Retrato de Ambrose Vollard
Picasso, 1910

Sociedad Chilena de Hematología

Trombosis y Cáncer

… Una nueva visión de un viejo problema …

Christopher J Tabilo Heavey
Becado H&O FALP

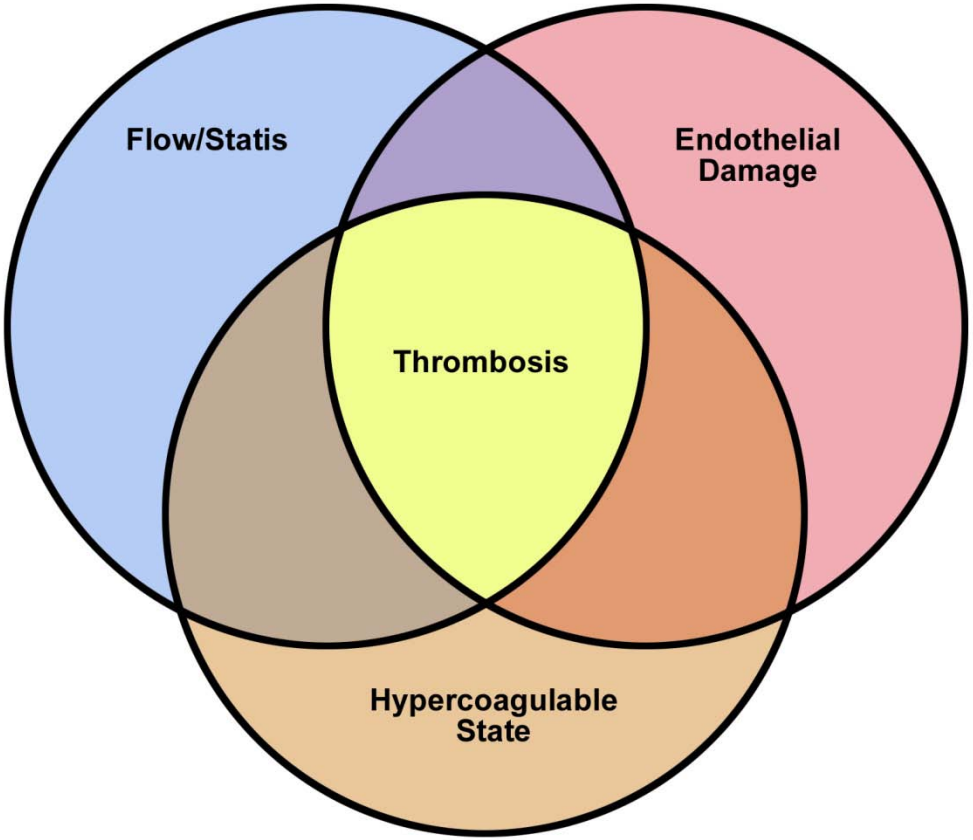
Introducción

- El tromboembolismo (TVE) es una complicación frecuente en pacientes con cáncer. La tasa de TVE en pacientes sanos es del 0.1 mientras que en pacientes con cancer parte en el 0.5 y puede alcanzar hasta una 10% en ciertas patologías (MM).
- En un 90% de los pacientes con cáncer se encuentra una hipercoagulabilidad, pero sólo un 4 – 15% desarrolla enfermedad tromboembólica detectable.
- Los estudios varían notoriamente en tipos histológicos, pero el cáncer de páncreas y el de pulmón dan cuenta de la mayoría de los casos de tromboembolismo.

Armand Trousseau
Tours 1801 - París 1867

En 1860 Trosseau describe casos de Tromboflebitis migratoria o generalizada asociada al hallazgo de neoplasias abdominales (pancreáticas).

Se recomienda ver revisión del Sd de Trousseau en
Blood 2007, Varki 110 (6): 1723



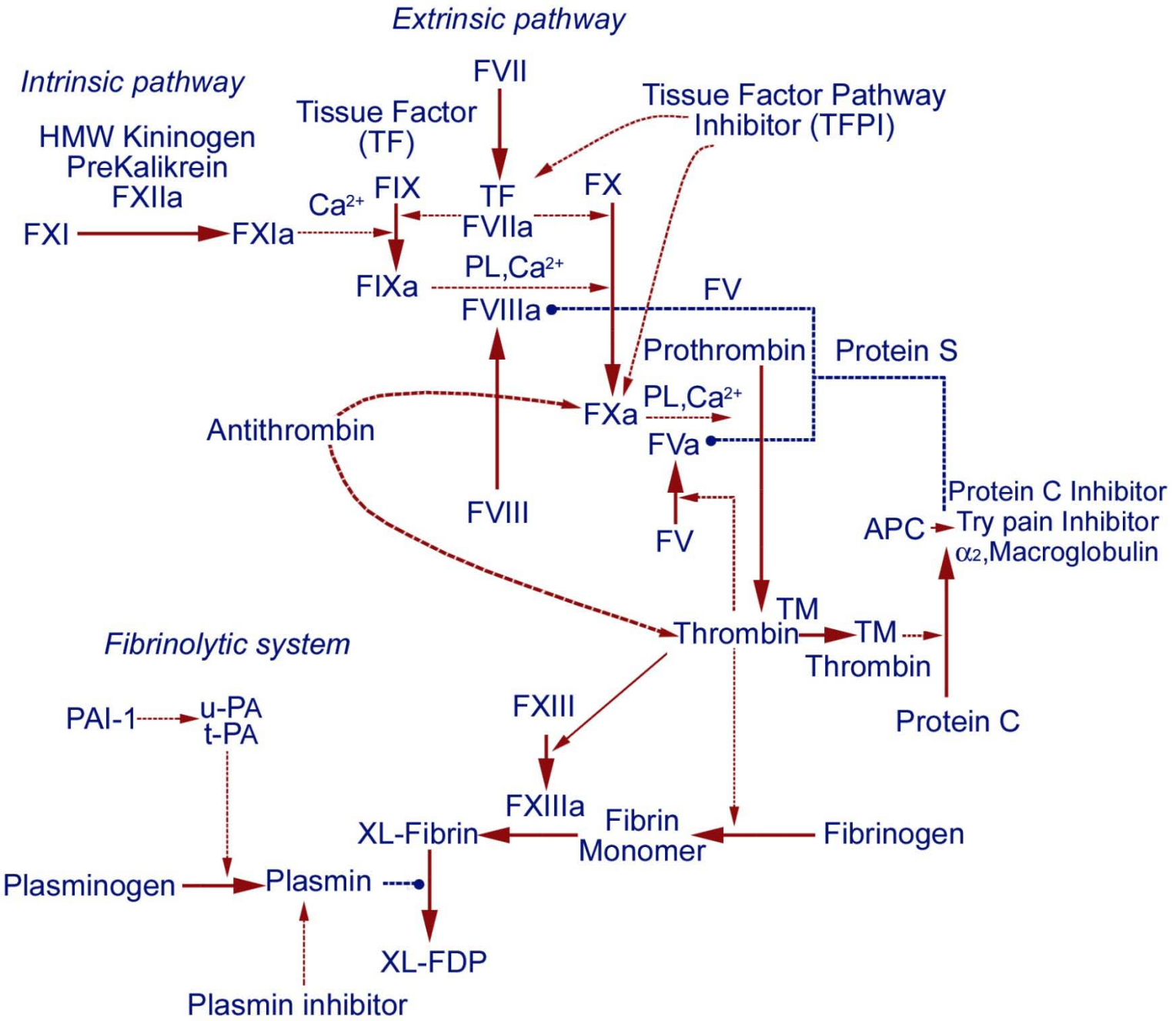
Triada de Wirchow

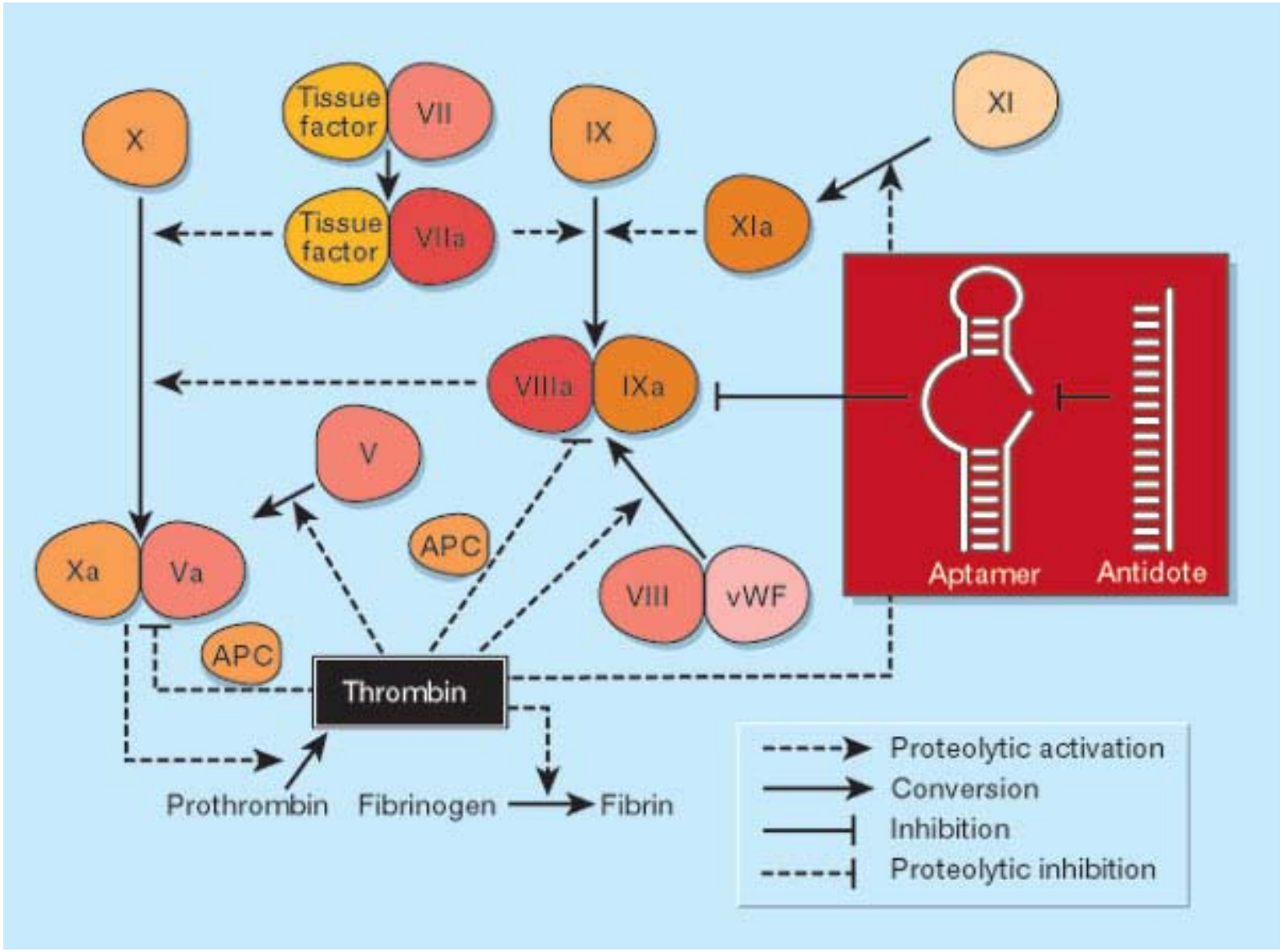
Descrita mucho antes de Virchow, éste la adaptó para explicar la fisiopatología del Tromboembolismo Pulmonar (1856), recibiendo su nombre después de su muerte.

Rudolf Virchow,
13 Octubre 1821 (Pomerania)
5 Septiembre 1902 (Berlin)

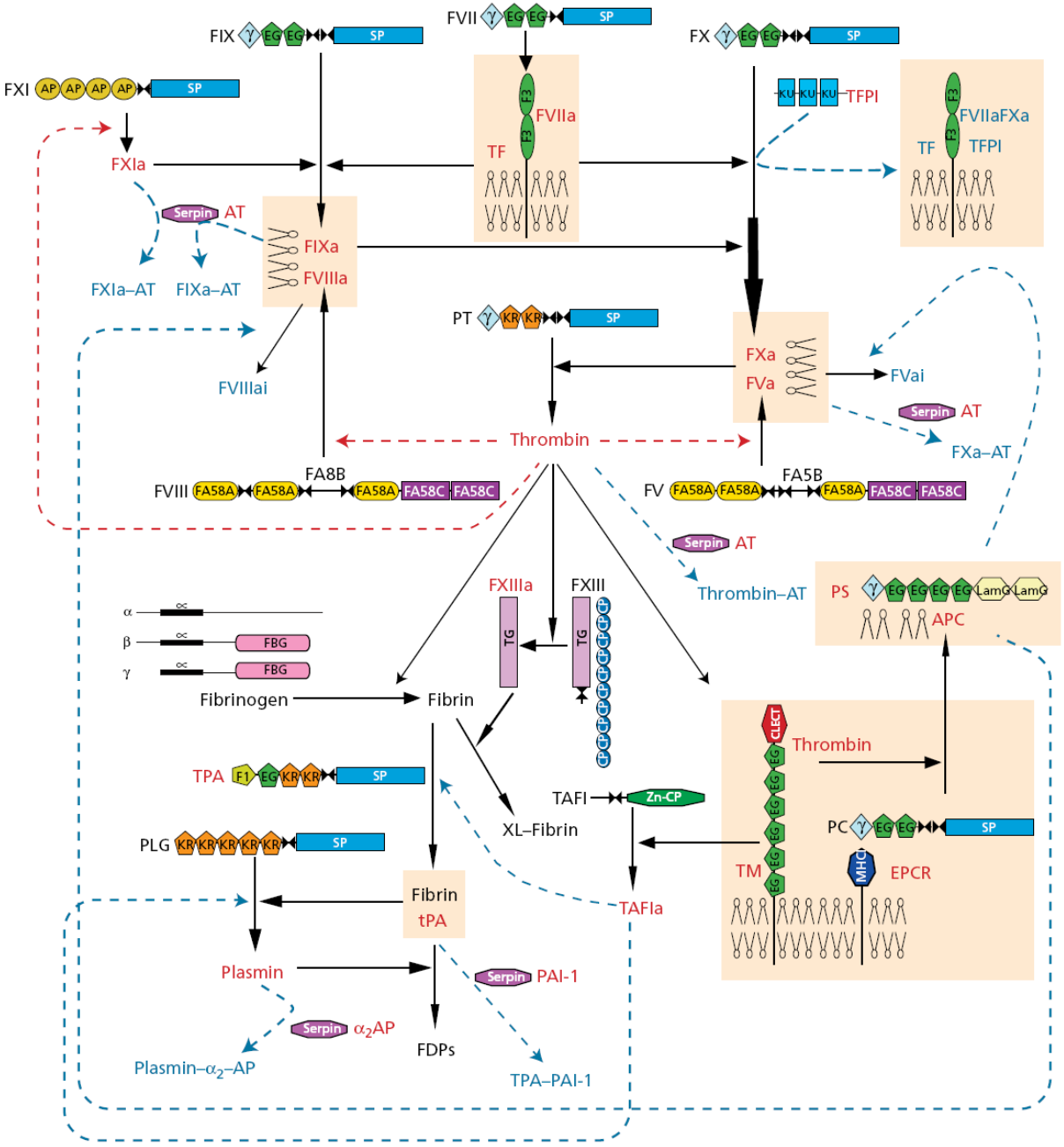
Introducción

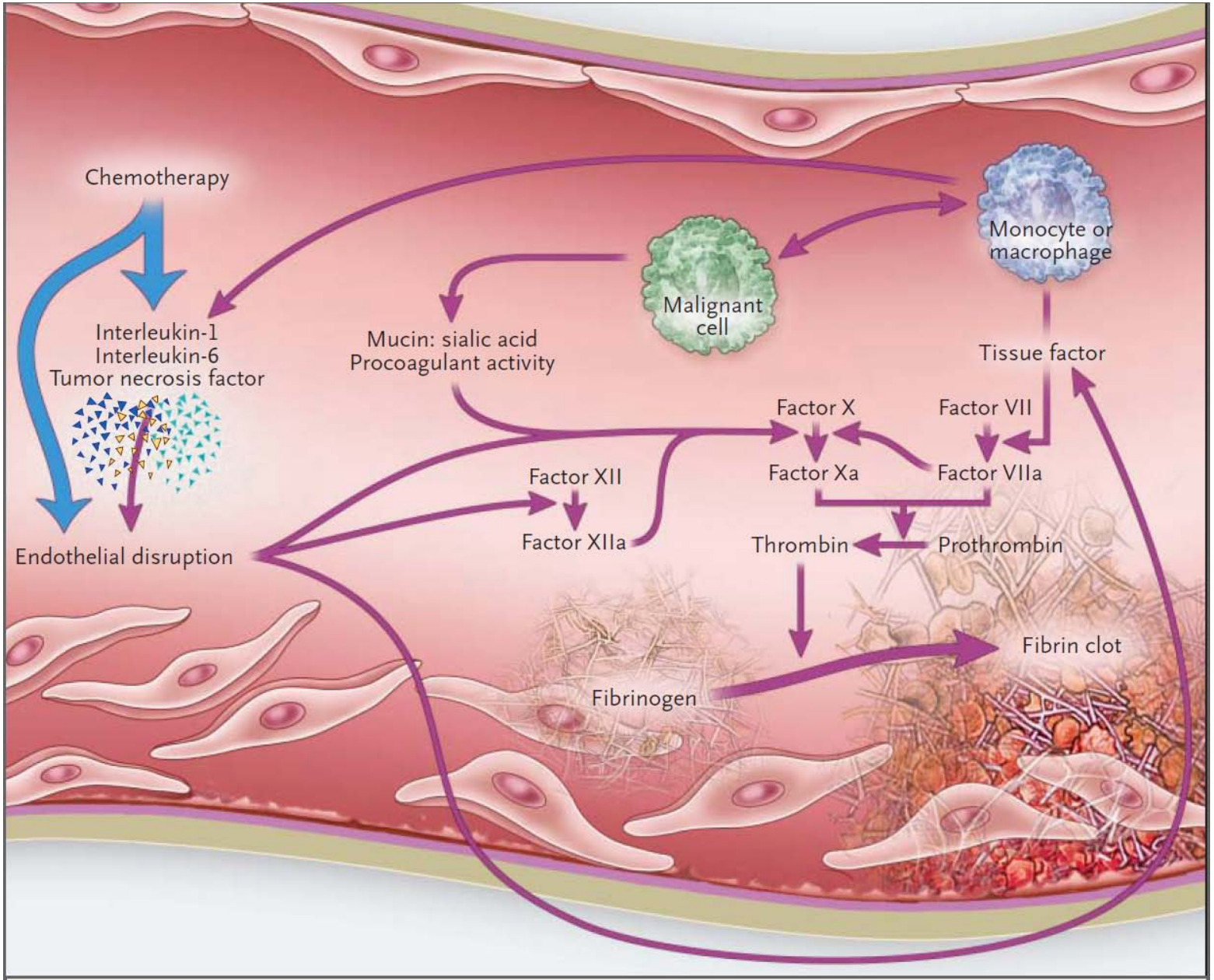
- El impacto de las terapias del cáncer (cirugía, quimioterapia, hormonoterapia), el uso de catéteres venosos centrales y la histología del tumor impactan en el riesgo de desarrollar enfermedad tromboembólica.
- Se ha objetivado que aún sin evidencias clínicas de enfermedad muchos pacientes con cáncer tienen un estado de hipercoagulabilidad subclínico (alteraciones del complejo trombina – antitrombina, fragmentos 1 y 2 de la protrombina, fibrinopéptido A, Dímero D, etc).


Extrinsic pathway
Intrinsic pathway
FVII
Tissue Factor
(TF)
Tissue Factor Pathway
Inhibitor (TFPI)
HMW Kininogen
PreKalikrein
FXIIa
FXI
FXIa
Ca2+
FIX
TF
FVIIa
FX
FIXa
PL,Ca2+
FVIIIa
FV
Prothrombin
Protein S
Antithrombin
FXa
PL,Ca2+
FVa
FVIII
FV
Protein C Inhibitor
APC
Try pain Inhibitor
α2,Macroglobulin
TM
Thrombin
TM
Thrombin
Fibrinolytic system
PAI-1
u-PA
t-PA
FXIII
Protein C
FXIIIa
XL-Fibrin
Fibrin
Monomer
Fibrinogen
Plasminogen
Plasmin
XL-FDP
Plasmin inhibitor

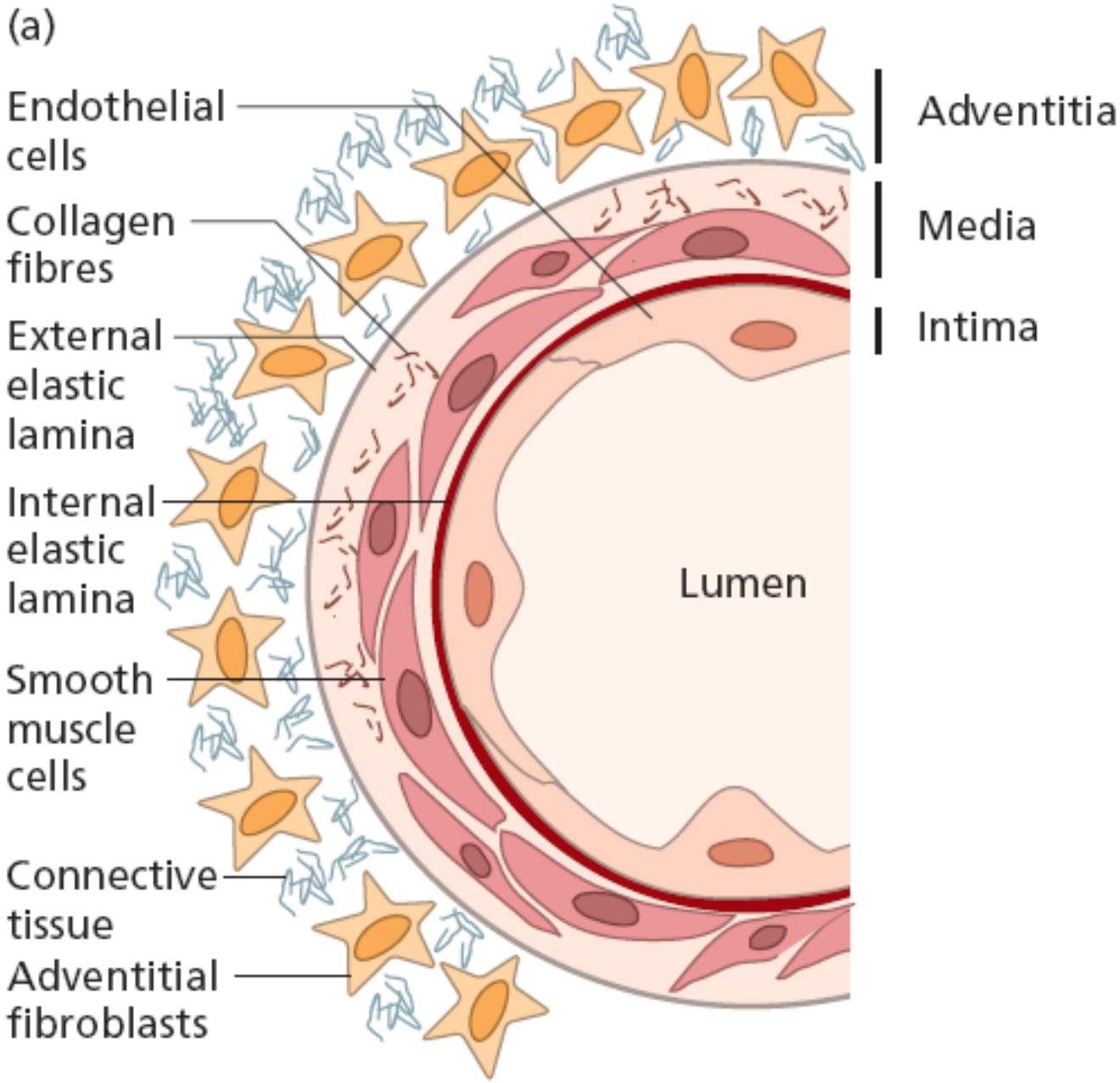


Nature **419**, 23-24(5 September 2002)

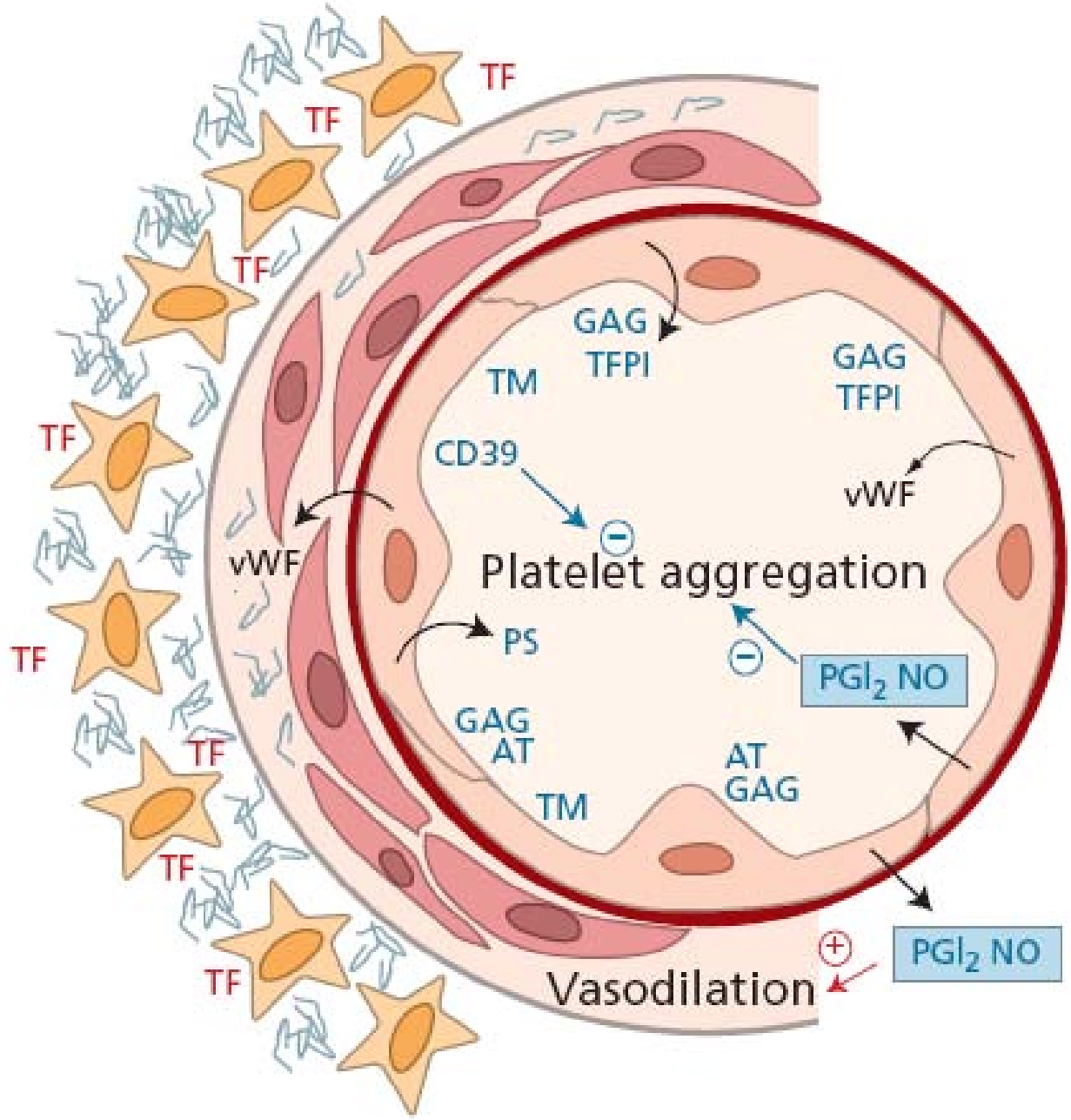

FIX
FVII
FX
FXI
SP
AP
FXIa
TF
FVIIa
TFPI
FVIIaFXa
Serpin
AT
FIXa
FVIIIa
FXIa–AT
FIXa–AT
FVIIIai
PT
KR
FXa
FVa
FVai
FXa–AT
Thrombin
FA8B
FVIII
FA58A
FA58C
FA5B
FV
Thrombin–AT
PS
APC
LamG
EG
FXIIIa
FXIII
TG
α
β
γ
FBG
Fibrinogen
Fibrin
TPA
F1
TAFI
Zn-CP
XL–Fibrin
PLG
CLECT
PC
TM
EPCR
MHC
TAFIa
Fibrin
tPA
Plasmin
PAI-1
α2AP
FDPs
Plasmin–α2–AP
TPA–PAI-1



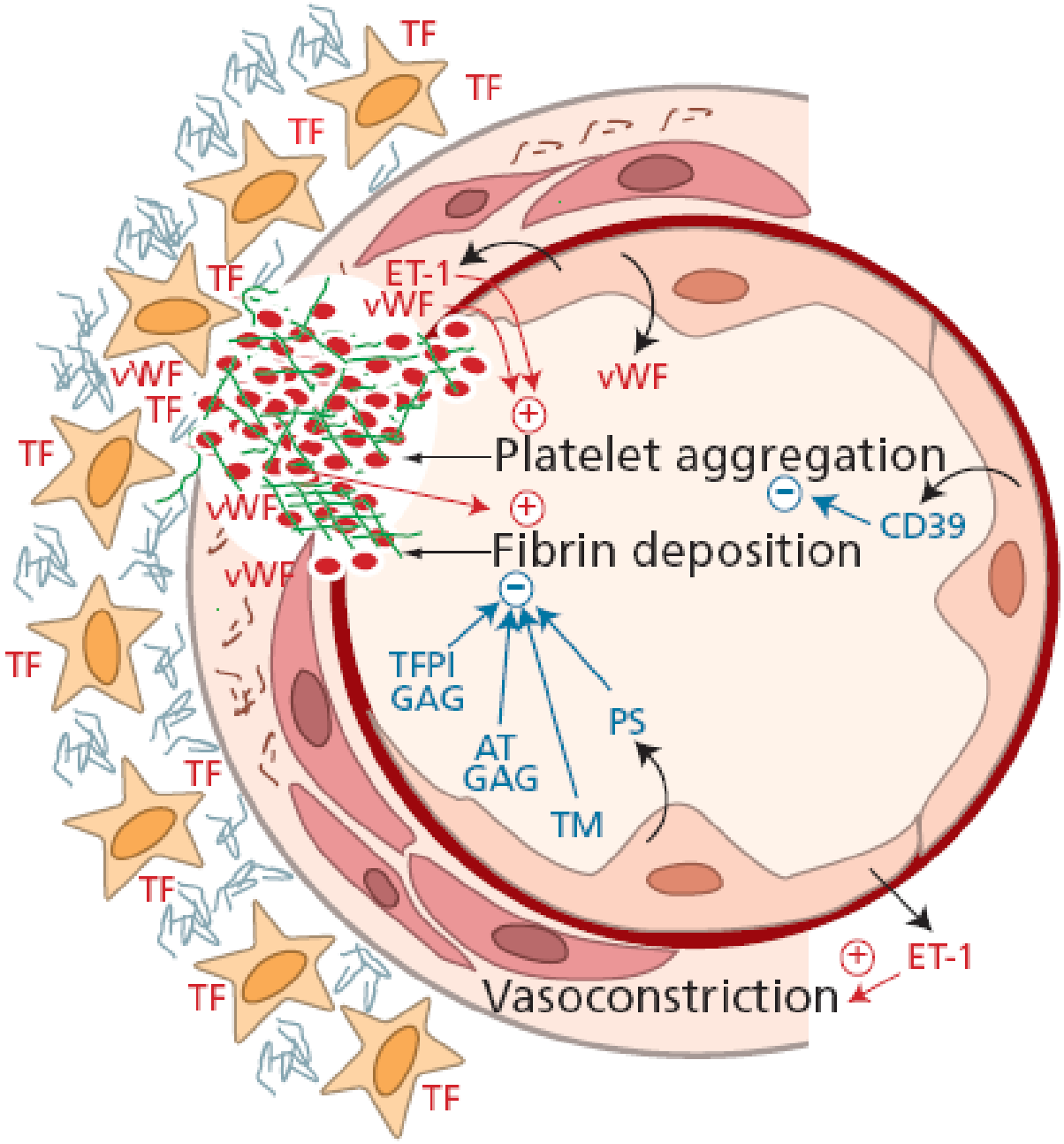
Mechanisms of Thrombosis in Cancer.

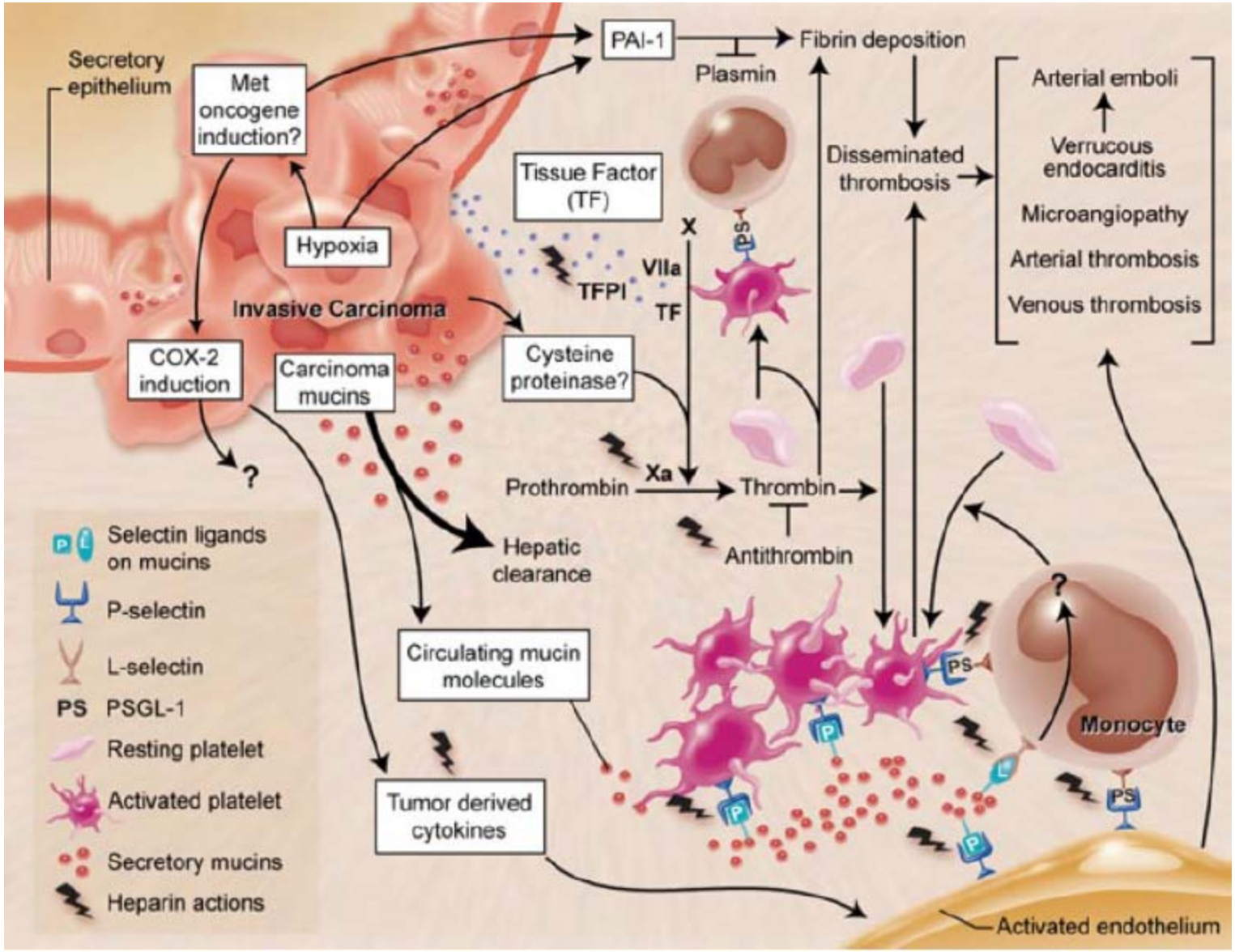

(a)
Endothelial cells
Collagen fibres
External elastic lamina
Internal elastic lamina
Smooth muscle cells
Connective tissue
Adventitial fibroblasts
Adventitia
Media
Intima
Lumen

(b)


TF
TF
TF
TF
TF
TF
TF
TF
GAG
TFPI
TM
GAG
TFPI
CD39
vWF
vWF
Platelet aggregation
PS
PGI2 NO
GAG
AT
AT
GAG
TM
PGI2 NO
Vasodilation

(c)


TF
TF
TF
TF
TF
TF
TF
TF
TF
TF
TF
ET-1
vWF
vWF
vWF
vWF
vWF
Platelet aggregation
Fibrin deposition
CD39
TFPI
GAG
AT
GAG
TM
PS
ET-1
Vasoconstriction

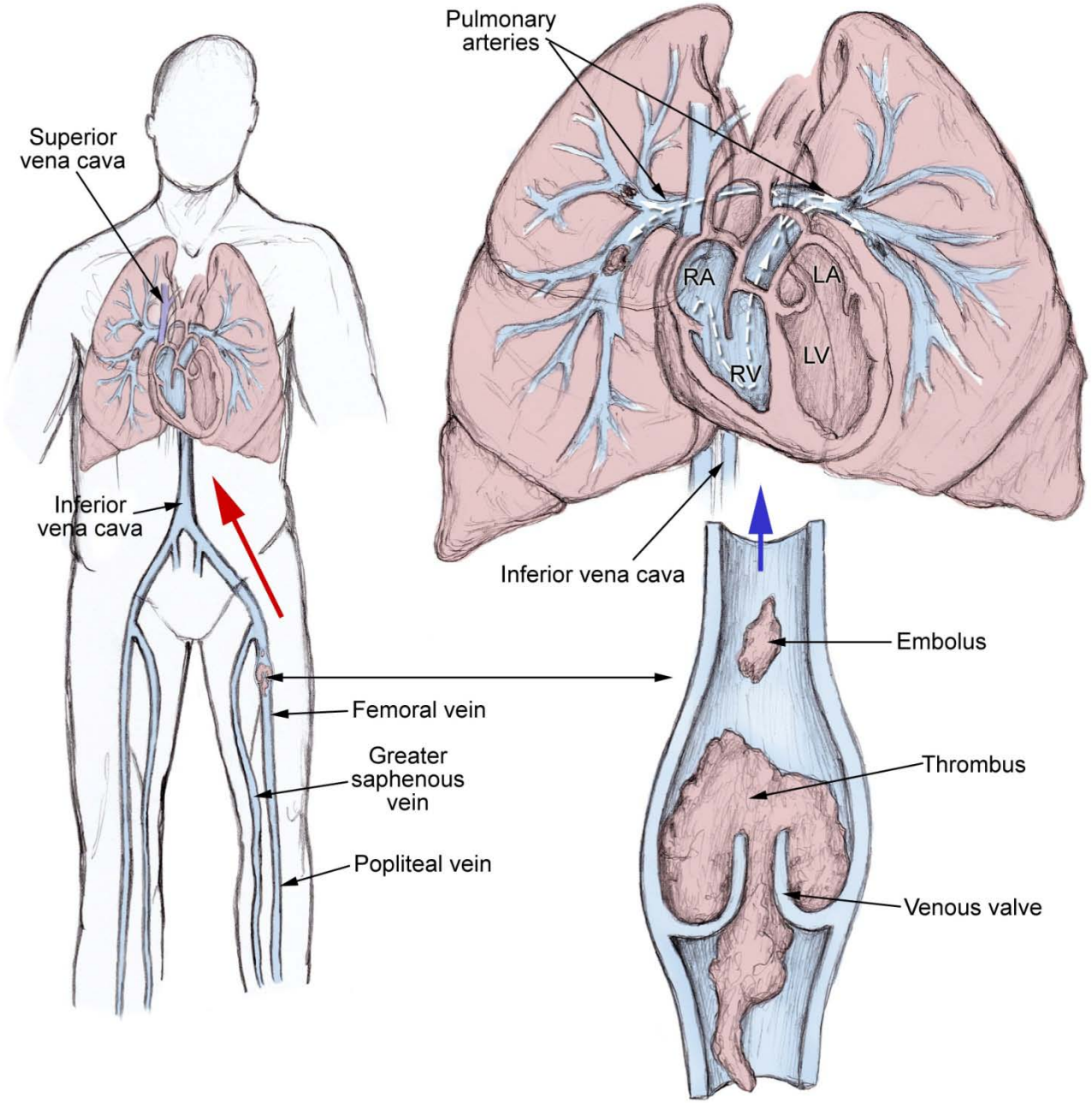


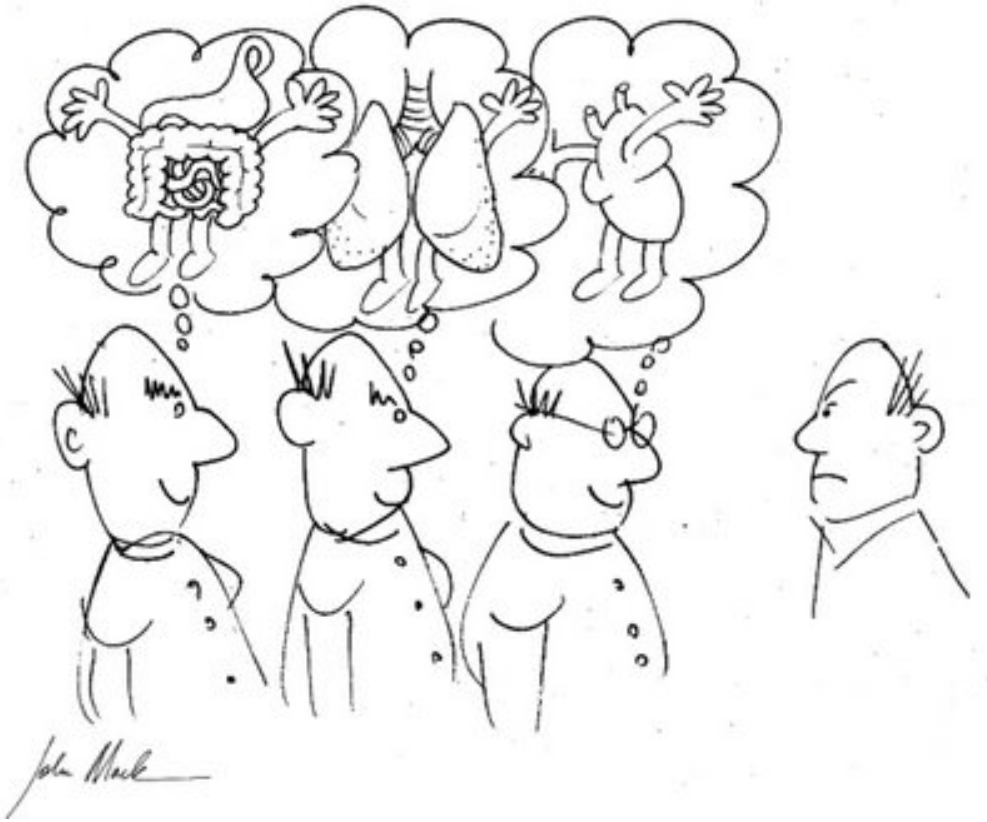
Multiple mechanisms in Trousseau's Syndrome

Blood 2007, Varki 110 (6): 1723

Table 1. The impact of cancer and its treatment on each element of Virchow's triad[2]

Venous Stasis	Endothelial Injury/ Alteration in Blood Vessels	Hypercoagulable State
• Increased blood viscosity • Mechanical blockage (tumor extrinsic compression or invasion) • Patient immobility (due to cancer complications or treatment)	• Mechanical endothelial trauma (due to cancer invasion or treatment) • Endothelial dysfunction/loss of antithrombotic properties • Angiogenic stimuli	• Increase in procoagulant activities • Decrease in anticoagulant activities • Increase in overall platelet activity • Decrease in fibrinolytic activity


Pulmonary arteries
Superior vena cava
RA
LA
RV
LV
Inferior vena cava
Inferior vena cava
Embolus
Femoral vein
Greater saphenous vein
Thrombus
Popliteal vein
Venous valve



Guitarrista,
Picasso

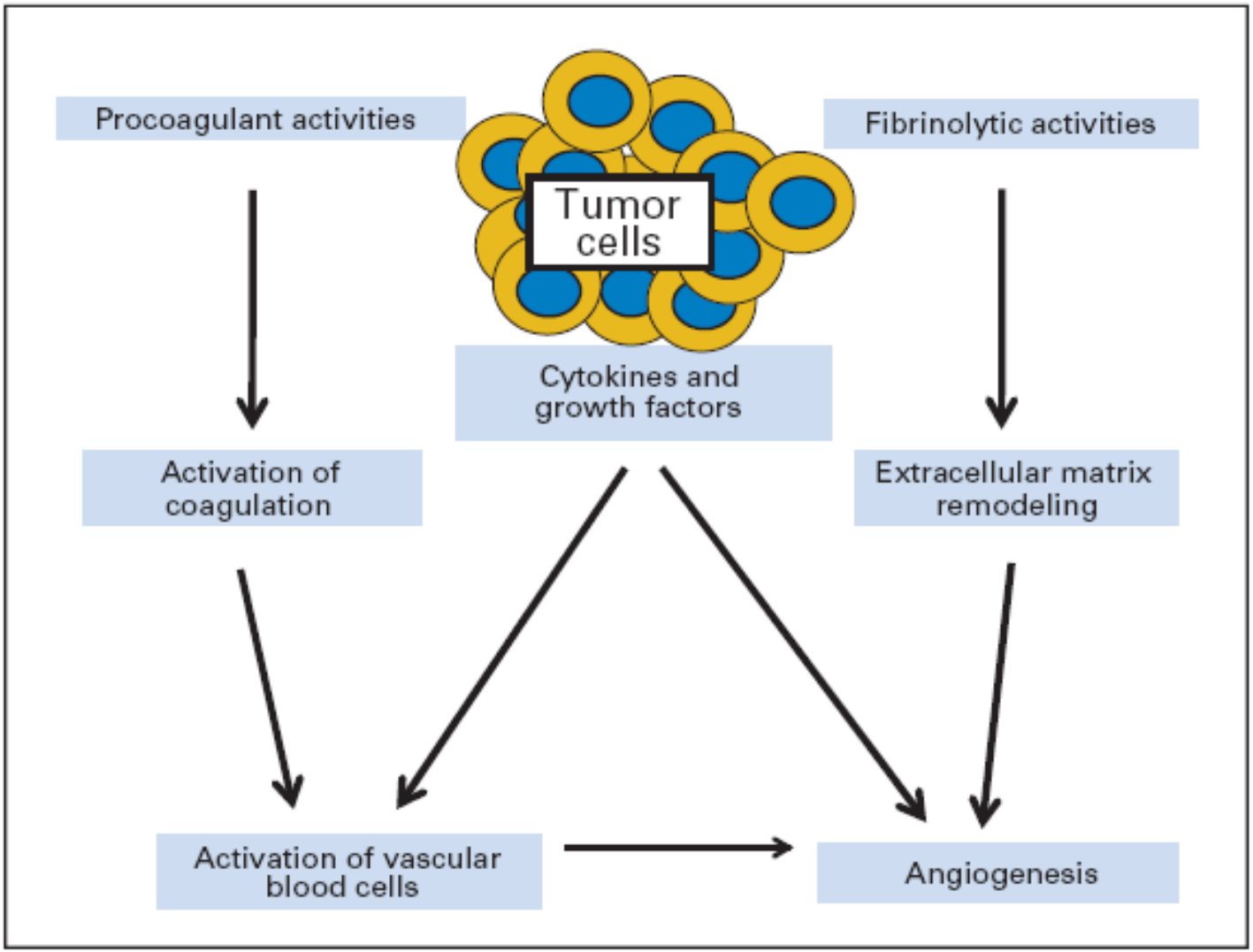
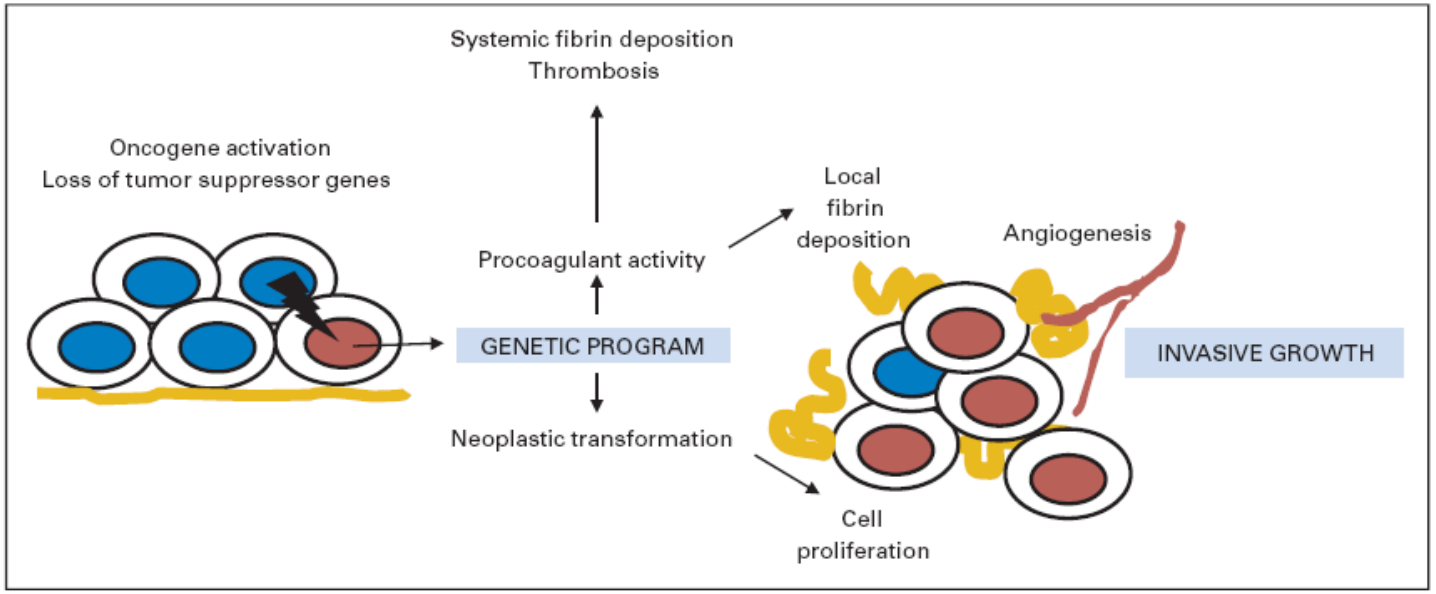
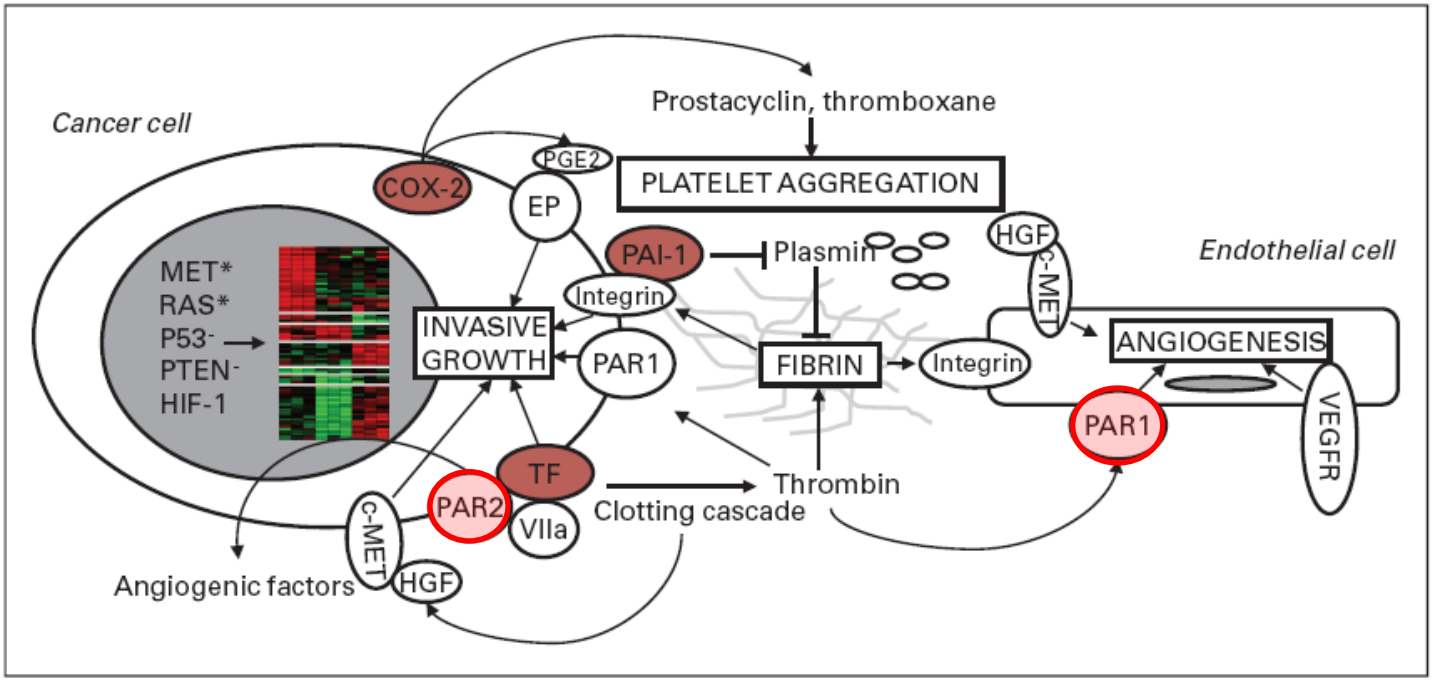


Fig 1. Schematic illustrating some of the interactions between tumor cells and the hemostatic system via procoagulant and fibrinolytic substances, various cytokines and growth factors, and their influence on hematopoietic elements and the vascular endothelium. Reproduced with permission.[9]

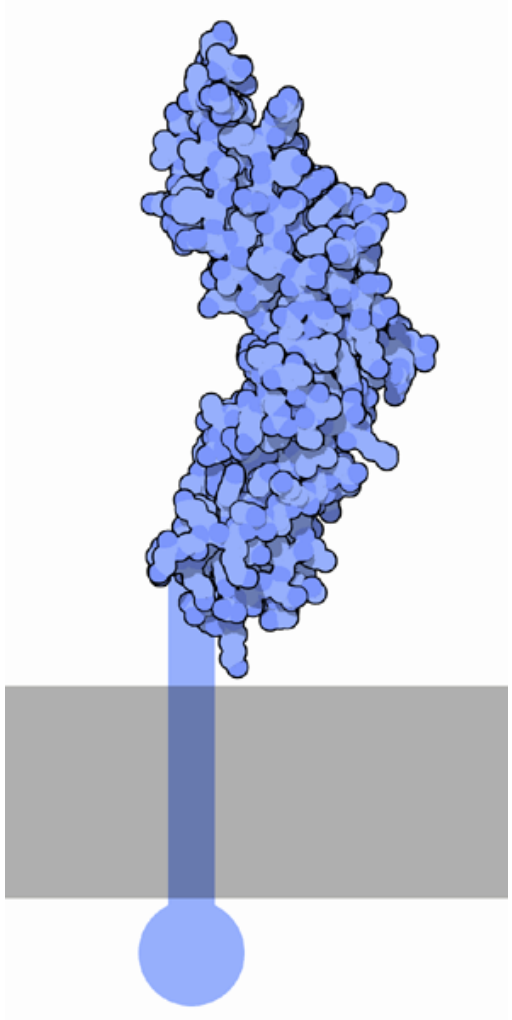
JCO 2009 27(29)4834

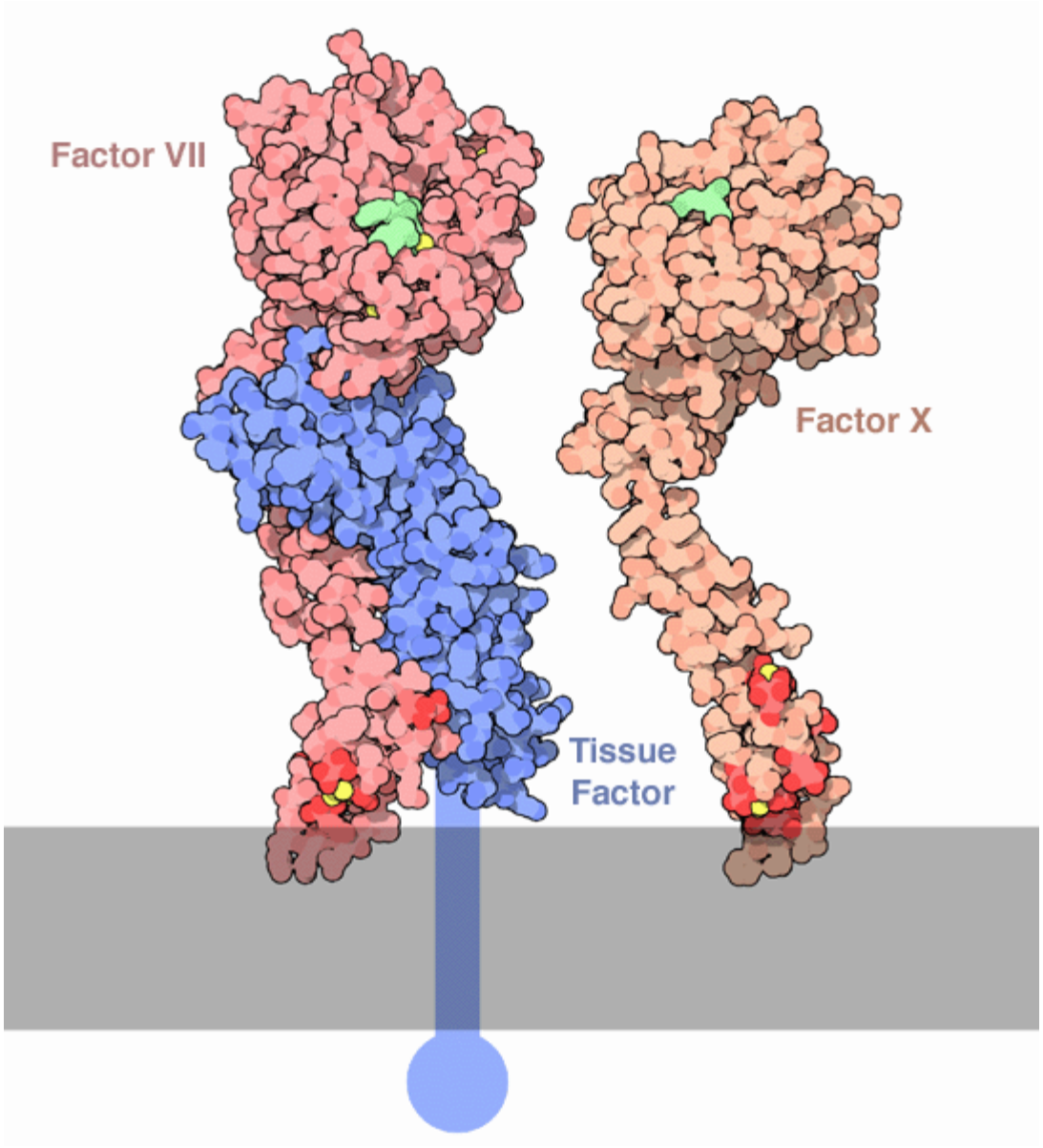




JCO 2009 27(29)4834

Tissue Factor ?





Conditions with increased TF expression

Pathology	TF upregulated in …
Lung injury	Type II alveolar cells
Vascular injury	Smooth muscle cells
Reperfusion injury (heart)	Cardiomyocytes
Glomerulonephritis	Infiltrating macrophages
Homocysteinemia	Monocyte/Macrophages and Endothelial cells
Extracorporeal circulation	Monocyte/Macrophages
Unstable angina	Monocyte/Macrophages
Anticardiolipin/lupus erythematosus	Monocyte/Macrophages and Endothelial cells
Sickle cell disease	Endothelial cells

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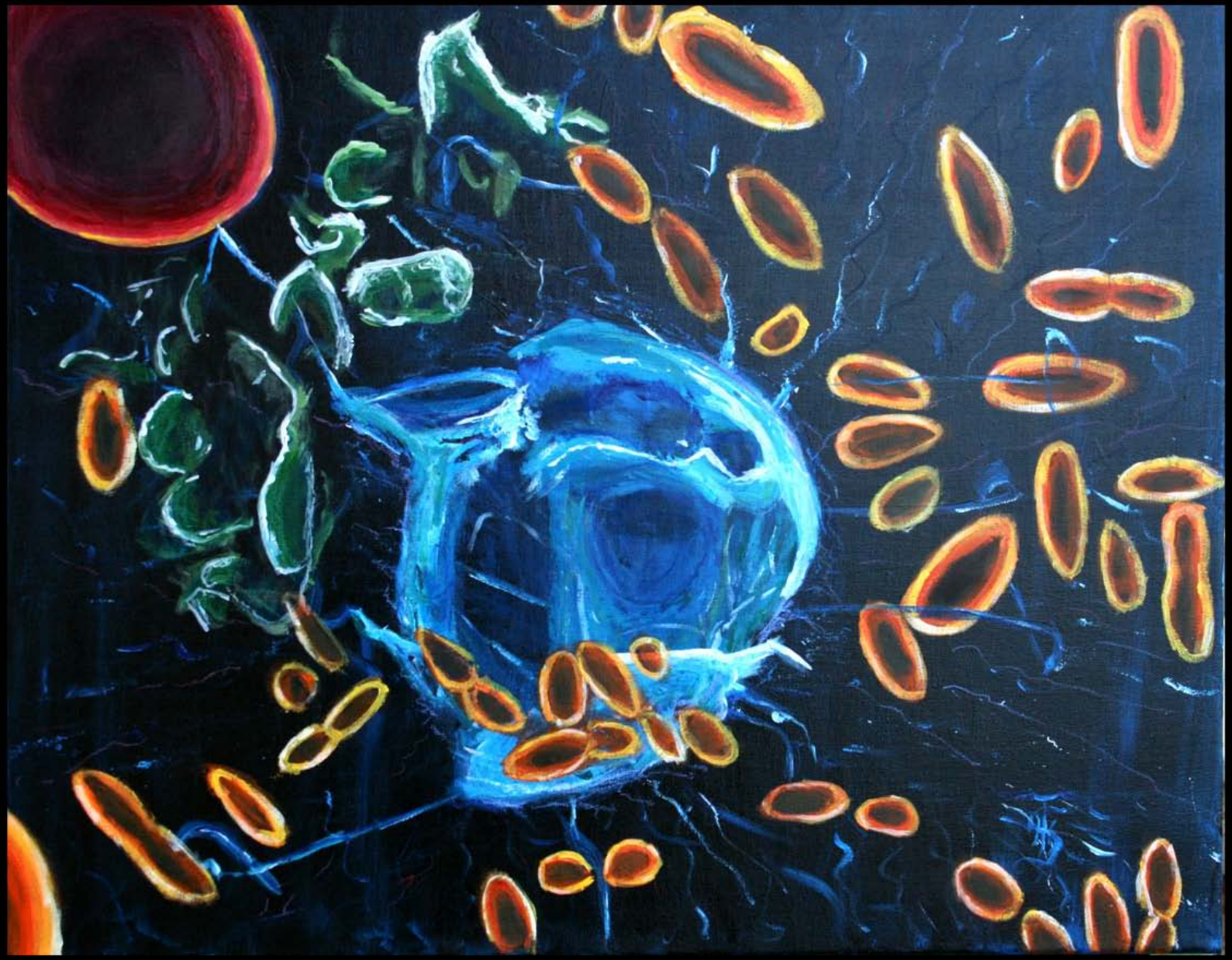
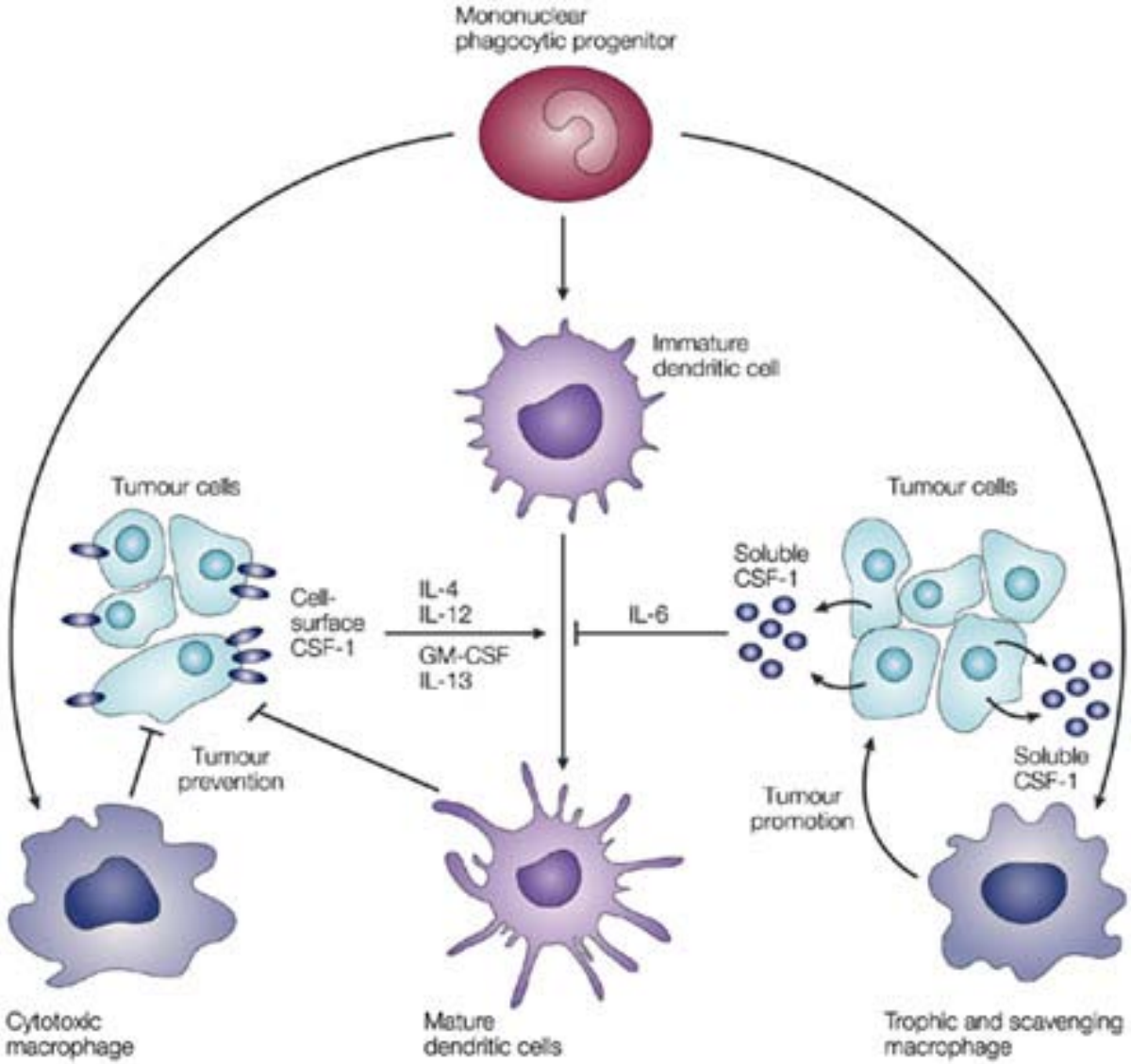
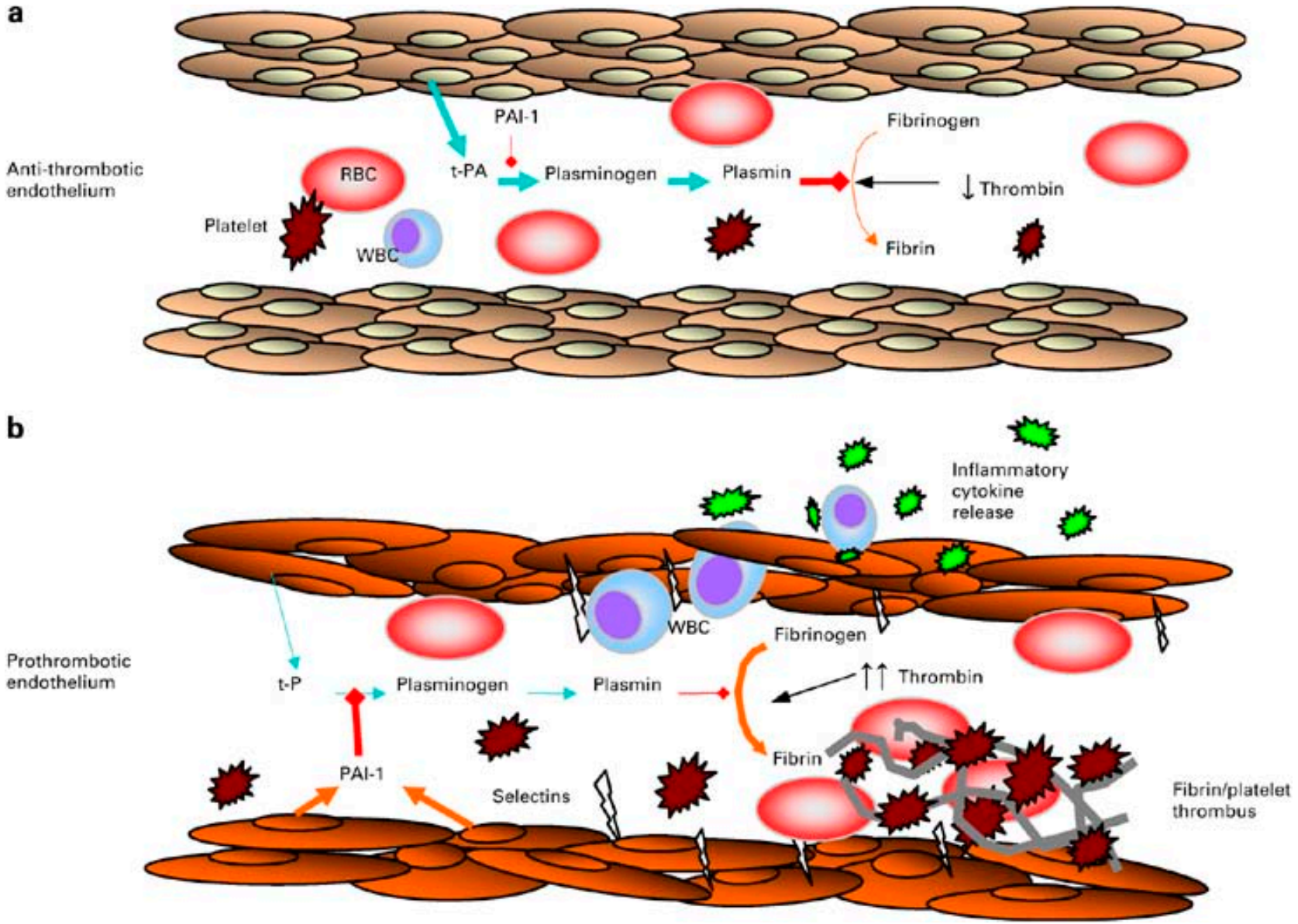


Macrophage, TS Hansen


Mononuclear phagocytic progenitor
Immature dendritic cell
Tumour cells
Cell-surface CSF-1
IL-4
IL-12
GM-CSF
IL-13
IL-6
Soluble CSF-1
Tumour cells
Soluble CSF-1
Tumour prevention
Tumour promotion
Cytotoxic macrophage
Mature dendritic cells
Trophic and scavenging macrophage



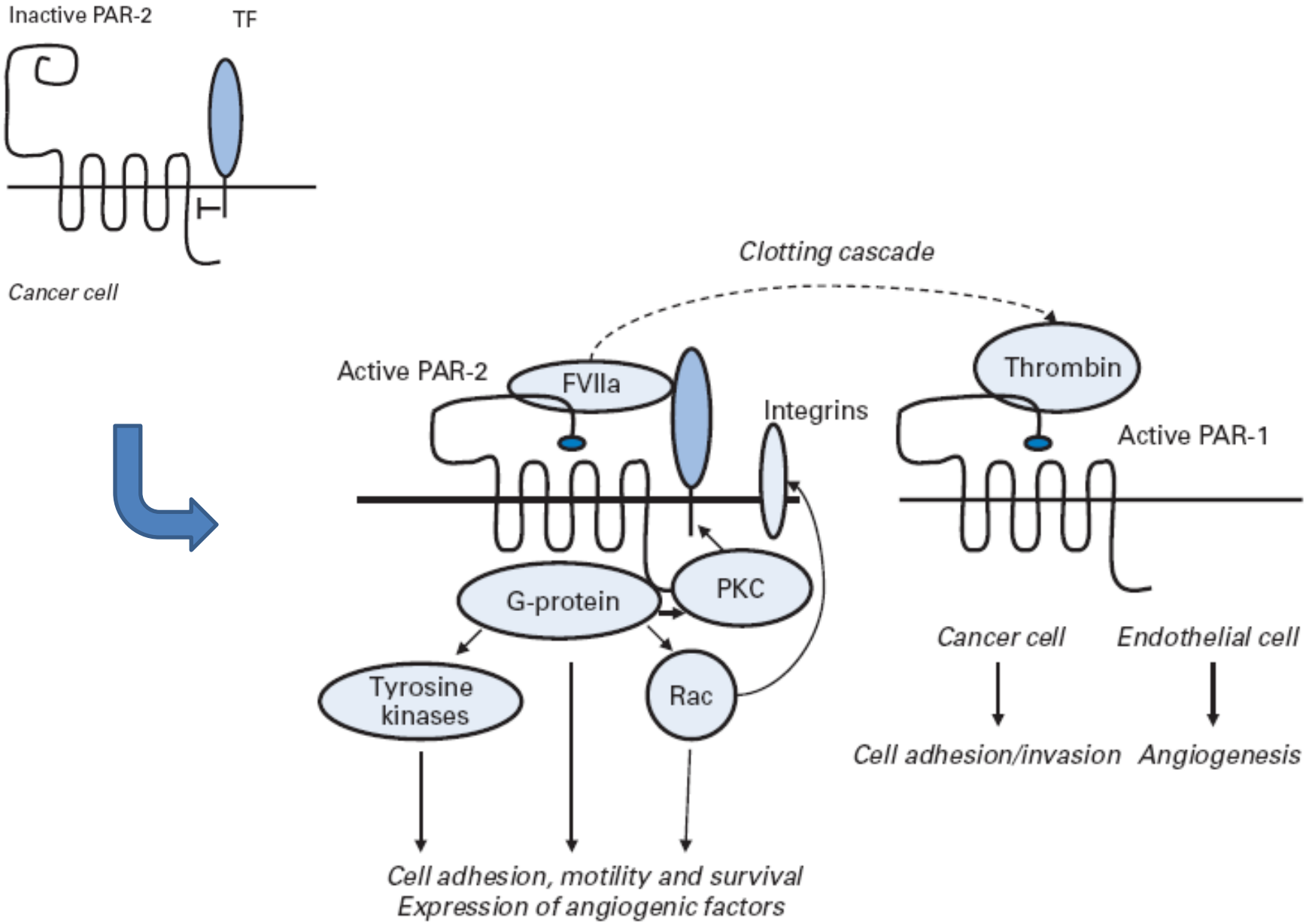
Bone Marrow Transplantation (2008) **41,** 677–686

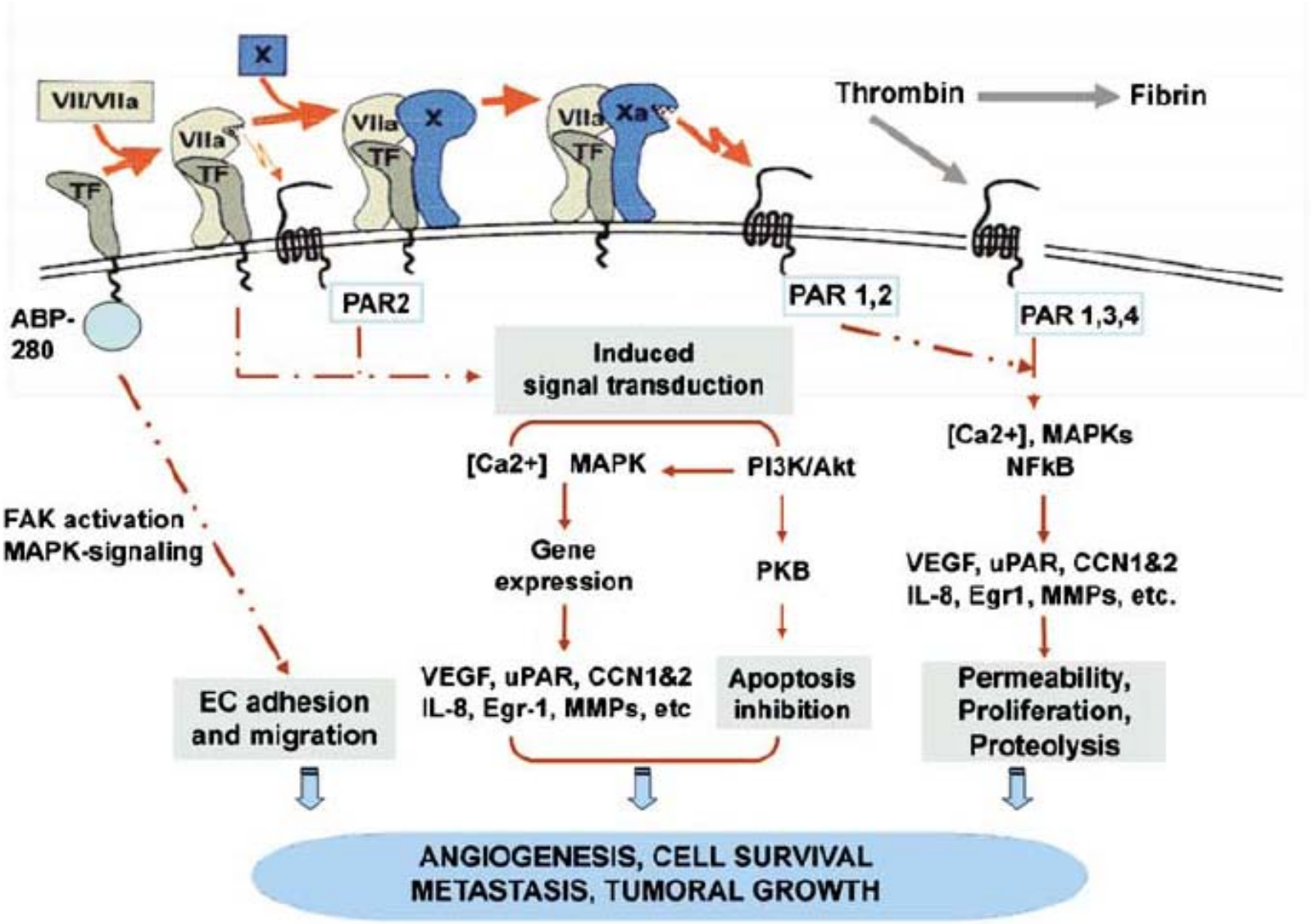
Table 1 TF-FVII(a)-induced intracellular signaling and their contribution to pathophysiological processes

Intracellular signaling induced	*Cell type*	*Pathophysiological effects*	*References*
PAR1 and PAR2 activation	VSMC cells Macrophages Various tumor cell types	Inflammation Angiogenesis Migration Tumor metastasis	Bromberg[35] Marutsuka, Thromb Res 107:271; 2002 Shi[13] Hjortoe[28] Morris, Cancer Res 66:307; 2006
P42/44 MAPK phosphorylation– p21 ras/MAPK pathway activation	BHK cells Fibroblasts HaCaT keratinocytes	Cell survival Tumor metastasis	Sorensen, J Biol Chem 274:21349; 1999 Camerer[29] Versteeg, J Thromb Haemost 1:1012; 2003
Intracellular Ca^{2+} oscillations	Endothelial cells J82 bladder carcinoma MDCK cells	Angiogenesis	Rottingen, J Biol Chem 270:4650; 1995 Camerer, J Biol Chem 271:29034; 1996
P38 ^{MAPK}/JNK phosphorylation	HaCaT keratinocytes	Inflammation	Camerer, J Biol Chem 274:32225; 1999
PI3K/Akt/PKB pathway activation	BHK cells Fibroblasts (A14 cells) HaCaT keratinocytes	Cell survival	Versteeg, J Biol Chem 275:28750; 2000
STAT phosphorylation via Jak2 activation	BHK(TF) cells	Cell survival	Versteeg, Circ Res 94:1032; 2004
P70/p85(S6K) and p90(RSK) phosphorylation	BHK cells HaCaT keratinocytes	Protein synthesis	Versteeg, J Biol Chem 277:27065; 2002
Gene transcripts: VEGF, uPAR, Egr-1, IL-8, etc	Fibroblasts Keratinocytes Various tumor cell types	Angiogenesis Tumor growth Tumor metastasis	Ollivier, Blood 91:2698; 1998 Taniguchi, Cancer Res 58:4461; 1998 Wang, J Biol Chem 277:23620; 2002
Altered expression of selected genes: CCN1 and CCN2	Fibroblasts Keratinocytes	Cell adhesion, proliferation Angiogenesis, tumor metastasis Wound healing	Pendurthi, J Biol Chem 275:14632; 2000
Phosphorylation of the TF cytoplasmic domain	Endothelial cells CHO/TF cells	Angiogenesis	Ahamed[27]

Abbreviations: HaCaT, human keratinocyte cell line; Jak2, Janus tyrosine kinase 2; JNK, Jun-N-terminal kinase; MAPK, mitogen activated protein kinase; PAR1, protease-activated receptor 1; PAR2, protease-activated receptor 2; TF, tissue factor; uPAR, urokinase-type plasminogen activator receptor; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cells

Leukemia 2006 20(8)1331


Inactive PAR-2
TF
Cancer cell
Clotting cascade
Active PAR-2
FVIIa
Integrins
Thrombin
Active PAR-1
G-protein
PKC
Tyrosine kinases
Rac
Cancer cell
Endothelial cell
Cell adhesion/invasion
Angiogenesis
Cell adhesion, motility and survival
Expression of angiogenic factors



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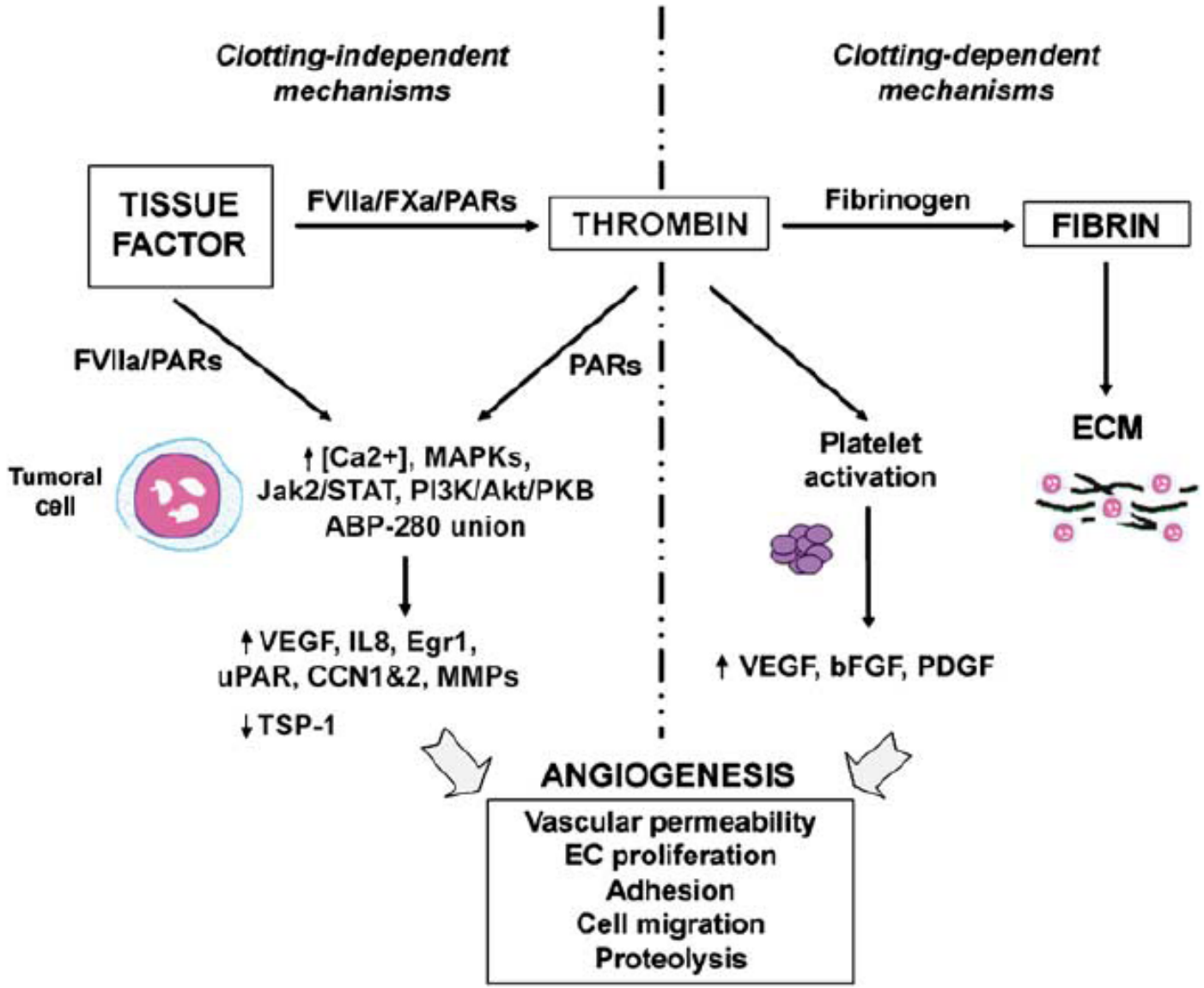

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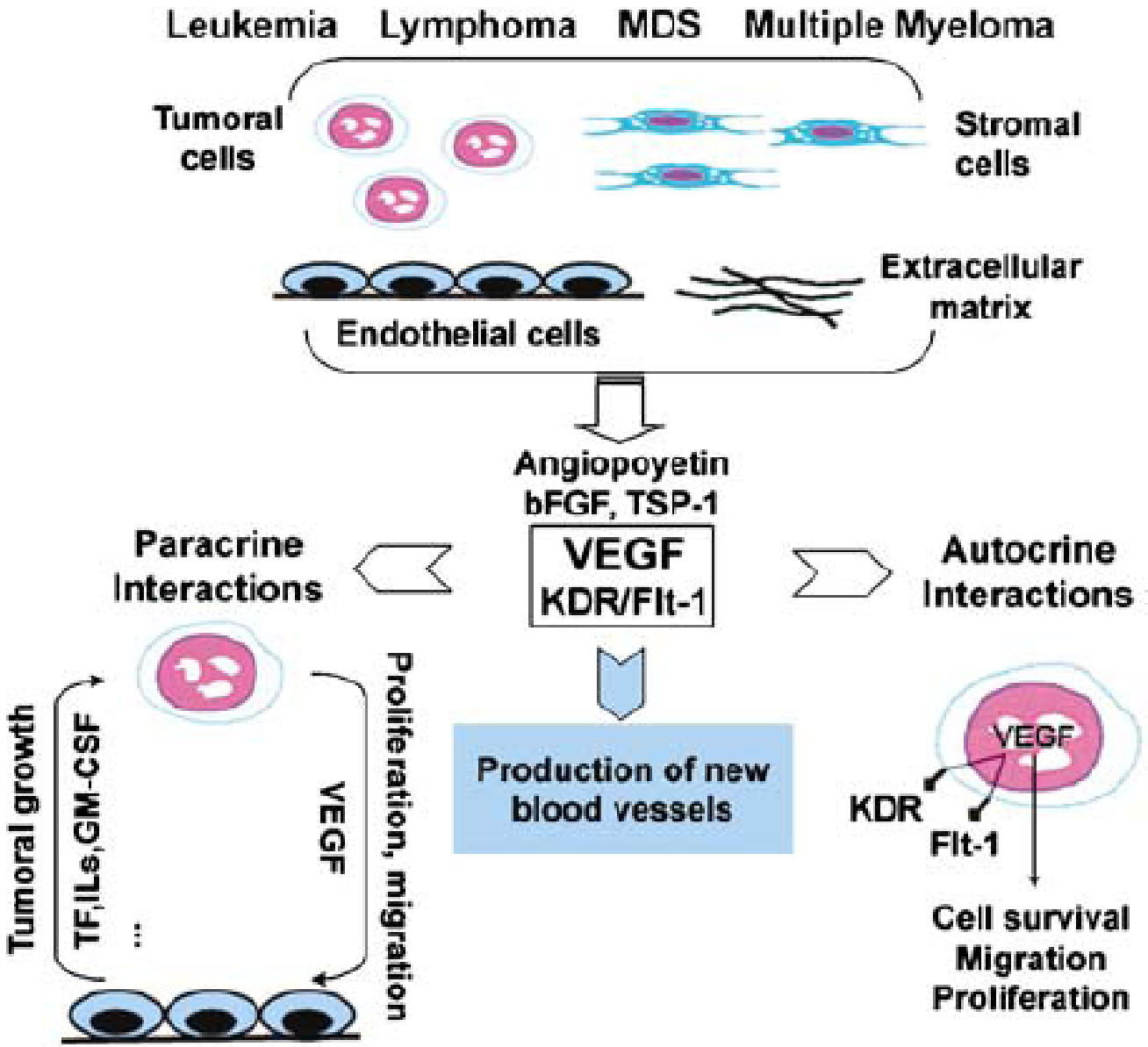

Leukemia 2006 20(8)1331

A Summary of the Major Known PAR-Activating Proteases, Cleavage Sites, Sequences of Activating Peptides, Signaling Mechanisms, and the Sites of PAR Expression

	PAR_1	PAR_2	PAR_3	PAR_4
Activating proteases	Thrombin Factor Xa Trypsin Activated protein C	Trypsin Tryptase Factor VIIa Factor Xa	Thrombin	Thrombin Trypsin Cathepsin G
Cleavage sites (✂)	$LDPR^{41}$ ✂ $S^{42}FLLRN$	$SKGR^{34}$ ✂ $S^{35}LIGKV$	$LPIK^{38}$ ✂ $T^{39}FRGAP$	$PAPR^{47}$ ✂ $G^{48}YPGQV^{53}$
Activating peptides	SFLLRN	SLIGKV	None	GYPGQV
Secondary messengers	$G\alpha_{q/11}$ → PLCβ → ⇧ IP_3+DAG $G\alpha_{12/13}$ → Rho → Rho-K, MLCK $G\alpha_i$ → ⇩ cAMP	$G\alpha_{q/11}$ → PLCβ → ⇧ IP_3+DAG ? → PLA_2 → ⇩ AA $G\alpha_s$? → PKA	Unknown	$G\alpha_{q/11}$ → ? → PKCδ
Locations	Platelets, endothelium, epithelium, neurons, myocytes	Sensory neurons, endothelium, epithelium, myocytes	Platelets, endothelium, myocytes	Platelets, endothelium, epithelium, myocytes

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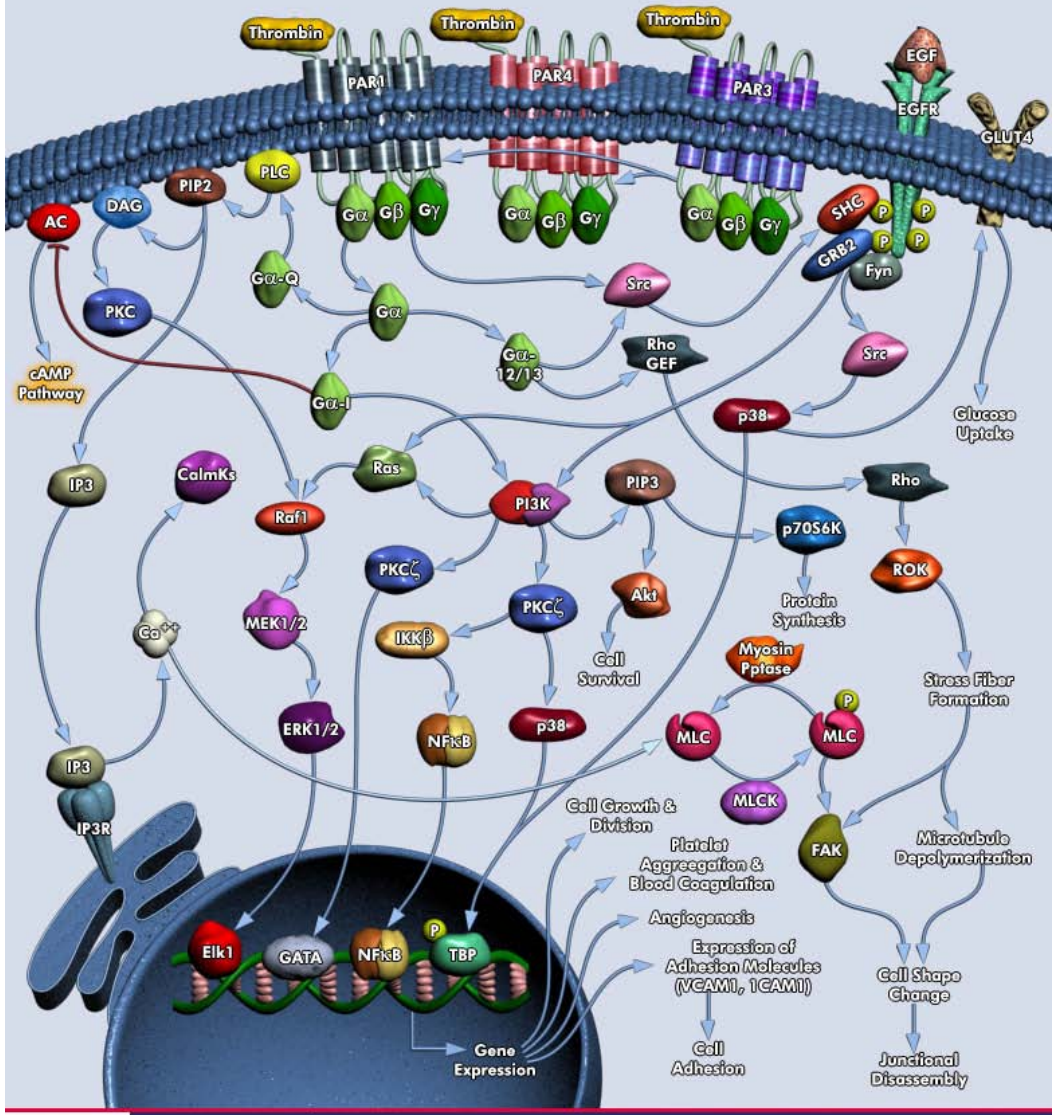
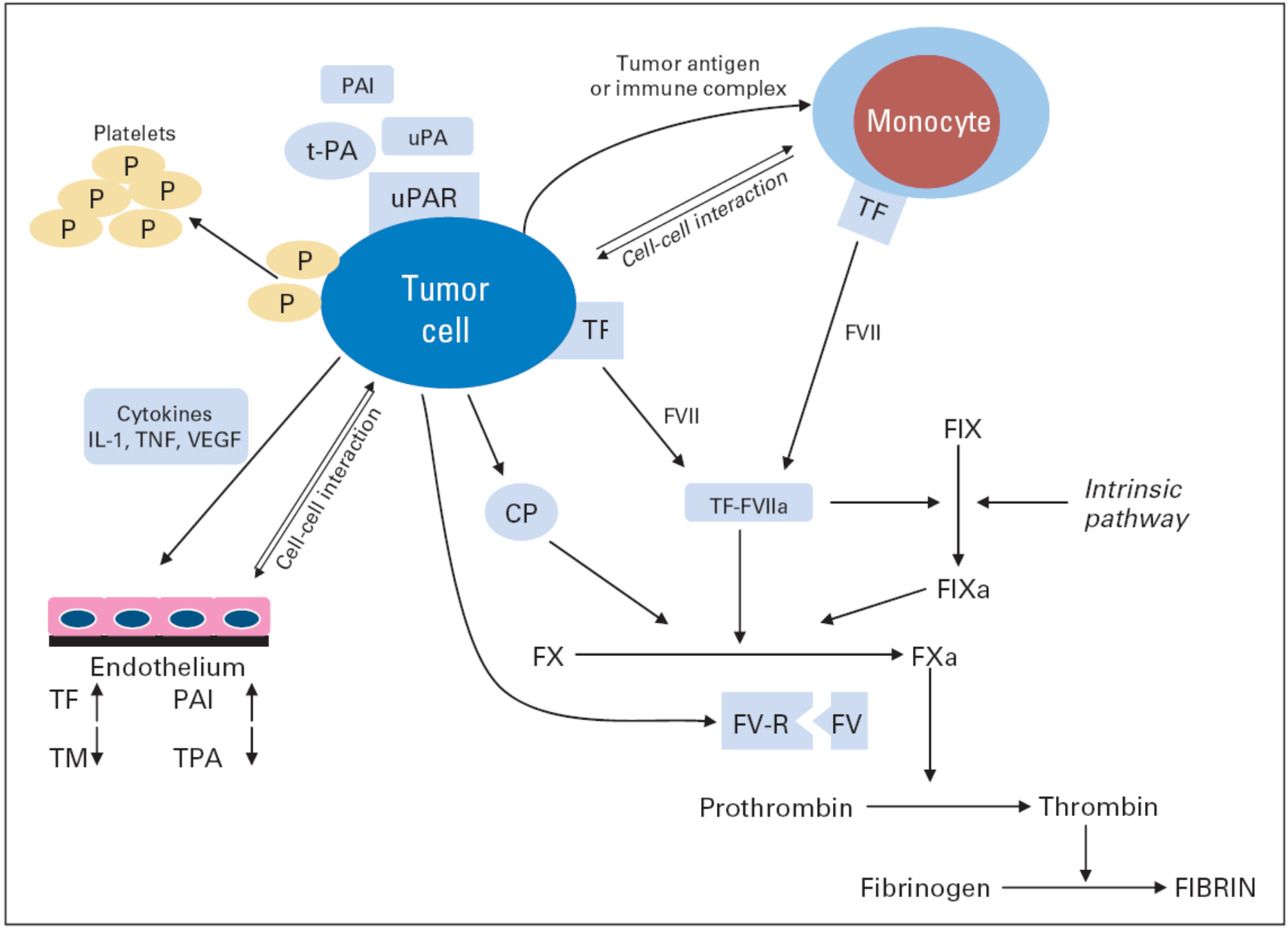
Thrombin Signaling




Tumor antigen
or immune complex
Monocyte
PAI
Platelets
t-PA
uPA
uPAR
P
P
P
P
P
P
Tumor
cell
TF
Cell-cell interaction
TF
FVII
FVII
Cytokines
IL-1, TNF, VEGF
Cell-cell interaction
CP
TF-FVIIa
FIX
Intrinsic
pathway
FIXa
Endothelium
TF
PAI
TM
TPA
FX
FXa
FV-R
FV
Prothrombin
Thrombin
Fibrinogen
FIBRIN

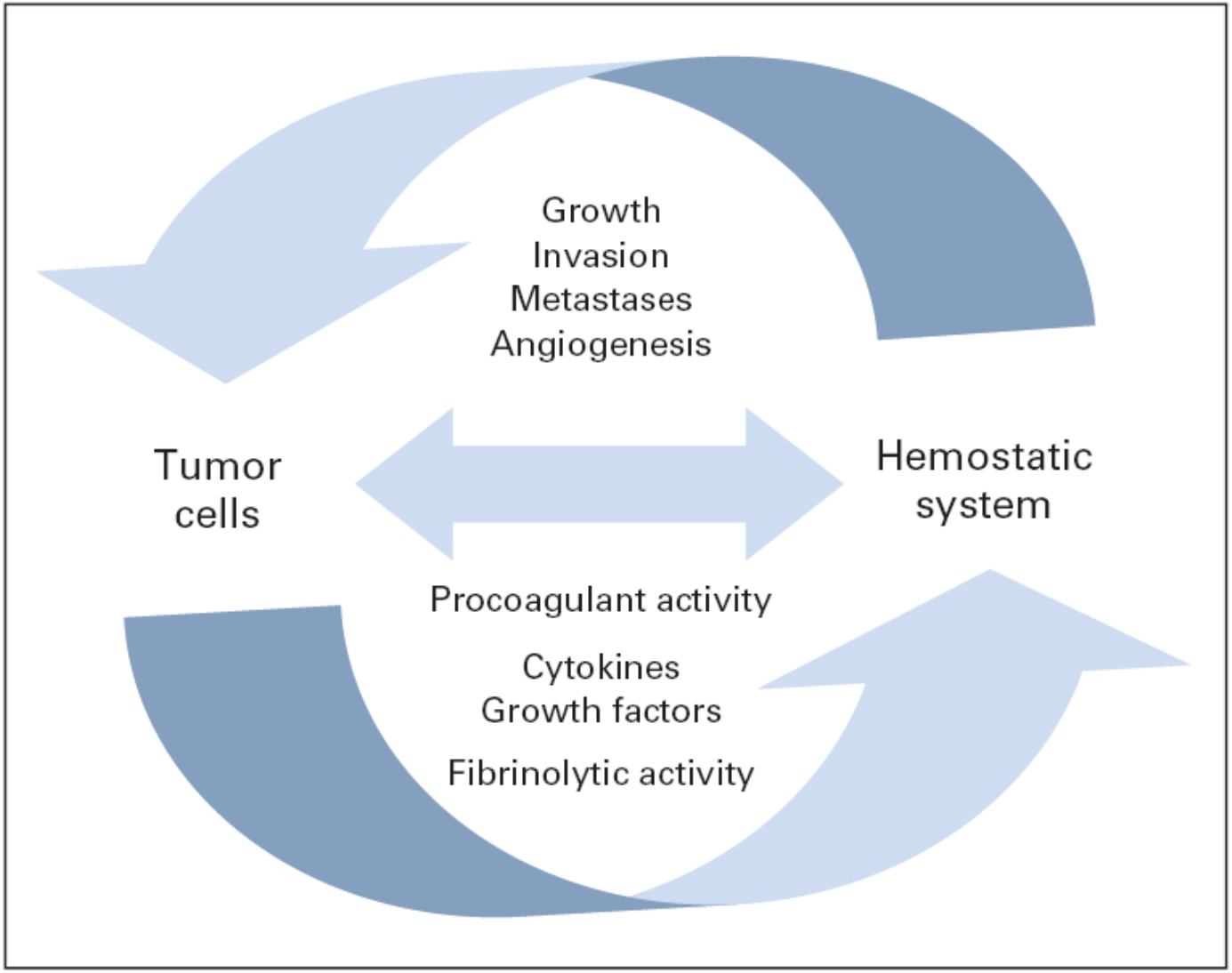
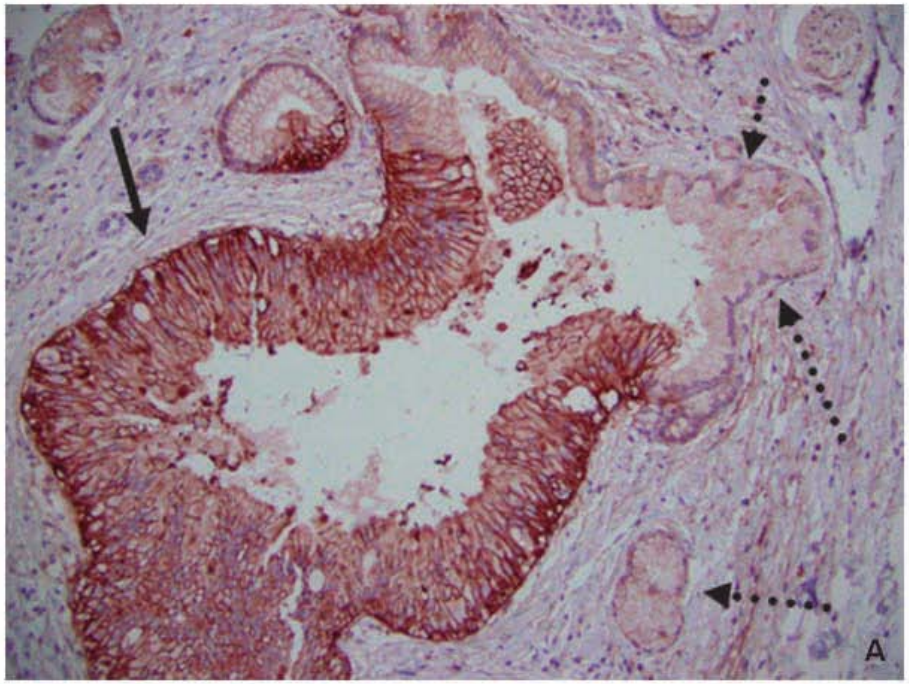


Fig 2. Positive feedback loop between tumor and the hemostatic system: tumor can promote a procoagulant state. Components of the activated hemostatic system, in particular the platelet-fibrin–rich tumor microthrombi, also promote tumor growth, angiogenesis, invasion, and metastasis formation.



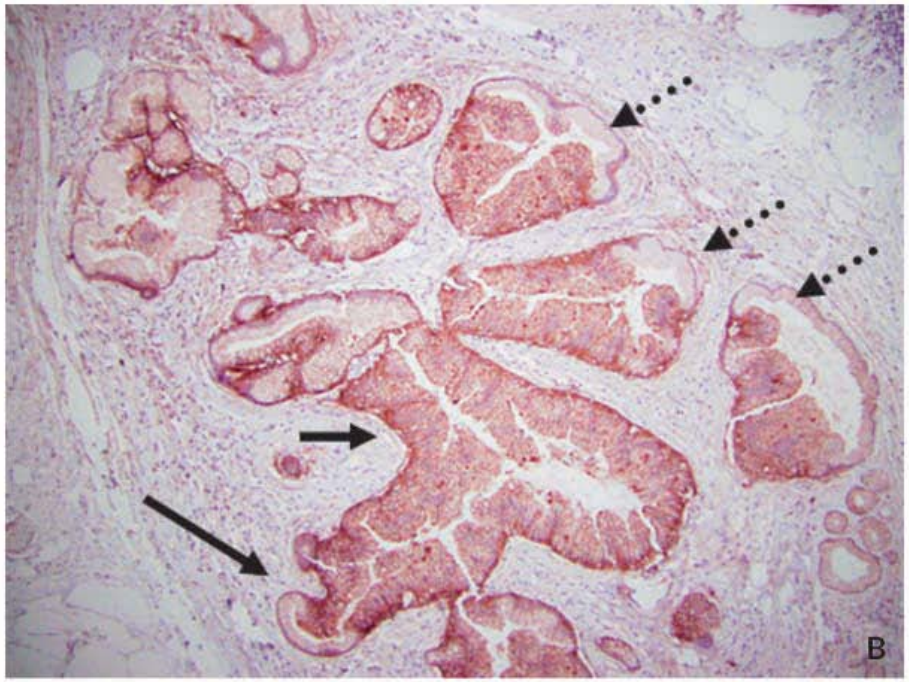
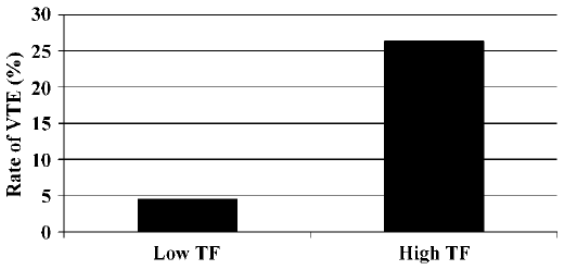


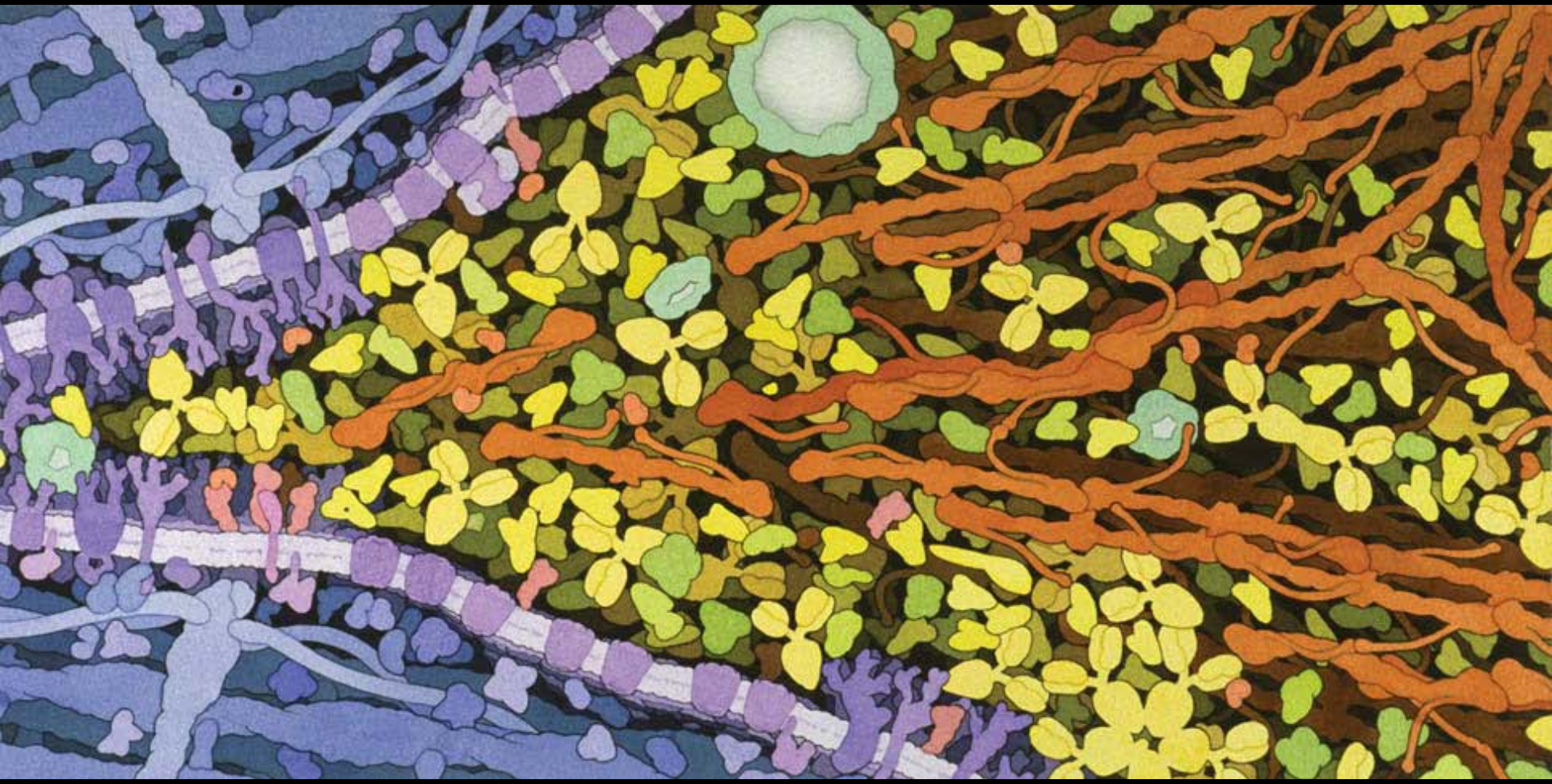
Fig. 1. TF expression in noninvasive pancreatic neoplasia. TF expression in noninvasive pancreatic neoplasia shown by strong immunostaining in the cytoplasm of morphologically dysplastic cells (*straight arrows*), compared with morphologically normal cells (*dashed arrows*) in the same duct showing no TF staining. Original magnification, ×250 (*A*) and ×400 (*B*).

Table 2. Correlation of TF expression with the expression of other angiogenesis variables in resected pancreatic cancer

	High TF expression	Low TF expression	*P*
VEGF expression			
Negative	13	41	<0.0001
Positive	53	15	
Microvessel density			
≤6 per tissue core	27	33	0.047
>6 per tissue core	39	23	
Median	8	6	0.01



Clin Cancer Res 2007;13(10)May 15, 2007



¿ Causa o Consecuencia ?

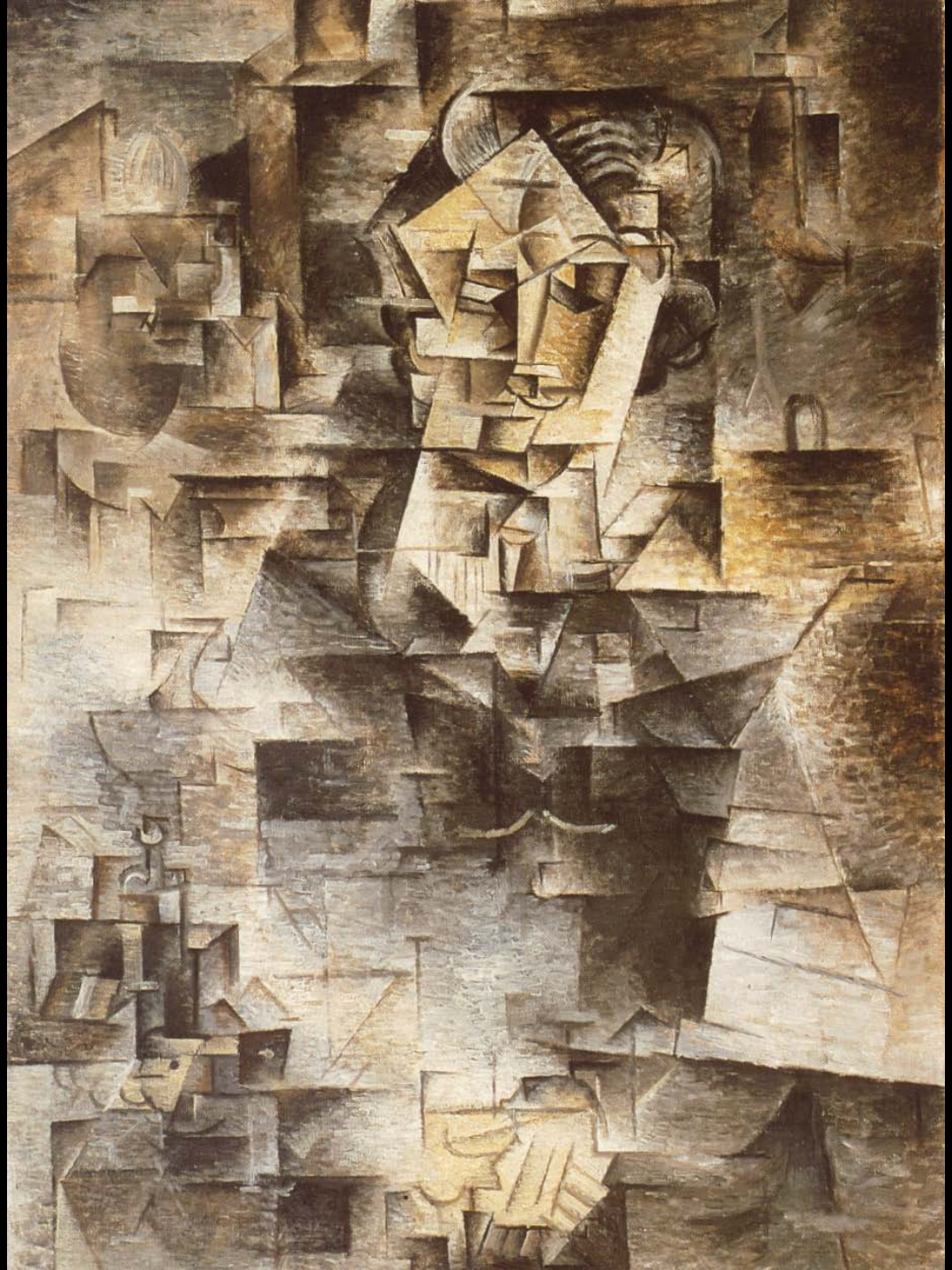


Table 2. American Society of Clinical Oncology VTE Prophylaxis and Treatment Guidelines Clinical Questions[19]

1.	Should patients with cancer receive anticoagulation for VTE prophylaxis while hospitalized?
2.	Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?
3.	Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?
4.	What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?
5.	Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?

Abbreviation: VTE, venous thromboembolism.

Development and validation of a predictive model for chemotherapy-associated thrombosis

Alok A. Khorana, Nicole M. Kuderer, Eva Culakova, Gary H. Lyman, and Charles W. Francis

Blood 2008 111: 4902

Desarrollo y validación de un Modelo Predictivo para trombosis asociada a Quimioterapia

UNIVERSITY of ROCHESTER

Introducción

- Sin embargo, en pacientes con cáncer avanzado sometidos a quimioterapia por su enfermedad NO se recomienda profilaxis con HBPM o HNF [Evidencia Nivel II, Recomendación B, Guías Clínicas AIOM y ASCO].
- En quienes sí se recomienda es en pacientes con cáncer hospitalizados por complicaciones agudas y confinados al decúbito [Evidencia Nivel I, Recomendación A].
- Se piensa que en pacientes en quimioterapia u hormonoterapia no se ha seleccionado claramente a la población que se beneficiaría claramente de esta intervención, por lo que faltarían elementos para indicar una profilaxis tan costosa.

Table 2. Clinical Risk Factors and Candidate Biomarkers for Cancer-Associated VTE

- Cancer-related factors
  - Primary site of cancer[1-5]: brain, pancreas, kidney, stomach, lung, gynecologic, lymphoma, myeloma
  - Advanced stage of cancer[4-6]
  - Initial period after diagnosis of cancer[1,17-19]
  - Histology[20,21]
- Treatment-related factors
  - Major surgery[6]
  - Hospitalization[2,9,13]
  - Cancer therapy
    - Chemotherapy[9,14,16,22]
    - Hormonal therapy[23]
    - Anti-angiogenic agents[24-32]: thalidomide, lenalidomide, bevacizumab
  - Erythropoiesis-stimulating agents[8,33]
  - Transfusions[34]
  - Central venous catheters[35-38]

Patient-related factors
Older age[2,6,39]
Female sex[2]
Race[2,21,40]
Higher in African Americans
Lower in Asians/Pacific Islanders
Comorbidities[9,15,21,40-42]: infection, renal disease, pulmonary disease, obesity, arterial thromboembolism
Inherited prothrombotic mutations[1,43,44]: Factor V Leiden, prothrombin gene mutation
Prior history of VTE[6,45-48]
Performance status[6,19,49]
Candidate biomarkers
Blood counts[8,15,39,50-52]
Prechemotherapy platelet count $\geq$ 350,000/μL
Prechemotherapy leukocyte count $>$ 11,000/μL
TF[10,11,53,54]
High grade of TF expression by tumor cells
Elevated systemic TF (antigen or activity)
D-dimer[49,55]
Soluble P-selectin[7]
C-reactive protein[9]

Abbreviations: VTE, venous thromboembolism; TF, tissue factor.

Table 1. Wells Clinical Deep Vein Thrombosis Model[8]

Clinical Characteristic	Score
Active cancer (patient receiving treatment for cancer within 6 months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster cast immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than the asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	−2

NOTE. A score of lower than 2 indicates that a deep vein thrombosis is unlikely. A score of 2 points or higher indicates that a deep vein thrombosis is likely.

Table 2. Wells Clinical Pulmonary Embolism Model[7]

Clinical Characteristic	Score
Active cancer (patient receiving treatment for cancer within 6 months or currently receiving palliative treatment)	1
Surgery or bedridden for 3 days or more during the past 4 weeks	1.5
History of deep venous thrombosis or pulmonary embolism	1.5
Hemoptysis	1
Heart rate $>$ 100 beats per minute	1.5
Pulmonary embolism judged to be the most likely diagnosis	3
Clinical signs and symptoms compatible with deep venous thrombosis	3

NOTE. A score of $\leq$ 4 indicates that pulmonary embolism is unlikely. A score of higher than 4 indicates that pulmonary embolism is likely.

OJO
NO SON ESPECÍFICAS PARA PACIENTES ONCOLÓGICOS

Table 6. Geneva Pulmonary Embolism Prognostic Index[49]

Risk Factor	Geneva Risk Scale (points)
Active cancer	2
Systolic blood pressure < 100 mmHg	2
Concomitant DVT at diagnosis	1
History of VTE	1
Heart failure	1
Hypoxia (arterial PaO2 < 60 mmHg)	

NOTE. Geneva risk score: low risk = 2 or fewer points; high risk = 3 or more points.

Pacientes y Método

- Datos Obtenidos del Registro Prospectivo "Awareness of Neutropenia in Chemotherapy (ANC) Study Group Registry", que abarca 115 centros en USA y el mundo.
- Se trata de un estudio observacional multicéntrico diseñado para evaluar neutropenia febril y otras complicaciones relacionadas con la quimioterapia en pacientes con cancer que están iniciando una nueva quimioterapia.

Pacientes y Método

- Se enroló 4066 pacientes entre Marzo 2002 y Agosto 2004, divididos aleatoriamente en una cohorte de derivación (n=2701) y otra de validación (n=1365).
- Se les siguió por un máximo de 4 ciclos, incluyéndose en este análisis todos aquellos con al menos 1 ciclo recibido.
- El estudio fue aprobado por un Comité Revisor Institucional Central y el de la University of Rochester, todos los pacientes tuvieron consentimiento informado.

- Inclusión
  - Diagnóstico Histológico de Cáncer
  - Tumores específicos (Mama, Pulmón, Ovario, Sarcoma, Colon y Linfomas).
  - Mayor de 18 años
  - Estar iniciando QMT y tener al menos 4 ciclos a recibir.
  - Consentimiento Informado Helsinski.

- Exclusión :
  - Terapia Concurrente (citotóxica, Inmunoterapia, biológica, etc).
  - Dg de Leucemia
  - Embarazo o Lactancia
  - Infección activa que requiera tratamiento
  - Participando en otro estudio doble ciego
  - Receptor de TMO

Variables

- Se registraron Variables demográficas asociadas a ETV : Edad, Performance Status, etnicidad, sitio y estadío de la Neoplasia, tipo de Quimioterapia empleada, IMC, comórbidos (especialmente cardiovasculares), cirugías recientes, terapias concomitantes y recuentos de laboratorio.
- En general la tasa de pérdida de datos del registro fue baja, excepto para Albúmina sérica (n=125, 3.1%).

Outcomes y Seguimiento

- Endpoint : Evento de Enfermedad Tromboembólica a 2.5 meses plazo, diagnosticado por el Clínico a cargo del paciente (No se describen detalles, en addenda se explica que sería con Eco Doppler de EEII y TAC AngioTAC de Tórax).
- Seguimiento : Pérdida de Seguimiento menor del 3%.

Análisis Estadístico

Desarrollo del Modelo Predictivo

- Análisis estadístico de las Cohortes:
  - Características Basales (univariado) por X_2.
  - Análisis Multivariado realizado por Regresión
  - El Modelo Predictivo se desarrolló a partir de la cohorte de derivación, analizando regresión de las variables significativas en el análisis univariado y otras preestablecidas por los investigadores.
  - Se validó el modelo en la cohorte de validación ya descrita, de manera de calibrar (Modelo de Hosmer-Lemeshow) bien el instrumento.
  - Software : SAS statistical software (SAS Institute, Cary, NC)

Resultados

- Se identificaron 5 variables con poder predictivo en el análisis multivariado :
  - Sitio del cáncer (2 pts para sitios de muy alto riesgo, 1 pt para sitios de alto riesgo) (1 pt)
  - Recuento de Plaquetas >350 10^9/L (1 pt)
  - Hemoglobina <100 g/L (10 g/dL) y/o uso de estimulantes de la Eritropoiesis (1 pt)
  - Leucocitos > 11 10^9/L (1 pt)
  - IMC >35 kg/m2 (1 pt).

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.

TABLE 3
Predictors of Venous Thromboembolism by Multivariate Logistic Regression Analysis

Patient characteristic	Odds ratio (95% CI)	*P* value
Site of cancer[a]		0.03
Upper gastrointestinal	3.88[b] (1.43–10.05)	0.0076
Lung	1.86[b] (0.99–3.49)	0.05
Lymphoma	1.50[b] (0.67–3.38)	0.32
Prechemotherapy platelet count $\geq 350{,}000/mm^3$	2.81 (1.63–4.93)	0.0002
Use of white cell growth factors[a]	2.09 (1.21–3.61)	0.008
Hemoglobin < 10 g/dL or use of red cell growth factors	1.83 (1.07–3.14)	0.03

[a] There was a significant interaction identified between cancer site and use of white cell growth factors (β-coefficient = 0.62, $P = 0.018$). For purpose of simplicity, this interaction was not considered in the above model.

[b] Odds ratio in comparison to other cancers.

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

Resultados

- Las tasas de ETV en ambas cohortes fueron similares a 2.5 meses plazo, al evaluar según las categorías de riesgo obtenidas del análisis multivariado.
- El análisis del instrumento generado permite un alto valor predictivo negativo, identificando a quienes NO necesitan una intervención para evitar la ETV.

VTE and Type of Malignancy

Type	Adjusted Odds Ratio (95% CI)
Hematologic	28 (4-199.7)
Lung	22.2 (3.6-136.1)
Gastrointestinal	20.3 (4.9-83)

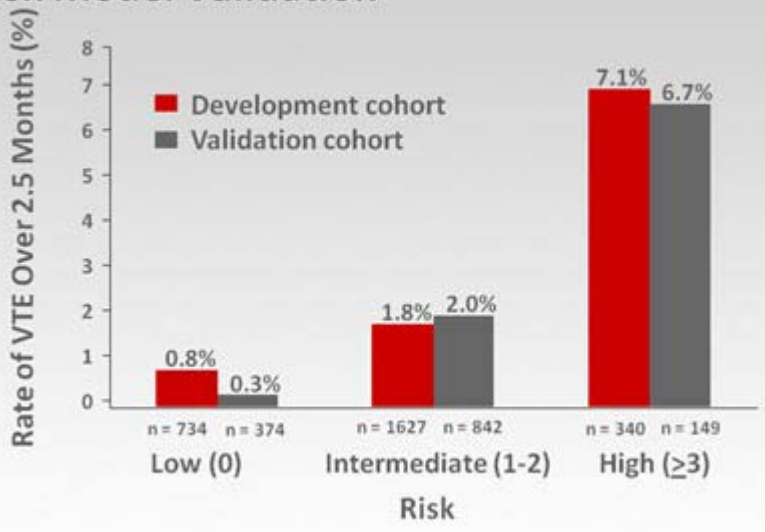
Blom JW, et al. *JAMA*. 2005;293:715-722.

Risk Model

Patient Characteristic	Score
Site of Cancer:	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, GU excluding prostate)	1
Platelet count $\geq$ 350,000/mm^3	1
Hb < 10g/dL or use of ESA	1
Leukocyte count > 11,000/mm^3	1
BMI $\geq$ 35 kg/m^2	1

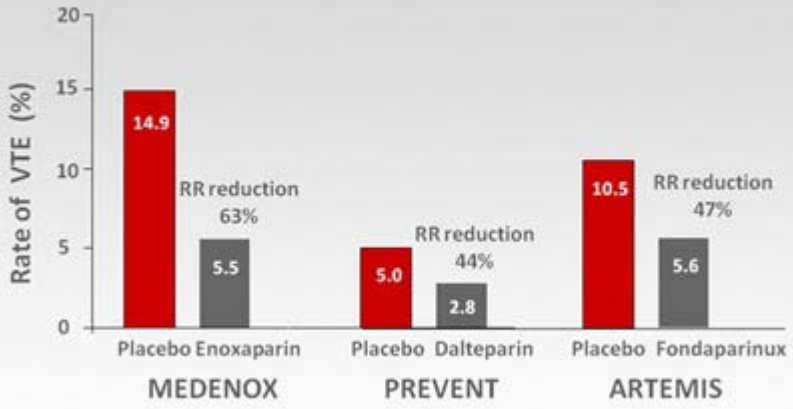
Khorana AA, et al. *Blood*. 2008;111:4902-4907.

Risk Model Validation



Khorana AA, et al. *Blood*. 2008;111:4902-4907.

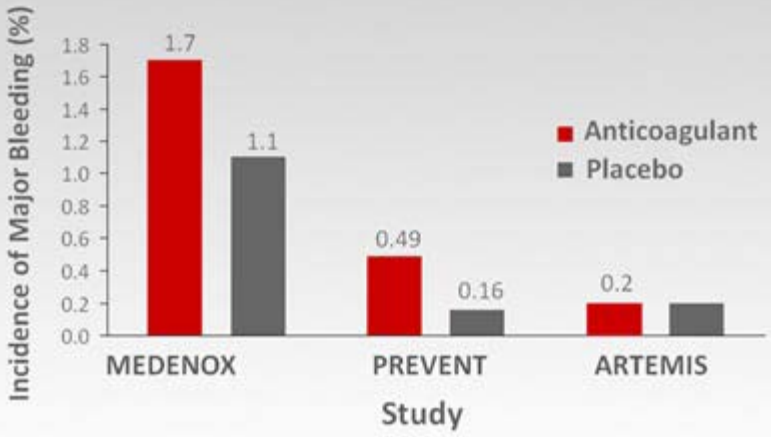
Prophylaxis in Hospitalized Medical Patients: Efficacy



RR = relative risk

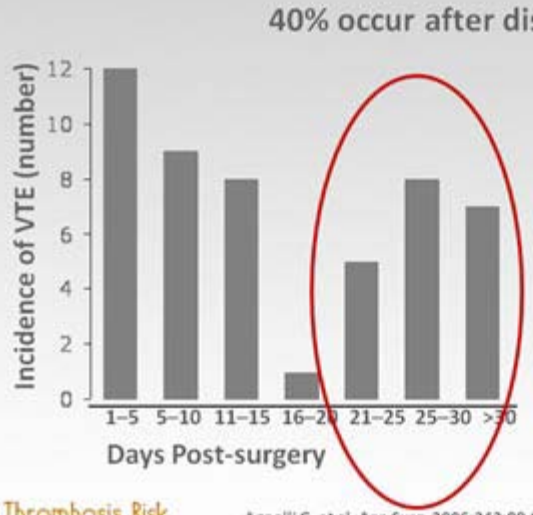
Francis CW. *N Engl J Med*. 2007;356:1438-1444.

Prophylaxis in Hospitalized Medical Patients: Safety



Samama MM, et al. *N Engl J Med*. 1999;341:793-800.
Leizorovicz A, et al. *Circulation*. 2004;110:874-879.
Cohen AT, et al. *J Thromb Haemost*. 2003;1(S1):P2046.

Surgical Patients: Extended Risk for VTE

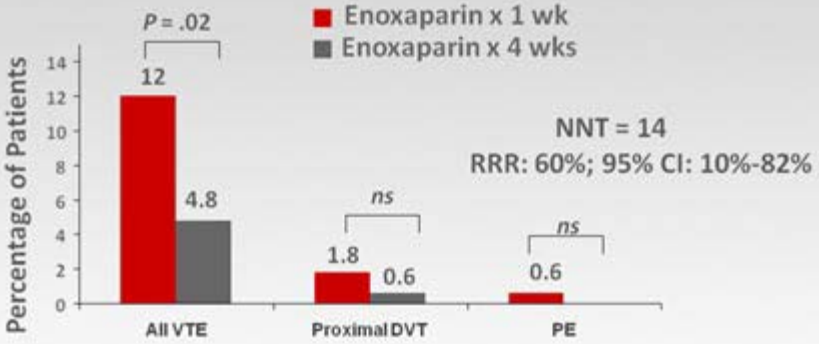


@RISTOS
- Prospective cohort
- N = 2373
- Symptomatic VTE 2.1%
- Overall mortality 1.7%

46% due to fatal PE

Agnelli G, et al. *Ann Surg*. 2006;243:89-95.

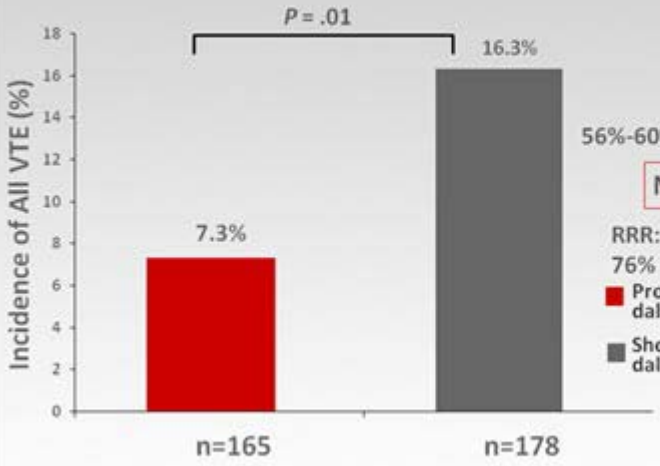
ENOXACAN II: Incidence of VTE



NNT = 14
RRR: 60%; 95% CI: 10%-82%

Bergqvist D, et al. *N Engl J Med*. 2002;346:975-980.

FAME: Incidence of VTE



56%-60% were cancer surgery

NNT: 12 (7-44)

RRR: 55%; 95% CI: 15%-76%

- Prolonged TP (28 day) with dalteparin
- Short-term TP (7 day) with dalteparin

Rasmussen MS, et al. *J Thromb Haemost*. 2006;4:2384-2390.

LMWH Thromboprophylaxis Studies in Cancer Outpatients

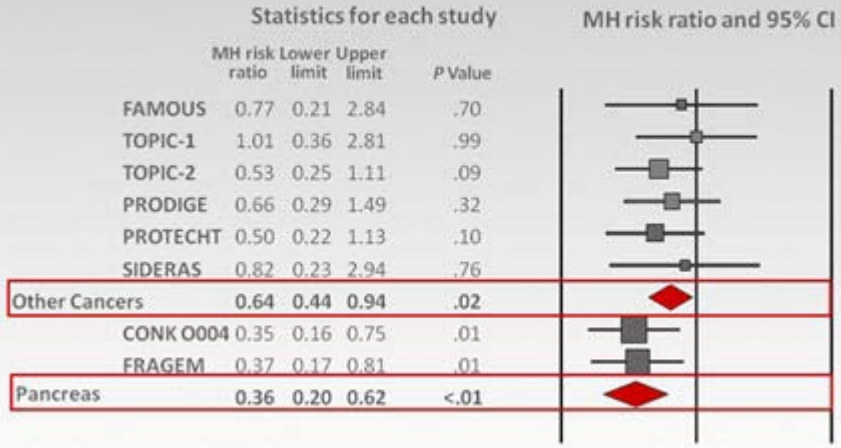
Study/Cancer Type	Year	Stage	N	LMWH/ Dose	Control Arm	Duration
FAMOUS Solid tumors	2004	III/IV	385	Dalteparin 5000 IU/d	Placebo	12 months
TOPIC-I Breast	2005	III/IV	353	Certoparin 3000 IU/d	Placebo	6 months
TOPIC-2 NSCLC	2005	III/IV	547	Certoparin 3000 IU/d	Placebo	6 months
PRODIGE Glioma	2007	Any	186	Dalteparin 5000 IU/d	Placebo	6-12 months
SIDERAS Solid tumors	2006	IV	141	Dalteparin 5000 IU/d	Nonplacebo	Indefinite
PROTECHT Solid tumors	2008	III/IV	1166	Nadroparin 3800 IU/d	2:1 Placebo	≤ 4 months with chemo
CONKO-04 Pancreas	2009	Advanced	312	Enoxaparin 1 mg/kg/d 40 mg/d	Nonplacebo	3 months (data to progression)
FRAGEM Pancreas	2009	Advanced	123	Dalteparin 200 IU/kg/d (w 1-4) 150 IU/kg/d (w 5-12)	Nonplacebo	3 months

Thrombosis Risk

Kuderer NM, et al. ASH. December 5-8, 2009; New Orleans, Louisiana. Abstract 490.

theheart.org | MedscapeCME

Benefit From LMWH Thromboprophylaxis by Cancer Type



Thrombosis Risk

Kuderer NM, et al. ASH. December 5-8, 2009; New Orleans, Louisiana. Abstract 490.

theheart.org MedscapeCME

Despite Evidence – Medical Patients at Risk Remain Unprotected

ENDORSE[1]

	Medical	Surgical
No. of patients	37,356	30,827
At risk for VTE	42%	64%
Receiving ACCP Tx	40%	59%

IMPROVE[2]

	United States	Other Countries
No. of patients	3410	11,746
VTE prophylaxis	1852 (54%)	5788 (49%)
LMWH	476 (14%)	4657 (40%)
UFH	717 (21%)	1014 (9%)

1. Cohen AT, et al. ISTH. July 6-12, 2007; Geneva, Switzerland. Abstract O-5-002.
2. Tapson VF, et al. *Chest*. 2007;132:936-945.

Thrombosis Risk

theheart.org MedscapeCME

ASCO Guidelines for Thromboprophylaxis

Hospitalized cancer patients:

- Should be considered candidates for VTE prophylaxis in the absence of contraindications

Surgical cancer patients:

- All patients undergoing major surgical intervention for malignant disease should be considered for prophylaxis
- Prophylaxis should be continued for at least 7-10 days postoperatively and may be extended into the postdischarge period for selected high-risk patients

Ambulatory cancer patients:

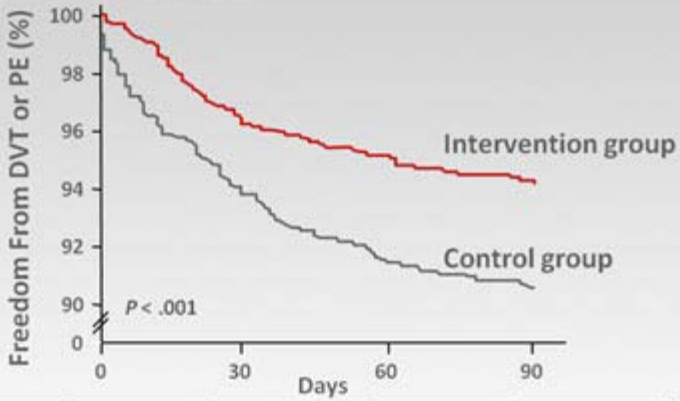
- Routine prophylaxis not recommended
- Exception: Patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone

Thrombosis Risk

Lyman GH, et al. *J Clin Oncol*. 2007;25:5490-5505.

theheart.org Medscape

Electronic Alerts to Prevent VTE in Hospitalized Patients



No. at Risk				
Intervention group	1255	977	900	853
Control group	1251	976	893	839

P < .001 by the log-rank test for the comparison of the outcome between groups at 90 days.

Thrombosis Risk

Reprinted with permission from:
Kucher N, et al. *N Engl J Med*. 2005;352:969-977.

theheart.org MedscapeCME

Resultados

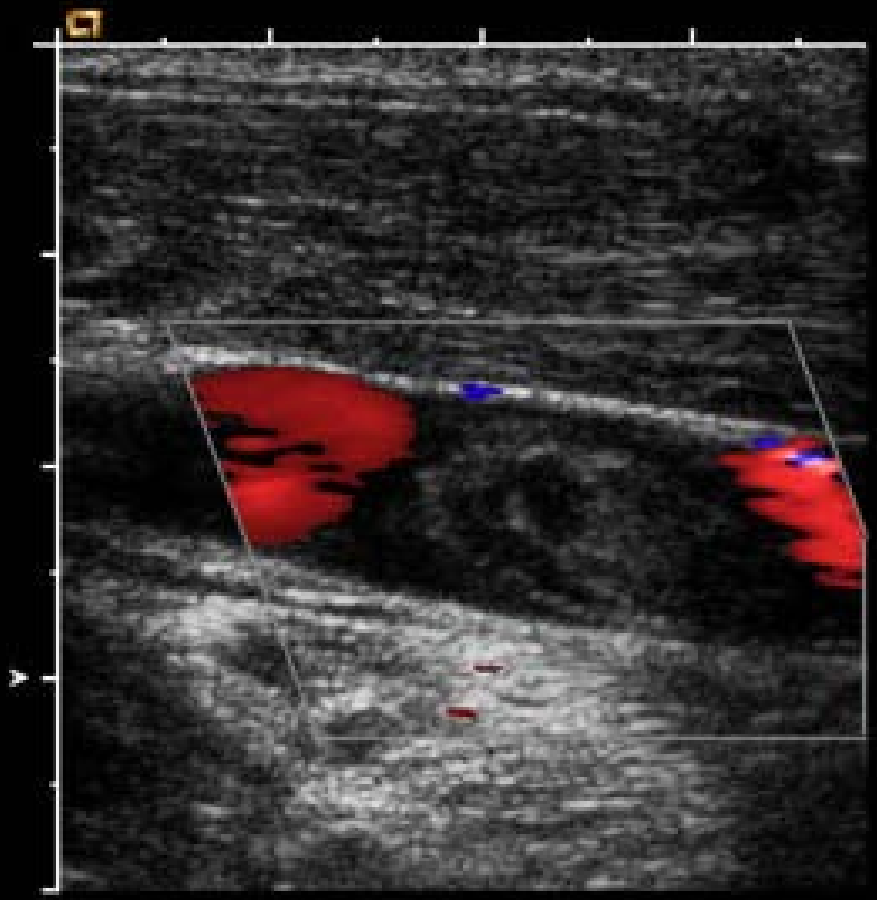
- Con un punto de corte de 7 (alto riesgo) el instrumento permite :

COHORTE	DERIVACIÓN	VALIDACIÓN
SENSIBILIDAD	40%	35.7%
ESPECIFICIDAD	88%	89.6%
VALOR PREDICTIVO NEGATIVO	98.5%	98.5%
VALOR PREDICTIVO POSITIVO	7.1%	6.7%

- El análisis de Hosmer-Lemeschow indica que no hubo diferencias en el rendimiento del instrumento, la precisión del mismo y la asignación de categorías entre ambas cohortes.

Conclusión

En resumen, este modelo puede identificar pacientes con un riesgo de ETV a 2.5 meses plazo de un 7%, lo cual permitiría seleccionar a pacientes ambulatorios de alto riesgo que pudieran beneficiarse de profilaxis anti ETV.



Trombosis Venosa Profunda

Ultrasound Clinics - Volume 4, Issue 2
(April 2009)

Table 1. Reported Incidence of VTE in Large Studies of Pooled Patients With Cancer

First Author	Stage	Type of Study	Years	Population	No. of Patients	Median Follow-Up	Incidence (%)	Risk Factors
Levitan[12]	NA	Retrospective cohort	1984-1990	Hospitalized medicare	1,211,944	NA	0.6	Type of cancer
Sallah[5]	I-IV	Retrospective cohort	1993-2000	Hospitalized with solid tumors	1,041	26 months	7.8	Type of cancer Advanced stage
Stein[3]	NA	Retrospective cohort	1979-1999	Hospitalized	40,787,000	NA	2.0	Type of cancer Year of hospitalization
Agnelli[6]	I-IV	Prospective cohort	1999-2002	Oncologic surgery	2,373	35 days	2.1	Age $\geq$ 60 years Previous VTE Advanced stage Immobility $>$ 3 days Anesthesia $\geq$ 2 hours
Khorana[13]	NA	Retrospective cohort	1995-2002	Hospitalized neutropenic	66,106	8 days	5.4	Age $\geq$ 65 years Comorbidity Type of cancer
Chew[4]	I-IV	Retrospective record linkage cohort	1993-1995	Hospitalized	235,149	2 years	1.6	Race Type of cancer Advanced stage
Blom[14]	I-IV	Retrospective record linkage cohort	1986-2002	Various	66,329	6 months	3.2	Type of cancer Advanced stage Chemotherapy Hormonal therapy
Khorana[2]	NA	Retrospective cohort	1995-2003	Hospitalized	1,015,598	8 days	4.1	Age $\geq$ 65 years Race Female sex Comorbidity Type of cancer Chemotherapy Year of hospitalization
Khorana[15]	I-IV	Prospective cohort	2002-2005	Ambulatory, receiving chemotherapy	4,066	73 days	2.2	Type of cancer BMI $\geq$ 35kg/m^2 Platelet count $\geq$ 350,000/μL Hemoglobin $<$ 10 g/dL and/or erythropoiesis-stimulating agents Leukocyte count $>$ 11,000/μL

Abbreviations: VTE, venous thromboembolism; NA, not available; BMI, body mass index.

Table 3. Therapeutic Options for Initial Treatment of Venous Thromboembolism in Patients With Cancer

Medication	Dose Regimens
Low molecular weight heparin	
Dalteparin	100 units/kg sc every 12 h
	200 units/kg sc daily
Enoxaparin	1 mg/kg sc every 12 h
	1.5 mg/kg sc daily
Renal insufficiency	1 mg/kg sc daily
Tinzaparin	175 units/kg sc daily
Pentasaccharide	
Fondaparinux	5 mg (< 50 kg)
	7.5 mg (50-100 kg)
	10 mg (> 100 kg)
Unfractionated heparin	80 unit/kg IV bolus followed by 18 unit/kg/h IV infusion adjusted to aPTT-based therapeutic range

Abbreviations: sc, subcutaneous; IV, intravenous; aPTT, activated partial thromboplastin time.

Table 4. Medications That Can Influence Vitamin K Antagonists

Increase in the International Normalized Ratio	Decrease in the International Normalized Ratio
Alcohol	Azathioprine
Amiodarone	Barbiturates
Anabolic steroids	Carbamazepine
Broad-spectrum antibiotics	Chlordiazepoxide
Capecitabine	Cholestyramine
Corticosteroids (eg, prednisone, dexamethasone)	Griseofulvin
Erlotinib	Methimazole
Erythromycin	Mitotane
Fluorouracil	Nafcillin
Fluconazole and other azole antifungals	Phenytoin
Flutamide	Rifampin
Gefitinib	Rifabutin
Gemcitabine	Spironolactone
Ifosfamide	Sucralfate
Imatinib	Vitamin K and vitamin K–rich foods
Isoniazid	
Metronidazole	
Omeprazole	
Piroxicam	
Propafenone	
Propranolol	
Quinidine	
Sulfinpyrazone	
Trastuzumib	
Trimethoprim/sulfamethoxazole	

NOTE. List is not all inclusive.

¿ Cumarínicos ?

Tratamiento del Tromboembolismo Venoso en pacientes con Cáncer.

- En pacientes con cáncer y Enfermedad Tromboembólica Aguda se recomienda iniciar tratamiento con HBPM subcutánea ajustada por kilos de peso. En pacientes con Insuficiencia Renal Severa (Clearance de Creatinina <25 a 30 ml/min) se sugiere HNF o HBPM monitorizando niveles de Xa [Evidencia Nivel III, Recomendación B].

Critical Reviews in Oncology/Hematology 59 (2006) 194–204

Tratamiento del Tromboembolismo Venoso en pacientes con Cáncer.

- Se recomienda mantener tratamiento en pacientes sin neoplasia activa con HBPM subcutánea por al menos 3 a 6 meses [Evidencia Nivel I, Recomendación A].
- En pacientes con neoplasia activa se recomienda mantener tratamiento con HBPM subcutánea hasta resolver la patología [Evidencia Nivel III, Recomendación C].

Critical Reviews in Oncology/Hematology 59 (2006) 194–204

Tratamiento del Tromboembolismo Venoso en pacientes con Cáncer.

- La terapia anticoagulante en pacientes con enfermedad tromboembólica recurrente, en particular si se ha mantenido INR terapéutico (INR 2.0 a 3.0), no está del todo estandarizada.
- Si la recurrencia ocurre con INR en rango NO terapéutico se recomienda manejar con HBPM o HNF y luego reasumir TACO logrando INR en rango terapéutico.

Critical Reviews in Oncology/Hematology 59 (2006) 194–204

Tratamiento del Tromboembolismo Venoso en pacientes con Cáncer.

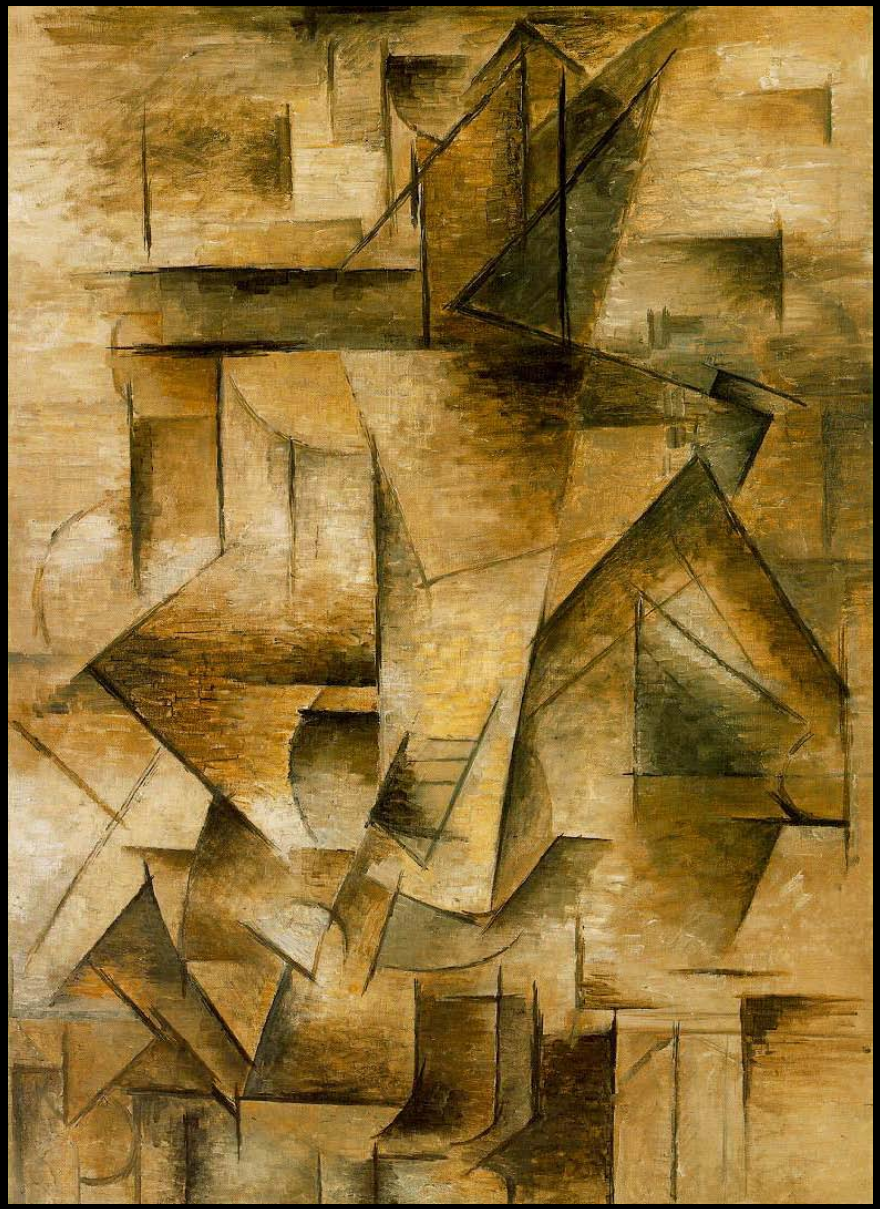
- Si la recurrencia ocurre con HBPM fuera de rango terapéutico se recomienda manejar con HBPM full dosis y mantenerla en el tiempo [Evidencia Nivel II, Recomendación B].
- En pacientes con cáncer y Contraindicaciones al tratamiento anticoagulante o con TEP recurrente DURANTE la anticoagulación se recomienda instalar un Filtro de Vena Cava Inferior. [Evidencia Nivel I, Rec A].

Critical Reviews in Oncology/Hematology 59 (2006) 194–204

Table 5. Contraindications to Outpatient Treatment of Venous Thromboembolism

Active bleeding or high risk of bleeding
Recent surgery (within 7 days)
Cardiopulmonary instability
Severe symptomatic venous obstruction
High risk pulmonary embolism*
Thrombocytopenia (platelets $< 50{,}000/\mu L$)
Medical/surgical condition requiring inpatient management
Medical non-compliance
Geographical or telephone inaccessibility
Poor hepatic function (international normalized ratio ≥ 1.5)
Unstable renal function (eg, rising serum creatinine)
Poor home health care support environment

NOTE. List may not be all inclusive.
*See Tables 6 to 8.



… Volverá ?

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

NEJM 349;2:146-153, July 10, 2003

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., Michael Gent, D.Sc. and 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

The NEW ENGLAND JOURNAL of MEDICINE

"HEPARINA DE BAJO PESO MOLECULAR VS CUMARÍNICOS PARA PREVENIR TROMBOEMBOLISMO VENOSO RECURRENTE EN PACIENTES CON CÁNCER"

Table 3. Primary Efficacy Outcome Events.

Event	Dalteparin (N=336)	Oral Anticoagulant (N=336)
	no. of patients	
Deep-vein thrombosis alone	14	37
Nonfatal pulmonary embolism	8	9
Fatal pulmonary embolism	5	7
Total	27	53

Primary Efficacy Outcome Events

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

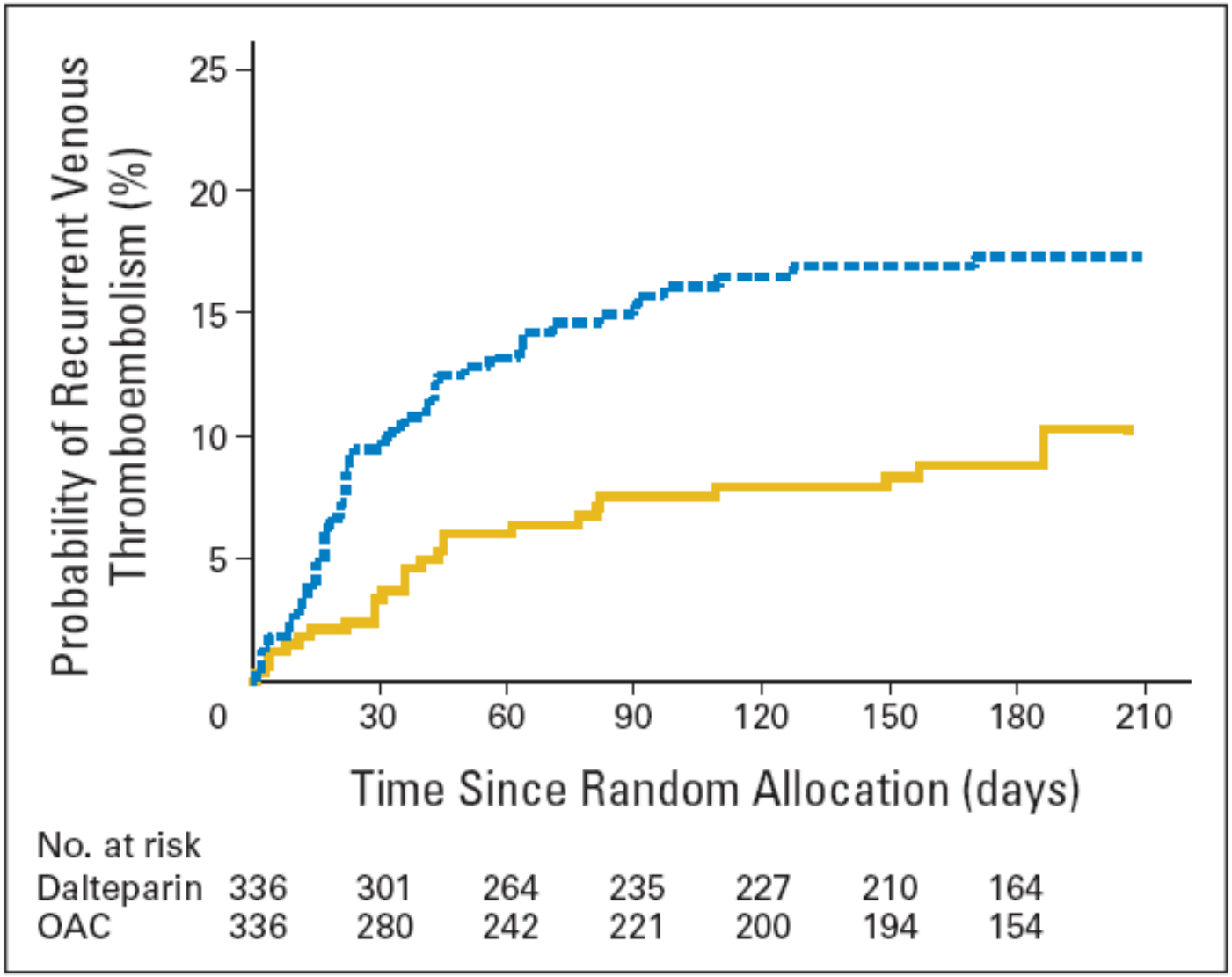
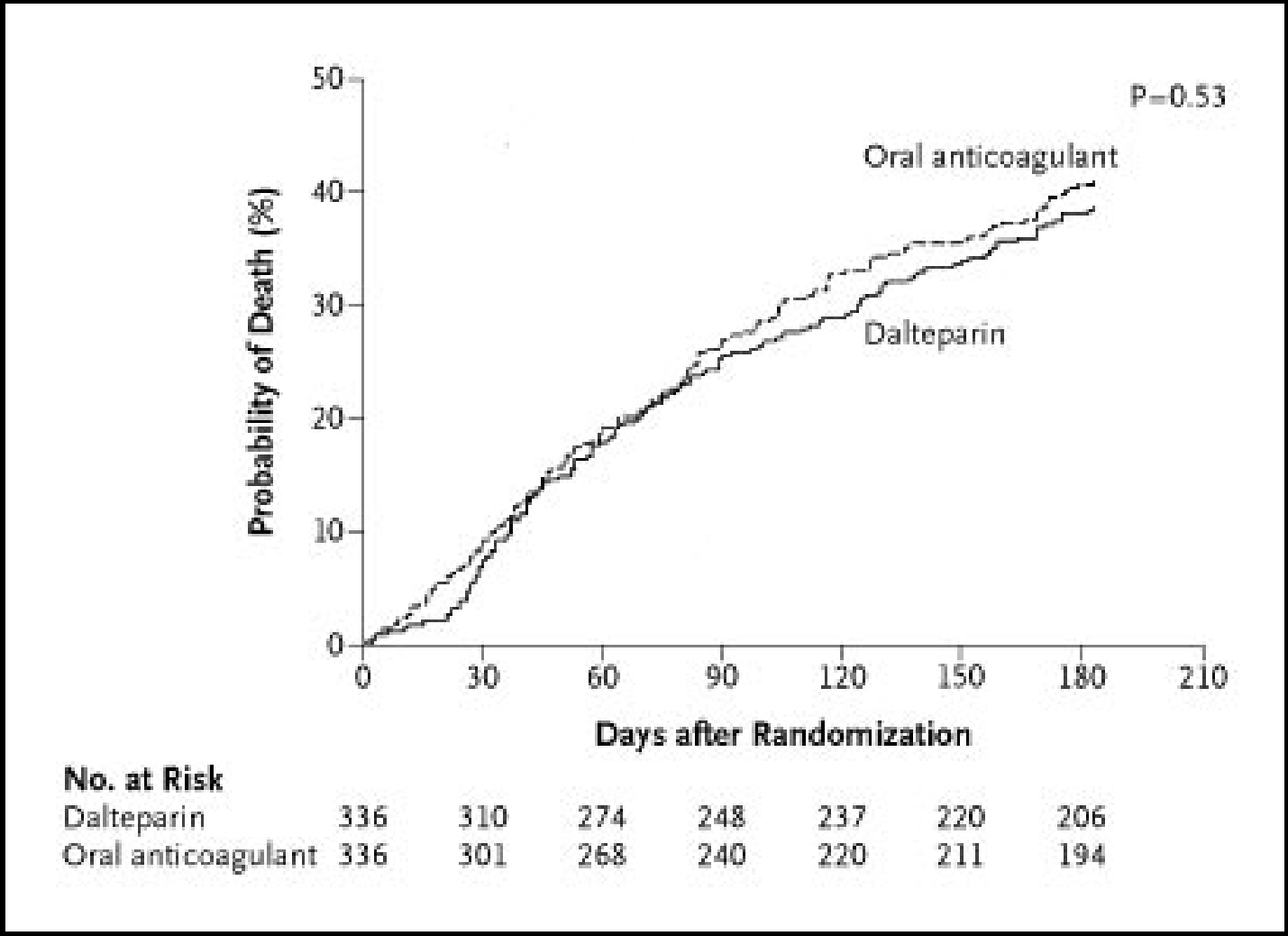


Fig 1. Cumulative risk of recurrent venous thromboembolism in patients treated with dalteparin versus vitamin K antagonist. Blue line indicates oral anticoagulant (OAC); gold line indicates dalteparin. Reprinted with permission.[7]

Kaplan-Meier Estimates of the Probability of Death from All Causes among Patients with Cancer, According to Whether They Received Secondary Prophylaxis with Dalteparin or Oral Anticoagulant Therapy for Acute Venous Thromboembolism



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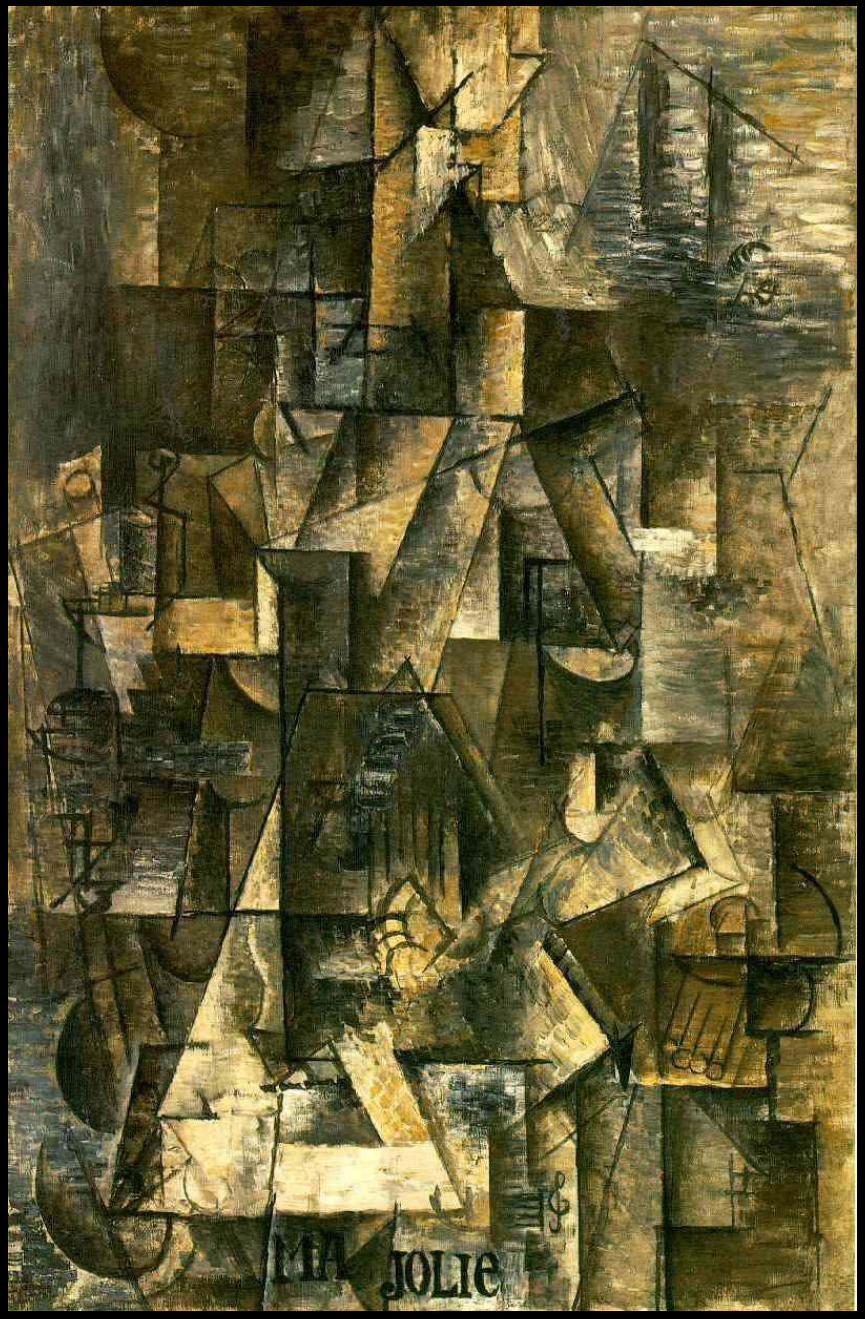
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Table 1. Clinical Trials of Long-Term Anticoagulation for the Prevention of Recurrent VTE in Cancer Patients

Study and Treatment Regimen	No. of Patients Evaluable for the Primary Outcome	Event Rates Reported During Treatment Period (%)			*P* for Primary Outcome
		Recurrent VTE	Major Bleeding	Death	
Lee et al,[7] 2003					.002*
Dalteparin (200 U/kg for 5-7 days) + vitamin K antagonist (INR 2-3 × 6 months)	336	17	4	41	
Dalteparin (200 U/kg OD for 1 month), then dalteparin (~150 U/kg OD × 5 months)	336	9	6	39	
Hull et al,[10] 2006					NS†
IV UFH (APTT adjusted for 6 days) + warfarin (INR 2-3 × 3 months)	100	10	7	19	
Tinzaparin (175 U/kg OD for 3 months)	100	6	7	20	
Meyer et al,[8] 2002					.09‡
Enoxaparin (1.5 mg/kg OD for at least 4 days) + warfarin (INR 2-3 × 3 months)	71	21.1		22.7	
Enoxaparin (1.5 mg/kg OD for 3 months)	67	10.5		11.3	
Deitcher et al,[9] 2006					NS§
Enoxaparin (1 mg/kg BID for 5 days) + warfarin (INR 2-3 for 180 days)	30	10.0	2.9	8.8	
Enoxaparin (1 mg/kg BID for 5 days), then enoxaparin (1 mg/kg OD for 175 days)	29	6.9	6.5	6.5	
Enoxaparin (1 mg/kg BID for 5 days), then enoxaparin (1.5 mg/kg OD for 175 days)	32	6.3	11.1	19.4	

Abbreviations: VTE, venous thromboembolism; INR, international normalized ratio; OD, once daily; NS, not significant; IV, intravenous; UFH, unfractionated heparin; APTT, activated partial thromboplastin time; BID, twice a day.

*Primary outcome of cumulative incidence of objectively documented recurrent VTE was assessed at 6 months. Hazard ratio in the dalteparin group compared with the control group was 0.48 (95% CI, 0.30 to 0.77; log-rank test, $P = .002$).

†Primary outcome measure of objectively documented recurrent VTE or death was assessed at 3 and 12 months. There was no significant difference between treatment groups at the end of study treatment at 3 months (difference = −4.0%; 95% CI, −12.0% to 4.1%).

‡Primary outcome was a composite end point of objectively documented recurrent VTE or major bleeding. There was no significant difference between treatment groups, with a relative risk of 2.02 (95% CI, 0.88 to 4.65).

§Primary objective was to evaluate the feasibility of recruitment and compliance with long-term (180 days) injections of enoxaparin. No difference was observed in overall compliance, with an average rate of 95% among all groups.

Table 2. Examples of LMWH Regimens Used for Treatment of Cancer-Associated Thrombosis

LMWH	Initial Period	Long-Term Treatment
Dalteparin	Prefilled syringe according to weight scale once daily (4 weeks): 45-56 kg = 10,000 U; 57-68 kg = 12,500 U; 69-82 kg = 15,000 U; 83-90 kg = 18,000 U	Prefilled syringes according to weight scale (weeks 5-26): 45-56 kg = 7,500 U; 57-68 kg = 10,000 U; 69-82 kg = 12,500 U; 83-90 kg = 15,000 U; 91-100 kg = 18,000 U
Dalteparin	Multidose vial 25,000 U/mL (4 weeks): 200 U/kg once daily	Multidose vial 25,000 U/mL (weeks 5-26): 150 U/kg once daily
Dalteparin	Multidose vial 25,000 U/mL (1 week): 200 U/kg once daily	Multidose vial 25,000 U/mL (week 2 through third month): 10,000 U once daily
Tinzaparin	Prefilled syringe* according to weight scale once daily (4 weeks): 45-56 kg = 10,000 U; 57-80 kg = 14,000 U; 81-110 kg = 18,000 U	Prefilled syringes* according to weight scale (weeks 5-26): 45-56 kg = 10,000 U; 57-80 kg = 14,000 U; 81-110 kg = 18,000 U
Tinzaparin	Multidose vial 20,000 U/mL (4 weeks): 175 U/kg once daily	Multidose vial 20,000 U/mL (5-26 weeks): 175 U/kg once daily
Enoxaparin	Prefilled syringe according to weight scale once daily (4 weeks): 46-59 kg = 80 mg; 60-72 kg = 100 mg; 73-89 kg = 120 mg; 90-110 kg = 150 mg	Prefilled syringes according to weight scale (weeks 5-26): 46-59 kg = 80 mg; 60-72 kg = 100 mg; 73-89 kg = 120 mg; 90-110 kg = 150 mg
Enoxaparin	Multidose vial 300 mg/3 mL (4 weeks): 1.5 mg/kg once daily	Multidose vial 300 mg/3 mL (weeks 5-26): 1.5 mg/kg once daily

NOTE. Not all of these regimens are approved by regulatory health agencies or based on published studies.
Abbreviation: LMWH, low molecular weight heparin.
*Syringes are graduated so finer dose adjustments can be made.

Anticoagulación y Pronóstico en pacientes con cáncer

- La información disponible es aún limitada para recomendar o no la anticoagulación como una manera de influenciar el pronóstico del cáncer [Evidencia Nivel II, Recomendación C].

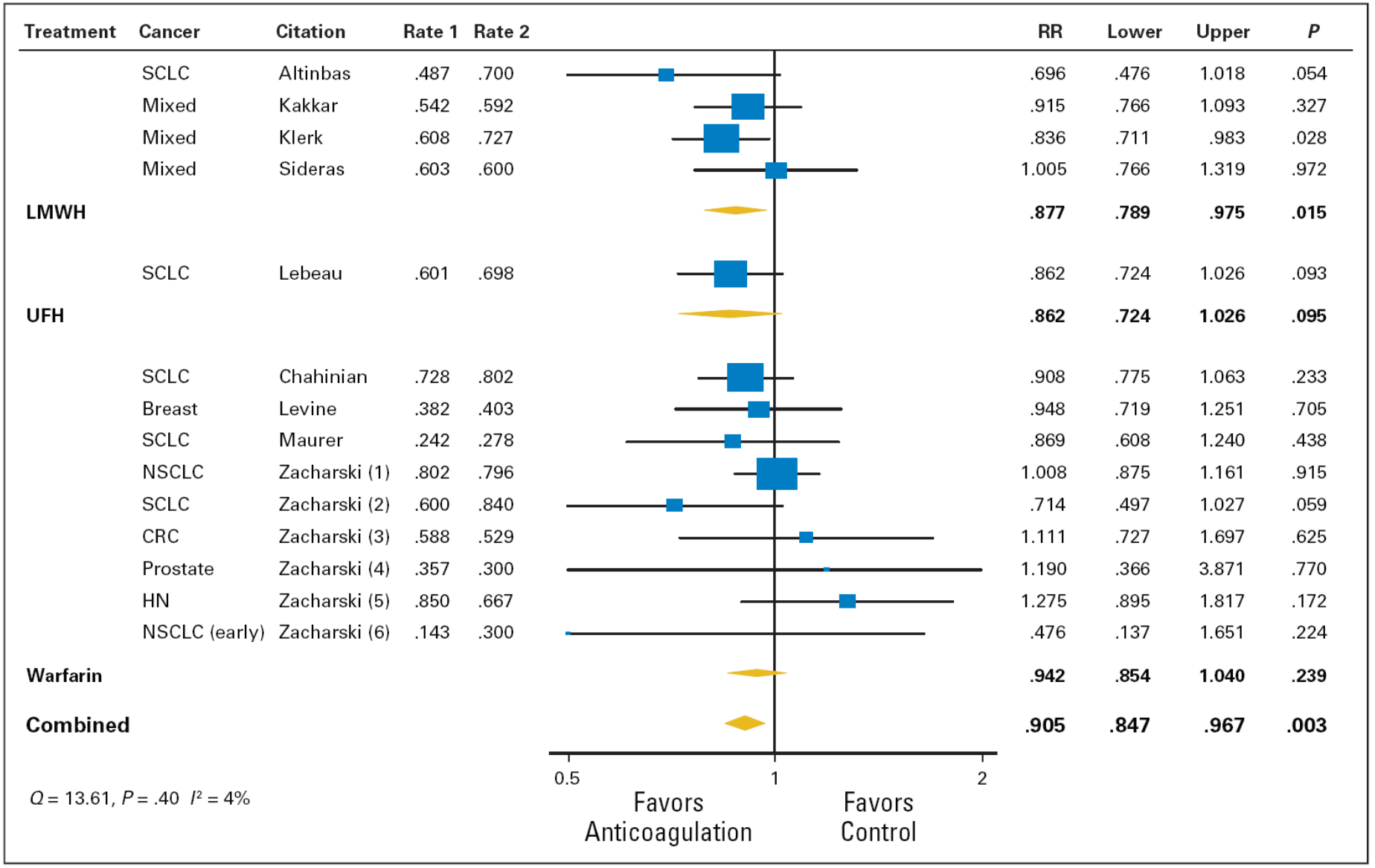


Fig 3. Meta-analysis of anticoagulation studies evaluating the impact on mortality in cancer patients without venous thrombosis: 1-year overall mortality by type of anticoagulation. SCLC, small-cell lung cancer; LMWH, low molecular weight heparin; UFH, unfractionated heparin; NSCLC, non–small-cell lung cancer; CRC, colorectal cancer; HN, head and neck cancer. Adapted from Kuderer et al.[176]

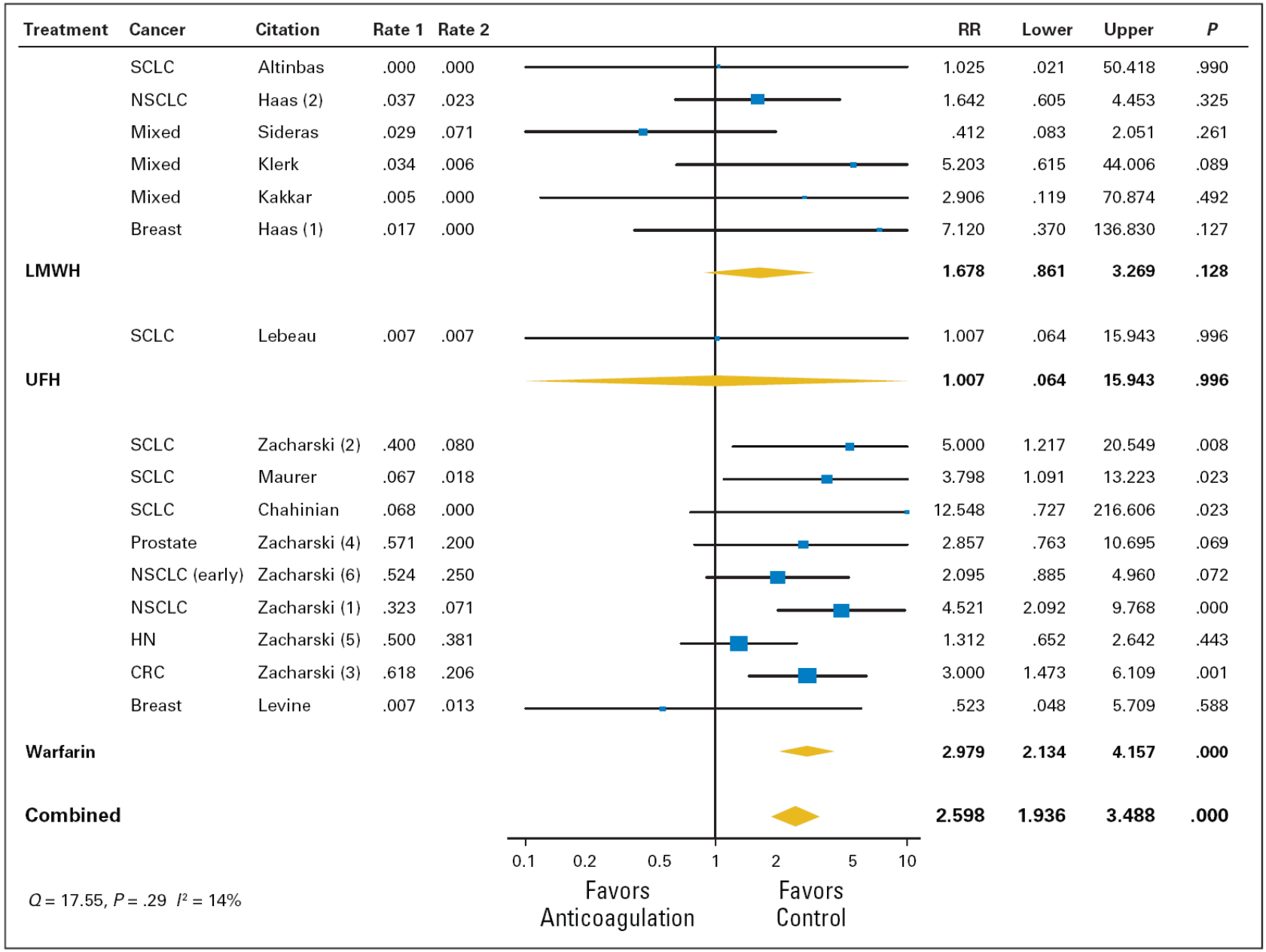
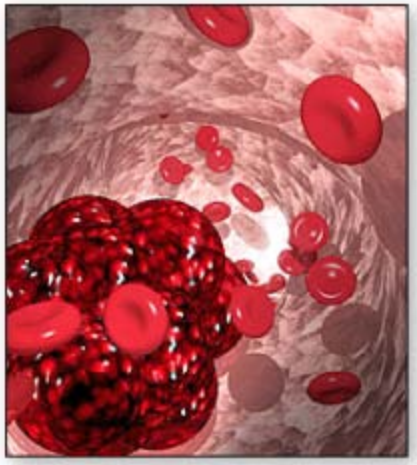
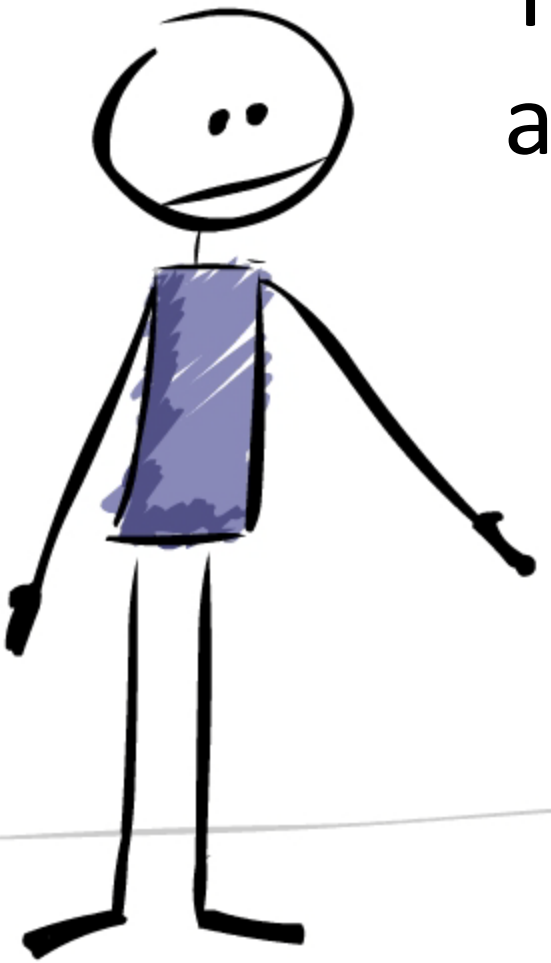


Fig 4. Meta-analysis of anticoagulation studies evaluating the impact on mortality in cancer patients without venous thrombosis: major bleeding complications by type of anticoagulation. SCLC, small-cell lung cancer; NSCLC, non–small-cell lung cancer; HN, head and neck cancer; CRC, colorectal cancer. Adapted from Kuderer et al.[176]





Hay algo nuevo
al final del día ?

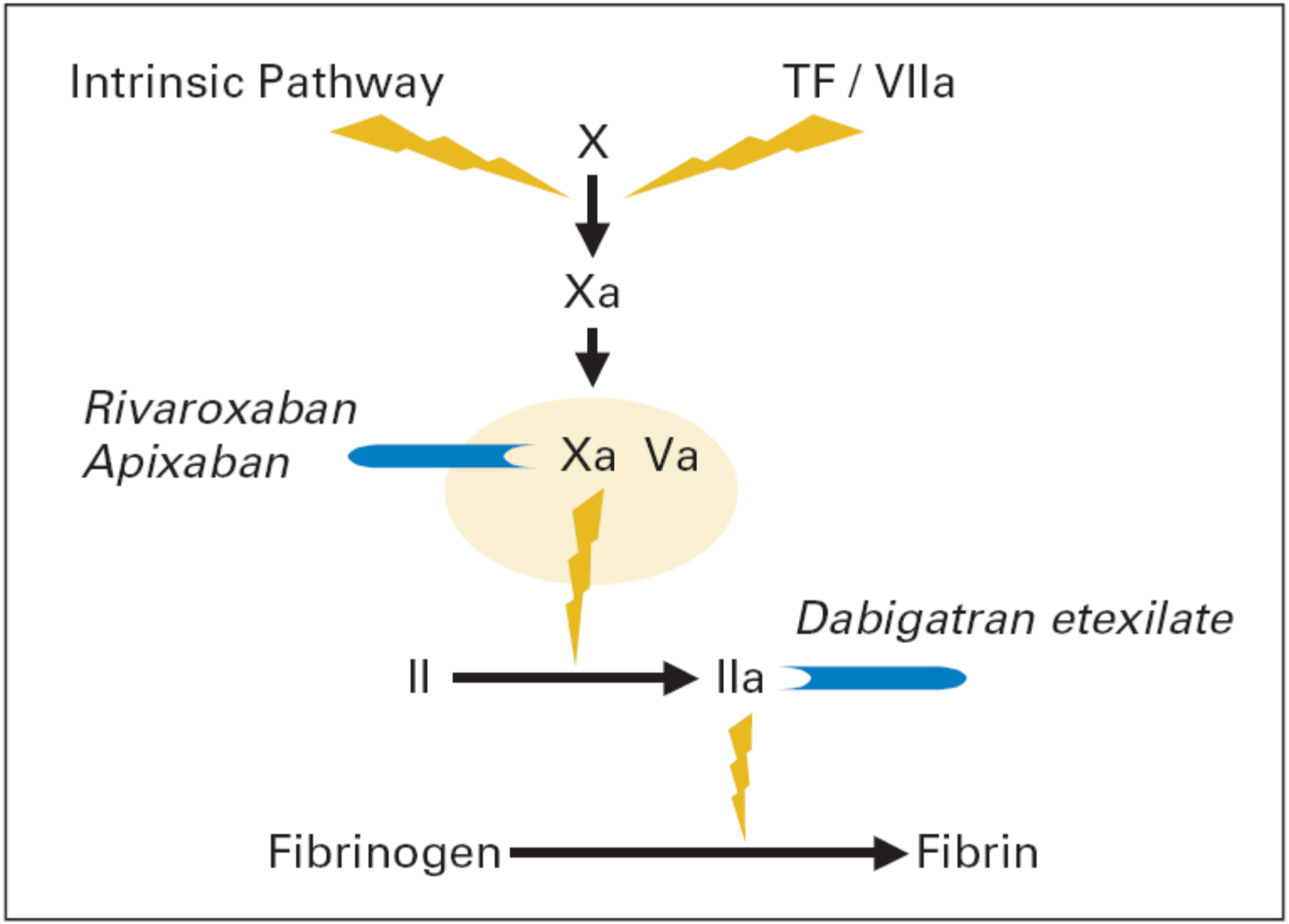


Fig 1. Action of new agents. TF, tissue factor; Xa, activated factor X; Va, activated factor V; VIIa, activated factor VII; IIa, thrombin.

Table 1. Trials of Factor Xa Inhibitors for the Treatment of VTE

Study and Treatment*	Indication	No. of Patients	Outcome	Efficacy (%)	Major Bleeding (%)
Buller (Matisse)[26]	PE		Recurrent VTE at 3 months		
Fondaprinux		1,103		3.9	1.3
LMWH		1,110		5.0	1.1
Buller (Matisse)[27]	DVT		Recurrent VTE at 3 months		
Fondaprinux		1,098		3.9	1.1
LMWH		1,107		4.1	1.2
Agnelli (ODIXa)[28]	DVT		Reduction in clot on ultrasound		
Rivaroxaban		112			
10 mg twice daily				53.0	1.7
20 mg twice daily				59.2	1.7
30 mg twice daily				56.9	3.3
40 mg once daily				43.8	1.7
LMWH		109		45.9	0
Buller (Einstein)[29]	DVT	543	Increase in clot burden on ultrasound and lung scan, or DVT/PE/VTE death		
Rivaroxaban					
20 mg UFH				6.1	5.9
30 mg UFH				5.4	6.0
40 mg UFH				6.6	2.2
LMWH				9.9	8.8
Buller (Botecelli)[30]	DVT	520	Increase in clot burden on ultrasound and lung scan, or DVT/PE/VTE death		
Apixaban					
5 mg twice daily				6.0	8.6
10 mg twice daily				6.5	4.5
20 mg once daily				2.6	8.9†
LMWH				4.2	7.9†

Abbreviations: Factor Xa, activated factor X; VTE, venous thromboembolism; LMWH, low molecular weight heparin; DVT, deep vein thrombosis; PE, pulmonary embolism; UFH, unfractionated heparin.

*Initial therapy followed by 3 months of vitamin K antagonist treatment.

†Major and clinically relevant nonmajor bleeding.


Gracias …