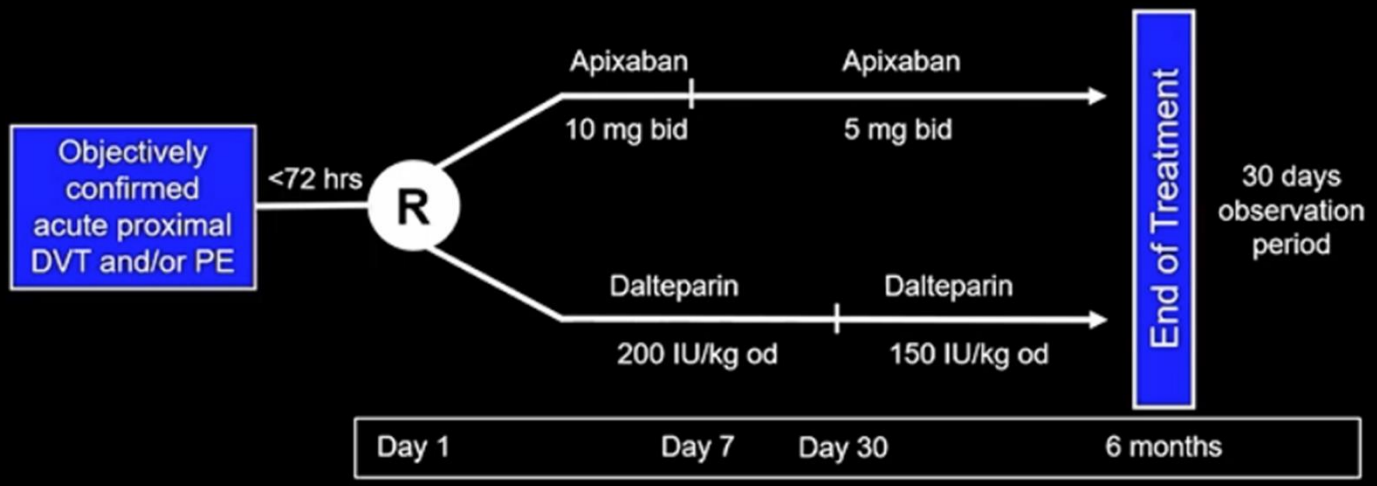
[a]normal renal function.

3A4, Cytochrome P450 3A4; *PTT,* partial thromboplastin time; *ECT,* ecarin clotting time; *INR,* international normalized ratio; *P-gp,* P glycoprotein; *PT,* prothrombin time; *TT,* thrombin time.

The Caravaggio study

Aim: To assess whether oral apixaban was non-inferior to subcutaneous dalteparin for the treatment of proximal DVT and/or PE in patients with cancer

Design: Randomized, open-label, PROBE, non-inferiority study



Investigator-Initiated Study supported by an unrestricted grant from the Bristol-Myers Squibb/Pfizer Alliance

Study background

- The high risk of recurrent venous thromboembolism and bleeding in patients with cancer requires specific studies on anticoagulant treatment
- Major guidelines recommend low-molecular-weight heparin and have recently added edoxaban and rivaroxaban
- The clinical benefit of these oral agents is limited by the high risk of bleeding, mainly occurring at gastrointestinal sites

Inclusion criteria (I)

Consecutive patients with cancer and objectively confirmed:

- symptomatic or incidental*, proximal lower-limb DVT or
- symptomatic pulmonary embolism or
- incidental* pulmonary embolism in a segmental or more proximal pulmonary artery

* Incidental DVT or PE were events detected on imaging tests performed for reasons other than clinical suspicion of venous thromboembolism. The maximum proportion of patients entering the study with incidental VTE was set at 20% of the overall study population

Inclusion criteria (II)

Any type of cancer other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor or known cerebral metastases and acute leukemia

- Active cancer

  defined as diagnosis of cancer within six months before the study inclusion, or receiving treatment for cancer at the time of inclusion or during 6 months prior to randomization, or recurrent locally advanced or metastatic cancer

- History of cancer*

  Cancer diagnosed within 2 years before the study inclusion

* The maximum proportion of patients entering the study with history of cancer was set at 20% of the overall study population

Study outcomes

Efficacy:

Objectively confirmed recurrent proximal DVT or PE occurring during the study treatment period:

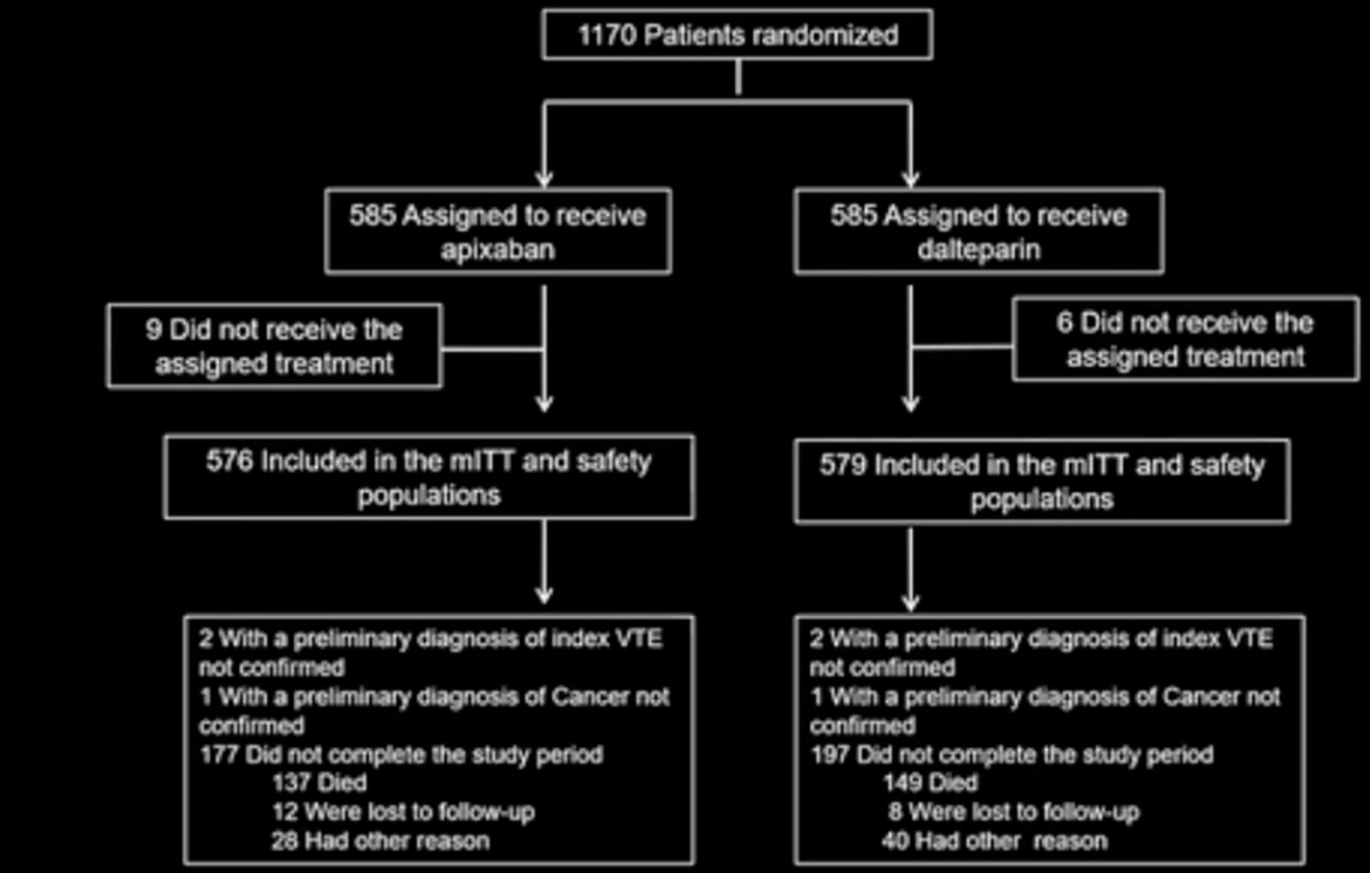
- proximal DVT of the lower limbs (symptomatic or incidental)
- DVT of the upper limbs (symptomatic)
- pulmonary embolism (symptomatic or incidental)

Safety:

Major bleeding (EMA definition*)

* EMA definition: ISTH criteria (acute clinically overt bleeding with ≥ 1 of the following: decrease in hemoglobin ≥ 2 g/dl; transfusion ≥ 2 units of packed red blood cells, occurring in at least one of the following critical sites: intracranial, intra-spinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal; fatal) and bleeding that necessitates acute surgical intervention

Patient disposition



Patient characteristics at baseline

	Apixaban N=576	Dalteparin N=579
Mean age, y (SD)	67.2 (11.3)	67.2 (10.9)
Male sex, n (%)	292 (50.7)	276 (47.7)
Mean weight, kg (SD)	75.7 (16.1)	76.1 (16.7)
PE with or without DVT	304 (52.8)	334 (57.7)
DVT only	272 (47.2)	245 (42.3)
Symptomatic DVT or PE	460 (79.9)	465 (80.3)
Incidental DVT or PE *	116 (20.1)	114 (19.7)
Active cancer, n (%)	559 (97.0)	565 (97.6)
Recurrent Locally Advanced or Metastatic cancer, n (%)	389 (67.5)	396 (68.4)
Treatment for cancer at the time of inclusion, n (%) §	350 (60.8)	367 (63.4)
Treatment for cancer within previous 6 months, n (%) §	143 (24.8)	129 (22.3)
Treatment for cancer during the study period, n (%) §	344 (59.7)	346 (59.8)
Previous venous thromboembolism, n (%)	45 (7.8)	61 (10.5)
Platelet count < 100,000 per mm^3, n (%)	21 (3.6)	22 (3.8)
Creatinine clearance ≤50 ml/min, n (%)	51 (8.9)	61 (10.5)

§ Cancer treatment includes anticancer drug therapy (cytotoxic, hormonal, targeted or immunomodulatory), radiotherapy, surgery, or a combination of these therapies

Type of cancer

	Apixaban N=576	Dalteparin N=579
Solid tumor, n(%)	543 (94.3)	527 (91.0)
Colorectal	121 (21.0)	113 (19.5)
Lung	105 (18.2)	95 (16.4)
Breast	79 (13.7)	76 (13.1)
Genitourinary	66 (11.5)	73 (12.6)
Gynecological	60 (10.4)	59 (10.2)
Pancreatic or hepatobiliary	44 (7.6)	43 (7.4)
Upper gastrointestinal	23 (4.0)	31 (5.4)
Head and Neck	14 (2.4)	8 (1.4)
Bone/soft tissue	11 (1.9)	7 (1.2)
Skin-melanoma	4 (0.7)	7 (1.2)
Other	16 (2.8)	15 (2.6)
Hematological malignancy, n (%)	33 (5.7)	52 (9.0)

Primary efficacy outcomes

	Apixaban N=576	Dalteparin N=579	Hazard Ratio (95% CI)	P Value
Recurrent VTE, n (%)	32 (5.6)	46 (7.9)	0.63 (0.37–1.07)	<0.001 for noninferiority 0.08 for superiority
Recurrent DVT, n (%)	13 (2.3)	15 (2.6)	0.87 (0.34–2.21)	
Recurrent PE, n (%)	19 (3.3)	32 (5.5)	0.54 (0.29–1.03)	
Fatal PE, n (%)	4 (0.7)	3 (0.5)	1.93 (0.40–9.41)	

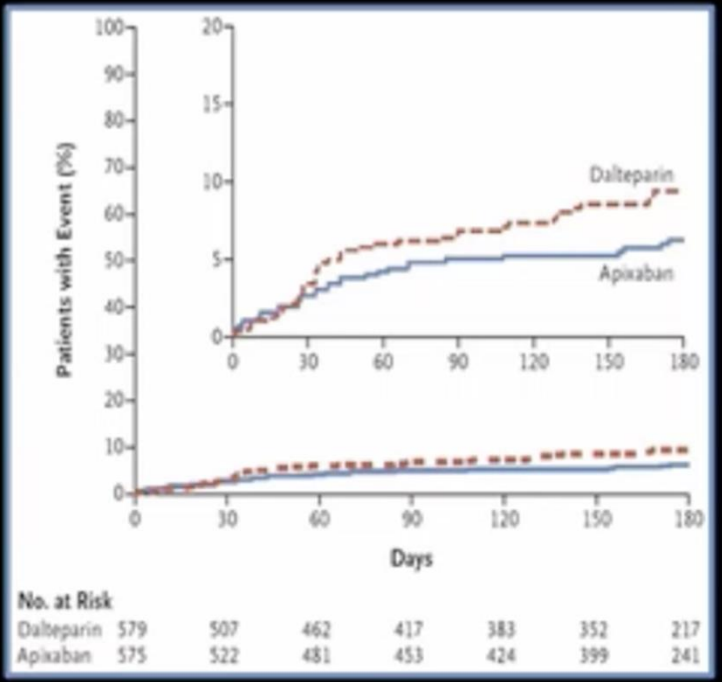
Primary and secondary safety outcomes

	Apixaban N=576	Dalteparin N=579	Hazard Ratio (95% CI)	P Value
Major Bleeding, n (%)	22 (3.8)	23 (4.0)	0.82 (0.40–1.69)	0.60
Major GI bleeding, n (%)	11 (1.9)	10 (1.7)	1.05 (0.44–2.50)	
Major non GI bleeding, n (%)	11 (1.9)	13 (2.2)	0.68 (0.21–2.20)	
CRNMB, n (%)	52 (9.0)	35 (6.0)	1.42 (0.88-2.30)	
MB & CRNMB, n (%)	70 (12.2)	56 (9.7)	1.16 (0.77-1.75)	

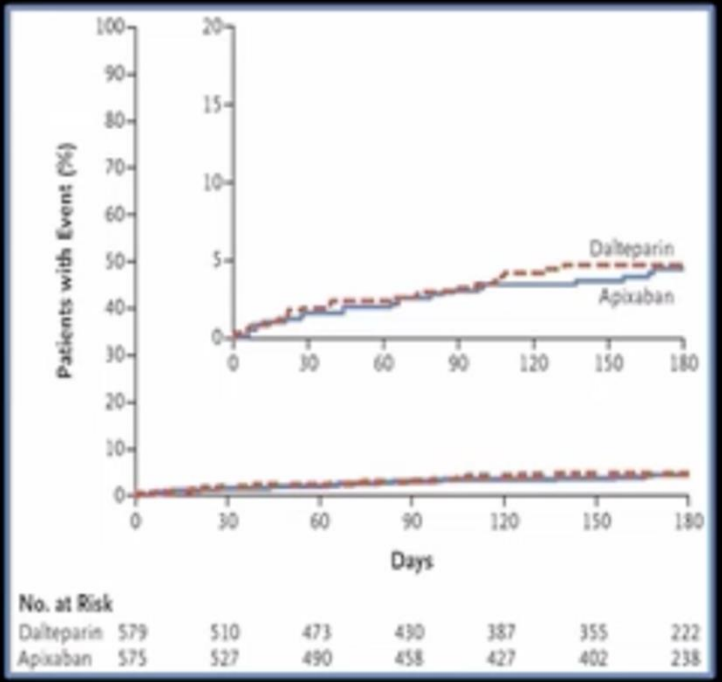
CRNMB, clinically relevant nonmajor bleeding

Cumulative event rate of VTE recurrences and major bleeding

Recurrent VTE



Major Bleeding



Conclusions

Oral apixaban was noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism

No increase in the risk of major bleeding was observed in particular at the gastrointestinal sites.

Findings of Caravaggio expand the proportion of patients with cancer-associated thrombosis who are eligible for treatment with the oral direct anticoagulants, including patients with gastrointestinal cancer