

XXXIV

Congreso Nacional de la Sociedad Española de Medicina Interna (SEMI)

XXIX Congreso de la
Sociedad Andaluza de
Medicina Interna (SADEMI)

21-23

Noviembre 2013

Palacio de Ferias y
Congresos de Málaga
Málaga



TROMBOPROFILAXIS PRIMARIA EN PACIENTES AMBULATORIOS CON CÁNCER Y TRATAMIENTO QUIMIOTERÁPICO

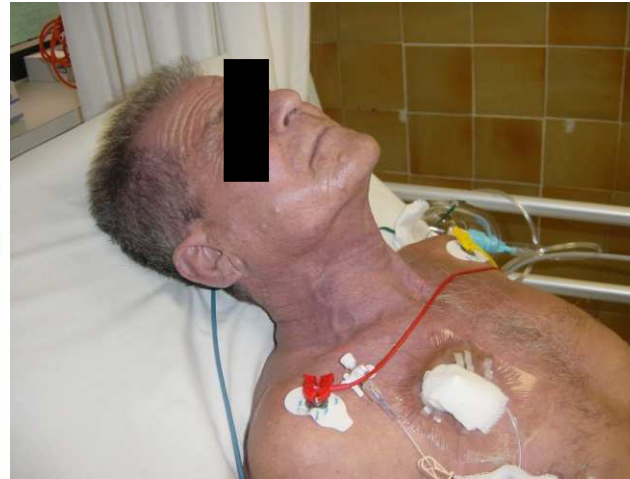
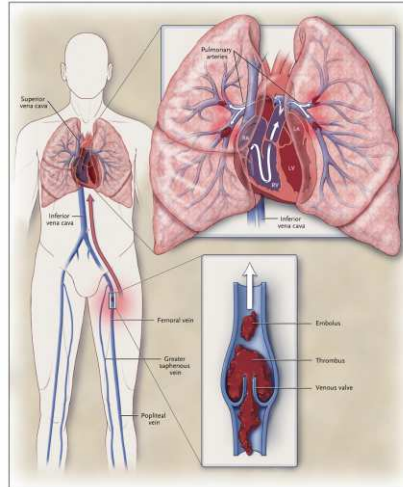
Carme Font

Departamento de Oncología Médica

Hospital Clínic i Provincial

Barcelona

Trombosis venosa asociada al cáncer



- **Segunda causa de muerte (9% de las muertes)**
- **Incidencia :** 4 al 20%
50% en autopsias
- **Morbilidad:** 21% riesgo anual de retrombosis
12% riesgo anual de hemorragias mayores
Anticoagulación crónica

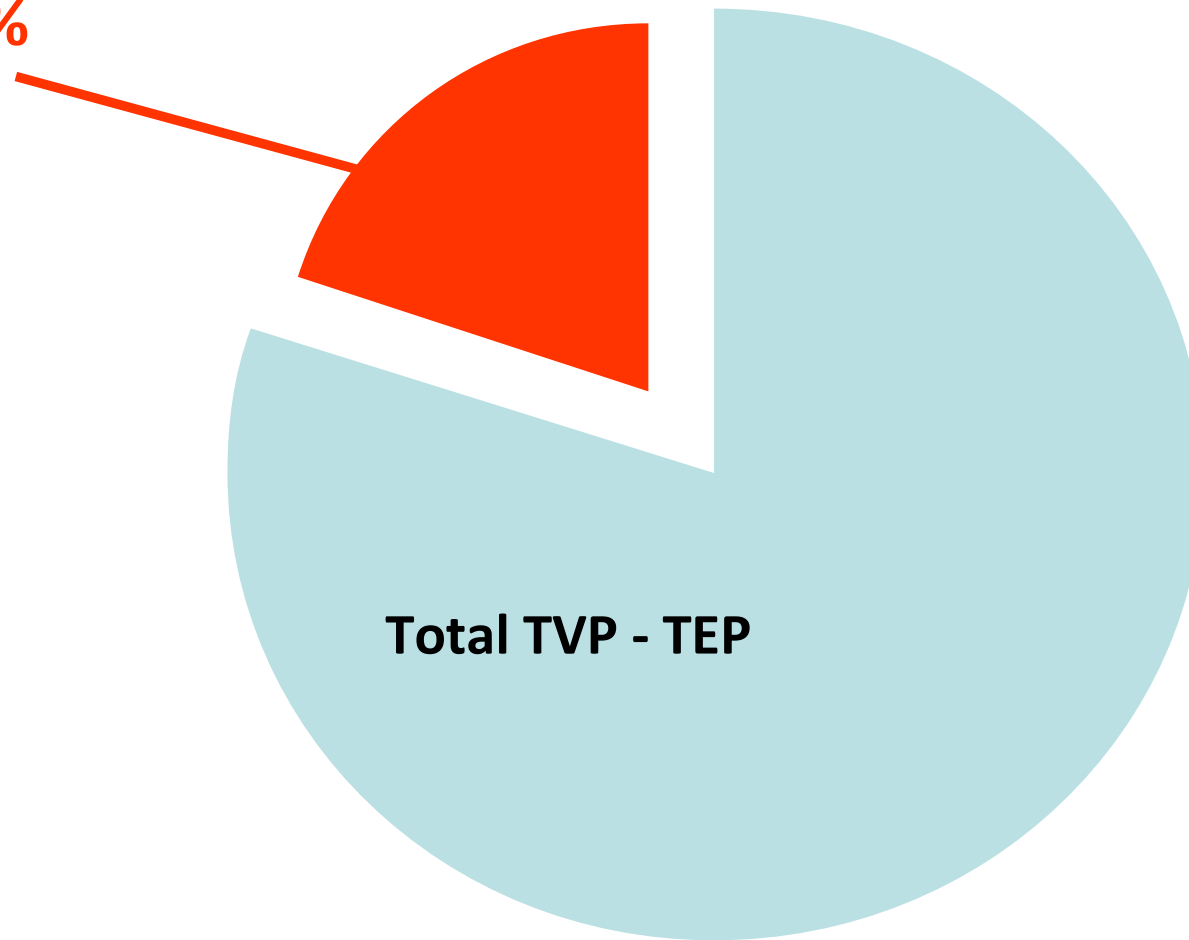
1. Khorana AA et al. *J Thromb Haemost* 2007

2. Prandoni P et al. *Blood*. 2002

Trombosis venosa asociada al cáncer

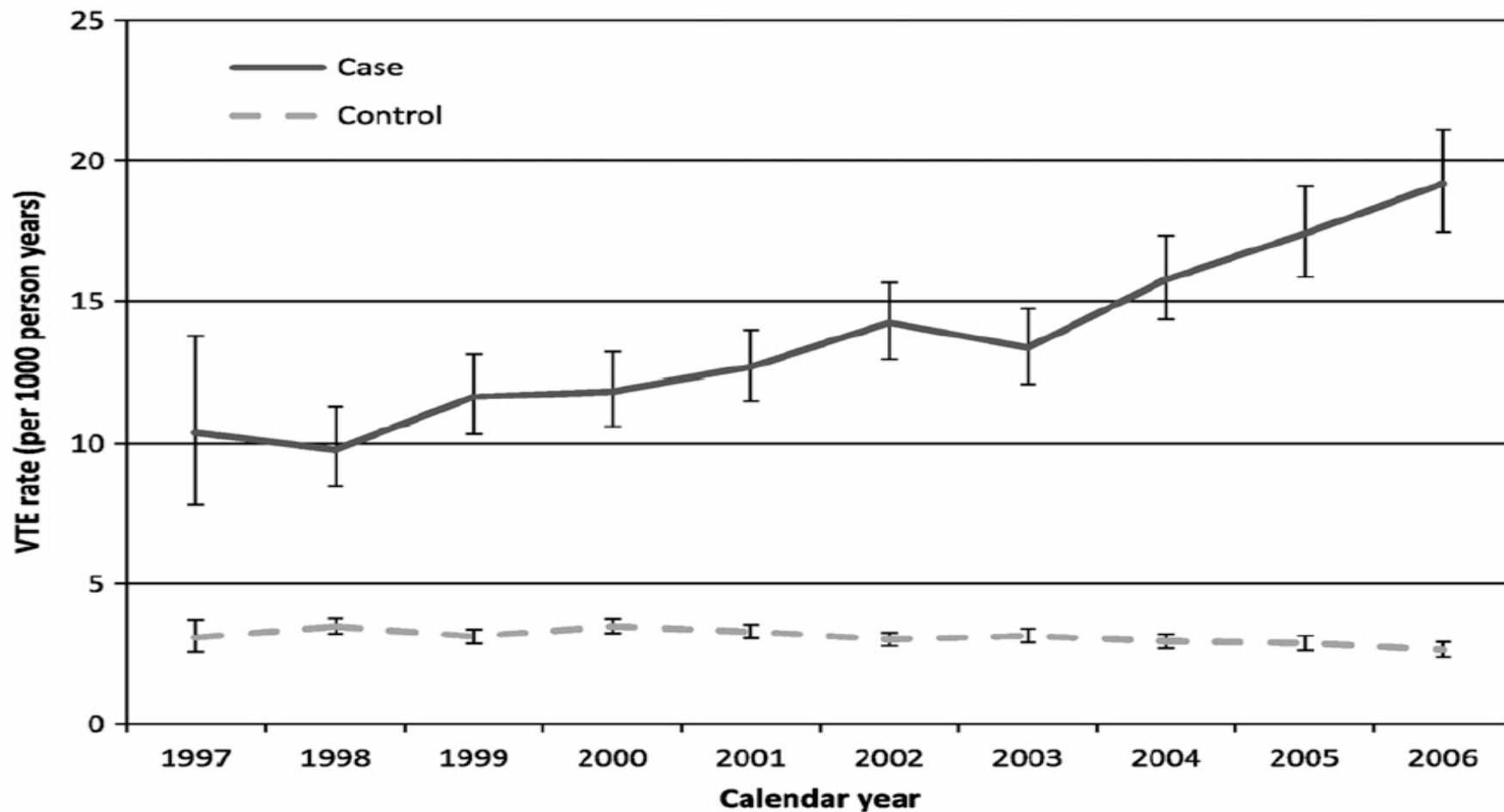
Pacientes con cáncer:

19.8%



Epidemiology of cancer-associated venous thrombosis

Jasmijn F. Timp, Sigrid K. Braekkan, Henri H. Versteeg and Suzanne C. Cannegieter



Cáncer y trombosis: factores de riesgo

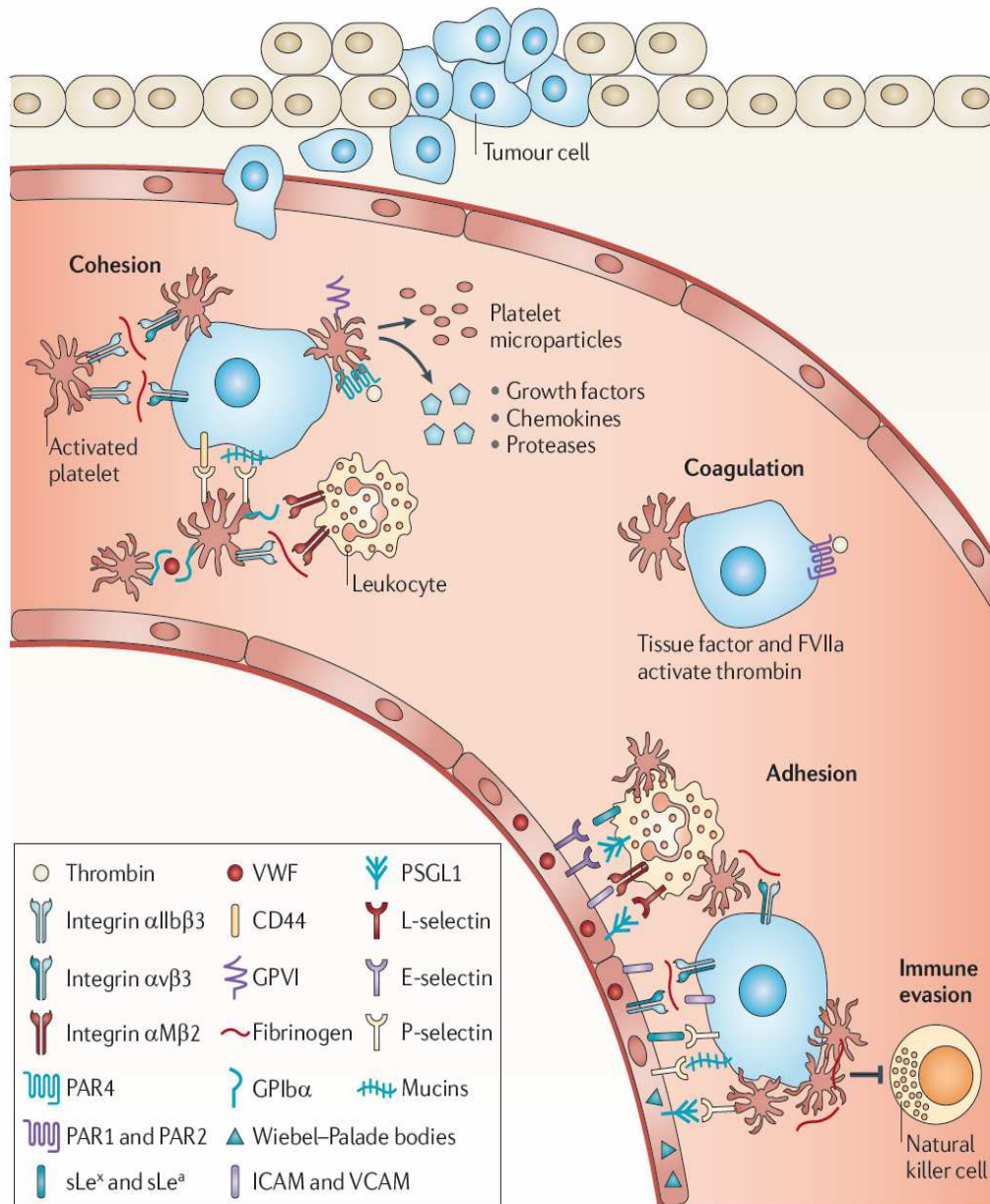


Figure 2 | **Molecular coordination between platelets and tumour cells supports metastasis from the bloodstream.** As platelets become activated, they undergo a shape change, increase

Table 1. Risk factors for VTE and candidate biomarkers

Cancer-related

Site
 Stage/metastatic disease
 Histology
 Initial period after diagnosis (3-6 months)
 Active disease
 Vascular compression due to tumoral mass or lymphadenopathy

Treatment-related

Chemotherapy
 Surgery
 Hospitalization
 Hormonal treatment
 Indwelling catheters
 Transfusions
 Erythropoietic stimulating agents
 Antiangiogenic agents

Patient-related

Older age
 Obesity
 African-american
 Female
 Prior thrombosis
 Comorbidities/medical problems (infection, pulmonary disease, others)
 Pregnancy
 Tobacco
 Low performance status
 Low level of activity/physical exercise
 Major trauma and immobilization
 Inherited thrombophilia (Factor V Leyden)

Cáncer y trombosis: factores de riesgo

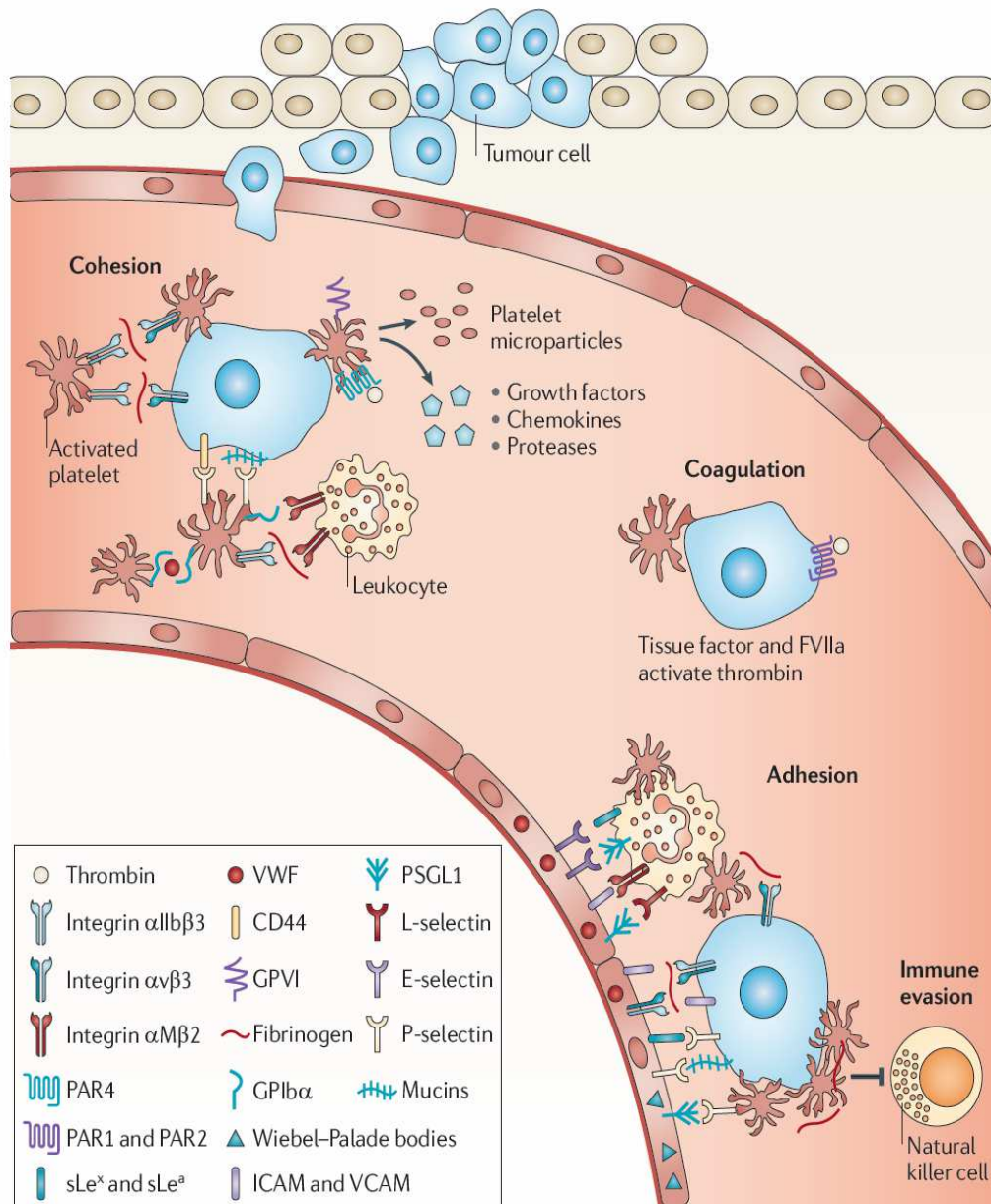


Figure 2 | **Molecular coordination between platelets and tumour cells supports metastasis from the bloodstream.** As platelets become activated, they undergo a shape change, increase

Table 1. Risk factors for VTE and candidate biomarkers

Cancer-related

- Site
- Stage/metastatic disease
- Histology
- Initial period after diagnosis (3-6 months)
- Active disease
- Vascular compression due to tumoral mass or lymphadenopathy

Treatment-related

- Chemotherapy
- Surgery
- Hospitalization
- Hormonal treatment
- Indwelling catheters
- Transfusions
- Erythropoietic stimulating agents
- Antiangiogenic agents

Patient-related

- Older age
- Obesity
- African-american
- Female
- Prior thrombosis
- Comorbidities/medical problems (infection, pulmonary disease, others)
- Pregnancy
- Tobacco
- Low performance status
- Low level of activity/physical exercise
- Major trauma and immobilization
- Inherited thrombophilia (Factor V Leyden)

Cáncer y trombosis: factores de riesgo

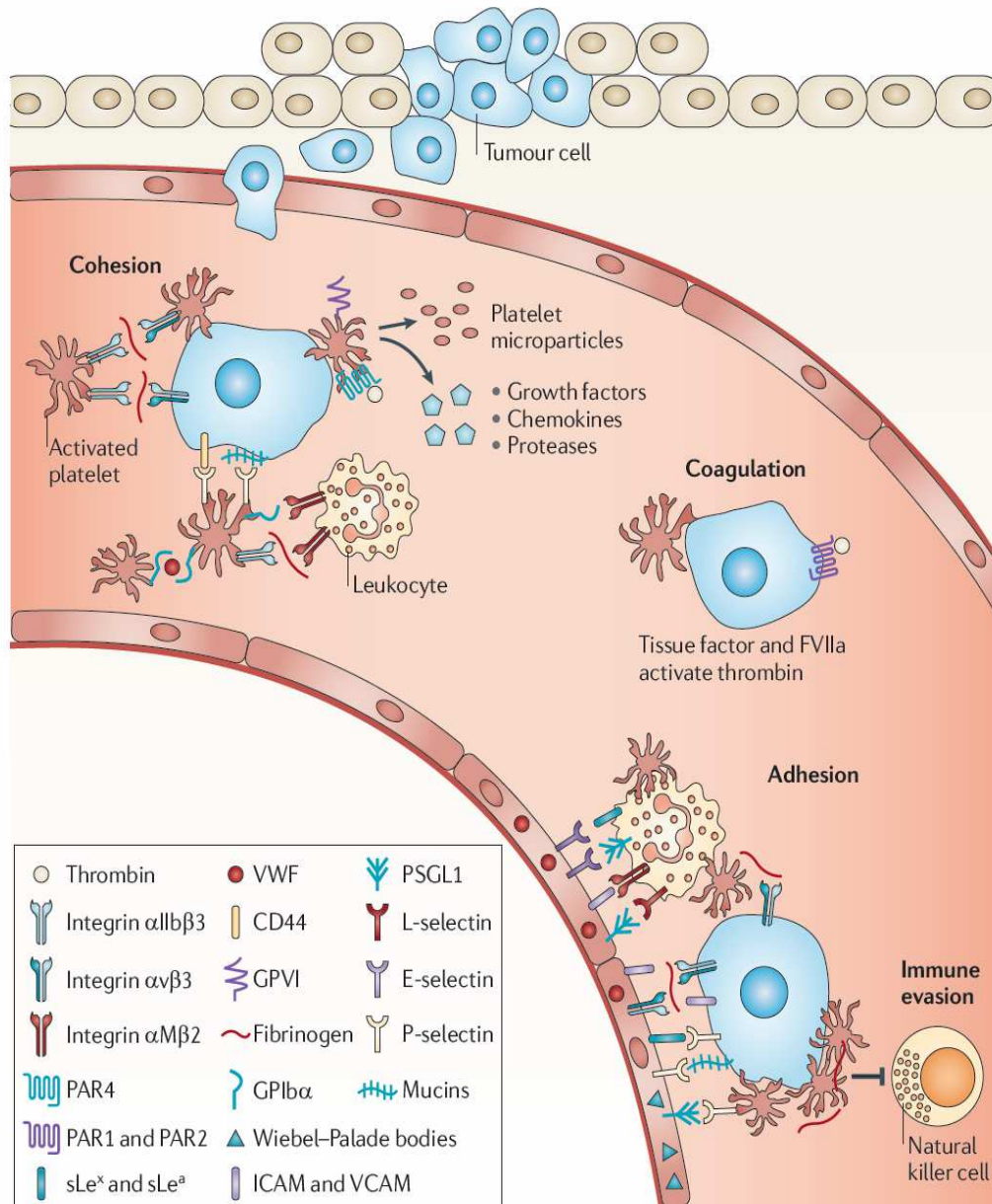


Figure 2 | **Molecular coordination between platelets and tumour cells supports metastasis from the bloodstream.** As platelets become activated, they undergo a shape change, increase

Table 1. Risk factors for VTE and candidate biomarkers

Cancer-related

- Site
- Stage/metastatic disease
- Histology
- Initial period after diagnosis (3-6 months)
- Active disease
- Vascular compression due to tumoral mass or lymphadenopathy

Treatment-related

- Chemotherapy
- Surgery
- Hospitalization
- Hormonal treatment
- Indwelling catheters
- Transfusions
- Erythropoietic stimulating agents
- Antiangiogenic agents

Patient-related

- Older age
- Obesity
- African-american
- Female
- Prior thrombosis
- Comorbidities/medical problems (infection, pulmonary disease, others)
- Pregnancy
- Tobacco
- Low performance status
- Low level of activity/physical exercise
- Major trauma and immobilization
- Inherited thrombophilia (Factor V Leyden)

Incidence and Predictors of Venous Thromboembolism (VTE) Among Ambulatory High-Risk Cancer Patients Undergoing Chemotherapy in the United States

Alok A. Khorana, MD¹; Mehul Dalal, PhD²; Jay Lin, PhD³; and Gregory C. Connolly, MD¹

N= 17,984

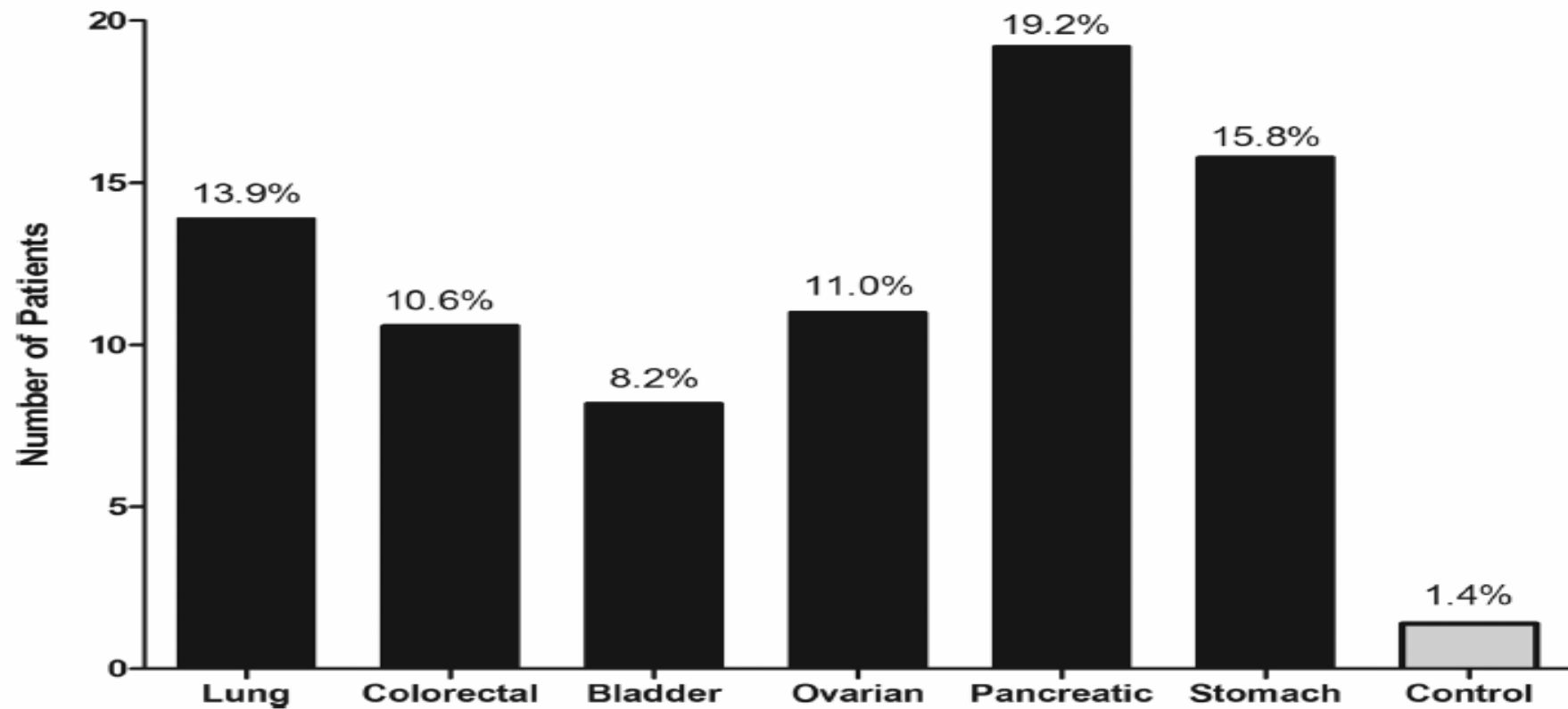


Figure 3. The incidence of venous thromboembolism is illustrated according to cancer type.

Incidence and Predictors of Venous Thromboembolism (VTE) Among Ambulatory High-Risk Cancer Patients Undergoing Chemotherapy in the United States

Alok A. Khorana, MD¹; Mehul Dalal, PhD²; Jay Lin, PhD³; and Gregory C. Connolly, MD¹

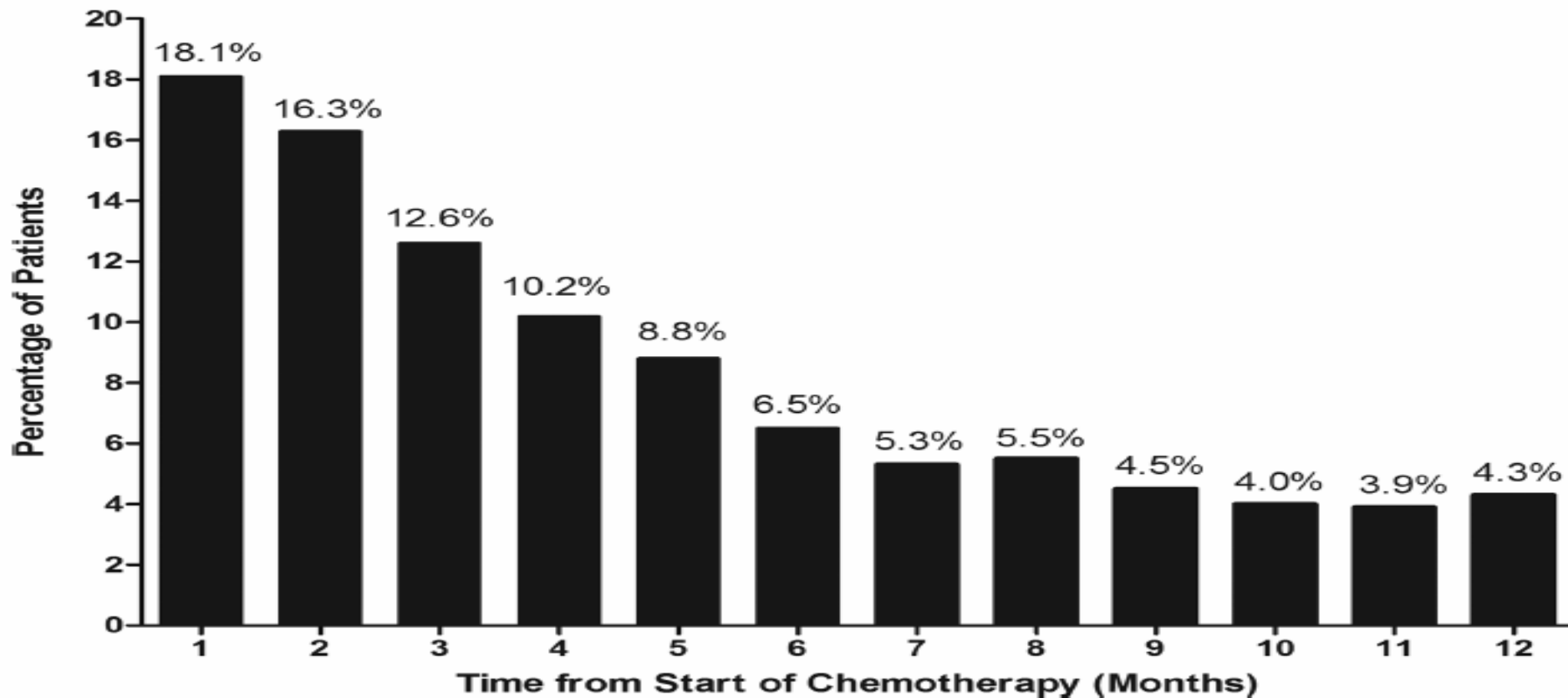
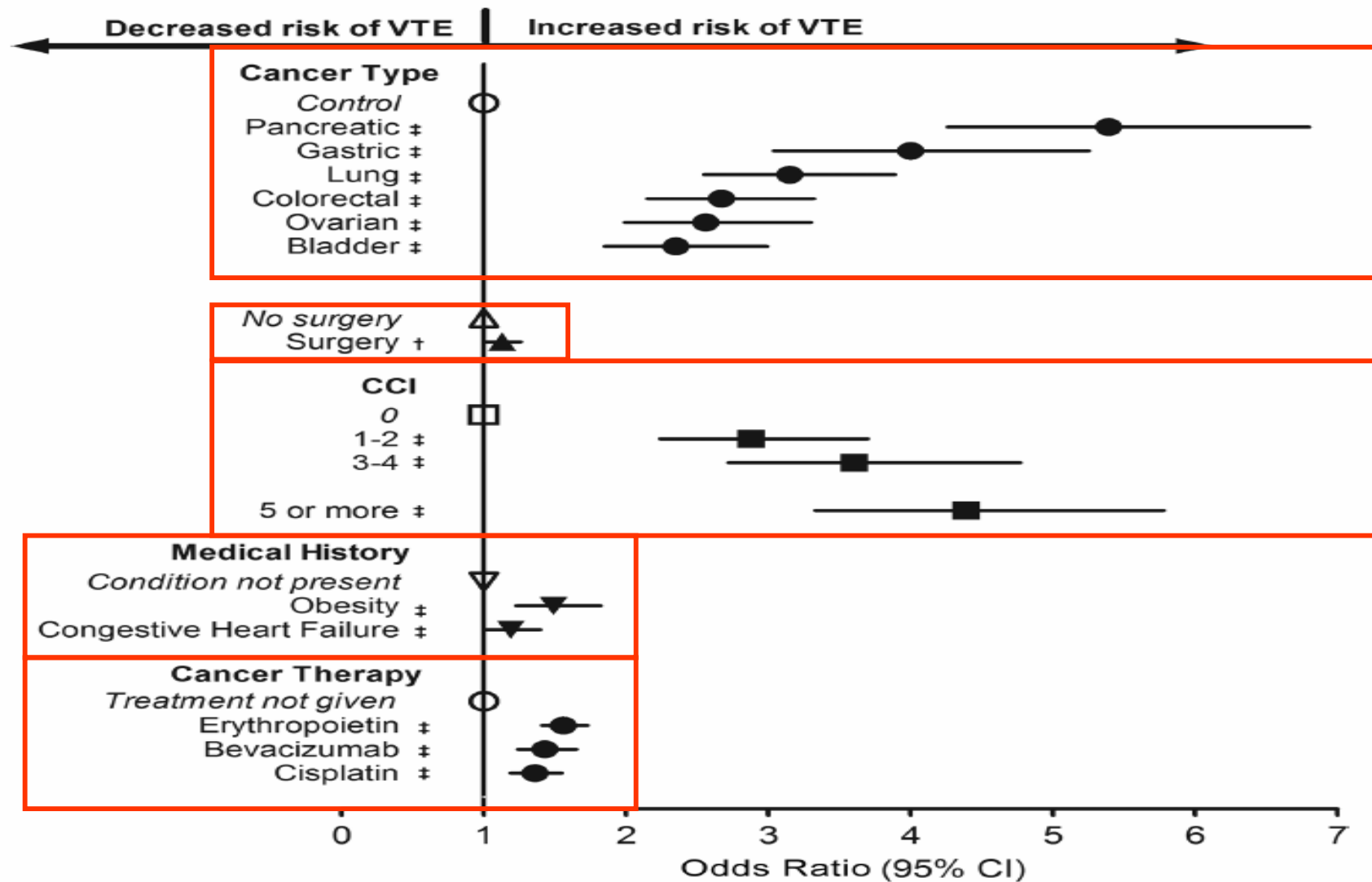


Figure 4. The distribution of venous thromboembolism events is illustrated for the cancer cohort after the initiation of chemotherapy.

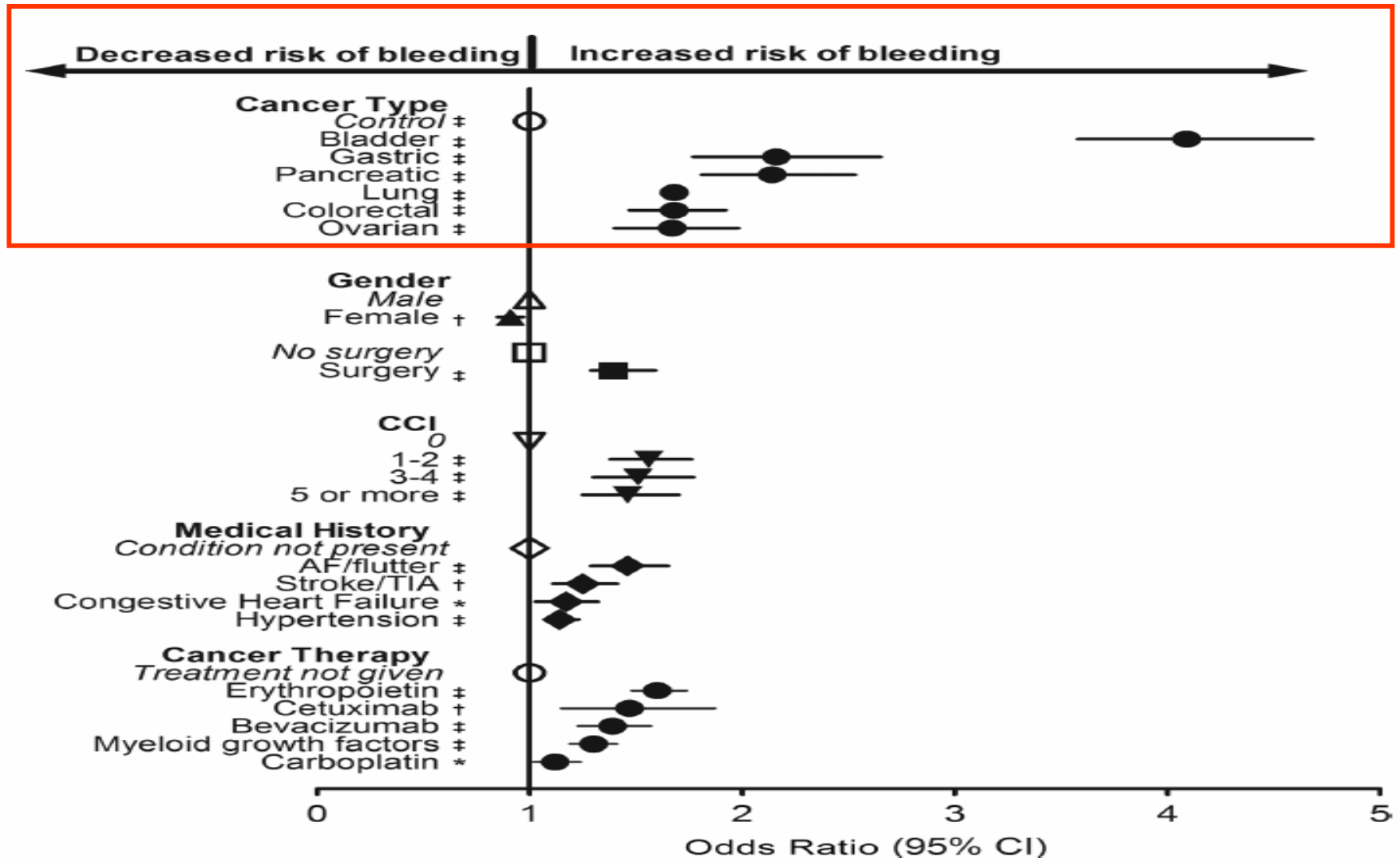
Incidence and Predictors of Venous Thromboembolism (VTE) Among Ambulatory High-Risk Cancer Patients Undergoing Chemotherapy in the United States

Alok A. Khorana, MD¹; Mehul Dalal, PhD²; Jay Lin, PhD³; and Gregory C. Connolly, MD¹



Incidence and Predictors of Venous Thromboembolism (VTE) Among Ambulatory High-Risk Cancer Patients Undergoing Chemotherapy in the United States

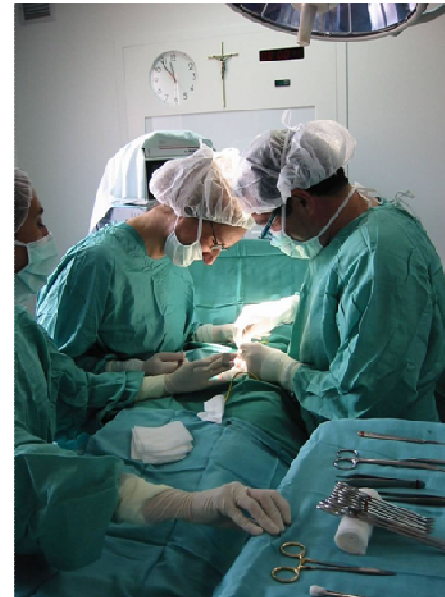
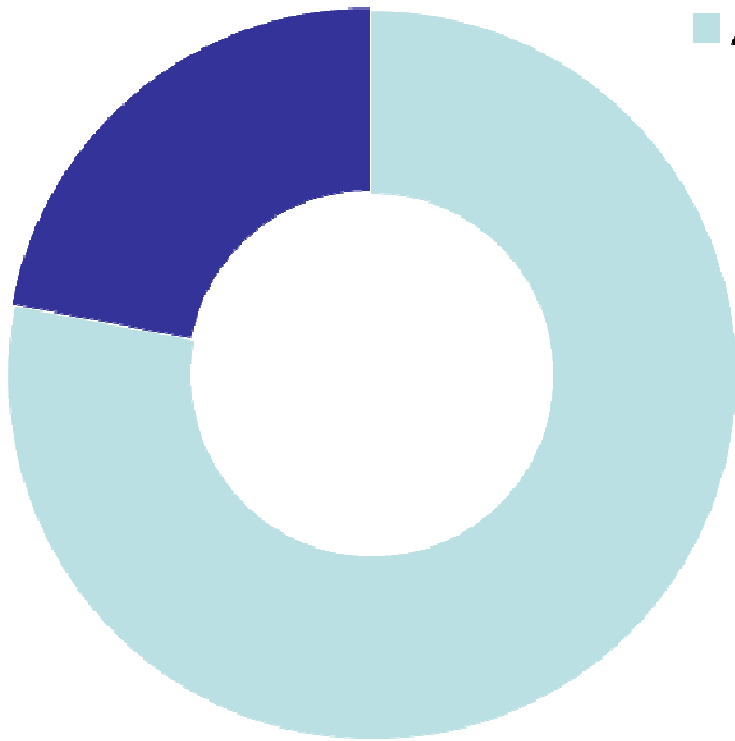
Alok A. Khorana, MD¹; Mehul Dalal, PhD²; Jay Lin, PhD³; and Gregory C. Connolly, MD¹



Trombosis venosa asociada al cáncer

Retrospectivo N = 17,874

■ Ambulatorios



Cáncer y trombosis: evidencia

- ✓ Poblaciones con cáncer muy heterogéneas
- ✓ Pocos estudios prospectivos dirigidos a estudiar la trombosis
- ✓ Ensayos clínicos de Oncología Médica

- ✓ Riesgo de sangrado tumoral

Antiangiogénicos: trombosis y hemorragia

Quimioterapia: trombosis y riesgo de plaquetopenia

- ✓ Trombosis venosa / arterial / visceral

- ✓ Trombosis sintomática / Incidental

➤ **Identificar grupos de mayor riesgo ?**

-

➤ **Trombopprofilaxis primaria?**

Trial	Tumor	n	Treatment	VTE	Major bleeding	Survival		
FAMOUS 2004	Solid tumors	385	Dalteparin Placebo	2.4 % 3.3 %	NS	0.5% 0 %	NS	P=0.03
SIDERAS	Adv / Met Solid tumors	141	Dalteparin Control	6 % 7 %		3 % 7 %		ND
TOPIC-1	Metastatic Breast	353	Certoparin Placebo	4 % 4 %		1.7% 0 %		ND
TOPIC-2	Metastatic Lung	547	Certoparin Placebo	4.5 % 8.3 %		3.7 % 2.2 %		ND
PRODIGE	Gliomas	186	Dalteparin Placebo	11 % 17 %		5.1 % 1.2 %		ND
CONKO-004	Adv / Met Pancreas	312	Enoxaparin Control	1.3 % 9.9 %		ND		ND
UK FRAGEM	Adv / Met Pancreas	123	Dalteparin Control	12 % 31 %		3 % 3 %		ND
PROTECHT	Adv / Met Solid tumors	1150	Nadroparina Placebo	2 % 3.9 %		0.7 % 0 %		ND
SAVE-ONCO	Adv / Met	3212	Semuloparin	1.2 %		1.2 %		ND

Trial	Tumor	n	Treatment	VTE	Major bleeding	Survival
FAMOUS	Solid tumors	385	Dalteparin Placebo	2.4 % 3.3 %	0.5% 0 %	P=0.03
SIDERAS 2005	Adv / Met Solid tumors	141	Dalteparin Control	6 % 7 %	3 % 7 %	ND
TOPIC-1 2005	Metastatic Breast	353	Certoparin Placebo	4 % 4 %	1.7% 0 %	NS ND
TOPIC-2	Metastatic Lung	547	Certoparin Placebo	4.5 % 8.3 %	3.7 % 2.2 %	ND
PRODIGE	Gliomas	186	Dalteparin Placebo	11 % 17 %	5.1 % 1.2 %	ND
CONKO-004	Adv / Met Pancreas	312	Enoxaparin Control	1.3 % 9.9 %	ND	ND
UK FRAGEM	Adv / Met Pancreas	123	Dalteparin Control	12 % 31 %	3 % 3 %	ND
PROTECHT	Adv / Met Solid tumors	1150	Nadroparina Placebo	2 % 3.9 %	0.7 % 0 %	ND
SAVE-ONCO	Adv / Met Solid tumors	3212	Semuloparin Placebo	1.2 % 3.4 %	1.2 % 1.1 %	ND

Trial	Tumor	n	Treatment	VTE	Major bleeding	Survival
FAMOUS	Solid tumors	385	Dalteparin Placebo	2.4 % 3.3 %	0.5% 0 %	P=0.03
SIDERAS	Adv / Met Solid tumors	141	Dalteparin Control	6 % 7 %	3 % 7 %	ND
TOPIC-1	Metastatic Breast	353	Certoparin Placebo	4 % 4 %	1.7% 0 %	ND
TOPIC-2 2005	Metastatic Lung	547	Certoparin Placebo	4.5 % 8.3 %	3.7 % 2.2 %	ND NS
PRODIGE	Gliomas	186	Dalteparin Placebo	11 % 17 %	5.1 % 1.2 %	ND
CONKO-004	Adv / Met Pancreas	312	Enoxaparin Control	1.3 % 9.9 %	ND	ND
UK FRAGEM	Adv / Met Pancreas	123	Dalteparin Control	12 % 31 %	3 % 3 %	ND
PROTECHT	Adv / Met Solid tumors	1150	Nadroparina Placebo	2 % 3.9 %	0.7 % 0 %	ND
SAVE-ONCO	Adv / Met Solid tumors	3212	Semuloparin Placebo	1.2 % 3.4 %	1.2 % 1.1 %	ND

Trial	Tumor	n	Treatment	VTE	Major bleeding	Survival
FAMOUS	Solid tumors	385	Dalteparin Placebo	2.4 % 3.3 %	0.5% 0 %	P=0.03
SIDERAS	Adv / Met Solid tumors	141	Dalteparin Control	6 % 7 %	3 % 7 %	ND
TOPIC-1	Metastatic Breast	353	Certoparin Placebo	4 % 4 %	1.7% 0 %	ND
TOPIC-2	Metastatic Lung	547	Certoparin Placebo	4.5 % 8.3 %	3.7 % 2.2 %	ND
PRODIGE 2007	Gliomas	186	Dalteparin Placebo P=0.03	11 % 17 %	5.1 % 1.2 % NS	ND
CONKO-004	Adv / Met Pancreas	312	Enoxaparin Control	1.3 % 9.9 %	ND	ND
UK FRAGEM	Adv / Met Pancreas	123	Dalteparin Control	12 % 31 %	3 % 3 %	ND
PROTECHT	Adv / Met Solid tumors	1150	Nadroparina Placebo	2 % 3.9 %	0.7 % 0 %	ND
SAVE-ONCO	Adv / Met Solid	3212	Semuloparin Placebo	1.2 % 3.4 %	1.2 % 1.1 %	ND

Trial	Tumor	n	Treatment	VTE	Major bleeding	Survival
FAMOUS	Solid tumors	385	Dalteparin Placebo	2.4 % 3.3 %	0.5% 0 %	P=0.03
SIDERAS	Adv / Met Solid tumors	141	Dalteparin Control	6 % 7 %	3 % 7 %	ND
TOPIC-1	Metastatic Breast	353	Certoparin Placebo	4 % 4 %	1.7% 0 %	ND
TOPIC-2	Metastatic Lung	547	Certoparin Placebo	4.5 % 8.3 %	3.7 % 2.2 %	ND
PRODIGE	Gliomas	186	Dalteparin Placebo	11 % 17 %	5.1 % 1.2 %	ND
CONKO-004 2009	Adv / Met Pancreas	312	Enoxaparin Control	1.3 % 9.9 %	ND	ND
UK FRAGEM 2009	Adv / Met Pancreas	123	Dalteparin Control	12 % 31 %	3 % 3 %	ND
PROTECHT	Adv / Met Solid tumors	1150	Nadroparina Placebo	2 % 3.9 %	0.7 % 0 %	ND
SAVE-ONCO	Adv / Met Solid	3212	Semuloparin Placebo	1.2 % 3.4 %	1.2 % 1.1 %	ND

P<0.01

P=0.02

VTE-related deaths n=5 (8,3%) vs 0 (100 days) (p 0.057)

Trial	Tumor	n	Treatment	VTE	Major bleeding	Survival
FAMOUS 2004	Solid tumors	385	Dalteparin Placebo	2.4 % 3.3 %	0.5% 0 %	P=0.03
SIDERAS	Adv / Met Solid tumors	141	Dalteparin Control	6 % 7 %	3 % 7 %	ND
TOPIC-1	Metastatic Breast	353	Certoparin Placebo	4 % 4 %	1.7% 0 %	ND
TOPIC-2	Metastatic Lung	547	Certoparin Placebo	4.5 % 8.3 %	3.7 % 2.2 %	ND
PRODIGE	Gliomas	186	Dalteparin Placebo	11 % 17 %	5.1 % 1.2 %	ND
CONKO-004	Adv / Met Pancreas	312	Enoxaparin Control	1.3 % 9.9 %	ND	ND
UK FRAGEM	Adv / Met Pancreas	123	Dalteparin Control	12 % 31 %	3 % 3 %	ND
PROTECHT 2009	Adv / Met Solid tumors	1150	Nadroparina Placebo P=0.02	2 % 3.9 %	0.7 % 0 %	ND
SAVEONCO 2012	Adv / Met Solid tumors	3212	Semuloparin Placebo P<0.001	1.2 % 3.4 %	1.2 % 1.1 %	ND

NS

PROTECHT Study

Agnelli et al Lancet Oncol 2009

Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study



Objetivo primario:

Eventos tromboembólicos sintomáticos arteriales o venosos

Objetivos secundarios:

Supervivencia a los 12 meses

Eventos trombóticos asintomáticos

PROTECHT Study

**Pulmón,
Gastrointestinal, Páncreas,
Mama, Ovario,
Cabeza y cuello**

**Randomizado 2:1
Doble ciego**

**Nadroparina SC + QT vs
QT + Placebo**

**Durante esquema QT
Fins máximo de 4 meses**

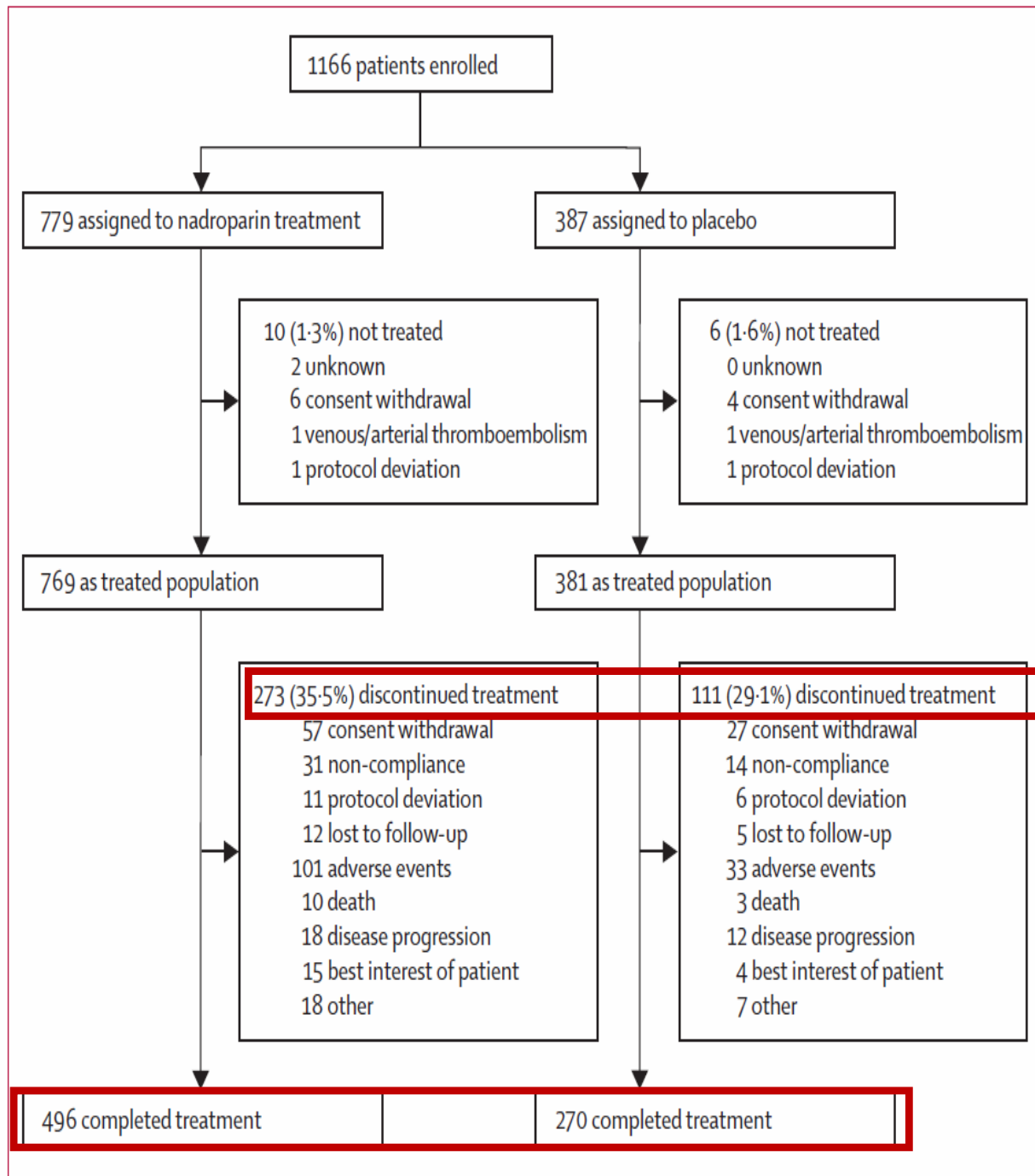


Figure 1: Trial profile

	Nadroparin (N=769)	Placebo (N=381)
Overall thromboembolic events	15 (2.0)	15 (3.9)
Deep-vein thrombosis	8 (1.0)	8 (2.1)
Pulmonary embolism	3 (0.4)	3 (0.8)
Visceral venous thrombosis	1 (0.1)	1 (0.3)
Stroke and peripheral thrombosis	3 (0.4)	3 (0.8)

P = 0.02

Thromboembolic event by cancer site

Lung	7/199 (3.5)	7/80 (8.8)
Gastrointestinal	4/272 (1.5)	4/148 (2.7)
Pancreas	3/36 (8.3)	1/17 (5.9)
Other	1/262 (0.4)	3/136 (2.2)

Data are n (%).

Table 3: Thromboembolic events by treatment group and cancer site

ORIGINAL ARTICLE

Semuloparin for Thromboprophylaxis in Patients Receiving Chemotherapy for Cancer

Objetivo primario:

Eventos tromboembólicos sintomáticos venosos

Muertes relacionadas con eventos tromboembólicos

Objetivos secundarios:

Supervivencia a los 12 meses

Hemorragias clínicamente relevantes

Cáncer localmente avanzado o metastásico

**Pulmón,
Gástrico, Páncreas, Colon,
Mama, Ovario,
Vejiga urinaria**

Randomizado 1:1

Doble ciego

Semuloparina SC + QT vs QT + placebo

Estudio durante un esquema de QT

Table 1. Primary Efficacy Outcome, According to Treatment Group.*

Outcome	Semuloparin (N=1608)	Placebo (N=1604)	P < 0.001
Any VTE or VTE-related death — no. (%)	20 (1.2)	55 (3.4)	0.36 (0.21–0.60)
Symptomatic deep-vein thrombosis	11 (0.7)	34 (2.1)	0.32 (0.15–0.62)
Upper limbs	3 (0.2)	9 (0.6)	0.33 (0.07–1.18)
Lower limbs	8 (0.5)	25 (1.6)	0.32 (0.13–0.69)
Proximal	4 (0.2)	19 (1.2)	0.21 (0.06–0.58)
Distal	4 (0.2)	12 (0.7)	0.33 (0.09–0.99)
Pulmonary embolism	10 (0.6)	24 (1.5)	0.41 (0.19–0.85)
Nonfatal	3 (0.2)	15 (0.9)	0.20 (0.05–0.63)
Symptomatic	3 (0.2)	12 (0.7)	0.25 (0.06–0.83)
Detected during tumor evaluation	0	3 (0.2)	NE
Any VTE-related death	7 (0.4)	9 (0.6)	0.77 (0.27–2.13)

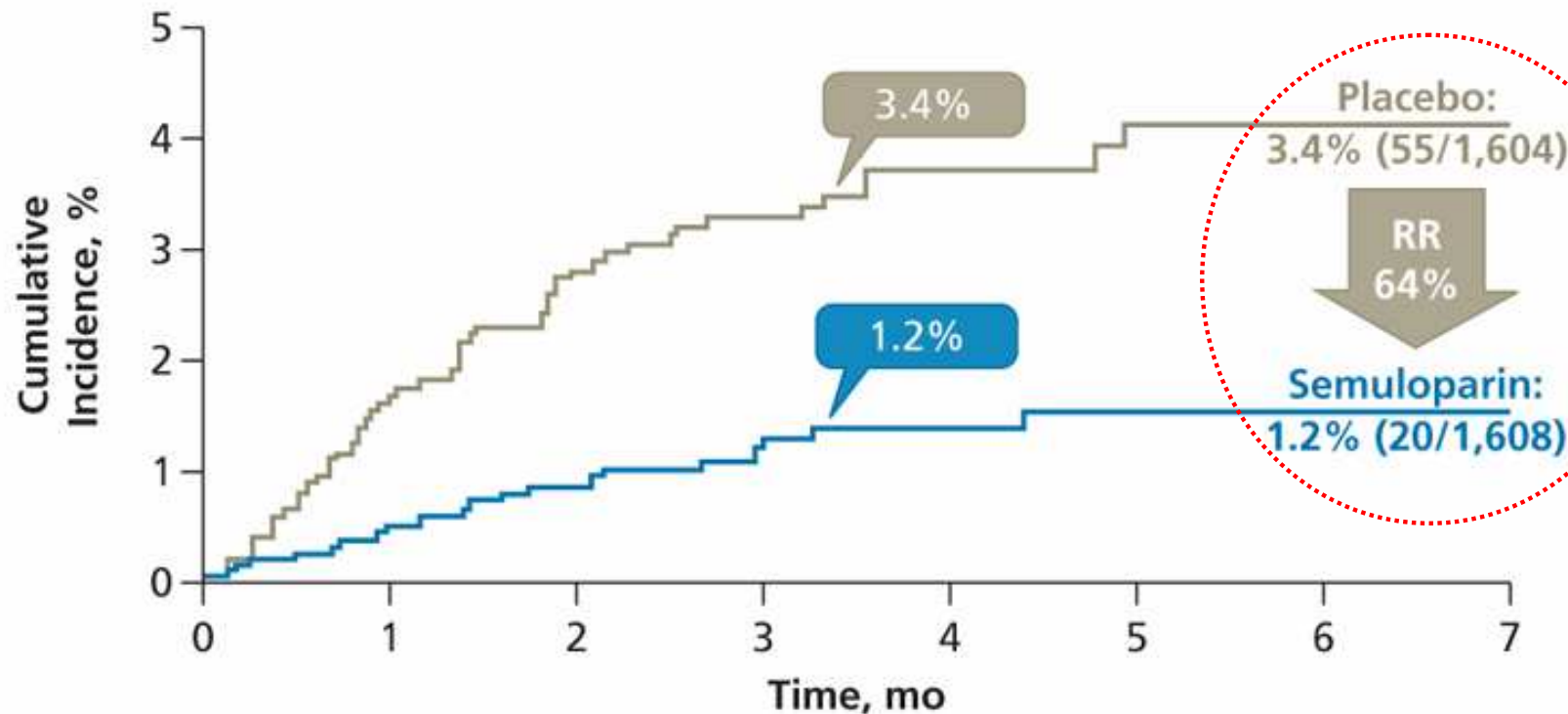
Table 1. Primary Efficacy Outcome, According to Treatment Group.*

Outcome	Semuloparin (N = 1608)	Placebo (N = 1604)	Hazard Ratio (95% CI) [†]
Outcome according to primary cancer site — no./total no. (%)			
Lung	9/591 (1.5)	25/589 (4.2)	0.36 (0.17–0.77)
Pancreas	3/126 (2.4)	14/128 (10.9)	0.22 (0.06–0.76)
Stomach	1/204 (0.5)	4/207 (1.9)	0.25 (0.03–2.20)
Colon or rectum	5/464 (1.1)	9/461 (2.0)	0.54 (0.18–1.60)
Bladder	1/32 (3.1)	3/31 (9.7)	0.30 (0.03–2.95)
Ovary	1/191 (0.5)	0/188	NE
Outcome according to stage of cancer — no./total no. (%)			
Metastatic	16/1097 (1.5)	38/1095 (3.5)	0.42 (0.23–0.75)
Locally advanced	4/511 (0.8)	17/509 (3.3)	0.23 (0.08–0.68)
Outcome according to no. of risk factors for VTE			
0	9/923 (1.0)	23/932 (2.5)	0.39 (0.18–0.84)
1 or 2	9/652 (1.4)	27/632 (4.3)	0.32 (0.15–0.68)
≥3	2/33 (6.1)	5/40 (12.5)	0.56 (0.11–2.93)

Primary Efficacy Endpoint: Decrease in VTE or VTE-Related Deaths

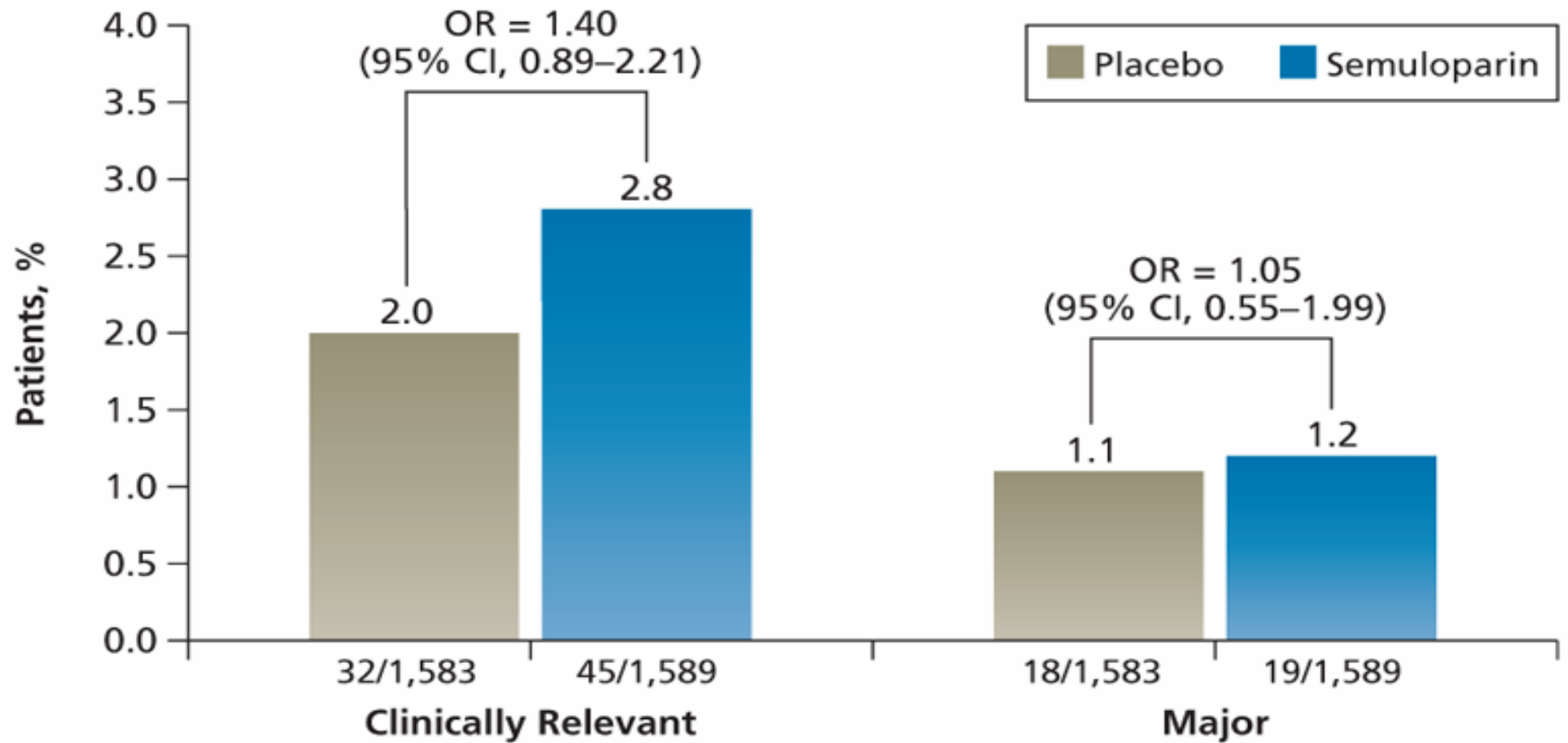
Primary Efficacy Endpoint

- Time to first occurrence of any component of a composite of symptomatic DVT, nonfatal PE, and VTE-related deaths



- Efficacy results were consistent for rates of DVT and PE
- RR = 59% for all PE (OR = 0.41, 95% CI, 0.19-0.85)

SAVE ONCO Safety Endpoints: Bleeding Outcomes



Trombopprofilaxis primaria en pacientes ambulatorios en tratamiento con QT?

PROTECHT

Es necesario tratar **53** pacientes para evitar un evento trombotic arterial o venoso

SAVE-ONCO

Es necesario tratar **45** pacientes para evitar un evento trombotico venoso

NO diferencias en mortalidad

High Incidence of Thromboembolic Events in Patients Treated With Cisplatin-Based Chemotherapy: A Large Retrospective Analysis

Table 2. Overall Incidence of Thromboembolic Events (N = 932)

Thromboembolic Event	No. of Patients	%
Thrombosis	169	18.1
Types of thromboses (n = 169)		
DVT alone	84	49.7
PE alone	43	25.4
DVT + PE	23	13.6
Arterial thrombosis alone	14	8.3
DVT + arterial thrombosis	5	3.0
Subtypes of DVTs (n = 112)		
Proximal lower extremity	22	19.6
Proximal lower and distal lower extremity	18	16.1
Proximal lower extremity and central*	5	4.4
Proximal lower extremity and central* and distal lower extremity	1	0.9
Proximal upper extremity	2	1.8
Proximal upper and distal upper extremity	3	2.7
Proximal upper and internal jugular vein and distal upper extremity	4	3.6
Internal jugular vein	5	4.4
Internal jugular vein and distal upper extremity	1	0.9
Central*	27	24.1
Distal lower extremity	20	17.9
Distal lower and distal upper extremity	1	0.9
Distal upper extremity	3	2.7
Subtypes of arterial events (n = 19)		
Central†	6	31.6
Myocardial infarction	2	10.5
Cerebrovascular accident	10	52.6
Transient ischemic attack	1	5.3
Symptomatic or incidental event (n = 169)		
Symptomatic	95	56.2
Incidental	74	43.8

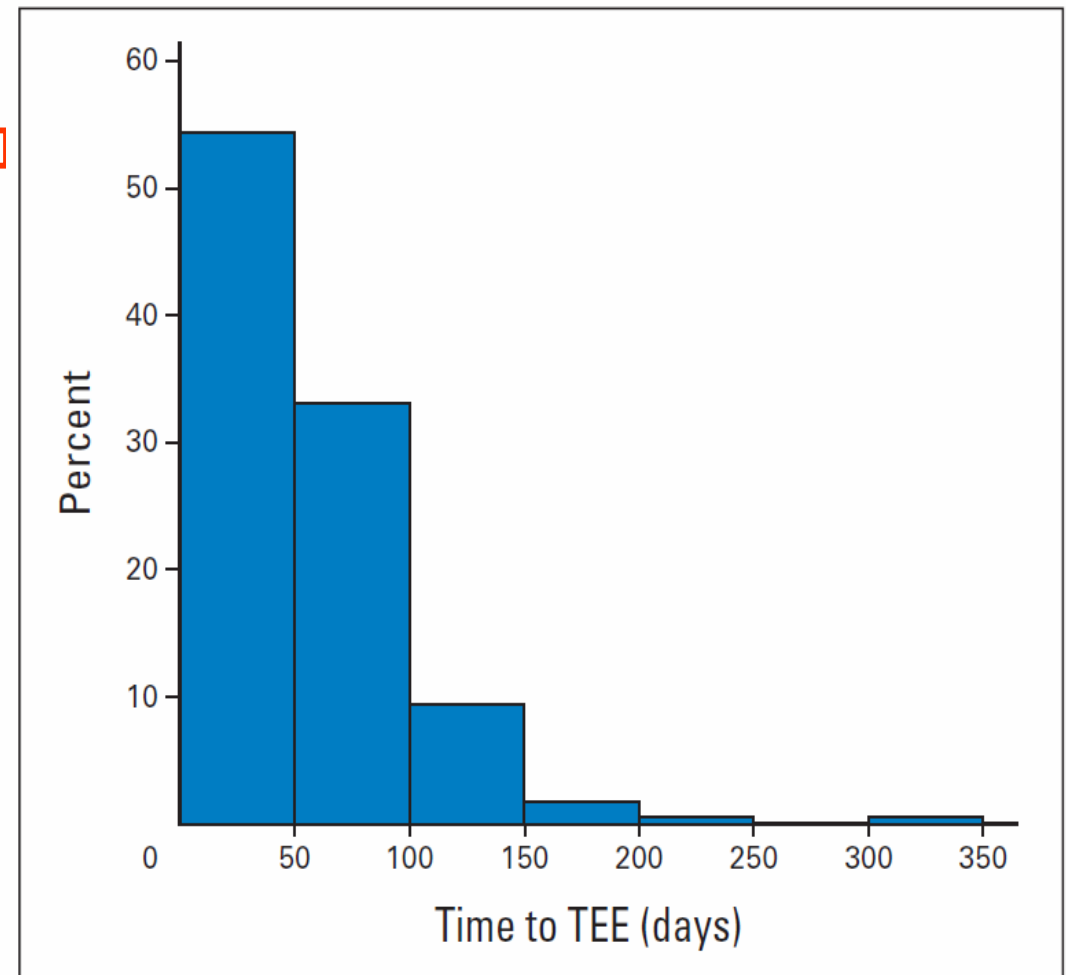


Fig 1. Time to thrombosis in patients who developed a thromboembolic event (TEE).

Table 4. Thromboembolic Rate According to Underlying Cancer and Treatment Regimen

Cancer Type and Treatment Regimen	No. of Patients*	%
Cancer diagnosis		
Colorectal/anal/small bowel	5/13	38.5
Pancreatic	29/79	36.7
Gallbladder/ampullary	3/10	30.0
Gastric/GE junction	31/114	27.2
Cholangiocarcinoma	5/18	27.8
Ovarian	12/57	21.0
Bladder	6/33	18.2
Sarcoma	2/11	18.2
Germ cell/seminoma	7/39	18.0
Esophageal	8/46	17.4
Endometrial	3/22	13.6
Melanoma	9/69	13.0
Head and neck	12/94	12.8
Lung	24/204	11.8
Cervical/uterine/vulvar	4/39	10.3
Hematologic malignancies	1/11	9.1
Neuroendocrine/carcinoid	0/11	0
Other	8/62	12.9
Chemotherapy regimens		
Cisplatin + docetaxel + fluorouracil/leucovorin + bevacizumab	11/16	68.8
Cisplatin + docetaxel + fluorouracil/leucovorin	7/11	63.6
Cisplatin IP + paclitaxel IV/IP + bevacizumab	6/13	46.2
Cisplatin + docetaxel + fluorouracil	5/17	29.4
Cisplatin + gemcitabine	38/134	28.4
Cisplatin + paclitaxel + ifosfamide	2/11	18.2
Cisplatin + irinotecan	15/89	16.9
Cisplatin + pemetrexed	6/43	14
Cisplatin + etoposide	10/80	12.5
Cisplatin + fluorouracil + epirubicin	2/16	12.5
Cisplatin + vinblastine + temozolomide	7/57	12.3
Cisplatin + pemetrexed + bevacizumab	4/33	12.1
Cisplatin + radiation	9/94	9.6
Cisplatin IP + paclitaxel IV/IP	3/33	9.1
Other cisplatin-based regimens	44/285	15.4

Moore RA
J Clin Oncol 2011

Profilaxis pacientes ambulatorios con QT

Modelo Predictivo

Table 2. Predictors of venous thromboembolism in the derivation cohort by multivariate logistic regression analysis

Patient characteristic	β	Odds ratio* (95% CI)
Site of cancer		
Very high risk (stomach, pancreas)	1.46	4.3 (1.2-15.6)
High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate)	0.43	1.5 (0.9-2.7)
Low risk (breast, colorectal, head and neck)	0.0	1.0 (reference)
Prechemotherapy platelet count $350 \times 10^9/L$ or more	0.60	1.8 (1.1-3.2)
Hemoglobin level less than 100 g/L or use of red cell growth factors	0.89	2.4 (1.4-4.2)
Prechemotherapy leukocyte count more than $11 \times 10^9/L$	0.77	2.2 (1.2-4)
BMI 35 kg/m^2 or more	0.90	2.5 (1.3-4.7)

*Odds ratios are adjusted for stage.

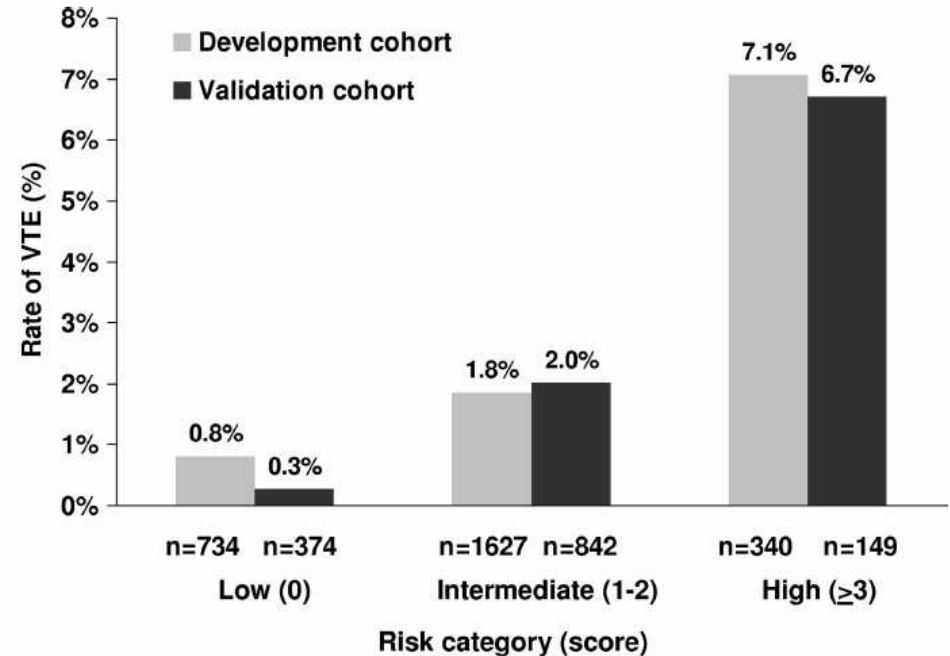


Figure 1. Rates of VTE according to scores from the risk model in the derivation and validation cohorts.

Table 3. Predictive model for chemotherapy-associated VTE

Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count $350 \times 10^9/L$ or more	1
Hemoglobin level less than 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count more than $11 \times 10^9/L$	1
BMI 35 kg/m^2 or more	1



Khorana et al. Blood 2008

Thaler et al. VTE in cancer patients – risk scores and trials

Table 1: VTE risk assessment scores in patients with cancer.

Khorana VTE Risk Assessment Score (13)			Points
– site of cancer:	very high risk:	stomach, pancreas	2
	high risk:	lung, lymphoma, gynaecologic, bladder, testicular	1
– platelet count		$\geq 350 \times 10^9 /l$	1
– haemoglobin and/or use of erythropoiesis-stimulating agents (ESAs)		$< 10 \text{ g/dl}$	1
– leukocyte count		$> 11 \times 10^9 /l$	1
– body mass index		$\geq 35 \text{ kg/m}^2$	1
Vienna VTE Risk Assessment Score* (15), addition of:			
– D-dimer		$\geq 1.44 \mu\text{g/ml}$	1
– sP-selectin		$\geq 53.1 \text{ mg/ml}$	1
*In the Vienna Cancer and Thrombosis Study brain tumours (high-grade glioma) were allocated to the “very high risk” sites of cancer.			

Thrombosis and cancer

Annie Young, Oliver Chapman, Carole Connor, Christopher Poole, Peter Rose and Ajay K. Kakkar

NATURE REVIEWS | CLINICAL ONCOLOGY

VOLUME 9 | AUGUST 2012 | 437



Ingrid Pabinger

Cihan Ay

Universidad de Viena

Box 1 | Potential biomarkers for venous thromboembolism in patients with cancer

- Blood count:^{56,78} prechemotherapy platelet count $\geq 350 \times 10^9/l$;
prechemotherapy white cell count $> 11 \times 10^9/l$
- Tissue factor:¹³⁸⁻¹⁴² high grade of tissue factor expression by tumour cells,
elevated systemic tissue factor (antigen or activity)
- D-dimer¹⁴³
- Soluble P-selectin¹⁴⁴
- C-reactive protein¹⁴⁵
- Prothrombin fragment 1 + 2¹⁴³
- Microparticles, selectin and D-dimer¹⁴⁶
- Circulating endothelial cells¹⁴⁷
- Nuclear retinoic acid receptors α and β ¹⁴⁸

Biomarcadores potenciales

Trombopprofilaxis primaria en
paciente ambulatorio que
recibe quimioterapia?

Recomendaciones de las Guías clínicas

American College of Chest Physicians (ACCP) Guidelines 2012

Cancer outpatients thromboprophylaxis



4.2.1. In outpatients with cancer who have **no additional risk factors for VTE, we suggest against routine prophylaxis** with LMWH or LDUH (*Grade 2B*) and recommend against the prophylactic use of vitamin K antagonists (*Grade 1B*) .

4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic dose LMWH or LDUH over no prophylaxis.

4.4. In outpatients with cancer and indwelling central venous catheters, we suggest against routine prophylaxis with LMWH or LDUH (*Grade 2B*) and suggest against the prophylactic use of vitamin K antagonists (*Grade 2C*).

Additional risk factors include: previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

American College of Chest Physicians (ACCP) Guidelines 2012

Cancer outpatients thromboprophylaxis



4.2.1. In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH or LDUH (*Grade 2B*) and recommend against the prophylactic use of vitamin K antagonists (*Grade 1B*) .

4.2.2. In outpatients with solid tumors who **have additional risk factors** for VTE and who are at low risk of bleeding, we **suggest prophylactic dose LMWH or LDUH** over no prophylaxis.

4.4. In outpatients with cancer and indwelling central venous catheters, we suggest against routine prophylaxis with LMWH or LDUH (*Grade 2B*) and suggest against the prophylactic use of vitamin K antagonists (*Grade 2C*).

Additional risk factors include: previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

NO incluye QT convencional !!

Patients with cancer at high risk for VTE (based on Khorana risk assessment score 3 or higher²⁵) could be considered for outpatient VTE prophylaxis on an individual basis. For these patients, the NCCN Guidelines panel recommends discussions with patients/caregivers regarding the potential risks and benefits of administering VTE prophylaxis in the outpatient setting. However, thromboprophylaxis in the majority of cancer outpatients receiving chemotherapy is controversial and its broader application using the Khorana risk assessment model or the Vienna risk assessment model should await the results of randomized controlled trials evaluating the efficacy of risk-adjusted thromboprophylaxis based upon these models.²⁵⁰

Published Ahead of Print on May 21, 2013 as 10.1200/JCO.2013.49.1118
The latest version is at <http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.49.1118>

JOURNAL OF CLINICAL ONCOLOGY

A S C O S P E C I A L A R T I C L E

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Gary H. Lyman, Nicole M. Kuderer, and Jeffrey M. Clarke, Duke University and Duke Cancer Institute, Durham; Nigel S. Key, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; Alok A. Khorana, Taussig Cancer

Gary H. Lyman, Alok A. Khorana, Nicole M. Kuderer, Agnes Y. Lee, Juan Ignacio Arcelus, Edward P. Balaban, Jeffrey M. Clarke, Christopher R. Flowers, Charles W. Francis, Leigh E. Gates, Ajay K. Kakkar, Nigel S. Key, Mark N. Levine, Howard A. Liebman, Margaret A. Tempero, Sandra L. Wong, Ann Alexis Prestrud, and Anna Falanga

Table 1. VTE Prophylaxis and Treatment Recommendations (continued)

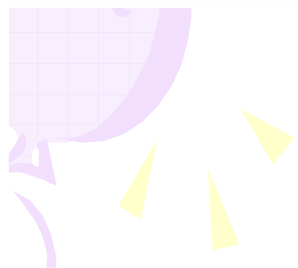
2013 Recommendation	Strength of Evidence Type and Strength of Recommendation	2007 Recommendation
<p>Outpatients</p> <p>2.1 Routine pharmacologic thromboprophylaxis is not recommended in cancer outpatients.</p>	<p>Evidence: moderate Recommendation type, strength: evidence based, strong</p>	<p>Routine prophylaxis with an antithrombotic agent is not recommended.</p>
<p>2.2 Based on limited RCT data, clinicians <u>may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumors receiving chemotherapy.</u> Consideration of such therapy <u>should be accompanied by a discussion with the patient about the uncertainty concerning benefits and harms as well as dose and duration of prophylaxis in this setting.</u></p>	<p>Evidence: moderate Recommendation type, strength: evidence based, weak</p>	
<p>2.3 Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients.</p>	<p>Evidence: moderate Recommendation type, strength: evidence based, strong</p>	<p>Patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone are at high risk for thrombosis and warrant prophylaxis. Until such time as data are available from RCTs, LMWH or adjusted-dose warfarin (INR approximately 1.5) is recommended in patients with myeloma receiving thalidomide plus chemotherapy or dexamethasone. This recommendation is based on extrapolation from studies of postoperative prophylaxis in orthopedic surgery and a trial of adjusted-dose warfarin in breast cancer. RCTs evaluating antithrombotic agents are needed in patients with multiple myeloma receiving thalidomide or lenalidomide plus chemotherapy and/or dexamethasone. Research identifying better markers of ambulatory patients with cancer most likely to develop VTE is urgently needed.</p>

Table 1. VTE Prophylaxis and Treatment Recommendations (continued)

2013 Recommendation	Strength of Evidence Type and Strength of Recommendation	2007 Recommendation
Risk assessment		
6.1 Based on consensus, the Panel recommends that patients with cancer <u>be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter</u> . Individual risk factors, including biomarkers or cancer site, 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 (Table 5).	Evidence: moderate Recommendation type, strength: <u>informal consensus, strong</u>	New for 2012 Update
6.2 Based on consensus, the Panel recommends that <u>oncologists educate patients regarding VTE</u> , particularly in settings that increase risk such as major surgery, hospitalization, and while receiving systemic antineoplastic therapy.	Evidence: insufficient Recommendation type, strength: informal consensus, strong	

JOURNAL OF CLINICAL ONCOLOGY

Low–Molecular Weight Heparin
Prophylaxis Should Not Be
Recommended Even in Highly
Selected Patients With Solid Cancer
Receiving Outpatient Chemotherapy



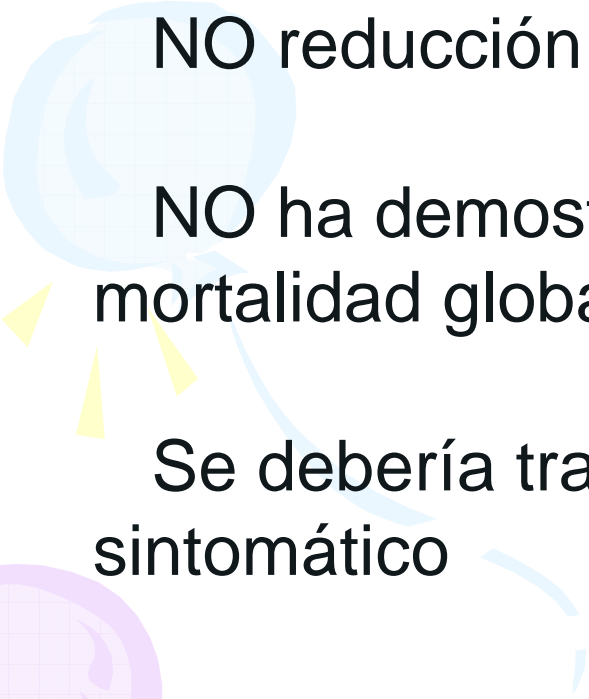
Thein Hlaing Oo

The University of Texas MD Anderson Cancer Center, Houston, TX



- Trombopprofilaxis primaria:

NO reducción en mortalidad por tromboembolismo



NO ha demostrado beneficio en supervivencia o en mortalidad global

Se debería tratar a 60 pacientes para evitar un trombo sintomático



Thein Hlaing Oo

The University of Texas MD Anderson Cancer Center, Houston, TX

CONCLUSIONES II

TROMBOPROFILAXIS PRIMARIA EN EL PACIENTE AMBULATORIO EN TRATAMIENTO QUIMIOTERÁPICO?

No indicado de manera rutinaria

Profilaxis con HBPM: Eficaz y segura en RCTs
 No diferencias en mortalidad
 Baja incidencia de trombosis en RCTs

Mayor incidencia de trombosis en la práctica clínica habitual

En desarrollo modelos predictivos de trombosis (clínicos / biomarcadores) que permitan identificar subgrupos de mayor riesgo

Individualizar la indicación en pacientes de especial riesgo

XXXIV

Congreso Nacional de la Sociedad Española de Medicina Interna (SEMI)

XXIX Congreso de la
Sociedad Andaluza de
Medicina Interna (SADEMI)

21-23

Noviembre 2013

Palacio de Ferias y
Congresos de Málaga
Málaga

