



LA VISION GLOBAL DE LA PERSONA ENFERMA



GRUPO DE  
TROMBOEMBOLISMO

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**Cáncer y ETV**

**FORUM**

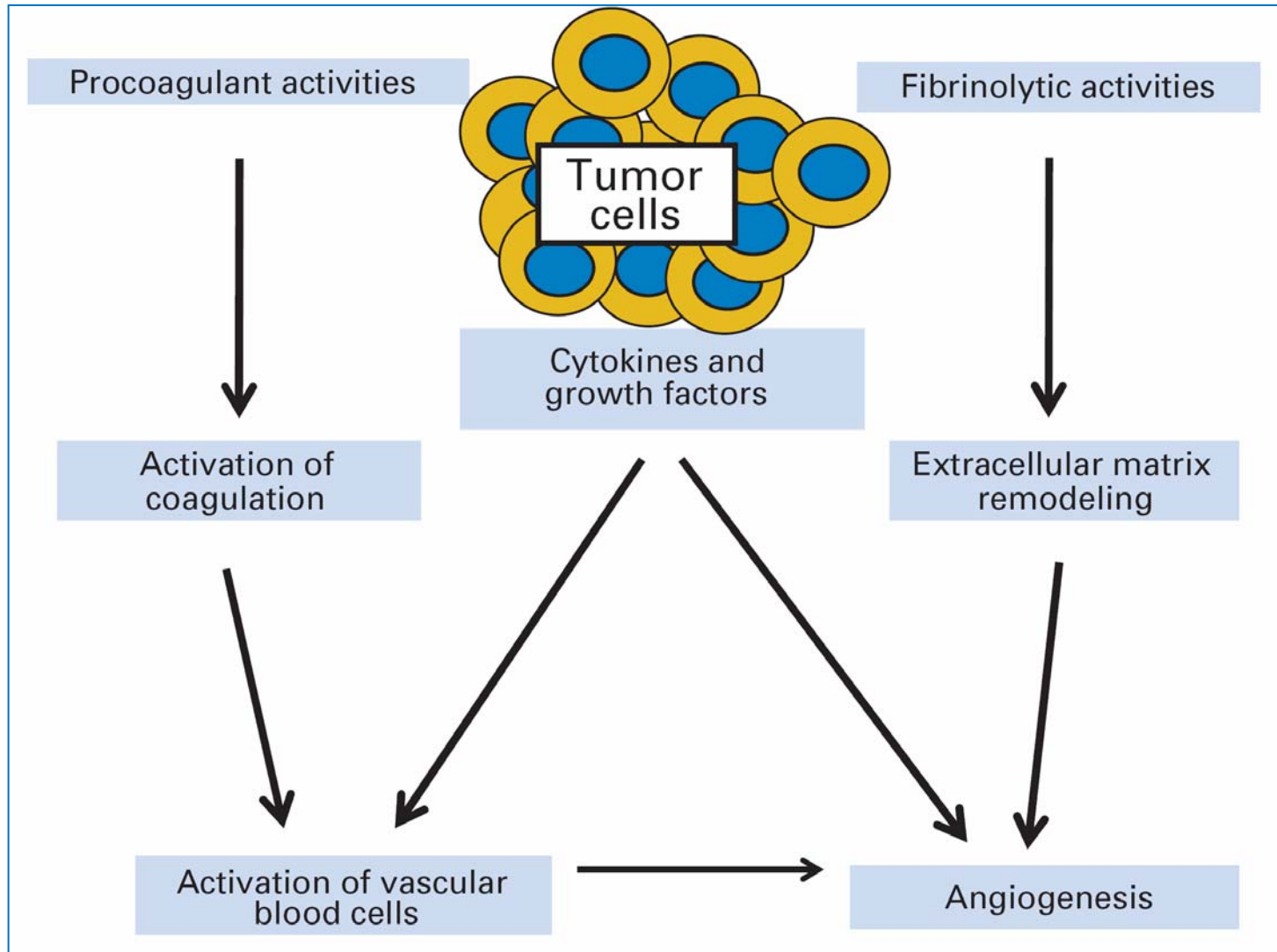
**MULTIDISCIPLINAR**

**DE LA ETV**

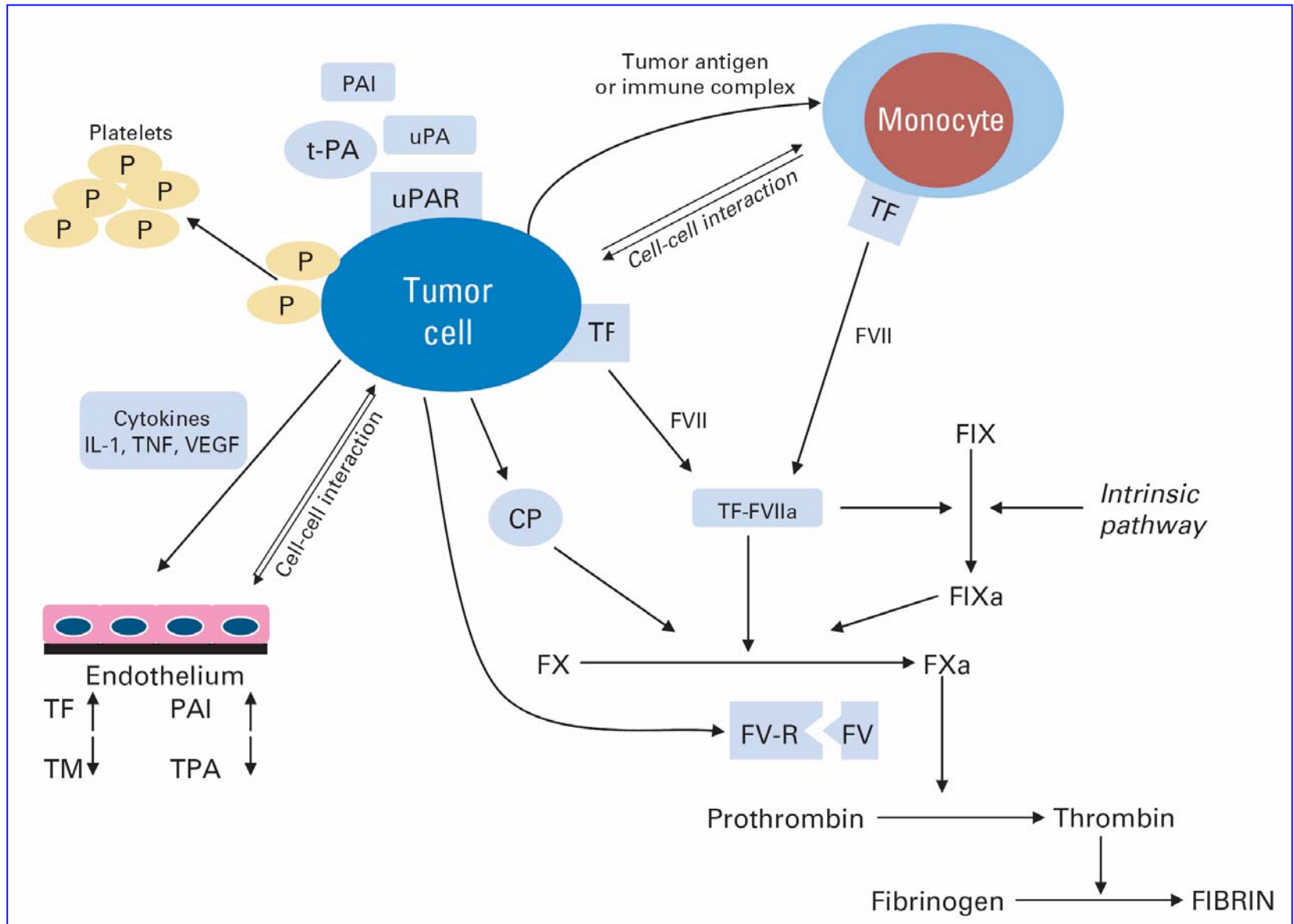
**21-22 OCTUBRE 2010**

HOTEL ABADES NEVADA PALACE - GRANADA

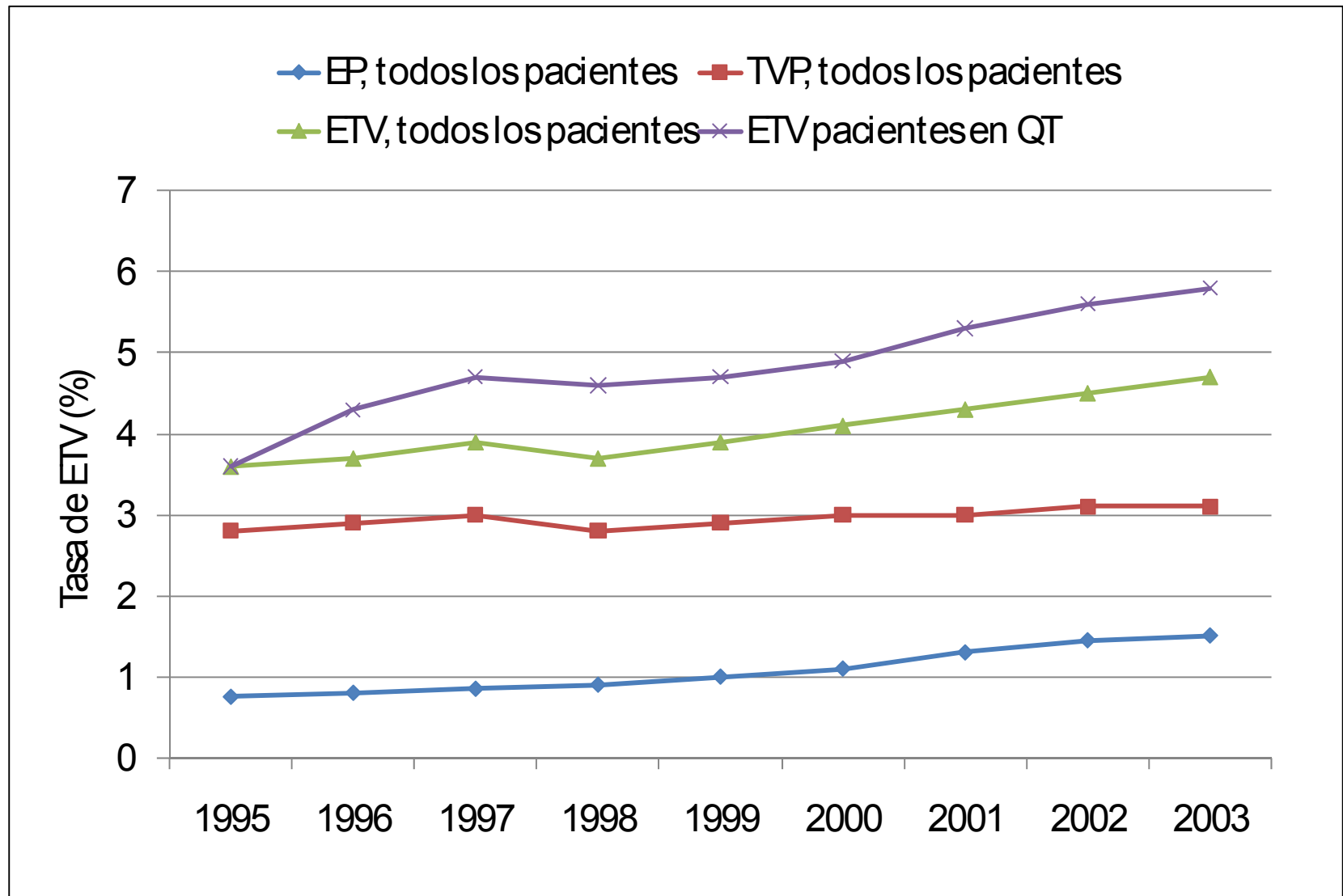
# Relación ETV-cáncer



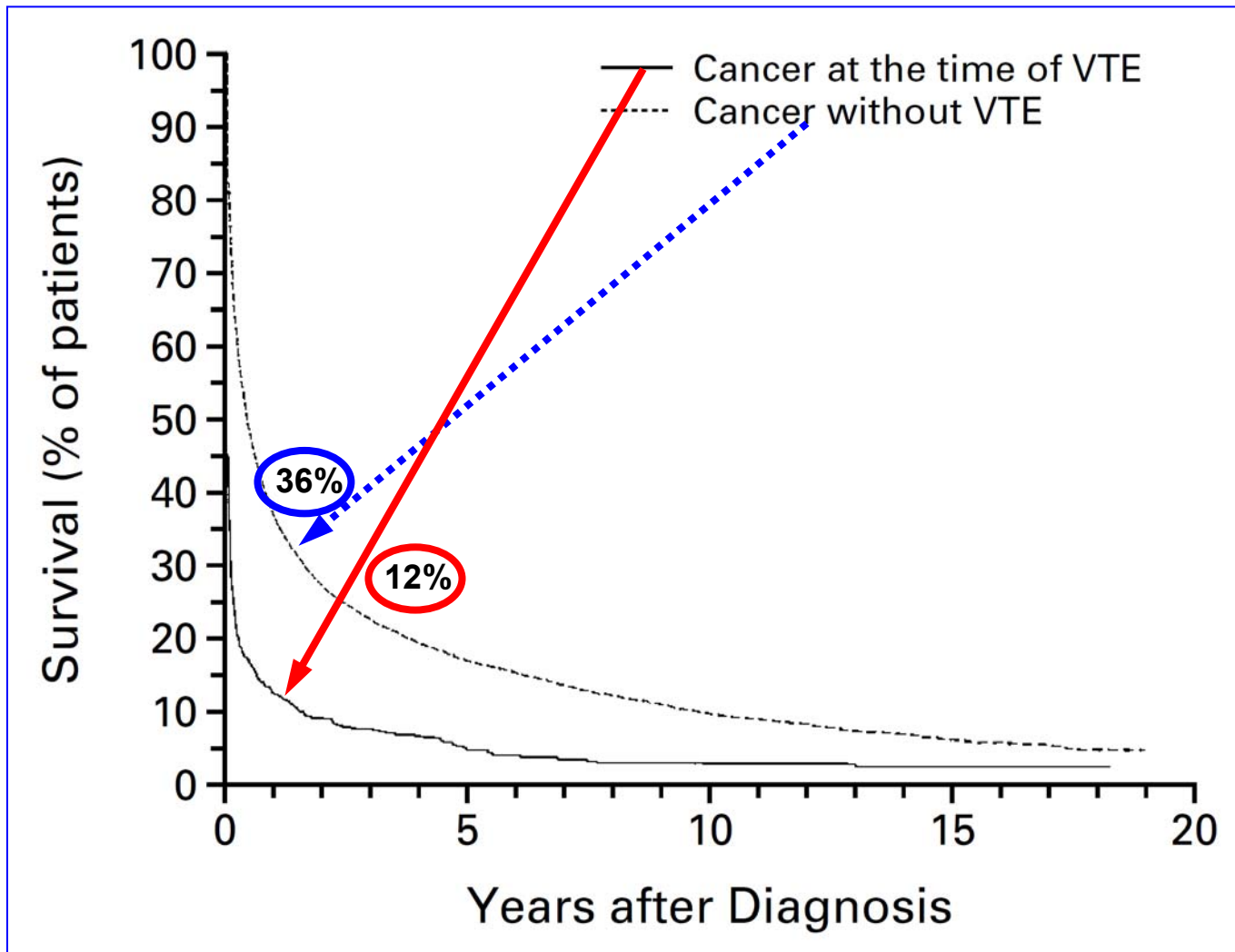
# Estado protrombótico del cáncer



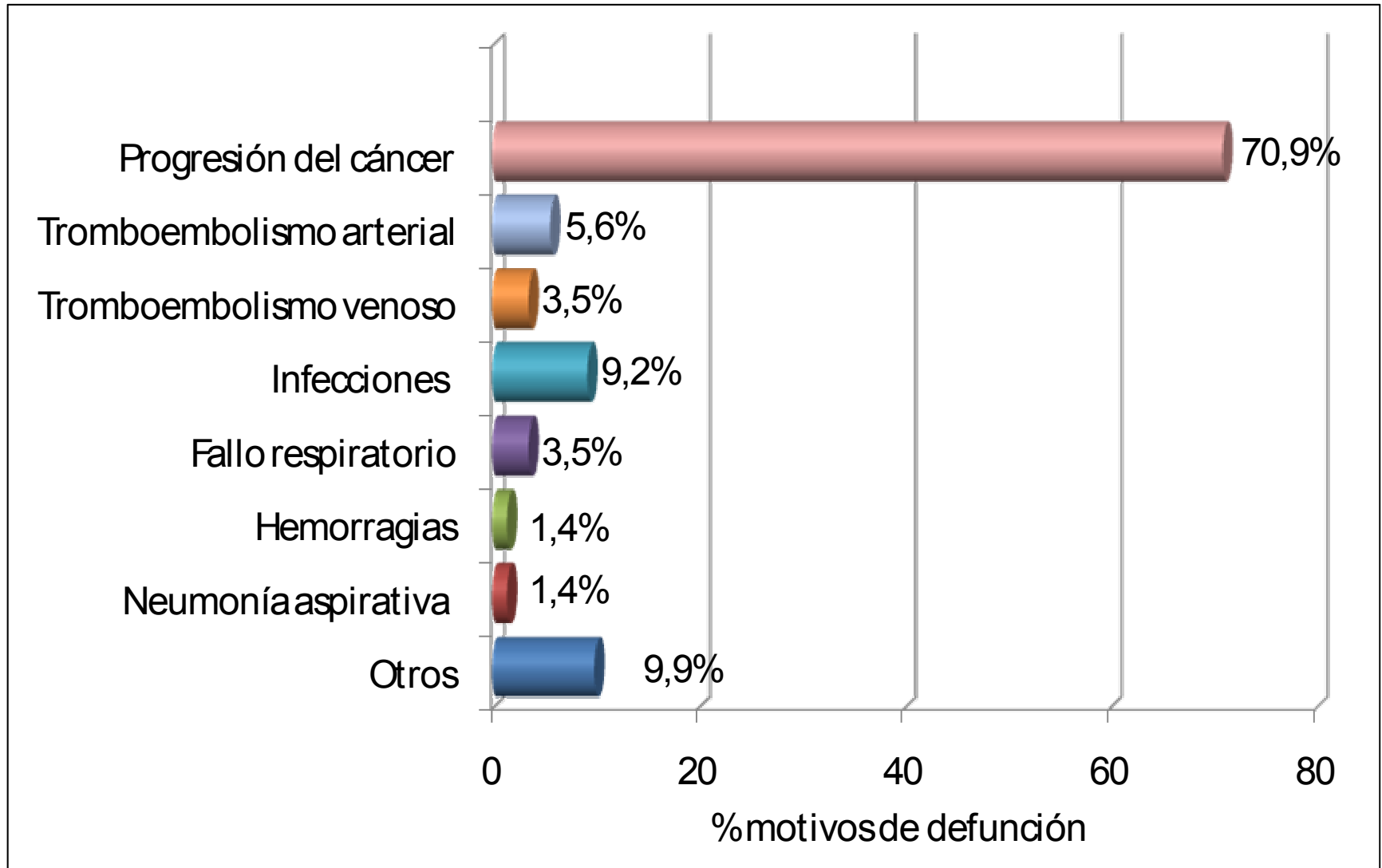
# Tendencia de la incidencia de ETV en pacientes con cáncer



# Pronóstico del cáncer asociado a ETV



# Causas de muerte en pacientes con cáncer en QT



# Guías de profilaxis y tto de la ETV en pacientes con cáncer



ESMO



AIOM



AMERICAN COLLEGE OF  
CHEST  
PHYSICIANS®



NCCN



ASCO®

American Society of Clinical Oncology



Fédération  
Nationale  
DES CENTRES DE LUTTE  
CONTRE LE CANCER



# Recomendaciones de prevención de ETV en pacientes con cáncer

Parameter	ASCO	NCCN	AIOM/ESMO
Prevention of VTE in the hospitalized cancer patient			
Recommendation	Prophylactic anticoagulation considered for all hospitalized cancer patients in the absence of contraindications	Prophylactic anticoagulation for all hospitalized cancer patients in the absence of contraindications	Prophylactic anticoagulation in immobilized hospitalized cancer patients with acute medical illness
Agent(s)	Low-dose UFH, LMWH, or fondaparinux		
Prevention of VTE in the surgical cancer patient			
Recommendation	Initial prophylaxis: prophylactic anticoagulation for patients undergoing laparotomy, laparoscopy, or thoracotomy lasting greater than 30 minutes; Prolonged prophylaxis: continue up to 4 weeks for major abdominal or pelvic surgery for cancer with high-risk features such as residual disease, obesity, or prior VTE	Initial prophylaxis: prophylactic anticoagulation is recommended; Prolonged prophylaxis: continue up to 4 weeks post-operation for high risk abdominal or pelvic cancer surgery	Initial prophylaxis: prophylaxis for cancer patients undergoing major cancer surgery; Prolonged prophylaxis: continue up to 28-35 days after major abdominal or pelvic surgery
Agent(s)	LMWH or UFH; add mechanical methods in highest-risk patients	LMWH, UFH, or fondaparinux ( $\pm$ pneumatic venous compression)	LMWH or UFH
Prevention of VTE in the ambulatory cancer patient			
Recommendation	Not recommended with the exception of patients with multiple myeloma receiving thalidomide-/lenalidomide-based combination regimens	Not recommended with the exception of patients with multiple myeloma receiving thalidomide-/lenalidomide-based combination regimens	Not recommended with the exception of patients with multiple myeloma receiving thalidomide-/lenalidomide-based combination regimens
Prevention of VTE in cancer patients with central venous catheters			
Recommendation	NA	Prophylactic anticoagulation not recommended	Prophylactic anticoagulation not recommended



# Recomendaciones de prevención de ETV en pacientes con cáncer

Parameter	ASCO	NCCN	AIOM/ESMO
Prevention of VTE in the hospitalized cancer patient			
Recommendation	Prophylactic anticoagulation considered for all hospitalized cancer patients in the absence of contraindications	Prophylactic anticoagulation for all hospitalized cancer patients in the absence of contraindications	Prophylactic anticoagulation in immobilized hospitalized cancer patients with acute medical illness
Agent(s)	Low-dose UFH, LMWH, or fondaparinux		

# Profilaxis de ETV en pacientes médicos ingresados

Study	Total No. of Patients	Patients With Cancer		Relative Risk	95% CI
		No.	%		
MEDENOX	579*	72	12.4	0.37	0.22 to 0.63
PREVENT	3,706	190	5.1	0.55	0.38 to 0.8
ARTEMIS	849†	131	15.4	0.47	0.08 to 0.69

Management phase	Dosage
<b>Prophylaxis</b>	
UFH	5000 U s.c. every 8 h
Dalteparin	5000 U s.c. daily
Enoxaparin	40 mg s.c. daily
Fondaparinux	2.5 mg s.c. daily <sup>b</sup>
Tinzaparin	4500 U s.c. or 75 U/kg s.c. daily

# Recomendaciones de prevención de ETV en pacientes con cáncer

## Prevention of VTE in the surgical cancer patient

Recommendation

Initial prophylaxis: prophylactic anticoagulation for patients undergoing laparotomy, laparoscopy, or thoracotomy lasting greater than 30 minutes; Prolonged prophylaxis: continue up to 4 weeks for major abdominal or pelvic surgery for cancer with high-risk features such as residual disease, obesity, or prior VTE

Initial prophylaxis: prophylactic anticoagulation is recommended; Prolonged prophylaxis: continue up to 4 weeks post-operation for high risk abdominal or pelvic cancer surgery

Initial prophylaxis: prophylaxis for cancer patients undergoing major cancer surgery; Prolonged prophylaxis: continue up to 28-35 days after major abdominal or pelvic surgery

Agent(s)

LMWH or UFH; add mechanical methods in highest-risk patients

LMWH, UFH, or fondaparinux ( $\pm$  pneumatic venous compression)

LMWH or UFH

# Profilaxis de ETV en pacientes quirúrgicos

## DURATION OF PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM WITH ENOXAPARIN AFTER SURGERY FOR CANCER

DAVID BERGQVIST, M.D., PH.D., GIANCARLO AGNELLI, M.D., ALEXANDER T. COHEN, M.D., AMIRAM ELDOR, M.D., PAUL E. NILSSON, M.D., PH.D., ANNE LE MOIGNE-AMRANI, M.S., AND FLAVIA DIETRICH-NETO, M.D., FOR THE ENOXACAN II INVESTIGATORS\*

**TABLE 3. INCIDENCE OF VENOUS THROMBOEMBOLIC EVENTS.**

EVENT	PLACEBO	ENOXAPARIN	RISK	P VALUE
	(N= 167)	(N= 165)	REDUCTION (95% CI)*	
	no. (%)		%	
During double-blind period				
All venous thromboembolism	20 (12.0)	8 (4.8)	60 (10–82)	0.02
Proximal deep-vein thrombosis	3 (1.8)	1 (0.6)		
Distal deep-vein thrombosis	17 (10.2)	7 (4.2)		
Pulmonary embolism	1 (0.6)†	0		
At 3 mo				
All venous thromboembolism	23 (13.8)	9 (5.5)	60 (17–81)	0.01‡
Proximal deep-vein thrombosis	4 (2.4)	2 (1.2)		
Distal deep-vein thrombosis	17 (10.2)	7 (4.2)		
Pulmonary embolism	2 (1.2)	0		

# Profilaxis de ETV en pacientes quirúrgicos

## Extended prophylaxis with bemparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer: the CANBESURE randomized study

V. V. KAKKAR,\* J. L. BALIBREA,† J. MARTÍNEZ-GONZÁLEZ‡, PAOLO PRANDONI§ and ON BEHALF OF THE CANBESURE STUDY GROUP<sup>¶</sup>

**Table 3** Incidence of events in the modified intention-to-treat population (main efficacy analysis)

Outcome, <i>n</i> (%)	Bemparin ( <i>n</i> = 248)	Placebo ( <i>n</i> = 240)	RRR (95% CI) (%)	<i>P</i> -value*
<i>Double-blind period</i>				
Primary efficacy outcome <sup>†</sup>	<b>25 (10.1)</b>	<b>32 (13.3)</b>	<b>24.4</b> (−23.7; 53.8)	<b>0.26</b>
DVT	19 (7.7)	29 (12.1)	36.6 (−10.0; 63.4)	0.10
Proximal DVT	1 (0.4)	8 (3.3)	87.9 (4.0; 98.5)	0.02
Distal DVT only	18 (7.3)	21 (8.8)	17.1 (−51.8; 54.7)	0.54
Non-fatal PE	0 (0.0)	0 (0.0)	–	–
Death (all-causes)	6 (2.4)	3 (1.3)	−93.6 (−665.1; 51.0)	0.50
Any DVT, nonfatal PE and VTE-related death	20 (8.1)	32 (13.3)	39.5 (−2.7; 64.4)	0.06
Major venous thromboembolism <sup>‡</sup>	2 (0.8)	11 (4.6)	82.4 (21.5; 96.1)	0.010
<i>Double-blind plus follow-up periods</i>				
Death (all-causes)	8 (3.2)	6 (2.5)	−29.0 (−266.4; 54.6)	0.63
Any DVT, nonfatal PE and VTE-related death	21 (8.5)	32 (13.3)	36.5 (−6.9; 62.3)	0.08
Major venous thromboembolism <sup>‡</sup>	3 (1.2)	11 (4.6)	73.6 (6.6; 92.5)	0.03

RRR, relative risk reduction; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism. \**P*-values were calculated using the  $\chi^2$ -test or Fisher's exact test, as appropriate. <sup>†</sup>Primary efficacy outcome was defined as the combined incidence at the end of double-blind period of total documented symptomatic and asymptomatic DVT, non-fatal PE and all-cause mortality. <sup>‡</sup>Major venous thromboembolism was the composite of symptomatic and asymptomatic proximal DVT, non-fatal PE and VTE-related deaths.

# Recomendaciones de prevención de ETV en pacientes con cáncer

Prevention of VTE in the ambulatory cancer patient

Recommendation

Not recommended with the exception of patients with multiple myeloma receiving thalidomide-/lenalidomide-based combination regimens

Not recommended with the exception of patients with multiple myeloma receiving thalidomide-/lenalidomide-based combination regimens

Not recommended with the exception of patients with multiple myeloma receiving thalidomide-/lenalidomide-based combination regimens



# Profilaxis de ETV en pacientes ambulatorios con cáncer

	Prophylaxis	VTE (%)
Thalidomide/dexamethasone		
Cavo et al, <sup>96</sup> Rajkumar et al <sup>100</sup>	No	20-26
Weber et al, <sup>101</sup> Cavo et al <sup>96</sup>	Warfarin 1.0/1.25 mg	25/13
Palumbo et al, <sup>102</sup> Dimopoulos et al <sup>10</sup>	No	2-7
Thalidomide/MP		
Palumbo et al <sup>103</sup>	No	18
Palumbo et al <sup>103</sup>	Enoxaparin 40 mg/d	5
Thalidomide/chemotherapy-doxorubicin		
Zangari et al <sup>11</sup>	No	34
Zangari et al <sup>11</sup>	Warfarin 1 mg	31
Zangari et al, <sup>11</sup> Minnema et al <sup>95</sup>	LMWH	10-15
Zangari et al <sup>35</sup>	No	16
Baz et al <sup>97</sup>	Aspirin 81 mg	19
Lenalidomide/dexamethasone		
Zonder et al <sup>38</sup>	No	14-75
Rajkumar et al, <sup>104</sup> Zonder et al <sup>38</sup>	Aspirin 81-325 mg	3-19
Klein et al <sup>105</sup>	LMWH	2
Dimopoulos et al <sup>12</sup>	No	11
Lenalidomide/MP		
Palumbo et al <sup>106</sup>	Aspirin 100 mg	5-10
Lenalidomide + chemotherapy-doxorubicin		
Baz et al <sup>97</sup>	Aspirin 81 mg	9

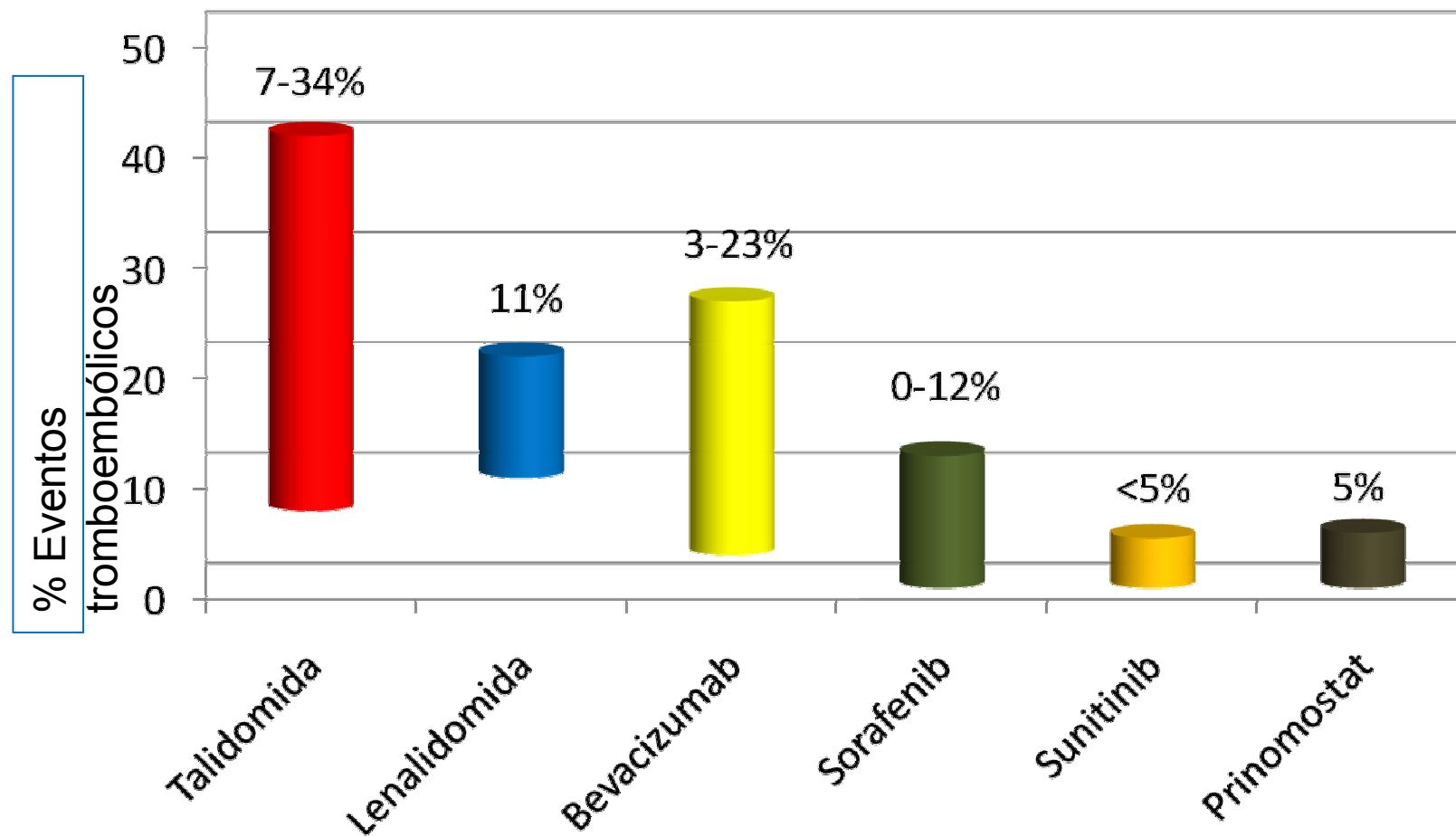


# Predicción de ETV en pacientes con cáncer en QT

Característica	Odds	Puntuación
<b>Localización del cáncer</b>		
<b>Bajo riesgo</b> (mama, colorrectal, cabeza y	1.0 (ref.)	0
<b>Alto riesgo</b> (pulmón, linfoma, ginecológico, genitourinario excluyendo próstata)	1.5	1
<b>Muy alto riesgo</b> (estómago, páncreas)	4.3	2
<b>Recuento plaquetario</b> $\geq 350.000 /\text{mm}^3$	1.8	1
<b>Hemoglobina</b> $< 10 \text{ g/dL}$ o tratamiento con factores estimulantes de hematíes	2.4	1
<b>Recuento leucocitario</b> $> 11.000/\text{mm}^3$	2.2	1
<b>Índice de masa corporal</b> $\geq 35 \text{ kg/m}^2$	2.5	1

Categoría de riesgo	Puntuación	Tasa de tromboembolismo venoso
<b>Bajo riesgo</b>	<b>0</b>	<b>0.3-0.8%</b>
<b>Alto riesgo</b>	<b>1-2</b>	<b>1.8-2.0%</b>
<b>Muy alto riesgo</b>	<b><math>\geq 3</math></b>	<b>6.7-7.1%</b>

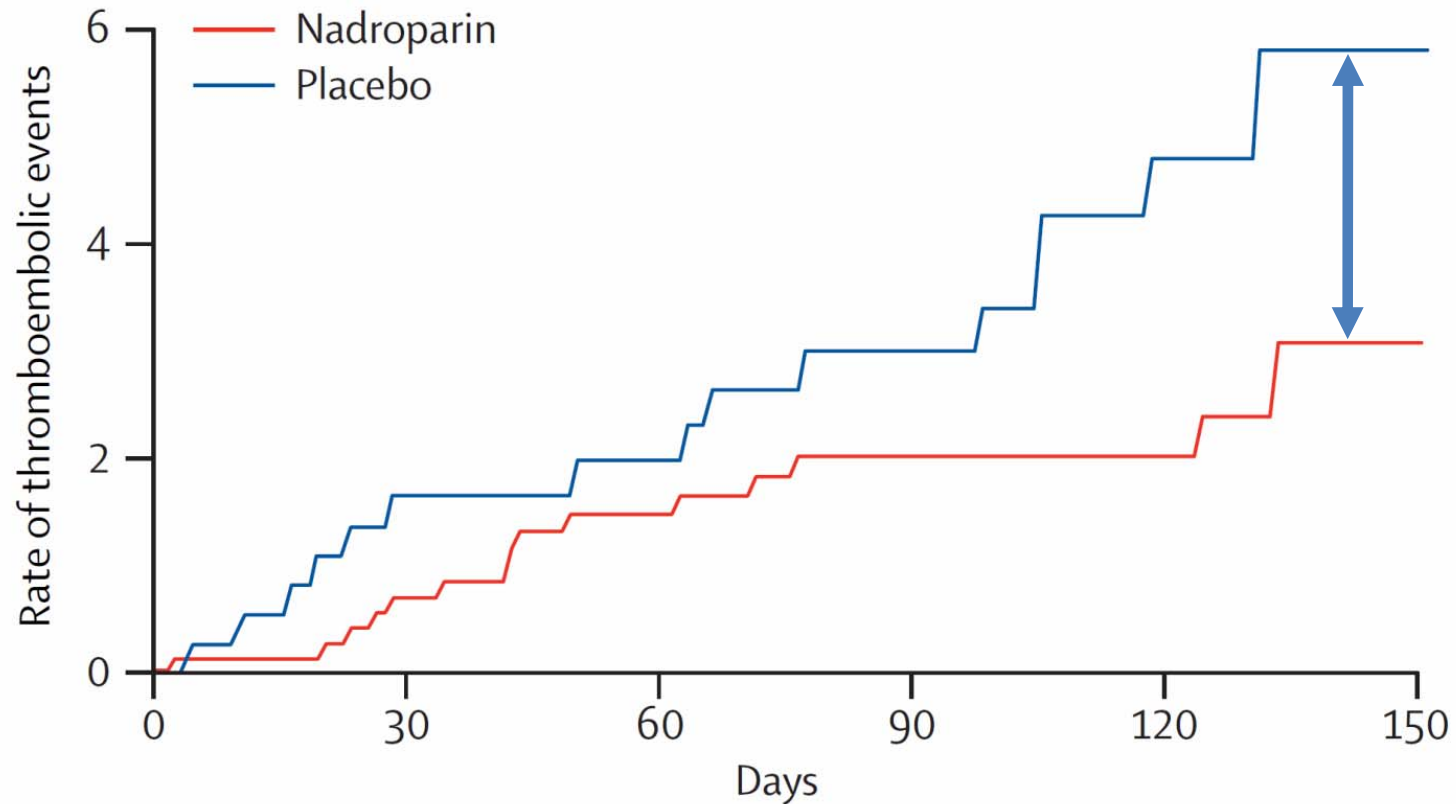
# Fármacos antiangiogénicos y ETV en pacientes con cáncer



# Profilaxis de ETV en pacientes con cáncer

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

*Giancarlo Agnelli, Gualberto Gussoni, Carlo Bianchini, Melina Verso, Mario Mandalà, Luigi Cavanna, Sandro Barni, Roberto Labianca, Franco Buzzi, Giovanni Scambia, Rodolfo Passalacqua, Sergio Ricci, Giampietro Gasparini, Vito Lorusso, Erminio Bonizzoni, Maurizio Tonato, on behalf of the PROTECT Investigators\**



**Figure 2: Cumulative hazard of thromboembolic events by treatment**

# Recomendaciones de prevención de ETV en pacientes con cáncer

Prevention of VTE in cancer patients  
with central venous catheters

Recommendation

NA

Prophylactic anticoagulation  
not recommended

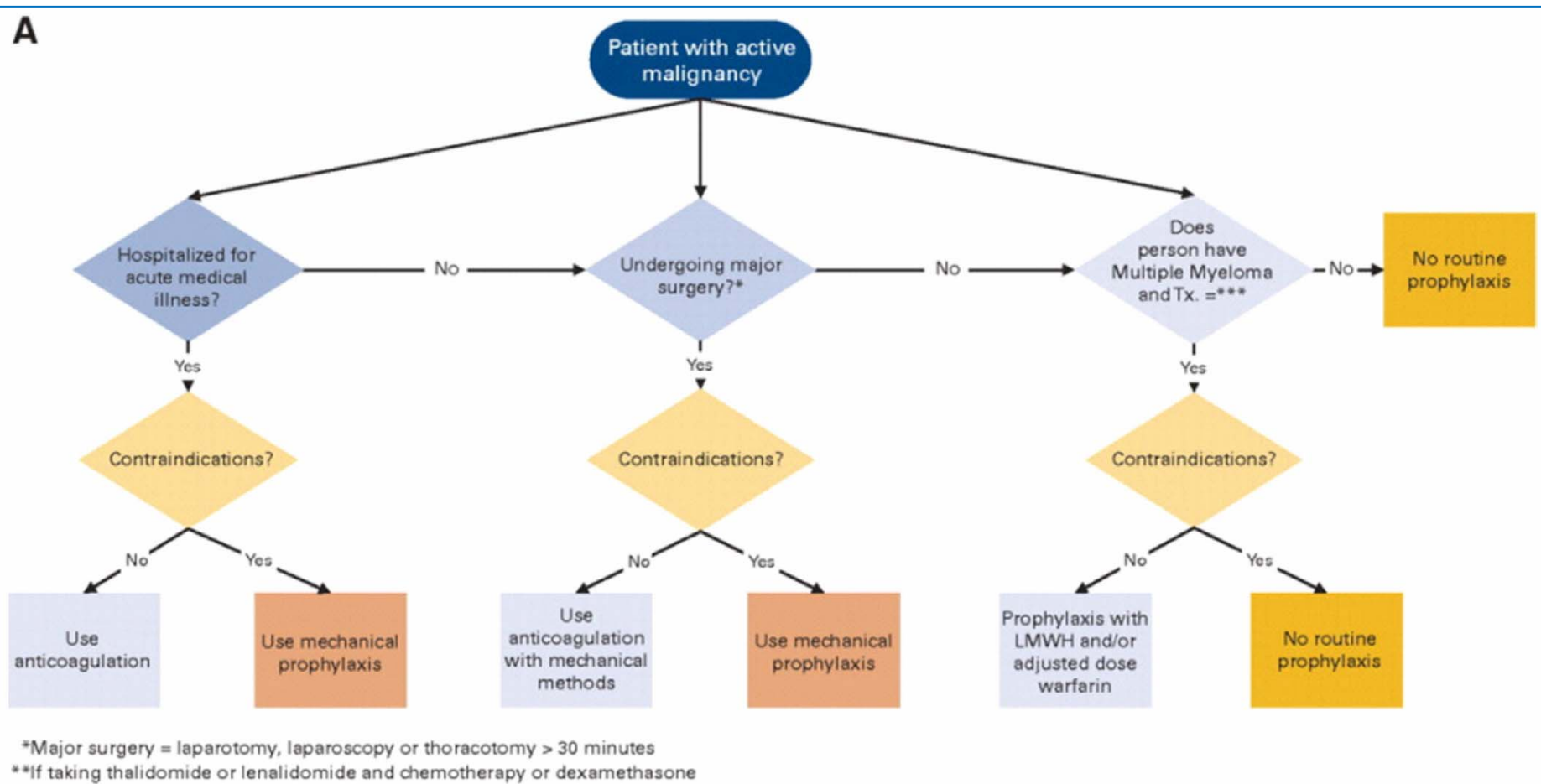
Prophylactic anticoagulation  
not recommended

# Profilaxis de ETV asociada a CVC en pacientes con cáncer

<b>Study</b>	<b>Anticoagulant</b>	<b>RR (CI 95%)</b>
Bern <i>et al.</i> (1990)	Warfarin	0.31 (0.11 – 0.88)
Monreal <i>et al.</i> (1996)	Dalteparin	0.16 (0.02 – 1.22)
Heaton <i>et al.</i> (2002)	Warfarin	1.91 (0.18 – 20.3)
Mismetti <i>et al.</i> (2003)	Nadroparin (vs. warfarin)	1.45 (0.46 – 4.59)
Abdelkefi <i>et al.</i> (2004)	UFH	0.19 (0.02 – 1.54)
Karthaus <i>et al.</i> (2005)	Dalteparin	0.99 (0.34 – 2.83)
Verso <i>et al.</i> (2005)	Enoxaparin	0.33 (0.07 – 1.63)
Couban <i>et al.</i> (2005)	Warfarin	1.15 (0.36 – 3.68)
Young <i>et al.</i> (2005)	Warfarin	0.75 (0.45 – 1.24)
Ruud <i>et al.</i> (2006)	Warfarin	0.95 (0.69 – 1.31)

# Recomendaciones de prevención de ETV en pacientes con cáncer

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

## Venous Thromboembolism Prophylaxis and Treatment in Cancer: A Consensus Statement of Major Guidelines Panels and **Call to Action**

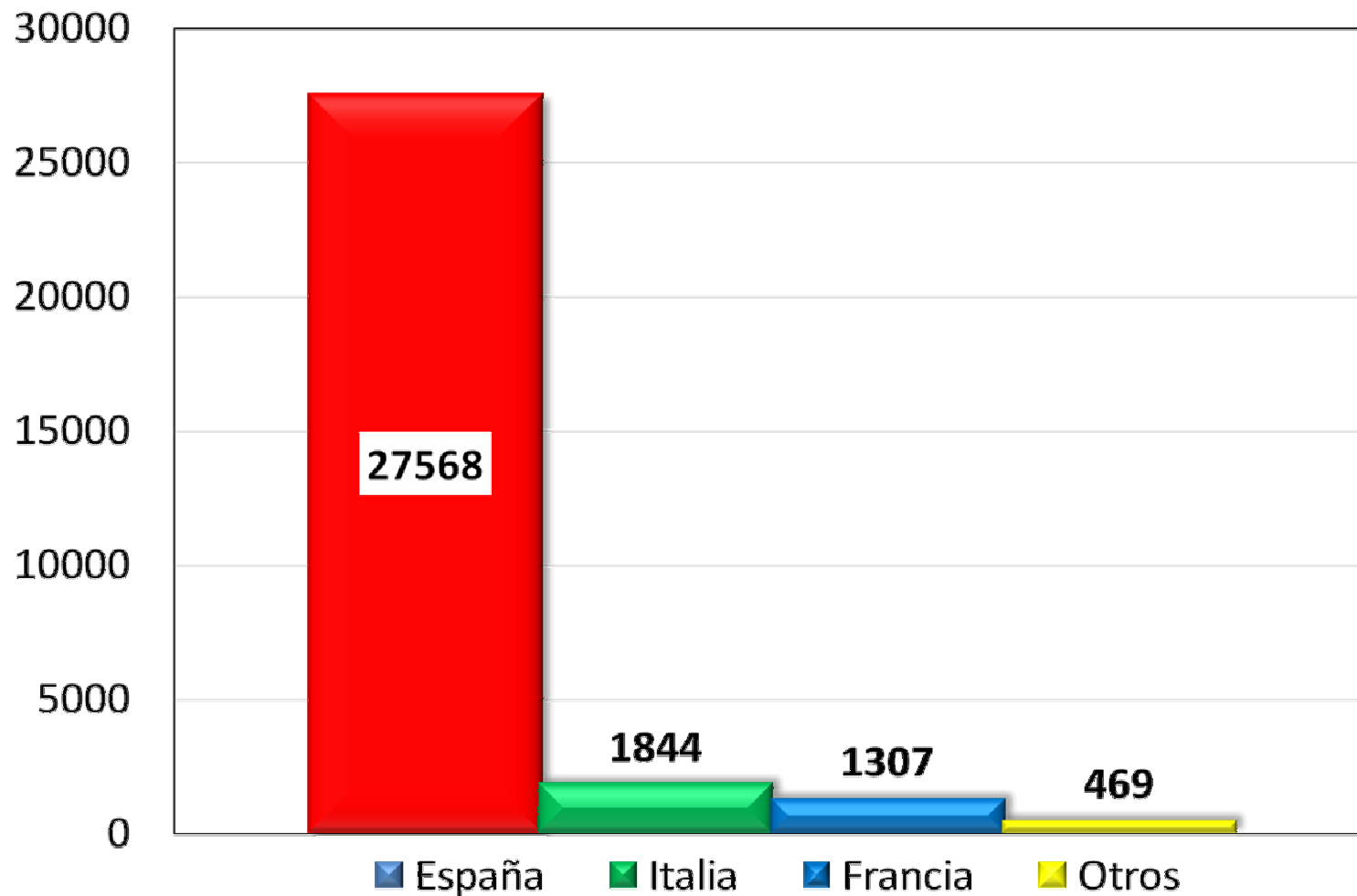


American Society of Clinical Oncology





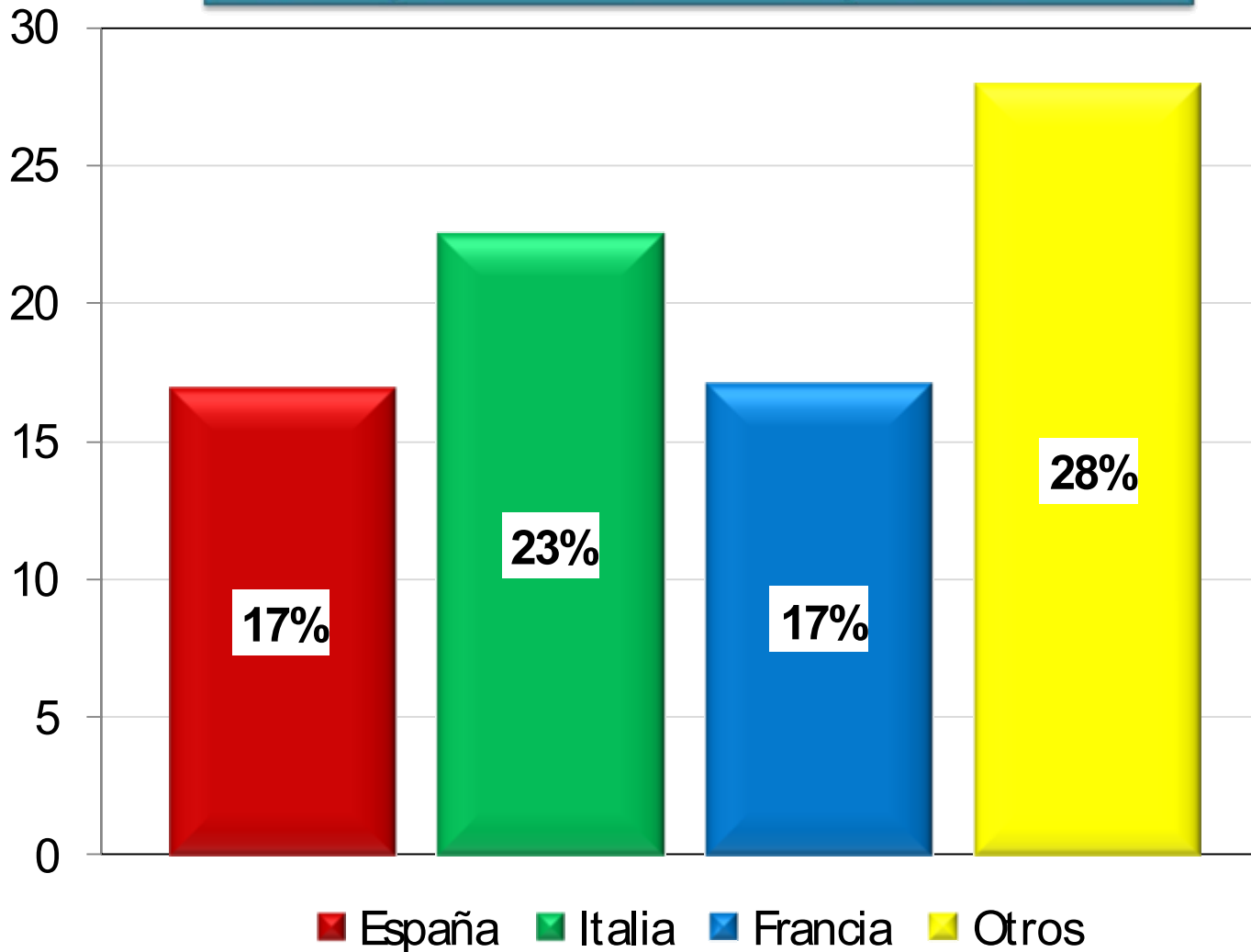
# Prevención de ETV en pacientes con cáncer: visión internacional



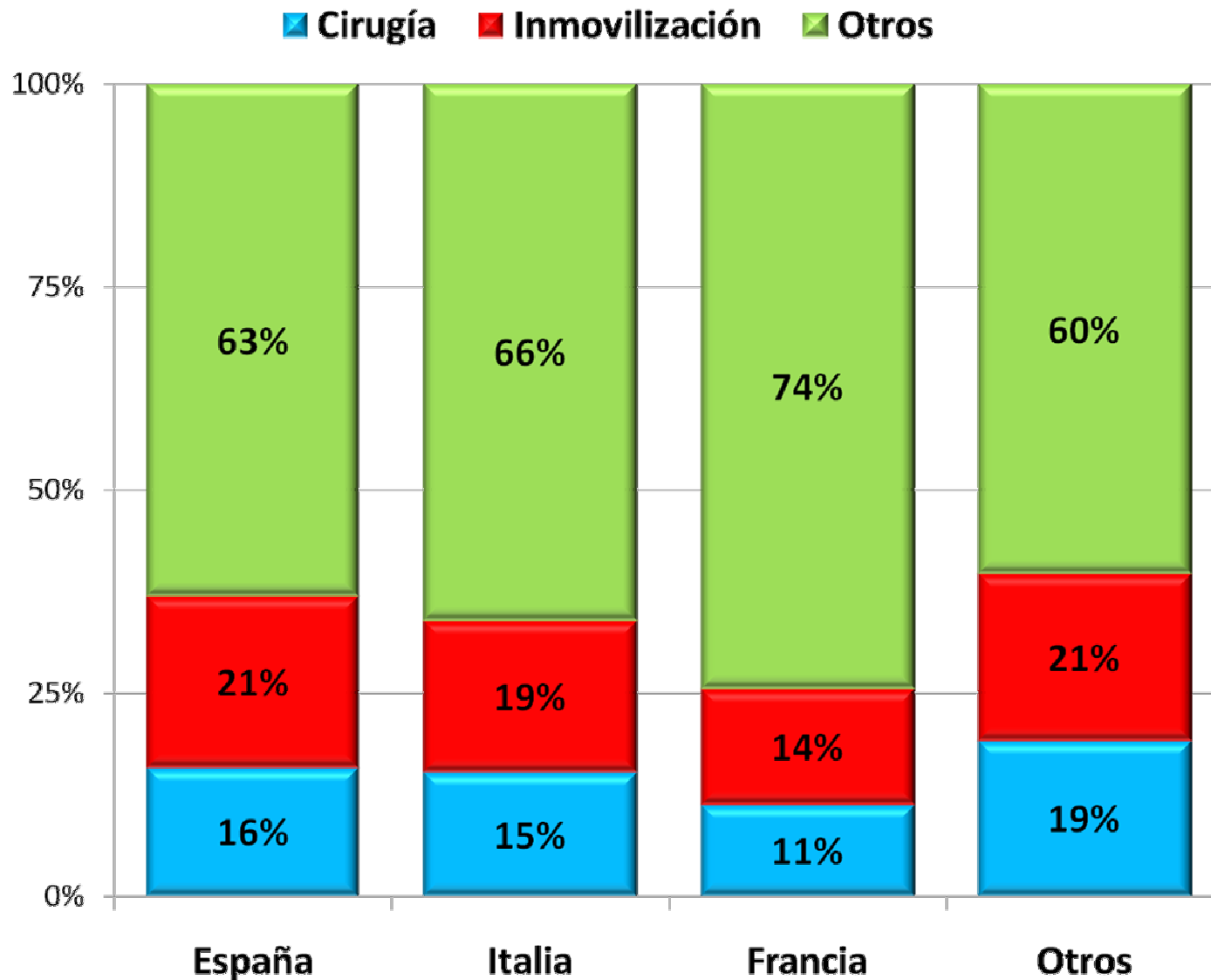
# Prevención de ETV en pacientes con cáncer: visión internacional



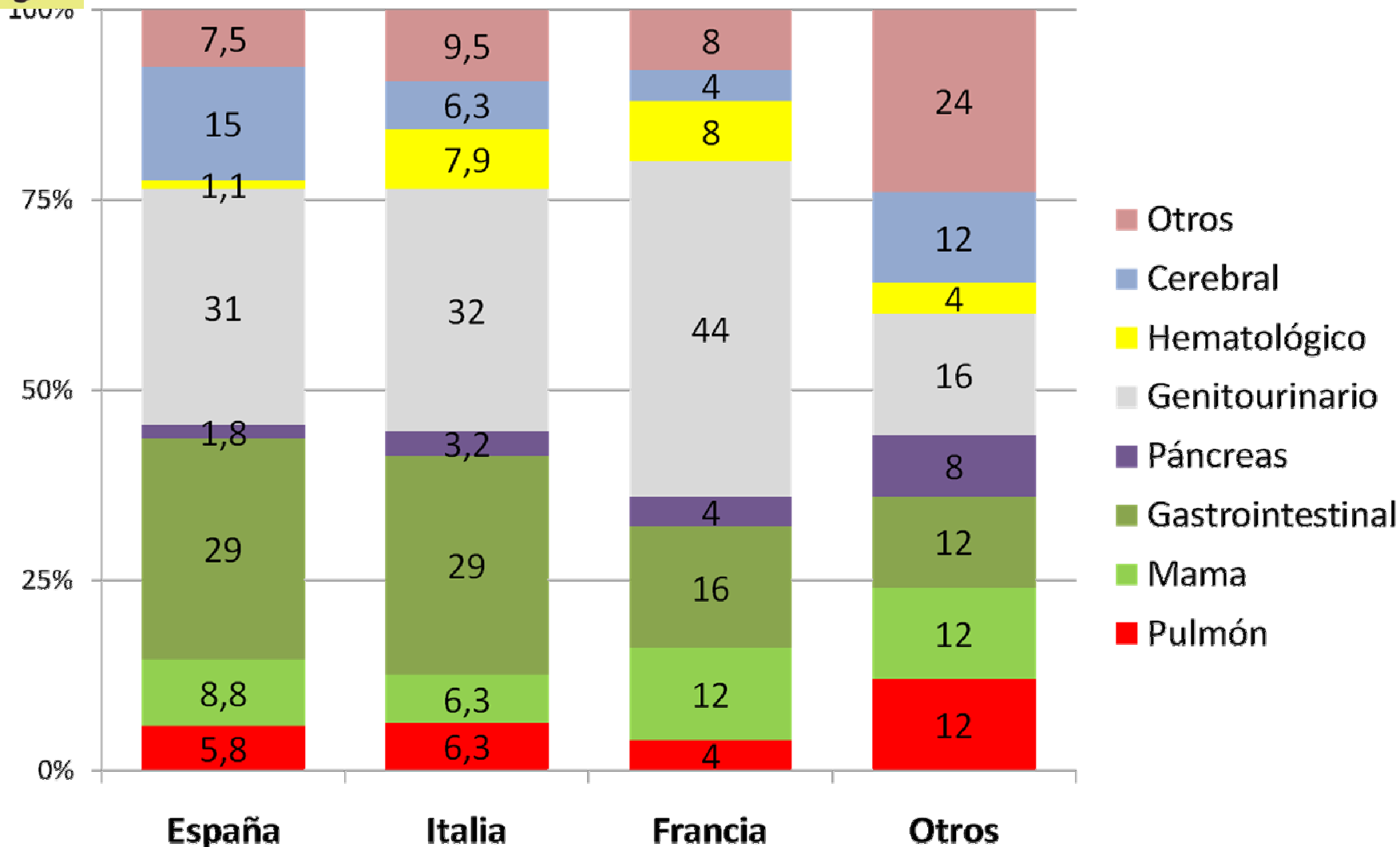
% de pacientes con neoplasia activa



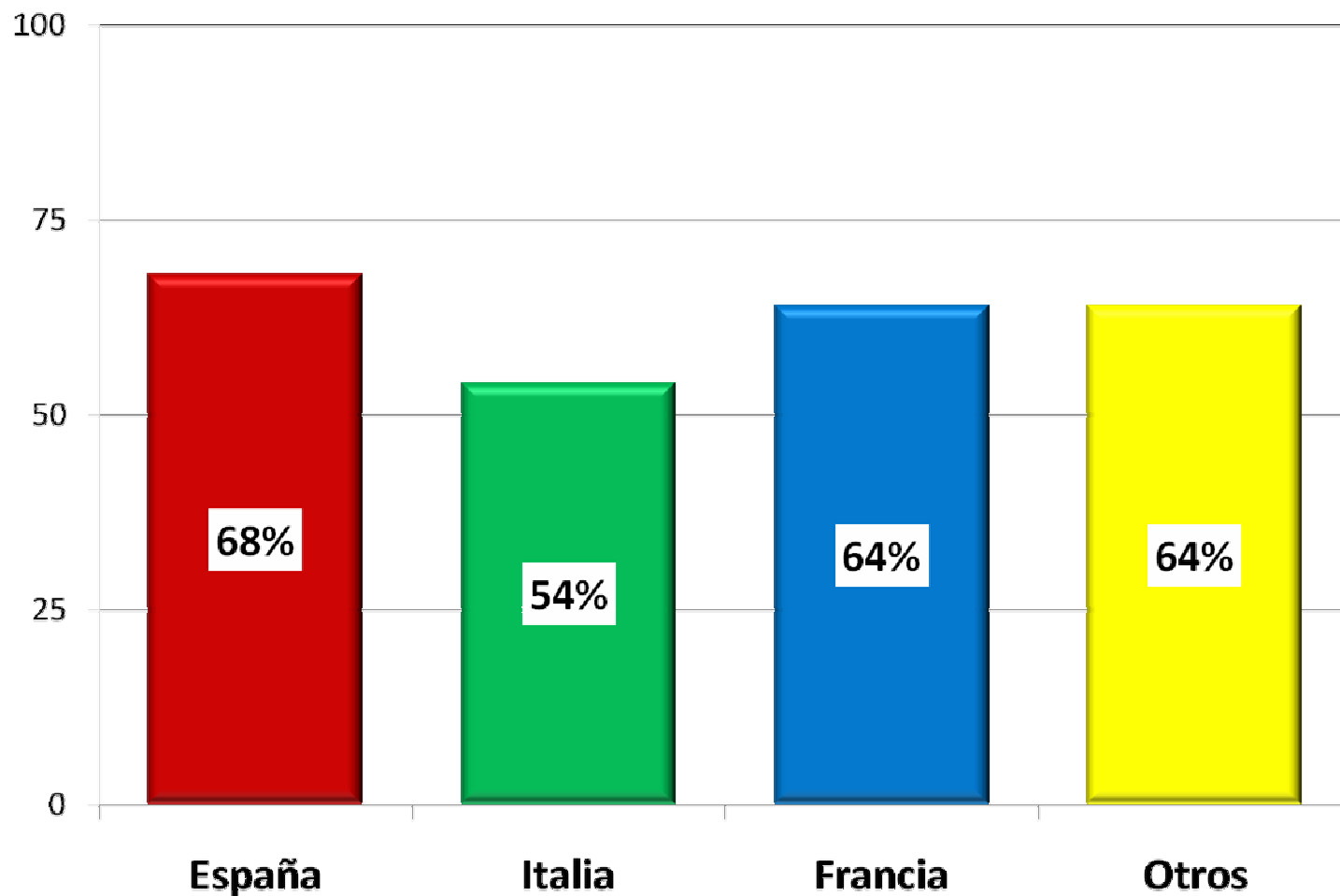
# Factores de riesgo en pacientes con cáncer activo



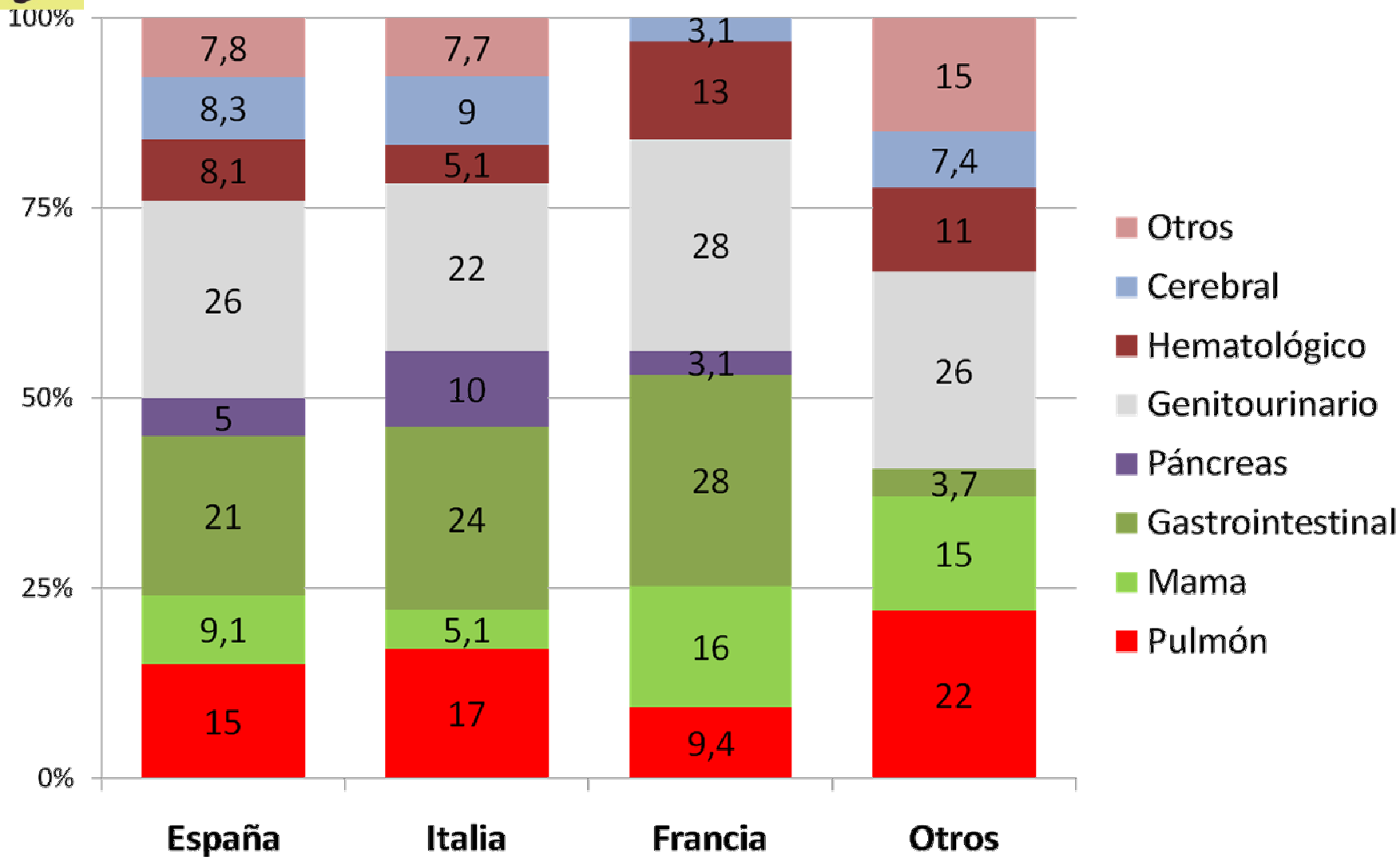
# % tipos de neoplasia activa en pacientes postquirúrgicos



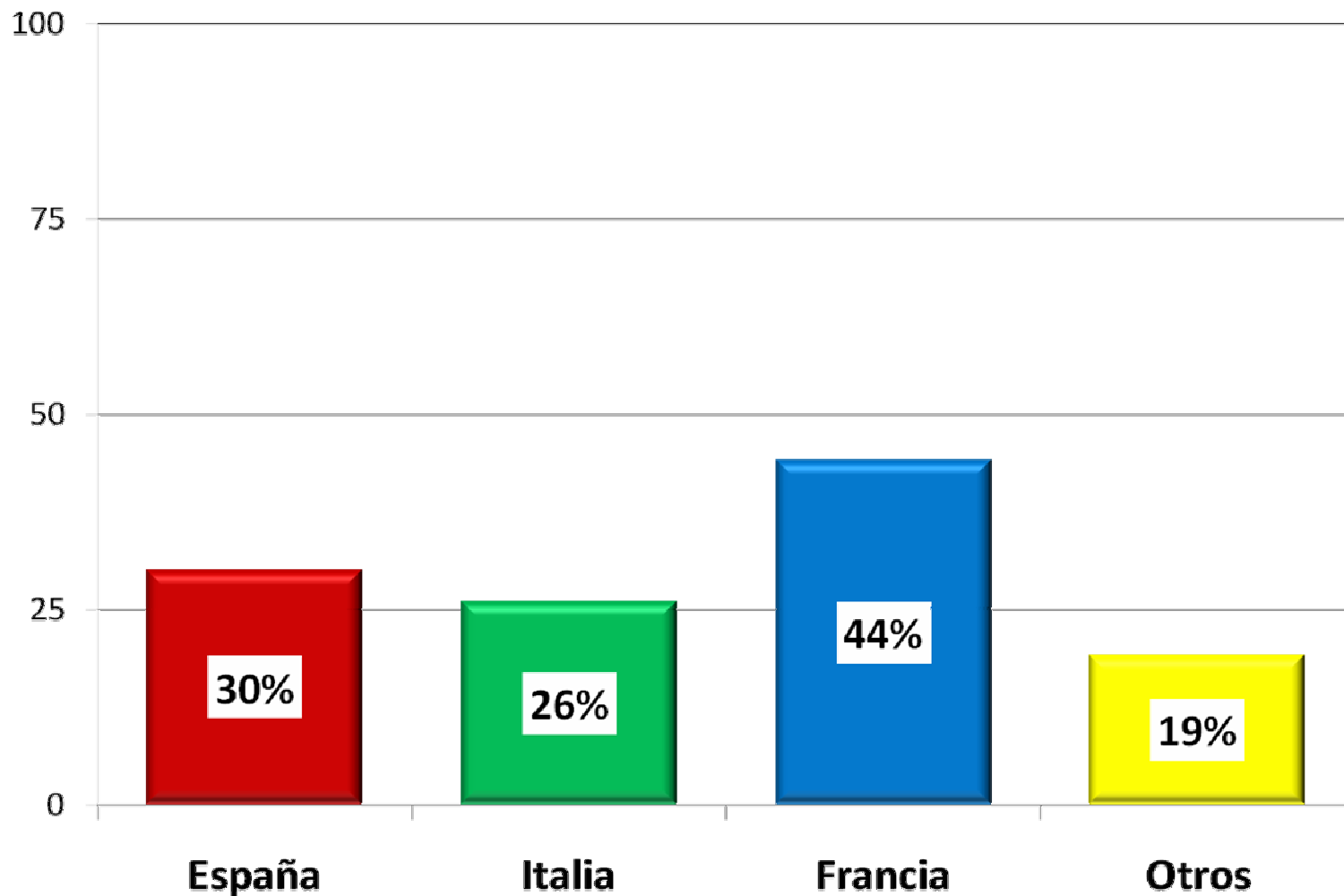
# % tromboprofilaxis en pacientes con cáncer y ETV postquirúrgicos



# % tipos de neoplasia en pacientes con cáncer y ETV inmovilizados



# % tromboprolifaxis en pacientes con cáncer y ETV inmovilizados





# Recomendaciones de tratamiento de ETV en pacientes con cáncer

Parameter	ASCO	NCCN
Initial treatment of VTE in patients with cancer	LMWH is the preferred approach for the initial 5-10 days	LMWH, UFH, or fondaparinux according to patient's characteristics and clinical situation
	AIOM/ESMO	FNCLCC
	Weight-adjusted dose LMWH if creatinine clearance < 25-30 mL, either UFH or LMWH with anti-Xa monitoring	LMWH, UFH, or fondaparinux for the first 10 days if severe renal failure, UFH, and early VKA
Long-term treatment of VTE in patients with cancer	LMWH for at least 6 months is preferred; VKA are acceptable when LMWH is not available; indefinite anticoagulation in patients with active cancer	LMWH is preferred; indefinite anticoagulation in patients with active cancer or persistent risk factors
	LMWH for at least 3-6 months; long-term LMWH for patients with active cancer	LMWH for 3-6 months; LMWH or VKA beyond 6 months

# Recomendaciones de tratamiento de ETV en pacientes con cáncer

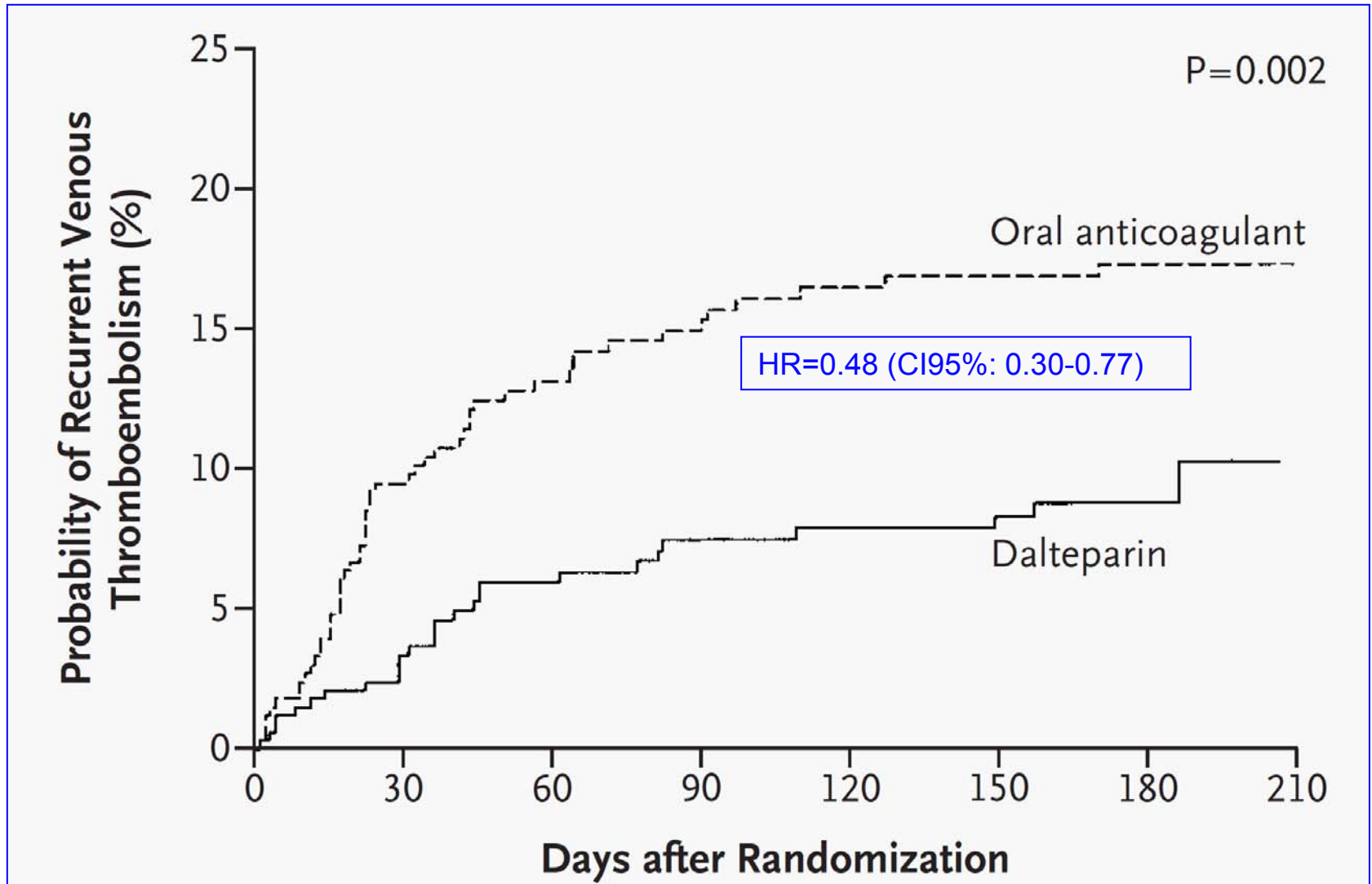
## Treatment: initial<sup>c</sup>

UFH	80 U/kg i.v. bolus, then 18 U/kg/h i.v. <sup>d</sup>
Dalteparin	100 U/kg s.c. every 12 h; 200 U/kg s.c. daily <sup>e</sup>
Enoxaparin	1 mg/kg s.c. every 12 h; 1.5 mg/kg s.c. daily <sup>e</sup>
Fondaparinux	<50 kg: 2.5–5 mg s.c. daily; 50–100 kg: 5–7.5 mg s.c. daily; >100 kg: 7.5–10 mg s.c. daily
Tinzaparin	175 U/kg s.c. daily

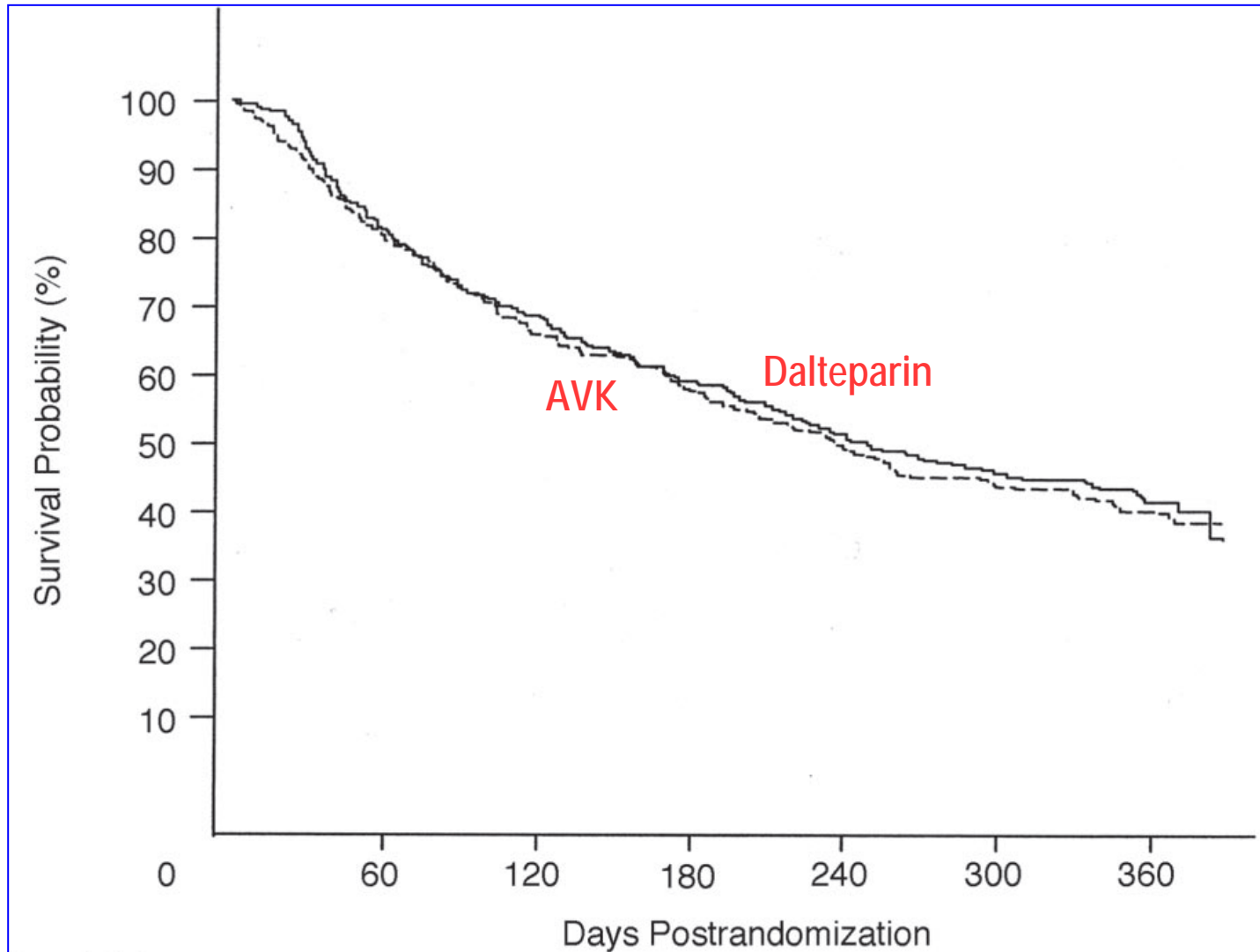
## Treatment: long term<sup>f</sup>

Dalteparin	200 U/kg s.c. daily × 1 month, then 150 U/kg s.c. daily
Warfarin	5–10 mg p.o. daily <sup>g</sup>

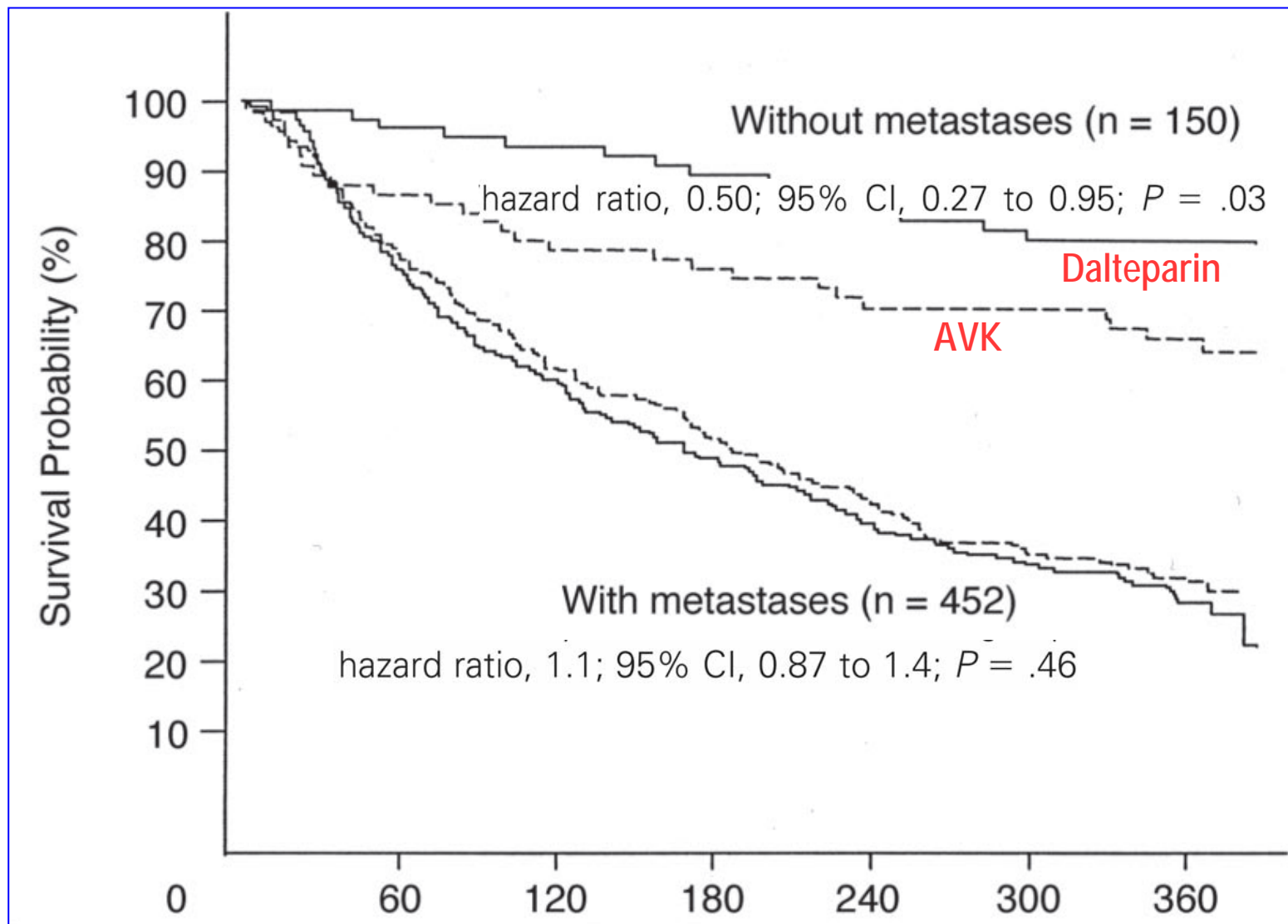
# Tratamiento de ETV en pacientes con cáncer: *CLOT trial*



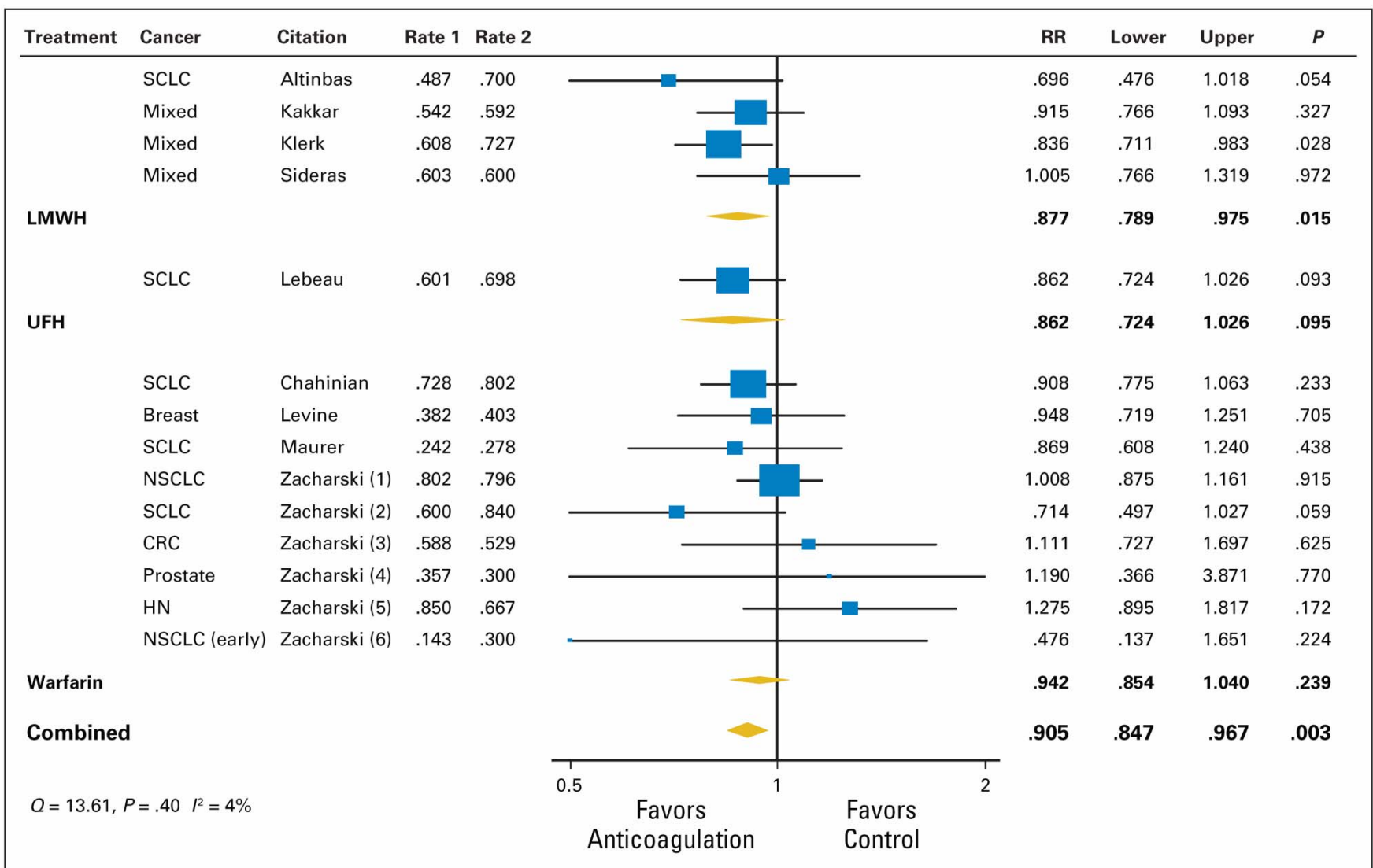
# Tratamiento de ETV en pacientes con cáncer: *CLOT trial*



# Tratamiento de ETV en pacientes con cáncer: *CLOT trial post-hoc*



# Influencia en la supervivencia de los anticoagulantes

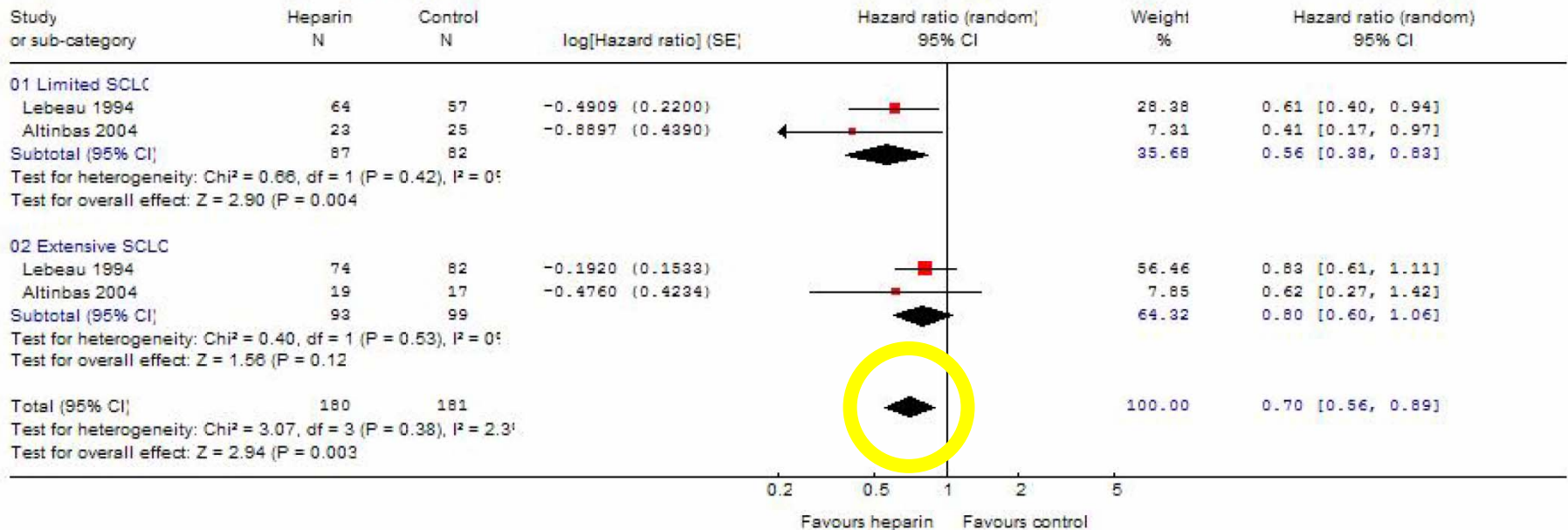


**Fig 3.** Meta-analysis of anticoagulation studies evaluating the impact on mortality in cancer patients without venous thrombosis: 1-year overall mortality by type of anticoagulation. SCLC, small-cell lung cancer; LMWH, low molecular weight heparin; UFH, unfractionated heparin; NSCLC, non-small-cell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



# Influencia en la supervivencia de los anticoagulantes

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation  
 Comparison: 01 Heparin vs placebo  
 Outcome: 04 Mortality SCLC, over duration of study



**Figure 4**

The effect of heparin therapy on survival in patients with small cell lung cancer.



# Factores pronósticos de Recurrencia ETV o Hemorragia Mayor



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

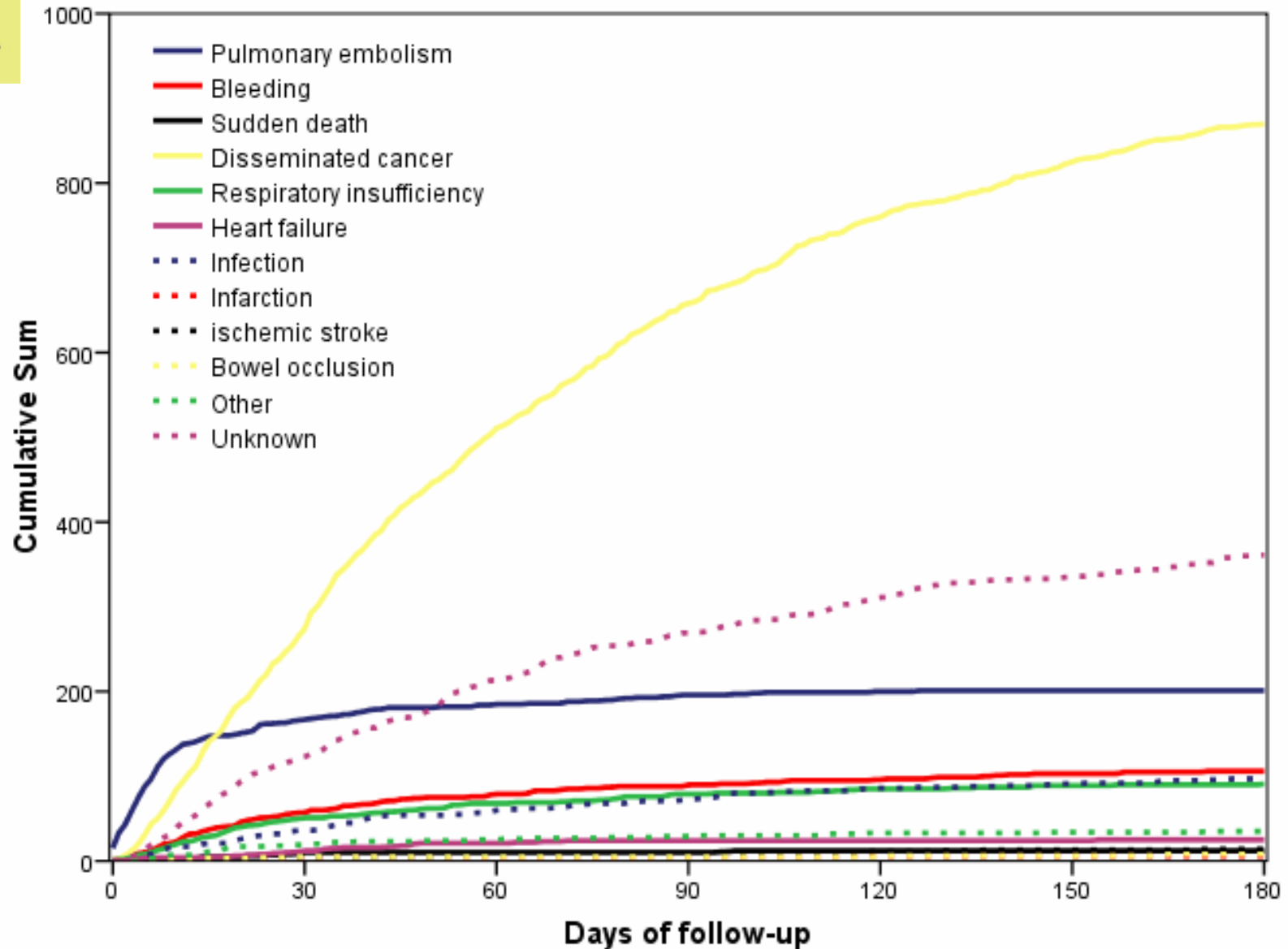
PE, pulmonary embolism; DVT, deep-vein thrombosis; CrCl, creatinine clearance; CI, confidence intervals.

# Predicción de EP y hemorragia fatales

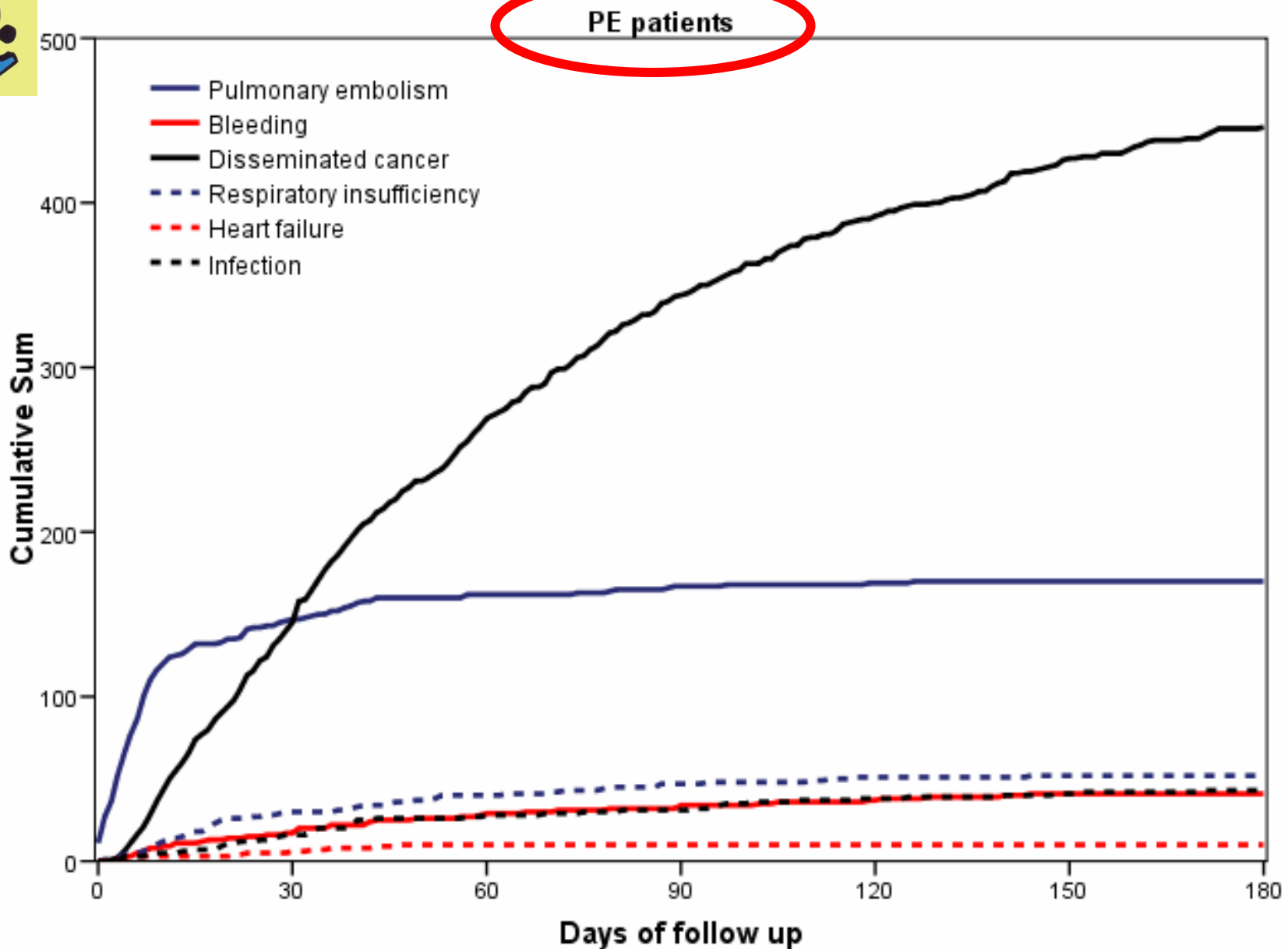


Variables	Fatal PE OR (95% CI)	Fatal bleeding OR (95% CI)
Body weight <60 kg	–	2.5 (1.1–5.3)
Recent major bleeding	2.8 (1.2–6.3)	3.0 (0.96–9.1)
Serum creatinine >1.2 mg/dL	2.6 (1.6–4.3)	2.8 (1.3–5.8)
Immobility $\geq$ 4 days	1.9 (1.1–3.2)	4.1 (1.9–8.7)
Surgery	0.6 (0.2–1.4)	–
Symptomatic PE	13.9 (6.3–30)	–
Metastatic cancer	2.9 (1.8–4.8)	3.1 (1.4–7.1)

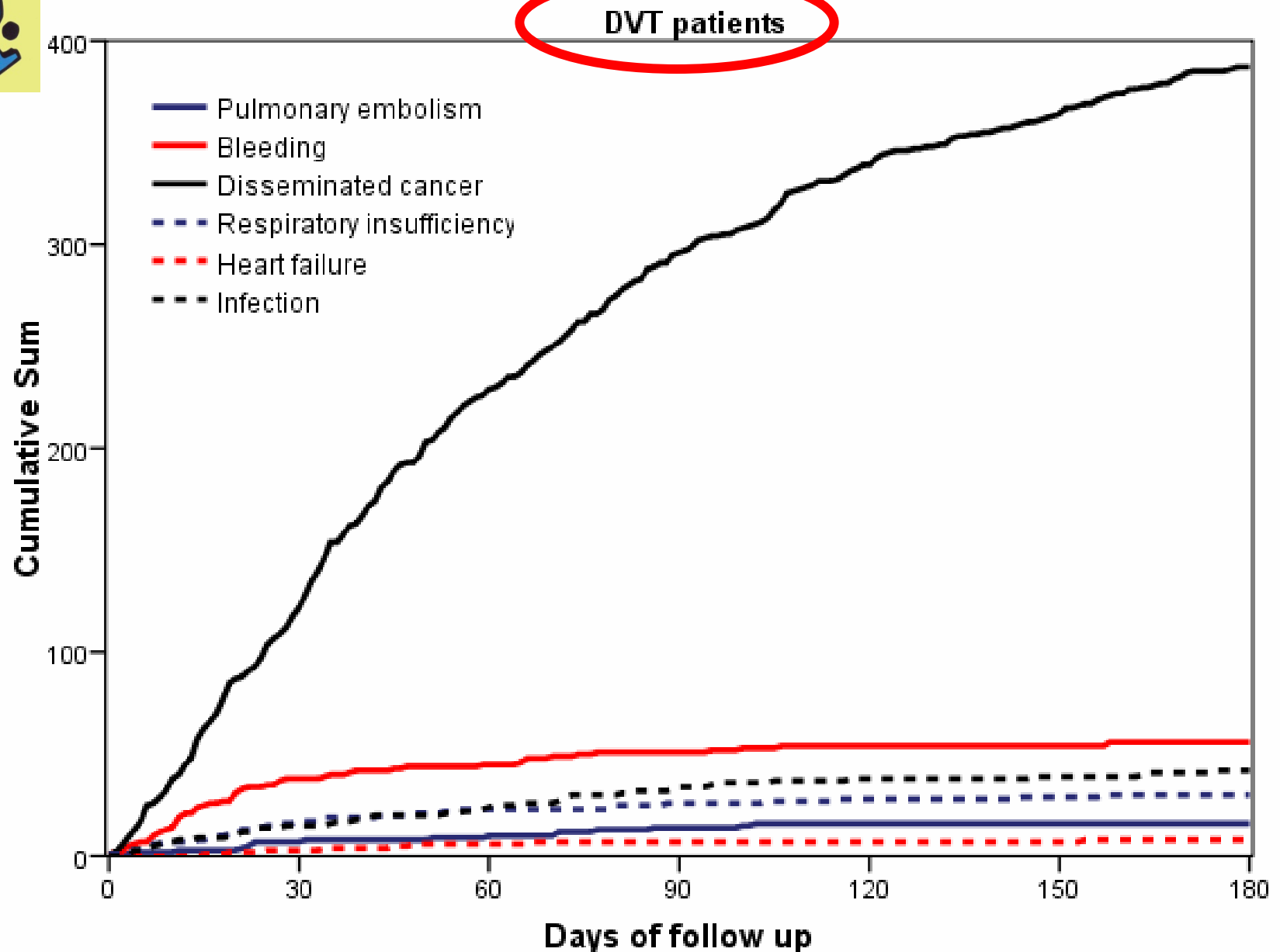
# Causas de muerte en pacientes con ETV y cáncer



# Causas de muerte en pacientes con EP y cáncer



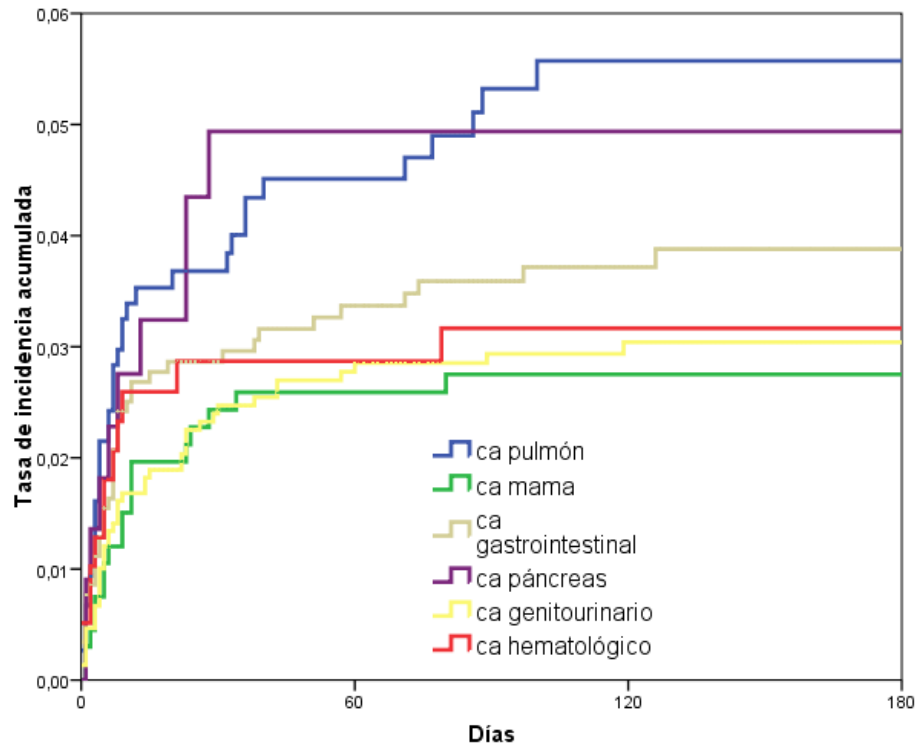
# Causas de muerte en pacientes con TVP y cáncer



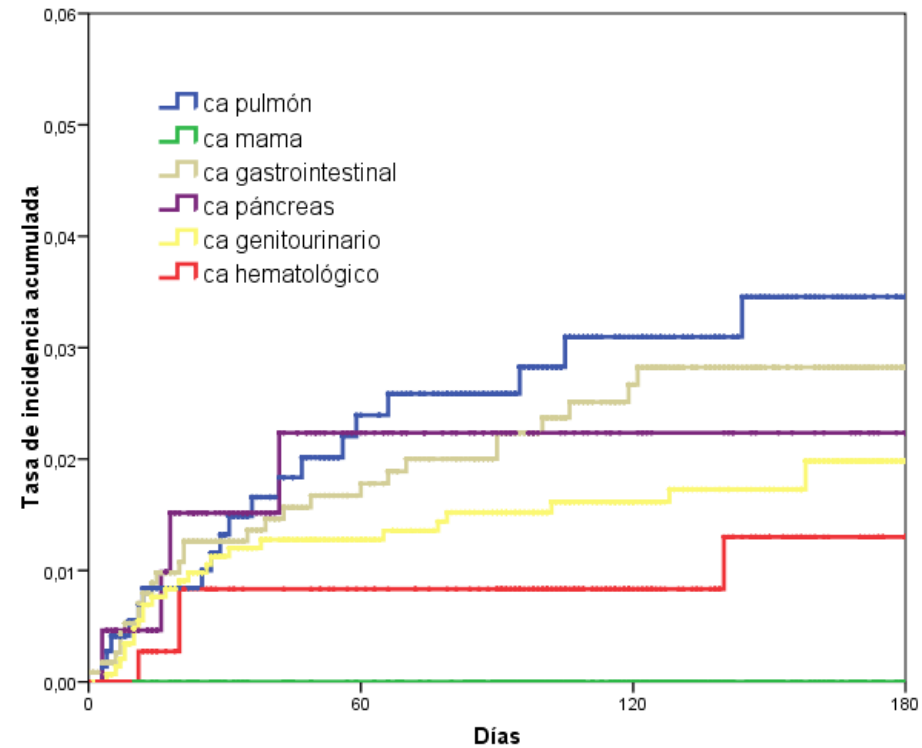
# EP y hemorragia fatales según tipo de neoplasia



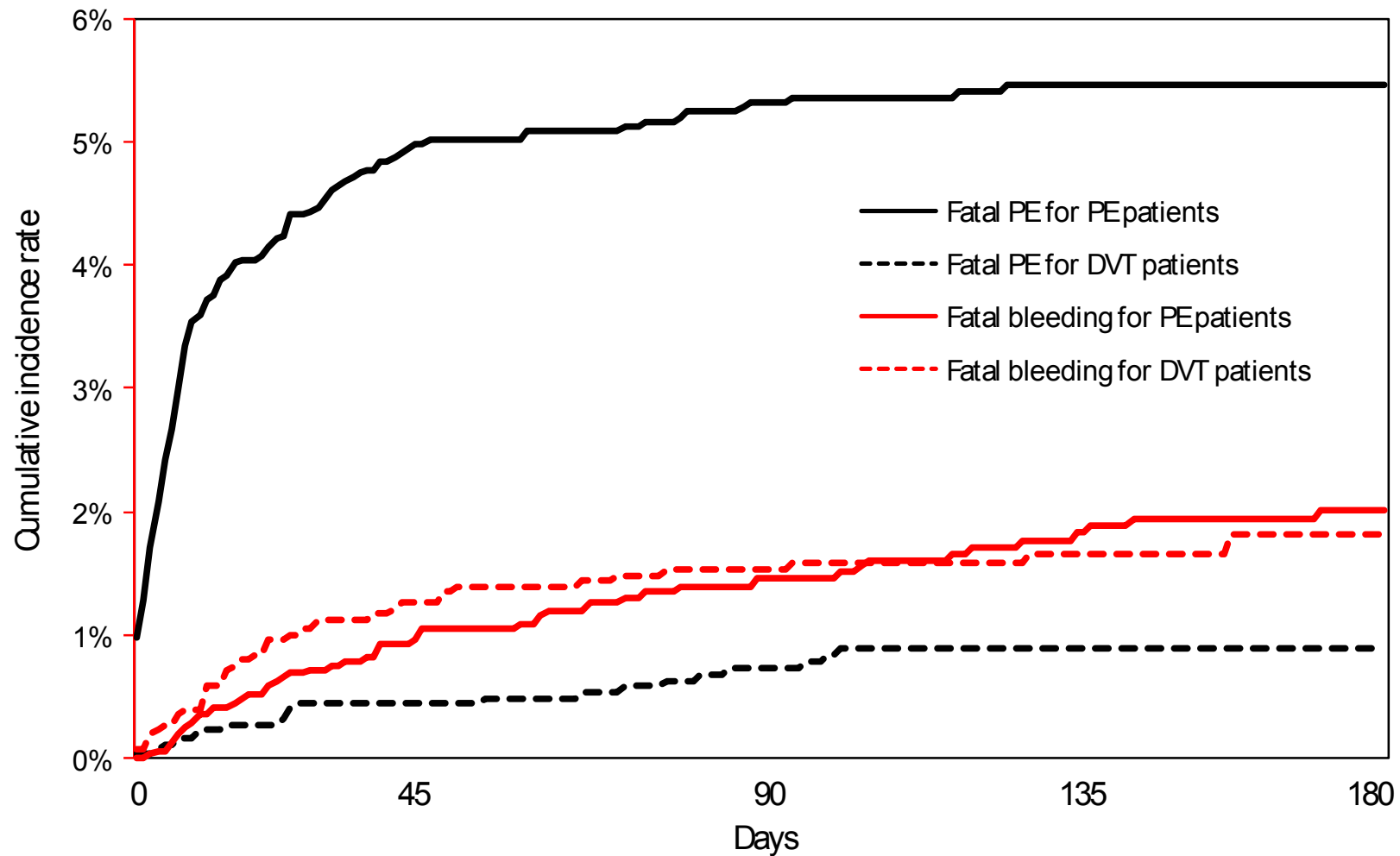
## EP fatal



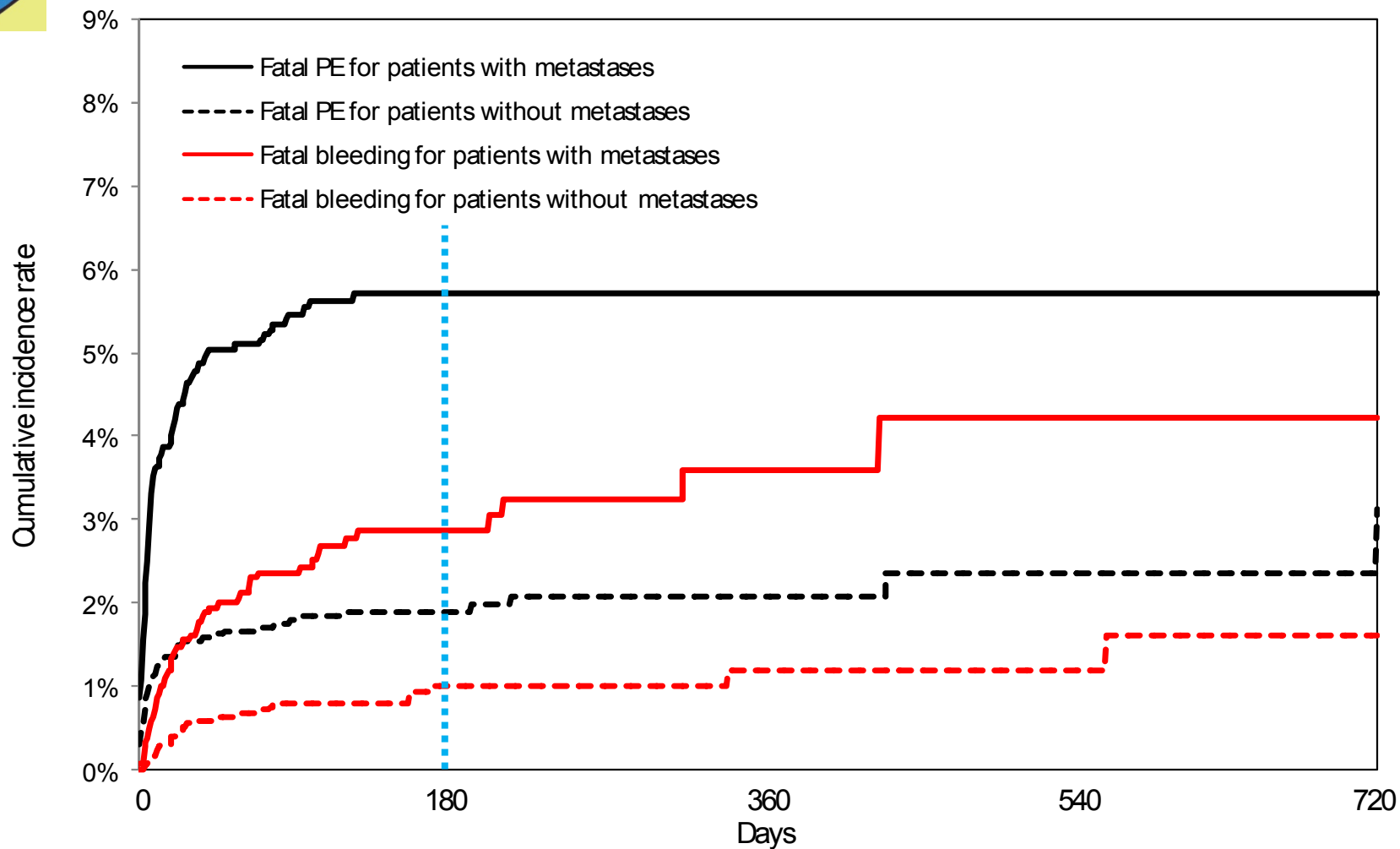
## Hemorragia fatal



# EP y hemorragia fatales según forma de presentación: EP vs TVP



# EP y hemorragia fatales según extensión de la neoplasia





## 1. Trombopprofilaxis farmacológica si alto riesgo de TEV

- preQT
- catéter venoso central

## 2. Tratamiento tras hemorragia mayor

## 3. Tratamiento tras recidiva TEV

## 4. Individualización del tratamiento anticoagulante

- metástasis vs cáncer localizado
- EP vs TVP
- según tipo de neoplasia
- según riesgo individual de recidiva vs hemorragia mayor

## 5. Duración del tratamiento anticoagulante