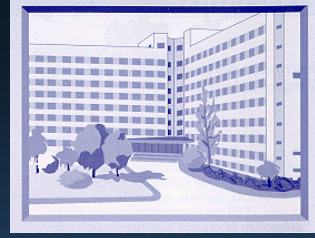


Tratamiento de los pacientes con recidiva de ETV a pesar de tratamiento anticoagulante oral

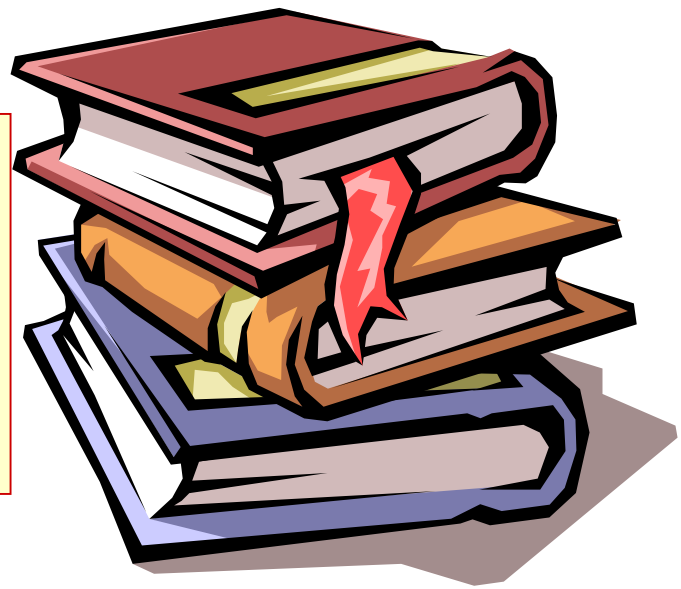
Dr Lobo
S de Neumología.
Hospital Txagorritxu. Vitoria

- anticoagulación oral con antivitaminas K (AVK) a largo plazo
- hep
me

4-7% presentan recidiva a pesar del tratamiento

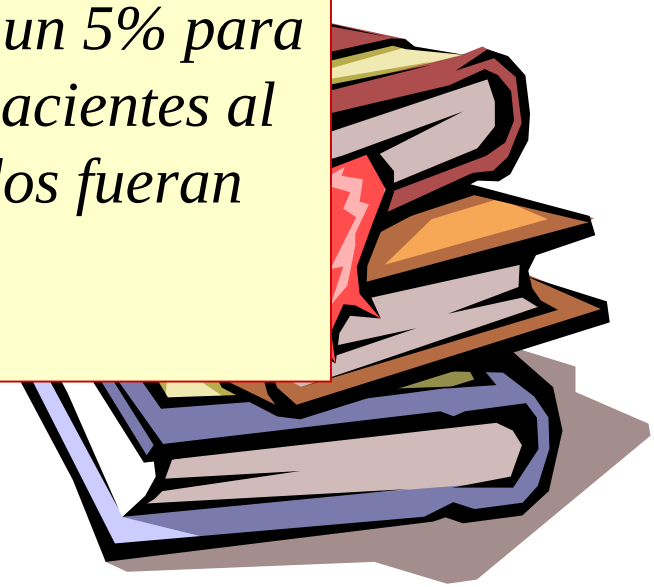
- El perfil clínico
- Evolución posterior

...los pacientes que recidivan tienen mayor riesgo de seguir recidivando....



- El perfil clínico
- Evolución
- **Manejo**

...100 centros con 100 pacientes al año que recidivaran en un 5% para poder aleatorizar 500 pacientes al año, asumiendo que todos fueran incluibles y dieran su consentimiento

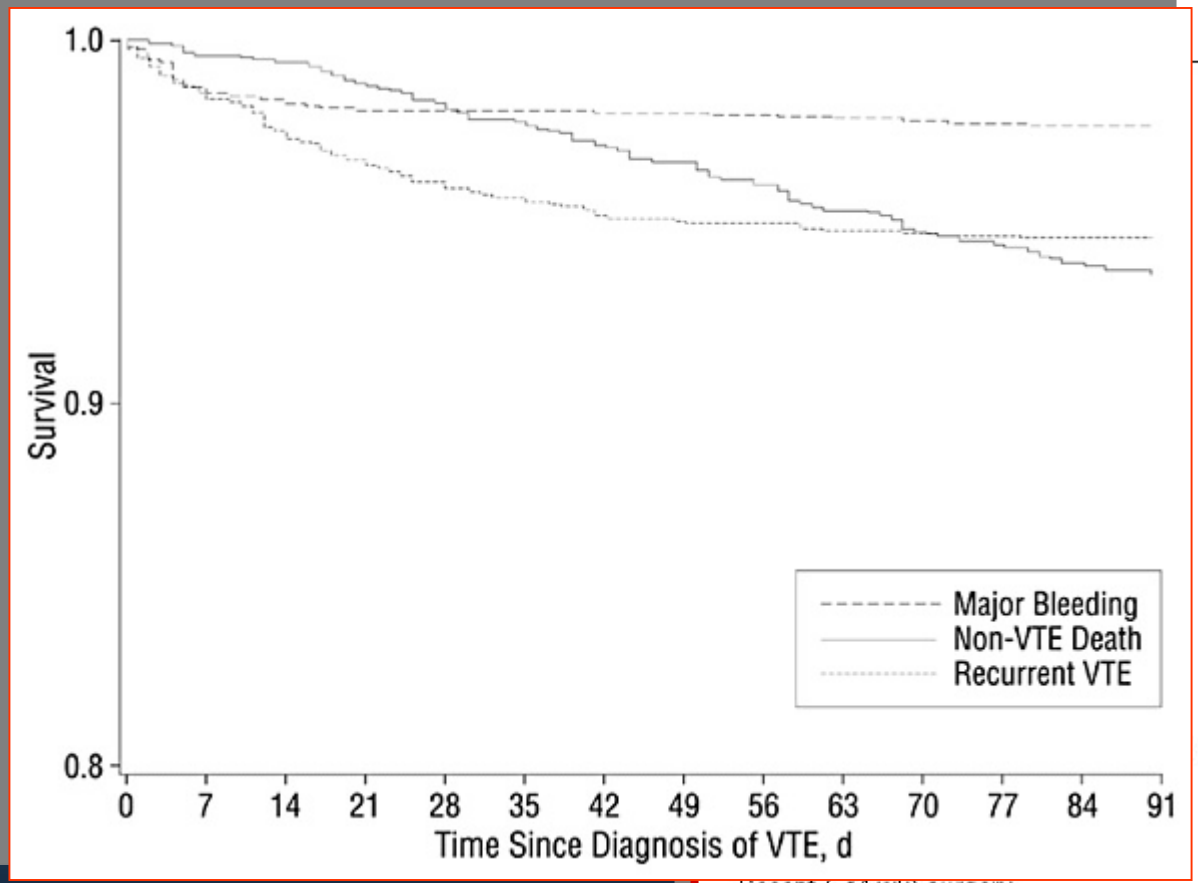


Clinical Risk Factors and Timing of Recurren Venous Thromboembolism During the Initial 3 Months of Anticoagulant Therapy

James D. Douketis, MD, FRCPC; Gary A. Foster, PhD; Mark A. Crowther, MD, MSc, FRCPC; Martin H. Prins, MD, PhD; Jeffrey S. Ginsberg, MD, FRCPC

ARCHIVES OF INTERNAL MEDICINE

1021 consec
objectively



	Patients, No. (%) (N = 1021)
	334 (33)
	222 (22)
	445 (44)
	496 (49)
	648 (63)
	102 (10)
	271 (26)
	372 (36)
	121 (12)
	36 (4)
	13 (1)
	47 (5)
	80 (8)
	72 (7)
	119 (12)
	155 (15)
	111 (11)
	337 (33)
Recent (<4 wk) surgery	294 (29)
Previous venous thromboembolism	219 (21)

*DVT indicates deep vein thrombosis; PE, pulmonary embolism.

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Clinical Outcome

Recurrent nonfata
Recurrent fatal PE
Major bleeding
Non-VTE death

**Data are given as*
vein thrombosis; PE,
thromboembolism.

recurrent VTE occurre

Clinical Characteristics	Odds Ratio (95% CI)	P
Variables in Final Model		
Cancer	2.72 (1.39-5.32)	<.01
Chronic cardiovascular disease	2.27 (1.08-4.97)	.03
Chronic respiratory disease	1.91 (0.85-4.26)	.11
Other concurrent disease†	1.79 (1.00-3.21)	.05
Older age (10-y increment)	0.76 (0.64-0.92)	<.01
Variables Not in Final Model		
Previous VTE	0.58 (0.26-1.32)	.19
Qualifying event (DVT or PE)	1.27 (0.69-2.34)	.44
Female	1.20 (0.69-2.11)	.52
Permanent risk factor‡ vs idiopathic	0.46 (0.17-1.26)	.14
Transient risk factor§ vs idiopathic	0.74 (0.37-1.49)	.40

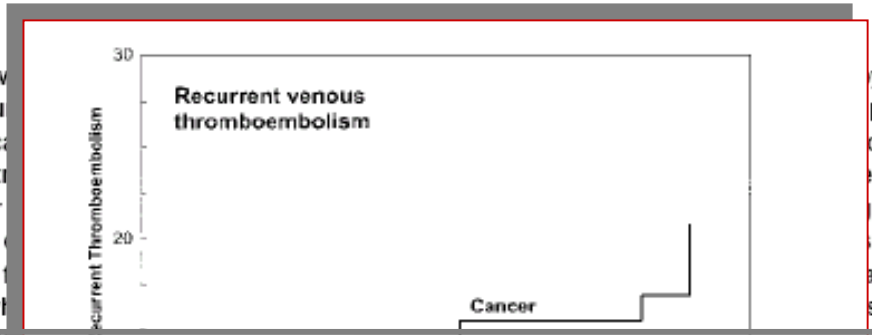
**CI indicates confidence interval; DVT, deep vein thrombosis; and PE, pulmonary embolism.*
†One or more of the following diseases: renal, hepatic, gastrointestinal, neurologic, hematologic, or multisystem.
‡Cancer or previous VTE.
§Recent surgery, trauma, or immobility.

blood

Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis

Paolo Prandoni, Anthonie W. A. Lensing, Andrea Piccioli, Enrico Bernardi, Paolo Simioni, Bruno Girolami, Antonio Marchiori, Paola Sabbion, Martin H. Prins, Franco Noventa, and Antonio Girolami

A small proportion of patients v … y sub- or overantico- vein thrombosis develop recu … patients with venous nous thromboembolic complica … ore likely to develop bleeding during anticoagulant tr … mbolic complications These complications may occur … during anticoagulant quently if these patients have … e without malignancy. tant cancer. This prospective … ate with the extent of study sought to determine wh … s for improvement us



Site of cancer	No. (%)	Follow-up, patient-y	Recurrent VTE hazard ratio (95% CI)
Genitourinary*	47 (26.0)	26.4	3.7 (1.7-8.0)
Gastrointestinal†	37 (20.4)	18.4	5.1 (2.3-11.3)
Breast	27 (15.0)	18.5	0.7 (0.1-4.9)
Myelolymphoproliferative‡	24 (13.3)	18.9	2.3 (0.7-7.5)
Lung	24 (13.3)	14.9	6.9 (3.0-15.9)
Brain	14 (7.7)	6.2	3.7 (0.8-14.1)
Other§	8 (4.4)	5.0	2.3 (0.3-16.7)

The Natural Course of Hemodynamically Stable Pulmonary Embolism*

Clinical Outcome and Risk Factors in a Large Prospective Cohort Study

Mathilde Nijkeuter, Pieter Willem Kampl Laurens Laterveer, M Marieke J. H. A. Kru and Menno V. Huism

Table 1—*Baseline Characteristics of the 674 Patients With PE

Characteristics	Data
Age, yr†	58 (19–100)
Age < 55 yr	296 (44)
Age ≥ 55 to < 65 yr	117 (17)
Age ≥ 65 yr	
Female gender	

Tabl

Variables	Pati and			R (95% CI)
Patients, No.				
Age, yr†				2 (0.99–1.05)
Female gender				3 (0.40–2.38)
Inpatients				2 (0.58–4.04)
Paralysis/paresis				7 (0.11–6.67)
Immobilization > 3 d				0 (1.40–8.77)
Travel by air or car				5 (0.35–6.88)
Surgery				9 (0.23–4.36)
Previous VTE				4 (0.21–2.57)
Previous PE				2 (0.23–4.52)
Heart failure				4 (0.92–0.96)
COPD	2 (10)	60 (9)	0.71	1.09 (0.25–4.83)
Malignancy	4 (20)	126 (19)	1.00	1.05 (0.34–3.18)
Signs of DVT	5 (25)	95 (15)	0.20	1.96 (0.70–5.51)
Tachycardia	9 (45)	240 (37)	0.45	1.41 (0.58–3.46)

*Data are presented as No. (%) or % unless otherwise indicated.

- Edad
- Comorbilidad cardiorespiratoria
- Neoplasia pulmonar o digestiva
- En las primeras 3-4 semanas
- Mortalidad ¿elevada?

- ¿Alternativas terapéuticas a largo plazo?

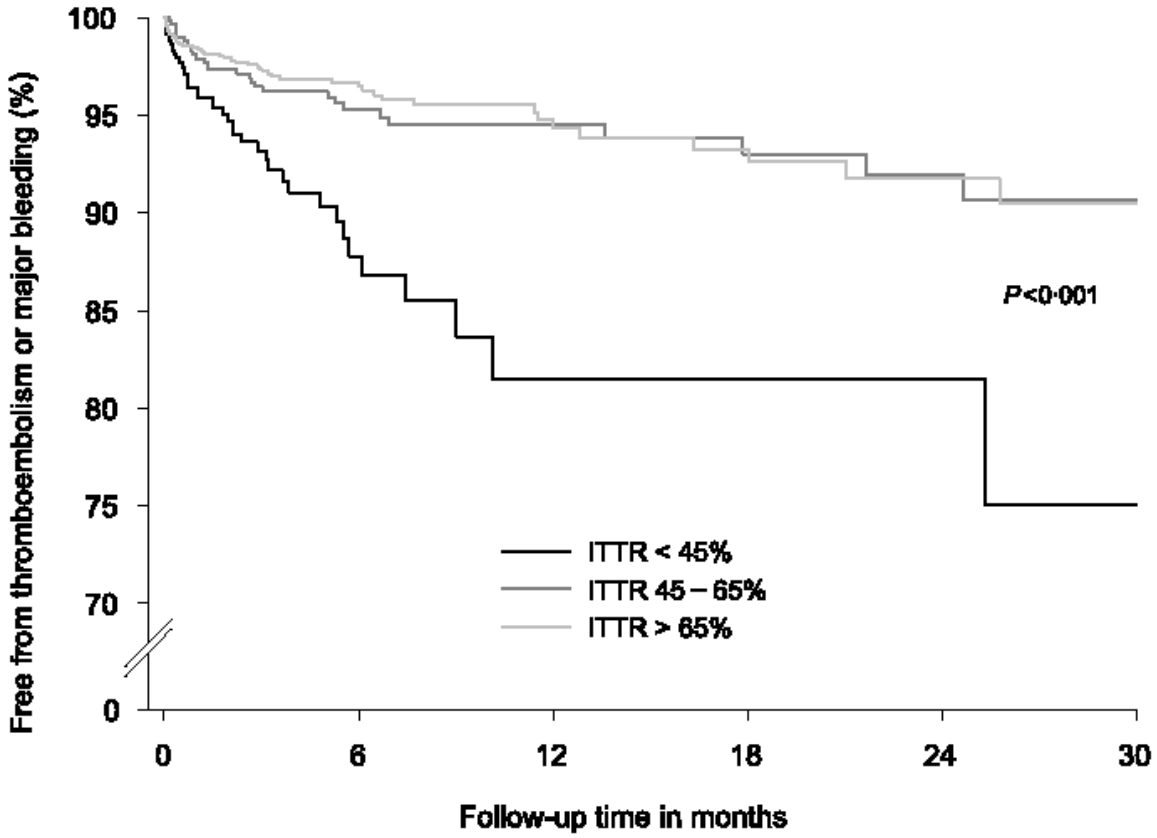
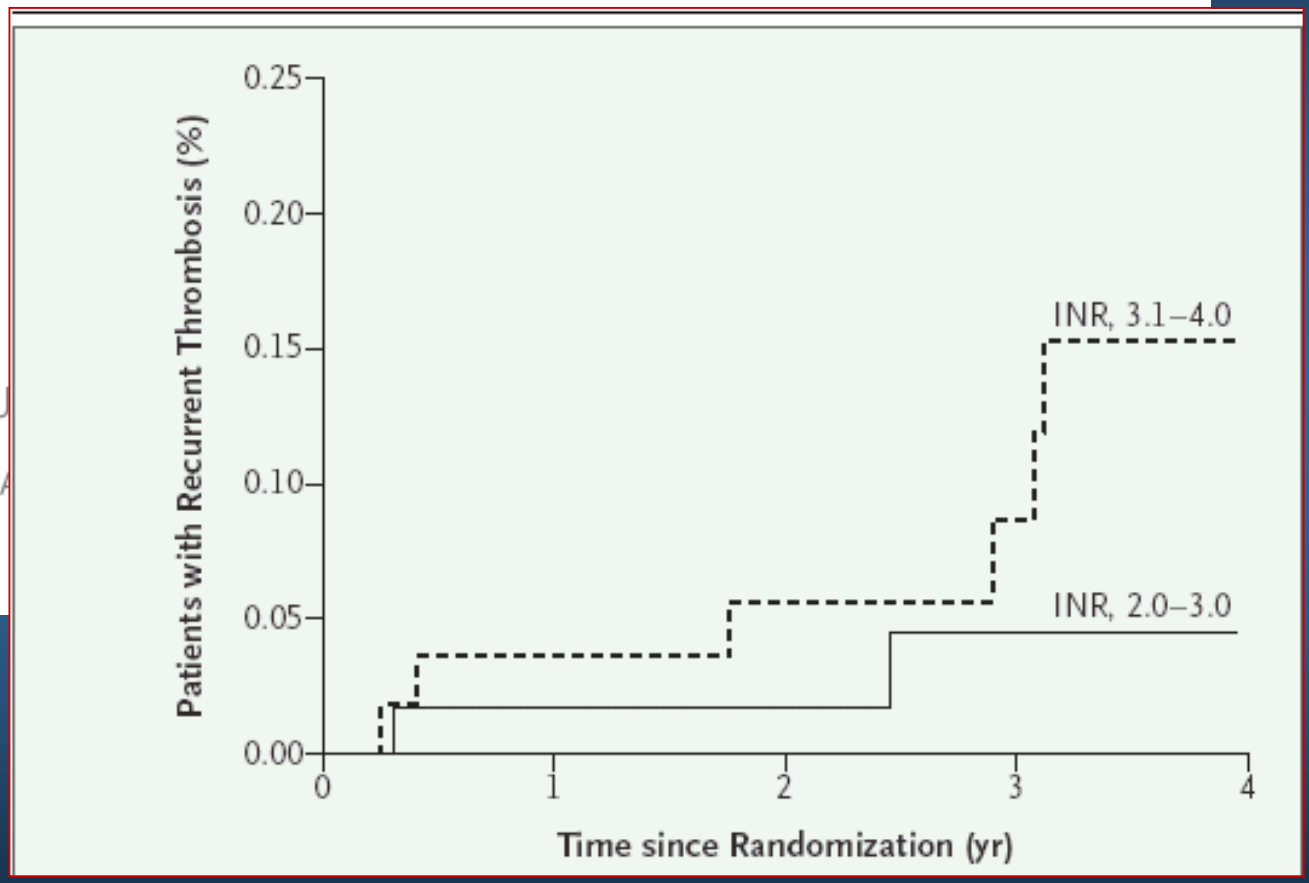


Fig 3. Freedom from recurrent thromboembolism and major bleeding in patients according to the percentage time within the therapeutic range (ITTR). $RR_{ITTR<45\%} = 2{\cdot}8$ (95% CI 1·9–4·3, $P < 0{\cdot}001$) and $RR_{ITTR45–65\%} = 1{\cdot}2$ (95% CI 0·7–1·8, $P = 0{\cdot}54$), compared with ITTR > 65%.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE



N Engl J Med 2003;349:1133-8.

Journal of Thrombosis and Haemostasis 2005;3:848

A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS).

Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, Baudo F, Berrettini M, Testa S, D'Angelo A, Tognoni G, Barbui T.
The Ospedali Riuniti, Bergamo, Italy.

BACKGROUND: The optimal intensity of oral anticoagulation for the prevention of recurrent thrombosis in patients with antiphospholipid antibody syndrome is uncertain. Retrospective studies show that only high-intensity oral anticoagulation [target international normalized ratio (INR) >3.0] is effective but a recent randomized clinical trial comparing high (INR range 3.0-4.0) vs. moderate (INR 2.0-3.0) intensities of anticoagulation failed to confirm this assumption. METHODS: We conducted a randomized trial in which 109 patients with antiphospholipid syndrome (APS) and previous thrombosis were given either high-intensity warfarin (INR range 3.0-4.5, 54 patients) or standard antithrombotic therapy (warfarin, INR range 2.0-3.0 in 52 patients or aspirin alone, 100 mg day(-1) in three patients) to determine whether intensive anticoagulation is superior to standard treatment in preventing symptomatic thromboembolism without increasing the bleeding risk. RESULTS: The 109 patients enrolled in the trial were followed up for a median time of 3.6 years. Mean INR during follow-up was 3.2 (SD 0.6) in the high-intensity warfarin group and 2.5 (SD 0.3) ($P < 0.0001$) in the conventional treatment patients given warfarin. Recurrent thrombosis was observed in six of 54 patients (11.1%) assigned to receive high-intensity warfarin and in three of 55 patients (5.5%) assigned to receive conventional treatment [hazard ratio for the high intensity group, 1.97; 95% confidence interval (CI) 0.49-7.89]. Major and minor bleeding occurred in 15 patients (two major) (27.8%) assigned to receive high-intensity warfarin and eight (three major) (14.6%) assigned to receive conventional treatment (hazard ratio 2.18; 95% CI 0.92-5.15). CONCLUSIONS: High-intensity warfarin was not superior to standard treatment in preventing recurrent thrombosis in patients with APS and was associated with an increased rate of minor hemorrhagic complications.

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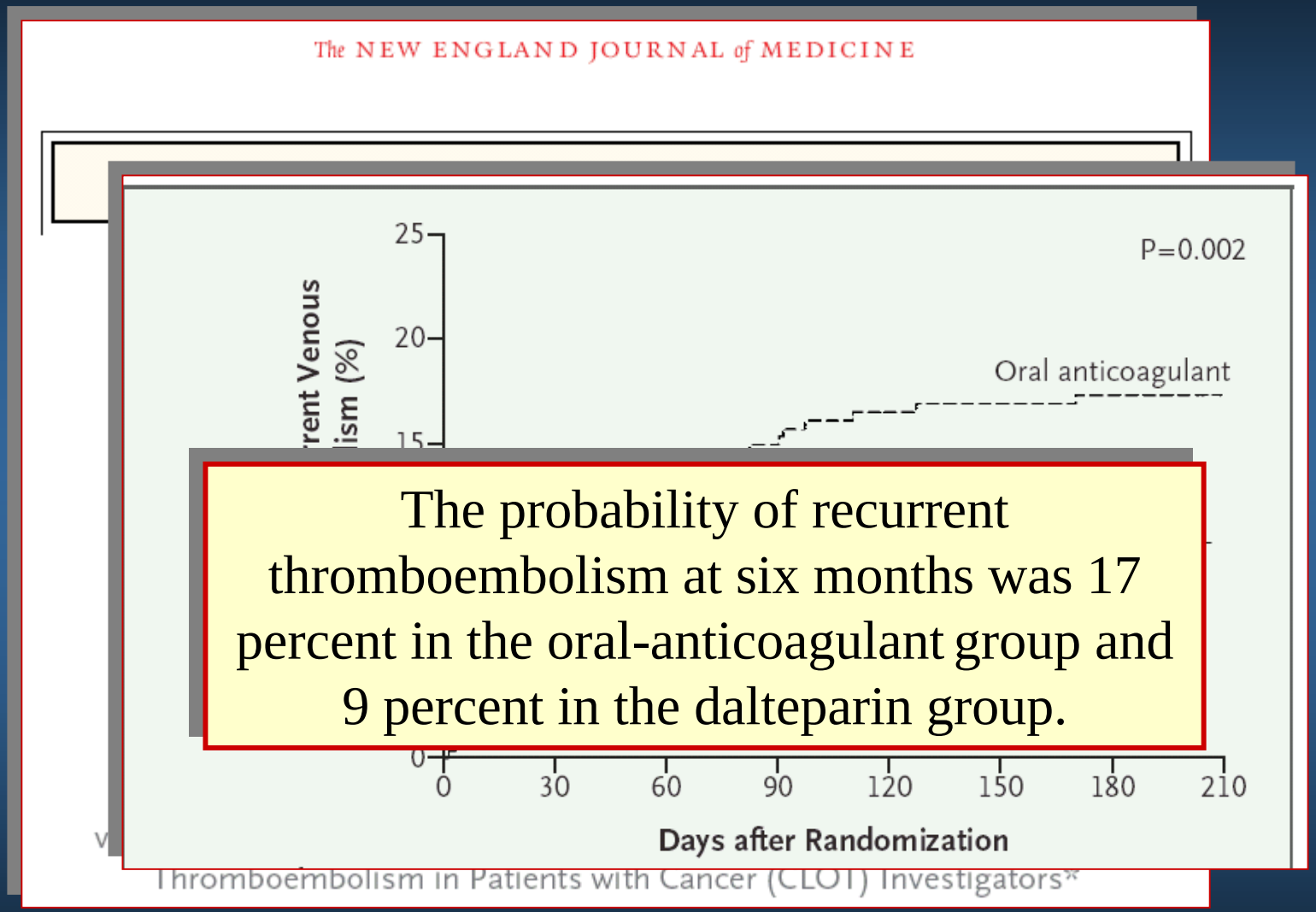
1.8.2. We suggest the placement of an inferior vena caval filter in patients with a contraindication for, or a complication of anticoagulant treatment (**Grade 2C**), as well as in those with recurrent thromboembolism despite adequate anticoagulation (**Grade 2C**).

Para los pacientes con EP



The probability of recurrent thromboembolism at six months was 17 percent in the oral-anticoagulant group and 9 percent in the dalteparin group.

N Engl J Med 2003;349:146-53.

Extended Outpatient Therapy with Low Molecular Weight Heparin for the Treatment of Recurrent Venous Thromboembolism Despite Warfarin Therapy

Cynthia Luk, MD, Philip S. Wells, MD, David Anderson, MD, Michael J. Kovacs, MD

2001

Table. Comparison of Patients with and without Recurrence of Venous Thromboembolism

	No Recurrence (n = 855)	Recurrence (n = 32)
	Number (%) or Mean ± SD	
Characteristic		
Male sex	410 (48)	15 (47)
Age (years)	64 ± 17	56 ± 17
Prior history of venous thromboembolism	129 (15)	4 (13)
Initial presentation		
Deep vein thrombosis	677 (79)	27 (84)
Pulmonary embolism	152 (18)	4 (13)
Deep vein thrombosi… pulmonary embol…	…	…
Risk Factor		
Cancer		
Idiopathic		
Transient (e.g., surge…		

(1–4). It would require 100 centers, each averaging 100 patients per year with a 5% recurrence rate, to provide 500 patients per year for a randomized study, assuming all patients consent and are eligible.

- Todos fueron tratados con 200 UI/Kg de Dalteparina, independientemente del INR.
- 15/32 fallecieron antes de finalizar el tratamiento de 12 semanas de Dalteparina.
- los otros 17/32 regresaron a las AVK tras períodos de 6-36 semanas; 3 (9%) presentaron recurrencia durante el tratamiento HBPM.

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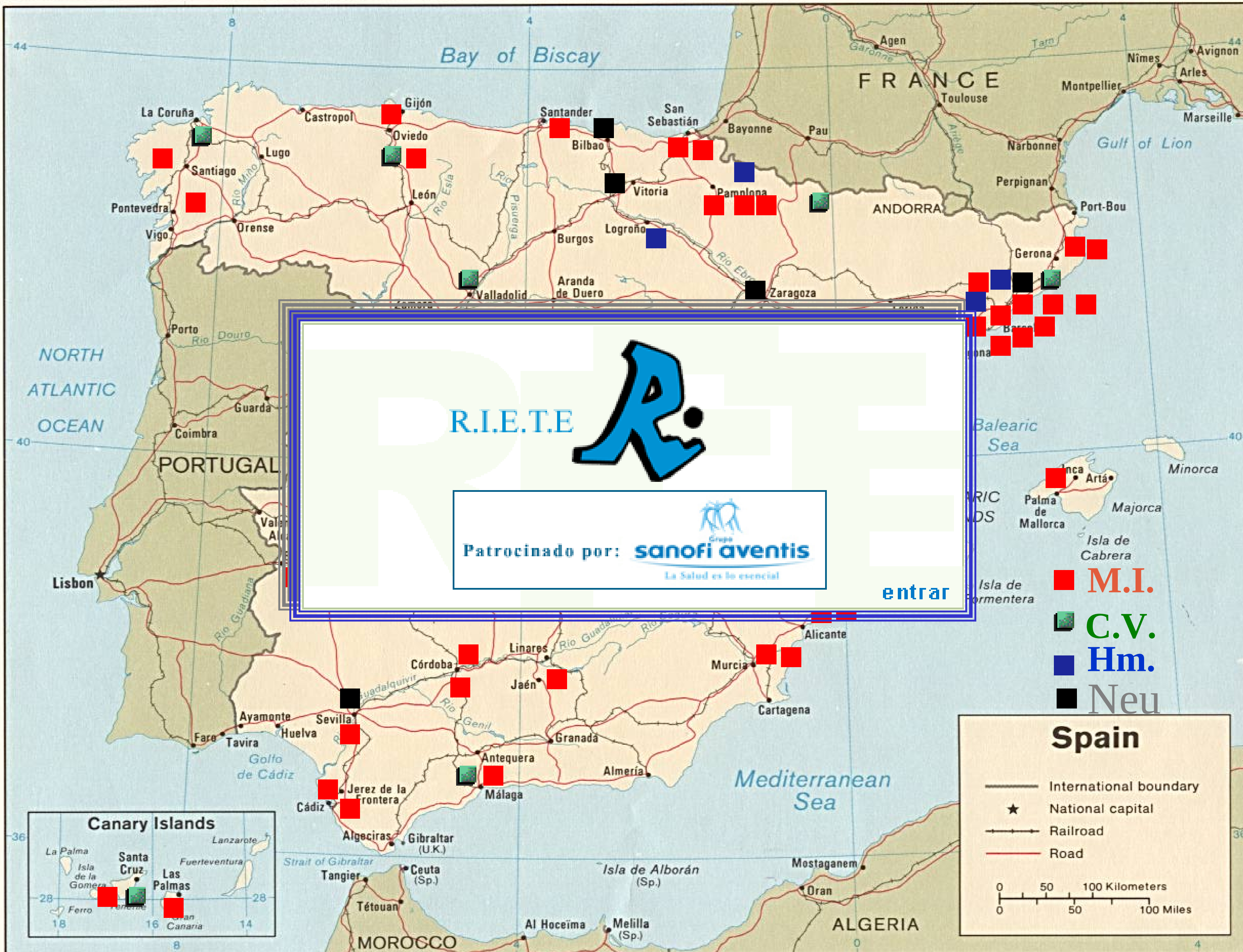
- un 9% de recurrencias con tratamiento HBPM a largo plazo es muy aceptable
- no tuvieron sangrados mayores durante el ttmto HBPM



R.I.E.T.E
Patrocinado por: sanofi aventis
Grupo
La Salud es lo esencial
entrar
M.I.
C.V.
Hm.
Neu
Spain
International boundary
National capital
Railroad
Road
0 50 100 Kilometers
0 50 100 Miles
Bay of Biscay
FRANCE
NORTH ATLANTIC OCEAN
PORTUGAL
ANDORRA
Balearic Sea
Gulf of Lion
Mediterranean Sea
Golfo de Cádiz
Strait of Gibraltar
Isla de Alborán (Sp.)
MOROCCO
ALGERIA
Canary Islands
La Palma
Isla de la Gomera
Ferro
Santa Cruz
Las Palmas
Gran Canaria
Lanzarote
Fuerteventura
Minorca
Majorca
Palma de Mallorca
Artá
Isla de Cabrera
Isla de Formentera
La Coruña
Santiago
Pontevedra
Vigo
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Zaragoza
Gerona
Port-Bou
Bayonne
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Cádiz
Algeciras
Gibraltar (U.K.)
Tangier
Ceuta (Sp.)
Tétouan
Al Hoceïma
Melilla (Sp.)
Mostaganem
Oran

Clinical characteristics, treatment details and outcome of 15,862 VTE patients, according to the existence of prior VTE and AVK therapy.

	Prior VTE, AVK	Prior VTE, no AVK	No prior VTE	AVK vs. no AVK	AVK vs. no prior VTE
	177	2361	13324		
Gender (males)	107 (61%)	1243 (53%)	6532 (49%)	1.4 (1.0-1.9)*	1.6 (1.2-2.2)†
Age >65 years	101 (57%)	1590 (67%)	8545 (64%)	0.6 (0.5-0.9)†	0.7 (0.6-1.0)*
Body weight >65 kg	125 (71%)	1848 (78%)	9713 (73%)	0.7 (0.5-0.9)*	0.9 (0.6-1.2)
Cancer	54 (31%)	426 (18%)	2772 (21%)	2.0 (1.4-2.8)‡	1.7 (1.2-2.3)†
Symptom PE	69 (39%)	1043 (44%)	6159 (46%)	0.8 (0.6-1.1)	0.7 (0.5-1.0)

	Prior VTE, AVK	Prior VTE, no AVK	No prior VTE	AVK vs. no AVK	AVK vs. no prior VTE
	177	2361	13324		
LMWH	135 (76%)	2143 (91%)	12143 (91%)	0.3 (0.2-0.5)‡	0.3 (0.2-0.4)‡
UFH	35 (20%)	193 (8.2%)	994 (7.5%)	2.8 (1.9-4.1)‡	3.1 (2.1-4.4)‡
IVC filter	24 (14%)	51 (2.2%)	255 (1.9%)	7.1 (4.2-12)‡	8.0 (5.1-13)‡
AVK drugs	107 (62%)	1802 (78%)	9145 (72%)	0.5 (0.3-0.6)‡	0.6 (0.5-0.9)†
LMWH	63 (37%)	490 (21%)	4531 (29%)	2.1 (1.5-3.0)‡	1.5 (1.1-2.0)*

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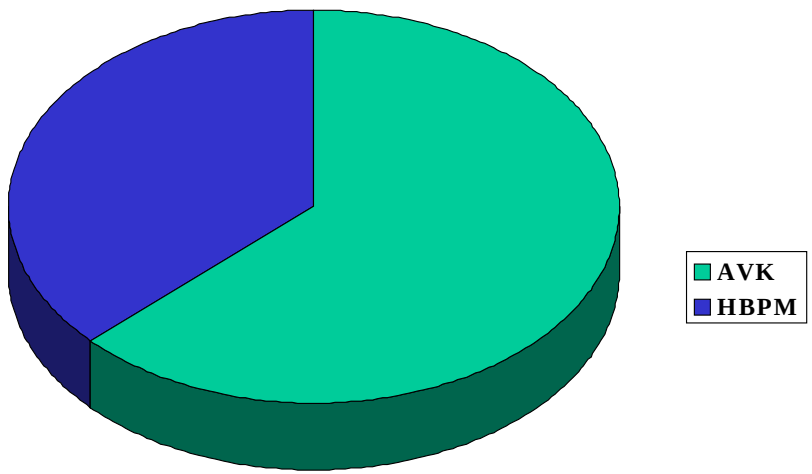
LMWH	63 (37%)	490 (21%)	4531 (29%)	2.1 (1.5-3.0)‡	1.5 (1.1-2.0)*

¿Utilizamos poco las HBPM como ttmto a largo plazo?



¿Qué pudo mover a uno u otro Ttmto?

	LMWH (n=66)	AVK (n=107)	Odds ratio (95% CI)	P value
A Protromb <40%	19 (29%)	46 (43%)	0.5 (0.3-1.0)	0.061
A Protromb >40%	47 (71%)	61 (57%)	1.9 (0.97-3.6)	0.061
IVC Filter	5 (7.6%)	18 (17%)	0.4 (0.1-1.1)	0.082

	LMWH (n=66)	**AVK (n=107)**	Odds ratio (95% CI)	P value
Symptomatic PE	25 (38%)	41 (38%)	1.0 (0.5-1.8)	0.954
Proximal DVT *(N=98)*	32 (82%)	47 (80%)	1.2 (0.4-3.3)	0.770

¿Qué pudo mover a uno u otro Ttmto?

	LMWH (n=66)	AVK (n=107)	Odds ratio (95% CI)	P value
Chronic lung disease	7 (11%)	13 (12%)	0.9 (0.3-2.3)	0.759
Chronic heart failure	3 (4.5%)	8 (7.5%)	0.6 (0.2-2.3)	0.443
Abnormal creatinine	13 (20%)	14 (13%)	1.6 (0.7-3.7)	0.224
Cancer	30 (46%)	22 (21%)	3.2 (1.6-6.3)	0.001

	Prior VTE, AVK 177	Prior VTE, no AVK	No prior VTE	AVK vs. no AVK	AVK vs. no prior VTE
Fatal, initial PE	2 (1.1)	14 (0.6)	171 (1.3)	1.9 (0.6-8.9)	0.9 (0.2-3.5)
Major bleeding	4 (2.3)	38 (1.6)	339 (2.5)	1.4 (0.5-3.5)	0.9 (0.3-2.4)
Fatal bleeding	3 (1.7)	6 (0.3)	70 (0.5)	**4.8 (1.9-12)** *	**3.2 (1.04-9.7)** *
Recurrent VTE	12 (**6.8%**)	57 (2.4%)	330 (2.5%)	**2.9 (1.5-5.5)**†	**2.9 (1.5-5.0)**†
Recurrent DVT	8 (4.5)	31 (1.3)	166 (1.2)	3.0 (1.6-5.7) †	3.6 (1.8-7.3) †
Recurrent PE	4 (2.3)	26 (1.1)	164 (1.2)	1.9 (0.8-4.9)	1.8 (0.7-4.9)
Fatal, recurrent PE	4 (2.3)	10 (0.4)	59 (0.4)	4.2 (1.8-9.7) †	4.9 (1.9-13) †
Overall death	24 (14%)	112 (4.7)	1179 (8.8%)	2.8 (1.9-4.1) ‡	1.6 (1.05-2.5 *

	VTE recurence *12*	No VTE recurrence ***165***	OR (95% CI)	P value
Cancer	5 (42%)	49 (30%)	1.7 (0.5-5.7)	0.201
Body weight >65 k	11 (92%)	114 (69%)	4.9 (0.8-108)	0.050
Protromb <35%	5 (42%)	83 (50%)	0.7 (0.2-2.4)	0.291
UFH	7 (58%)	28 (17%)	6.7 (1.9-2.5)	0.001
IVC filter	3 (25%)	21 (13%)	2.3 (0.5-8.8)	0.136
Long-term AVK	6 (50%)	101 (61%)	0.6 (0.2-2.2)	0.230
Long-term LMWH	6 (50%)	57 (35%)	1.9 (0.6-6.5)	0.151

Desenlace a 15 días

	LMWH (n=66)	AVK (n=107)	Odds ratio (95% CI)	P value
Major bleeding	0 (0%)	1 (0.9%)		0.431¡
Fatal bleeding	0 (0%)	1 (0.9%)		0.431¡
Recurrent VTE	2 (3.0%)	1 (0.9%)	3.3 (0.3-37)	0.305¡
Overall death	1 (1.5%)	2 (1.9%)	0.8 (0.1-9.1)	0.862¡

Desenlace a 15-90 días

	LMWH (n=66)	AVK (n=107)	Odds ratio (95% CI)	P value
Major bleeding	2 (3.0%)	1 (0.9%)	3.3 (0.3-37)	**0.309¡**
Fatal bleeding	2 (3.0%)	0 (0%)		**0.071¡**
Recurrent VTE	4 (6.3%)	5 (4.7%)	1.3 (0.3-5.2)	**0.665¡**
Overall death	12 (19%)	5 (4.8%)	4.5 (1.5-14)	**0.004**

Conclusiones

- Los pacientes recidivantes a pesar de AVK son varones, jóvenes, de menor peso y con frecuente (no siempre) neoplasia.

- Muestran mayor tendencia (moderada) a volver a recidivar y a sangrar

Conclusiones II

- El Ttmto agudo con HNF no ofrece ventajas
- Si el ***perfil INR*** previo al episodio fuera manifiestamente mejorable debe considerarse AVK con monitorización más estrecha
- Para los casos con EP parece razonable considerar la adición de Filtro de cava.

Conclusiones III

- Los pacientes neoplásicos deberían ser tratados con HBPM
- No parece haber base para recomendar sistemáticamente HBPM a largo plazo.

9-15%

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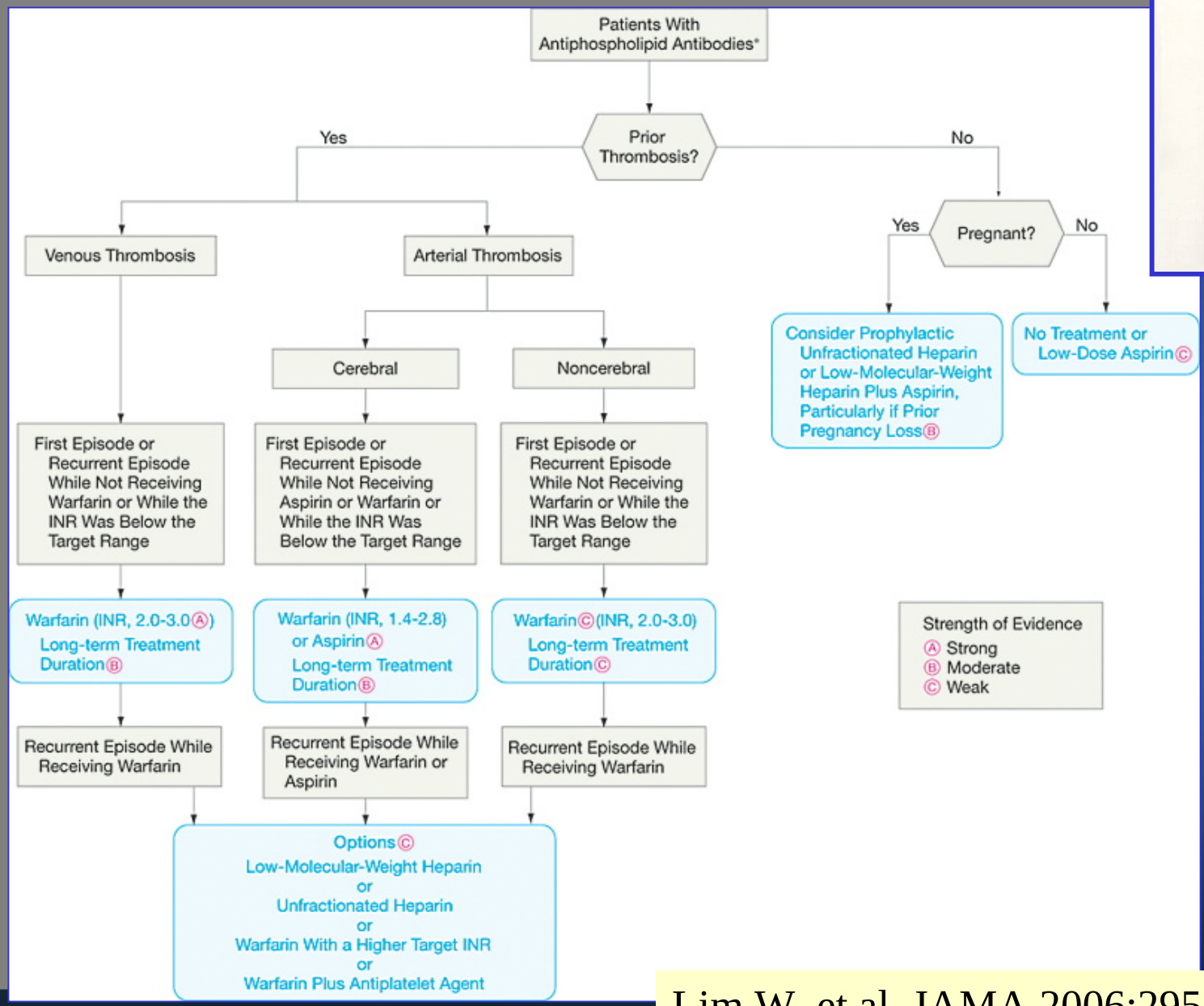
Treatment at Recurrence	Patient-years of Follow-up	Recurrent Events	Events per Year of Follow-up	*P*†
Warfarin only	64.2	0	0.000	. . .
None	127.5	14	0.110	.008
Warfarin plus aspirin	30.6	0	0.000	>.99
Aspirin only	36.6	1	0.027	.19
Any prednisone	33.1	8	0.242	<.001

** Warfarin was given as warfarin sodium.*

† Statistical significance according to Poisson heterogeneity test, when compared with warfarin plus aspirin therapy.

Krnic-Barrie S, et al. Arch Intern Med 1997;157:2101-2108



Lim W, et al. JAMA 2006;295:1050-7