NOVES DIANES ONCOLÒGIQUES I RISC TROMBÒTIC

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Barcelona, 22 de gener de 2016

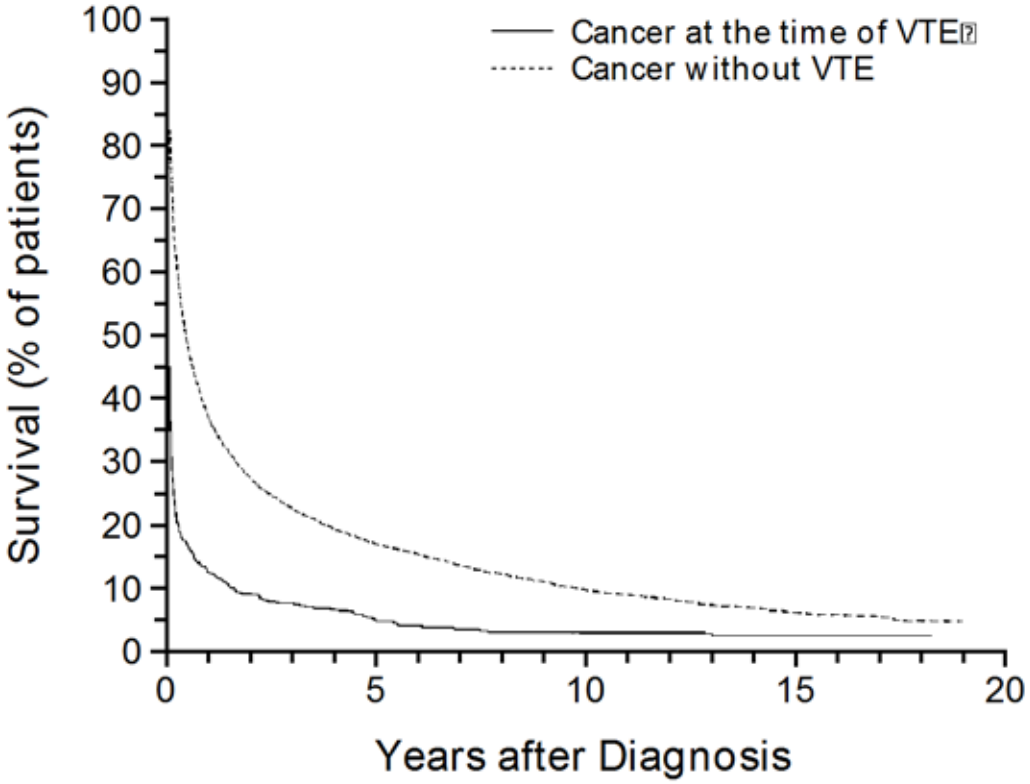
LA ENFERMEDAD TROMBOEMBÓLICA ES LA 2ª CAUSA DE MUERTE EN PACIENTES CON CÁNCER

Cause of death	*n* (%)
All	141 (100)
Progression of cancer	100 (70.9)
Thromboembolism	13 (9.2)
Arterial	8 (5.6)
Venous	5 (3.5)
Infection	13 (9.2)
Respiratory failure	5 (3.5)
Bleeding	2 (1.4)
Aspiration pneumonitis	2 (1.4)
Other	9 (6.4)
Unknown	5 (3.5)

4466 pacientes en curso de QT

Khorana AA. J Thromb Haemost 2007;5:632-4

TEV EMPEORA EL PRONÓSTICO DEL TUMOR



No. at Risk				
Cancer at the time of VTE	668	23	10	3
Cancer without VTE	6668	913	338	87

Sørensen HT, et al. N Engl J Med 2000;343:1846-50

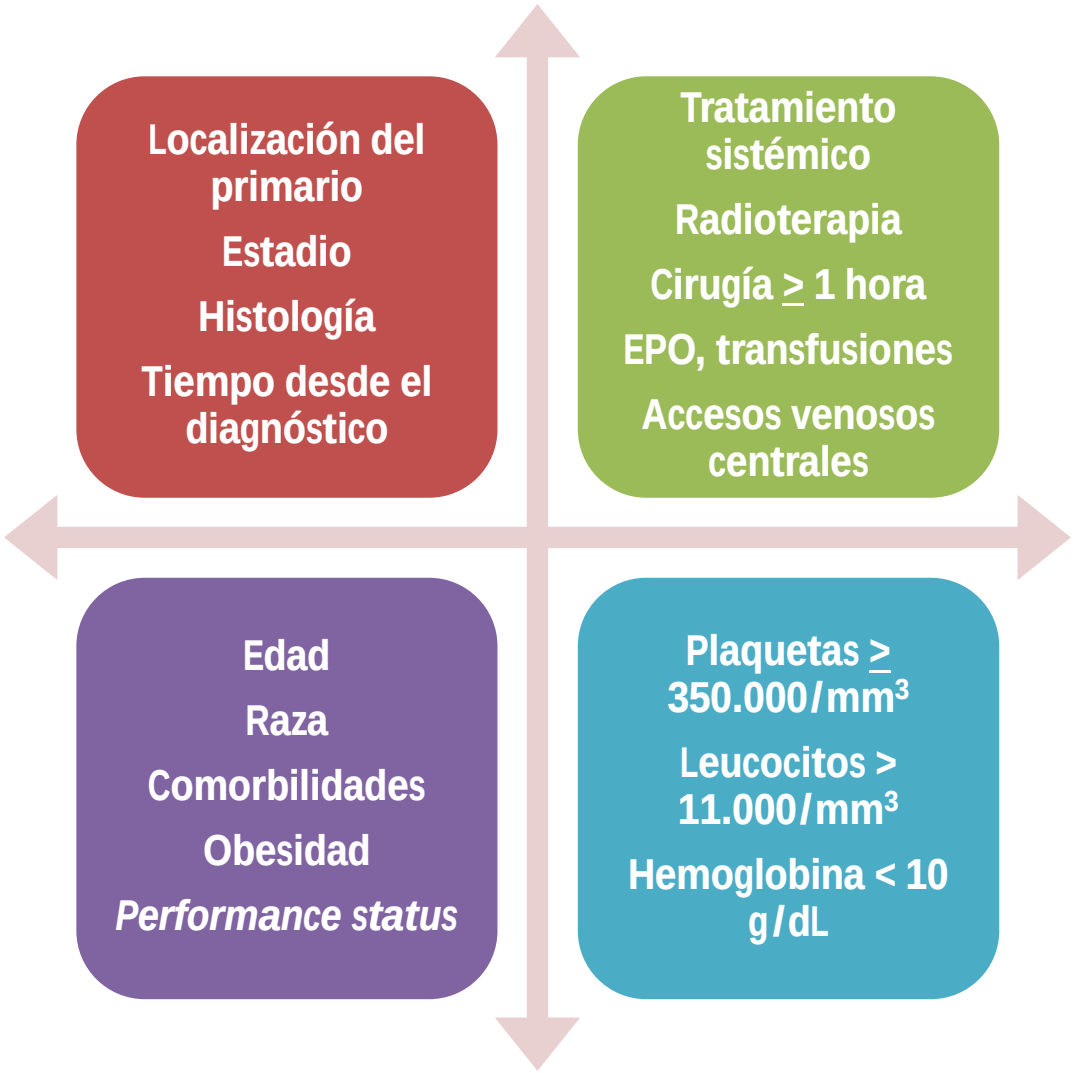
TEV EMPEORA EL PRONÓSTICO DEL TUMOR

Table 4. Effect of Venous Thromboembolism on the Risk of Death Within 1 Year of Cancer Diagnosis Stratified by Stage, Adjusted for Age and Race

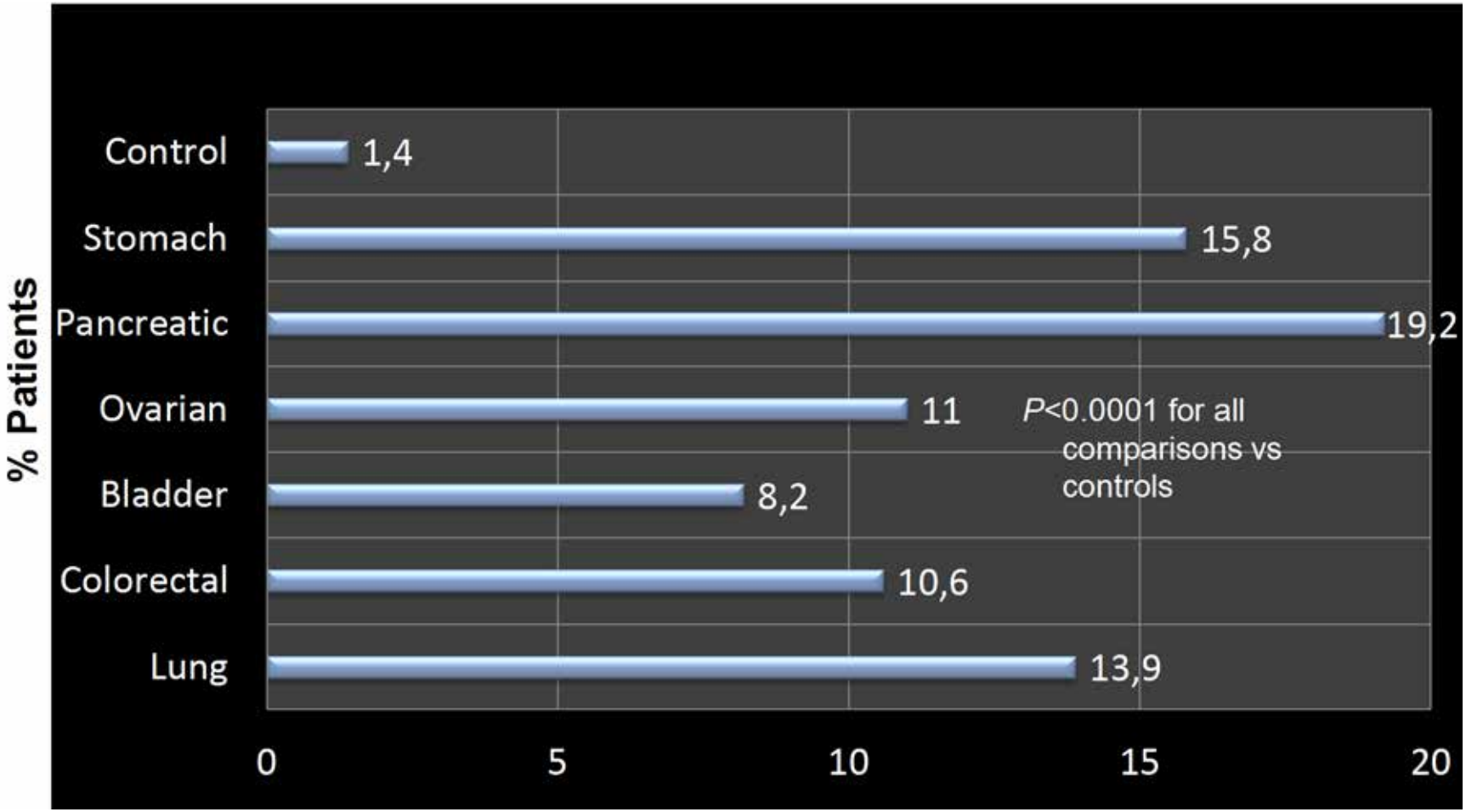
	Hazard Ratio (95% CI), by Stage		
Cancer	**Local**	**Regional**	**Remote**
Prostate	5.6 (3.8-8.5)*	4.7 (1.9-11.5)*	2.8 (1.5-5.0)†
Breast	6.6 (3.7-11.8)*	2.4 (1.3-4.5)†	1.8 (1.1-2.9)‡
Lung	3.1 (2.1-4.5)*	2.9 (2.3-3.5)*	2.5 (2.3-2.7)*
Colon/rectum	3.2 (1.8-5.5)*	2.2 (1.7-3.0)*	2.0 (1.7-2.4)*
Melanoma	14.4 (4.6-45.2)*	NA§	2.8 (1.5-5.3)†
Non-Hodgkin lymphoma	3.2 (1.9-5.3)*	2.0 (1.3-3.2)†	2.3 (1.7-3.1)*
Uterus	7.0 (3.4-14.2)*	9.1 (4.8-17.2)*	1.7 (1.0-3.0)‡
Bladder	3.2 (1.7-6.2)*	3.3 (1.7-6.4)*	3.3 (1.8-6.2)*
Pancreas	2.3 (1.2-4.6)‡	3.8 (2.8-5.1)*	2.3 (1.9-2.7)*
Stomach	2.4 (1.1-5.1)‡	1.5 (1.0-2.1)‡	1.8 (1.4-2.3)*
Ovary	11.3 (2.5-51.7)†	4.8 (1.1-20.4)‡	2.3 (1.7-3.0)*
Kidney	3.2 (1.2-8.8)‡	1.4 (0.6-3.2)	1.3 (0.9-2.0)

Chew HK, et al. Arch Intern Med 2006;166(4):458-64

FACTORES DE RIESGO PARA ETEV RELACIONADA CON CÁNCER

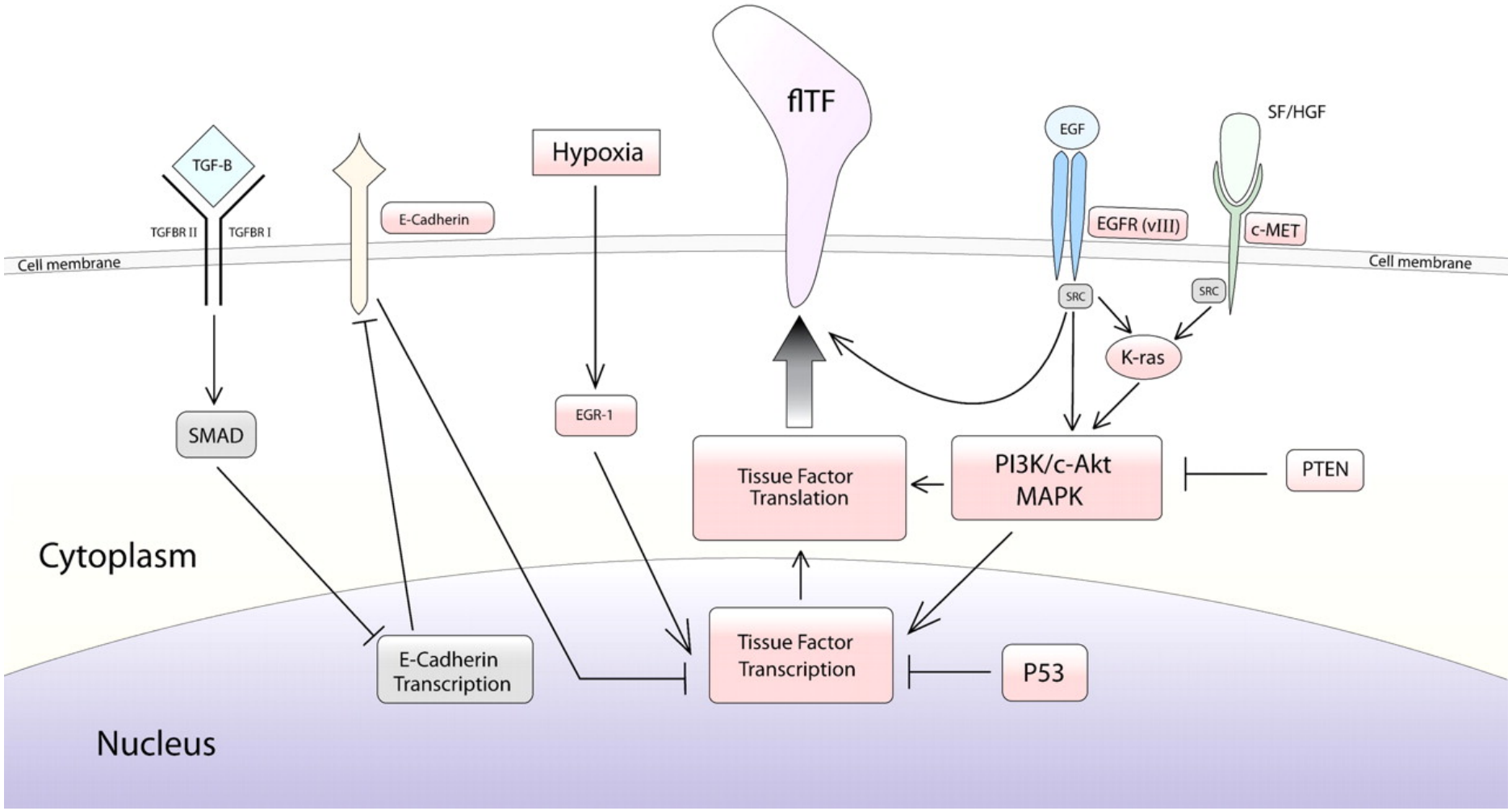


RISK OF VTE BY PRIMARY SITE



Khorana AA, et al. Cancer 2012

DEFINED ONCOGENIC TRANSFORMATIONS DRIVE TF EXPRESSION IN CANCER



Yascha W. van den Berg et al. Blood 2012;119:924-932

MECHANISMS OF CANCER-ASSOCIATED THROMBOSIS

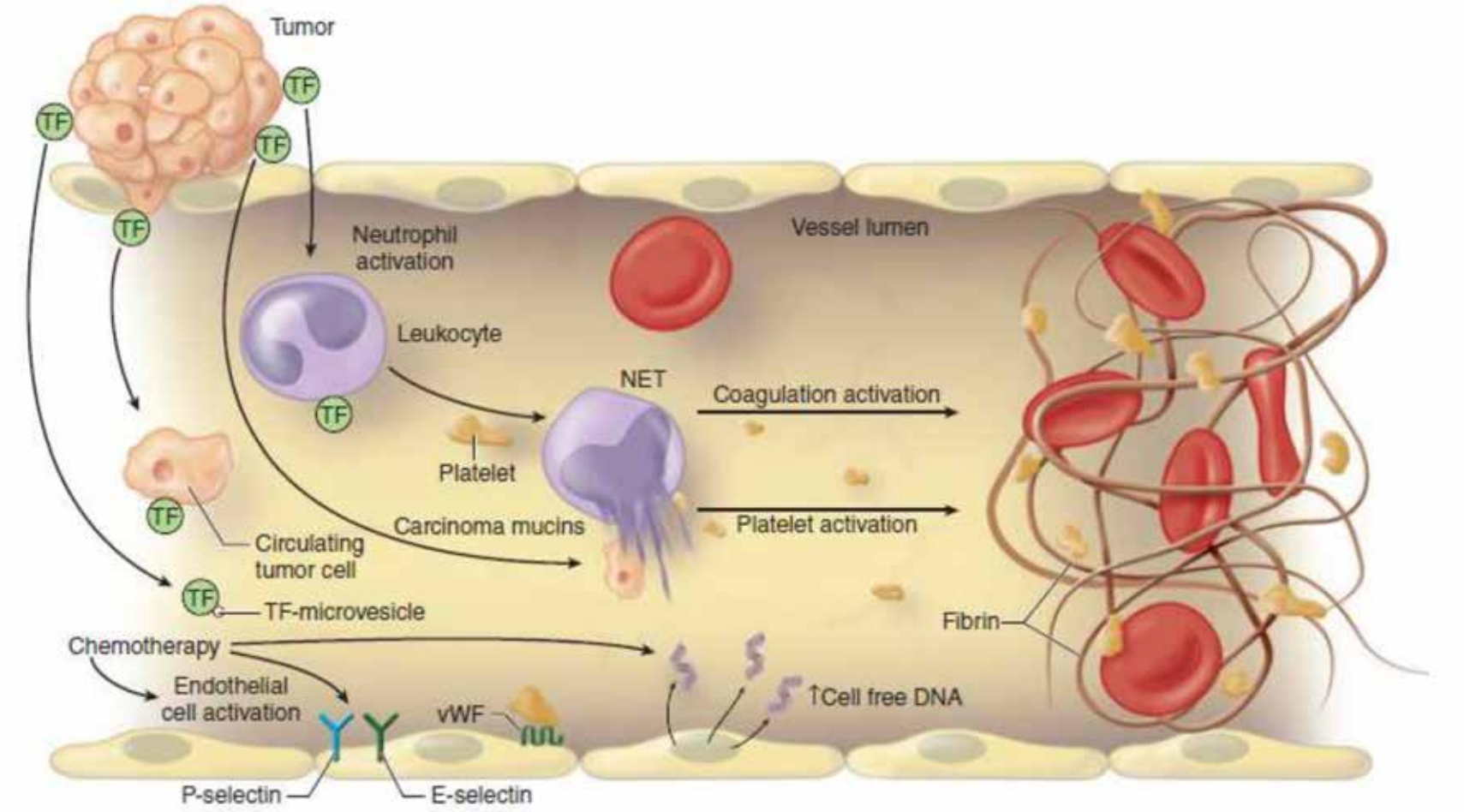


Figure 134.1 Proposed mechanisms for cancer-associated thrombosis. Multiple mechanisms have been postulated including tissue factor upregulation on tumor cell surface as well as release associated with microvesicles into the systemic circulation, platelet activation by carcinoma mucins and other factors, endothelial cell activation by chemotherapy, release of cell-free DNA by chemotherapy, and formation of neutrophil extracellular traps.

Lee and Khorana, DeVita et al (Eds) 10th Ed., 2015

CANCER-ASSOCIATED THROMBOSIS RISK SCORES

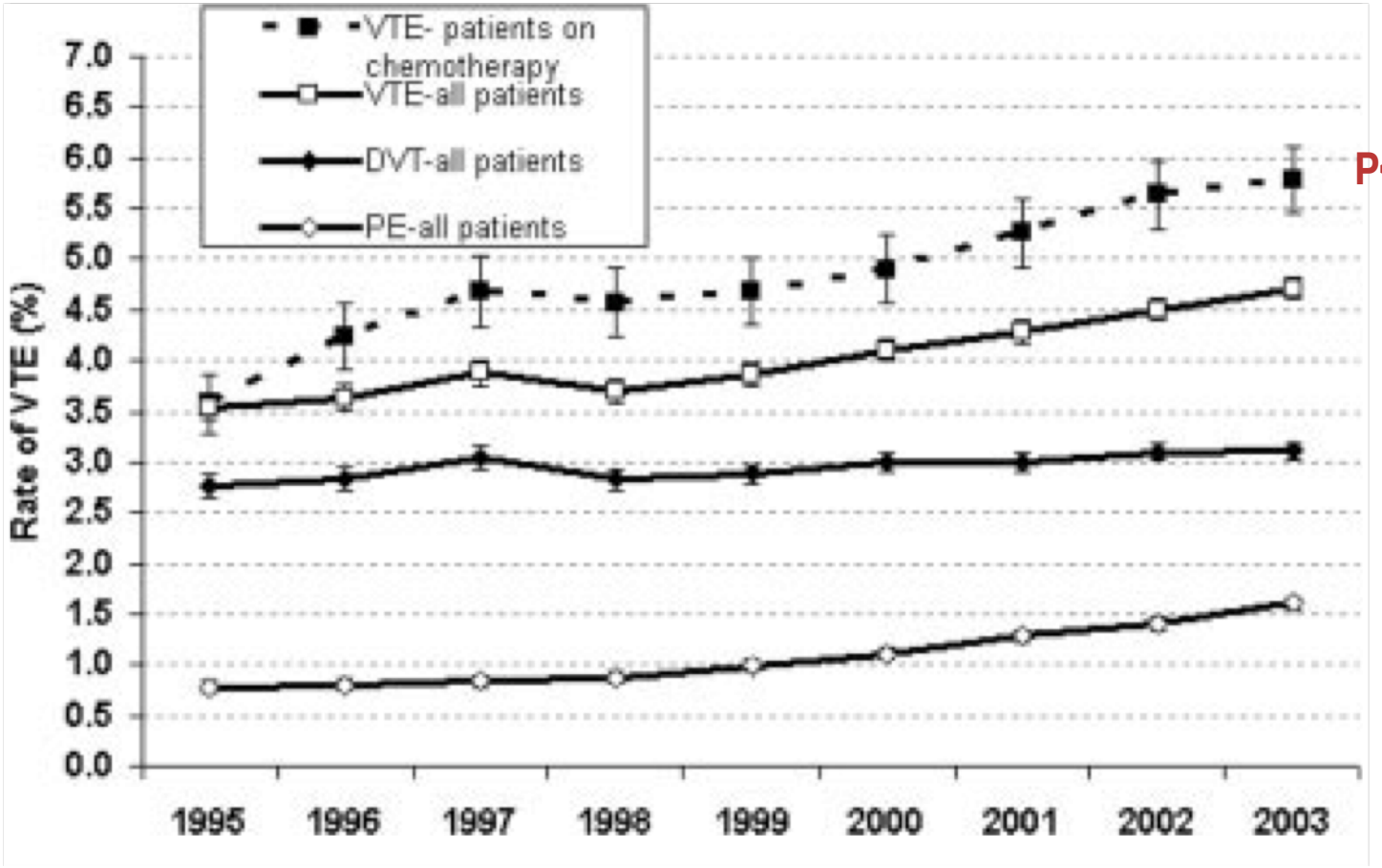
Table 2. Two different risk models for identification of cancer patients at high risk of VTE

Khorana VTE risk assessment score[5]			Points
Site of cancer	Very high risk	Stomach, pancreas	2
	High risk	Lung, lymphoma, gynecologic, bladder, testicular	1
Platelet count		≥350 × 10^9/L	1
Hemoglobin and/or use of erythropoiesis-stimulating agents		<10 g/dL	1
Leukocyte count		>11 × 10^9/L	1
Body mass index		≥35 kg/m^2	1
Vienna VTE risk assessment score,[19] addition of			
D-dimer		≥1.44 μg/mL	1
sP-selectin		≥53.1 mg/mL	1

In the CATS, brain tumors (high-grade glioma) were allocated to the very high risk sites of cancer.

Pabinger I, et al. Blood 2013

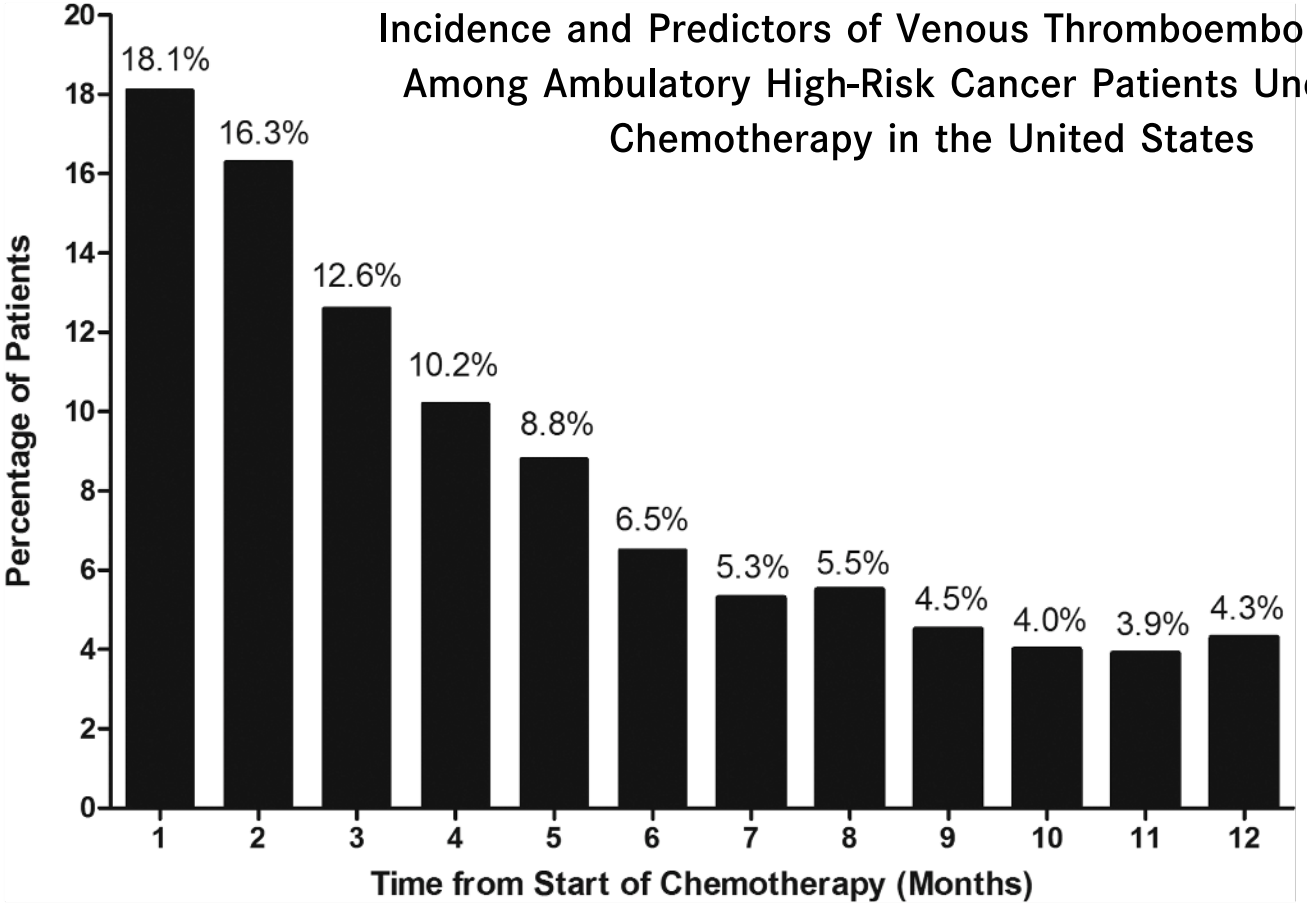
VTE INCREASE IS GREATER IN PATIENTS RECEIVING CHEMOTHERAPY



P<0.0001

Khorana AA, et al. Cancer 2007;110(10):2339-46

VTE OCCURS SINCE THE BEGINNING OF CHEMOTHERAPY



Khorana AA, et al. Cancer 2013;119:648-55

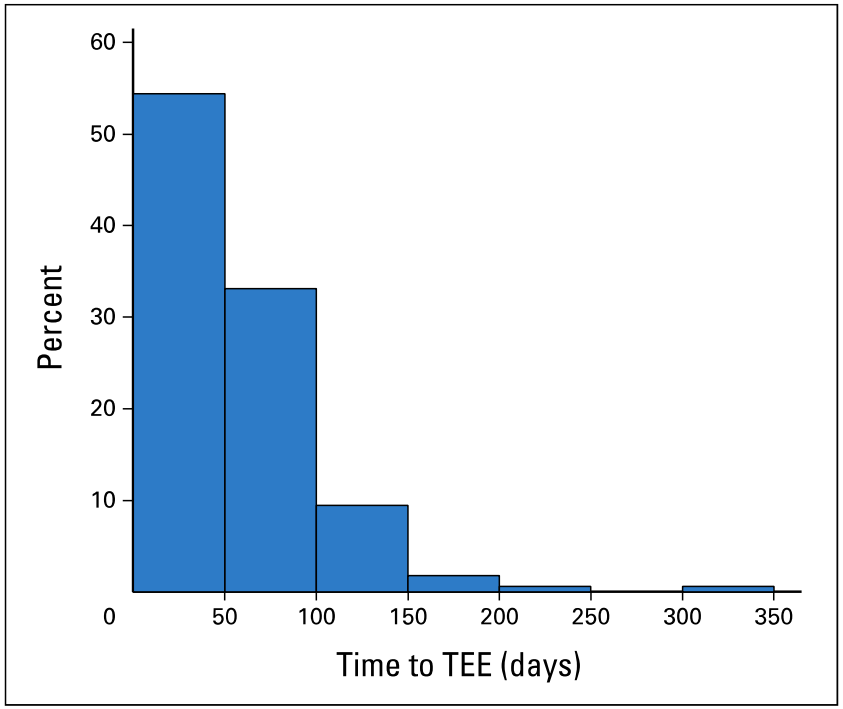
QUIMIOTERAPIA Y RIESGO DE ETE

VOLUME 29 · NUMBER 26 · SEPTEMBER 1 2011
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

Russell A. Moore, Nelly Adel, Elyn Riedel, Manisha Bhutani, Darren R. Feldman, Nora Elsa Tabbara, Gerald Soff, Rekha Parameswaran, and Hani Hassoun

- 932 patients, 169 (18.1%) experienced TEE during treatment or within 4 weeks of the last dose
- Arterial thromboembolism 11.3%
- VTE: PE 39%, DVT 66.3%
- 88% occurred within 100 days of initiation of treatment



Fármaco con más riesgo de ETV: CISPLATINO

Moore RA, et al. J Clin Oncol 2011;29:3466-73

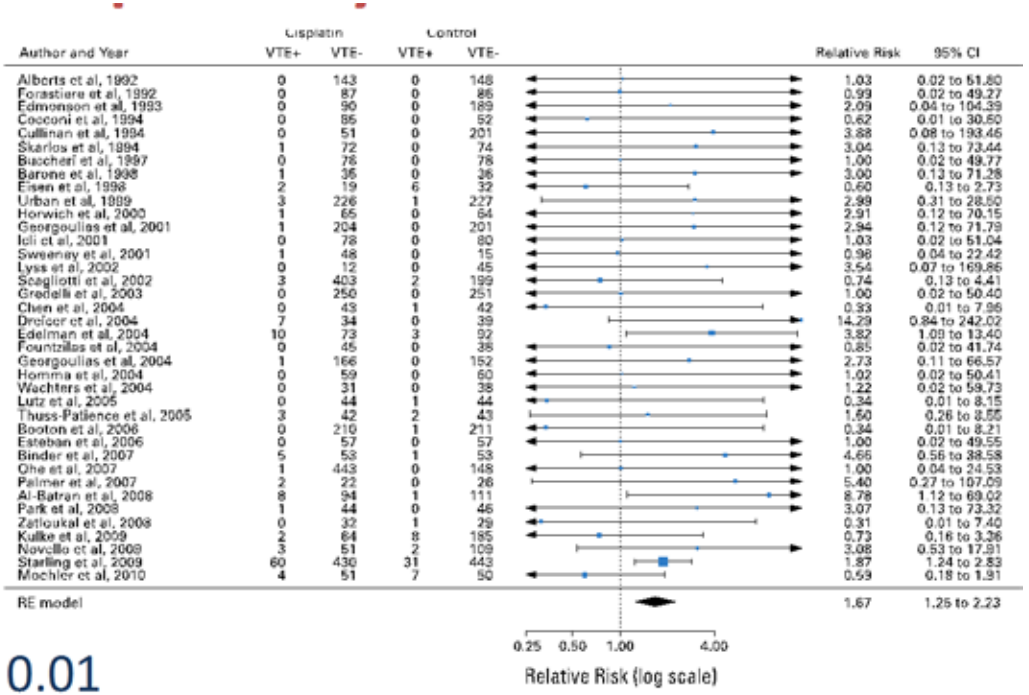
METAANÁLISIS CISPLATINO Y TEV

Published Ahead of Print on November 13, 2012 as 10.1200/JCO.2012.42.4358
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.42.4358

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Risk of Venous Thromboembolism in Patients With Cancer Treated With Cisplatin: A Systematic Review and Meta-Analysis

Seng Seng, Yiyue Liu, Sophia V. Chiu, Tracy Proverbs-Singh, Gina Lesperance, Toni K. Choueiri,



8,216 patients

Various advanced solid tumors

38 randomized controlled trials

Significantly increased risk of VTEs:

RR 1.67; 95% CI, 1.25 to 2.23; p= 0.01

Highest RR of VTEs:

Patients receiving a weekly equivalent cisplatin dose 30 mg/m2 (2.71; 95% CI, 1.17 to 6.30; p=0.02)

Trials reported during 2000 to 2010 (RR 1.72; 95% CI, 1.27 to 2.34; p=0.01

Increase all types of events (PE, DVT and thromboembolism unspecified)

Seng S, et al. J Clin Oncol. 2012 Dec 10;30(35):4416-26

HORMONOTERAPIA Y TEV

Tamoxifeno

- Riesgo ETV: aumento del riesgo 1,5 - 7,1 (Deitcher et al. Cancer 2004)
- Riesgo asociado a la edad

Anastrozol adyuvante, ATAC trial

- Anastrozol 2,8% vs Tam 4,5% eventos tromboembólicos global, RR: 0,61; IC95%: 0,47-0,8); p = 0,0004 (Howell et al. Lancet 2005)

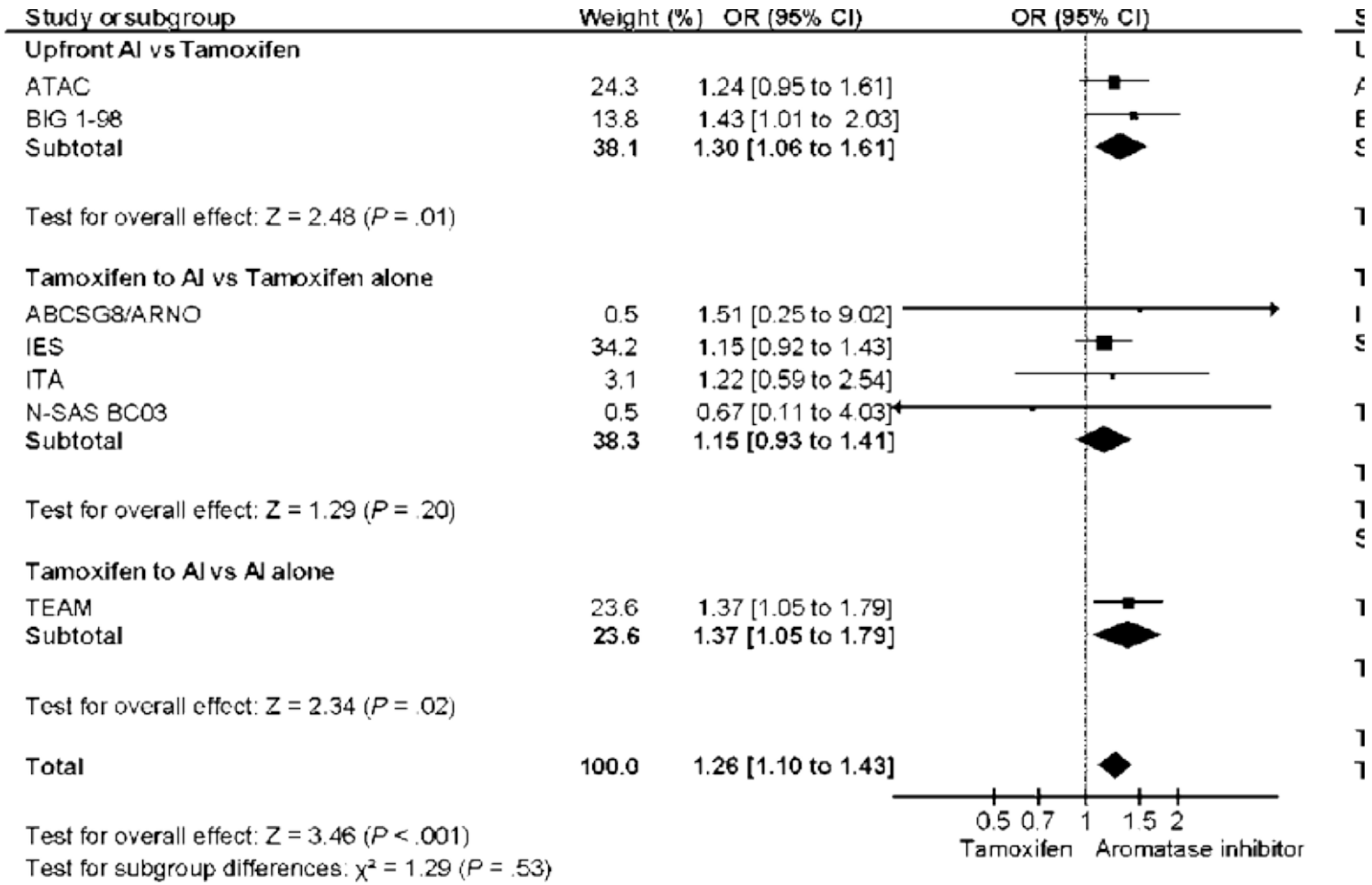
Letrozol adyuvante

- Incidencia de eventos tromboembólicos 1,5-2,1% a 5 años, grado ¾ 0,8%
- Continuación tras 5 años incidencia de eventos tromboembólicos 0,9%
- BIG 1.98 1,5% Let vs 3,5% Tam, p <0,001

Exemestano adyuvante

- TamExe 2% vs 1% Exe, p<0,0001 (Van de Velde et al. Lancet 2011)

HORMONOTERAPIA Y TEV



Amir E, et al. J Natl Cancer Inst. 2011;103(17):1299-309

TERAPIAS ONCOLÓGICAS ACTUALES

- Citostáticos
- Hormonoterapia
- Anticuerpos monoclonales antiangiogénicos
- Anticuerpos monoclonales no antiangiogénicos
- Inhibidores tirosin-kinasa antiangiogénicos
- Inhibidores tirosin-kinasa no antiangiogénicos

PEGPH20 – Hialuronidasa humana recombinante pegilada

PEGPH20 – Hialuronidasa humana recombinante pegilada

- 42% VTE PEGPH20+NP-GEM vs 25% NP-GEM
- Clinical hold, protocol amendment
- Add enoxaparin prophylaxis 40 mg/day 13% - 1 mg/kg/day 0%

ENSAYOS CLÍNICOS Y ETE

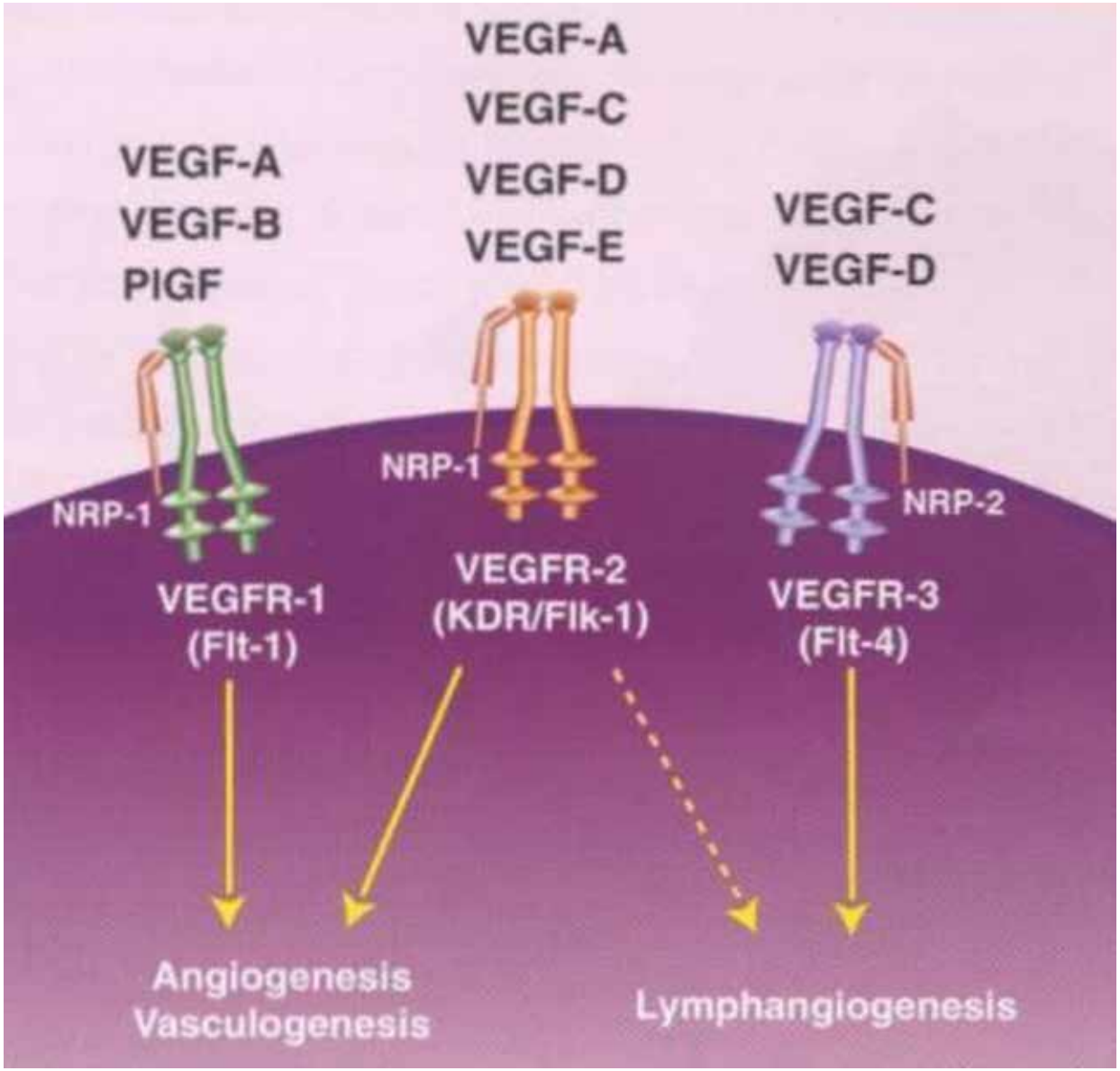
- Actualmente se dispone de pocos ensayos clínicos aleatorizados que hayan analizado de forma pormenorizada la incidencia y probabilidad de ETV y ETA asociada a los tratamientos antitumorales:
  - Localización
  - Tipo de evento (incidental vs sintomático)
  - Tiempo de ocurrencia
  - Posibilidad relación con los tratamientos recibidos
  - Asociación con peor pronóstico

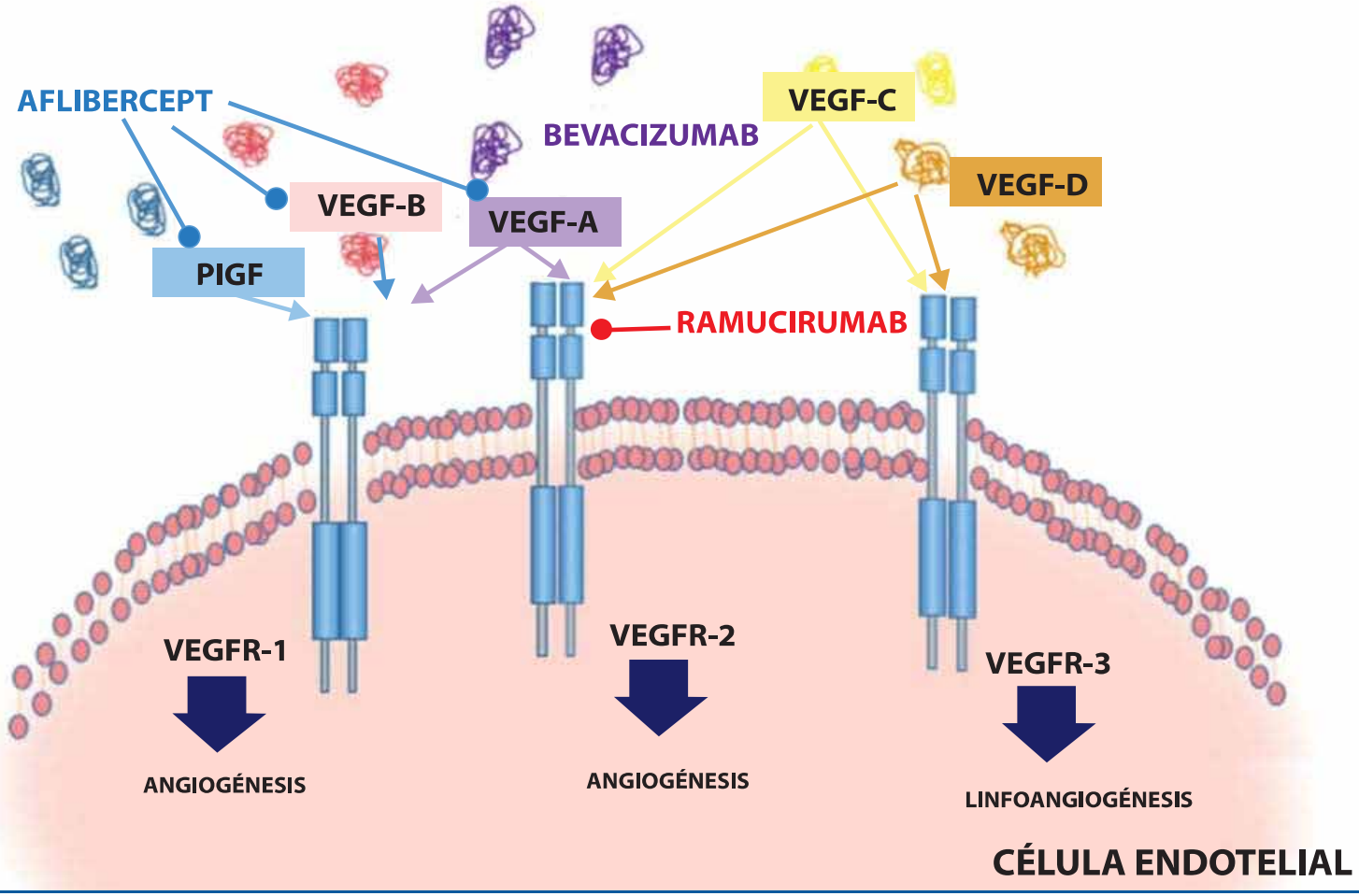
- Infraestimación en la incidencia de ETV en los EC
  - CCR avanzado FOLFIRI: recogida como toxicidad 2 de 27 ensayos

- Ensayos clínicos de poliquimioterapia
  - Análisis de varios fármacos de forma simultánea (asignación complicada)
  - Múltiples factores de riesgo

Mandalà M, et al. Eur J Cancer 2009;45(1):65-73

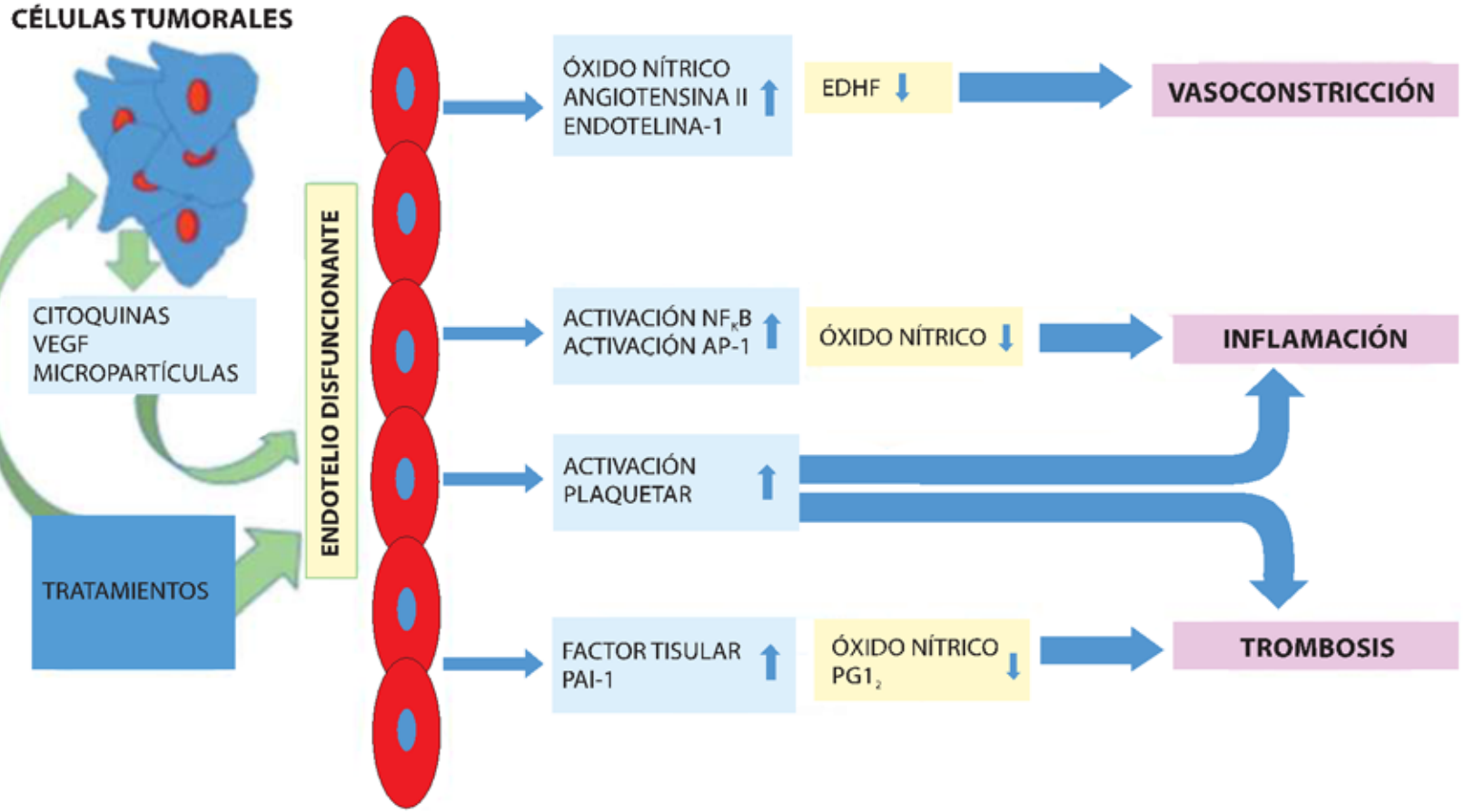
ANGIOGÉNESIS – VEGFR





humano	lonal	Antagonista del VEGFR-2 (receptor del VEGF-A)	ADC gástrico o de la UEG CPNM

MECANISMOS PROTROMBÓTICOS DE ANTICUERPOS MONOCLONALES ANTIANGIOGÉNICOS



AP-1: activador proteico 1; EDHF: factor de hiperpolarizacïon derivado del endotelio; NF-KB: factor de transcripcïon nuclear kappa B; PAI-1: inhibidor del activador del plasmiǹogeno 1; PGI2: prostaciclina 2; VEGF: factor de crecimiento del endotelio vascular

BEVACIZUMAB Y RIESGO TROMBÓTICO

2004

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 3, 2004 VOL. 350 NO. 23

Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer

Herbert Hurwitz, M.D., Louis Fehrenbacher, M.D., William Novotny, M.D., Thomas Cartwright, M.D., John Hainsworth, M.D., William Heim, M.D., Jordan Berlin, M.D., Ari Baron, M.D., Susan Griffing, B.S., Eric Holmgren, Ph.D., Napoleone Ferrara, M.D., Gwen Fyfe, M.D., Beth Rogers, B.S., Robert Ross, M.D., and Fairooz Kabbinavar, M.D.

INCREMENTO RIESGO ENFERMEDAD TROMBOEMBÓLICA ARTERIAL Y PROBABLE VENOSA

BEVACIZUMAB Y RIESGO TROMBÓTICO

2007

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer

Kathy Miller, M.D., Molin Wang, Ph.D., Julie Gralow, M.D., Maura Dickler, M.D., Melody Cobleigh, M.D., Edith A. Perez, M.D., Tamara Shenkier, M.D., David Cella, Ph.D., and Nancy E. Davidson, M.D.

Table 2. Treatment-Related Toxic Effects.*

Effect	Paclitaxel plus Bevacizumab (N=365)			Paclitaxel (N=346)		P Value
Thrombosis or embolism	1.6	0.5		0.6	0.9	
Cerebrovascular ischemia	0.8	1.1	*percent*	0	0	0.02

Aumento significativo trombosis arterial
No incremento trombosis venosas

INCIDENCIA DE EVENTOS TROMBOEMBÓLICOS EN ESTUDIOS RANDOMIZADOS FASE III

Estudio	Regimen	N	Incidencia		
			TE	TEV	ATE
Hurwitz 2004	IFL+BEV IFL	402 411	**19.4%** **16.2%**	-	**3.3%** **1%**
Miller 2005	Capecitabina/Bev Capecitabina	229 215	**7.4%** **5.6%**	-	-
Escudier 2007	Interferon alfa-2ª/Bev Interferon alfa-2a	325 316		**3%** **1%**	**1.5%** **0.7%**
Miller 2007	Paclitaxel/Bev Paclitaxel	365 346	**2.2%** **1.4%**	-	-
Saltz 2008	Oxaliplatino/fluoropirimidin/BEV Oxaliplatino/fluoropirimidin	694 675	-	**8%** **5%**	**2%** **1%**

Ferroni et al. Curr Vasc Pharm 2010;8:102-113

METAANÁLISIS DE RIESGO DE TROMBOSIS Y BEVACIZUMAB

Estudio	N	TEV				TEA			
		Bev	Control	p	RR	Bev	Control	p	RR
Scappaticci	1.745	9,97%	9,85%	0,44	0,89	3,8%	1,7%	0,031	2,0
Nalluri*	7.956	12,9%	9,9%	0,03	1,29				
Ranpura	12.617					3,3%	1,34%	0,013	1,44
Schutz	13.026					2,2%	1,33%	0,007	1,46
Hurwitz	6.055	10,9%	9,8%	0,13	1,14				

Bev: bevacizumab; RR: riesgo relativo; TEA: tromboembolismo arterial; TEV: tromboembolismo venoso. Datos correspondientes únicamente a seis estudios aleatorizados entre bevacizumab y control.

- **Bevacizumab does not appear to be associated to an increase in the risk of VTD.**
- **Bevacizumab is associated to a modest, but significant increase in the risk of arterial TED of approximately 1-3%.**

Scappaticci FA, et al. J Natl Cancer Inst. 2007. Nalluri SR, et al. JAMA. 2008. Ranpura V, et al. Acta Oncol 2010. Schutz FA, et al. Ann Oncol 2011. Hurwitz HI, et al. J Clin Oncol 2011.

BEVACIZUMAB AND ARTERIAL THROMBOSIS

Pivotal phase III trial AVF2107 in CRC (Hurwitz NEJM 2004)

- ATE BVZ 3.3 versus 1% controls

BRiTE registry (Sugrue ASCO 2007)

- Incidence of ATD found was 1.8%
- Overall rate of ATD 2.2 per 100 patient-years of exposure
- Greater incidence in patients with a history of ATD

BEAT (Van Cutsem Ann Oncol 2009)

- Incidence of ATD is 0.8%
- Severe adverse events with Bv are infrequent including ATD
- Survival benefit can be seen in all subgroups

Metaanálisis ETEA
Scappaticci et al. JNCI 2007

Development of an arterial thromboembolic event was associated with:

- **A prior arterial thromboembolic event (p<0.001)**
- **Age of 65 years or older (p=0.01)**

Table 3. Cox proportional hazards regression analysis of potential baseline risk factors for an arterial thromboembolic event*

Risk factor	Comparison†	Univariate HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*†
Bevacizumab treatment	Yes/no (728/963)	1.99 (1.05 to 3.75)	.03	1.95 (1.04 to 3.67)	.04
Age, y	≥65/<65 (618/1127)	3.00 (1.69 to 5.30)	<.001	2.17 (1.17 to 4.01)	.01
Sex	Male/female (760/985)	0.57 (0.32 to 1.01)	.05		
Hypertension at baseline	Yes/no (799/946)	1.89 (1.06 to 3.34)	.03		
History of ATE	Yes/no (148/1597)	5.18 (2.86 to 9.39)	<.001	3.65 (1.92 to 6.92)	<.001
History of atherosclerosis	Yes/no (192/1553)	4.17 (2.32 to 7.49)	<.001		
History of diabetes mellitus	Yes/no (224/1521)	1.91 (0.98 to 3.73)	.06		
History of myocardial infarction	Yes/no (110/1635)	4.90 (2.56 to 9.38)	<.001		
History of stroke or TIA	Yes/no (25/1720)	3.16 (0.77 to 13.02)	.11		
History of venous thrombosis	Yes/no (79/1666)	0.47 (0.07 to 3.41)	.46		

INCIDENCIA DE ATEs POR SUBGRUPOS

Baseline patient characteristic	sATE, n (%)
Age <65 years without Arterial Disease History (n=963)	13 (1.4)
Age <65 years with Arterial Disease History (n=94)	2 (2.1)
Age ≥65 years without Arterial Disease History (n=638)	9 (1.4)
Age ≥65 years with Arterial Disease History (n=258)	11 (4.3)
ECOG PS 0 without Arterial Disease History (n=707)	6 (0.8)
ECOG PS 0 with Arterial Disease History (n=130)	2 (1.5)
ECOG PS ≥1 without Arterial Disease History (n=764)	14 (1.8)
ECOG PS ≥1 with Arterial Disease History (n=197)	9 (4.6)

Note: Patients with unknown ECOG PS were not included; 4 patients had an sATE in ECOG PS unknown group.

Sugrue et al. ASCO 2007. Abs 4136

Metaanálisis
Hurwitz et al. JCO 2011

Outcome	Control* (n = 2,607)		Bevacizumab* (n = 3,448)	
	No.	%	No.	%
Total patients with at least one VTE	256	9.8	377	10.9
Total No. of VTEs	293		432	
Deep vein thrombosis†	114	4.4	175	5.1
Pulmonary embolism, venous embolism, or pulmonary thrombosis	62	2.4	86	2.5
Catheter- or phlebitis-related thrombosis	89	3.4	126	3.7
Thrombosis NOS	28	1.1	45	1.3

Abbreviations: VTE, venous thromboembolism; NOS, not otherwise specified.
*Patients in the bevacizumab group had a 63% longer total exposure to treatment than those in the control group (2,111.9 patient-years *v* 1,295.6 patient-years, respectively).
†Thrombosis to the jugular, limb, portal, pelvic, mesenteric, subclavian, axillary, splenic, and hepatic vene as well as to the vena cava superior and the atrium were grouped to "deep" venal thrombosis.

Incidence by Location of VTEs in Patients Treated With Bevacizumab or Control

The risk of VTD was not affected by the dose of Bv used

Multivariate risk factor analysis

Risk Factor	Patients With VTE: Control No.	Control %	Bevacizumab No.	Bevacizumab %	Overall Risk Factor Effect on VTE Event Rate*: Rate Ratio	95% CI	Within Subgroup Treatment Comparison†: Rate Ratio	95% CI
Age, years								
≤ 65	169	9	240	10	1		1.16	0.81 to 1.67‡
> 65	87	11	137	14	1.30	1.10 to 1.54§	1.33	0.89 to 1.99‡
BMI, kg/m^2								
< 35	243	10	350	11	1		1.22	0.86 to 1.72‡
≥ 35	13	11	24	15	1.29	0.91 to 1.84‡	1.23	0.59 to 2.56‡
Diabetes								
No	224	10	332	11	1.18	0.92 to 1.51‡	1.20	0.85 to 1.70‡
Yes	32	10	45	11	1		1.30	0.76 to 2.25‡
Performance status								
0	108	9	170	10	1		1.41	0.95 to 2.08‡
1/2	148	11	207	12	1.38	1.17 to 1.62¶	1.11	0.77 to 1.60‡
Sex								
Male	139	11	190	11	1.02	0.86 to 1.21‡	1.12	0.77 to 1.63‡
Female	117	9	187	10	1		1.34	0.91 to 1.97‡
Prior VTE								
No	243	10	349	10	1		0.86	0.73 to 1.02‡
Yes	13	17	28	29	2.31	1.64 to 3.27¶	1.72	0.89 to 3.35‡
Prior surgery								
No	181	9	248	10	1		1.18	0.82 to 1.69‡
Yes	75	12	129	14	1.34	1.10 to 1.64§	1.30	0.86 to 1.96‡
Prior oral anticoagulants (coumarins)								
No	224	9	324	10	1		1.17	0.82 to 1.68‡
Yes	32	18	53	24	1.89	1.47 to 2.42¶	1.40	0.84 to 2.32‡
Prior nonoral anticoagulants (heparins)								
No	239	10	355	11	1		1.22	0.85 to 1.75‡
Yes	17	13	22	16	1.13	0.80 to 1.59‡	1.22	0.64 to 2.35‡
Prior NSAID/PAA								
No	142	9	195	9	1.10	0.94 to 1.30‡	1.05	0.72 to 1.52‡
Yes	114	10	182	13	1		1.45	0.94 to 1.30‡
Tumor type								
Breast	30	7	49	7	4.89	2.44 to 9.81¶	1.14	0.67 to 1.97‡
Colorectal	134	11	185	14	7.90	4.06 to 15.38¶	1.39	0.95 to 2.03‡
NSCLC	37	10	91	13	9.85	4.93 to 19.66¶	1.13	0.69 to 1.84‡
Pancreatic	52	18	43	15	13.64	6.80 to 27.39¶	0.87	0.53 to 1.43‡
Renal	3	1	9	3	1		2.95	0.77 to 11.31‡
Treatment								
Bevacizumab	—		377	11	1.22	0.87 to 1.72‡	N/A	
Control	256	10	—		1		N/A	

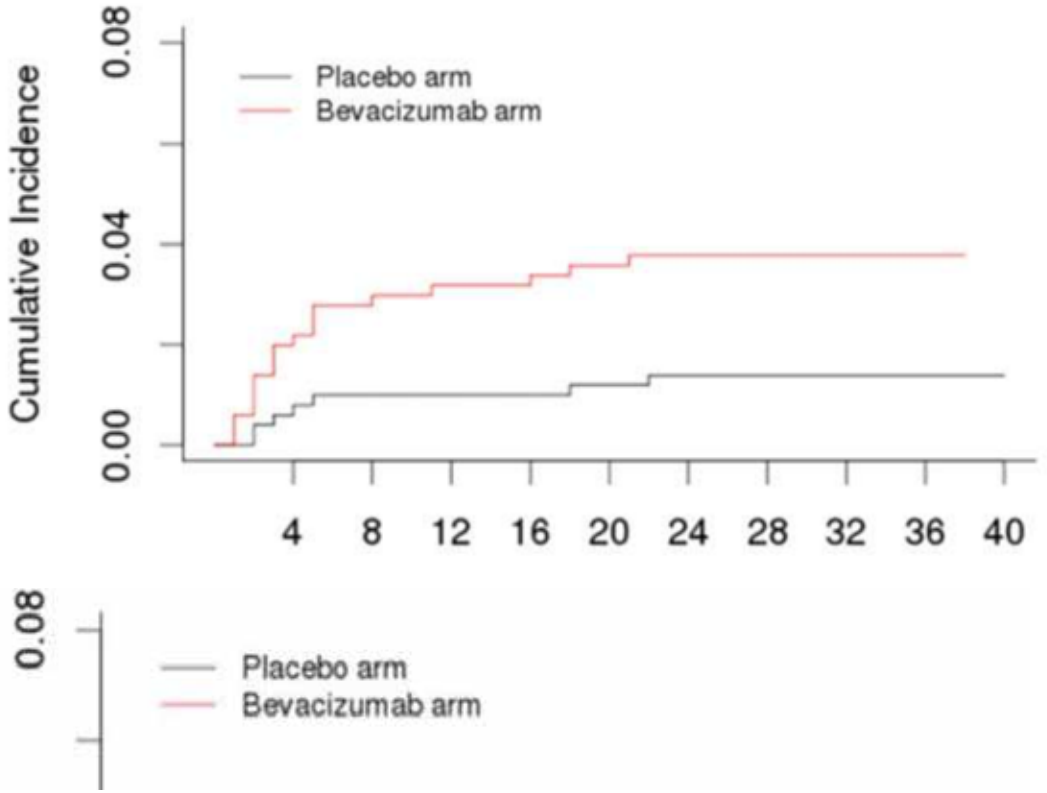
No significant difference between the BVZ and control groups in the effect of any of these factors (lack of a statistically significant difference in the treatment interaction terms)

Hurwitz HI, et al. J Clin Oncol 2011

Original Article

Bevacizumab and the Risk of Arterial and Venous Thromboembolism in Patients With Metastatic, Castration-Resistant Prostate Cancer Treated on Cancer and Leukemia Group B (CALGB) 90401 (Alliance)

Jai N. Patel, PharmD[1]; Chen Jiang, PhD[2]; Daniel I. Hertz, PharmD, PhD[3]; Flora A. Mulkey, MS[2]; Kouros Owzar, PhD[2,4]; Susan Halabi, PhD[2,4]; Mark J. Ratain, MD[5]; Paula N. Friedman, PhD[5]; Eric J. Small, MD[6]; Michael A. Carducci, MD[7]; John F. Mahoney, MD[1]; Michael J. Kelley, MD[8]; Michael J. Morris, MD[9]; William K. Kelly, MD[10]; and Howard L. McLeod, PharmD[11]



ATE

Figure 1. This is a cumulative incidence curve for grade 3 or greater (>3) arterial thromboembolism (ATE) stratified by treatment arm. There were 19 events among 503 patients (3.78%) in the bevacizumab arm and 7 events among 505 patients (1.39%) in the placebo arm. The hazard ratio for the cumulative incidence of grade ≥3 ATE in the patients who received bevacizumab was 2.76 (95% confidence interval, 1.16-6.55; $P = .021$).

Patel JN, et al. Cancer 2014

Original Article

Bevacizumab and the Risk of Arterial and Venous Thromboembolism in Patients With Metastatic, Castration-Resistant Prostate Cancer Treated on Cancer and Leukemia Group B (CALGB) 90401 (Alliance)

Jai N. Patel, PharmD[1]; Chen Jiang, PhD[2]; Daniel L. Hertz, PharmD, PhD[3]; Flora A. Mulkey, MS[3]; Kouros Owzar, PhD[2,4]; Susan Halabi, PhD[2,4]; Mark J. Ratain, MD[5]; Paula N. Friedman, PhD[5]; Eric J. Small, MD[6]; Michael A. Carducci, MD[7]; John F. Mahoney, MD[1]; Michael J. Kelley, MD[8]; Michael J. Morris, MD[9]; William K. Kelly, MD[10]; and Howard L. McLeod, PharmD[11]

VTE

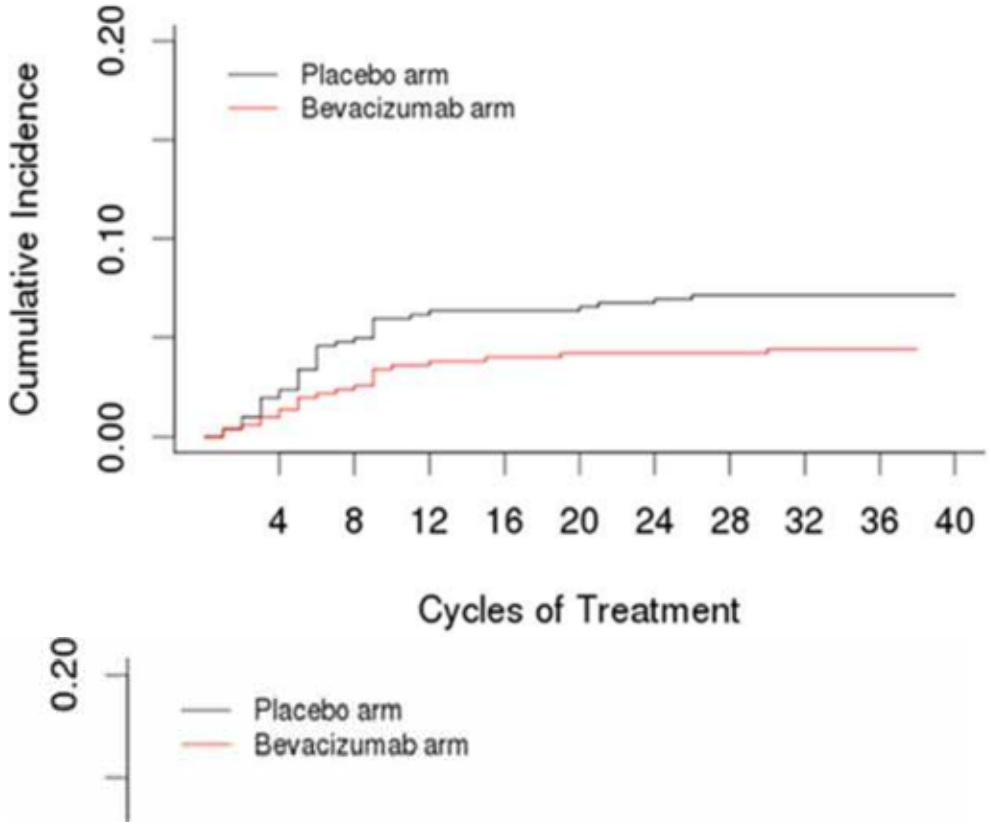


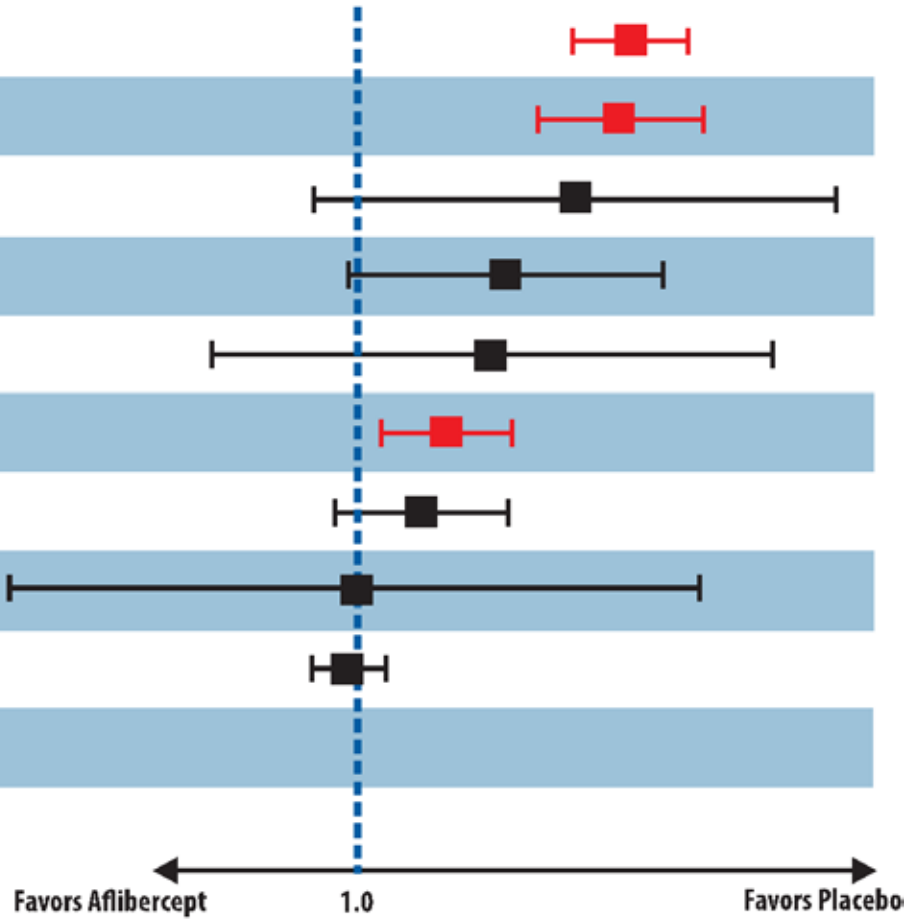
Figure 2. This is a cumulative incidence curve for grade 3 or greater (≥3) venous thromboembolism (VTE) stratified by treatment arm. There were 22 events among 503 patients (4.37%) in the bevacizumab arm and 36 events among 505 patients (7.13%) in the placebo arm. The hazard ratio for the cumulative incidence of grade ≥3 VTE in the patients who received bevacizumab was 0.60 (95% confidence interval, 0.35-1.02; $P = .059$).

Patel JN, et al. Cancer 2014

AFLIBERCEPT Y RIESGO DE ETE

Grade 3-4 Adverse Events	Percentage of Patients		
	Placebo (N=1329)	Aflibercept (N=1333)	Relative Risk (95% CI)
Hypertension*	1.6	14.6	9.21 (5.91 to 14.36)**
Proteinuria	0.8	6.3	8.37 (4.37 to 16.06)**
Cardiac dysfunction	<0.1	0.5	5.98 (0.72 to 49.62)
Gastrointestinal perforation	0.2	0.8	3.32 (0.92 to 12.05)
Fistula	<0.1	0.2	2.99 (0.31 to 28.72)
Hemorrhage	<1.5	3.1	2.04 (1.20 to 3.47)**
Arterial thromboembolic event	1.0	1.7	1.69 (0.85 to 3.34)
Osteonecrosis of the jaw	<1.0	<0.1	1.00 (0.06 to 15.92)
Venous thromboembolic event (VTE)	6.4	6.1	0.95 (0.71 to 1.28)
Impaired wound healing	0	0.2	Not assessable

*Grade 3:2 drugs needed to control blood pressure
**Statistically significant



Allegra C, Tabernero J, et al. ASCO. Abs 561 ASCO GI 2012

AFLIBERCEPT Y RIESGO DE ETE

- Mayor capacidad de inhibir angiogénesis.
- ETEA en el rango de la observada con bevacizumab.
- Aparición precoz eventos tromboembólicos y no repetidos.

Ruff P, et al. Eur J Cancer 2015. Tabernero J, et al. J Clin Oncol 2012

RAMUCIRUMAB Y RIESGO DE ETE

- Anticuerpo monoclonal humano IgG1 que se une al dominio extracelular del VE- GFR-2 y bloquea su activacïon al impedir la interaccïon con su ligando, VEGF.

Trombosis venosa

Estudio	Esquemas (N)	TEV de cualquier grado	TEV de grado ≥3
REGARD (2ª línea ADCG/AUEG) Fuchs *et al.*[37]	RM (236) Placebo (115)	4% 7%	1% 4%
RAIBOW (2ª línea ADCG/AUEG) Wilke *et al.*[40]	RM + paclitaxel (327) Placebo + paclitaxel (329)	4% 5,5%	2,4% 3,3%
REVEL (2ª línea CPNM) Garon *et al.*[38]	RM + docetaxel (627) Placebo + docetaxel (618)	3% 6%	2% 3%
ROSE/TRIO-12 (1ª línea CMm) Mackey *et al.*[39]	RM + docetaxel (752) Placebo + docetaxel (382)	2,4% 4,2%	1,3%* 3,1%*

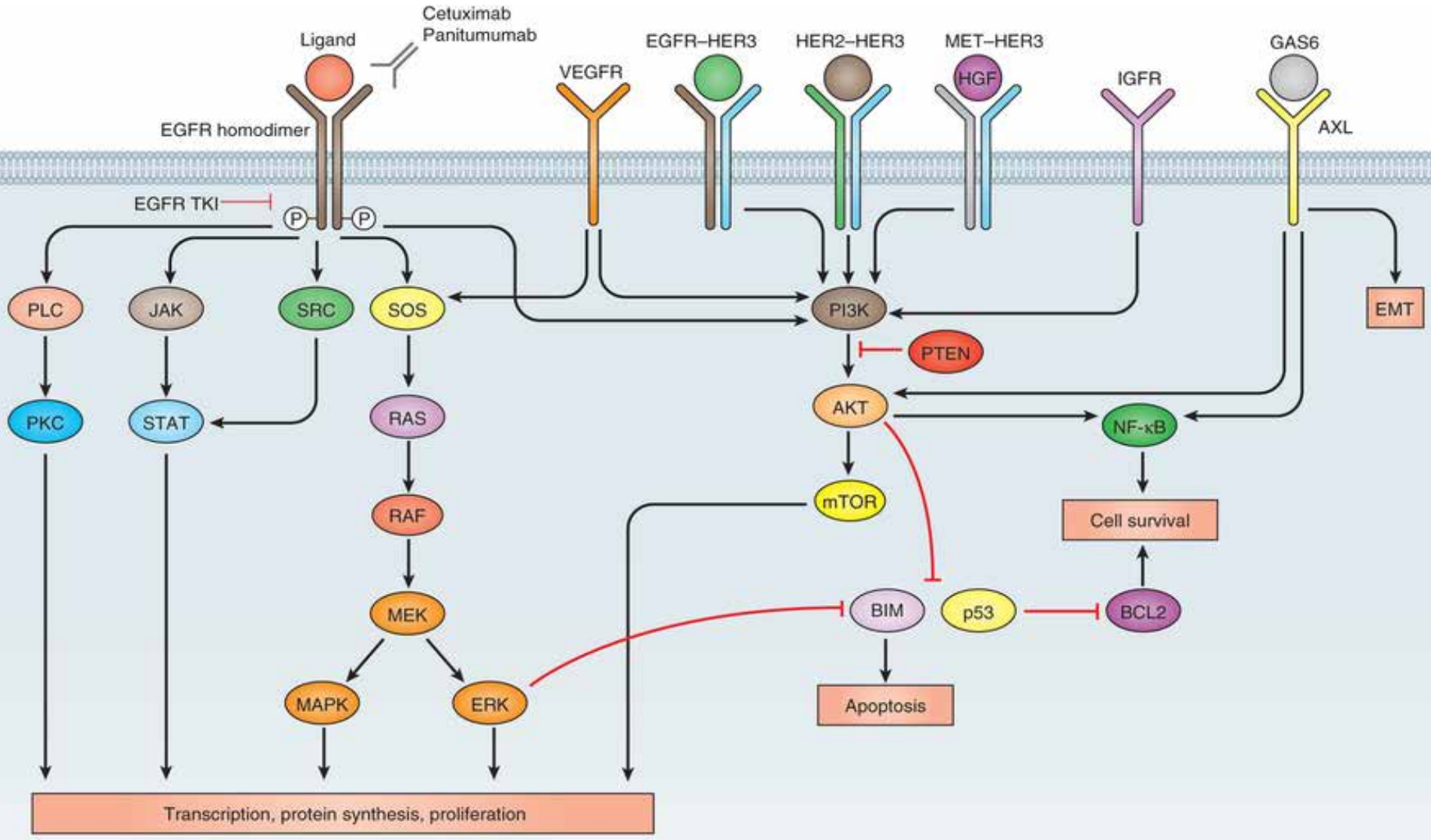
Salgado M. Oncology Thrombosis Risk 2015.
Saif MW. Cancer Manag Res 2013

RAMUCIRUMAB Y TROMBOSIS ARTERIAL

Estudio	Esquemas (N)	TEA de cualquier grado	TEV de grado ≥3
REGARD (2ª línea ADCG/AUEG) Fuchs *et al.*[37]	RM (236)	2%	1%
	Placebo (115)	0%	0%
RAIBOW (2ª línea ADCG/AUEG) Wilke *et al.*[40]	RM + paclitaxel (327)	1,5%	0,9%
	Placebo + paclitaxel (329)	1,8%	0,9%
REVEL (2ª línea CPNM) Garon *et al.*[38]	RM + docetaxel (627)	2%	1%
	Placebo+docetaxel (618)	2%	1%
ROSE/TRIO-12 (1ª línea CMm) Mackey *et al.*[39]	RM + docetaxel (752)	1,1%	0,7%
	Placebo+docetaxel (382)	1,3%	0,3%

Salgado M. Oncology Thrombosis Risk 2015

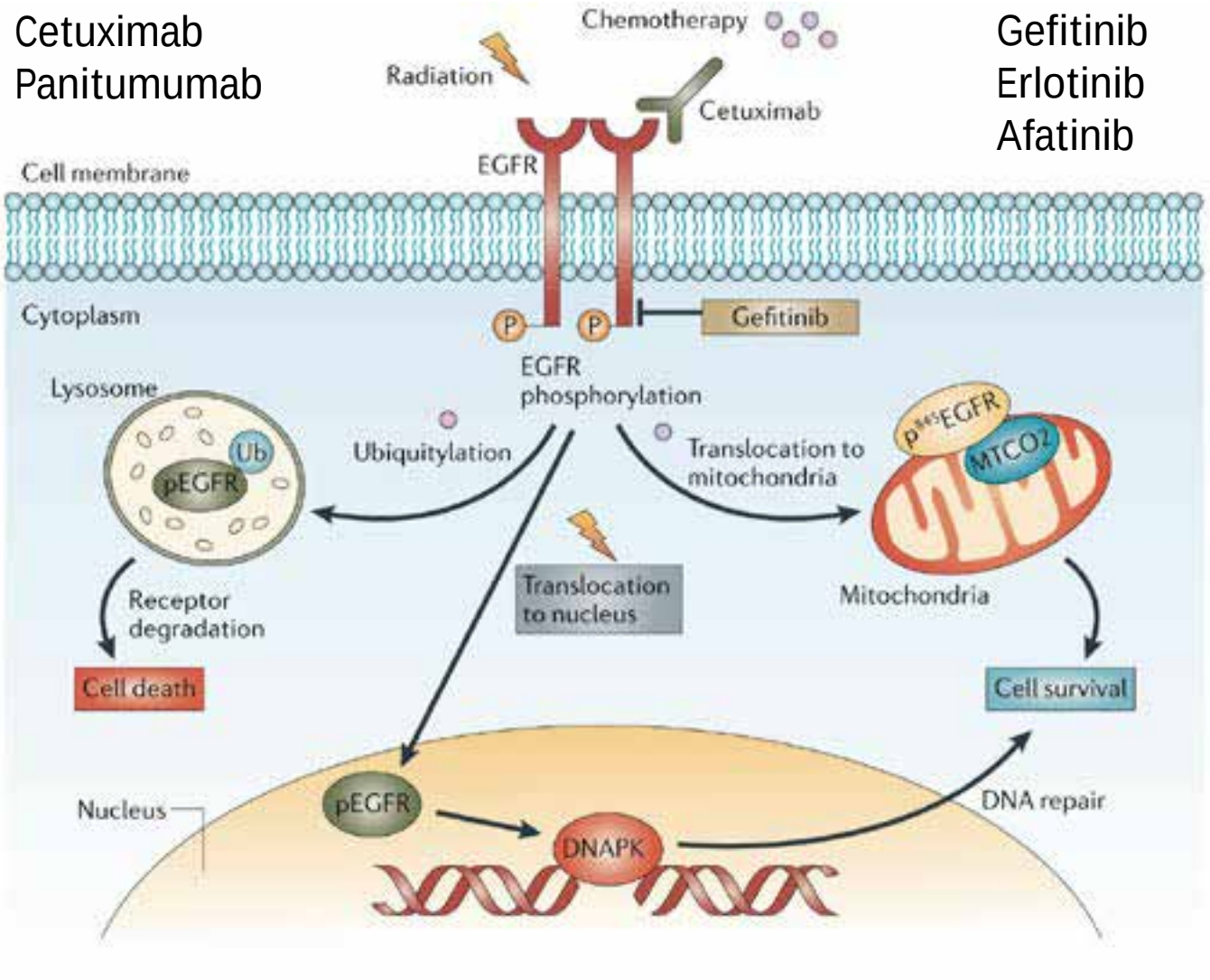
RECEPTORES HER – EGFR



FÁRMACOS ANTI-EGFR

AcMo
Cetuximab
Panitumumab

ITK
Gefitinib
Erlotinib
Afatinib



Annals of Oncology Advance Access published January 11, 2012

review

Annals of Oncology
doi:10.1093/annonc/mds592

Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials

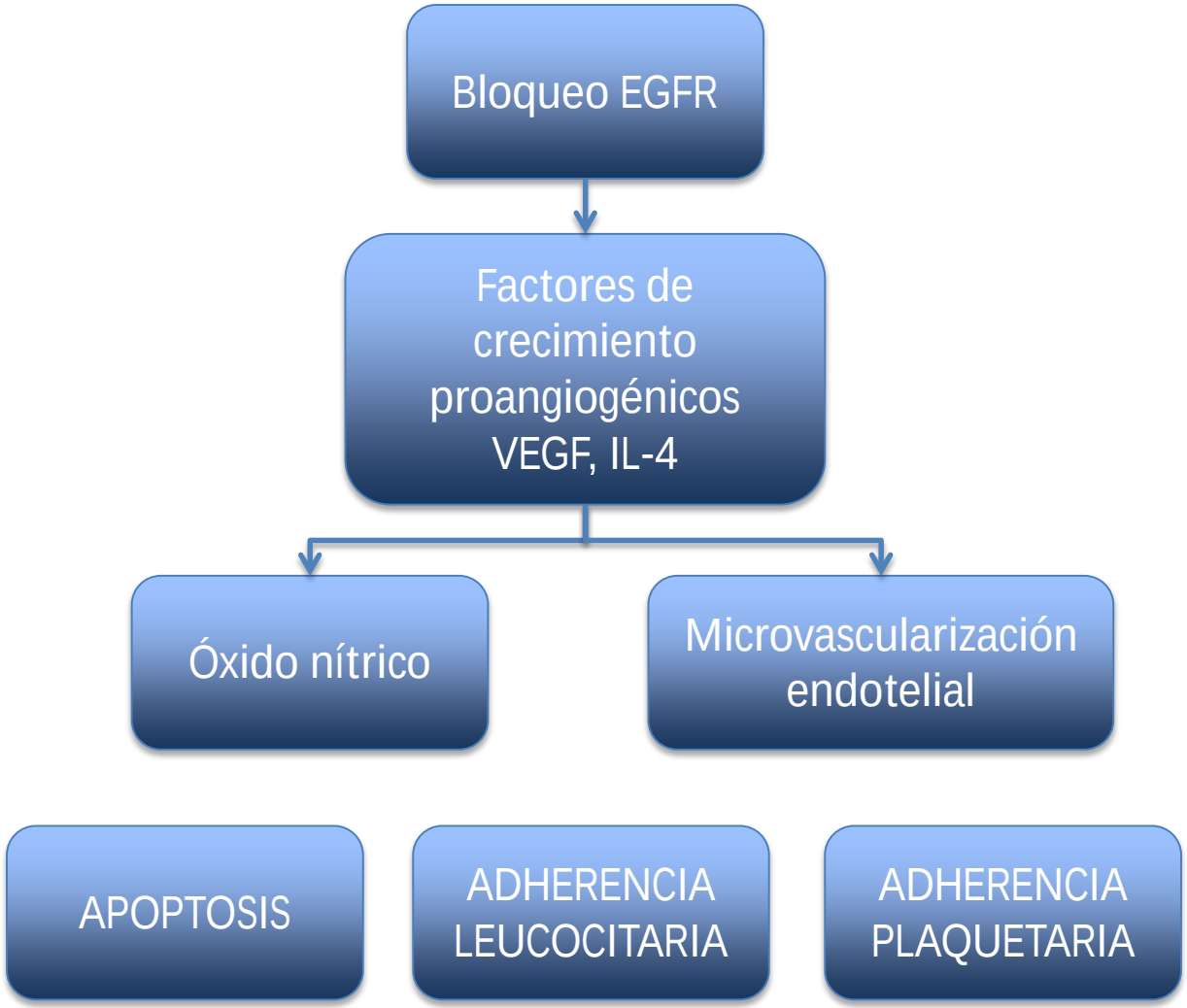
F. Petrelli[1]*, M. Cabiddu[1], K. Borgonovo[1] & S. Barni[1]

[1]Medical Oncology Unit, Oncology Department, Azienda Ospedaliera Treviglio-Caravaggio, Treviglio, Italy

- **Metaanálisis: 13 estudios – 7611 pacientes (cetuximab, panitumumab, erlotinib y gefitinib)**
- **ETEV 11 estudios:**
  - **RR 1,32 IC95% 1,07-1,63; p=0,01**
- **ETEA 5 estudios:**
  - **RR 1.34 IC95% 0,94–1,9; p=0,11**
- **VTE: MoAbs RR 1,34; p=0,01 and oral TKIs RR 1,16; p=0,65**

Petreli F, et al. Ann Oncol 2012

MECANISMO PROTROMBÓTICO AcMo ANTIEGFR



OTROS ANTICUERPOS

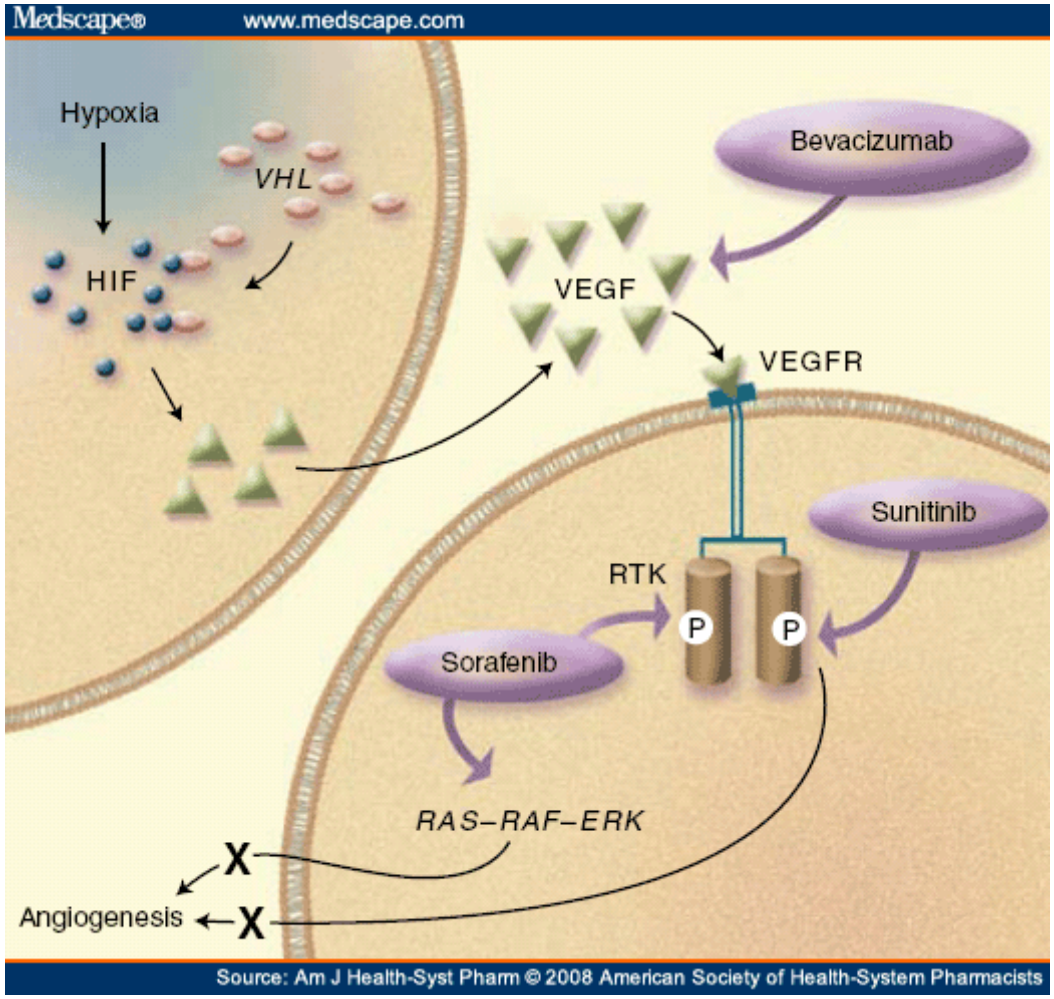
- Anti-HER
  - Trastuzumab
  - Pertuzumab
  - TDM-1 (AcMo conjugado)

SIN EVIDENCIA INCREMENTAR RIESGO DE TROMBOSIS

- Anticuerpos empleados en neoplasias hematológicas
  - Anti-CD20: rituximab
  - Anti-CD52: alemtuzumab
  - Anti-CD30: brentuximab
  - 90Y-ibritumomab (AcMo conjugado)
- Anticuerpos anti-PD1-PD-L1, CTLA-4
  - Ipilimumab (<1%)
  - Nivolumab
  - Pembrolizumab

INHIBIDORES TIROSIN-KINASA ANTIANGIOGÉNICOS

- Sunitinib
- Sorafenib
- Pazopanib
- Axitinib
- Vandetanib
- Lenvatinib
- Nintedanib



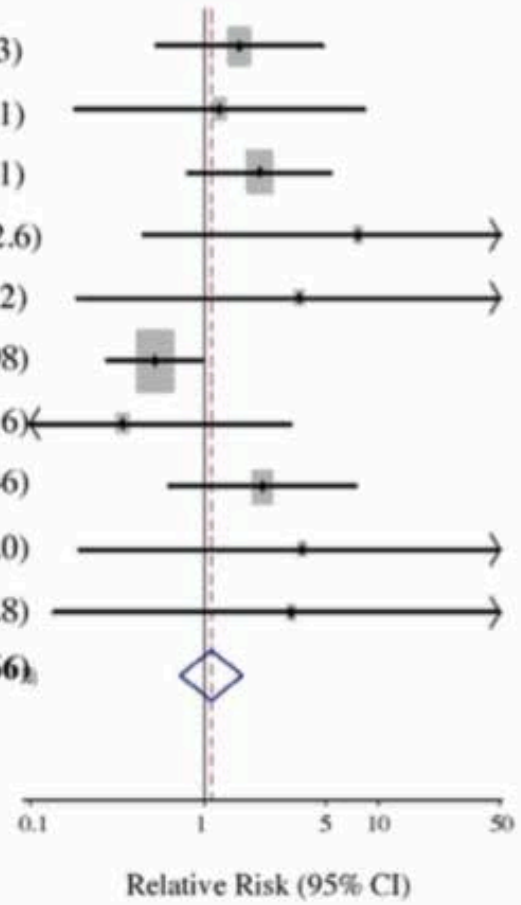
Venous thromboembolic events with vascular endothelial growth factor receptor tyrosine kinase inhibitors: A systematic review and meta-analysis of randomized clinical trials

Guru Sonpavde[a], Youjin Je[b], Fabio Schutz[c], Matthew D. Galsky[d], Ravikumar Paluri[a], Jonathan E. Rosenberg[e], Joaquim Bellmunt[f], Toni K. Choueiri[g,*]

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

Source	No. of events/Total no. VEGFR TKI	Control	Relative Risk (95% CI)	*P* value
Scagliotti et al, 2010	8/464	5/462	1.59 (0.53-4.83)	.41
Krege et al, 2010	2/40	2/49	1.23 (0.18-8.31)	.84
Motzer et al, 2009	13/375	6/360	2.08 (0.80-5.41)	.13
Demetri et al, 2006	7/207	0/105	7.64 (0.44-132.6)	.16
Rugo et al, 2011	3/112	0/56	3.53 (0.19-67.2)	.40
Herbst et al, 2011	14/694	27/697	0.52 (0.28-0.98)	.05
Arnold et al, 2007	1/52	3/53	0.34 (0.04-3.16)	.34
Van Der Graaf et al, 2011	13/246	3/123	2.17 (0.63-7.46)	.22
Monk et al, 2010	3/150	0/78	3.66 (0.19-70.0)	.39
Ward et al, 2012	1/18	0/19	3.16 (0.14-72.8)	.47
Overall	**65/2358**	**46/2002**	**1.10 (0.73-1.66)**	**.64**

Test for heterogeneity: Q=13.11, P=.158, I^2=31.3%



All grade VTE events

Sonpavde G, et al. Crit Rev Oncol Hematol 2013

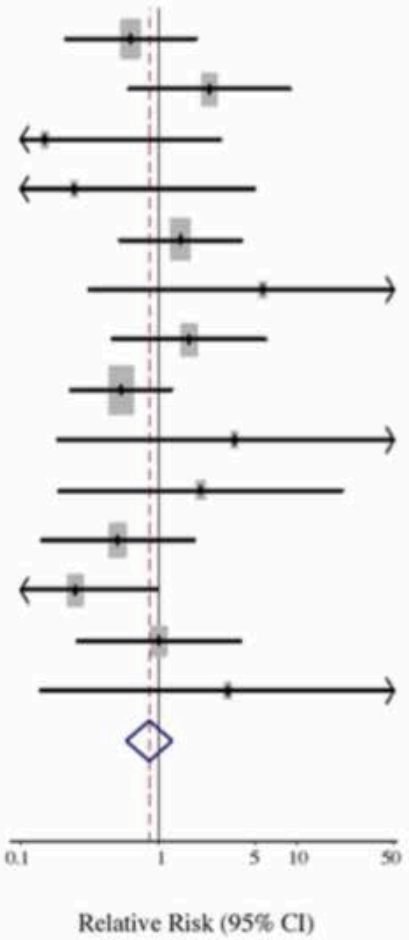
Venous thromboembolic events with vascular endothelial growth factor receptor tyrosine kinase inhibitors: A systematic review and meta-analysis of randomized clinical trials

Guru Sonpavde[a], Youjin Je[b], Fabio Schutz[c], Matthew D. Galsky[d], Ravikumar Paluri[a], Jonathan E. Rosenberg[e], Joaquim Bellmunt[f], Toni K. Choueiri[g,*]

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

Source	No. of events/Total no. VEGFR TKI	Control	Relative Risk (95% CI)	*P* value
Hauschild et al, 2009	5/134	8/134	0.63 (0.21-1.86)	.40
Scagliotti et al, 2010	7/464	3/462	2.32 (0.60-8.93)	.22
Abou-Alfa et al, 2011	0/47	3/49	0.15 (0.01-2.81)	.20
Krege et al, 2010	0/40	2/49	0.24 (0.01-4.94)	.36
Motzer et al, 2009	9/375	6/360	1.44 (0.52-4.00)	.49
Demetri et al, 2006	5/207	0/105	5.61 (0.31-100.4)	.24
Michaelson et al, 2011	10/584	3/289	1.65 (0.46-5.95)	.44
Kindler et al, 2007	8/316	15/316	0.53 (0.23-1.24)	.14
Rugo et al, 2011	3/112	0/56	3.53 (0.19-67.2)	.40
Horti et al, 2011	2/43	1/43	2.00 (0.19-21.2)	.57
Heymach et al, 2008	5/129	4/52	0.50 (0.14-1.80)	.29
Lee et al, 2012	3/617	6/307	0.25 (0.06-0.99)	.05
Van Der Graaf et al, 2011	6/246	3/123	1.00 (0.25-3.93)	>.99
Ward et al, 2012	1/18	0/19	3.16 (0.14-72.8)	.47
Overall	**64/3332**	**54/2364**	**0.85 (0.58-1.25)**	**.41**

Test for heterogeneity: Q=15.15, P=.298, I^2=14.2%



High grade VTE events

Sonpavde G, et al. Crit Rev Oncol Hematol 2013

VOLUME 28 · NUMBER 13 · MAY 1 2010

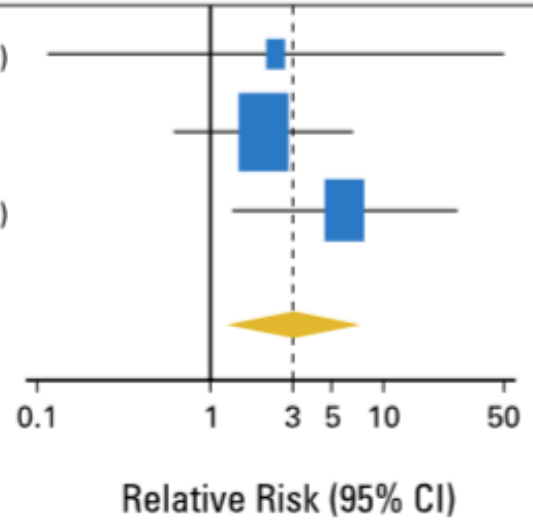
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Risk of Arterial Thromboembolic Events With Sunitinib and Sorafenib: A Systematic Review and Meta-Analysis of Clinical Trials

Toni K. Choueiri, Fabio A.B. Schutz, Youjin Je, Jonathan E. Rosenberg, and Joaquim Bellmunt

Study	No. cases/sample size TKI	Control	Relative Risk (95% CI)	*P*
Demetri et al (2008)	2/241	0/115	2.39 (0.12 to 49.41)	.573
Llovet et al (2008)	8/297	4/302	2.03 (0.62 to 6.68)	.242
Escudier et al (2007)	12/451	2/451	6.00 (1.35 to 26.66)	.019
Overall Test for heterogeneity: Q = 1.261, *P* = .532, I^2 = 0%			3.03 (1.25 to 7.37)	.015



Incidence ATE 1.4%

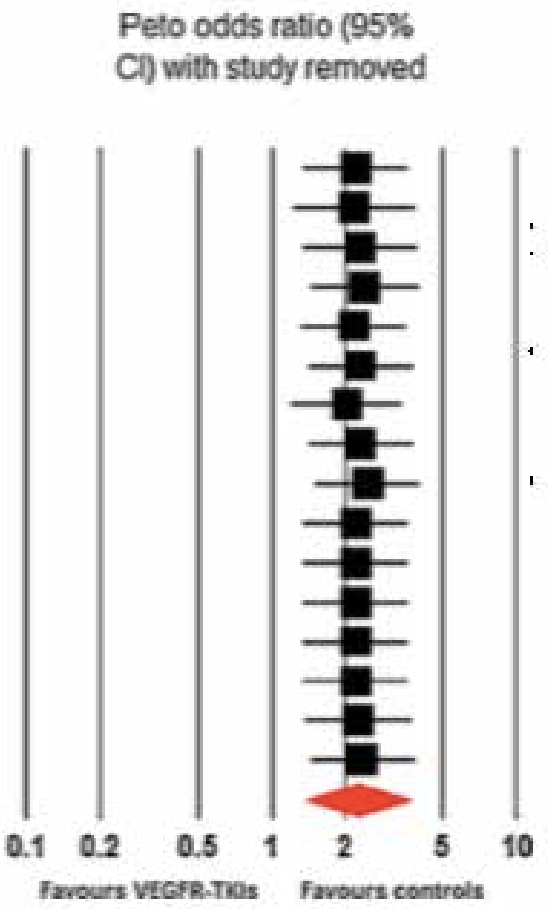
Choueiri TK, et al. J Clin Oncol 2010;28:2280-5

Risk of arterial thromboembolic events with vascular endothelial growth factor receptor tyrosine kinase inhibitors: An up-to-date meta-analysis

Wei-Xiang Qi *, Zan Shen, Li-Na Tang, Yang Yao

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Demetri G.D. et al.2006	2.211	1.346	3.632	3.132	0.002
Escudier B. et al.2007	2.177	1.225	3.869	2.652	0.008
Llovet J.M. et al.2008	2.315	1.347	3.980	3.037	0.002
Spano J.P. et al.2008	2.394	1.433	4.001	3.334	0.001
Abou-Alfa G.K. et al.2010	2.167	1.318	3.563	3.049	0.002
Scagliotti G. et al.2010	2.315	1.408	3.807	3.309	0.001
Sternberg C.N. et al.2010	2.041	1.210	3.442	2.676	0.007
Kindler H.L. et al.2011	2.314	1.408	3.805	3.307	0.001
Natale R.B. et al.2011	2.470	1.502	4.061	3.563	0.000
Goncalves A. et al.2012	2.213	1.351	3.625	3.156	0.002
Carrato A et al.2013	2.214	1.352	3.625	3.157	0.002
Gradishar W.J. et al.2013	2.212	1.351	3.623	3.155	0.002
Groen H.J.M. et al.2013	2.213	1.351	3.625	3.156	0.002
Hyams D.M. et al.2013	2.213	1.351	3.625	3.156	0.002
Llovet J.P. et al.2013	2.265	1.359	3.776	3.137	0.002
Serve H. et al.2013	2.360	1.441	3.866	3.412	0.001
	2.255	1.382	3.679	3.256	0.001



Qi WX, et al. Crit Rev Oncol Hematol 2014

Risk of arterial thromboembolic events with vascular endothelial growth factor receptor tyrosine kinase inhibitors: An up-to-date meta-analysis

Wei-Xiang Qi *, Zan Shen, Li-Na Tang, Yang Yao

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

19 EC

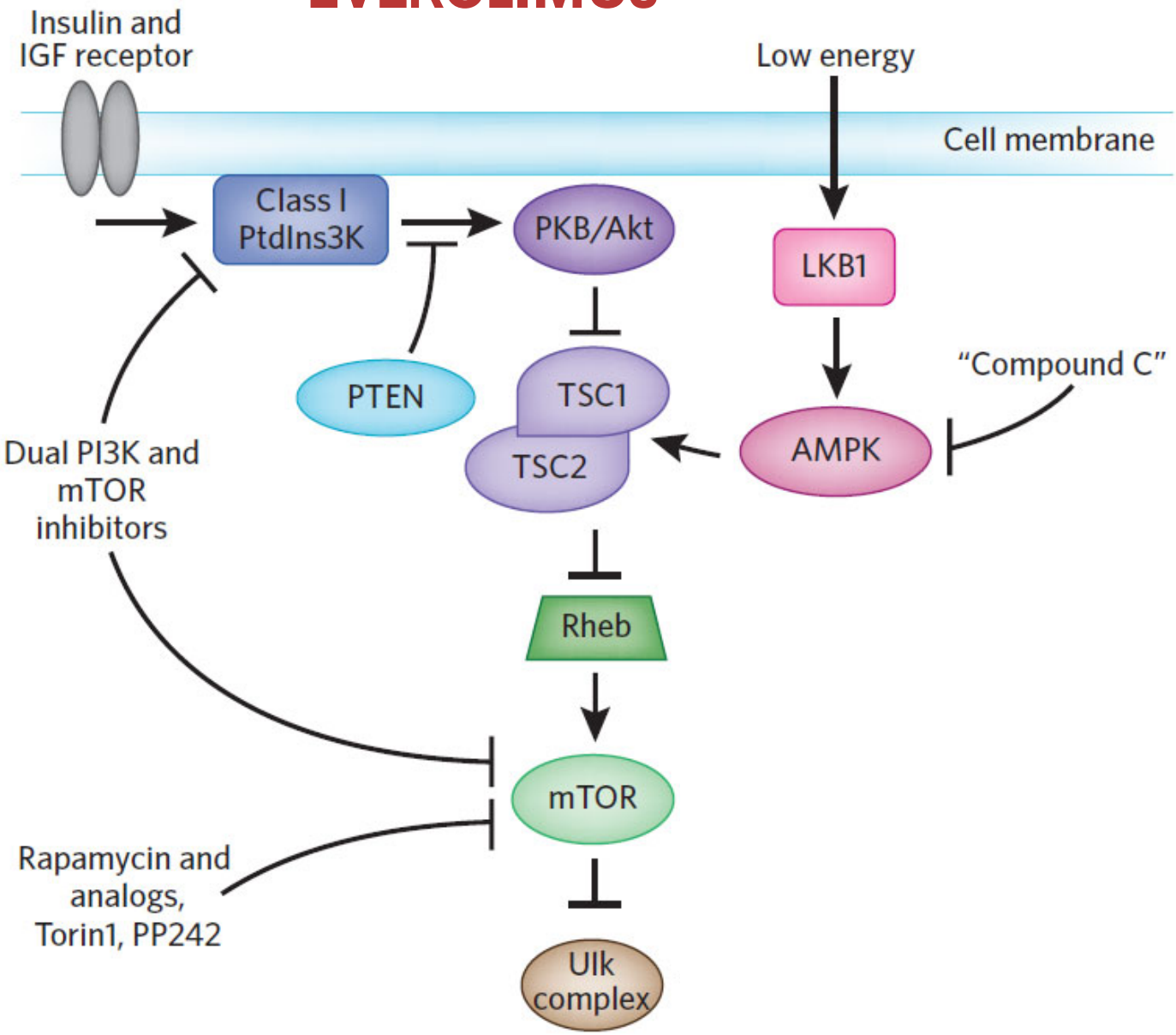
9711 pacientes

Incidencia total ATE 1,5%

OR 2,26 IC95% 1,38-3,68; P=0,001

Evento más frecuente: isquemia cardíaca 67,4%

EVEROLIMUS


Insulin and
IGF receptor
Low energy
Cell membrane
Class I
PtdIns3K
PKB/Akt
LKB1
PTEN
TSC1
TSC2
"Compound C"
AMPK
Dual PI3K and
mTOR
inhibitors
Rheb
mTOR
Rapamycin and
analogs,
Torin1, PP242
Ulk
complex

EVEROLIMUS

Inhibidor de mTOR

No parece incrementar el riesgo de ETE

Sin embargo en pacientes con trasplante renal y tratados con everolimus se observa[1]:

- Alteración de la fibrinolisis
- Formación de trombina
- Activación del endotelio

Se sugiere un incremento del riesgo de ETE

[1]Baas MC, et al. Thromb Res 2013

EVEROLIMUS – RADIANT 3

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D.,

Incidencia no descrita en la publicación

Adverse Event	Everolimus (N=204)		Placebo (N=203)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	no. of patients (%)			
Stomatitis*	131 (64)	14 (7)	34 (17)	0
Rash	99 (49)	1 (<1)	21 (10)	0
Diarrhea	69 (34)	7 (3)	20 (10)	0
Fatigue	64 (31)	5 (2)	29 (14)	1 (<1)
Infections†	46 (23)	5 (2)	12 (6)	1 (<1)
Nausea	41 (20)	5 (2)	37 (18)	0
Peripheral edema	41 (20)	1 (<1)	7 (3)	0
Decreased appetite	40 (20)	0	14 (7)	2 (1)
Headache	39 (19)	0	13 (6)	0
Dysgeusia	35 (17)	0	8 (4)	0
Anemia	35 (17)	12 (6)	6 (3)	0
Epistaxis	35 (17)	0	0	0
Pneumonitis‡	35 (17)	5 (2)	0	0
Weight loss	32 (16)	0	9 (4)	0
Vomiting	31 (15)	0	13 (6)	0
Pruritus	30 (15)	0	18 (9)	0
Hyperglycemia	27 (13)	11 (5)	9 (4)	4 (2)
Thrombocytopenia	27 (13)	8 (4)	1 (<1)	0
Asthenia	26 (13)	2 (1)	17 (8)	2 (1)
Nail disorder	24 (12)	1 (<1)	2 (1)	0
Cough	22 (11)	0	4 (2)	0
Pyrexia	22 (11)	0	0	0
Dry skin	21 (10)	0	9 (4)	0

Yao JC, et al. N Engl J Med 2011

Everolimus – BOLERO 2
Cáncer de mama

Table 2. Adverse Events Irrespective of Relationship to Study Treatment (with at Least 10% Incidence in the Everolimus–Exemestane Group).

Adverse Event	Everolimus and Exemestane (N=482)			Placebo and Exemestane (N=238)		
	Any Event	Grade 3 Event	Grade 4 Event	Any Event	Grade 3 Event	Grade 4 Event
	percent					
Stomatitis	56	8	0	11	1	0
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Decreased appetite	29	1	0	10	0	0
Nausea	27	<1	<1	27	1	0
Cough	22	1	0	11	0	0
Dysgeusia	21	<1	0	5	0	0
Headache	19	<1	0	13	0	0
Decreased weight	19	1	0	5	0	0
Dyspnea	18	4	0	9	1	<1
Arthralgia	16	1	0	16	0	0
Anemia	16	5	1	4	<1	<1
Epistaxis	15	0	0	1	0	0
Vomiting	14	<1	<1	11	<1	0
Peripheral edema	14	1	0	6	<1	0
Pyrexia	14	<1	0	6	<1	0
Aspartate aminotransferase level increased	13	3	<1	6	1	0
Constipation	13	<1	0	11	<1	0
Hyperglycemia	13	4	<1	2	<1	0
Pneumonitis	12	3	0	0	0	0
Thrombocytopenia	12	2	1	<1	0	<1
Asthenia	12	2	0	3	0	0
Alanine aminotransferase level increased	11	3	<1	3	2	0
Pruritus	11	<1	0	3	0	0
Insomnia	11	<1	0	8	0	0
Back pain	11	0	0	8	1	0

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D.,

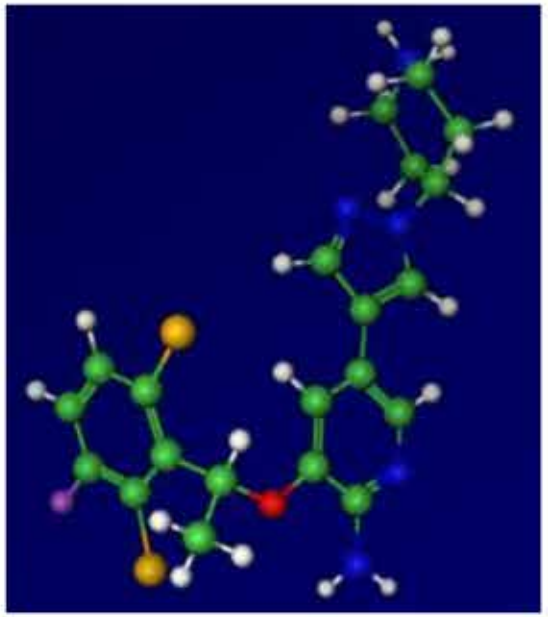
Incidencia no descrita en la publicación

Baselga J, et al. N Engl J Med 2012

OTROS INHIBIDORES TIROSIN-KINASA

Crizotinib: no incrementa el riesgo de ETE

Potent and selective ATP competitive oral inhibitor of ALK and MET tyrosine kinases and their oncogenic variants



AGENTES ESTIMULADORES DE LA ERITROPOYESIS

Trasfusiones de hematíes se han asociado con un mayor riesgo de:

ETV OR 1,60, IC95% 1,53-1,67; p<0,05

ETEA OR 1,53; IC95% 1,46-1,61; p<0,05

Mortalidad OR 1,34; IC95% 1,29-1,38; p<0,05

AEE

Relaciones complicaciones tromboembólicas con valores de hemoglobina

11 g/dL

También se ha sugerido efecto prototrombótico independiente de la cifra de hemoglobina (activación endotelial+reactividad plaquetaria)

Martínez de Castro, et al. Monografía Thrombosis Risk

AAE Y TROMBOSIS

Tabla 3. Resumen de los principales metaanálisis sobre seguridad de los agentes estimulantes de la eritropoyesis.

Autor	Año	Estudios incluidos	Mortalidad global	Mortalidad estudios con quimioterapia	Riesgo de trombosis
Bohlius *et al.*[15]	2006	Pacientes oncológicos que reciben AEE, tanto **con anemia como sin ella, con y sin quimioterapia**	HR: 1,08; IC95%: 0,99-1,18; 42 estudios, 8.167 pacientes	RR: 1,02; IC95%: 0,90-1,15; 30 estudios, 6.282 pacientes	RR: 1,67; IC95%: 1,35-2,06; 35 estudios, 6.769 pacientes
Bennett *et al*[18]	2008	Pacientes oncológicos en tratamiento **con quimioterapia** y *darbepoetina alfa*	HR: 1,10; IC95%: 1,01-1,2; 51 estudios, 13.611 pacientes	⇧50%	RR: 1,57; IC95%: 1,31- 1,87; 31 estudios, 8.172 pacientes
Ludwig *et al.*[19]	2009	Pacientes oncológicos con **anemia inducida por quimioterapia** tratados con *darbepoetina alfa*	HR: 0,97; IC95%: 0,85- 1,1; 6 estudios, 2.122 pacientes	Riesgo	HR: 1,57; IC95%: 1,10-2,26; 6 estudios, 2.122 pacientes
Glaspy *et al.*[20]	2010	Pacientes oncológicos que reciben AEE tanto **con anemia como sin ella, con y sin quimioterapia**	OR: 1,06; IC95%: 0,97-1,15; 60 estudios, 15.323 pacientes	OR: 1,03; IC95%: 0,93-1,13; 47 estudios, 12.108 pacientes	OR: 1,48; IC95%: 1,28-1,72; 44 estudios, 13.196 pacientes
Tonia *et al.*[12]	2012	Pacientes oncológicos que reciben AEE tanto **con anemia como sin ella, con y sin quimioterapia**	HR: 1,17; IC95%: 1,06-1,29; 70 estudios, 15.935 pacientes		RR: 1,52; IC95%: 1,34-1,74; 57 estudios, 15.498 pacientes

Martínez de Castro, et al. Monografía Thrombosis Risk

AAE Y TROMBOSIS

No diferencias de riesgo entre las distintas EPOs (riesgo similar)

Sin datos sobre la eficacia de tromboprofilaxis (AAS-HBPM)

Incremento de ACVA

Darbepoetina HR 1,92; IC95%: 1,38 a 2,68

Martínez de Castro, et al. Monografía Thrombosis Risk

ANTANGIOGÉNICOS Y RIESGO HEMORRÁGICO

Tabla 8.5. Riesgo relativo de fenómenos hemorrágicos en ensayos con bevacizumab o inhibidores de la tirosina cinasa

Estudio	Fármaco	N.º ensayos	N	Incidencia		RR		RR (dosis de Bev)	
				Todos los grados (%, IC 95%)	Grados 3-5 (%, IC 95%)	Todos los grados (IC 95%)	Grados 3-5 (IC 95%)	2,5 mg/kg/sem (IC 95%)	5 mg/kg/sem (IC 95%)
Hapani	Bev	20	12.617	30,4% (21,5-40,9)	3,5% (2,2-5,7)	2,48 (1,93-3,18)	1,91 (1,36-2,68)	2,01 (1,43-2,83)	3,02 (2,42-3,78)
Hang	Bev	22	14.277	25% (18-34)	2,8% (2,1-3,8)	2,65 (2,08-3,38)	1,60 (1,19-2,15)	1,27 (0,95-1,71)	3,02 (1,85-4,95)
Je	Su-So	23	6.779	16,7% (12,7-21,5)	2,4% (1,6-3,9)	2,0 (1,14-3,49)	1,16 (0,70-1,92)	-	-

So: sorafenib; Su: sunitinib.

Hapani S, et al. Oncology 2010
Hang XF, et al. Eur J Clin Pharmacol 2011
Je Y, et al. Lancet Oncol 2009

Increased Risk of Serious Hemorrhage with Bevacizumab in Cancer Patients: A Meta-Analysis

Sanjaykumar Hapani[a] Amna Sher[a] David Chu[b] Shenhong Wu[a]

Incidencia de hemorragias grado 3-4

	Studies n	High-grade hemorrhage (bevacizumab) n/total n	High-grade hemorrhage (control) n/total n	Incidence (95% CI) %	RR (95% CI)
Overall	19	256/6,635	103/5,866	3.5 (2.2–5.7)	1.91 (1.36–2.68)
Colorectal cancer	6	44/1,698	27/1,652	2.8 (2.1–3.7)	1.45 (0.88–2.38)
NSCLC	4	128/1,191	24/841	11.5 (5.8–21.3)	2.84 (1.87–4.32)
NSCLC-NSQ	3	120/1,125	24/809	11.3 (4.7–24.8)	2.77 (1.81–4.23)
Breast cancer	3	9/1,091	3/794	0.9 (0.5–1.7)	1.59 (0.45–5.59)
Renal cell carcinoma	2	16/703	2/653	2.4 (1.5–3.8)	7.0 (1.59–30.68)
Pancreatic cancer	2	30/573	21/550	5.8 (4.0–8.1)	1.38 (0.8–2.37)
Malignant mesothelioma	1	4/53	1/55	7.5 (2.9–18.4)	4.15 (0.47–35.94)

Hapani J, et al. Oncology 2010:79,27-38

Incidencia de mortalidad por hemorragia

	Studies n	Grade 5 hemorrhage (bevacizumab) n/total n	Grade 5 hemorrhage (control) n/total n	Incidence (95% CI) %	RR (95% CI)
Overall	14	29/5,100	8/4,575	0.8 (0.4–1.7)	3.56 (1.71–7.41)
Colorectal cancer	6	5/2,872	0/2,823	0.3 (0.1–0.8)	10.81 (0.60–105.45)
NSCLC	4	22/1,218	2/841	2.7 (1.1–6.3)	5.02 (1.52–16.66)
NSCLC-NSQ	3	18/1,152	2/809	1.8 (1.2–2.9)	5.16 (1.38–19.24)
Renal cell carcinoma	2	2/413	0/344	0.6 (0.2–2.1)	4.17 (0.20–86.50)
Breast cancer	2	0/694	0/561	0	NA

RECOMENDACIONES

PROFILAXIS TEV EN PACIENTE MÉDICO AMBULATORIO

Pacientes con cáncer y quimioterapia ambulatoria:

- No se recomienda profilaxis farmacológica de forma rutinaria.
- Pacientes con **mieloma múltiple** en tratamiento con *talidomida o lenalidomida + quimioterapia o dexametasona a dosis altas* se recomienda HBPM
  - o AVK (INR 1.5)

ASCO 2015

Lyman GH, et al. J Clin Oncol 2015

ANTIANGIOGÉNICOS Y ETE – MANEJO

- **TE Arterial**
  - Se recomienda suspender el tratamiento con antiangiogénicos en los pacientes que han presentado un episodio de TEA
  - Respecto a la profilaxis, no está claramente establecido el papel de la aspirina u otros antiagregantes en la prevención de TEA relacionados con los fármacos anti-VEGF
- **TE Venoso**
  - Anticoagulación preferentemente con HBPM
  - Suspender anti-VEGF. Reiniciar en función de ratio riesgo-beneficio
  - Profilaxis: No demostrada

CONCLUSIONES

- El tratamiento oncológico aumenta el riesgo de eventos tromboembólicos, tanto venosos como arteriales.
- Previo al inicio de un tratamiento sistémico farmacológico en un paciente con cáncer se debe realizar una valoración específica del riesgo de trombosis asociado a la terapia a emplear.

CONCLUSIONES

- Sería deseable que los ensayos clínicos analizaran con más detalle la incidencia, las características clínicas y la posible relación con los fármacos empleados con la enfermedad tromboembólica.
- ¿Debemos incluir en los futuros scores de riesgo de los pacientes que reciben tratamiento oncológico sistémico en un medio extrahospitalario variables relacionadas con el tratamiento?

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