La embolia pulmonar en España
Prevención y tratamiento

Manuel Monreal

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La embolia pulmonar en España
Prevención y tratamiento

- **1.- Profilaxis**
- **2.- Tratamiento**
- **3.- Escalas de riesgo**
- **4.- Trombolisis en la EP**
- **5.- Nuevos anticoagulantes**

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AAOS American Academy of Orthopaedic Surgeons
American Association of Orthopaedic Surgeons

Summary of Recommendations

The following recommendations are based on a systematic review of the literature and are evidence-based

Recommendation 3.3 **Chemoprophylaxis of patients undergoing hip or knee replacement**

Recommendation 3.3.1 **Patients at standard risk of both PE and major bleeding** should be considered for one of the chemoprophylactic agents evaluated in this guideline, including-in alphabetical order: **Aspirin, LMWH, synthetic pentasaccharides, and warfarin.** (Level III, Grade B (choice of prophylactic agent), Grade C (dosage and timing))

CHEST ONLINE

Prevention of Venous Thromboembolism* : American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

3.1.2. For patients undergoing THR, we recommend against the use of any of the following: aspirin, dextran, LDUH, GCS, or venous foot pump (VFP) as the sole method of thromboprophylaxis (all Grade 1A).

Venous thromboembolism and bleeding after total knee and hip arthroplasty

Findings from the Spanish National Discharge Database

Ricardo Guijarro[1]; Julio Montes[2]; Carlos San Roman[3]; Juan Ignacio Arcelus[4]; Giovanni Barillari[5]; Xavier Granero[6]; Manuel Monreal[7]

Venous thromboembolism and bleeding after total knee and hip arthroplasty

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Table 1: Univariable analysis for VTE and death for 58,037 patients undergoing TKA in the Spanish National Discharge Database.

	VTE	No VTE	Death	No death
Patients, N	436	57601	54	57983
Clinical characteristics				
Age (mean years ± SD)	71 ± 6.7	71 ± 7.3	75 ± 6.3‡	71 ± 7.3
Age > 70 years	258 (59%)	32489 (56%)	43 (80%)†	32704 (56%)
Gender (males)	89 (20%)†	15330 (27%)	24 (44%)†	15395 (27%)
Hospital stay (mean days ± SD)	14 ± 11‡	9.1 ± 5.8	14 ± 24†	9.2 ± 5.8
Hospital stay >10 days	243 (56%)‡	14265 (25%)	14 (26%)	14494 (25%)

	VTE	No VTE	Death	No death
Patients, N	436	57601	54	57983
Bleeding complications				
Surgical haematoma	17 (3.4%)‡	583 (1.0%)	2 (3.7%)	598 (1.0%)
Gastrointestinal	2 (0.5%)	59 (0.1%)	3 (5.6%)‡	58 (0.1%)
Cerebral	0	2 (0.003%)	0	2 (0.003%)
Other	3 (0.7%)†	42 (0.07%)	2 (3.7%)‡	43 (0.1%)
Any bleeding	22 (5.0%)†	677 (1.2%)	7 (13%)‡	692 (1.2%)
Bleeding during admission	20 (4.6%)‡	677 (1.2%)	7 (13%)‡	690 (1.2%)
Bleeding during readmission	2 (0.4%)‡	0	0	2 (0.0%)
Wound infection				
Yes	11 (2.5%)‡	331 (0.6%)	2 (3.7%)*	340 (0.6%)
Venous thromboembolism				
DVT during hospital stay	254 (58%)	-	1 (1.8%)	253 (0.4%)
PE during hospital stay	56 (13%)	-	8 (15%)‡	48 (0.08%)
DVT after discharge	76 (17%)	-	1 (1.8%)	75 (0.13%)
PE after discharge	50 (11%)	-	3 (5.5%)‡	47 (0.08%)
Any VTE	436 (100%)	-	13 (24%)‡	423 (0.7%)

	VTE	No VTE	Death	No death
Patients, N	436	57601	54	57983
Bleeding complications				
Surgical haematoma	17 (3.4%)‡	583 (1.0%)	2 (3.7%)	598 (1.0%)
Gastrointestinal	2 (0.5%)	59 (0.1%)	3 (5.6%)‡	58 (0.1%)
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Bleeding during readmission	2 (0.4%)‡	0	0	2 (0.0%)
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Any VTE	436 (100%)	-	13 (24%)‡	423 (0.7%)

Table 2: Univariable analysis for VTE and death for 31,769 patients undergoing THA in the Spanish National Discharge Database.

	VTE	No VTE	Death	No death
Patients. N	213	31556	52	31717
Clinical characteristics				
Age (mean years ± SD)	69 ± 10	67 ± 12	77 ± 10‡	67 ± 12
Age > 70 years	118 (55%)†	14495 (46%)	44 (85%)‡	14569 (46%)
Gender (males)	113 (53%)	15795 (50%)	24 (46%)	15884 (50%)
Hospital stay (mean days ± SD)	19 ± 18‡	10 ± 6.7	16 ± 17	10 ± 7.1
Hospital stay >10 days	130 (61%)‡	9439 (30%)	25 (48%)†	9544 (30%)
Bleeding complications				
Surgical haematoma	2 (0.9%)	312 (1.0%)	2 (3.8%)*	312 (1.0%)
Gastrointestinal	0	41 (0.1%)	2 (3.8%)‡	39 (0.1%)
Cerebral	1 (0.5%)*	2 (0.0%)	1 (1.9%)	2 (0.0%)
Other	2 (0.9%)*	36 (0.1%)	0	38 (0.1%)
Any bleeding	5 (2.3%)	381 (1.2%)	5 (9.6%)‡	381 (1.2%)
Bleeding during admission	3 (1.4%)	381 (1.2%)	4 (7.7%)†	380 (1.2%)
Bleeding during readmission	2 (0.9%)	0	1 (1.9%)†	1 (0.0%)
Wound infection				
Yes	12 (5.6%)‡	264 (0.8%)	2 (3.8%)	374 (1.2%)
Venous thromboembolism				
DVT during hospital stay	94 (44%)	-	0	94 (0.3%)
PE during hospital stay	31 (16%)	-	3 (5.8%)‡	28 (0.1%)
DVT after discharge	46 (22%)	-	0	46 (0.1%)
PE after discharge	42 (20%)	-	4 (7.7%)‡	38 (0.1%)
Any VTE	213 (100%)	-	7 (3.3%)‡	206 (0.6%)

Table 2: Univariable analysis for VTE and death for 31,769 patients undergoing THA in the Spanish National Discharge Database.

	VTE	No VTE	Death	No death
Patients. N	213	31556	52	31717
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Hospital stay (mean days ± SD)	19 ± 18‡	10 ± 6.7	16 ± 17	10 ± 7.1
Hospital stay >10 days	130 (61%)‡	9439 (30%)	25 (48%)†	9544 (30%)
Bleeding complications				
Surgical haematoma	2 (0.9%)	312 (1.0%)	2 (3.8%)*	312 (1.0%)
Gastrointestinal	0	41 (0.1%)	2 (3.8%)‡	39 (0.1%)
Cerebral	1 (0.5%)*	2 (0.0%)	1 (1.9%)	2 (0.0%)
Other	2 (0.9%)*	36 (0.1%)	0	38 (0.1%)
Any bleeding	5 (2.3%)	381 (1.2%)	5 (9.6%)‡	381 (1.2%)
Bleeding during admission	3 (1.4%)	381 (1.2%)	4 (7.7%)†	380 (1.2%)
Bleeding during readmission	2 (0.9%)	0	1 (1.9%)†	1 (0.0%)
Wound infection				
Yes	12 (5.6%)‡	264 (0.8%)	2 (3.8%)	374 (1.2%)
Venous thromboembolism				
DVT during hospital stay	94 (44%)	-	0	94 (0.3%)
PE during hospital stay	31 (16%)	-	3 (5.8%)‡	28 (0.1%)
DVT after discharge	46 (22%)	-	0	46 (0.1%)
PE after discharge	42 (20%)	-	4 (7.7%)‡	38 (0.1%)
Any VTE	213 (100%)	-	7 (3.3%)‡	206 (0.6%)

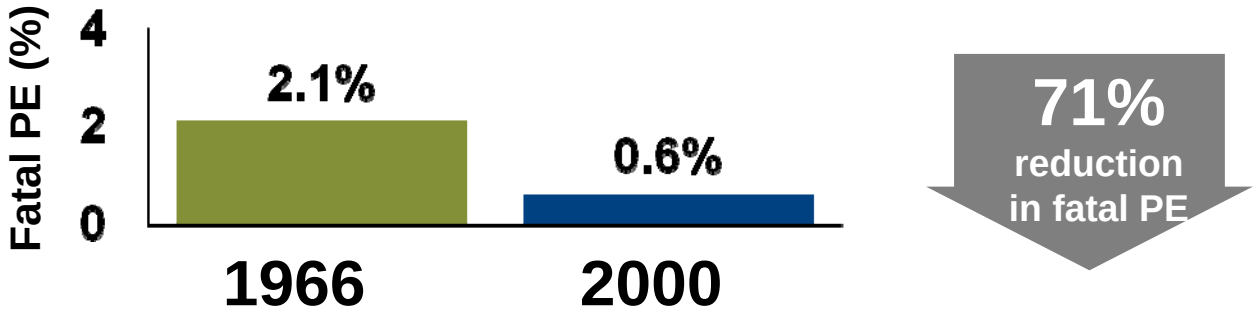
MINISTERIO DE SANIDAD Y CONSUMO

	TKA		THA	
	Acute VTE OR (95%CI)	Overall death OR (95%CI)	Acute VTE OR (95%CI)	Overall death OR (95%CI)
Clinical characteristics				
Gender (males)	0.7 (0.5–0.9)†	2.3 (1.3–4.0)†	-	-
Age >70 years	-	2.9 (1.5–5.8)†	1.5 (1.1–1.9)*	4.7 (2.2–10)‡
Underlying diseases				
Obesity	1.7 (1.2–2.3)†	-	-	-
Chronic lung disease	1.5 (1.02–2.1)*	-	-	-
Chronic heart failure	-	4.1 (1.6–11)†	-	10 (4.7–21)‡
Ischaemic heart disease	-	3.0 (1.3–7.0)†	-	3.4 (1.5–7.6)†
Cancer	2.2 (1.03–4.6)*	4.8 (1.4–16)*	-	7.8 (3.1–19)‡
Complications				
Any bleeding	-	8.5 (3.6–20)‡	-	6.4 (2.3–17)‡
Pulmonary embolism	-	157 (75–328)‡	-	65 (26–160)‡
Deep-vein thrombosis	-	6.3 (1.5–27)*	-	-

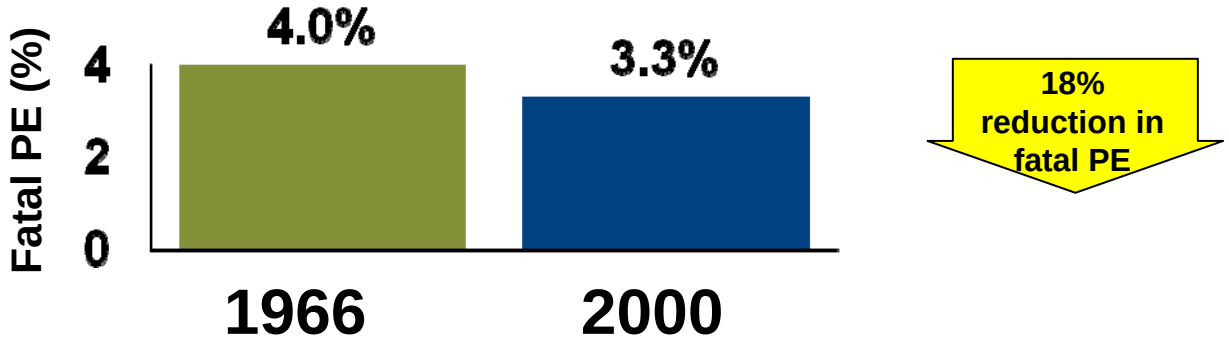
Thromb Haemost 2011; 105: 610-615.

Autopsy-Detected Fatal PE in Surgical and Medical Patients (21,515):1966–2000

Surgical patients[1,2]



Medical patients[1,2]



PE = Pulmonary embolism.

1. Cohen AT, et al. Haemostasis. 1996;26:65-71. 2. Alikhan R, et al. J Clin Pathol. 2004;57:1254-1257.

MINISTERIO
DE SANIDAD
Y CONSUMO

Venous thromboembolism and bleeding in acutely ill hospitalized patients. Findings from the Spanish National Discharge Database.

October 2005 to October 2006

1,184,652 patients

MINISTERIO DE SANIDAD Y CONSUMO

Venous thromboembolism and bleeding in acutely ill hospitalized patients. Findings from the Spanish National Discharge Database.

	Bleeding	No bleeding	VTE	No VTE	Death	No Death
Patients, N	35567	1112734	13751	1134550	99163	1049138
Bleeding complications,						
Gastrointestinal	17246	-	382	16864	4170	13076
Cerebral	2294	-	74	2220	866	1428
Other	17361	-	410	16951	2782	14579
Any bleeding	35567	-	798	34769	7405	28162
Bleeding during admission	35465	-	697	34768	7374	28091
Bleeding during readmission	110	-	110	-	32	79
Venous thromboembolism,						
DVT during hospital stay	431	7369	7800	-	1091	6709
PE during hospital stay	207	3047	3254	-	1260	1994
DVT during readmission	73	1216	1292	-	103	1186
PE during readmission	98	1407	1505	-	272	1233
Any VTE	798	12953	13751		2710	11041

CHEST Original Research

ANTITHROMBOTIC THERAPY

Factors at Admission Associated With Bleeding Risk in Medical Patients

Findings From the IMPROVE Investigators

Hervé Decousus, MD; Victor F. Tapson, MD, FCCP; Jean-François Bergmann, MD; Beng H. Chong, MD, PhD; James B. Froehlich, MD, MPH; Ajay K. Kakkar, MD, PhD; Geno J. Merli, MD; Manuel Monreal, MD; Mashio Nakamura, MD; Ricardo Pavanello, MD; Mario Pini, MD; Franco Piovella, MD; Frederick A. Spencer, MD; Alex C. Spyropoulos, MD, FCCP; Alexander G. G. Turpie, MD; Rainer B. Zotz, MD; Gordon FitzGerald, PhD; and Frederick A. Anderson, PhD; for the IMPR Investigators

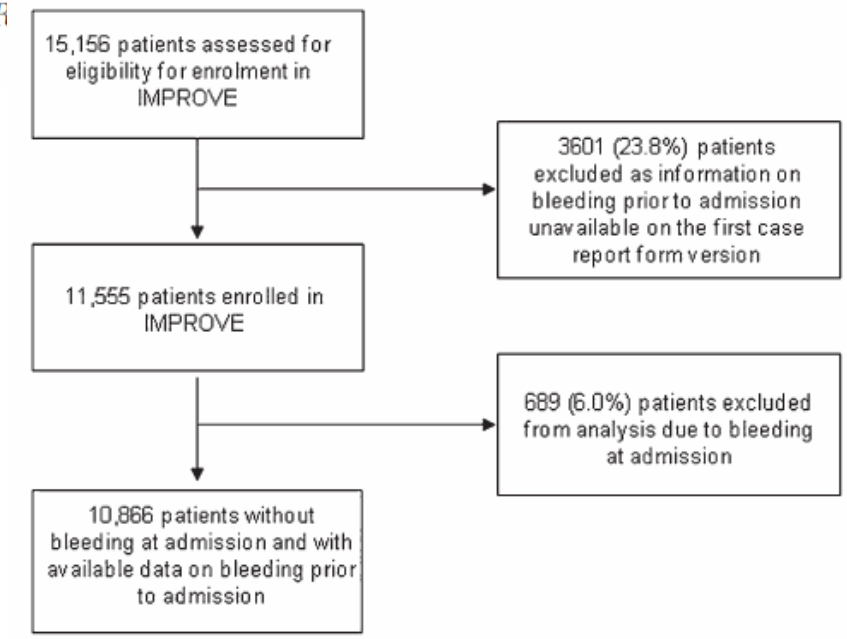


FIGURE 1. Patients included in this analysis of IMPROVE (data collected through September 2006). IMPROVE = International Medical Prevention Registry on Venous Thromboembolism.

CHEST 2011; 139(1):69–79

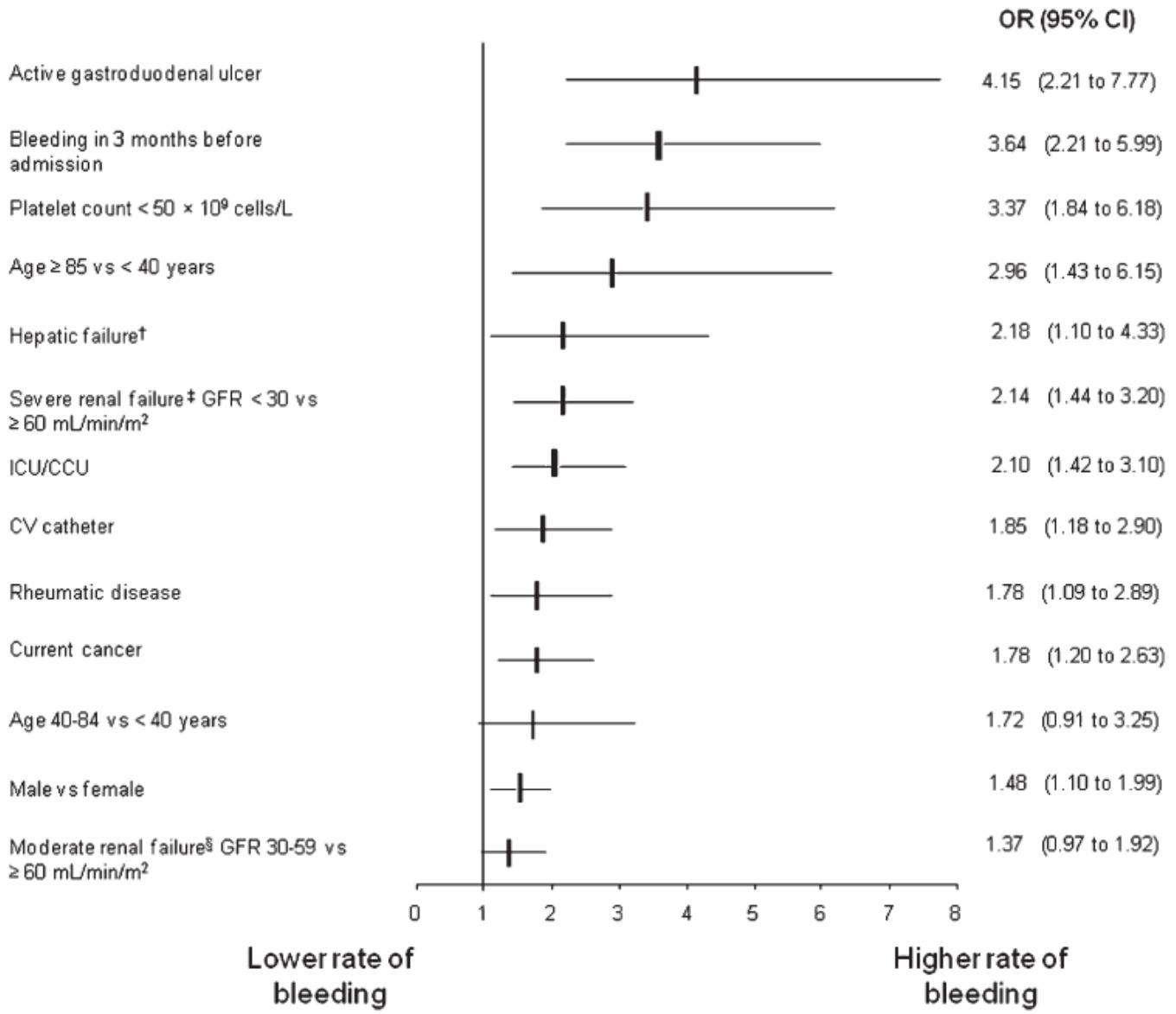


FIGURE 3. Multiple logistic regression model results for characteristics at admission independently associated with in-hospital bleeding in acutely ill medical patients in IMPROVE (9,388 patients with complete data, 198 with in-hospital bleeding within 14 days of admission). Note that 1,478 patients had no covariates observation to be included in the analysis. †Hepatic failure defined as an international normalized ratio > 1.5. ‡Severe renal failure defined as GFR < 30 mL/min/m². §Moderate renal failure defined as GFR 30 to 59 mL/min/m². CCU = coronary care unit; CV = central venous; GFR = glomerular filtration

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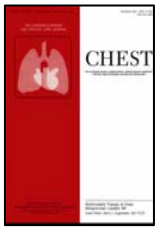
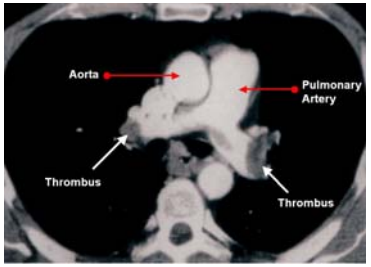
Caso clínico



- Mujer 77 años, 76 kg
- Hipertensión, diabetes
- **Abril 1: Hemorragia cerebral**
- **Abril 21: Dispnea + fibrilación auricular: Embolia pulmonar**

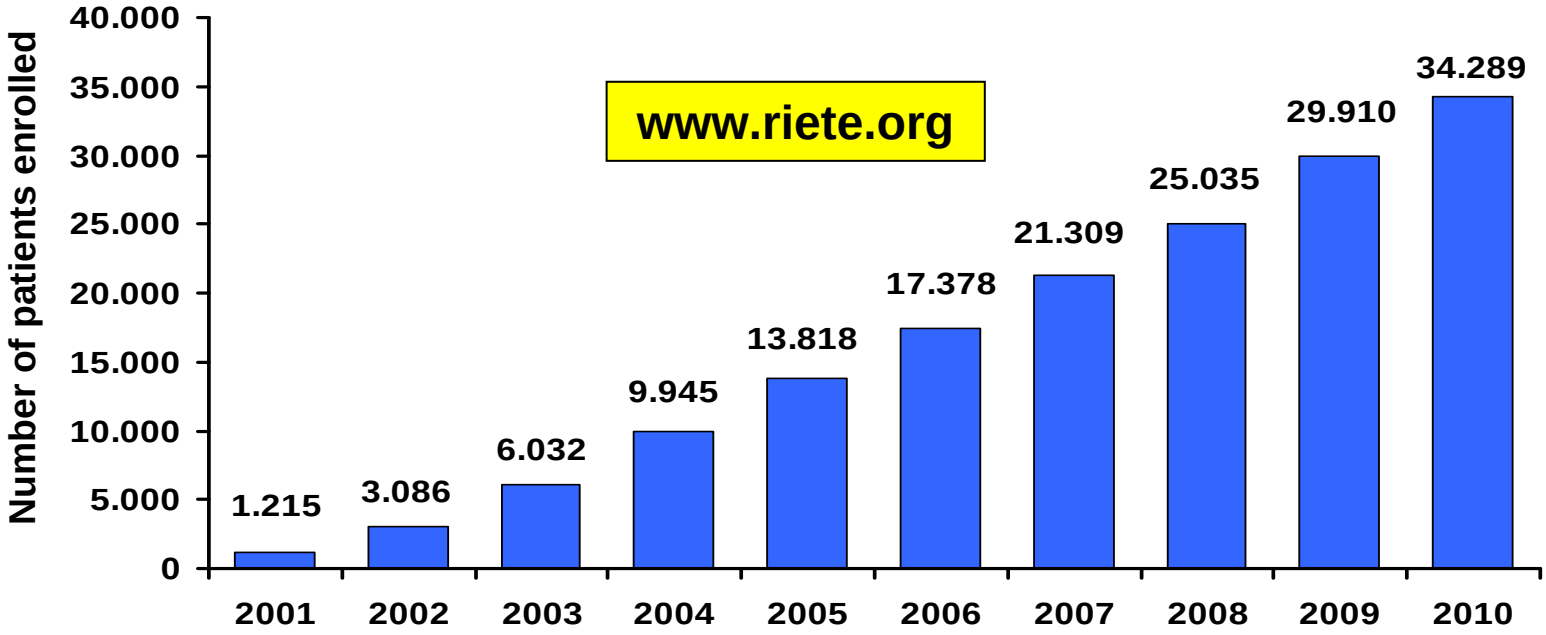
Tratamiento:

1. HBPM sc, 200 UI/kg/d
2. HBPM sc, 100 UI/kg/d
3. HNF iv.
4. Filtro vena cava + heparina
5. Filtro vena cava solo



Registro RIETE

36,281



30,921 patients

2,107 patients

1,580 patients

611 patients

105 patients

74 patients

62 patients

39 patients

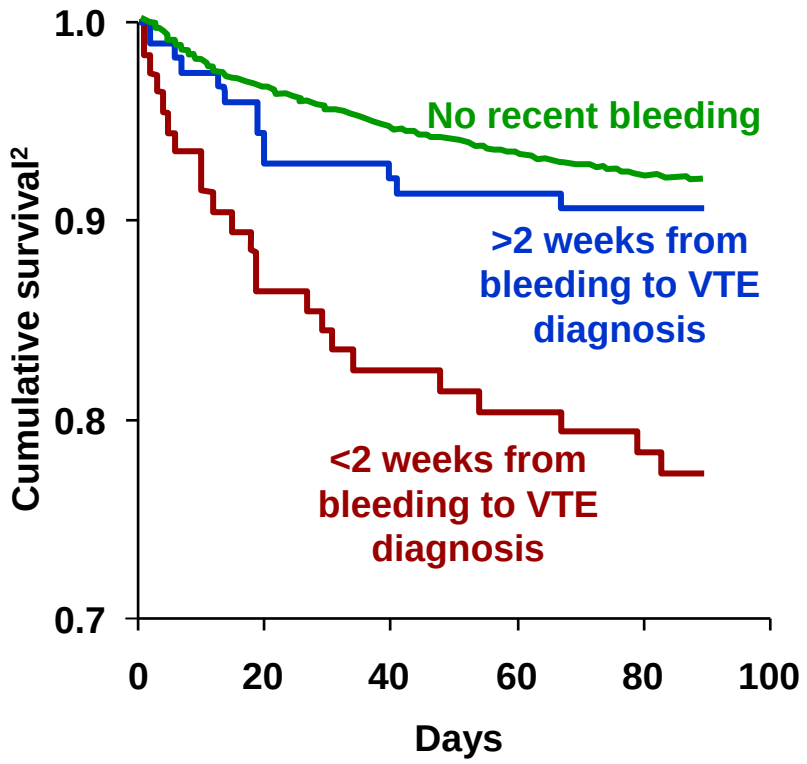
35 patients

10 patients

Hemorragia grave reciente

Clinical outcomes of VTE patients with and without recent episode of major bleeding

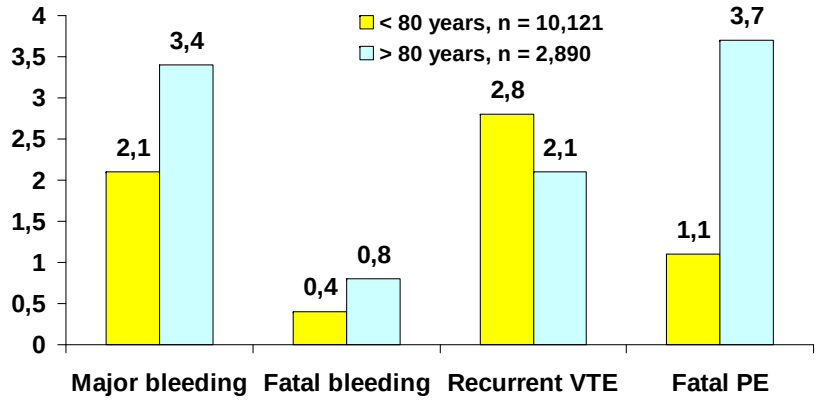
3-month outcome	Recent major bleeding (n=170) n (%)	No recent major bleeding (n=6,191) n (%)	Odds ratio (95% CI)	*p*-value
Fatal bleeding	7 (4.1)	41 (0.6)	**6.4** (2.6–15)	<0.001
Major bleeding	12 (7.1)	146 (2.3)	3.1 (1.6–5.9)	0.001
Minor bleeding	12 (7.1)	172 (2.8)	2.6 (14–5.0)	<0.005
Fatal initial PE	1 (0.6)	14 (0.2)	2.6 (0.2–19)	ns
Fatal recurrent PE	4 (2.4)	33 (0.5)	**4.5** (1.3–14)	<0.05
Recurrent VTE	8 (4.7)	184 (2.9)	1.6 (0.7–3.4)	ns
Overall mortality	25 (15)	479 (7.7)	2.1 (1.3–3.2)	<0.005



J Thromb Haemost 2005;3:703–709

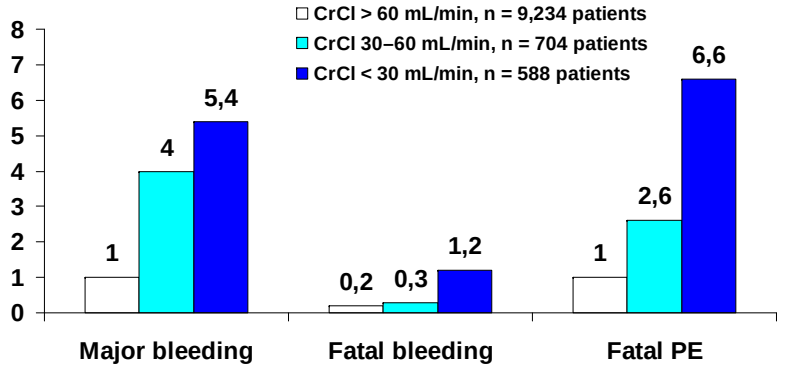
J Thromb Haemost 2006;4:2367–2372

Elderly patients



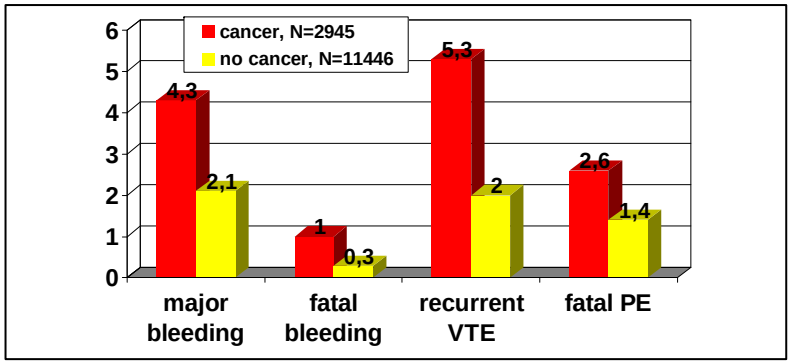
Haematologica 2006; 91: 1046-1051
Thromb Haemost 2009; 101: 1112-1118

Renal insufficiency: 15 days



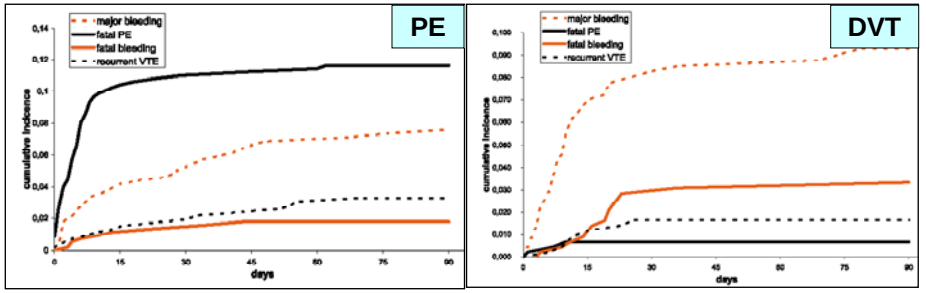
Am J Med 2006; 119: 1073-1079

Cancer and 3-month outcome



J Thromb Haemost, 2006: 4: 1950-1956

Renal insufficiency: 3 months



Thromb Haemost 2007; 98: 771-776

Intensidad del tratamiento

Summary of Recommendations

1.1 Initial Anticoagulation of Acute DVT of the Leg

1.1.1. For patients with objectively confirmed DVT, we recommend short-term treatment with SC LMWH (Grade 1A), **IV UFH** (Grade 1A), **monitored SC UFH** (Grade 1A), **fixed-dose SC UFH** (Grade 1A), **or SC fondaparinux** (Grade 1A) **rather than no such short-term treatment.**

1.1.2. For patients with a high clinical suspicion of DVT, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (Grade 1C).

1.1.3. In patients with acute DVT, we recommend initial treatment with LMWH, UFH, or fondaparinux for at least 5 days and until the INR is ≥ 2.0 for 24 h (Grade 1C).

1.1.4. In patients with acute DVT, we recommend initiation of VKA together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation of VKA (Grade 1A).

4.0 Initial Treatment of Acute PE

Treatment regimens for DVT and PE are similar because the two conditions are manifestations of the same disease process. When patients with VTE are carefully studied, the majority of those with proximal DVT also have PE (symptomatic or asymptomatic) and vice versa.[185] Furthermore, clinical trials of anticoagulant therapy have yielded similar estimates for efficacy and safety in patients with DVT alone, in those with both DVT and PE, and in patients with only PE. The

CHEST
Official publication of the American College of Chest Physicians
CHEST ONLINE

Antithrombotic Therapy for Venous Thromboembolic Disease*

Clive Kearon, Susan R. Kahn, Giancarlo Agnelli, Samuel Goldhaber, Gary E. Raskob and Anthony J. Comerota

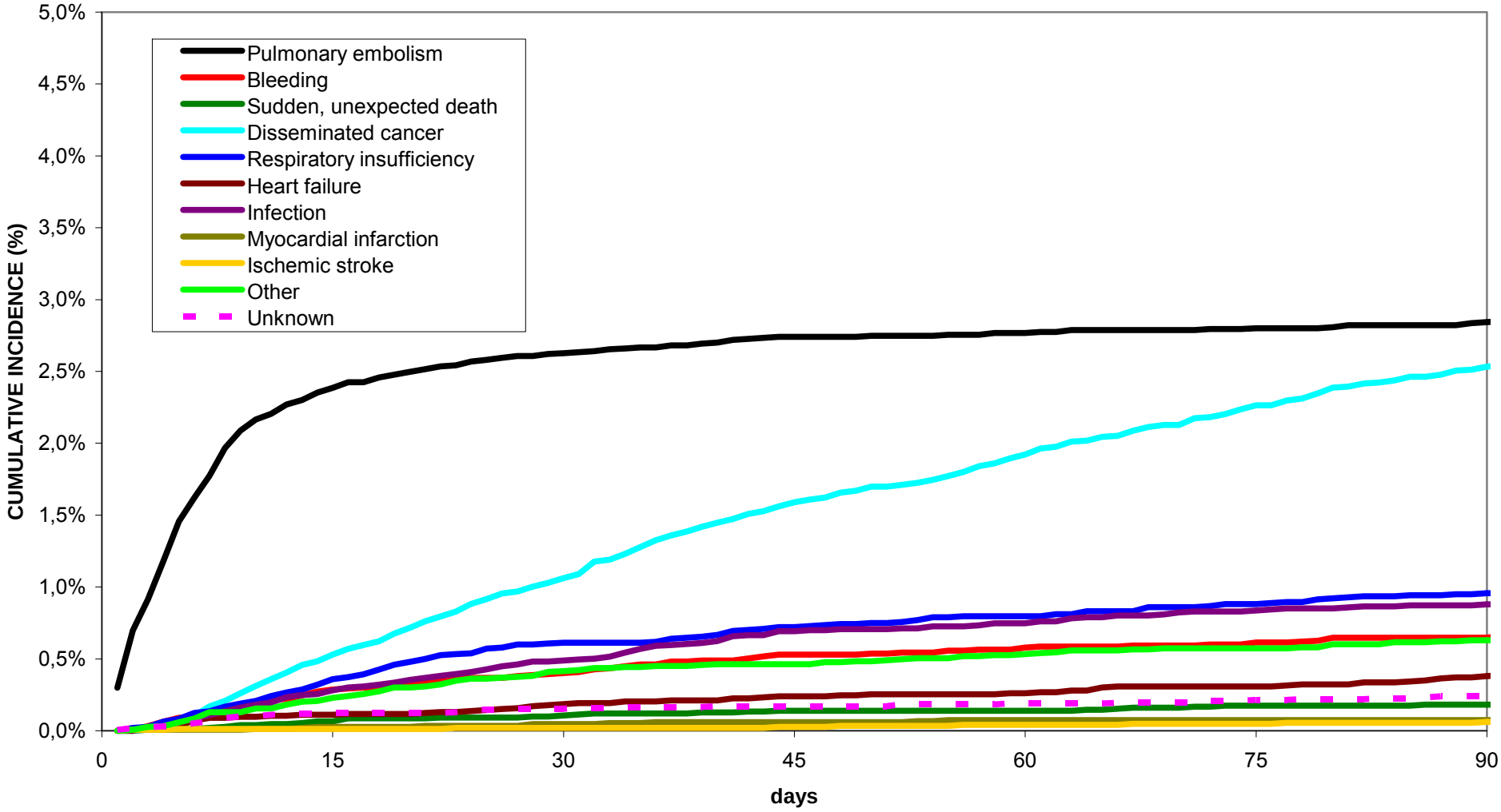
Mortality rate at different intervals

15,761 patients with PE	Day 7	Day 15	Day 30	Day 60	Day 90
Pulmonary embolism					
Disseminated cancer					
Dyspnea					
Infection					
Bleeding					
Heart failure					
Sudden, unexpected					
Myocardial infarction					
Ischemic stroke					
Other					
Unknown					
TOTAL	467 (3.0%)	710 (4.5%)	954 (6.1%)	1240 (7.9%)	1433 (9.1%)

Mortality rate at different intervals

15,761 patients with PE	Day 7	Day 15	Day 30	Day 60	Day 90
Pulmonary embolism	309 (2.0%)				
Disseminated cancer	32 (0.2%)				
Dyspnea	26 (0.2%)				
Infection	21 (0.1%)				
Bleeding	23 (0.1%)				
Heart failure	14 (0.1%)				
Sudden, unexpected	4 (0.0%)				
Myocardial infarction	1 (0.0%)				
Ischemic stroke	2 (0.0%)				
Other	20 (0.1%)				
Unknown	15 (0.1%)				
TOTAL	467 (3.0%)	710 (4.5%)	954 (6.1%)	1240 (7.9%)	1433 (9.1%)

Mortality rate in 15,761 patients with PE



Mortality rate at different intervals

15,761 patients with PE	Day 7	Day 15	Day 30	Day 60	Day 90	
Pulmonary embolism	309	380 (2.4%)	412 (2.6%)	433 (2.8%)	444 (2.8%)	135
Disseminated cancer		87 (0.6%)	165 (1.1%)	294 (2.0%)	378 (2.5%)	
Dyspnea		57 (0.4%)	93 (0.6%)	120 (0.8%)	143 (1.0%)	
Infection		46 (0.3%)	75 (0.5%)	114 (0.8%)	131 (0.9%)	
Bleeding	23	45 (0.3%)	62 (0.4%)	88 (0.6%)	99 (0.7%)	76
Heart failure		18 (0.1%)	29 (0.2%)	40 (0.3%)	57 (0.4%)	
Sudden, unexpected		13 (0.1%)	17 (0.1%)	21 (0.1%)	27 (0.2%)	
Myocardial infarction		4 (0.0%)	7 (0.0%)	11 (0.1%)	11 (0.1%)	
Ischemic stroke		2 (0.0%)	3 (0.0%)	6 (0.0%)	9 (0.1%)	
Other		37 (0.2%)	64 (0.4%)	81 (0.5%)	94 (0.6%)	
Unknown		21 (0.1%)	27 (0.2%)	32 (0.2%)	40 (0.2%)	
TOTAL	467	710 (4.5%)	954 (6.1%)	1240 (7.9%)	1433 (9.1%)	

17,128 patients with DVT

	Day 7	Day 15	Day 30	Day 60	Day 90
Disseminated cancer	28 (0.2%)				
Infection	19 (0.1%)				
Bleeding	15 (0.1%)				
Dyspnea	13 (0.1%)				
Pulmonary embolism	15 (0.1%)				
Heart failure	3 (0.0%)				
Sudden, unexpected	3 (0.0%)				
Other	31 (0.2%)				
TOTAL	112 (0.7%)	287 (1.7%)	520 (3.0%)	834 (4.9%)	1056 (6.2%)

17,128 patients with DVT

	Day 7	Day 15	Day 30	Day 60	Day 90	
Disseminated cancer		65 (0.4%)	136 (0.8%)	262 (1.6%)	347 (2.1%)	
Infection		34 (0.2%)	60 (0.4%)	88 (0.5%)	108 (0.6%)	
Bleeding	15	42 (0.2%)	66 (0.4%)	81 (0.5%)	91 (0.5%)	76
Dyspnea		22 (0.1%)	37 (0.2%)	49 (0.3%)	59 (0.4%)	
Pulmonary embolism	15	21 (0.1%)	27 (0.2%)	32 (0.2%)	40 (0.2%)	35
Heart failure		6 (0.0%)	15 (0.1%)	20 (0.1%)	25 (0.2%)	
Sudden, unexpected		7 (0.0%)	12 (0.1%)	18 (0.1%)	20 (0.1%)	
Other		90 (0.5%)	167 (1.0%)	284 (1.6%)	366 (2.2%)	
TOTAL		287 (1.7%)	520 (3.0%)	834 (4.9%)	1056 (6.2%)	

La embolia pulmonar en España
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Table 1: The Pulmonary Embolism Severity Index.

Predictors	Points assigned
Age, per year	**Age, in years**
Male sex	+10
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Pulse ≥110/minute	+20
Systolic blood pressure < 100 mm Hg	+30
Respiratory rate ≥30/minute*	+20
Temperature < 36°C	+20
Altered mental status†	+60
Arterial oxygen saturation < 90%*	+20

A total point score for a given patient is obtained by summing the patient's age in years and the points for each applicable predictor. Points assignments correspond with the following risk classes: ≤65 class I; 66–85 class II; 86–105 class III; 106–125 class IV; and > 125 class V. Patients in risk classes I and II are defined as low-risk. *Assessed with or without the administration of supplemental oxygen. †Defined as confusion, disorientation, or somnolence.

Table 1. Original and Simplified Pulmonary Embolism Severity Index (PESI)

Variable	Score	
	Original PESI[a]	Simplified PESI[b]
Age >80 y	Age in years	1
Male sex	+10	
History of cancer	+30	1
History of heart failure	+10	1[c]
History of chronic lung disease	+10	
Pulse ≥110 beats/min	+20	1
Systolic blood pressure <100 mm Hg	+30	1
Respiratory rate ≥30 breaths/min	+20	
Temperature <36°C	+20	
Altered mental status	+60	
Arterial oxyhemoglobin saturation level <90%	+20	1

ORIGINAL INVESTIGATION

Simplification of the Pulmonary Embolism Severity Index for Prognostication in Patients With Acute Symptomatic Pulmonary Embolism

David Jiménez, MD, PhD; Drahomir Aujesky, MD; Lisa Moores, MD; Vicente Gómez, MD; José Luis Lobo, MD, PhD; Fernando Uresandi, MD, PhD; Remedios Otero, MD, PhD; Manuel Monreal, MD, PhD; Alfonso Muriel, MSc; Roger D. Yusen, MD; for the RIETE Investigators

Table 4. Original and Simplified PESI Prediction Rule Test Characteristics for 30-Day Mortality in This Study's Derivation Cohort[a]

Characteristic	Original PESI Variable (95% CI)	Simplified PESI Variable (95% CI)
Sensitivity, %	88.5 (81.4-95.5)	96.1 (91.9-100.0)
Specificity, %	38.4 (35.2-41.5)	32.9 (29.9-36.0)
Positive predictive value, %	10.9 (8.5-13.3)	10.9 (8.5-13.2)
Negative predictive value, %	97.5 (95.9-99.1)	99.0 (97.9-100.0)
Positive likelihood ratio	1.44 (1.31-1.58)	1.43 (1.35-1.53)
Negative likelihood ratio	0.30 (0.16-0.56)	0.12 (0.04-0.36)

Arch Intern Med 2010;170:1383–1389

Age	N	Dead	Low-risk	Dead	NPV
PESI					
All	*12019*	*778 (6.5%)*			
<20 y	44	1 (2.3%)			
20-29	311	2 (0.6%)			
30-39	542	6 (1.1%)			
40-49	725	17 (2.3%)			
50-59	1079	61 (5.7%)			
60-69	2061	84 (4.1%)			
70-79	3938	234 (5.9%)			
80-89	2884	294 (10%)			
>89 y	435	79 (18%)			
$_{s}$PESI					
All	*12019*	*778 (6.5%)*			
<20 y	44	1 (2.3%)			
20-29	311	2 (0.6%)			
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70-79	3938	234 (5.9%)			
80-89	2884	294 (10%)			
>89 y	435	79 (18%)			

Age	N	Dead	Low-risk	Dead	NPV
PESI					
All	*12019*	*778 (6.5%)*	*4302 (36%)*	*49 (1.1%)*	*98.9 (98.5-99.1)*
<20 y	44	1 (2.3%)	43 (98%)		
20-29	311	2 (0.6%)	295 (95%)		
30-39	542	6 (1.1%)	486 (90%)		
40-49	725	17 (2.3%)	555 (77%)		
50-59	1079	61 (5.7%)	632 (59%)		
60-69	2061	84 (4.1%)	869 (42%)		
70-79	3938	234 (5.9%)	1094 (28%)		
80-89	2884	294 (10%)	328 (11%)		
>89 y	435	79 (18%)	0		
$_{s}$PESI					
All	*12019*	*778 (6.5%)*	*3399 (28%)*	*39 (1.1%)*	*98.9 (98.4-99.2)*
<20 y	44	1 (2.3%)	26 (59%)		
20-29	311	2 (0.6%)	176 (57%)		
30-39	542	6 (1.1%)	301 (56%)		
40-49	725	17 (2.3%)	345 (48%)		
50-59	1079	61 (5.7%)	444 (41%)		
60-69	2061	84 (4.1%)	738 (36%)		
70-79	3938	234 (5.9%)	1263 (32%)		
80-89	2884	294 (10%)	106 (3.7%)		
>89 y	435	79 (18%)	0		

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Variable	Score: Original PESI[a]	Score: Simplified PESI[b]
Age >80 y	Age in years	1
Male sex	+10	
History of cancer	+30	1
History of heart failure	+10	1[c]
History of chronic lung disease	+10	
Pulse ≥110 beats/min	+20	1
Systolic blood pressure <100 mm Hg	+30	1
Respiratory rate ≥30 breaths/min	+20	
Temperature <36°C	+20	
Altered mental status	+60	
Arterial oxyhemoglobin saturation level <90%	+20	1

[a] A total point score for a given patient is obtained by summing the patient's age in years and the points for each predictor when present. The score corresponds with the following risk classes: 65 or less, class I; 66 to 85, class II; 86 to 105, class III; 106 to 125, class IV; and more than 125, class V. Patients in risk classes I and II are defined as being at low risk.

[b] A total point score for a given patient is obtained by summing the points. The score corresponds with the following risk classes: 0, low risk; 1 or more, high risk. Empty cells indicate that the variable was not included.

[c] The variables were combined into a single category of chronic cardiopulmonary disease.

Age	N	Dead	Low-risk	Dead	NPV
PESI					
All	*12019*	*778 (6.5%)*	*4302 (36%)*	*49 (1.1%)*	*98.9 (98.5-99.1)*
<20 y	44	1 (2.3%)	43 (98%)	1 (2.3%)	97.7 (87.9-99.6)
20-29	311	2 (0.6%)	295 (95%)	2 (0.7%)	99.3 (97.6-99.8)
30-39	542	6 (1.1%)	486 (90%)	0	100 (99.2-100)
40-49	725	17 (2.3%)	555 (77%)	5 (0.9%)	99.1 (97.9-99.6)
50-59	1079	61 (5.7%)	632 (59%)	6 (0.9%)	99.1 (98.0-99.6)
60-69	2061	84 (4.1%)	869 (42%)	6 (0.7%)	99.3 (98.5-99.7)
70-79	3938	234 (5.9%)	1094 (28%)	16 (1.5%)	98.5 (97.6-99.1)
80-89	2884	294 (10%)	328 (11%)	13 (4.0%)	96.0 (93.3-97.7)
>89 y	435	79 (18%)	0	0	-
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All	*12019*	*778 (6.5%)*	*3399 (28%)*	*39 (1.1%)*	*98.9 (98.4-99.2)*
<20 y	44	1 (2.3%)	26 (59%)	0	100 (87.1-100)
20-29	311	2 (0.6%)	176 (57%)	0	100 (97.9-100)
30-39	542	6 (1.1%)	301 (56%)	0	100 (98.7-100)
40-49	725	17 (2.3%)	345 (48%)	2 (0.6%)	99.4 (97.9-99.8)
50-59	1079	61 (5.7%)	444 (41%)	4 (0.9%)	99.1 (97.7-99.7)
60-69	2061	84 (4.1%)	738 (36%)	3 (0.4%)	99.6 (98.8-99.9)
70-79	3938	234 (5.9%)	1263 (32%)	24 (1.9%)	98.1 (97.2-98.7)
80-89	2884	294 (10%)	106 (3.7%)	6 (5.7%)	94.3 (88.2-97.4)
>89 y	435	79 (18%)	0	0	

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3.- Trombolisis en la EP

Population	15-day mortality OR (95% CI)	30-day mortality OR (95% CI)	90-day mortality OR (95% CI)
Entire cohort* (n = 15,944)	2.28 (1.49-3.47) < 0.001	1.93 (1.30-2.86) 0.001	1.48 (1.02-2.15) 0.038

*Adjusted for age >80 years (vs. other), SBP <100 mm Hg (vs. other), previous bleeding, cancer, surgery, immobilization, abnormal creatinine levels, and SaO2 < 90% (vs. other).

3.- Trombolisis en la EP

Population	15-day mortality OR (95% CI)	30-day mortality OR (95% CI)	90-day mortality OR (95% CI)
Entire cohort* (n = 15,944)	2.28 (1.49-3.47) < 0.001	1.93 (1.30-2.86) 0.001	1.48 (1.02-2.15) 0.038
SBP <100 mm Hg (n = 94 matched pairs)	0.75 (0.34-1.67)	0.65 (0.29-1.42)	0.72 (0.36-1.46)
SBP ≥100 mm Hg (n = 217 matched pairs)	2.21 (0.99-4.28)	1.72 (0.88-3.33)	2.32 (1.15-4.68) 0.02

*Adjusted for age >80 years (vs. other), SBP <100 mm Hg (vs. other), previous bleeding, cancer, surgery, immobilization, abnormal creatinine levels, and SaO2 < 90% (vs. other).

3.- Trombolisis en la EP

Population	15-day mortality OR (95% CI)	30-day mortality OR (95% CI)	90-day mortality OR (95% CI)
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SBP ≥100 mm Hg (n = 217 matched pairs)	2.21 (0.99-4.28)	1.72 (0.88-3.33)	2.32 (1.15-4.68) 0.02
SBP <90 mm Hg (n =61 matched pairs)	0.69 (0.30-1.55)	0.62 (0.27-1.40)	0.71 (0.31-1.60)
SBP ≥90 mm Hg (n = 250 matched pairs)	5.93 (1.98-17.76) 0.001	3.51 (1.61- 7.67) 0.002	2.13 (1.14-4.00) 0.018

*Adjusted for age >80 years (vs. other), SBP <100 mm Hg (vs. other), previous bleeding, cancer, surgery, immobilization, abnormal creatinine levels, and SaO2 < 90% (vs. other).

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VTE treatment: clinical studies

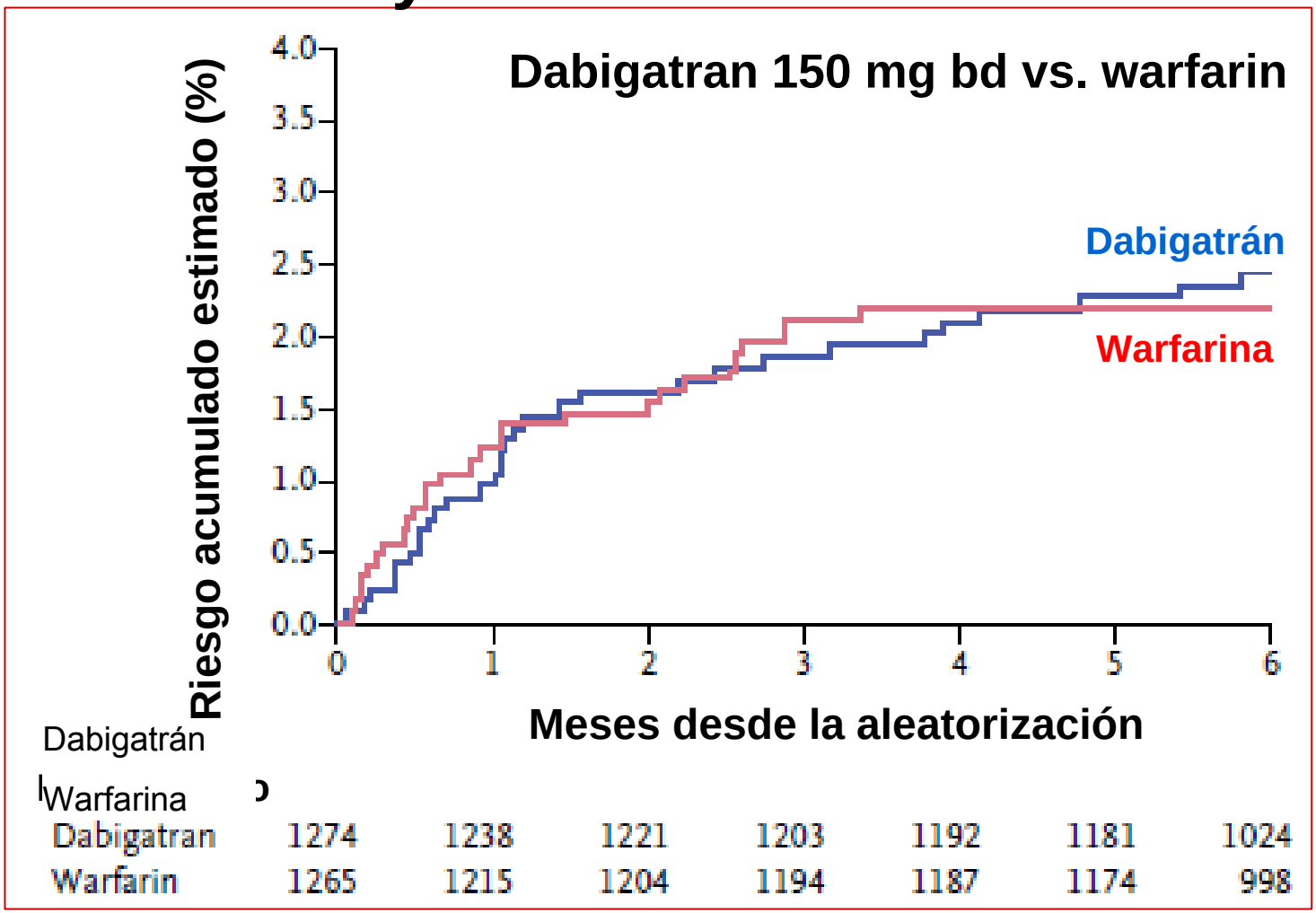
	Phase II	Phase III
Dabigatran Oral, direct thrombin inhibitor		**RE-COVER & RE-COVER II** 5–10 days pre-treatment with LMWH bridging to dabigatran or VKA for 6 months **RE-MEDY** 3–6 months' treatment with approved anticoagulant; switch to dabigatran or VKA **RE-SONATE** 6–18 months' VKA treatment followed by 6 months dabigatran or placebo
Rivaroxaban Oral, direct Factor Xa inhibitor	**EINSTEIN DVT** Rivaroxaban vs LMWH/UFH followed by VKA **ODIXa-DVT** Rivaroxaban vs enoxaparin followed by VKA	**EINSTEIN DVT/PE** Rivaroxaban for 3, 6 or 12 months vs enoxaparin for ≥5 days followed by VKA for 3, 6, or 12 months **EINSTEIN EXT** Pre-treatment with rivaroxaban or VKA for 6 or 12 months followed by rivaroxaban or placebo for 6 or 12 months
Apixaban Oral, direct Factor Xa inhibitor	**Botticelli-DVT** Apixaban vs LMWH or fondaparinux followed by VKA	**AMPLIFY** Apixaban 10 mg bid followed by 5 mg bid for 6 months vs enoxaparin followed by VKA **AMPLIFY-EXT** Apixaban 2.5 mg bid or 5 mg bid for extended 12 months period vs placebo

- Oral prodrug, converted to dabigatran, a potent reversible direct **thrombin** inhibitor (DTI)
- Rapid onset of action
- Half life of 12-17 h,
- ~ 80% renally excreted
- Predictable and consistent anticoagulant effects
- Low potential for drug-drug interactions, no drug-food interactions
- No requirement for routine coagulation monitoring

- Direct, specific, competitive **Factor Xa** inhibitor
- Rapid onset of action
- Half-life: 7–11 hours
- Dual mode of elimination:
  - 1/3 of drug excreted unchanged by the kidneys
  - 2/3 of drug metabolized by the liver: half excreted renally; half excreted by the fecal route
- No dietary restrictions

RECOVER™
Study of treatment of venous thromboembolism

Riesgo acumulado de recurrencias y muerte relacionada



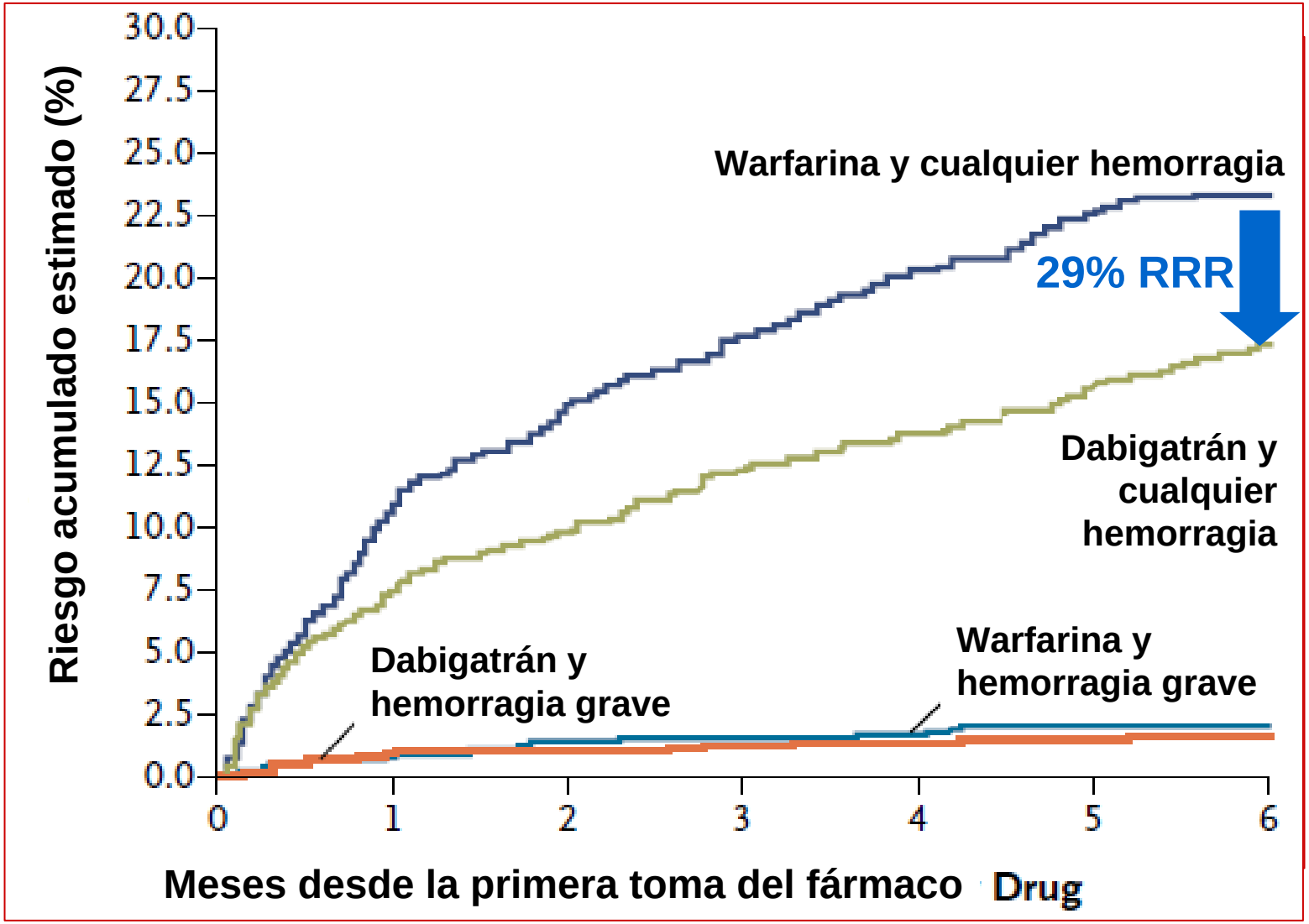
Schulman S, et al. N Engl J Med 2009;361:2342–2352

Criterios de valoración secundarios de la eficacia

	Dabigatrán 150 mg bid n = 1274	Warfarina n = 1265	Cociente de riesgos instantáneos ($IC_{95\%}$)
TVP sintomática (%)	16 (1,3)	18 (1,4)	0,87 (0,44-1,71)
EP sintomática no mortal (%)	13 (1,0)	7 (0,6)	1,85 (0,74-4,64)
Mortalidad relacionada con TEV	1 (0,1)	3 (0,2)	0,33 (0,03-3,15)
Mortalidad total	21 (1,7)	21 (1,7)	0,98 (0,53-1,79)

RECOVER™
Study of treatment of venous thromboembolism

Riesgo acumulado de hemorragia

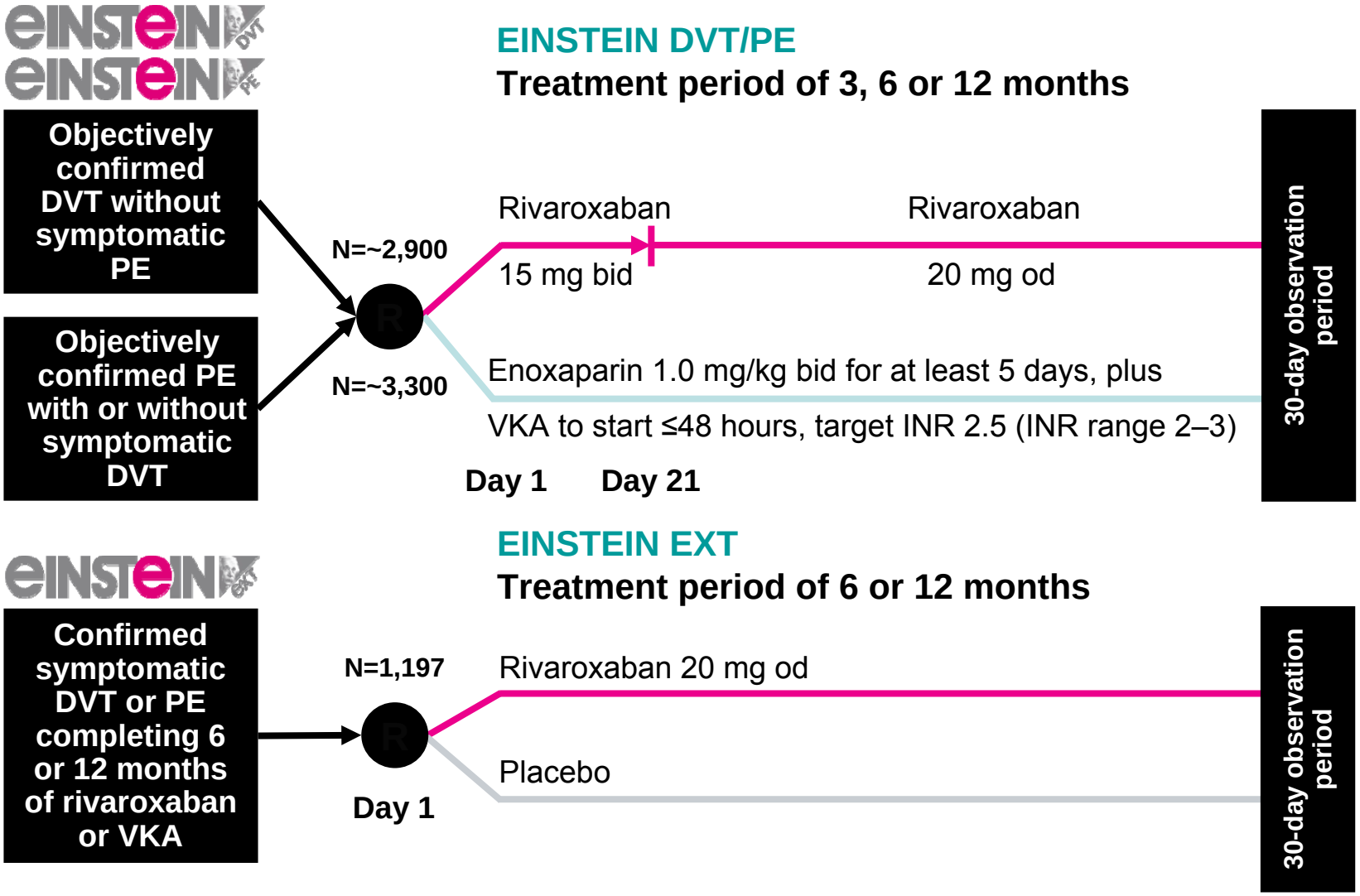


Schulman S, et al. N Engl J Med 2009;361:2342–2352

Localizaciones de hemorragia grave

	Dabigatran n = 1273	Warfarina n = 1266
Hemorragia mortal	1	1
Hemorragia en órganos críticos	1	9
Intracraneal	0	3
Hemartrosis	1	5
Hemoptisis	0	1

EINSTEIN phase III: study designs



EINSTEIN DVT, PE, Extension Evaluation Study Information available at: http://clinicaltrials.gov

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

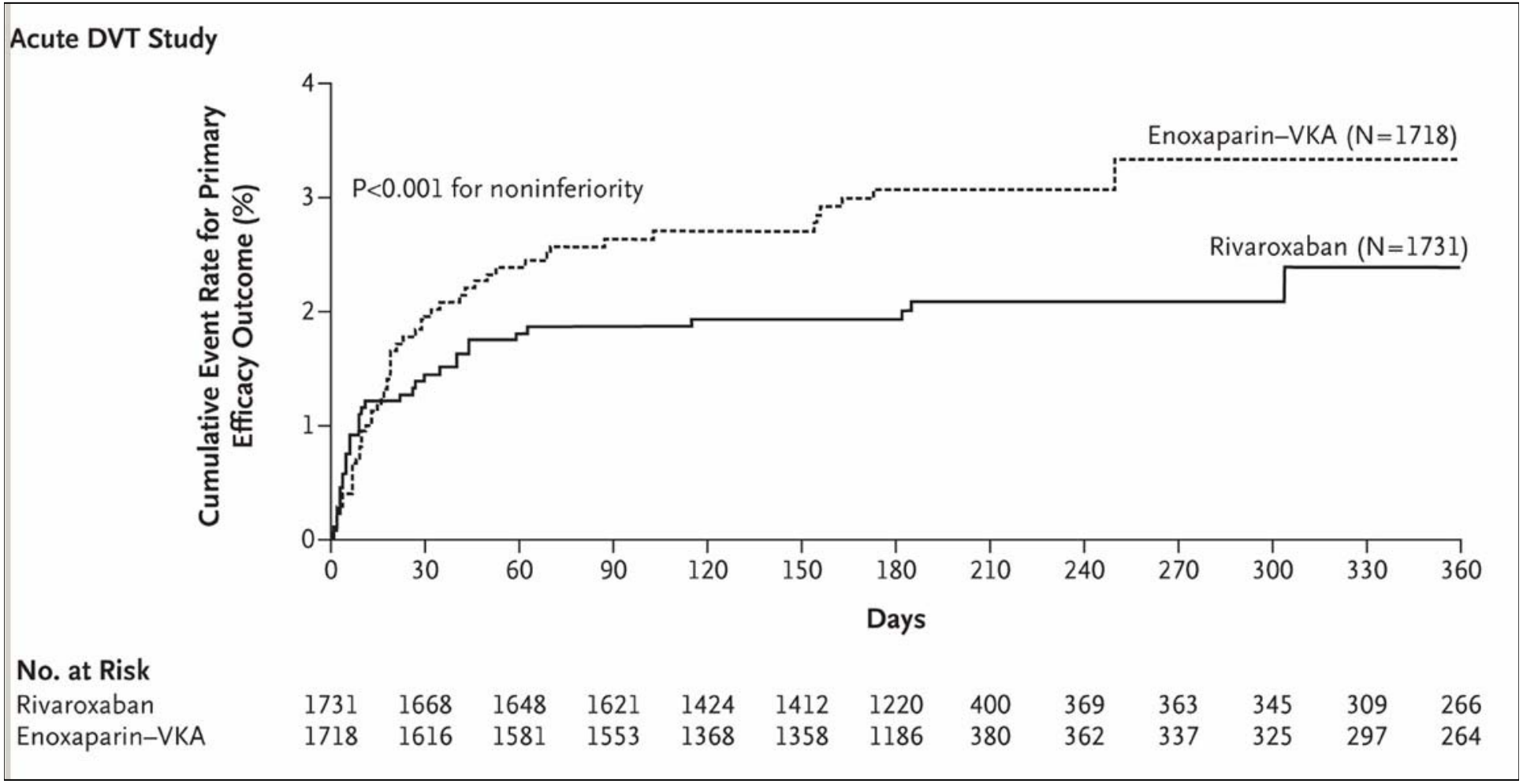
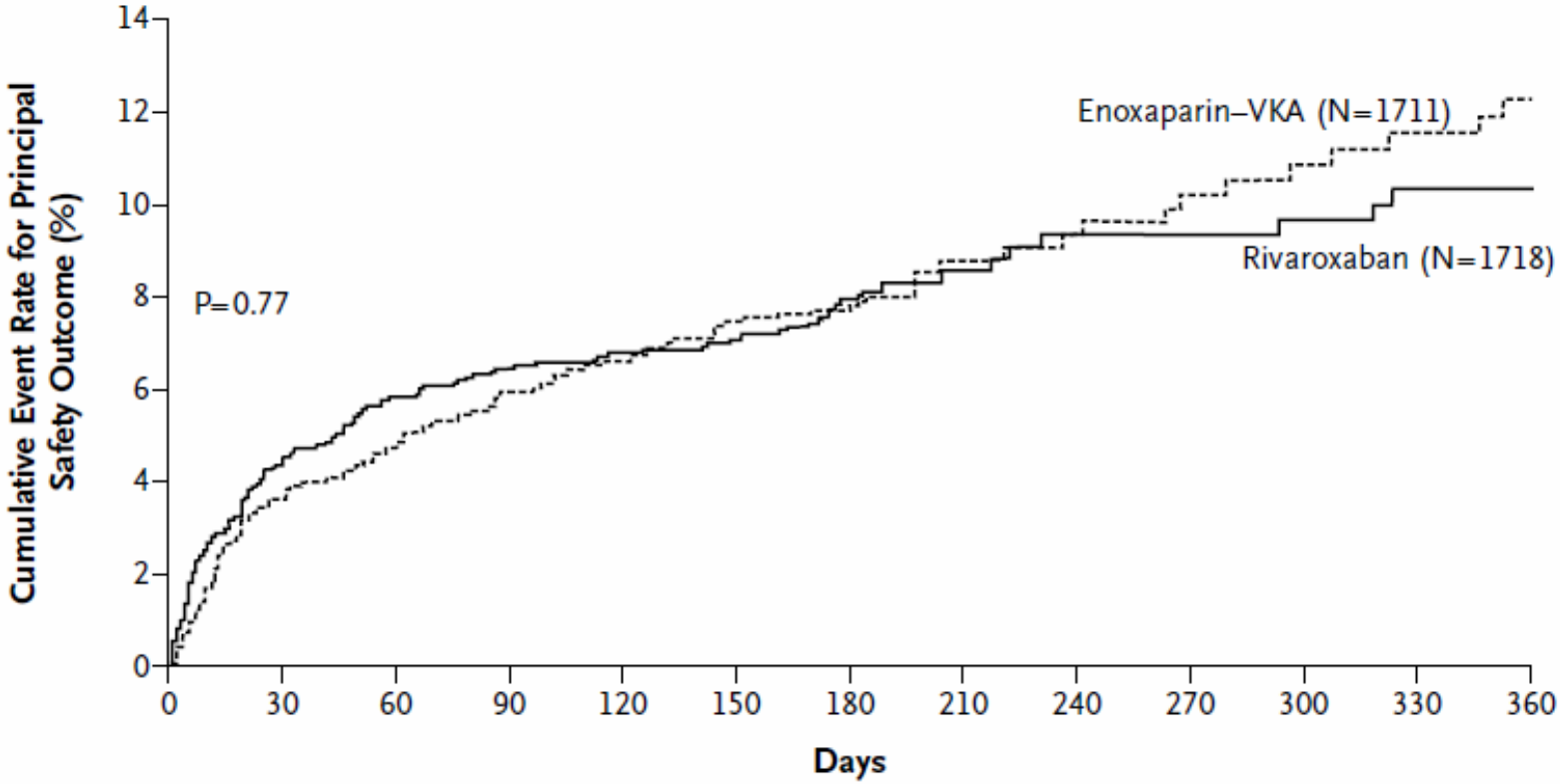


Table 3. Clinical Outcomes in the Acute DVT Study.*

Outcome	Rivaroxaban	Enoxaparin–VKA	Hazard Ratio (95% CI)	P Value
	no. (%)			
Efficacy				
Intention-to-treat population	1731	1718		
Recurrent VTE	36 (2.1)	51 (3.0)	0.68 (0.44–1.04)	<0.001†
Type of recurrent VTE				
Fatal PE	1	0		
PE could not be ruled out	3	6		
Nonfatal PE	20	18		
Recurrent DVT plus PE	1	0		
Recurrent DVT	14	28		
Net clinical benefit in terms of VTE plus major bleeding	51 (2.9)	73 (4.2)	0.67 (0.47–0.95)	0.03
Safety				
Safety population	1718	1711		
First major or clinically relevant nonmajor bleeding occurring during treatment	139 (8.1)	138 (8.1)	0.97 (0.76–1.22)	0.77
Major bleeding	14 (0.8)	20 (1.2)	0.65 (0.33–1.30)	0.21
Contributing to death	1 (<0.1)	5 (0.3)		
In a critical site	3 (0.2)	3 (0.2)		
Associated with a fall in hemoglobin of ≥2 g per deciliter, transfusion of ≥2 units, or both	10 (0.6)	12 (0.7)		
Clinically relevant nonmajor bleeding	126 (7.3)	119 (7.0)		
Total deaths through end of intended treatment period	38 (2.2)	49 (2.9)	0.67 (0.44–1.02)	0.06
Cause of death				
PE, or PE not ruled out	4	6		
Bleeding	2‡	5		
Cancer	25	20		
Cardiovascular disease	2	4		
Other	6	14		



No. at Risk

Rivaroxaban	1718	1585	1538	1382	1317	1297	715	355	338	304	278	265	140
Enoxaparin–VKA	1711	1554	1503	1340	1263	1238	619	338	321	287	268	249	118

Figure 3. Kaplan–Meier Cumulative Event Rates for the Principal Safety Outcome in the Acute DVT Study.

VKA denotes vitamin K antagonist.