CANCER AND THROMBOSIS
WHAT IS THE ROLE OF DIRECT ORAL ANTICOAGULANTS?

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THROMBOSIS IN THE ONCOLOGIC PATIENT: FROM HEPARINOID PRODUCTS TO THROMBIN INHIBITORS

NO RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

The Medical Educator Consortium

13th Annual New Orleans Summer Cancer Meeting
July 20-22, 2018

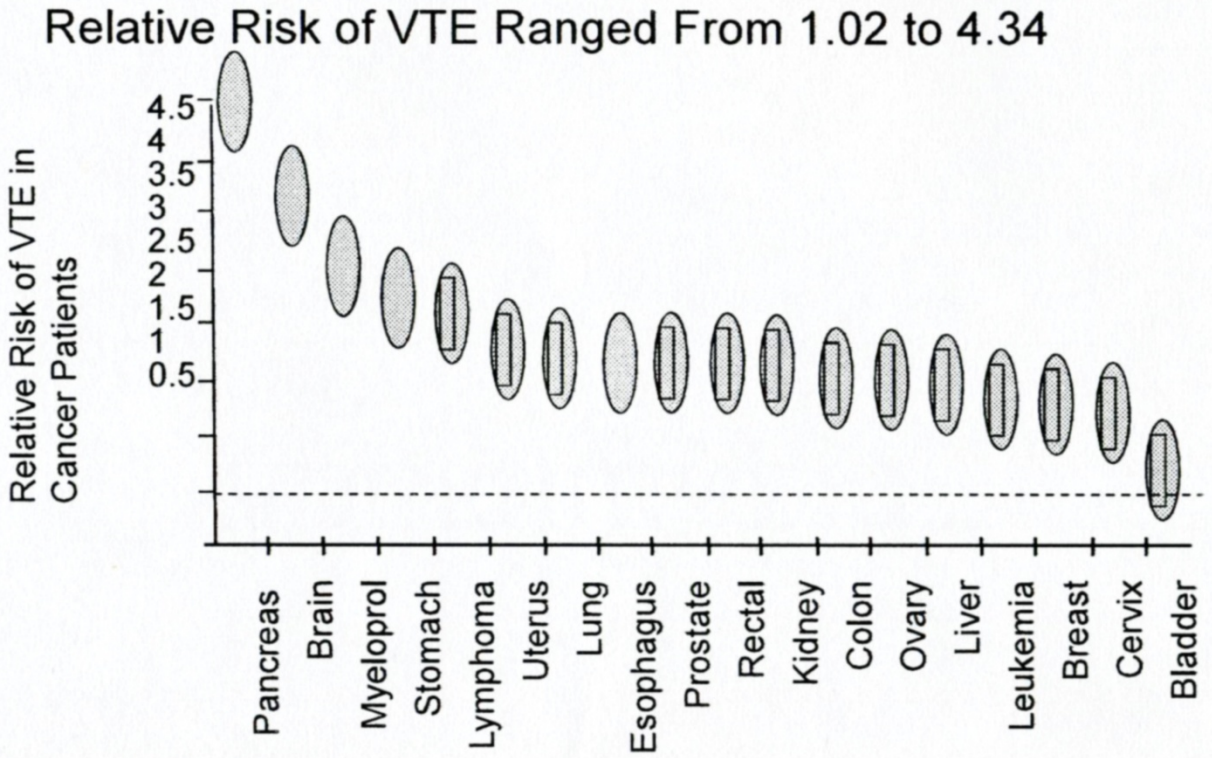
RISK FACTORS FOR HYPERCOAGULABILITY IN CANCER PATIENTS

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

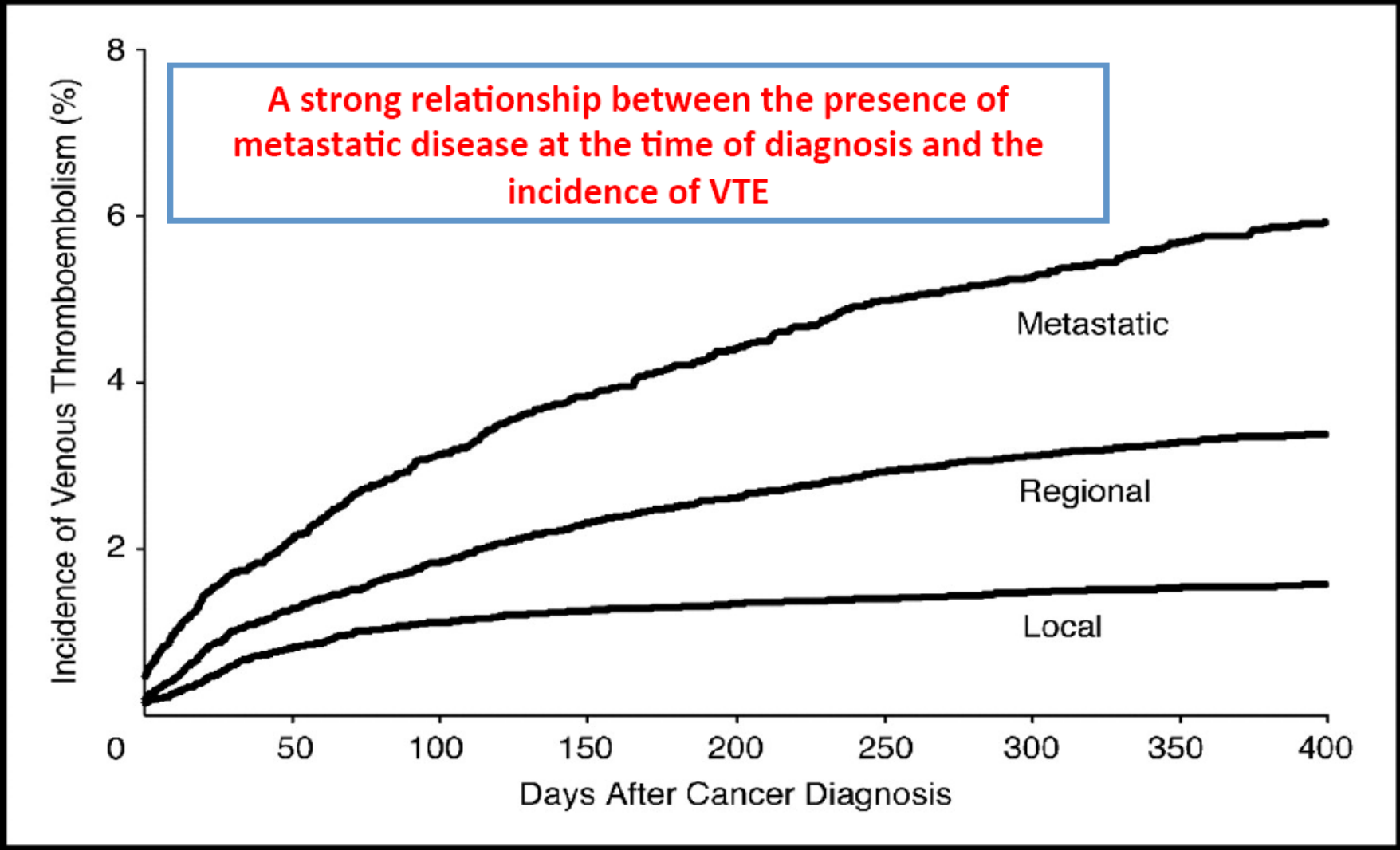
1) Virchow's Triad: stasis, vascular injury, hypercoagulability
2) Tumors and hypercoagulability procoagulants
   - Tissue factor
   - Mucinous secretions
   - Reduced endothelial secretion of tPA
   - Enhanced thrombin generation
3) Cancer and inflammation
   - Increased WBCs
   - Increased cytokines,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

VTE Risk and Cancer Type: "Solid and Liquid"



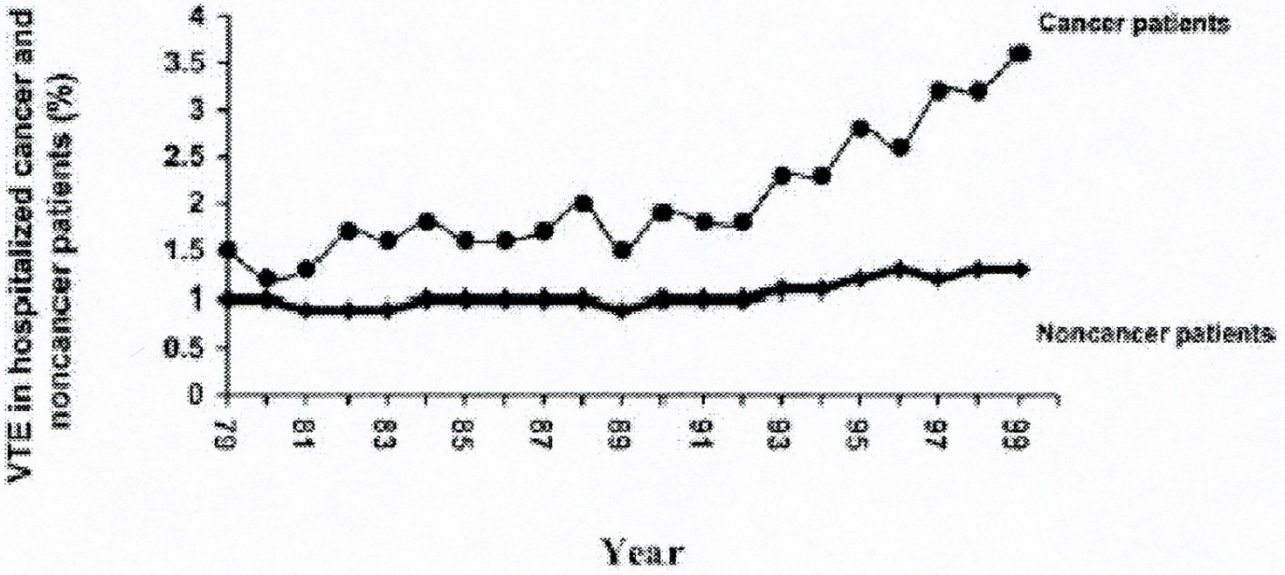
Stein PD, et al. Am J Med 2006; 119: 60-68

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



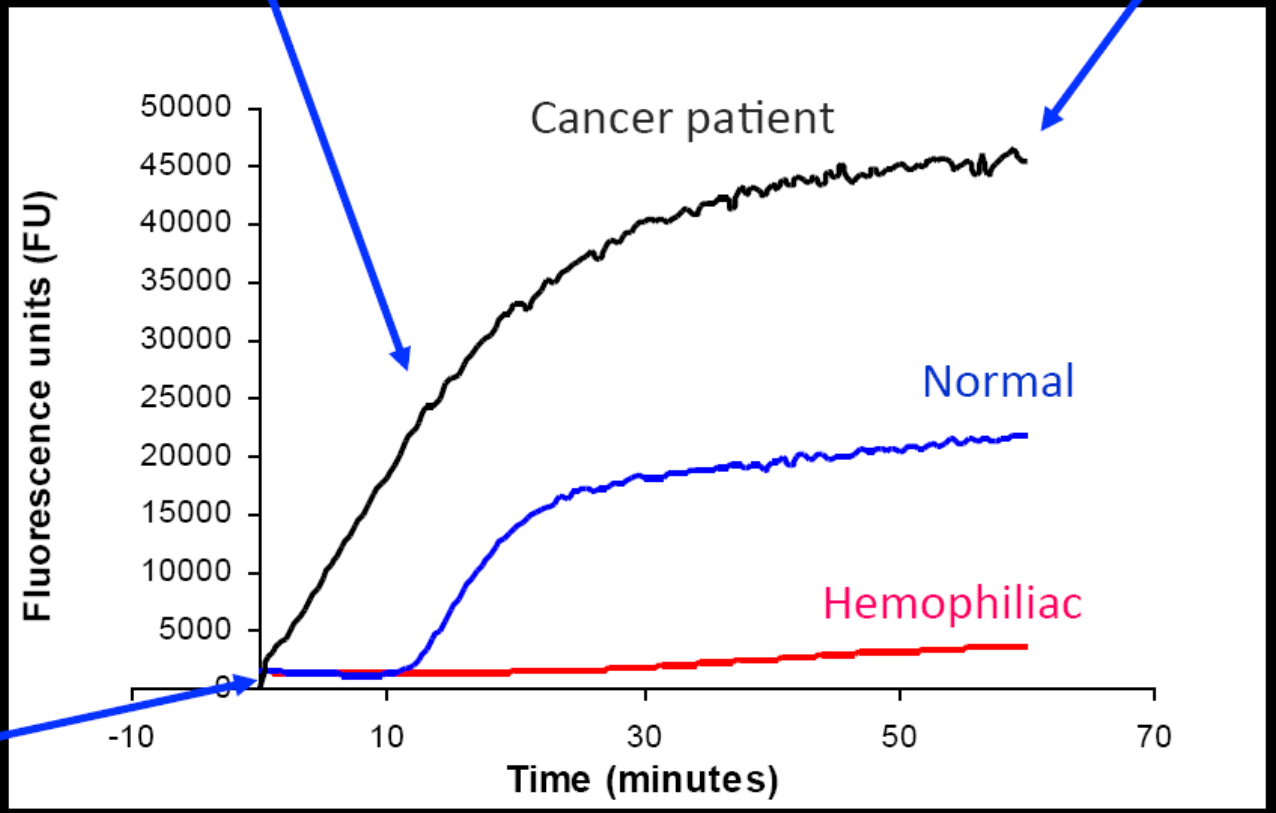
Alcalay A et al. JCO. 2006;24:1112

As Number of Cancer Survivors Increase, VTE Rates Increase



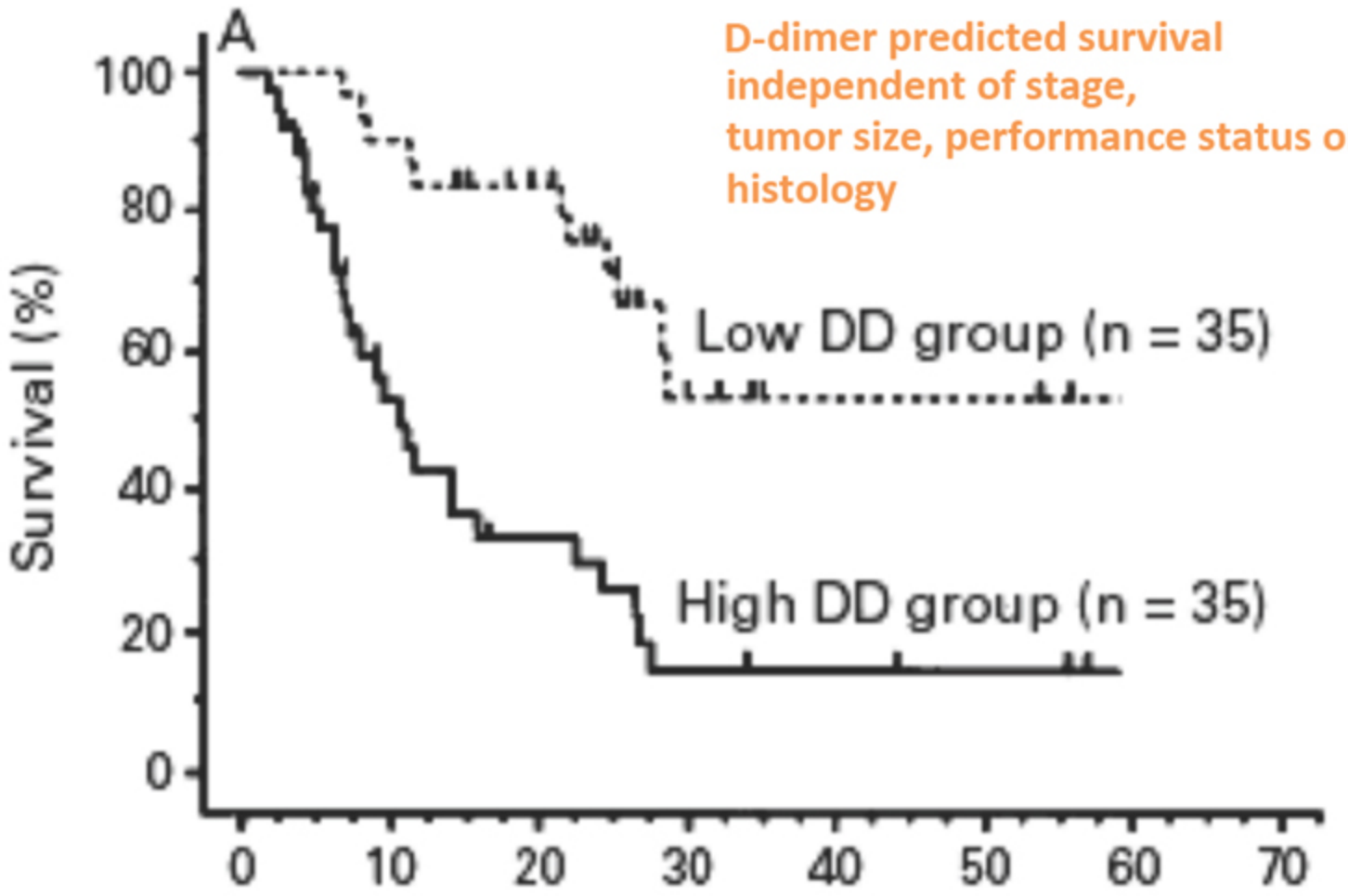
Stein PD, et al. Am J Med 2006; 119: 60-68

Thrombin Generation in Cancer



Adapted from J Francis

Elevated levels of D-dimer are predictive of survival in NSC lung cancer



D-dimer predicted survival independent of stage, tumor size, performance status or histology

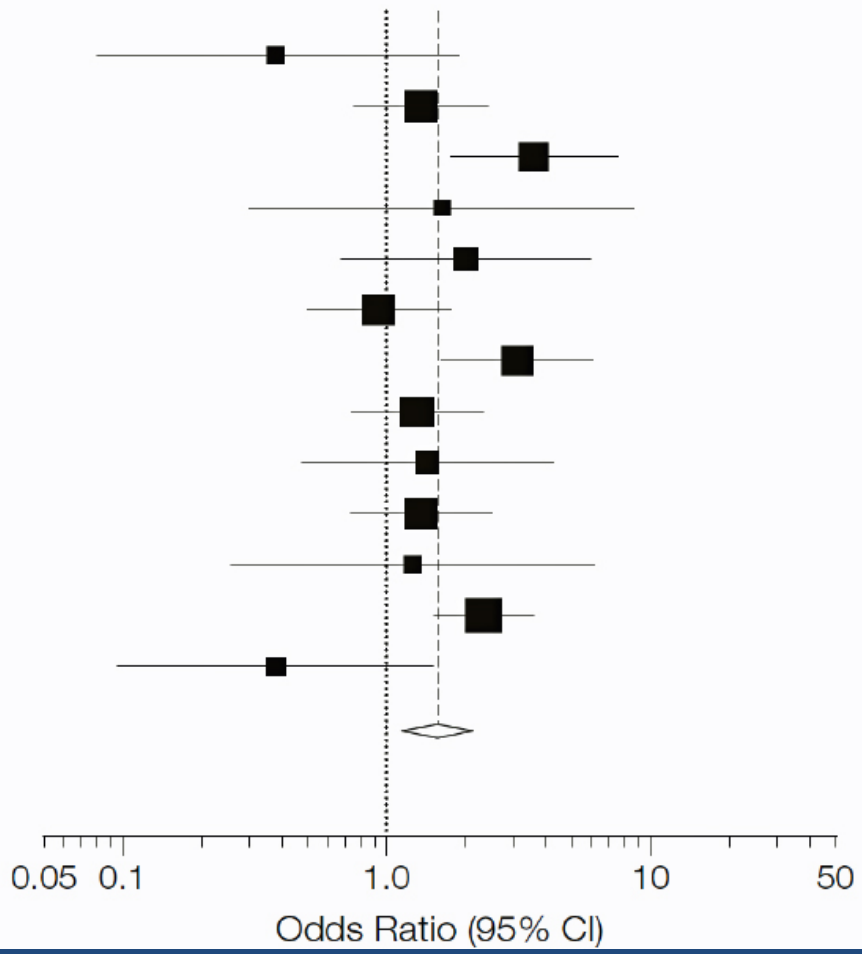
Taguchi O. et al. *Thorax* 1997;**52**:563–5.

RECURRENCE RATE WITH FACTOR V LEIDEN

Probands heterozygous for factor V Leiden mutation

Source	Odds Ratio (95% CI)
Kearon et al,[23] 1999	0.38 (0.08-1.87)
Lindmarker et al,[14] 1999	1.35 (0.75-2.43)
Simioni et al,[15] 2000	3.62 (1.74-7.53)
Høibraaten et al,[20] 2001	1.61 (0.30-8.62)
Miles et al,[25] 2001	1.99 (0.67-5.90)
Eichinger et al,[18] 2002	0.94 (0.50-1.76)
Palareti et al,[17] 2003	3.12 (1.61-6.04)
Christiansen et al,[13] 2005	1.30 (0.73-2.31)
González-Porras et al,[19] 2006	1.43 (0.48-4.29)
Wåhlander et al,[22] 2006[a]	1.36 (0.73-2.51)
Wåhlander et al,[22] 2006[b]	1.26 (0.26-6.14)
Prandoni et al,[21] 2007	2.33 (1.51-3.61)
Kearon et al,[24] 2008	0.38 (0.10-1.50)
Overall	**1.56 (1.14-2.12)**

Test for heterogeneity: $I^2 = 48\%$; $P = .03$
Test for overall effect: $P = .005$



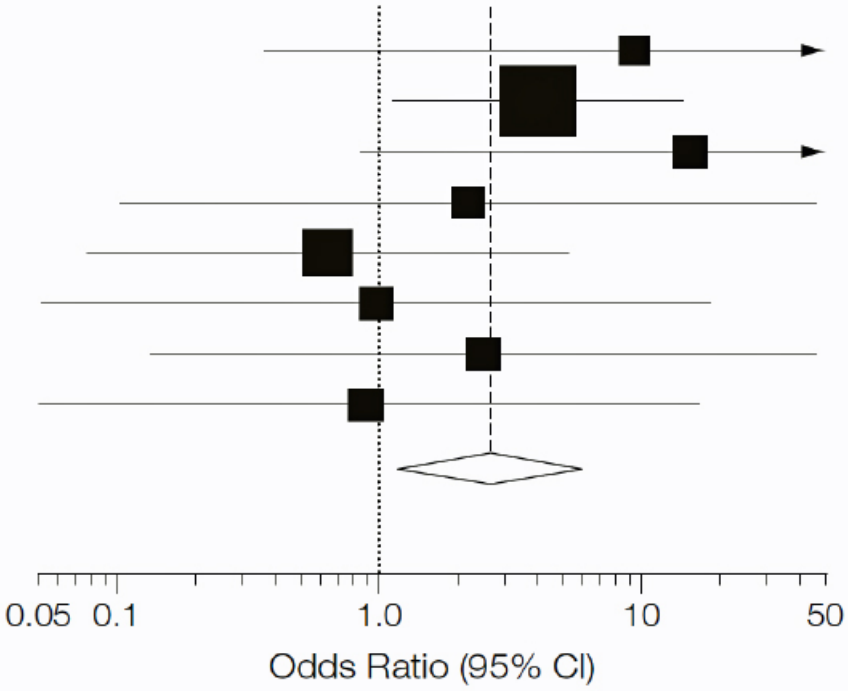
Segal JM. JAMA 2009; 301:2472-2485. Review.

RECURRENCE RATE WITH FACTOR V LEIDEN

Probands homozygous for factor V Leiden mutation

Source	Odds Ratio (95% CI)
Kearon et al,[23] 1999	9.44 (0.36-245.69)
Lindmarker et al,[14] 1999	4.03 (1.13-14.34)
Høibraaten et al,[20] 2001	15.33 (0.85-276.51)
Palareti et al,[17] 2003	2.18 (0.10-46.20)
Christiansen et al,[13] 2005	0.64 (0.08-5.26)
Wåhlander et al,[22] 2006[a]	0.98 (0.05-18.50)
Wåhlander et al,[22] 2006[b]	2.50 (0.13-46.47)
Kearon et al,[24] 2008	0.89 (0.05-16.72)
Overall	**2.65 (1.18-5.97)**

Test for heterogeneity: $I^2 = 0\%$; $P = .62$
Test for overall effect: $P = .08$



Segal JM. JAMA 2009; 301:2472-2485. Review.

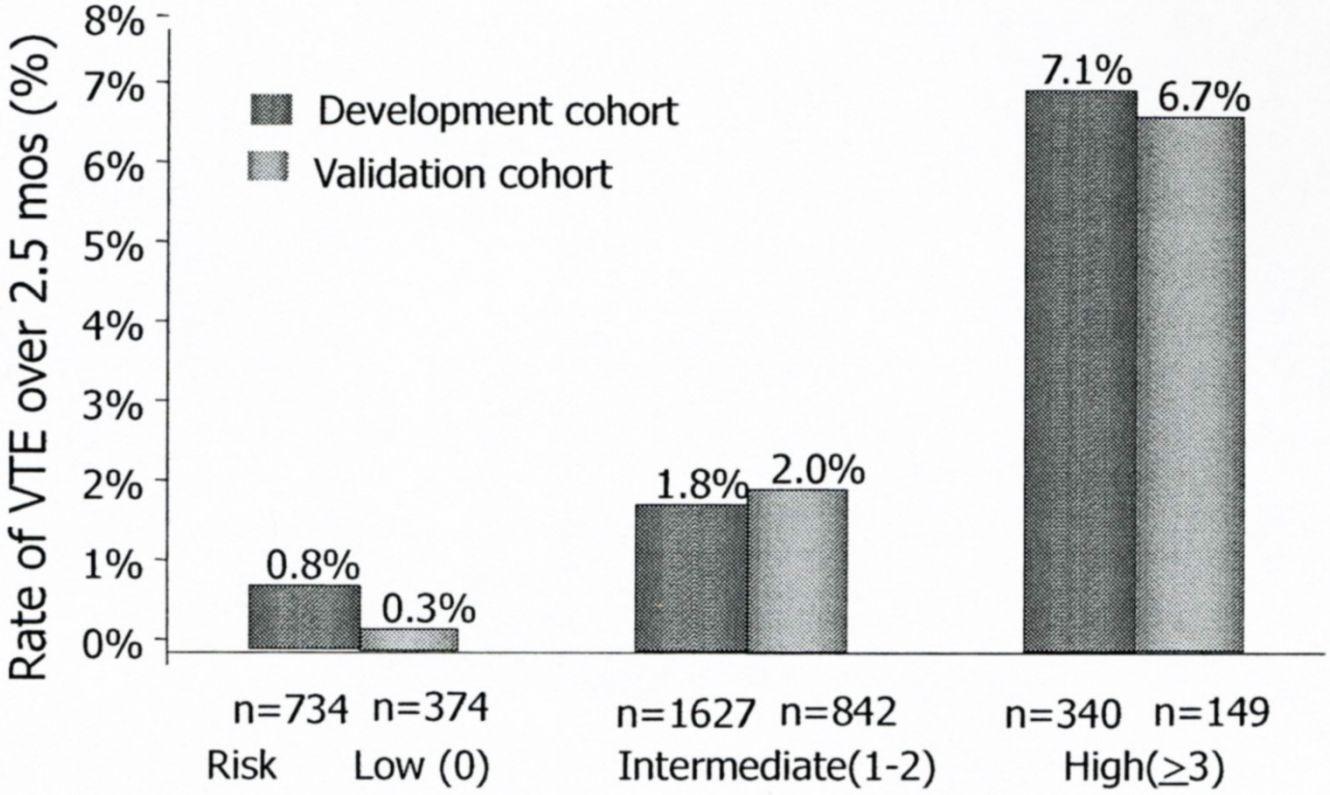
TABLE 23-3 Predictive Model for Chemotherapy-Associated Venous Thromboembolism

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

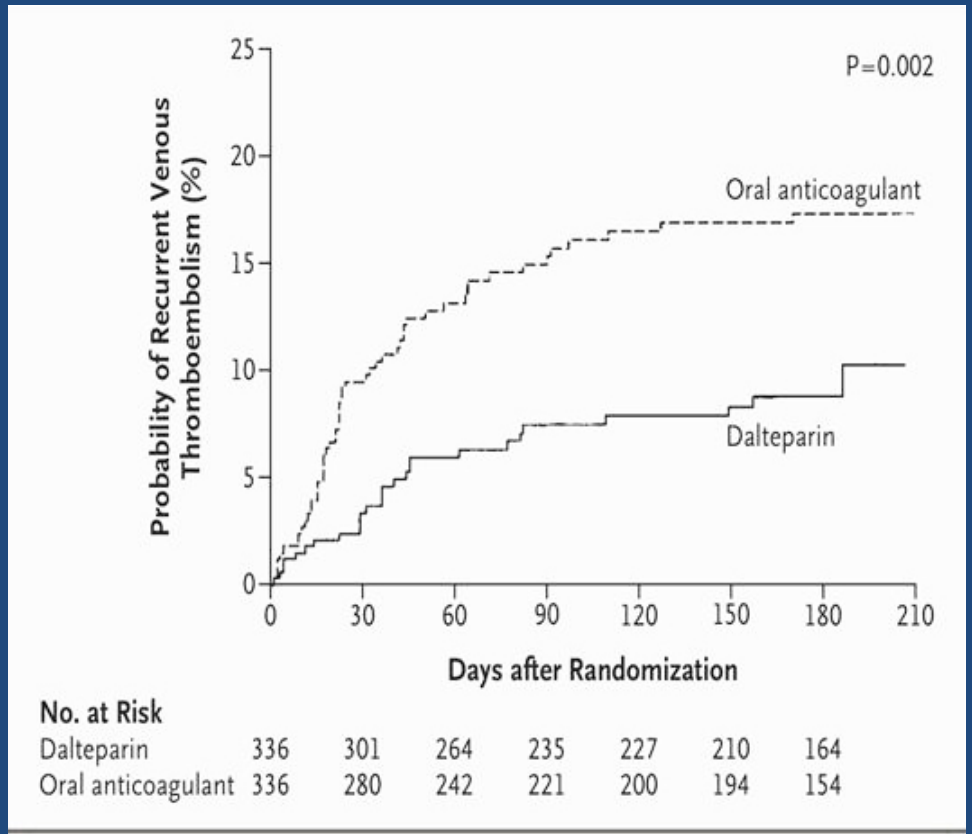


Figure 1. Kaplan–Meier Estimates of the Probability of Symptomatic Recurrent Venous Thromboembolism among Patients with Cancer, According to Whether They Received Secondary Prophylaxis with Dalteparin or Oral Anticoagulant Therapy for Acute Venous Thromboembolism.

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.

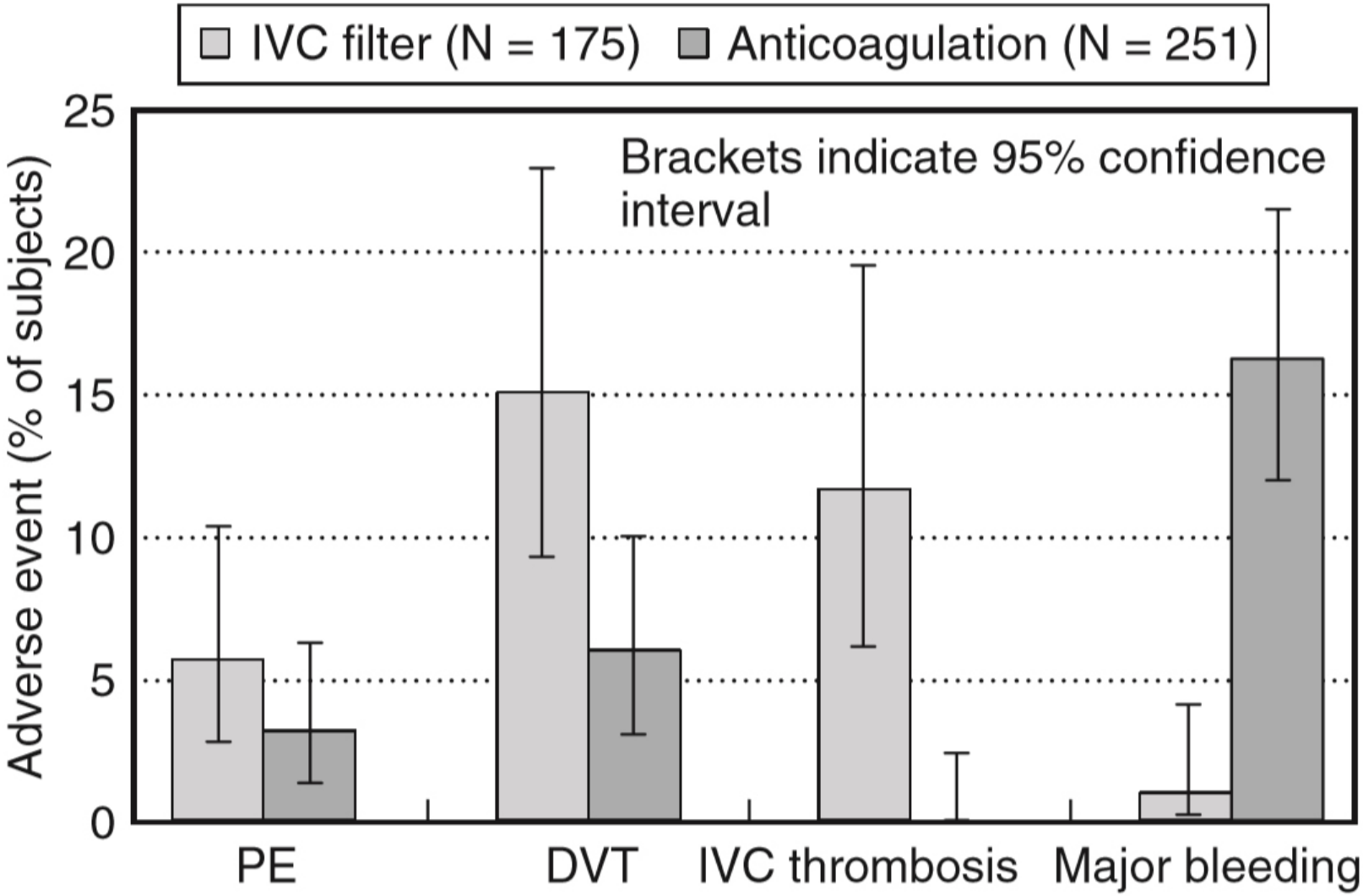


Figure 31-3 Frequency of adverse clinical events in studies of vena cava filter placement or anticoagulation for treatment of cancer patients with venous thromboembolism (VTE). *DVT*, Deep vein thrombosis; *IVC*, inferior vena cava; *PE*, pulmonary embolism.

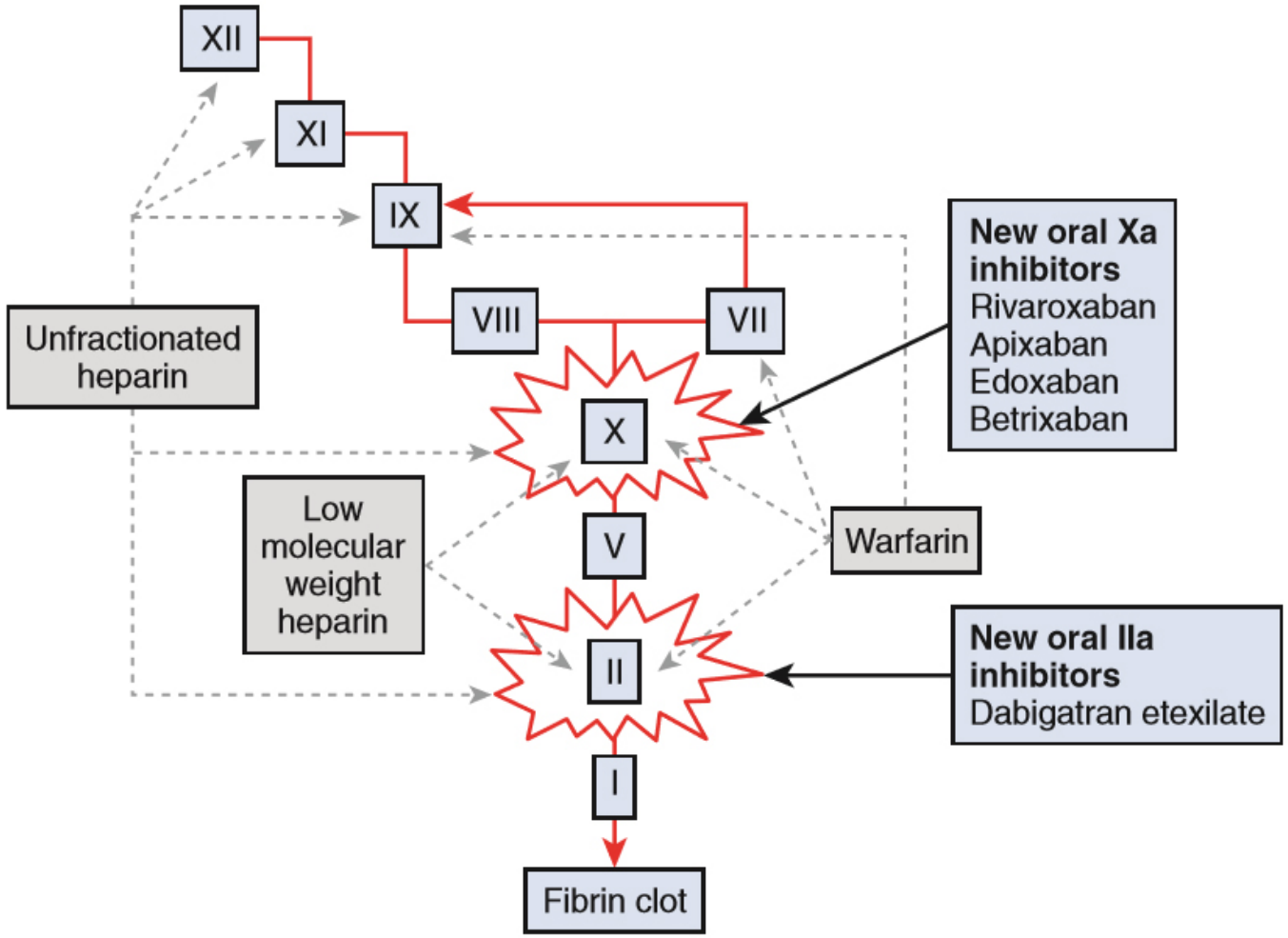


FIG 37.2 Coagulation cascade and factors inhibited or impaired by both standard anticoagulants and new target-specific oral anticoagulants.

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.

TABLE 37.12 Characteristics of the Direct Oral Anticoagulants Versus Warfarin

Characteristic	Warfarin	Direct Oral Anticoagulant
Onset of anticoagulant effect	Slow	Rapid
Half-life	Long	Short (with normal renal function)
Dosing	Variable	Fixed (some variability)
Food effect	Yes	No
Drug interactions	Many	Few
Monitoring of anticoagulant effect	Yes	No
Antidote	Yes	Yes