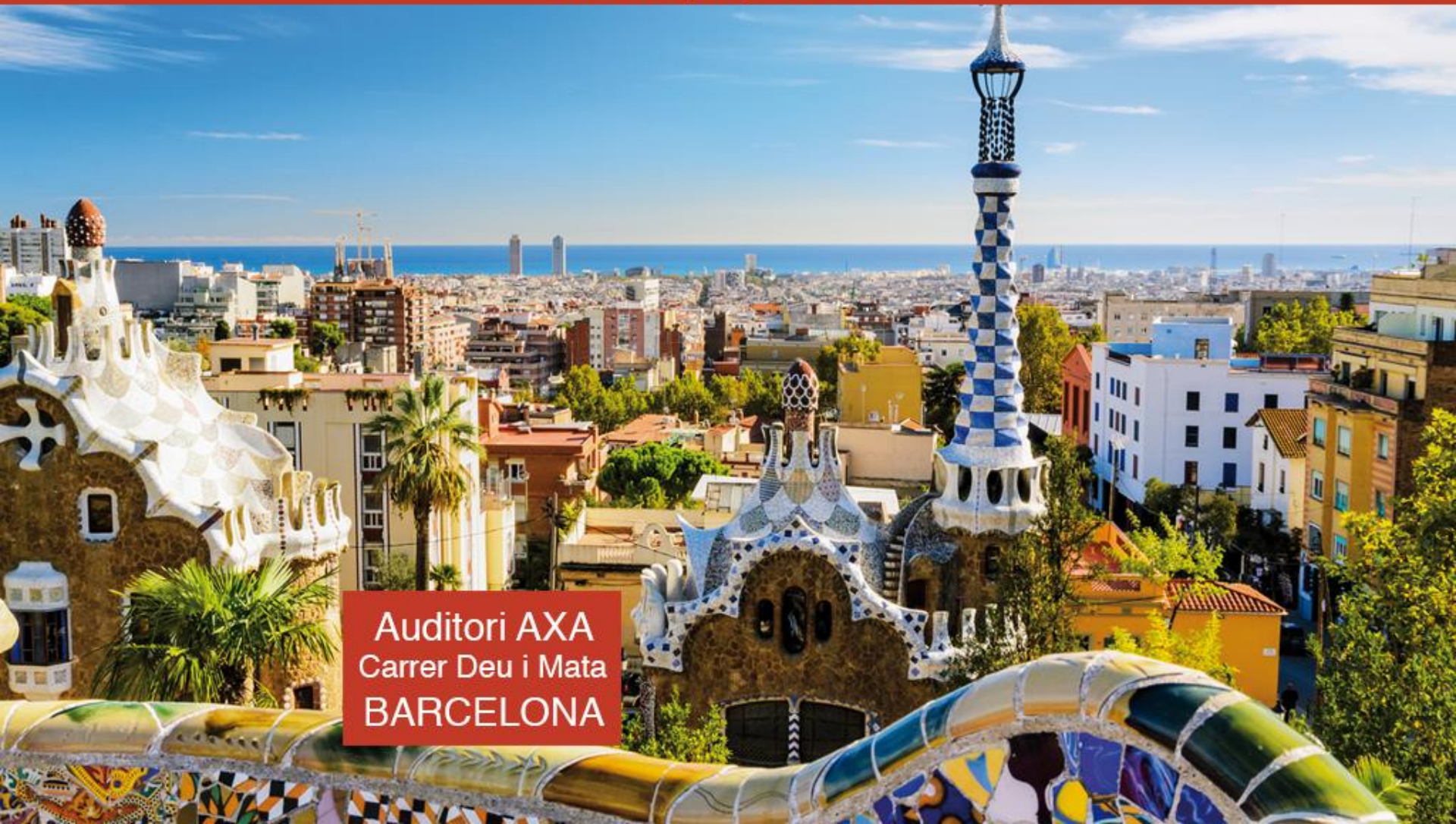
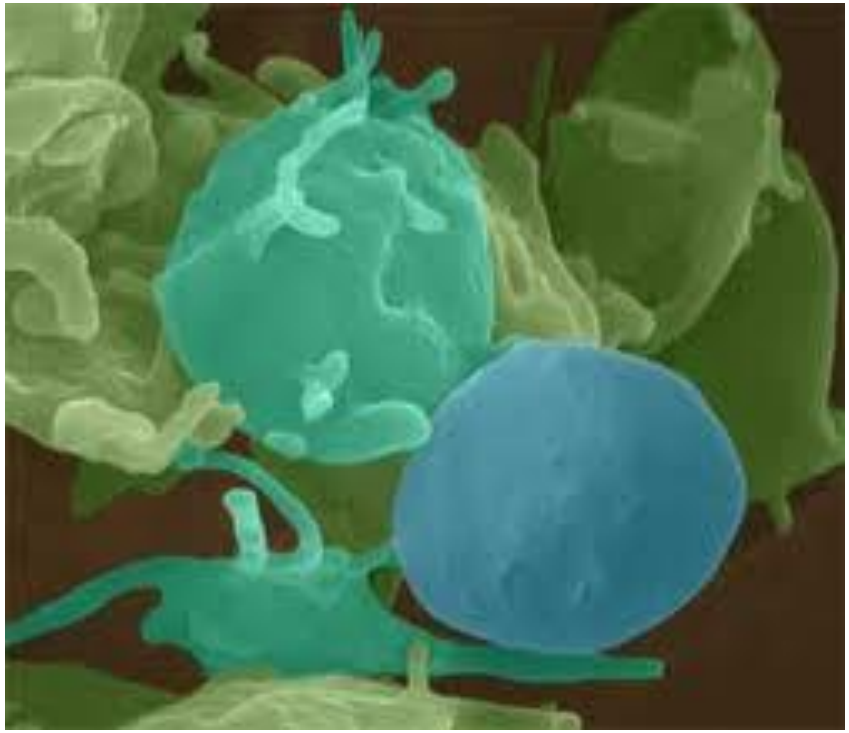
SOCIETAT CATALANOBALEAR DE MEDICINA INTERNA

XVI Congres de la Societat Catalano-Balear de Medicina Interna

2 i 3 de juny de 2016



TROMBOSI I CÀNCER



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Juny 2016

Hipercoagulabilitat i càncer. Síndrome de Trousseau.

- 1865: Tromboflebitis migratòria i neoplàsia oculta visceral.

- **Síndrome de Trousseau:**

- **Tromboembolisme venós.**
- Tromboembolisme arterial.
- Endocarditis trombòtica no bacteriana.
- Microangiopatia trombòtica.
- Coagulació intravascular disseminada.

Varki A, Blood 2007

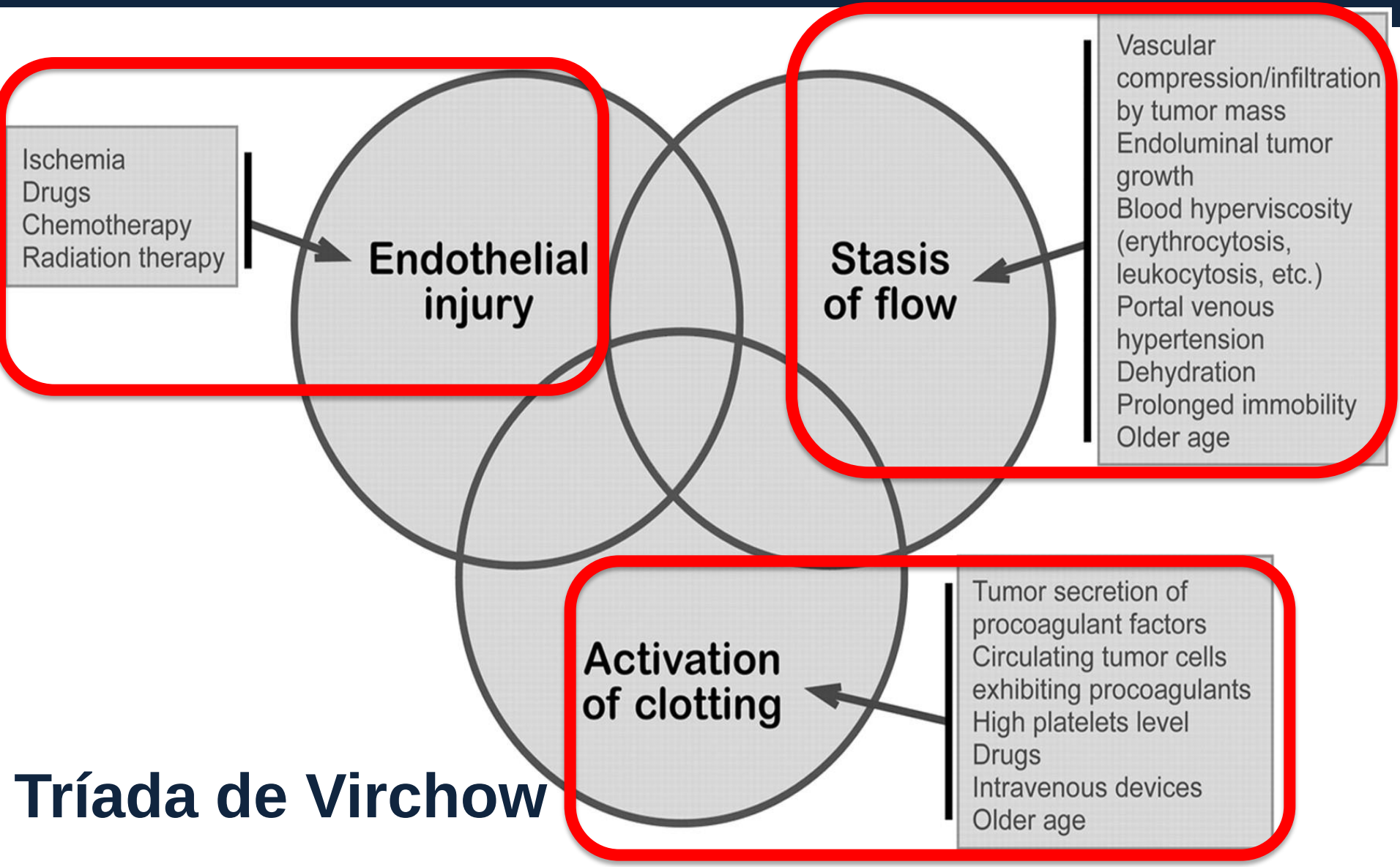
Cancer and Venous Thromboembolism

Cancer causes Thrombosis

CANCER

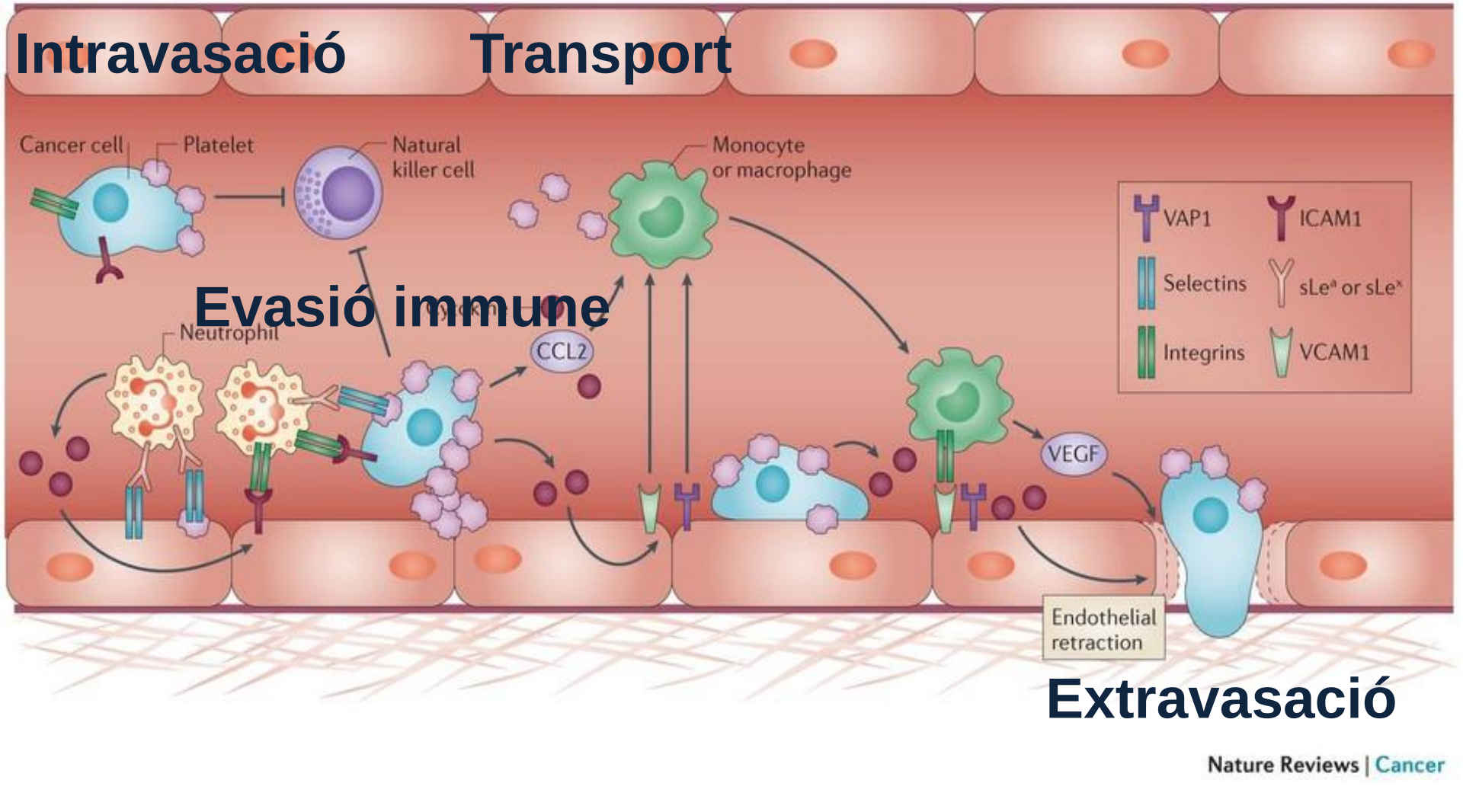
THROMBOSIS

Càncer –> Hipercoagulabiliat



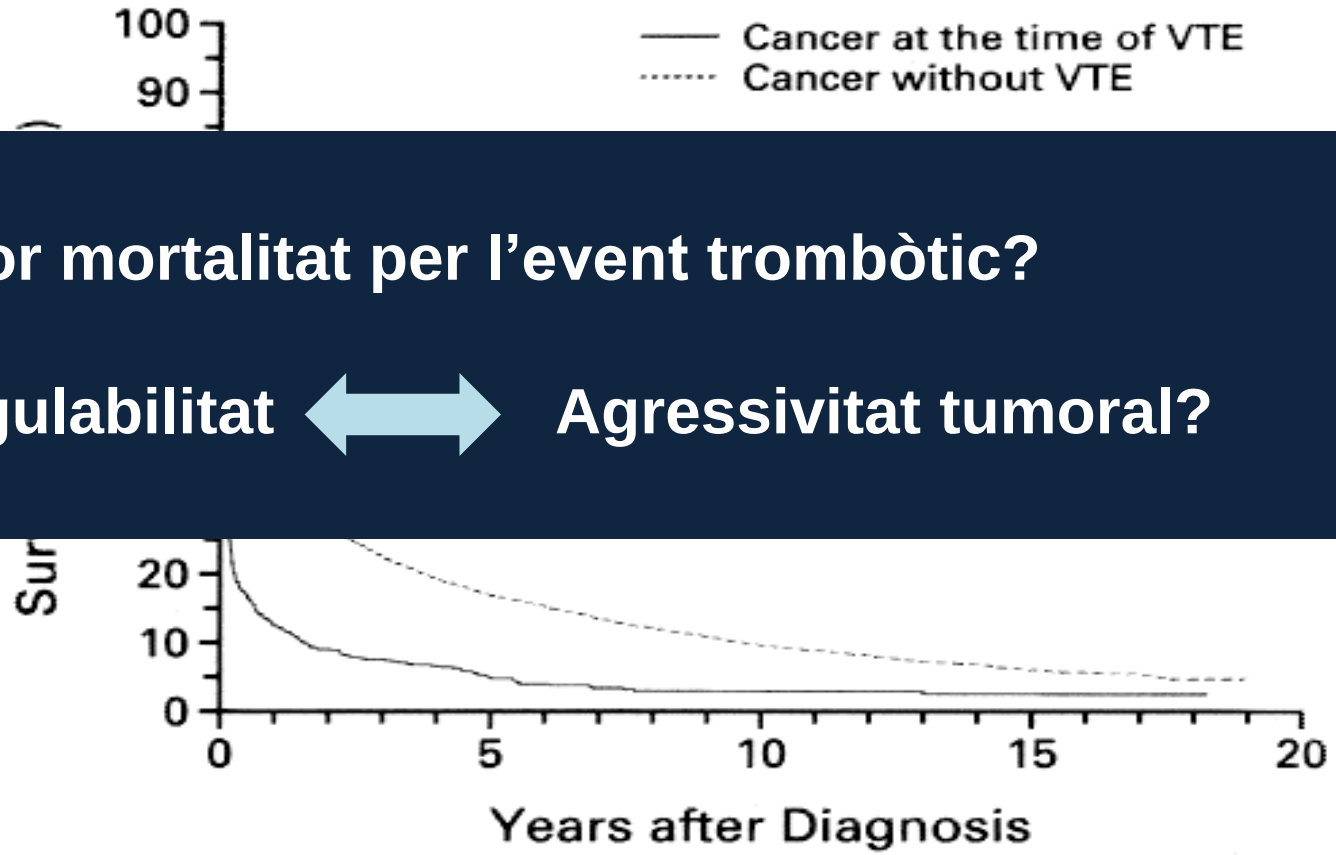
Tríada de Virchow

Inflamació – Hemostàsia –> Progressió Càncer



Prognosis of cancers associated with venous thromboembolism.

Sorensen HT. N Engl J Med 2000



Major mortalitat per l'event trombòtic?

Hipercoagulabilitat ⟺ Agressivitat tumoral?

No. at Risk

Cancer at the time of VTE	668	23	10	3
Cancer without VTE	6668	913	338	87

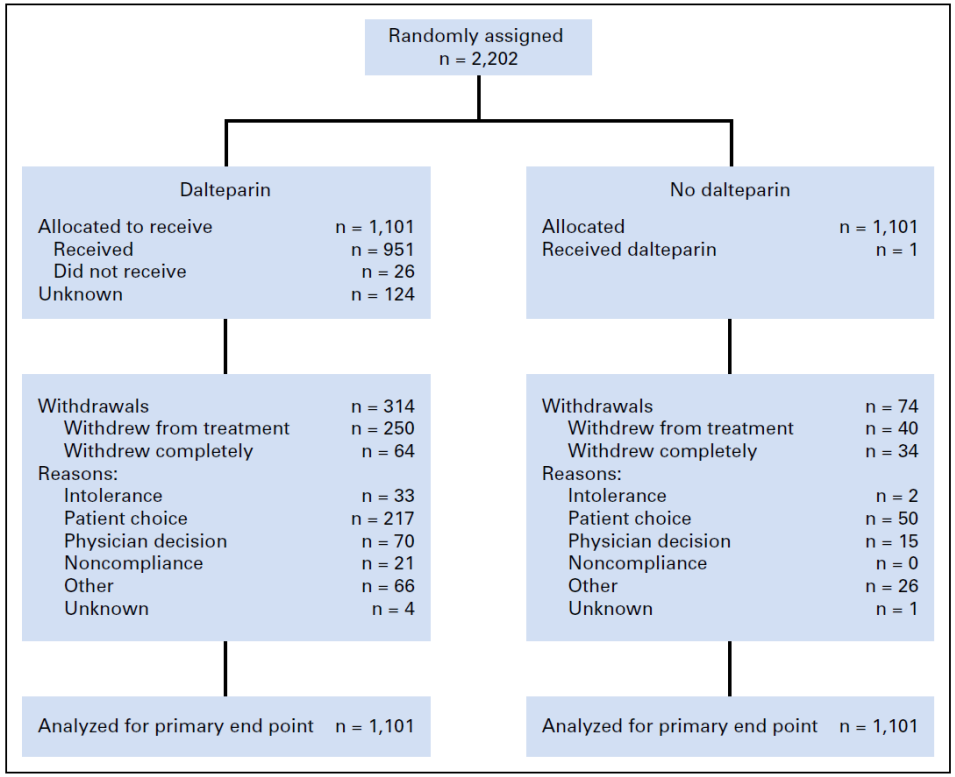
Published Ahead of Print on December 23, 2015 as 10.1200/JCO.2015.64.0268
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.64.0268

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial of Standard Therapy Plus Low Molecular Weight Heparin in Patients With Lung Cancer: FRAGMATIC Trial

Fergus Macbeth, Simon Noble, Jessica Evans, Sheikh Ahmed, David Cohen, Kerenza Hood, Dana Knoyle, Seamus Linnane, Mirella Longo, Barbara Moore, Penella J. Woll, Wiebke Appel, Jeanette Dickson, David Ferry, Caroline Brammer, and Gareth Griffiths



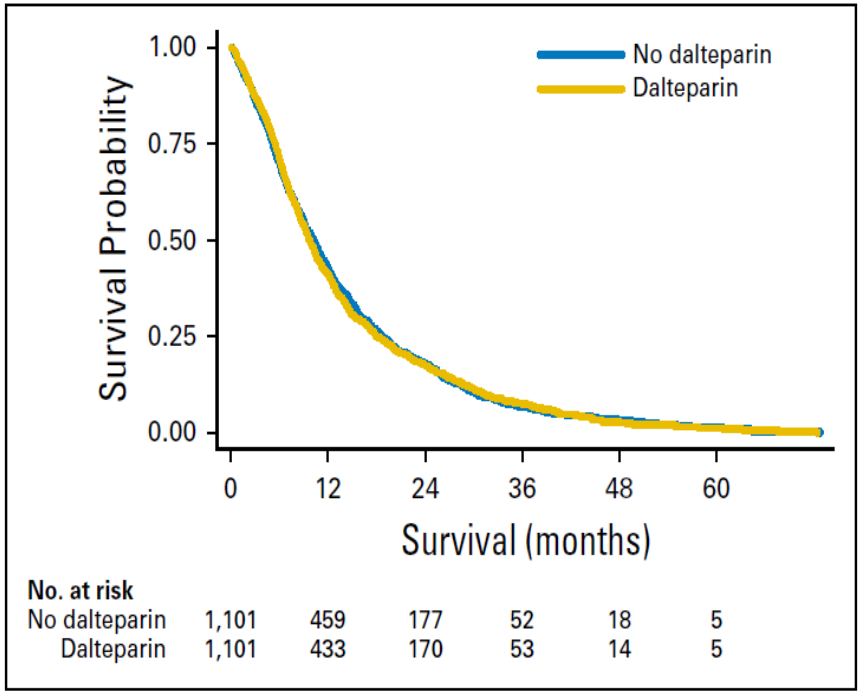


Fig 2. Kaplan-Meier curve of overall survival by treatment group.

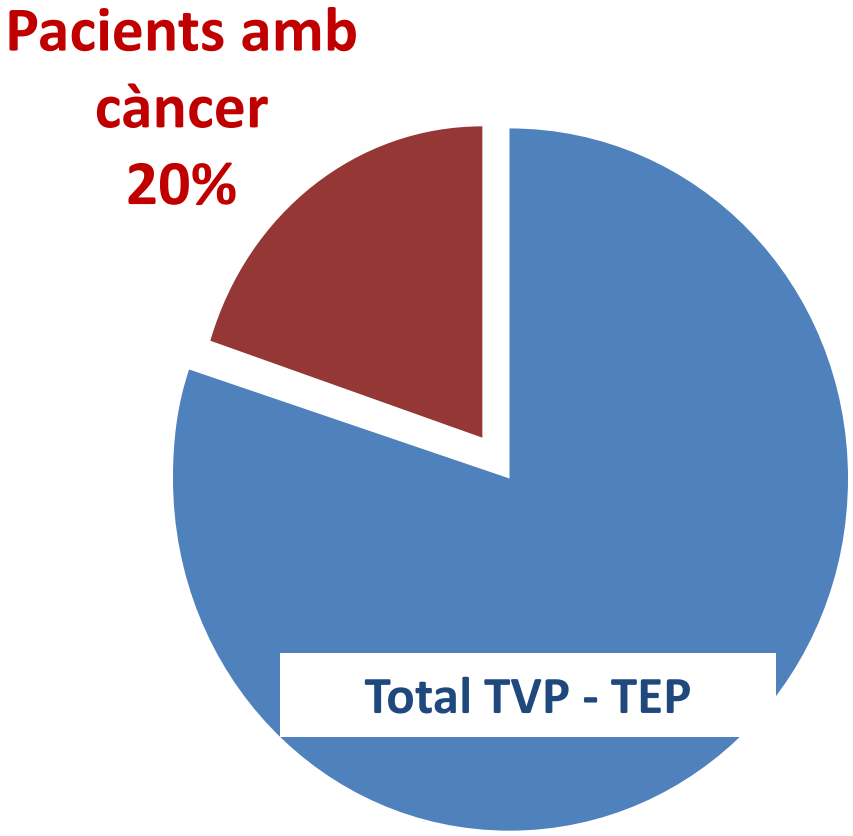
Addition of low molecular weight heparin to adjuvant chemotherapy after surgery for early stage NSCLC

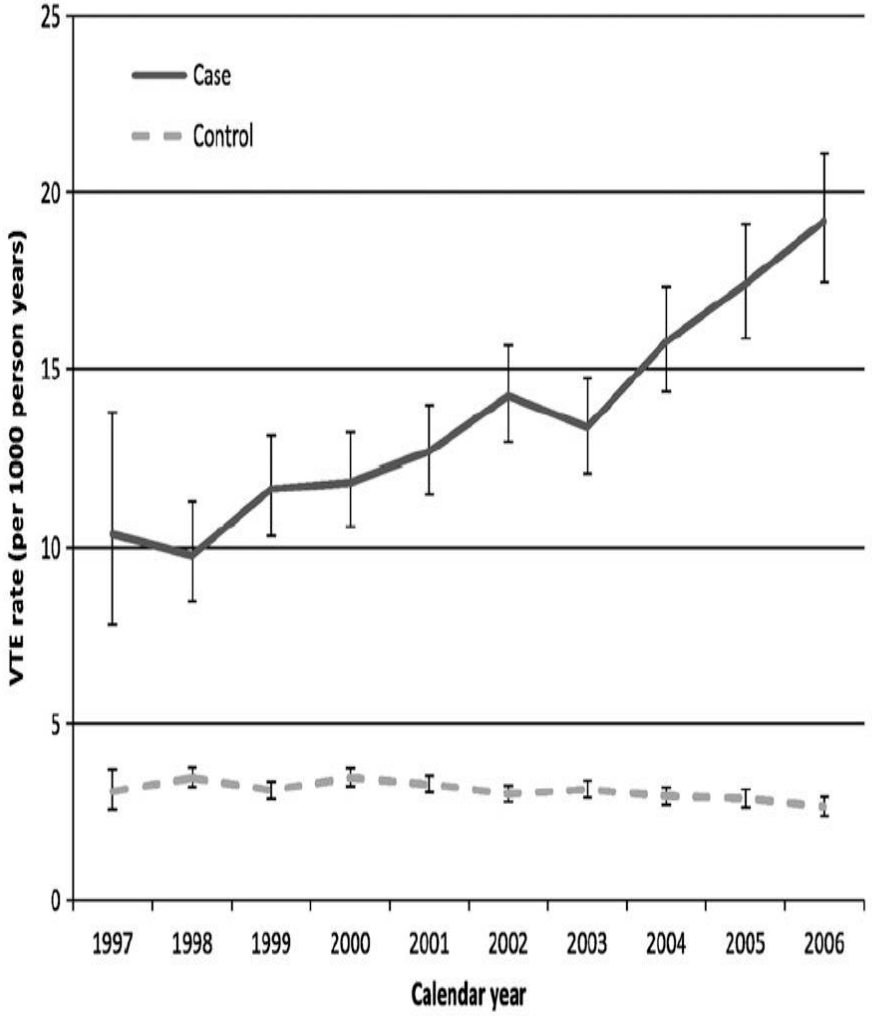
- Does addition of a low-molecular weight heparin during adjuvant chemo improve recurrence-free survival (RFS) in pts with resected early stage NSCLC & getting adjuvant chemo?
- 202 pts randomized to cis/gemcitabine (for squamous NSCLC) or cis/Alimta (pemetrexed) (for non-squamous NSCLC), with or without daily nadroparin under the skin daily x 16 weeks
- Higher neutropenia (low white blood cell count) level w/nadro, but no other differences in side effects
- Median RFS 47.8 vs. 36.1 mo, 3 yr RFS 57% vs. 50%, favoring nadroplatin
- Not likely to change practice yet, but very provocative

Abstract #8506, Groen & colleagues

ASCO Meeting 2016

Tromboembolisme venós associat al càncer

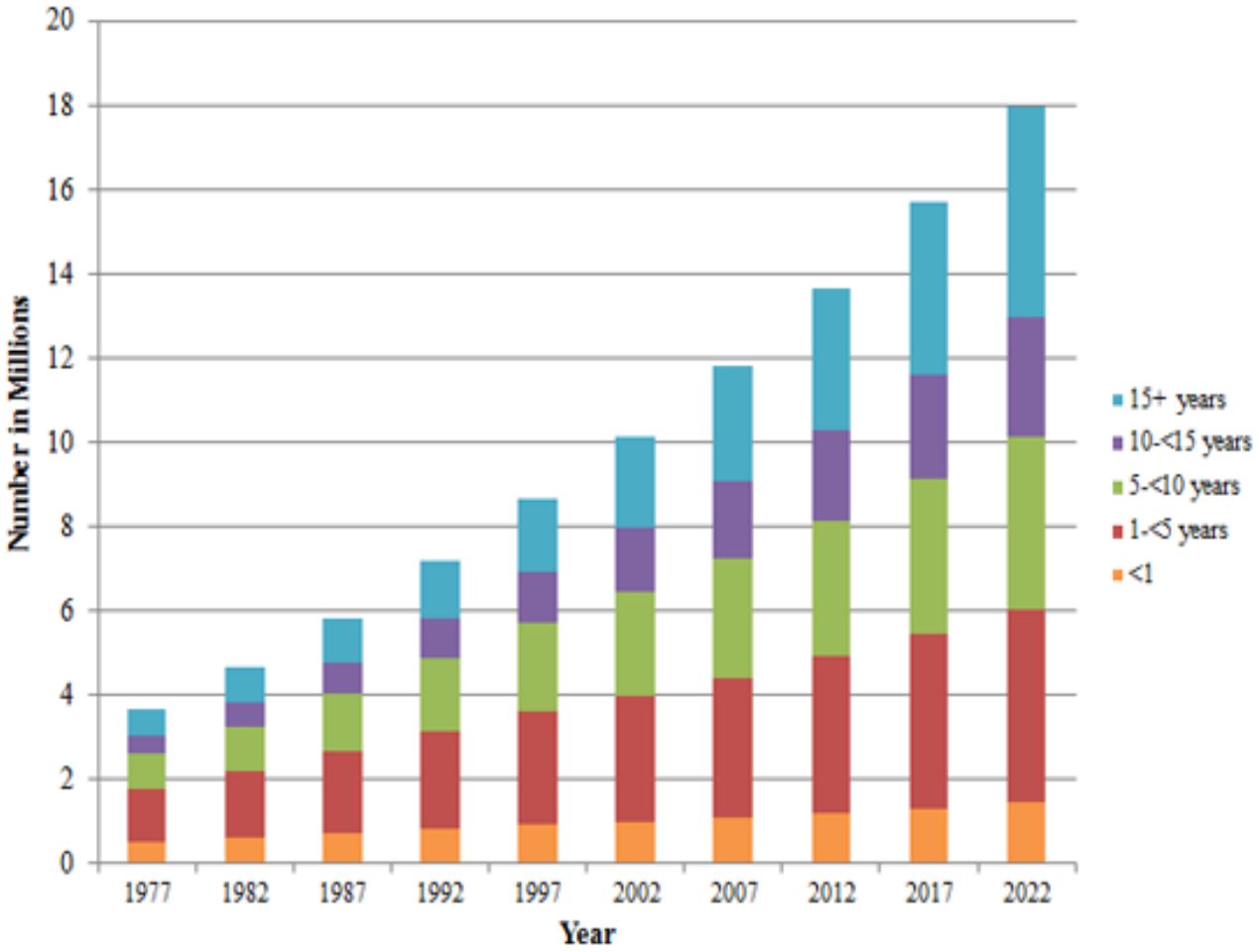




Heit JA et al. *Arch Intern Med.* 2002

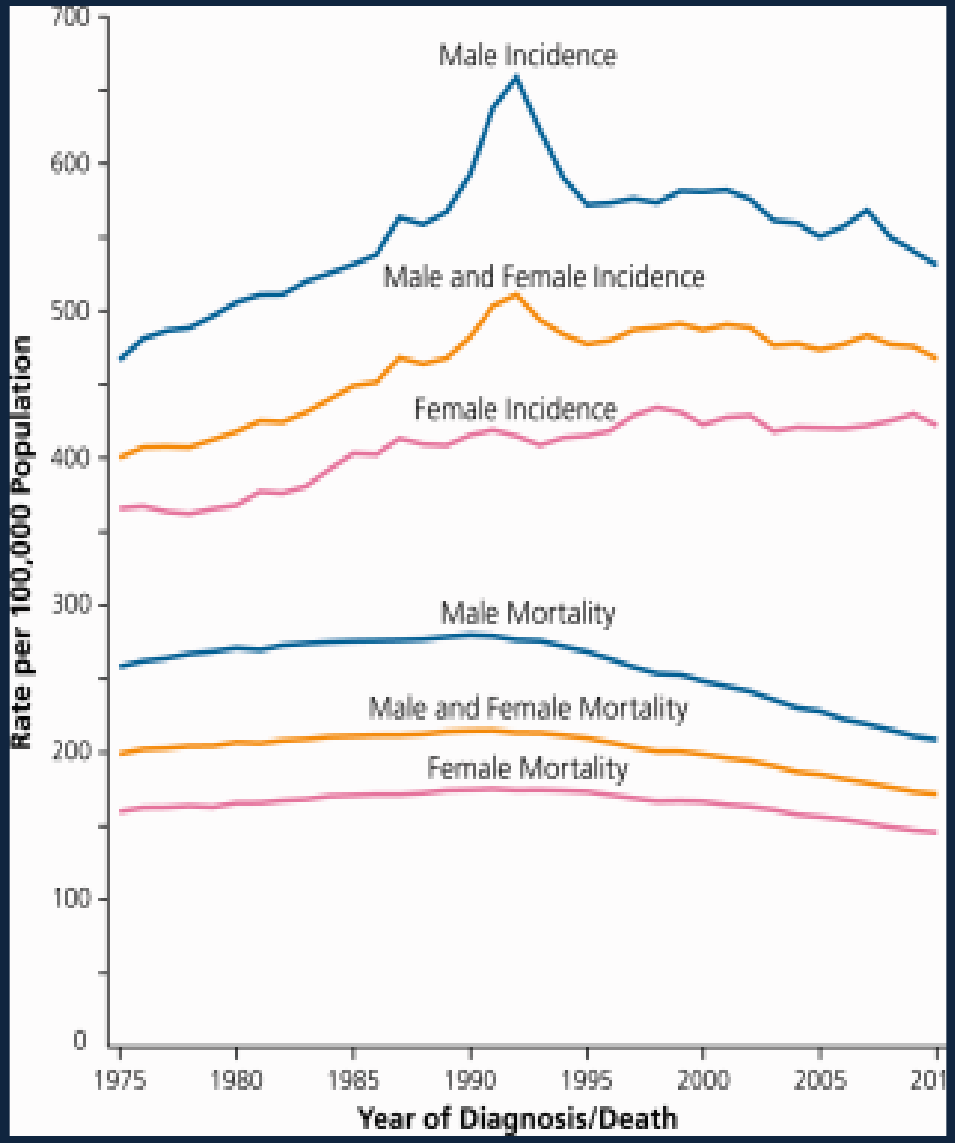
Trends in Cancer Statistics

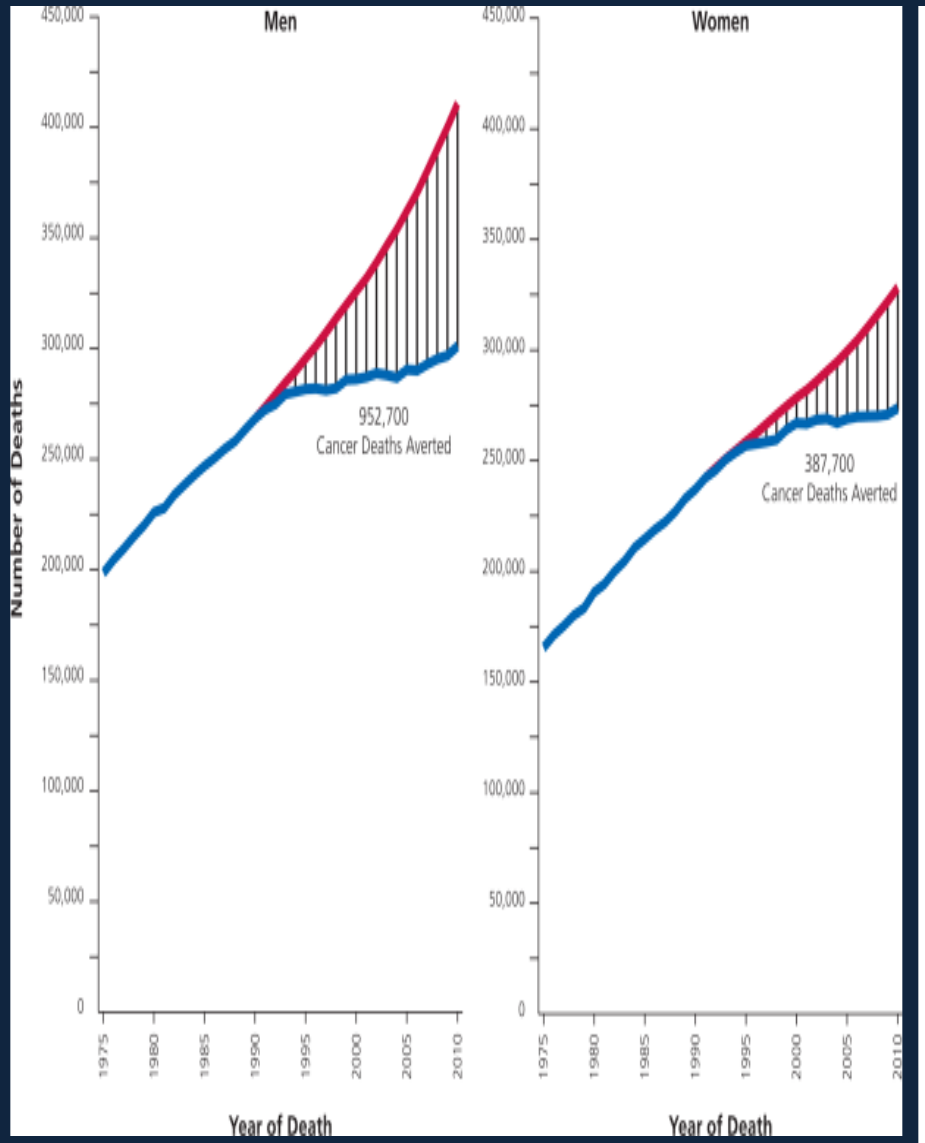
Estimated and projected number cancer survivors in the United States from 1977-2022 by years since diagnosis



de Moor JS, Mariotto AB, Parry C, Alfano CM, Padgett L, Kent EE, Forsythe L, Scoppa S, Hachey M, and Rowland JH. Cancer Survivors in the United States: Prevalence across the Survivorship Trajectory and Implications for Care. Cancer Epidemiol Biomarkers Prev. 2013 Apr;22(4):561-70. doi: 10.1158/1055-9965.EPI-12-1356. Epub 2013 Mar 27.

Trends in Cancer Statistics

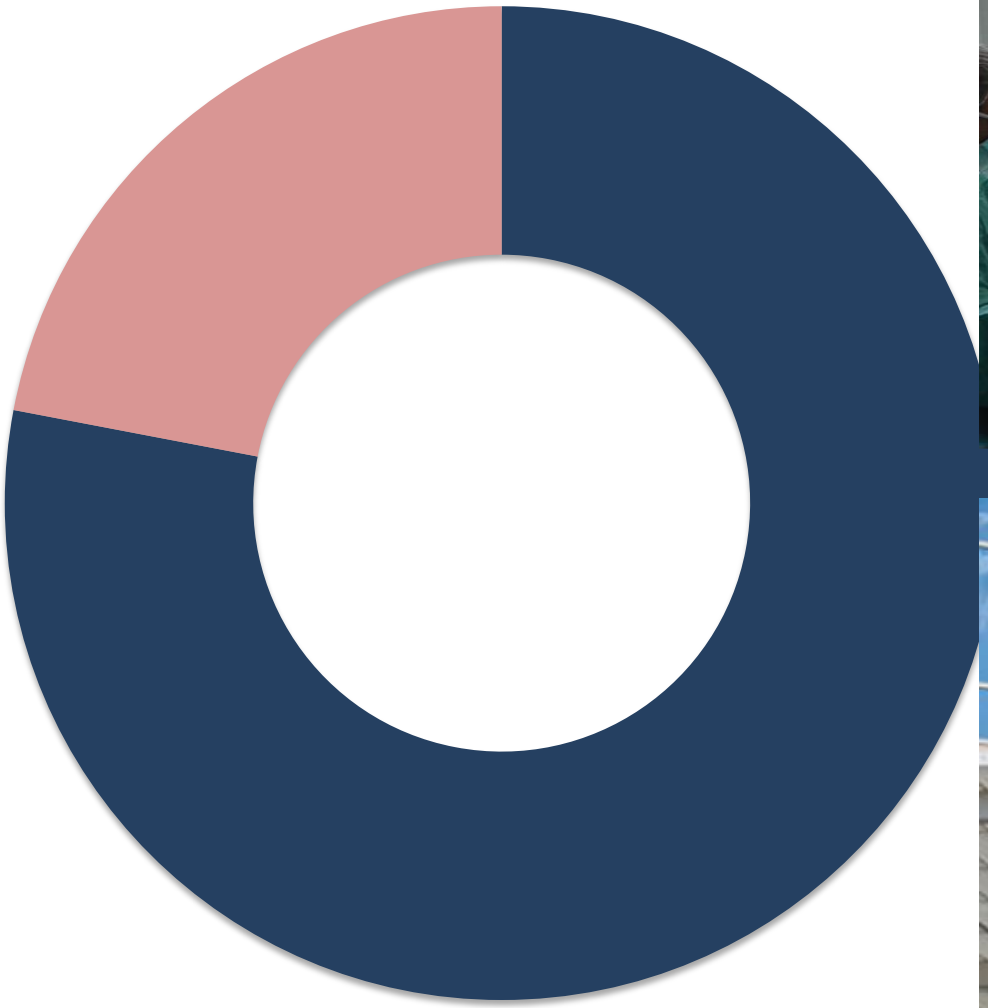




CA: A Cancer Journal for Clinicians; Volume 64, Issue 1, pages 9-29, 7 JAN 2014 DOI: 10.3322/caac.21208

Tromboprofilaxi primària en càncer

Retrospectiu N = 17,874
76% ambulatoris



Khorana et al. Blood 2012

Tromboprofilaxi primària en pacients ambulatoris que reben quimioteràpia?

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 Solis umors	141	Dalteparin Control	6 % 7 %	3 % 7 %	ND
TOPIC-1	Metastatic Breast	353	Certaparin 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 2015	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 2009	Adv / Met Solid tumors	1150	Nadroparina Placebo	2 % 3.9 %	0.7 % 0 %	ND
SAVEONCO 2012	Adv / Met Solid tumors	3212	Semuloparin Placebo	1.2 % 3.4 %	1.2 % 1.1 %	ND

P<0.01

P=0.02

Trial	Tumor	n	Treatment	VTE	Major bleeding	Survival
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SAVEONCO 2012	Adv / Met Solid tumors	3212	Semuloparin Placebo **P<0.001**	1.2 % 3.4 %	1.2 % 1.1 % **NS**	ND

¿Tromboprofilaxi primària en pacients ambulatoris en QUIMIOTERÀPIA?

PROTECHT Caldria tractar **53** pacients per evitar un event trombòtic arterial o venós

SAVE-ONCO Caldria tractar **45** pacients per evitar un event trombòtic venós

NO diferències en mortalitat

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

Alok A. Khorana, MD[1]; Mehul Dalal, PhD[2]; Jay Lin, PhD[3]; and Gregory C. Connolly, MD[1]

N= 17,984

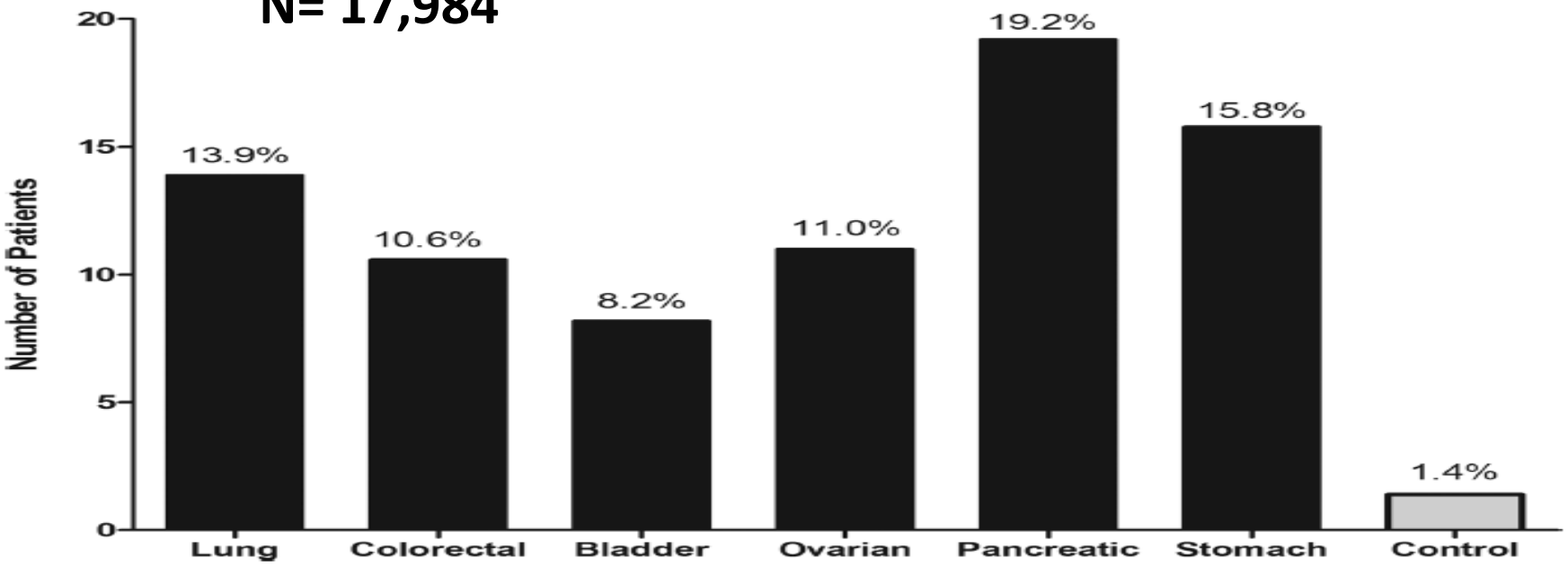

Figure 3. The Incidence of venous thromboembolism is illustrated according to cancer type.

Model Predictiu de risc d'MTV per pacients ambulatoris en tractament amb quimioteràpia

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 × 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 × 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.

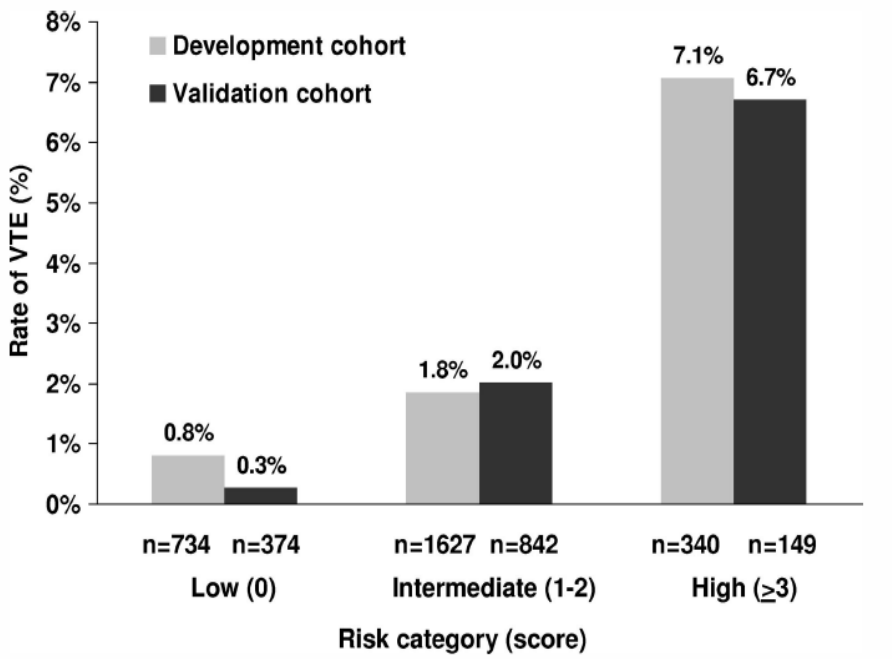

Figure 1. Rates of VTE according to scores from the risk model in the derivation and validation cohorts.

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 × 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 × 10^9/L	1
BMI 35 kg/m^2 or more	1

Khorana et al. Blood 2008

Biomarcadors potencials

Ingrid Pabinger
Cihan Ay

Universitat de Viena

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

- Blood count:[56,78] prechemotherapy platelet count ≥350 x 10^9/l; prechemotherapy white cell count >11 x 10^9/l
- Tissue factor:[138–142] high grade of tissue factor expression by tumour cells, elevated systemic tissue factor (antigen or activity)
- D-dimer[143]
- Soluble P-selectin[144]
- C-reactive protein[145]
- Prothrombin fragment 1+2[143]
- Microparticles, selectin and D-dimer[146]
- Circulating endothelial cells[147]
- Nuclear retinoic acid receptors α and β[148]

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, blader, testicular	1
– platelet count		≥ 350 x 10^9 /l	1
– haemoglobin and/or use of erythropoiesis -stimulating agents (ESAs)		< 10 g/dl	1
– leukocyte count		> 11 x 10^9 /l	1
– body mass index		≥ 35 kg/m^2	1
Vienna VTE Risk Assessment Score* (15), addition of:			
– D-dimer		≥ 1.44 µg/ml	1
– sP-selectin		≥ 53.1 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.

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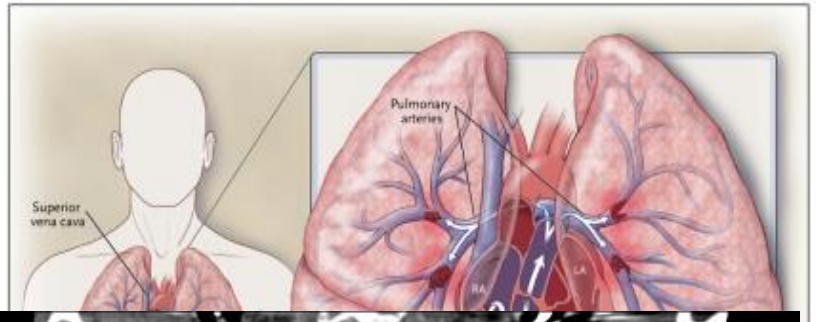
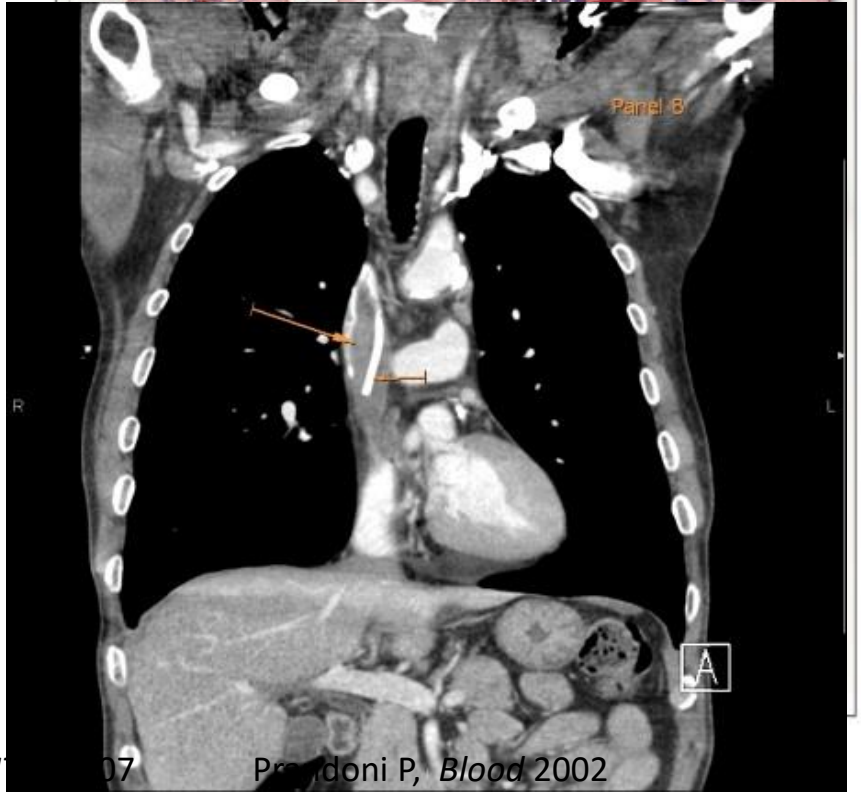
Additional risk factors include: previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

Malaltia tromboembòlica venosa (MTV) en el pacient oncològic

- Incidència 4 - 20%
- 50% en autòpsies
- Segona causa de mort
- Morbilitat





Khorana AA, *J* 07 Pr doni P, *Blood* 2002

Risc hemorràgic

- Sagnat tumoral
- Plaquetopènia per quimioteràpia / infiltració medul.lar
- Coagulopatia per disfunció hepàtica / malabsorció vit K
- Coagulació intravascular disseminada / Sepsis
- Anticoagulació

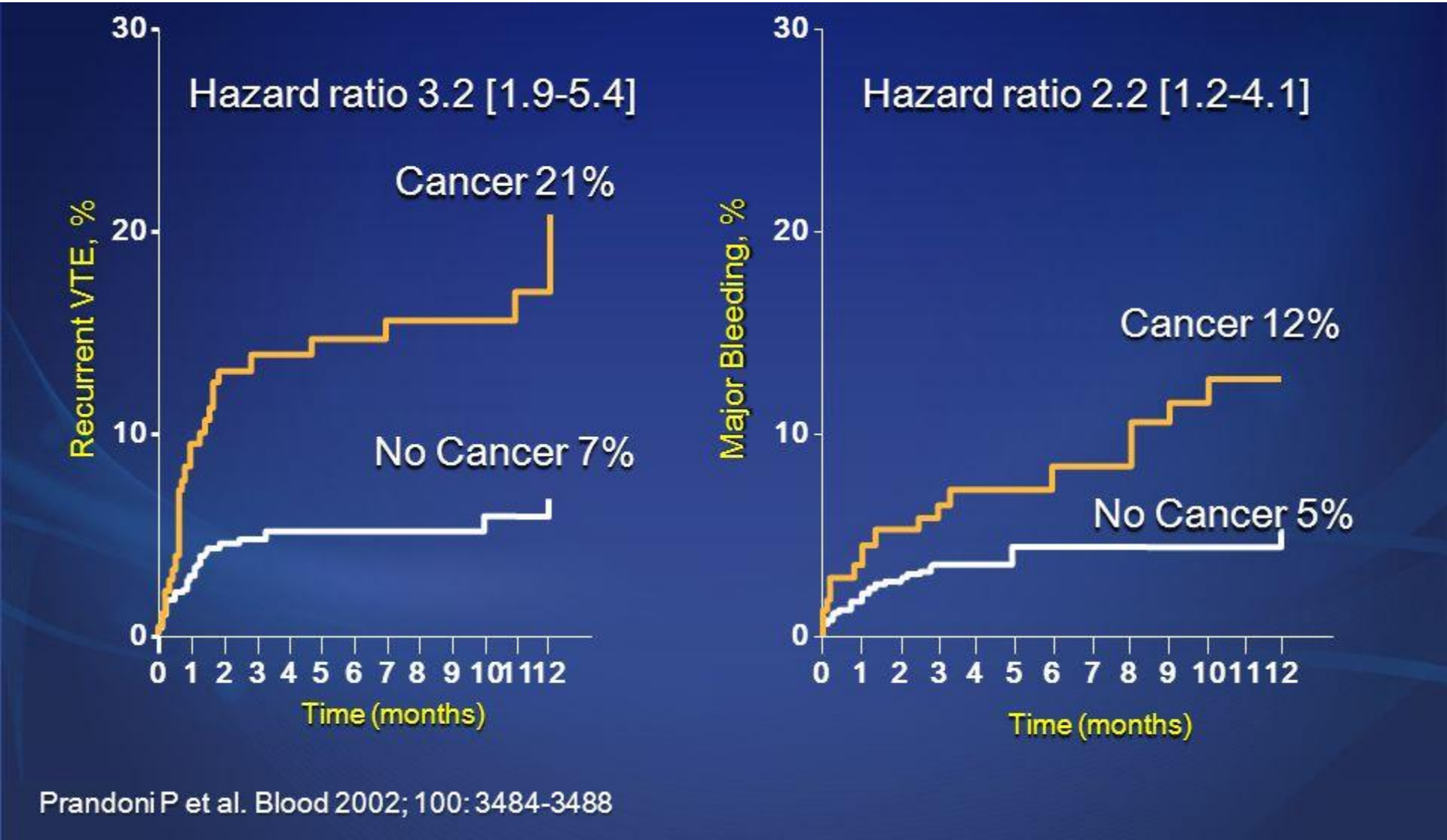
- **Controlar causa**
  - Corregir alteracions coagulació
  - Embolització arterial
  - Cirurgia
  - Radioteràpia hemostàtica
- **Filtre de cava removible**
  - Contraindicació anticoagulació

Lee AY, Blood 2013

Morbilitat associada a MTV en càncer:

21% risc anual de recorrència

12% risc anual d'hemorràgies majors



Prandoni P et al. Blood 2002; 100: 3484-3488

The NEW ENGLAND JOURNAL of MEDICINE

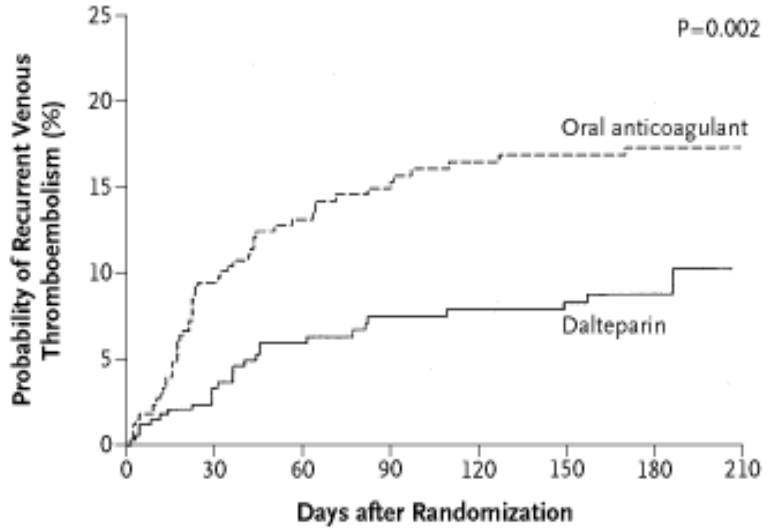
CLOT Investigators

N Engl J Med 2003

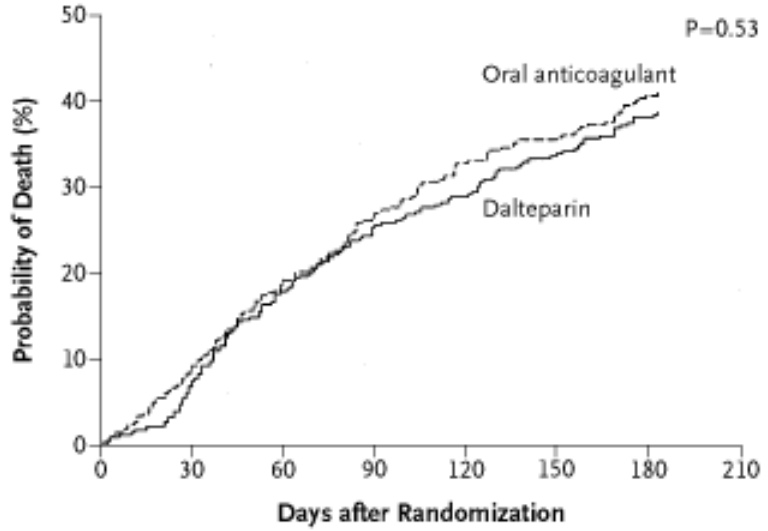
ORIGINAL ARTICLE

Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer

Agnes Y.Y. Lee, M.D., Mark N. Levine, M.D., Ross I. Baker, M.D., Chris Bowden, M.D., Ajay K. Kakkar, M.B., Martin Prins, M.D., Frederick R. Rickles, M.D., Jim A. Julian, M.Math., Susan Haley, B.Sc., Michael J. Kovacs, M.D., and Michael Gent, D.Sc., for the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators*



No. at Risk							
Dalteparin	336	301	264	235	227	210	164
Oral anticoagulant	336	280	242	221	200	194	154



No. at Risk							
Dalteparin	336	310	274	248	237	220	206
Oral anticoagulant	336	301	268	240	220	211	194

Cancer-associated thrombosis treatment

Trial	Study drug	N	Observation period	Recurrent VTE	Major bleeding	Survival
CLOT 2003	Dalteparin 25% dose reduction after 1 month	672	6 months	17% vs 9% P=0.02	4% vs 6% P=NS	41% vs 39% P= NS

Recorrència MTV

10-21% AVK vs. 7-10% HBPM

CATCH 2015	Tinzaparin Full dose	900	6 months	10% vs 7% P=0.07	1% vs 1% P=NS	34% vs 32% P=NS

Table 1. Consensus guidelines on treatment of deep vein thrombosis or pulmonary embolism in patients with cancer

	ACCP 2012[21]	NCCN 2011[13]	ASCO 2013[14]
Long-term treatment	LMWH preferred to VKA [2B].*	LMWH is preferred for first 6 mo as monotherapy without warfarin in patients with proximal DVT or PE and metastatic or advanced cancer.	LMWH is preferred for long-term therapy.
	In patients not treated with LMWH, VKA therapy is preferred to dabigatran or rivaroxaban [2C].* Patients receiving extended therapy should continue with the same agent used for the first 3 mo of treatment [2C].*	Warfarin 2.5-5 mg every day initially with subsequent dosing based on INR value targeted at 2-3.	VKAs (target INR, 2-3) are acceptable for long-term therapy if LMWH is not available.

1ª elecció HBPM:

- **Disminució 50% risc recorrència TEV**
- **Facilitat interrupcions temporals (puncions, plaquetopènia…)**
- **No interaccions farmacològiques warfarina**

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Alternativa: anti vitK INR 2-3

- No accés HBPM
- Insuficiència renal FG <30 mL/min
- Hipersensibilitat a heparina

AMERICAN COLLEGE OF CHEST PHYSICIANS
The Global Leader in Clinical Chest Medicine

In patients with DVT of the leg or PE and **no cancer**, as **long-term (first 3 months)** anticoagulant therapy, we suggest:

Dabigatran
Rivaroxaban
Apixaban or
Edoxaban **over VKA** (Grade 2B).

For patients who are not treated with dabigatran, rivaroxaban, apixaban or edoxaban, we suggest

VKA therapy **over LMWH** (Grade 2C).

ACCP Guidelines 2016

Factor	Preferred anticoagulant
Cancer	LMWH
Pregnancy or pregnancy risk	LMWH
Liver disease and coagulopathy	LMWH
Renal disease FG <30ml/min	AVK
Poor compliance	AVK
Cost, coverage, licensing	Varies among regions and individual circumstances
	2016

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The Global Leader in Clinical Chest Medicine

Nous anticoagulants directes per MTV associada al càncer?

Assajos clínics fase III en ETV: NOACs vs Warfarina

	RE-COVER I[1]	EINSTEIN DVT[2]	EINSTEIN PE[3]	AMPLIFY[4]	Hokusai-VTE[5]
	Dabigatran	Rivaroxaban	Rivaroxaban	Apixaban	Edoxaban
Eficàcia					
	No inferior	No inferior	No inferior	No inferior	No inferior
Seguretat					
Sagnat major + CRNM	Menor	NS	NS	Menor	Menor
Sagnat major	NS	NS	Menor	Menor	NS
Sagnat CRNM	NI	NS	NS	Menor	Menor
Cualsevol sagnat	Menor	NI	NI	NI	Menor

NI=no informado; NS=no significativo estadísticamente CRMN= no mayor clínicamente relevante.

1. RE-COVER: N Engl J Med 2009
2. EINSTEIN DVT; N Engl J Med 2010
3. EINSTEIN–PE N Engl J Med 2012
4. AMPLIFY: N Engl J Med 2013
5. Hokusai-VTE : N Engl J Med 2013

NOACs vs Warfarina per TEV: característiques basals

	RE-COVER[1#] Dabigatran	EINSTEIN DVT[2] Rivaroxaban	EINSTEIN PE[3] Rivaroxaban	AMPLIFY[4] Apixaban	Hokusai-VTE[5] Edoxaban
Pacients, N	2539	3449	4832	5395	8292
Edat (anys)	55	56	58	57	56
Dones (%)	42	43	47	41	43
Aclarament de creatinina <50 mL/min (%)	NI	7	8	6	7
TVP (%)	69	99	-	65	59
EP±TVP (%)	31	0,6	100	35	40
Sense causa (%)	NR	62	65	90	65
Càncer (%)	5	6	5	3	9†
TEV previ	26	19	19	16	18

1. RE-COVER: N Engl J Med 2009
2. EINSTEIN DVT; N Engl J Med 2010
3. EINSTEIN–PE N Engl J Med 2012
4. AMPLIFY: N Engl J Med 2013
5. Hokusai-VTE : N Engl J Med 2013

Journal of Thrombosis and Haemostasis, **12**: 1116–1120 DOI: 10.1111/jth.12605

BRIEF REPORT

Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism

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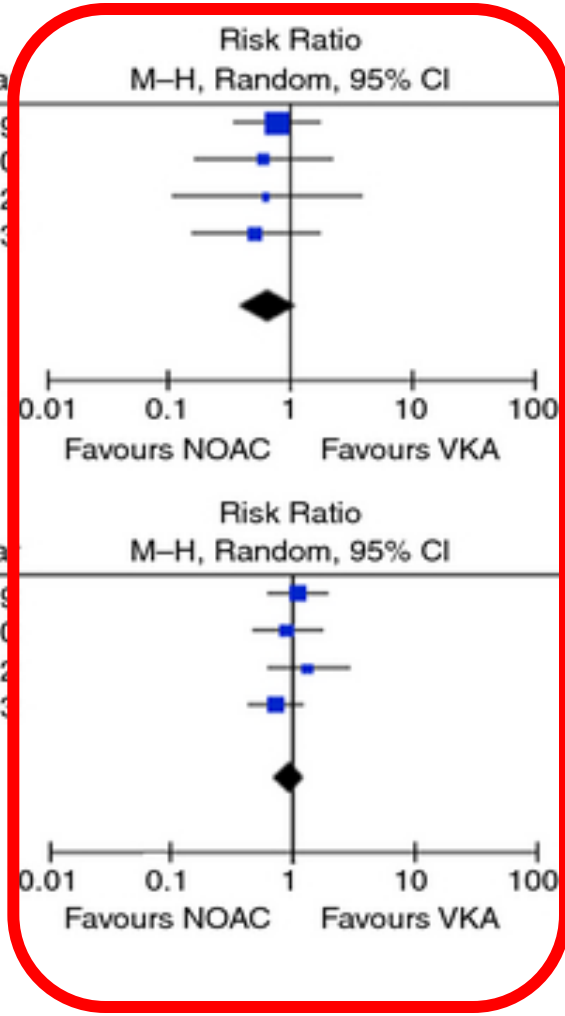
*Department of Thrombosis and Hemostasis, LUMC; and †Department of Medical Oncology, LUMC, Leiden, the Netherlands

Five studies were included, with 19 060 patients, of whom **973 (5.1%) had active cancer**.

The pooled incidence rates of
Recurrent VTE were
4.1% (95% CI 2.6-6.0) with NOACs, and
6.1% (95% CI 4.1-8.5) with VKAs (RR 0.66, 95% CI 0.38-1.2).

Major or non-major clinically relevant bleeding were
15% (95% CI 12-18) with NOACs, and
16% (95% CI 9.9-22) with VKAs (RR 0.94, 95% CI 0.70-1.3).

Solid basis for a head-to-head comparison of NOACs with LMWH in cancer patients.



Journal of Thrombosis and Haemostasis 2014

- **Estudis no dissenyats per avaluar eficàcia i seguretat en càncer.**
- **NOACs vs AVK i NO comparat HBPM (tractament estàndar).**
- **No antídots.**
- **Interacció potencial amb quimioteràpia / hormonoteràpia / antiangiogènics…**

BLOOD, 3 OCTOBER 2013 • VOLUME 122, NUMBER 14

Table 2. Interactions between chemotherapeutic agents and immunosuppressants with NOACs based on known metabolic pathway activity

Interaction effect*	Dabigatran	Rivaroxaban	Apixaban
	P-glycoprotein	P-glycoprotein CYP3A4	P-glycoprotein CYP3A4
Increases NOAC plasma levels†	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib
Reduces NOAC plasma levels‡	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine

Duració de tromboprofilaxi secundària

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ONCOLOGY GRAND ROUNDS

How Long Is Long Enough? Extended Anticoagulation for the Treatment of Cancer-Associated Deep Vein Thrombosis

Jeffrey I. Zwicker and Kenneth A. Bauer, *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

Table 2: Multivariate analysis on the risk to develop recurrent PE, recurrent DVT, or major bleeding.

	Odds ratio (95% CI)	P-value
Recurrent PE		
Age <65 years	3.0 (1.9–4.9)	<0.001
Diagnosis <3 months earlier	2.0 (1.2–3.2)	0.005
Clinically overt PE	1.9 (1.2–3.1)	0.01
Recurrent DVT		
Diagnosis <3 months earlier	2.4 (1.5–3.6)	<0.001
Age <65 years	1.6 (1.0–2.4)	0.04
Major bleeding		
Recent major bleeding	2.4 (1.1–5.1)	0.03
CrCl <30 ml/min	2.2 (1.5–3.4)	<0.001
Immobility ≥4days	1.8 (1.2–2.7)	0.005
Metastatic cancer	1.6 (1.1–2.3)	0.03

PE, pulmonary embolism; DVT, deep-vein thrombosis; CrCl, creatinine clearance; CI, confidence intervals.

Models predictius per identificar a pacients amb baix risc de recorrència de MTV

	Rodger MA 2008	Vienna 2010	DASH score 2012	Ottawa score 2012 derivation	Ottawa score 2012 validation
N	646	929	1818	543	819
Cohort	Prospective	Prospective	Meta-anaysis	Retrospective derivative cohort	Pooled data CLOT + Canthanox
Predictive variables	Men: none Women: . Age ≥ 60yr . PTS . BMI ≥ 30 . D-dimer ≥ 250 during anticoagulation	Gender Location first VTE D-dimer after anticoagulation	Male Age< 50 yr Hormonal therapy Abnormal D-dimer after anticoagulation	Female sex +1 Prior VTE +1 Lung cancer +1 Breast cancer -1 TNM 1 -2	Female sex +1 Prior VTE +1 Lung +1 Breast -1 TNM 1-2 -1
VTE recurrence Low risk	≤ 1 point 1.6% (95%CI 0.3%-4.6%)	≤ 180 points 4.4% (95%CI 2.7%-6.2%)	≤ 1 point 3.1% (95%CI 2.3-3.9)	≤ 0 LOW 4.5% ≥ 1 HIGH 19%	≤ -1 LOW 5.1% 0 INTERMEDIATE 9.9% ≥ 1 HIGH 15.8%

Unable to validate 2015 Lee AY et al.

N=900

CATCH study

Kyrle PA Thromb Res 2014; Khorana AA Thromb Res 2016

Predictors of recurrent venous thromboembolis

Laurel A. Menapace, Keith R. McCrae, Alok A. Khorana*

Taussig Cancer Institute, Department of Hematology Oncology, Cleveland Clinic, Cleveland, Ohio, USA

Clinical Risk Factors and Candidate Biomarkers for Cancer-Associated Recurrent VTE

Patient-Related Risk Factors	Cancer-Related Risk Factors	Candidate Biomarkers
Age < 65 years	Diagnosis of malignancy within 3 months of VTE event	Tissue factor (TF)
Female gender	Locally advanced or metastatic cancer	D-dimer
Prior history of VTE	Primary tumor site (lung, hepatobiliary)	C Reactive protein (CRP)
	Venous compression secondary to tumor or malignant adenioathy	

Thrombosis Research 140S1 (2016) S93–S98

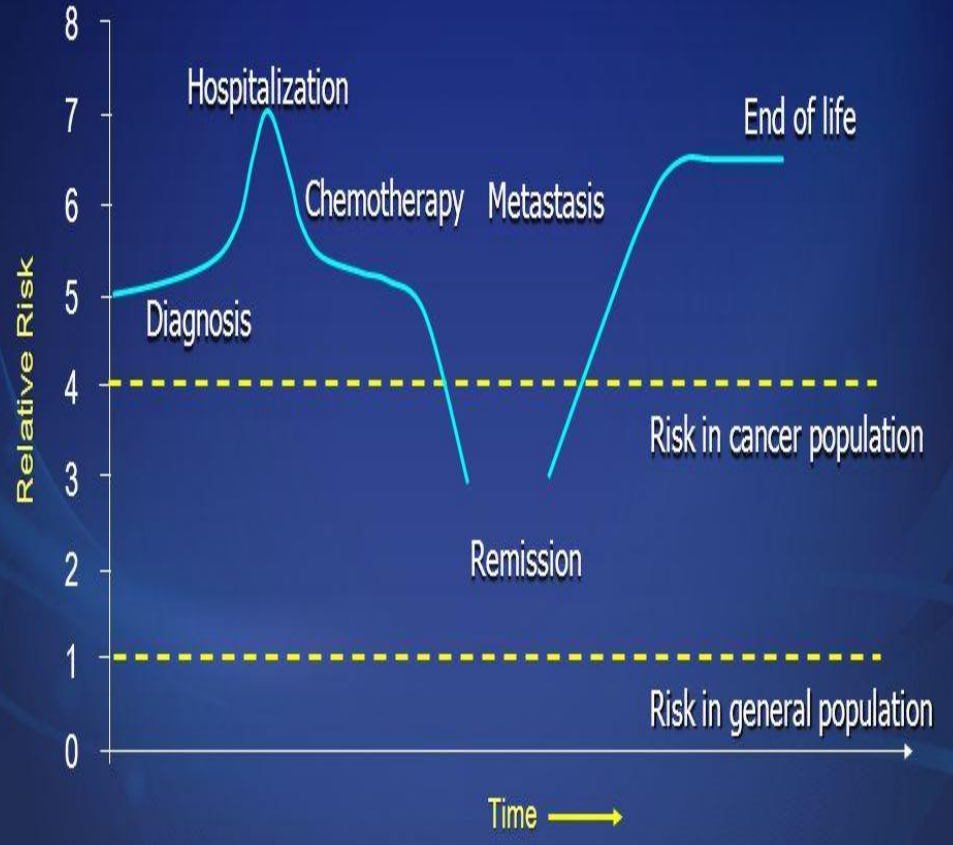
Factors de risc de MTV múltiples i canviants

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 lymphadenopaty

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, other
Pregnancy
Tobacco
Low performance status
Low level of activity/physical exercise
Major trauma and immobilization
Inherited thrombophilia (Factor V Leyden)



Rao MV, et al. In: Khorana and Francis, eds. *Cancer-Associated Thrombosis*; 2007

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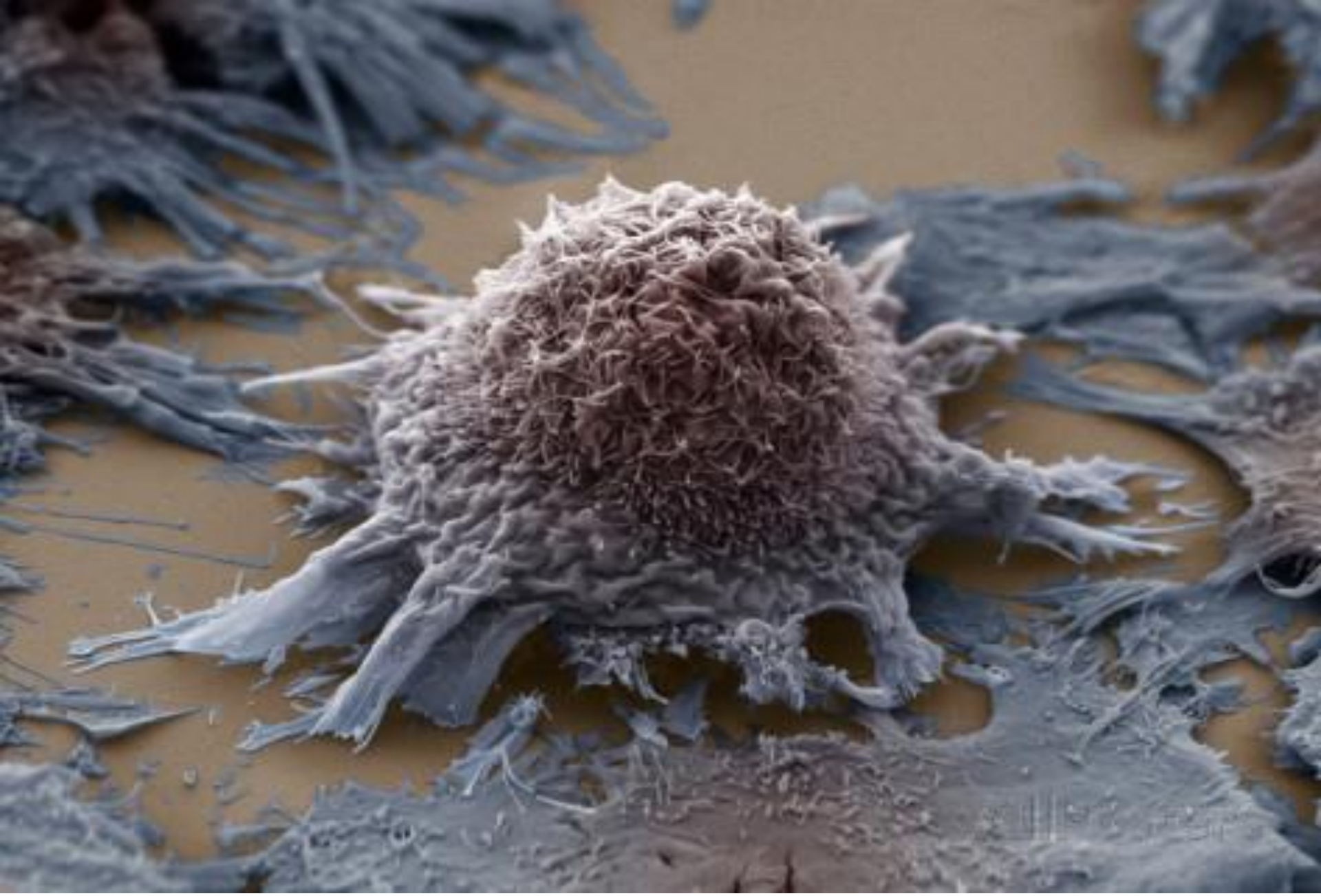
See accompanying article on page 3607

FACTOR	A FAVOR	EN CONTRA
Tumor	Neoplàsia activa	Remissió
Tractament	Quimioteràpia Hormonoteràpia Eritropoyetina	- -
Gravetat event	Risc vital Sd posflebítica	No risc vital
Risc hemorràgic	Baix	Alt
Factors adicionals	Obesitat Performance status Gènere femení Catèter venós central	Factors adicionals en event inicial com cirurgia …
Preferència pacient	Evitar recorrència	Evitar sagnat



Moltes gràcies !