Embolia polmonare in pronto soccorso: casi clinici tutti uguali ?

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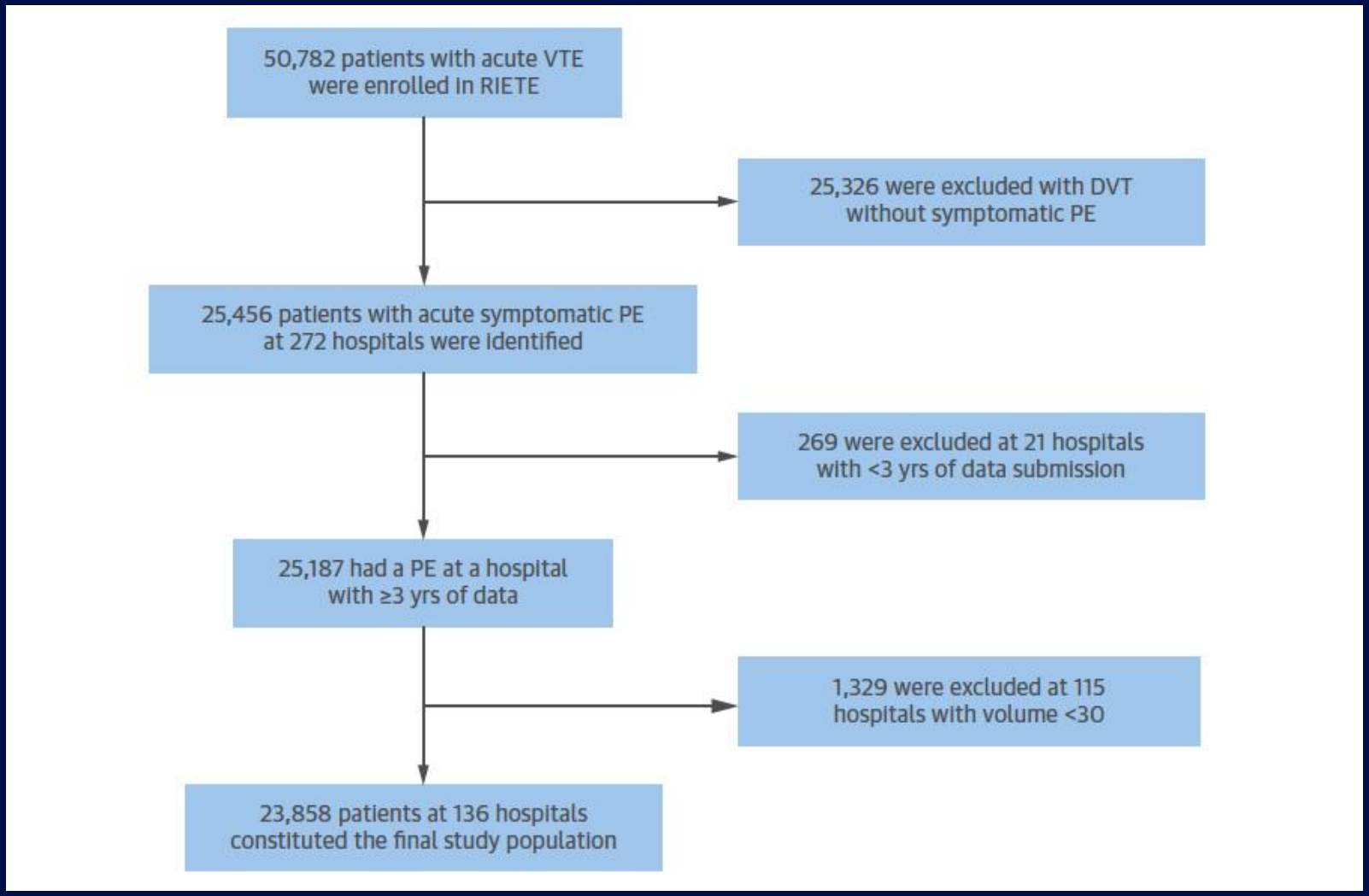
Dichiarazione conflitto d'interessi

Grant per collaborazioni scientifiche (advisory board, studi clinici, presentazioni a convegni):

- Actelion
- Bayer
- Dompè
- GSK
- MSD
- Pfizer
- United Therapeutics

The improvement in PE treatment RIETE Registry



Jimenez D. J Am Coll Cardiol 2016;67:162–70

The improvement in PE treatment RIETE Registry

	Year Group			
	2001-2005 (n = 7,323)	2006-2009 (n = 8,644)	2010-2013 (n = 7,891)	p Value for Trend
Clinical characteristics				
Age, yrs	68.5 ± 16.0	67.5 ± 17.1	67.3 ± 17.0	<0.001
Age >80 yrs	1,670 (22.8)	2,035 (23.5)	1,897 (24.0)	0.07
Male	3,374 (46.1)	3,969 (45.9)	3,655 (46.3)	0.59
Weight, kg	73.8 ± 14.5	74.9 ± 15.8	76.0 ± 16.1	<0.001
Risk factors for VTE				
History of VTE	1,139 (15.6)	1,236 (14.3)	1,188 (15.1)	0.10
Cancer†	1,552 (21.2)	2,030 (23.5)	1,785 (22.6)	<0.01
Recent surgery‡	953 (13.0)	1,015 (11.7)	899 (11.4)	<0.01
Immobilization for ≥4 days§	1,892 (25.8)	2,035 (23.5)	1,668 (21.1)	<0.001
Comorbid diseases				
Chronic lung disease	1,016 (13.9)	1,095 (12.7)	1,290 (16.3)	<0.001
Chronic heart disease	630 (8.6)	711 (8.2)	836 (10.6)	<0.001
Recent major bleeding	176 (2.4)	178 (2.1)	183 (2.3)	0.84
Clinical symptoms and signs at presentation				
Pulse, beats/min	94.1 ± 19.9	93.3 ± 19.9	91.5 ± 20.2	<0.001
Pulse ≥110 beats/min	1,629 (22.7)	1,763 (21.0)	1,475 (19.4)	<0.001
Systolic blood pressure, mm Hg	130.1 ± 24.9	129.3 ± 24.3	129.1 ± 23.9	<0.001
Systolic blood pressure <100 mm Hg	533 (7.3)	683 (7.9)	711 (9.0)	<0.001
Arterial oxyhemoglobin saturation (SaO_2) <90%	1,822 (31.1)	1,689 (29.0)	1,322 (29.9)	0.29
sPESI (21)				
Low risk	1,559 (27.1)	1,660 (28.8)	1,169 (26.8)	0.66
High risk	4,203 (72.9)	4,110 (71.2)	3,185 (73.2)	0.66
Laboratory findings				
Abnormal creatinine levels (>2 mg/dl)	1,283 (17.6)	1,541 (18.3)	1,519 (19.8)	<0.01
Hemoglobin, g/dl	13.04 ± 2.0	12.99 ± 2.0	12.97 ± 2.0	<0.01

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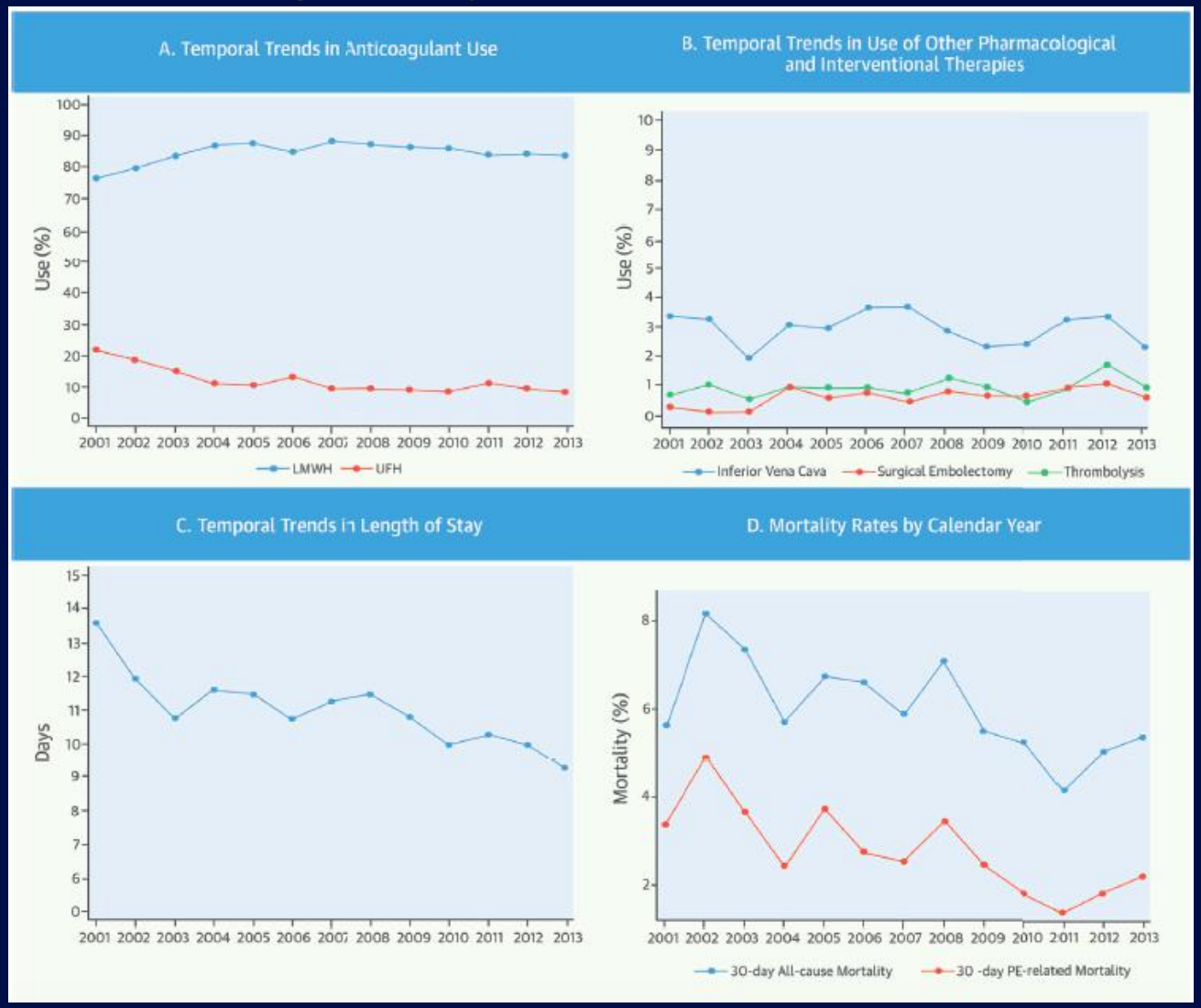
The improvement in PE treatment RIETE Registry



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The improvement in PE treatment RIETE Registry

	Risk-Adjusted Rates (%)*			Adjusted Rate Ratio Per Period (95% CI)†	p Value for Trend†
	2001-2005	2006-2009	2010-2013		
30-day all-cause mortality	6.6	6.1	4.9	0.84 (0.73-0.97)	0.02
7-day all-cause mortality	2.9	2.7	1.9	0.81 (0.67-0.98)	0.03
30-day PE-related mortality	3.3	2.7	1.8	0.73 (0.60-0.89)	<0.01
7-day PE-related mortality	2.2	1.9	1.1	0.72 (0.58-0.90)	<0.01
Nonfatal complications					
30-day VTE recurrences	1.1	0.6	0.6	0.72 (0.58-0.91)	<0.01
30-day major bleeding	4.0	2.7	3.1	0.89 (0.77-1.03)	0.11

Calendar year (per 1 yr)	0.96	0.93-0.99	0.02
Age (per 1 yr)	1.03	1.02-1.04	<0.001
Sex (female vs. male)	0.74	0.65-0.85	<0.001
Weight (per 1 kg)	0.98	0.97-0.98	<0.001
History of VTE	0.62	0.51-0.75	<0.001
Cancer†	3.33	2.85-3.88	<0.001
Recent surgery‡	0.56	0.44-0.71	<0.001
Immobilization for ≥4 days§	2.09	1.81-2.41	<0.001
Chronic lung disease	1.04	0.75-1.44	0.80
Chronic heart disease	1.35	1.01-1.80	0.04
Recent major bleeding	1.29	0.94-1.77	0.12
Pulse (per 1 beat/min)	1.01	1.01-1.02	<0.001
Systolic blood pressure (per mm Hg)	0.99	0.985-0.993	<0.001
Arterial oxyhemoglobin saturation (SaO_2) (per 1%)	0.97	0.96-0.97	<0.001
Abnormal creatinine levels (>2 mg/dl)	1.57	1.35-1.83	<0.001
Hemoglobin (per 1 g/dl)	0.87	0.84-0.91	<0.001

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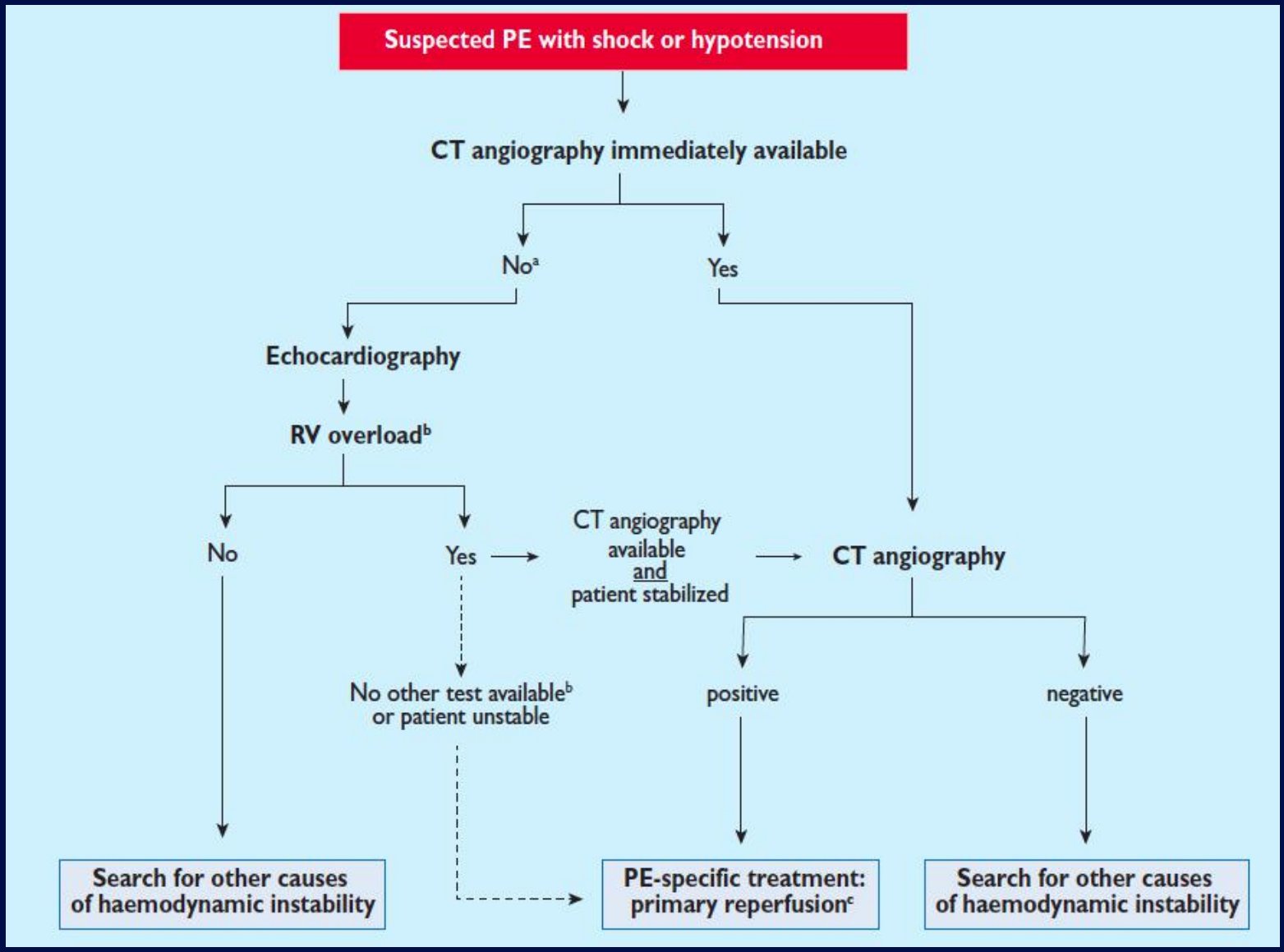
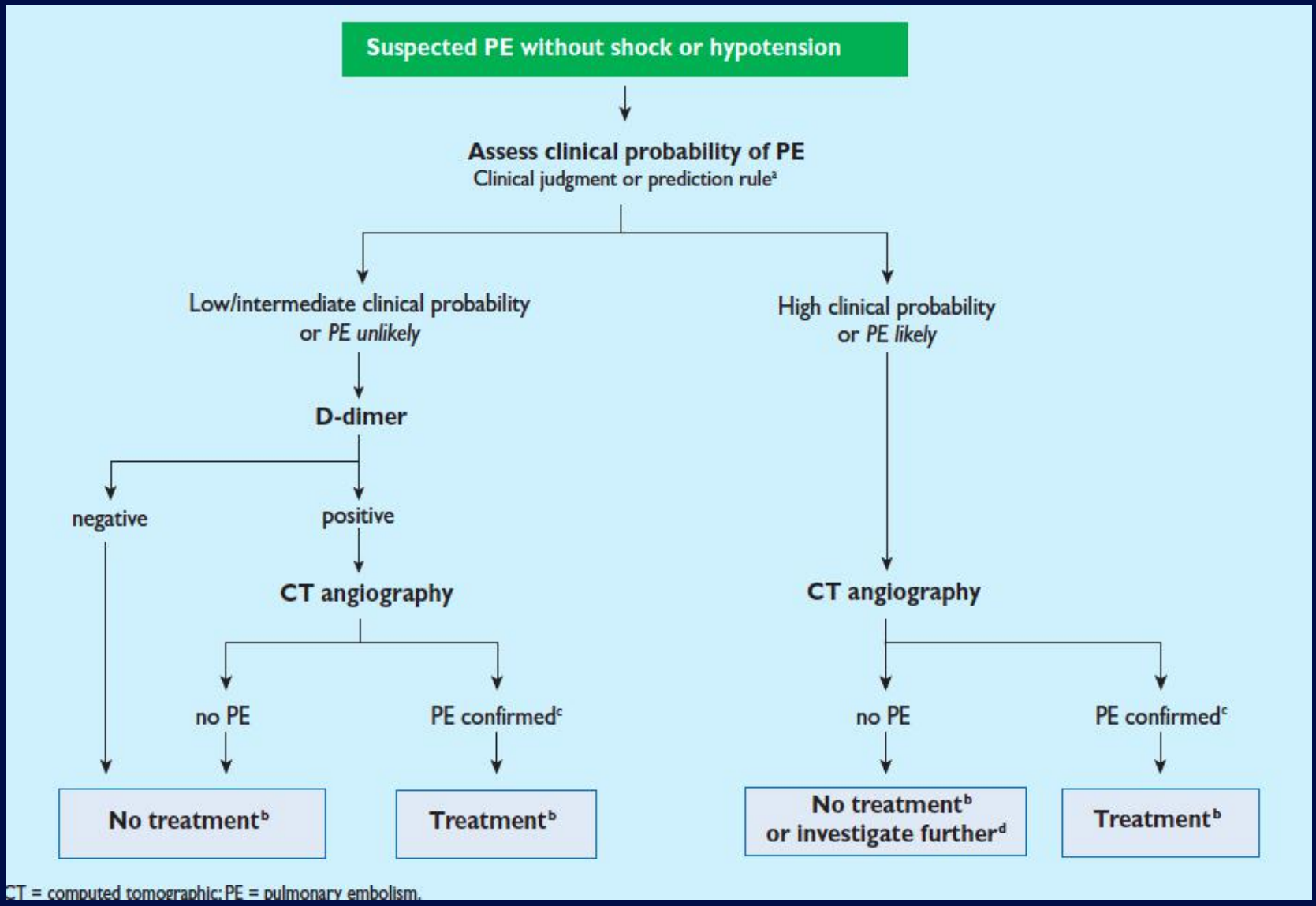
Diagnostic approach: instable pts



ESC guideline Acute Pulmonary Embolism 2014

Diagnostic approach: stable pts

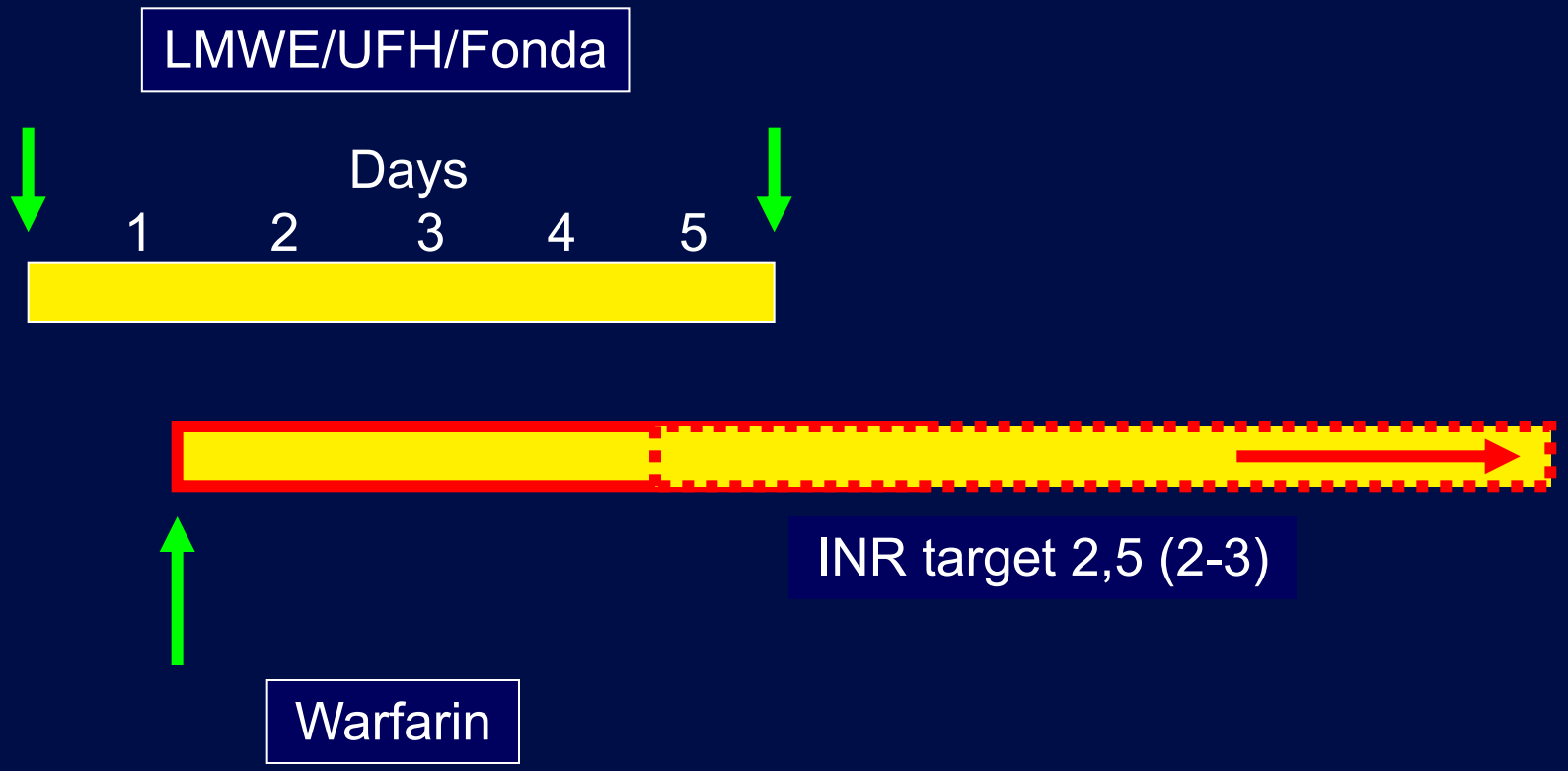


ESC guideline Acute Pulmonary Embolism 2014

Quando iniziare la terapia anticoagulante ?

PE without shock or hypotension (intermediate or low risk)[c]		
Anticoagulation - combination of parenteral treatment with VKA		
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is ongoing.	I	C

2008
Acute pulmonary embolism: patient stable



ESC guideline 2008

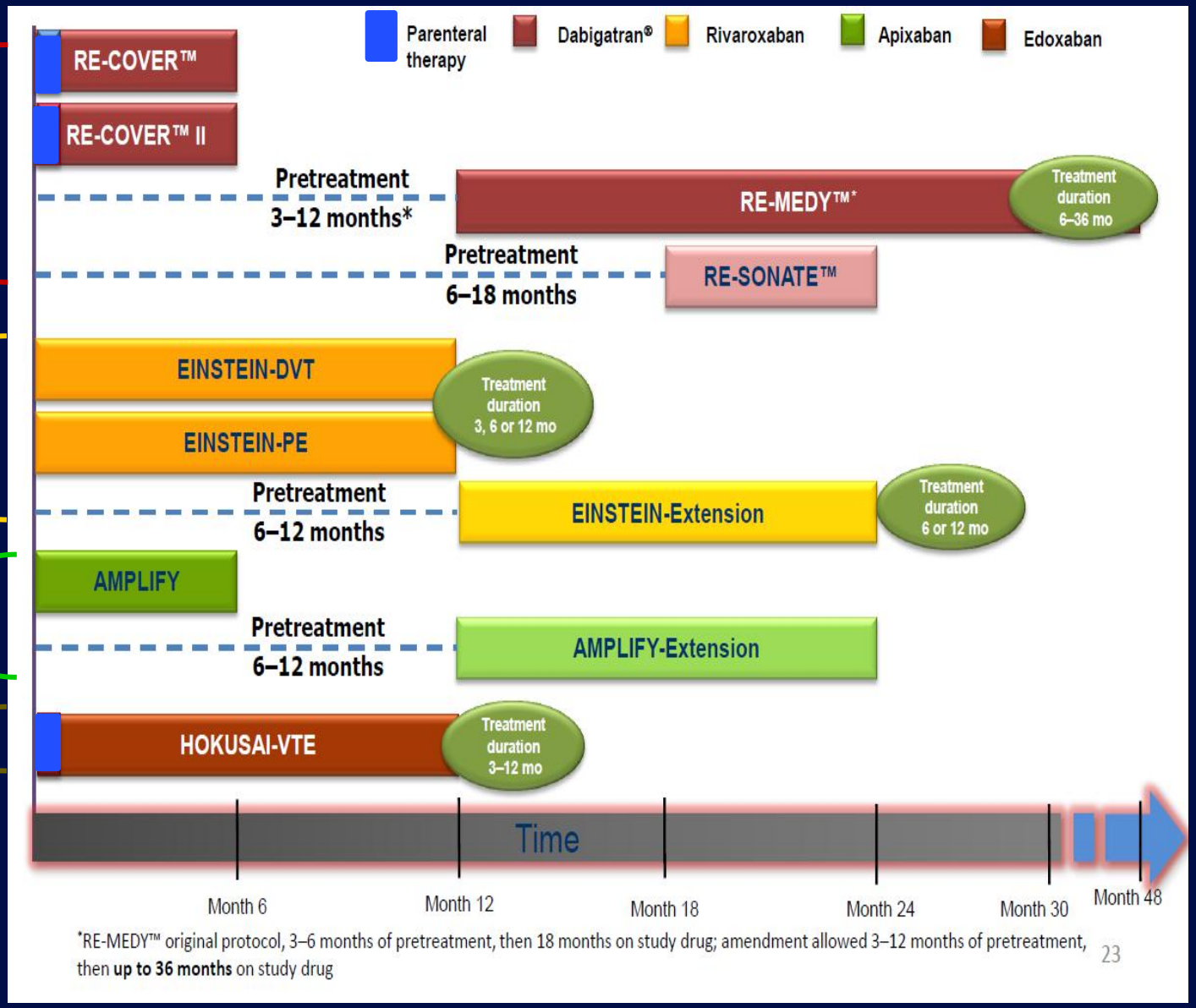
Anticoagulanti orali diretti nella TVP/EP

Dabigatran

Rivaroxaban

Apixaban

Edoxaban



*RE-MEDY™ original protocol, 3–6 months of pretreatment, then 18 months on study drug; amendment allowed 3–12 months of pretreatment, then **up to 36 months** on study drug

23

Studi ……

Trial	Study Drug	Comparator	Design	Tx Before Randomisation	Number of Patients*	Length of Tx (months)
AMPLIFY[1]	Apixaban 10 mg BD for 7d, then 5 mg BD	Enoxaparin/ Warfarin	Double-blind	Not required	5395 DVT: 3532 PE: 1836	6
EINSTEIN-DVT[2]	Rivaroxaban 15 mg BD for 21d, then 20 mg OD	Enoxaparin/ VKA	Open-label	Not required	3449	3, 6, or 12 †
EINSTEIN-PE[3]					4832	
RE-COVER[4]	Dabigatran 150 mg BD	Warfarin	Double-blind	LMWH or UFH	2564 DVT:1749 PE: 786	6
RE-COVER II[5,6]	Dabigatran 150 mg BD	Warfarin	Double-blind	LMWH or UFH	2568 DVT: 1750 PE: 816	6
HOKUSAI-VTE[7]	Edoxaban 60 mg OD (30 mg OD in selected pts)	Warfarin	Double-blind	LMWH or UFH	8292 DVT: 4921 PE: 3319	3-12

*DVT indicates DVT only; PE indicates a diagnosis of PE with or without DVT.
†Duration of treatment was determined by the treating physician before randomisation. Most patients received 6 or 12 months of therapy.

1. Agnelli G et al. *N Engl J Med*. 2013;369:799–808.
2. The EINSTEIN Investigators. *N Engl J Med*. 2010;363:2499–2510.
3. The EINSTEIN-PE Investigators. *N Engl J Med*. 2012; 366:1287–1297.
4. Schulman S et al. *N Engl J Med*. 2009;361:2342–2352.
5. Schulman S et al. *Blood* (ASH Annual Meeting Abstracts) 2011;118: Abstract 205.
6. ClinicalTrials.gov Identifier: NCT00680186. Study results. Available at: http://clinicaltrials.gov/ct2/show/results/NCT00680186 Accessed 26/09/13.
7. The HOKUSAI-VTE Investigators. *N Engl J Med*. 2013. DOI: 10.1056/NEJMoa1306638.

Proporzione dei pazienti con EP

Study	Study Drug/Control, %
Rivaroxaban	
• EINSTEIN-PE	100/100
Dabigatran	
• RE-COVER	21.2/21.4
• RE-MEDY	22.7/23.5
• RE-SONATE	26.9/26.9
Apixaban	
• AMPLIFY	25.2/25.2
• AMPLIFY-Extension	35.2/33.5
Edoxaban	
• Hokusai-VTE	40/40

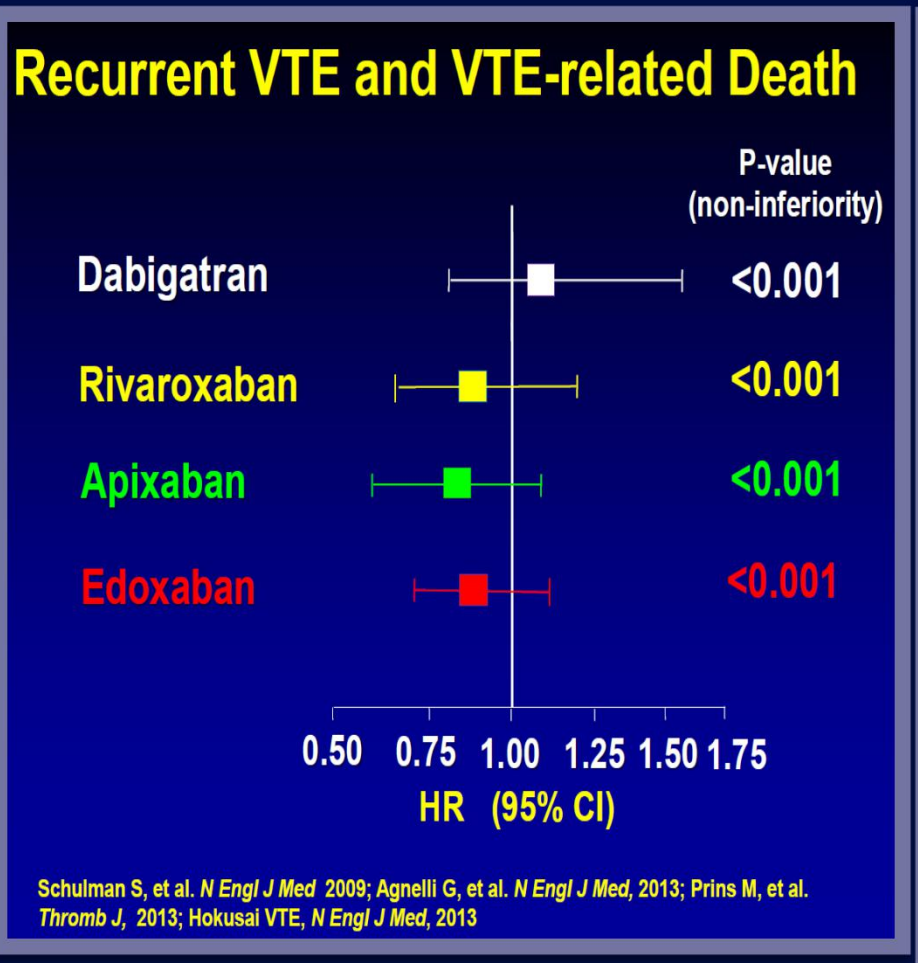
NOACs VTE Trials: Anatomic extent of qualifying PE

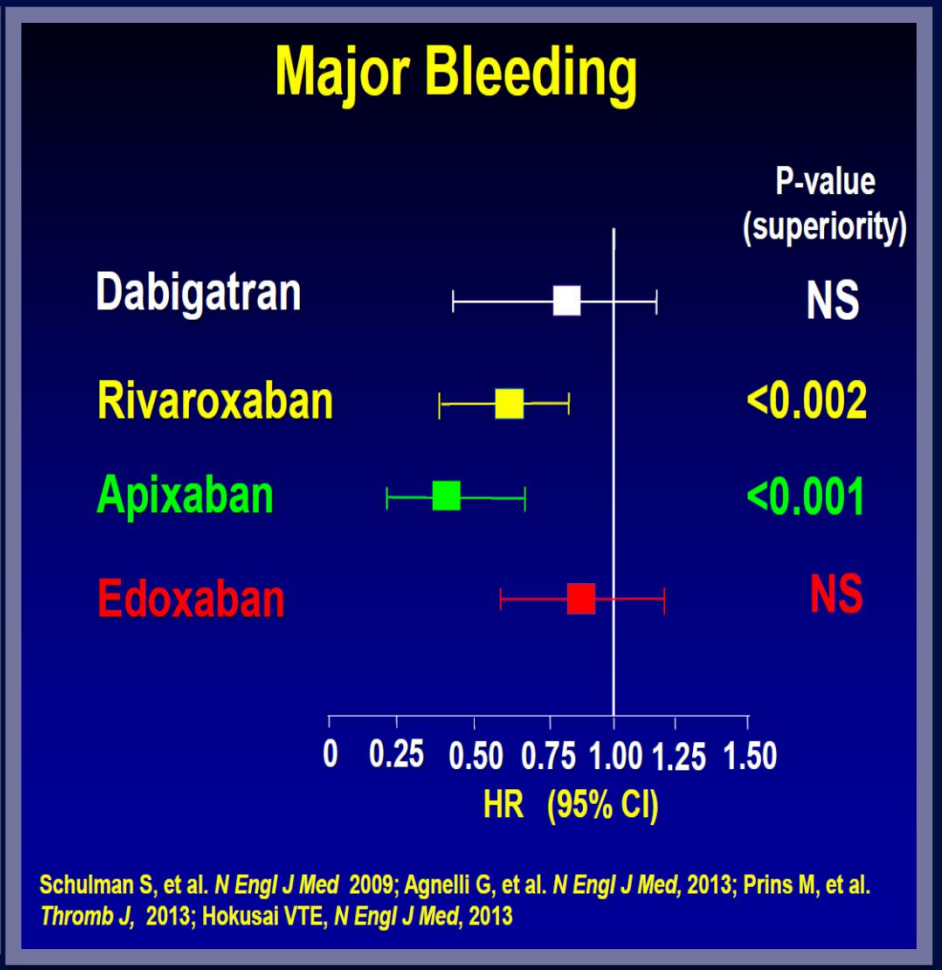
	EINSTEIN-PE[1]	AMPLIFY[2]	Hokusai-VTE[3]
Patients with PE ± DVT, n	4832	1836	3319
Anatomic extent of qualifying PE, n (%)			
Limited: ≤25% of vasculature of a single lobe	608 (13)	79 (9)	251 (8)
Intermediate	2816 (58)	787 (43)	1361 (41)
Extensive: ≥2 lobes with ≥25% of entire vasculature	1173 (24)	683 (37)†	1521 (46)
Not assessable	235 (5)	198 (11)	186 (6)

Dabigatran RE-COVER trial – anatomic extent of qualifying PE not reported
†Extensive: ≥2 lobes with ≥50% of vasculature for each lobe

1. EINSTEIN–PE Investigators. N Engl J Med 2012;366:1287–1297
2. Agnelli et al. N Engl J Med 2013. doi:10.1056/NEJMoa.1302507
3. The Hokusai-VTE Investigators. N Engl J Med 2013

Risultati





Rivaroxaban nella vita reale: Studio XALIA

Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study

Walter Ageno, Lorenzo G Mantovani, Sylvia Haas, Reinhold Kreutz, Danja Monje, Jonas Schneider, Martin van Eickels, Martin Gebel, Elizabeth Zell, Alexander G G Turpie

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Popolazione

	Rivaroxaban (n=2619)	Standard anticoagulation therapy* (n=2149)	p value	Early switchers (n=368)
Age, years	59·0 (45·0–71·0)	66·0 (47·0–73·0)	<0·0001	61·0 (47·5–73·0)
Age group, years	..	..	<0·0001	..
<60	1366 (52%)	824 (38%)	..	172 (47%)
≥60	1253 (48%)	1325 (62%)	..	196 (53%)
Sex			0·074	
Men	1428 (55%)	1116 (52%)	..	211 (57%)
Women	1191 (45%)	1033 (48%)	..	157 (43%)
Bodyweight	..	..	0·0092	..
<50 kg	22 (1%)	34 (2%)	..	2 (1%)
≥50 to <70 kg	525 (20%)	505 (23%)	..	75 (20%)
≥70 kg to <90 kg	881 (34%)	713 (33%)	..	131 (36%)
≥90 kg	636 (24%)	500 (23%)	..	93 (25%)
Missing	555 (21%)	397 (19%)	..	67 (18%)
First available CrCl	..	..	<0·0001	..
<30 mL/min	13 (1%)	61 (3%)	..	4 (1%)
≥30 to <50 mL/min	88 (3%)	157 (7%)	..	20 (5%)
≥50 to <80 mL/min	419 (16%)	398 (19%)	..	71 (19%)
≥80 mL/min	1125 (43%)	797 (37%)	..	169 (46%)
Missing	974 (37%)	736 (34%)	..	104 (28%)
Index diagnosis	..	..	<0·0001	..
Deep-vein thrombosis only	2399 (92%)	1894 (88%)	..	291 (79%)
Deep-vein thrombosis with pulmonary embolism	220 (8%)	255 (12%)	..	77 (21%)
Type of deep-vein thrombosis†	..	..	0·0033	..
Provoked	896 (34%)	823 (38%)	..	126 (34%)
Unprovoked	1692 (65%)	1300 (61%)	..	232 (63%)
Missing	31 (1%)	26 (1%)	..	10 (3%)
Previous venous thromboembolism	630 (24%)	481 (22%)	..	79 (22%)
Active cancer at baseline	146 (6%)	411 (19%)	<0·0001	30 (8%)
Known thrombophilic condition	157 (6%)	112 (5%)	0·24	25 (7%)
Previous major bleeding episode	37 (1%)	64 (3%)	0·0002	17 (5%)

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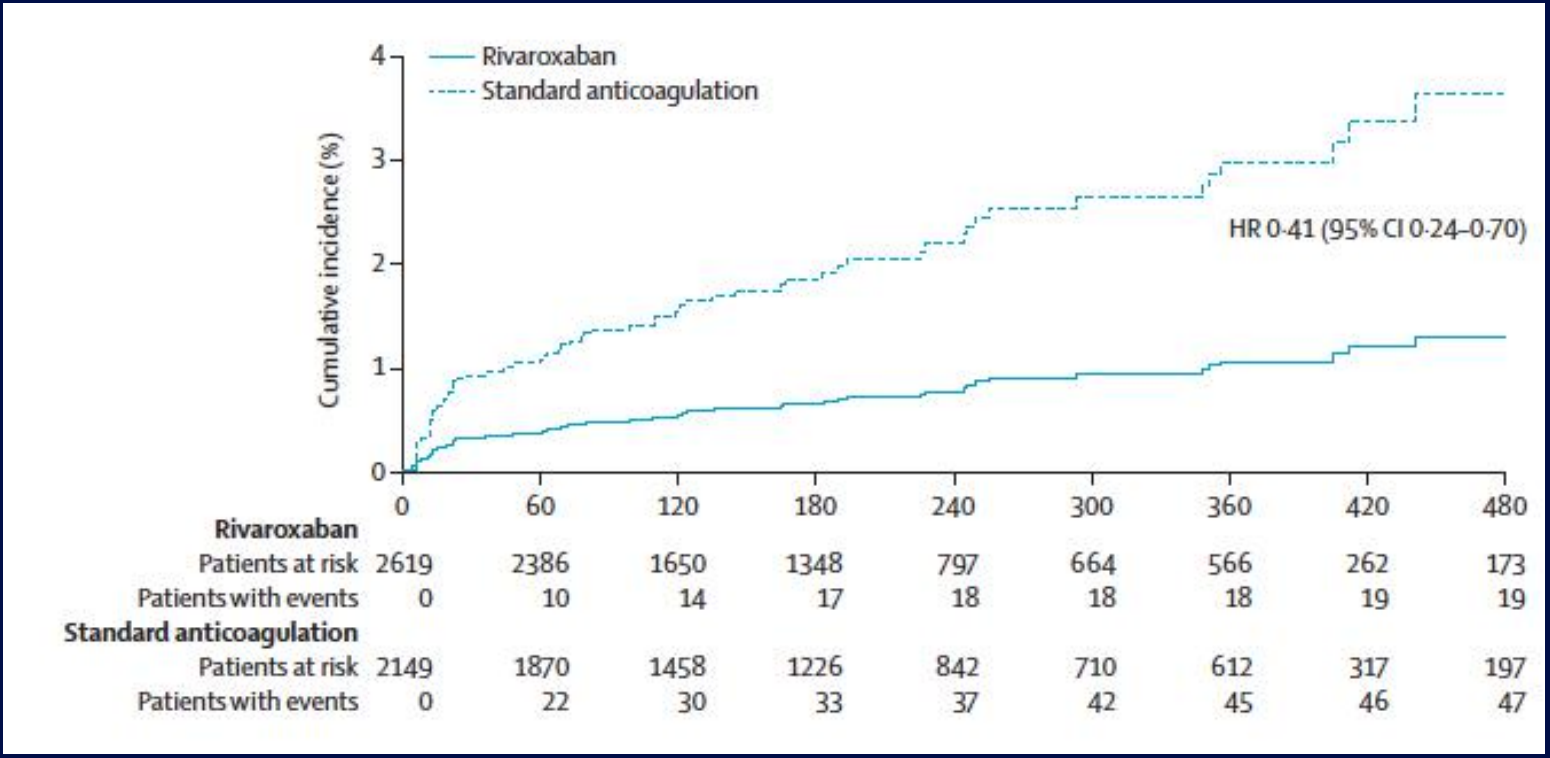
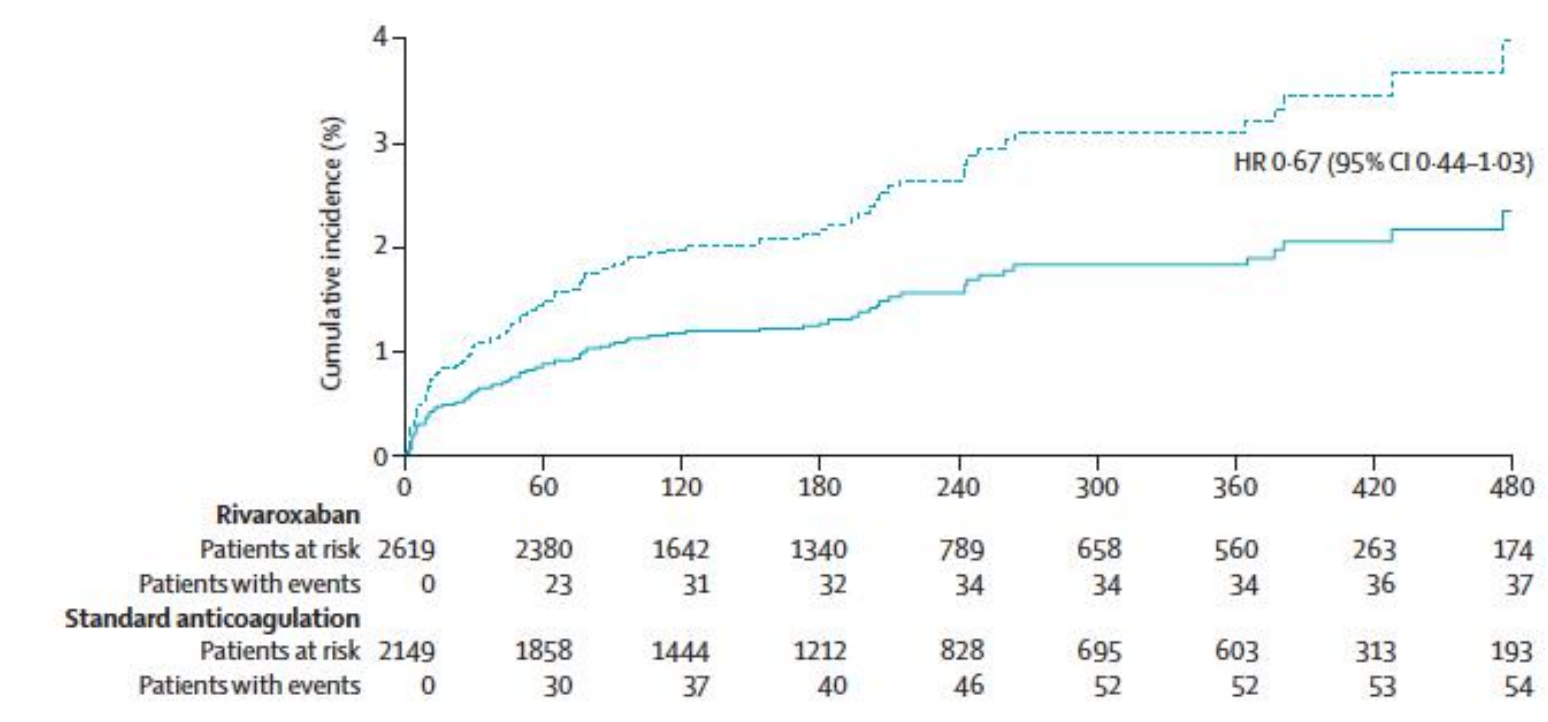
Safety: Major bleeding

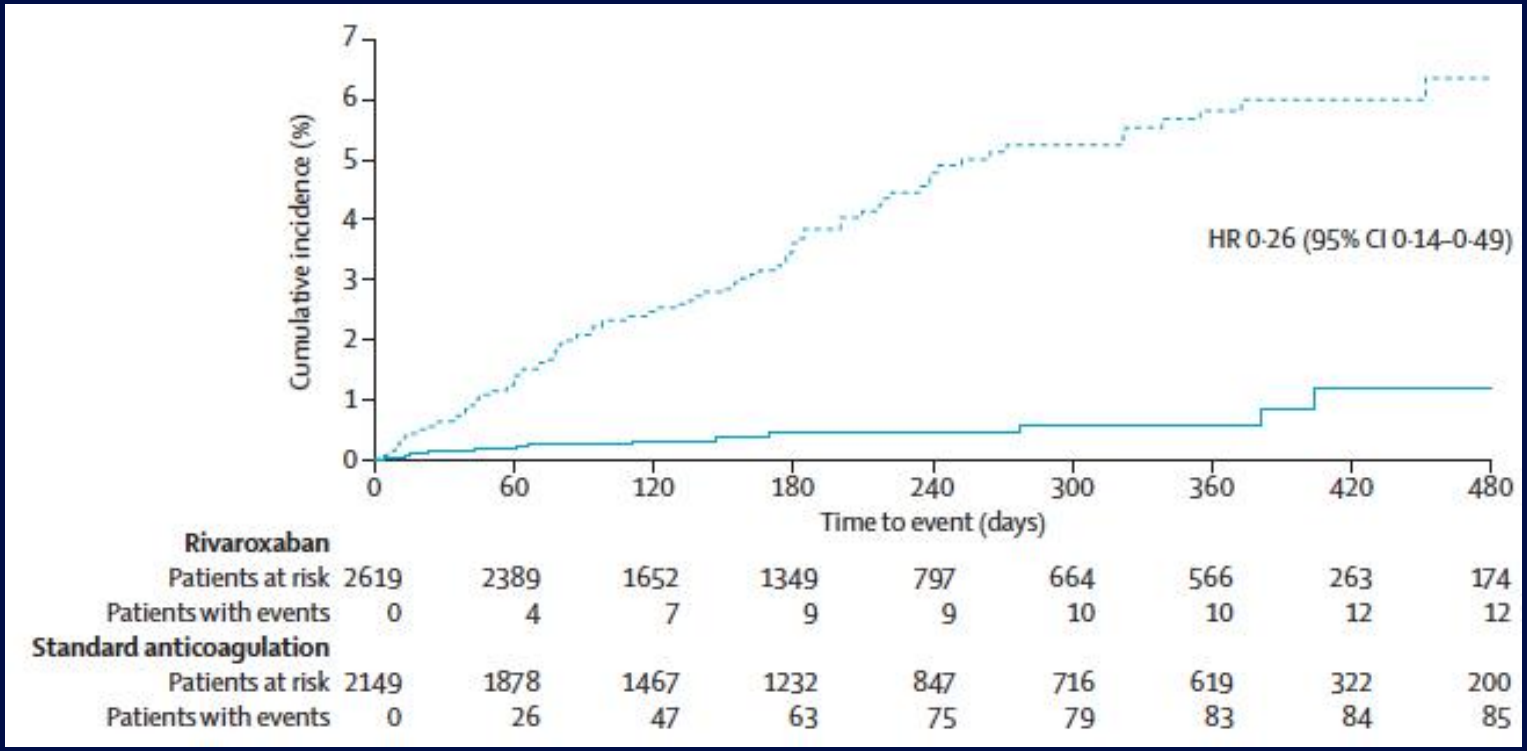


Rivaroxaban									
Patients at risk	2619	2386	1650	1348	797	664	566	262	173
Patients with events	0	10	14	17	18	18	18	19	19
Standard anticoagulation									
Patients at risk	2149	1870	1458	1226	842	710	612	317	197
Patients with events	0	22	30	33	37	42	45	46	47

Efficacy: Recurrent VTE



All cause mortality

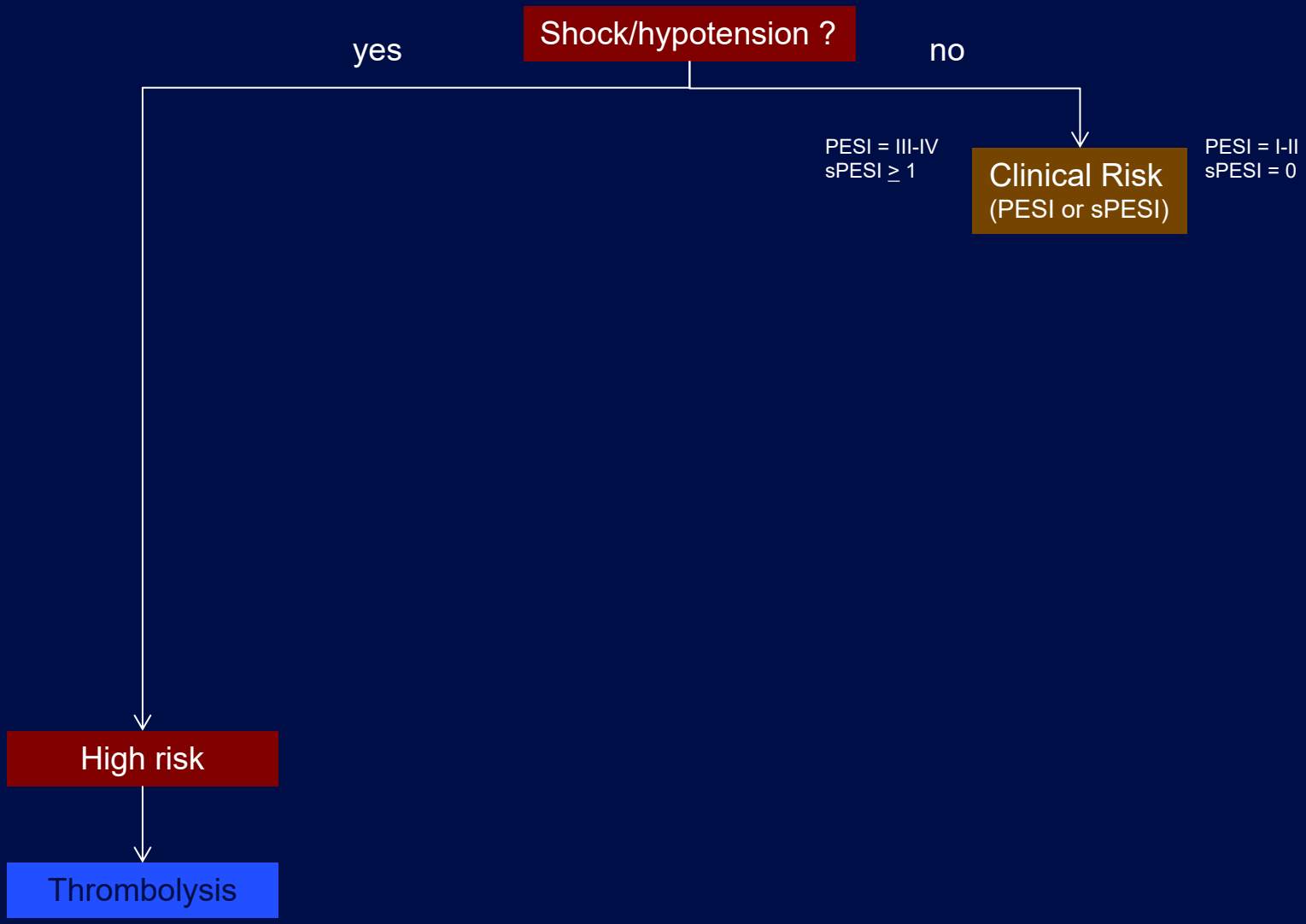


Rivaroxaban									
Patients at risk	2619	2389	1652	1349	797	664	566	263	174
Patients with events	0	4	7	9	9	10	10	12	12
Standard anticoagulation									
Patients at risk	2149	1878	1467	1232	847	716	619	322	200
Patients with events	0	26	47	63	75	79	83	84	85

XALIA: Key points

- incidence rates of major bleeding events are also consistent with those reported in the long-running RIETE registry (3.3% per year in XALIA and 2.6% per year in RIETE)
- In patients treated with a vitamin K antagonist, the mean time in therapeutic range was 56.2% (SD 38.2).
- Hospital admission for venous thromboembolism; Rivaroxaban 29% vs 46% VKA
- Duration of hospital stay was Rivaroxaban 5.0 days (SE 0.07) vs VKA (95% CI 0.61–0.72, p<0.001.

PE Treatment 2014:



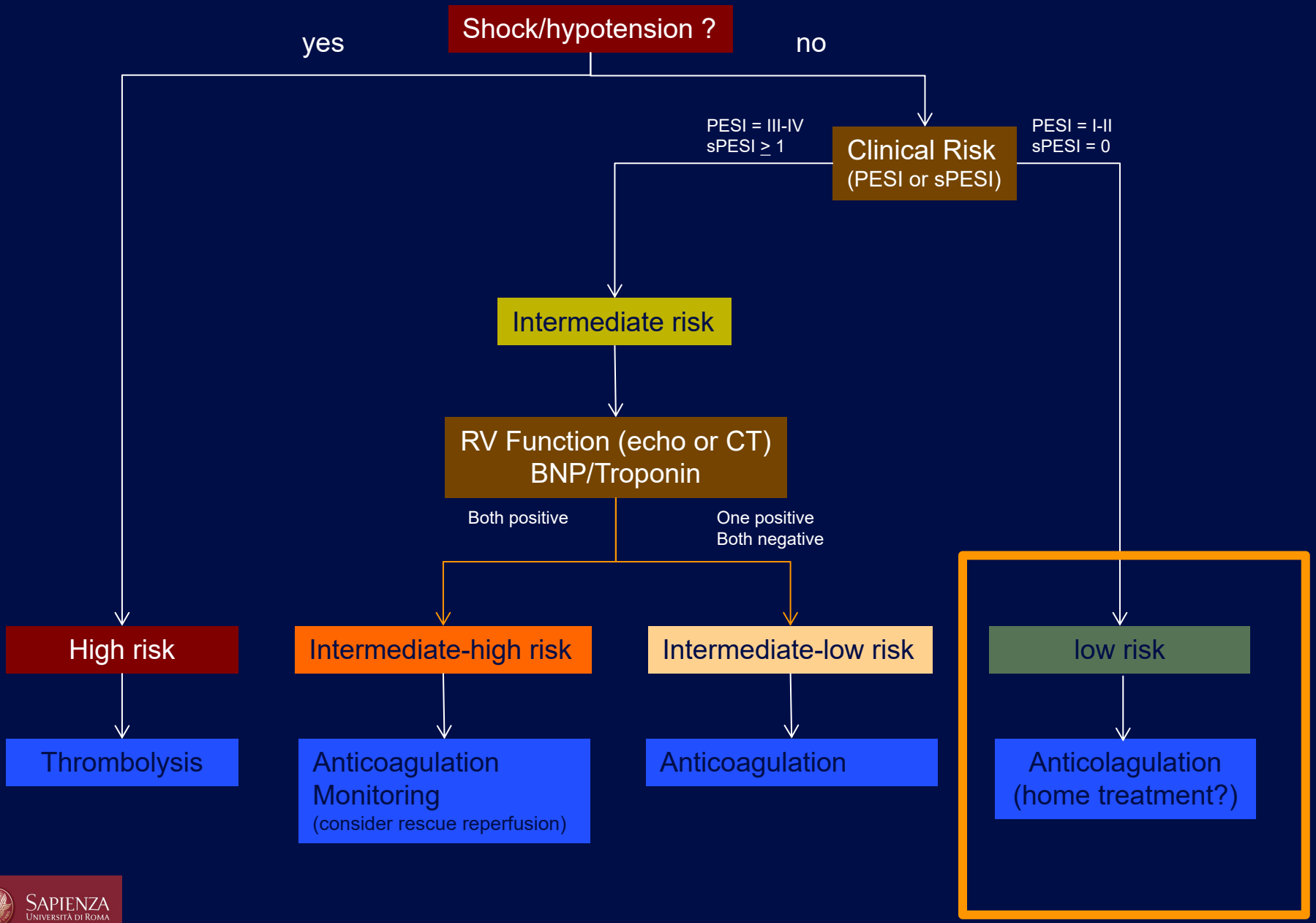
Pulmonary Embolism Score Index (PESI)

Predictors	Simplified PESI
Age >80 years	1
Cancer	1
Chronic cardiopulmonary disease	1
Heart rate ≥110 bpm	1
Systolic blood pressure <100 mm Hg	1
SaO_2 <90%	1
TOTAL	

PESI>1 = 30 days mortality risk 10.9%

ESC guideline Acute Pulmonary Embolism 2014

PE Treatment 2014:



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Early discharge and home treatment		
Patients with acute low-risk PE should be considered for early discharge and continuation of treatment at home if proper outpatient care and anticoagulant treatment can be provided.	IIa	B

Impatto economica di rivaroxaban nell'EP: Regione Lazio

Circa 4.969 pazienti affetti da EP siano ogni anno

Scenario 1 : Sostituzione completa EBPM/VKA con rivaroxaban

	EBPM/VKA	RIVAROXABAN	Differenza RIVAROXABAN VS EBPM/VKA
Farmaci	€ 628.880	€ 2.156.231	€ 1.527.351
Monitoraggio	€ 2.091.936	€ 349.512	-€ 1.742.424
Eventi	€ 1.595.664	€ 1.198.083	-€ 397.581
Spesa complessiva	€ 4.316.480	€ 3.703.826	-€ 612.654
N° di Giornate di Degenza risparmiate			4.472

Tabella 1 : Totale differenza COSTI trattamento con EBPM/VKA vs trattamento con rivaroxaban € a livello regionale

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* ***Roggeri DP, Roggeri A, Pengo V. Farmacoeconomia. Health economics and therapeutic pathways 2014; 15(4): 113-127***

Impatto economico di rivaroxaban nella TVP: Regione Lazio*

Circa 9.326 pazienti affetti da TVP ogni anno

Scenario 1 : Sostituzione completa EBPM/VKA con rivaroxaban

	EBPM/VKA	RIVAROXABAN	Differenza RIVAROXABAN VS EBPM/VKA
Farmaci	€ 1.002.529	€ 3.553.947	€ 2.551.418
Monitoraggio	€ 3.406.470	€ 617.018	-€ 2.789.452
Eventi	€ 2.934.244	€ 2.119.746	-€ 814.497
Spesa complessiva	€ 7.343.243	€ 6.290.711	-€ 1.052.531
N° di Giornate di Degenza risparmiate			14.549

Tabella 1 : Totale differenza COSTI trattamento con EBPM/VKA vs trattamento con rivaroxaban € a livello regionale

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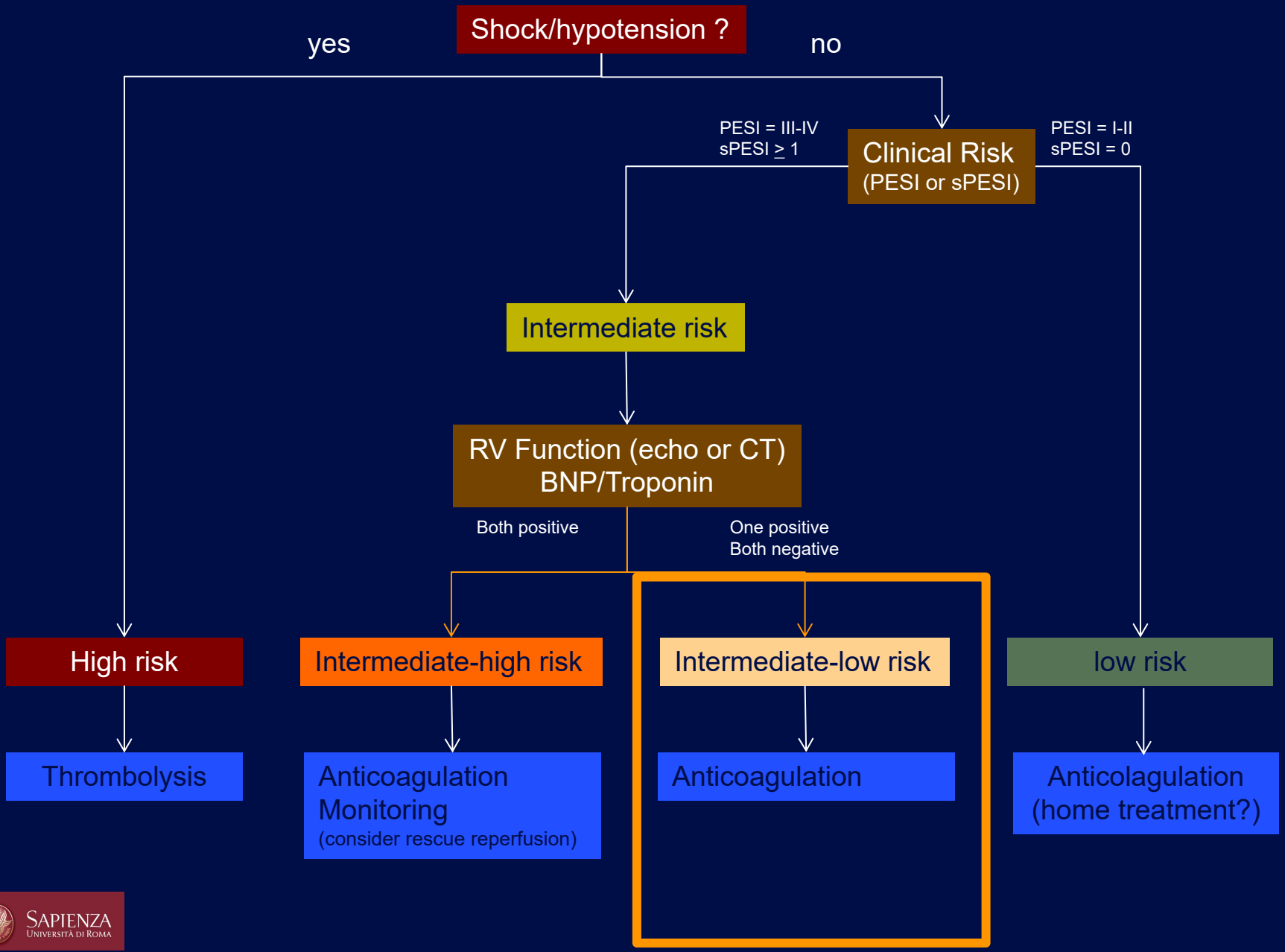
* *Roggeri DP, Roggeri A, Pengo V. Farmacoeconomia. Health economics and therapeutic pathways 2014; 15(4): 113-127*

PE Treatment 2014:



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PE Treatment: Intermediate-low risk

Parenteral + oral approach

4-7 days

LMWH or

VKA (INR 2-3) or Dabigatran Edoxaban

3 months

VKA or Dabigatran Edoxaban

Extended treatmement

Single oral drug approach

Rivaroxaban 15 mg bid 3 wks – 20 mg qd

Apixaban 10 mg bid 1 wks – 5 mg bid

3 months

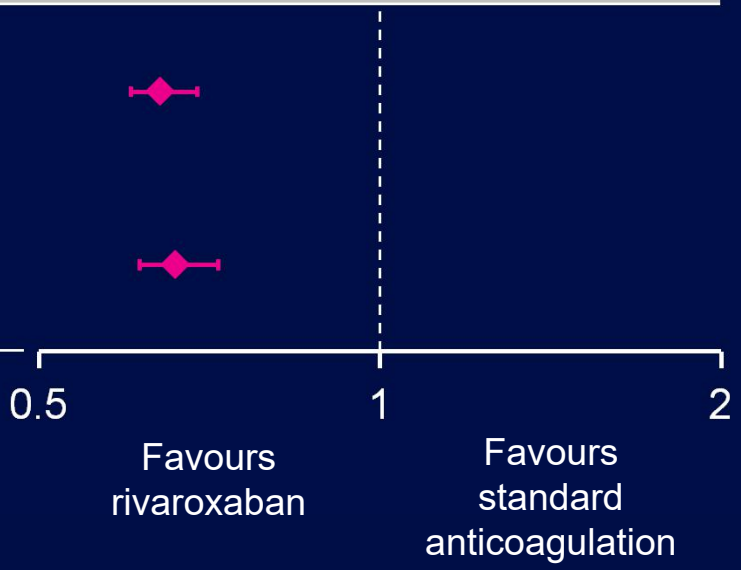
Rivaroxaban 20 mg qd

Apixaban 5 mg bid

Extended treatmement

Length of Hospital Stay

Analysis	Length of stay (LS mean, days)		Ratio (95% CI)*
	Rivaroxaban	Standard anticoagulation	
Before propensity score adjustment	4.8	7.5	
Propensity score adjusted	5.0	7.7	



*Mean length of stay calculated from hospitalized patients only; ratio based on ANOVA of log-transformed LOS data

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Ageno W *et al, Lancet Haematol* 2016;3(1):e12–e21

TRENDS IN LOS IN ACUTE PE OVER THE YEARS. WHAT IS CHANGING IN THE ERA OF DOACS?

	DOACs	No DOACs	Total	*p*
Number	100	228	328	-
Males/Females	41%/59%	44,7%/55,3%	43,6%/56,4%	ns
Mean age ± SD (years)	77 ± 13	75 ± 13	76 ± 13	ns
Median age (IQR) (years)	80 (72-85)	77 (69-84)	78 (69-85)	ns
Mean LOS ± SD (days)	9± 5	11± 6	10 ± 6	<0.005
		VKAs 11± 6		
		LMWH/fondaparinux 11± 6		
Median LOS (IQR) (days)	7 (5-10)	10 (6-14)	9 (6-13)	<0.001
		VKAs 9 (7-14)		
		LMWH/fondaparinux 10 (5-14)		

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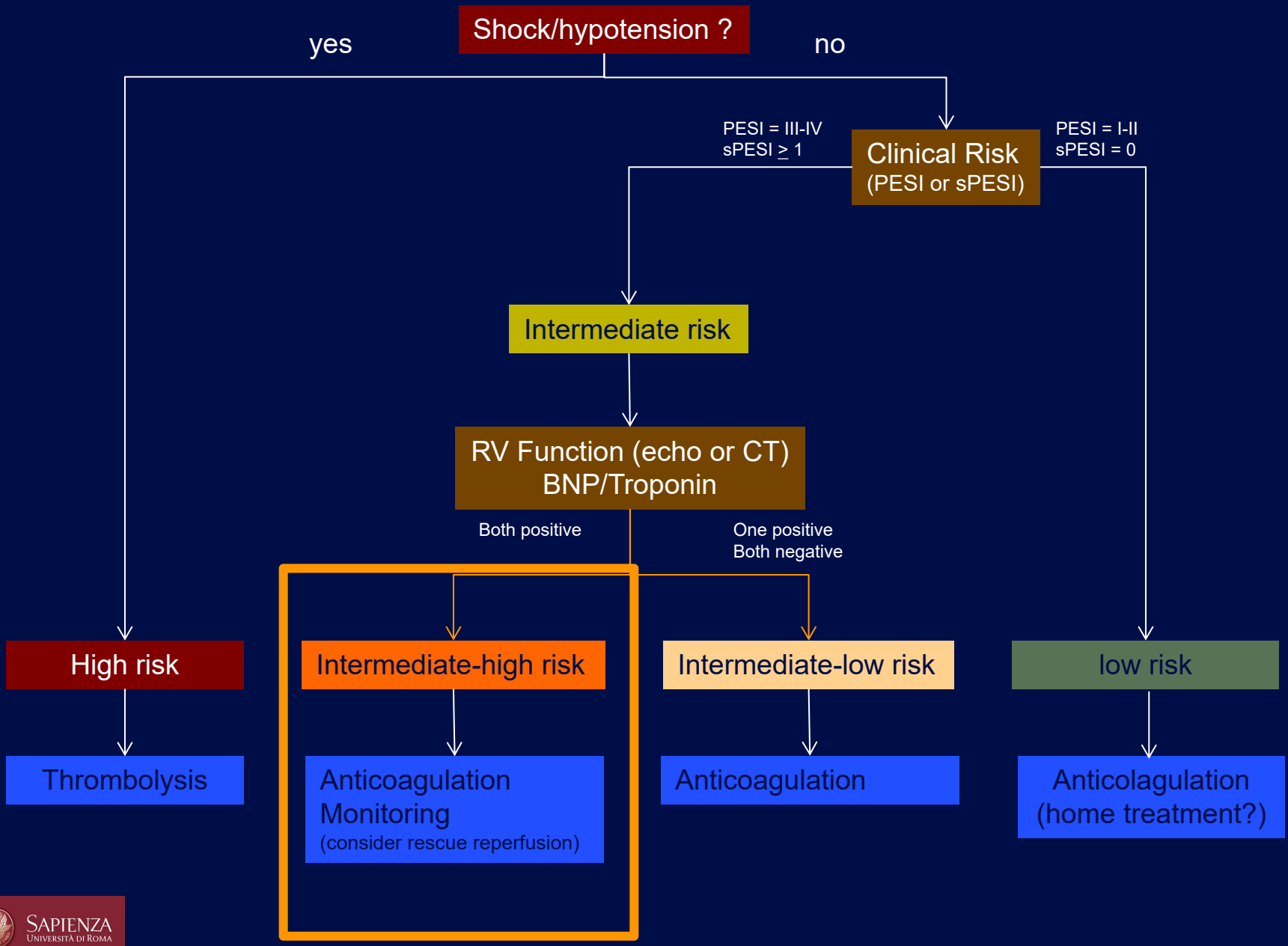
Masotti L. et al. J Cardiovasc Med 2016;

PE Treatment 2014:



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Thrombolysis in intermediate-risk PE PEITHO study: tenecteplase

Characteristic	Tenecteplase (N=506)	Placebo (N=499)
Demographic data		
Age — yr		
Mean	66.5±14.7	65.8±15.9
Median (interquartile range)	70.0 (59.0–77.0)	70.0 (57.0–78.0)
Male sex — no. (%)	242 (47.8)	231 (46.3)
Mean weight — kg	82.5±17.9	82.6±18.2
Clinical status		
Systolic blood pressure — mm Hg	130.8±18.3	131.3±18.5
Missing data — no. (%)	3 (0.6)	4 (0.8)
Heart rate — beats per min	94.5±17.1	92.3±16.7
Missing data — no. (%)	6 (1.2)	7 (1.4)
Respiratory rate — breaths per min	21.8±5.8	21.6±5.7
Missing data — no. (%)	95 (18.8)	107 (21.4)
Oxygen treatment — no. (%)	436 (86.2)	421 (84.4)
Medical history		
Chronic pulmonary disease — no. (%)	26 (5.1)	34 (6.8)
Missing data	6 (1.2)	6 (1.2)
Chronic heart failure — no. (%)	21 (4.2)	26 (5.2)
Missing data	5 (1.0)	7 (1.4)
Previous venous thromboembolism — no. (%)	126 (24.9)	147 (29.5)
Missing data	2 (0.4)	9 (1.8)
Active cancer — no. (%)	41 (8.1)	32 (6.4)
Missing data	20 (4.0)	20 (4.0)
Surgery or major trauma in previous month — no. (%)	31 (6.1)	27 (5.4)
Missing data	1 (0.2)	4 (0.8)
Immobilization — no. (%)	55 (10.9)	56 (11.2)
Missing data	5 (1.0)	9 (1.8)
Estrogen use — no. (%)	30 (5.9)	33 (6.6)
Missing data	7 (1.4)	5 (1.0)

Meyer G. N Engl J Med 2014;370:1402-11.

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Thrombolysis in intermediate-risk PE PEITHO study: tenecteplase

Characteristic	Tenecteplase (N=506)	Placebo (N=499)
	no. (%)	
Confirmation of pulmonary embolism		
CT	480 (94.9)	472 (94.6)
Ventilation–perfusion lung scanning	31 (6.1)	35 (7.0)
Pulmonary angiography	6 (1.2)	8 (1.6)
Confirmation of right ventricular dysfunction		
Echocardiography	278 (54.9)	255 (51.1)
CT	74 (14.6)	72 (14.4)
Both echocardiography and CT	154 (30.4)	172 (34.5)
Confirmation of myocardial injury		
Elevated cardiac troponin I	364 (71.9)	361 (72.3)
Elevated cardiac troponin T	164 (32.4)	164 (32.9)
Either troponin I or troponin T elevation	502 (99.2)	494 (99.0)
Low-molecular-weight heparin or fondaparinux given before randomization	170 (33.6)	133 (26.6)

Meyer G. N Engl J Med 2014;370:1402-11.

Thrombolysis in intermediate-risk PE
PEITHO study: tenecteplase

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12
Fatal	0	3 (0.6)		
Nonfatal	1 (0.2)	2 (0.4)		
Other in-hospital complications and procedures — no. (%)				
Mechanical ventilation	8 (1.6)	15 (3.0)		
Surgical embolectomy	1 (0.2)	2 (0.4)		
Catheter thrombus fragmentation	1 (0.2)	0 (0.0)		
Vena cava interruption	5 (1.0)	1 (0.2)		
Thrombolytic treatment other than study medication	4 (0.8)	23 (4.6)		
Death from any cause between randomization and day 30 — no. (%)	12 (2.4)	16 (3.2)	0.73 (0.34–1.57)	0.42
Patient still hospitalized at day 30 — no. (%)	59 (11.7)	50 (10.0)		
Rehospitalization between randomization and day 30 — no. (%)	22 (4.4)	15 (3.0)		

Meyer G. N Engl J Med 2014;370:1402-11.

Thrombolysis in intermediate-risk PE
PEITHO study: tenecteplase

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
	no. (%)			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7	12 (2.4)	1 (0.2)	12.10 (1.57–93.39)	0.003
Ischemic stroke	2 (0.4)	0		
Hemorrhagic stroke‡	10 (2.0)	1 (0.2)		
Serious adverse events between randomization and day 30	55 (10.9)	59 (11.8)	0.91 (0.62–1.34)	0.63

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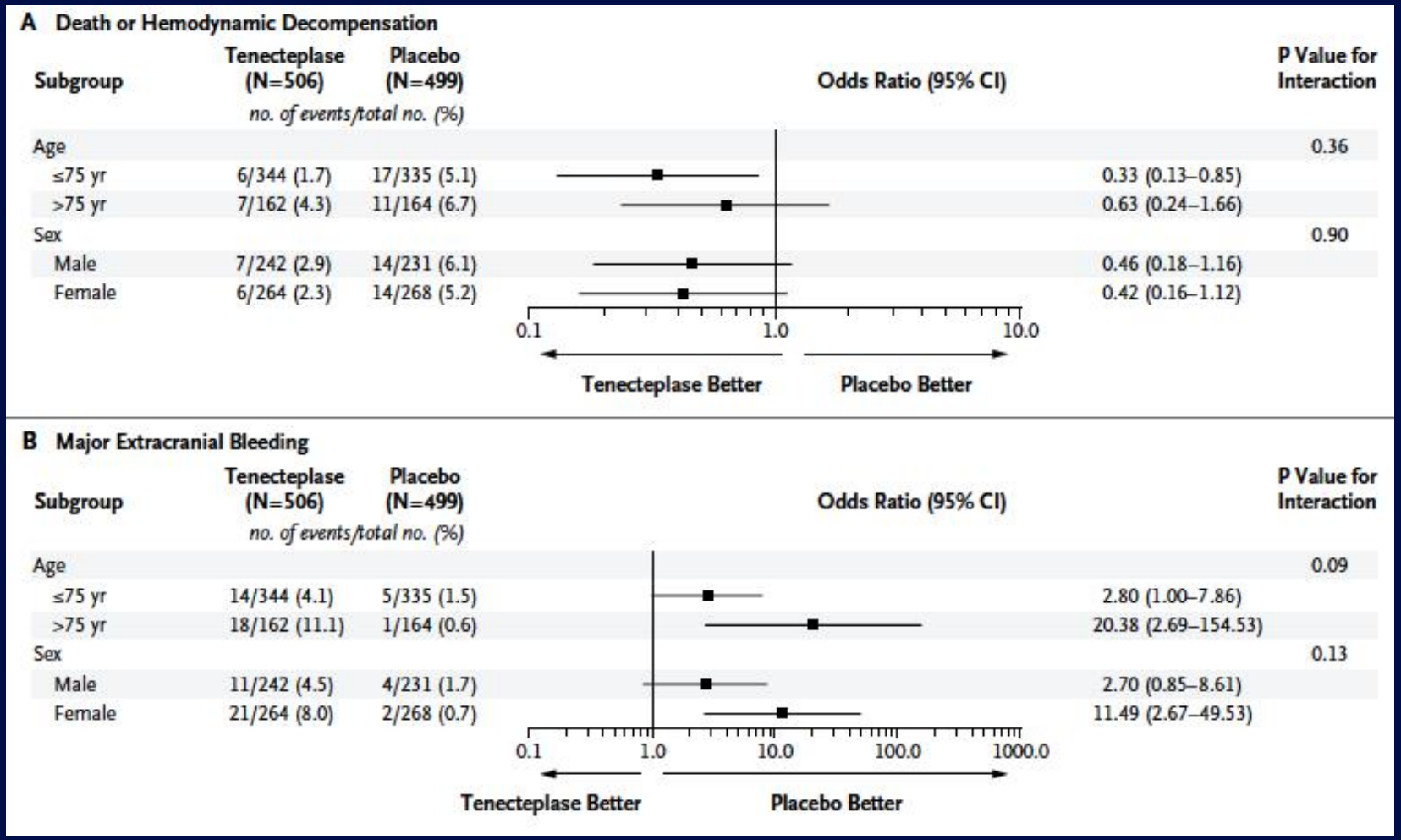
Meyer G. N Engl J Med 2014;370:1402-11.

Thrombolysis in intermediate-risk PE
PEITHO study: tenecteplase



Meyer G. N Engl J Med 2014;370:1402-11.

Thrombolysis in intermediate-risk PE MOPPET trial: low-dose rtPA

Variable	TG (n = 61; 100%)	CG (n = 60; 100%)	p Value
Men	28 (46%)	27 (45%)	0.92
Age (yrs)	58 ± 9	59 ± 10	0.56
Weight (kg)	84 ± 14	83 ± 13	0.68
Previous or concomitant disease			
Hypertension	32 (52%)	31 (52%)	0.93
Diabetes mellitus	23 (38%)	25 (40%)	0.66
Cardiovascular	35 (57%)	37 (62%)	0.80
Hypercholesterolemia*	27 (33%)	25 (30%)	0.77
Pulmonary	22 (36%)	25 (42%)	0.53
Renal	8 (13%)	9 (15%)	0.77
Current smoker	12 (20%)	15 (25%)	0.48
Unprovoked pulmonary embolism	28 (46%)	27 (45%)	0.92
Estrogen therapy	6 (10%)	7 (12%)	0.75
Cancer			
Active	8 (13%)	9 (15%)	0.77
History	3 (5%)	3 (5%)	0.98
Known prothrombotic state	6 (10%)	5 (8%)	0.77
Previous venous thromboembolism	13 (21%)	12 (20%)	0.86
Concomitant deep venous thrombosis	35 (57%)	33 (55%)	0.79

Sharifi M. Am J Cardiol 2013;111:273-277.

Thrombolysis in intermediate-risk PE MOPPET trial: low-dose rtPA

Primary end points at 28 ± 5 mo of follow-up

Variable	TG (n = 58; 100%)	CG (n = 56; 100%)	p Value
Pulmonary hypertension*	9 (16%)	32 (57%)	<0.001
Pulmonary hypertension plus recurrent pulmonary embolism	9 (16%)	35 (63%)	<0.001

* Pulmonary artery systolic pressure ≥40 mm Hg.

Table 3
Secondary end points

Variable	TG (n = 61; 100%)	CG (n = 60; 100%)	p Value
Recurrent pulmonary embolism	0	3 (5%)	0.08
Total mortality	1 (1.6%)	3 (5%)	0.30
Total mortality plus recurrent pulmonary embolism	1 (1.6%)	6 (10%)	0.049
Hospital stay (days)	2.2 ± 0.5	4.9 ± 0.8	<0.001
Bleeding	0	0	—

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Sharifi M. Am J Cardiol 2013;111:273-277.

Thrombolysis in intermediate-risk PE
MOPPET trial: low-dose rtPA

Timing	Pulmonary Artery Systolic Pressure (mm Hg)		p Value
	TG	CG	
On admission	50 ± 6	51 ± 7	0.4
Within 48 h	34 ± 7	41 ± 4	<0.001
6 mo	31 ± 6	49 ± 8	<0.001
28 ± 5 mo	28 ± 7	43 ± 6	<0.001

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Sharifi M. Am J Cardiol 2013;111:273-277.

Durata della TAO

- TEV associata a fattori di rischio temporanei
  - Gravidanza (entro i 3 mesi)
  - Terapia estrogenica
  - Trauma/frattura arti inferiori (entro i 3 mesi)
  - Chirurgia maggiore (entro i 3 mesi)
  - Allettamento > 1 sett
  - Viaggi > 6 ore

3 mesi

- TEV associata a fattori di rischio persistenti
  - Neoplasie in fase di attività

Indefinita

- TEV idiopatica o non provocata

Almeno 3 mesi ?

- 2° episodio di TEV idiopatica
  - Trombofilia !

Indefinita

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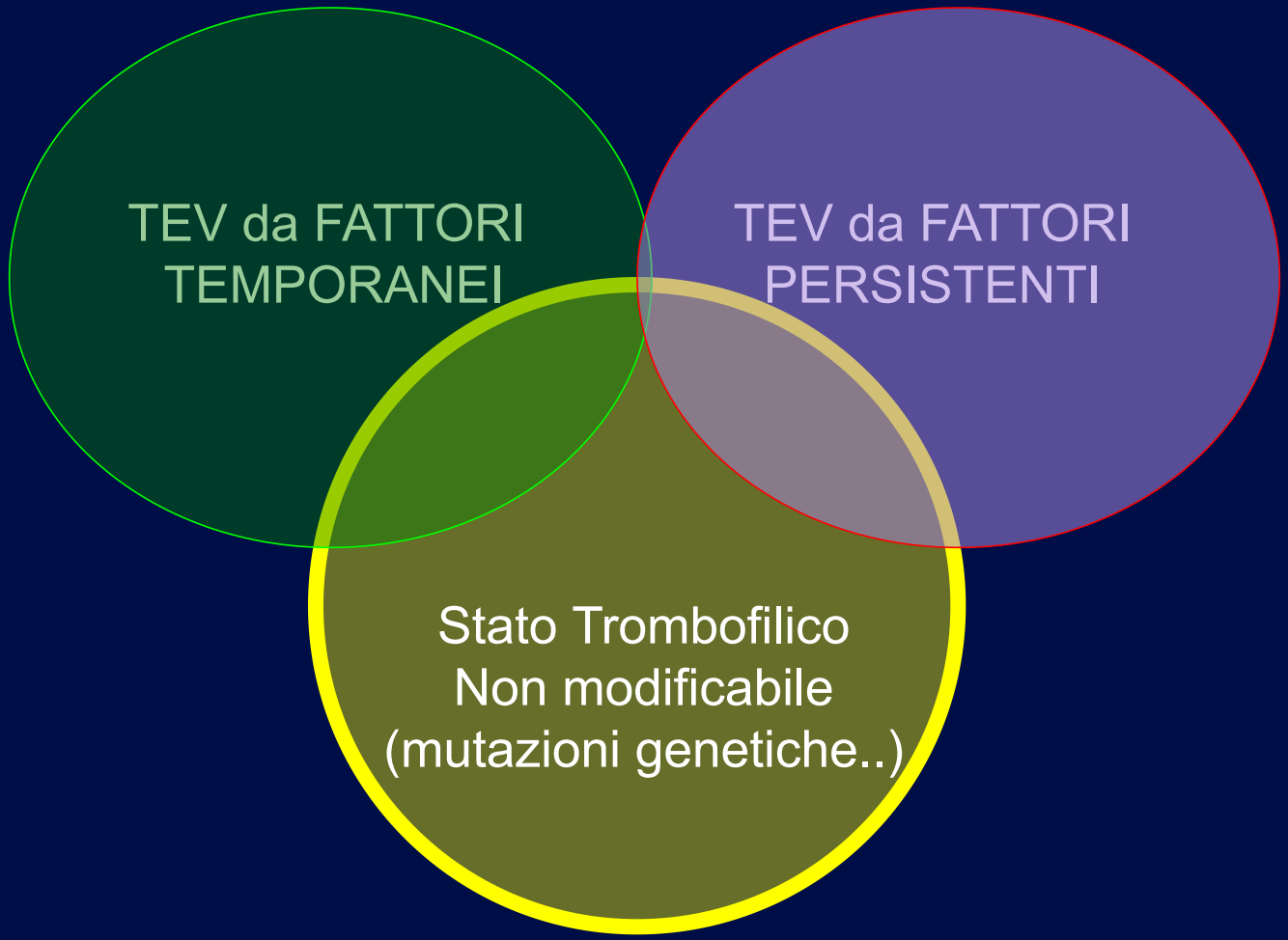
Agnelli G. et al.,Ital Heart J. 2005 ESC guidelines 2008ACCP Consensus 2012

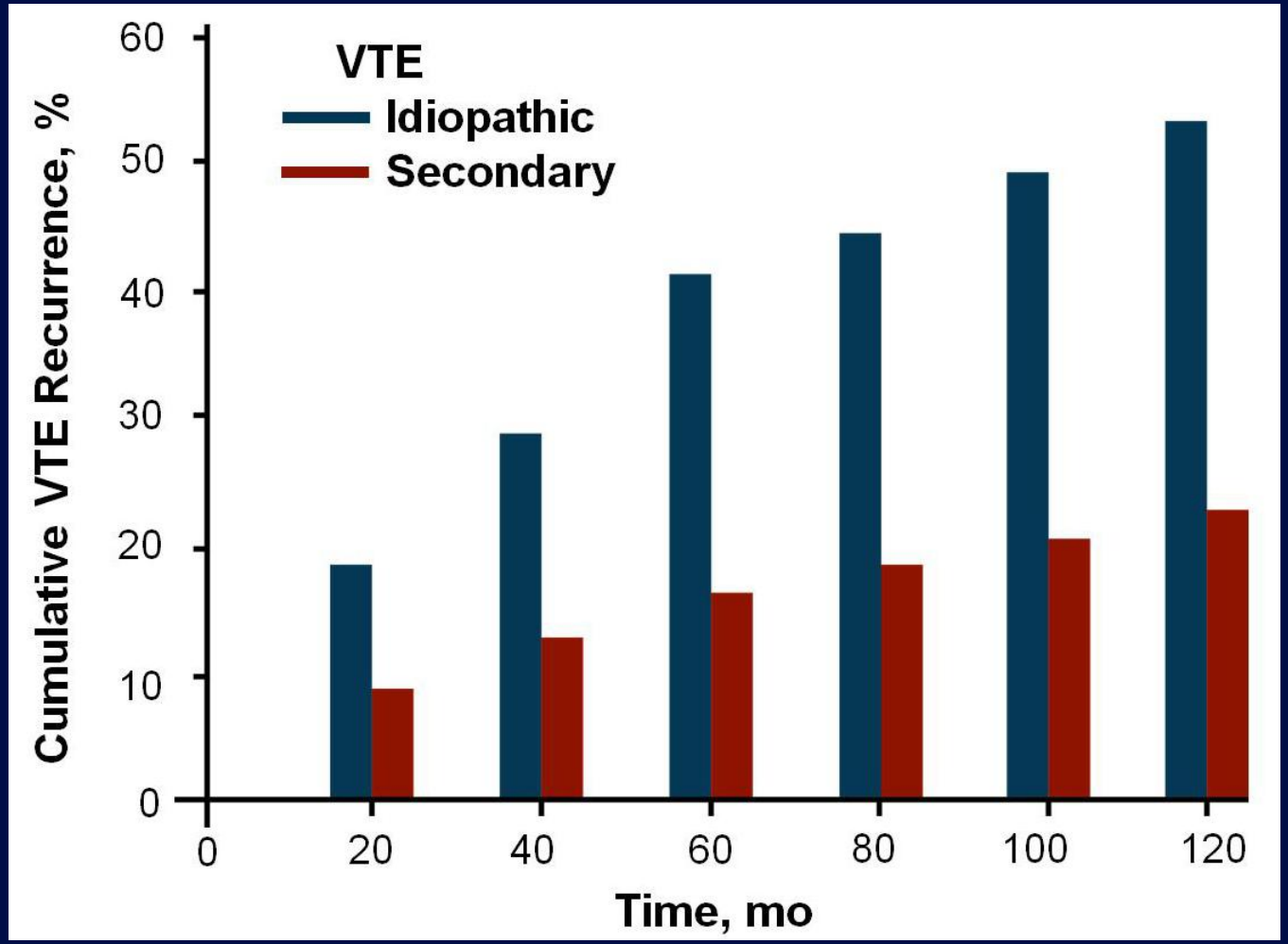
Stratificazione del rischio di sanguinamento

- Storia di sanguinamento (specie gastro-intestinale)
- Pregresso stroke (non cardioembolico)
- Insufficienza renale, anemia, ipertensione
- Epatopatie
- Gravi patologie (acute o croniche)
- Età avanzata (>75 anni)
- Alcolismo
- Valori di PT INR elevati (specie se>5)
- Scarso controllo della TAO
- Terapia antiaggregante concomitante

Overlap tra le diverse forme …

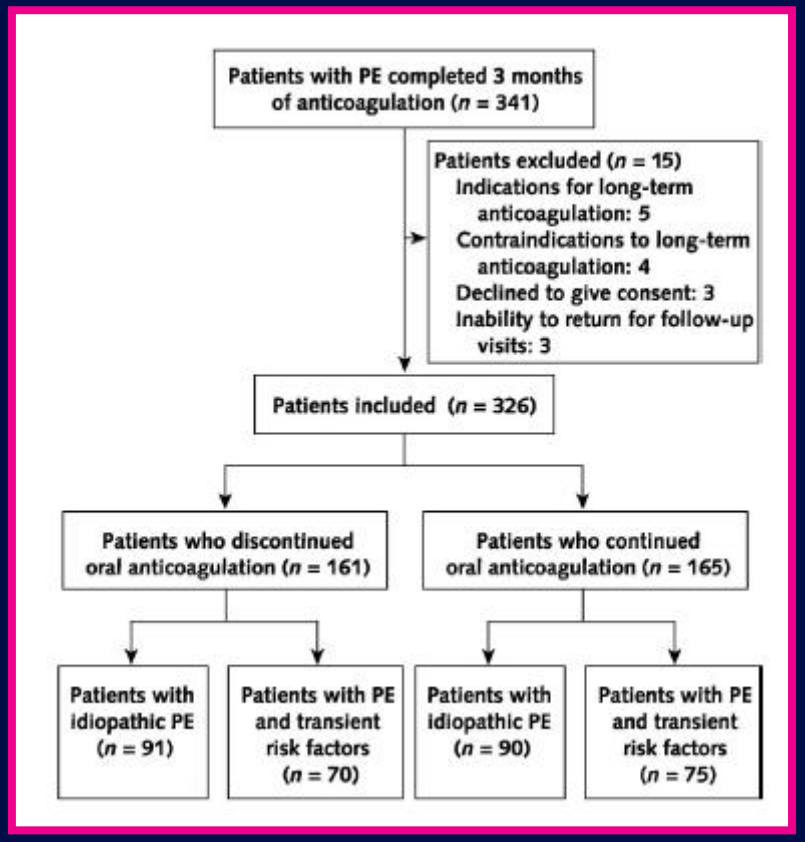


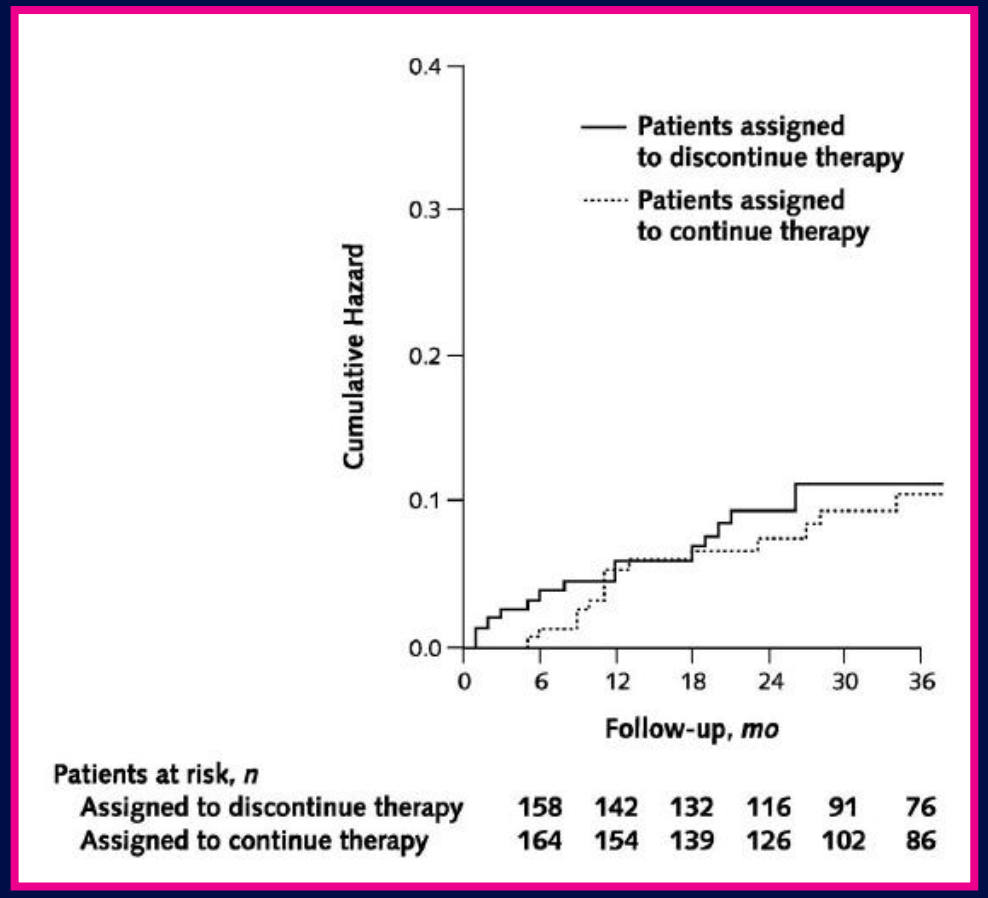
Rischio di recidive di TEV dopo sospensione di TAO



Prandoni P. Haematologica 2007; 92:199-205

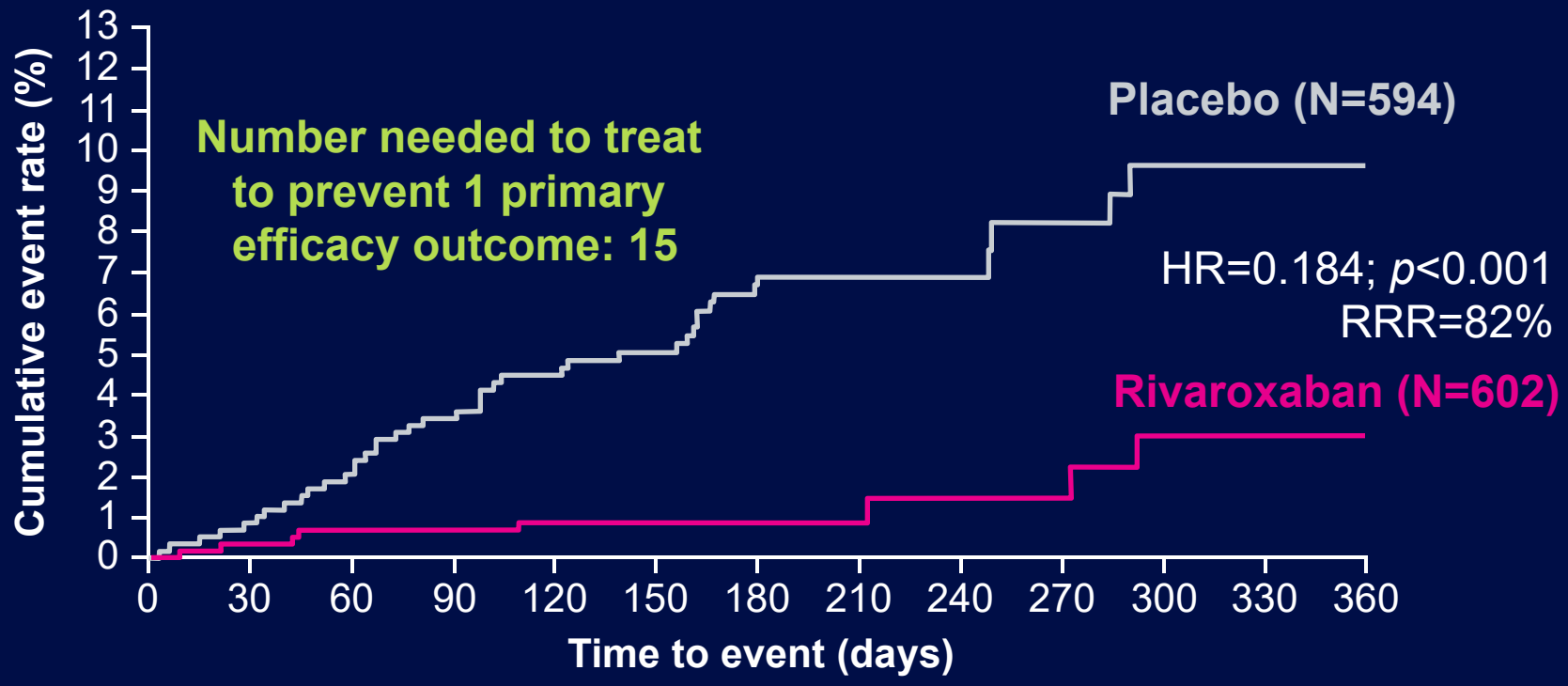
Extended Oral Anticoagulant Therapy (Warfarin) after a First Episode of Pulmonary Embolism





Giancarlo Agnelli, *Ann Intern Med.* 2003;139:19-25.

EINSTEIN Extension: recurrence of VTE



Number of subjects at risk													
Rivaroxaban	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	555	522	468	444	164	138	133	110	93	85

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EINSTEIN Investigators. *N Engl J Med* 2010

EINSTEIN Extension: primary efficacy outcome and individual components

	Rivaroxaban (n=602)		Placebo (n=594)	
	n	(%)	n	(%)
Symptomatic recurrent VTE*	**8**	**(1.3)#**	**42**	**(7.1)**
Recurrent DVT	5	(0.8)	31	(5.2)
Non-fatal PE	2	(0.3)	13	(2.2)
Fatal PE	0		1	(0.2)
Unexplained death (where PE cannot be excluded)	1	(0.2)	0	

ITT population; *Some patients experienced more than one event; #$p<0.001$

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

Major bleeding

	Placebo (n=590) n (%)	Rivaroxaban (n=598) n (%)
Major bleeding	0	4 (0.7)*
Bleeding contributing to death	0	0
Bleeding in a critical site	0	0
Associated with fall in hemoglobin ≥2 g/dL and/or transfusion of ≥2 units	0	4
Gastrointestinal bleeding	0	3 (0.5)
Menorrhagia	0	1 (0.2)

*p=0.11

- Number needed to harm: approximately 139

Safety population

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EINSTEIN Investigators. *N Engl J Med* 2010

Low dose Rivaroxaban ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 30, 2017 VOL. 376 NO. 13

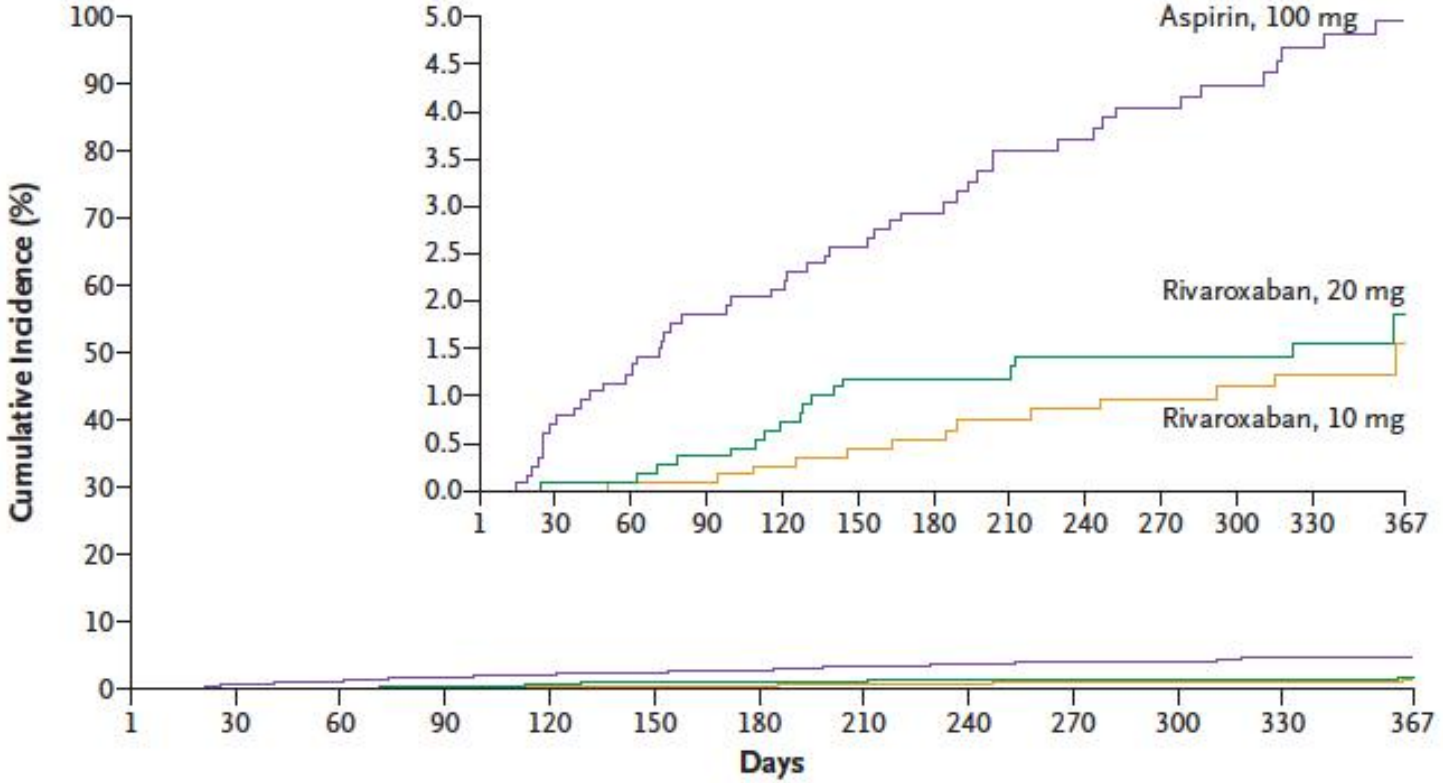
Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

Population

Characteristic	Rivaroxaban		Aspirin
	20 mg (N=1107)	10 mg (N=1127)	100 mg (N=1131)
Male sex — no. (%)	602 (54.4)	620 (55.0)	643 (56.9)
Age — yr			
Mean ±SD	57.9±14.7	58.8±14.7	58.8±14.7
Median (IQR)	59.0 (48.0–69.0)	60.0 (48.0–69.0)	60.0 (48.0–69.0)
Weight — no. (%)			
<70 kg	276 (24.9)	283 (25.1)	277 (24.5)
70 to ≤90 kg	471 (42.5)	480 (42.6)	508 (44.9)
>90 kg	360 (32.5)	364 (32.3)	346 (30.6)
Body-mass index†			
<30	712 (64.3)	751 (66.6)	756 (66.8)
≥30	394 (35.6)	376 (33.4)	375 (33.2)
Missing data	1 (0.1)	0	0
Creatinine clearance — no. (%)			
<30 ml/min	1 (0.1)	2 (0.2)	1 (0.1)
30 to <50 ml/min	40 (3.6)	49 (4.3)	63 (5.6)
50 to <80 ml/min	279 (25.2)	302 (26.8)	277 (24.5)
≥80 ml/min	787 (71.1)	774 (68.7)	790 (69.8)
Index event — no. (%)			
Isolated deep-vein thrombosis	565 (51.0)	565 (50.1)	577 (51.0)
Isolated pulmonary embolism	381 (34.4)	381 (33.8)	366 (32.4)
Both deep-vein thrombosis and pulmonary embolism	155 (14.0)	179 (15.9)	181 (16.0)
Index event asymptomatic or unconfirmed	6 (0.5)	2 (0.2)	7 (0.6)
Classification of index venous thromboembolism — no. (%)			
Provoked	666 (60.2)	647 (57.4)	663 (58.6)
Unprovoked	441 (39.8)	480 (42.6)	468 (41.4)
Hormonal therapy — no. (%)			
Estrogens	8 (0.7)	6 (0.5)	8 (0.7)
Progestins	29 (2.6)	30 (2.7)	30 (2.7)
Known thrombophilia — no. (%)	79 (7.1)	74 (6.6)	70 (6.2)
Previous venous thromboembolism — no. (%)	198 (17.9)	197 (17.5)	194 (17.2)
Active cancer — no. (%)	25 (2.3)	27 (2.4)	37 (3.3)
Median duration of study-drug administration (IQR) — days	349 (189–362)	353 (190–362)	350 (186–362)
Individual intended study duration — no. (%)			
6 mo	206 (18.6)	209 (18.5)	212 (18.7)
9 to <12 mo	229 (20.7)	240 (21.3)	238 (21.0)
12 mo	672 (60.7)	678 (60.2)	681 (60.2)

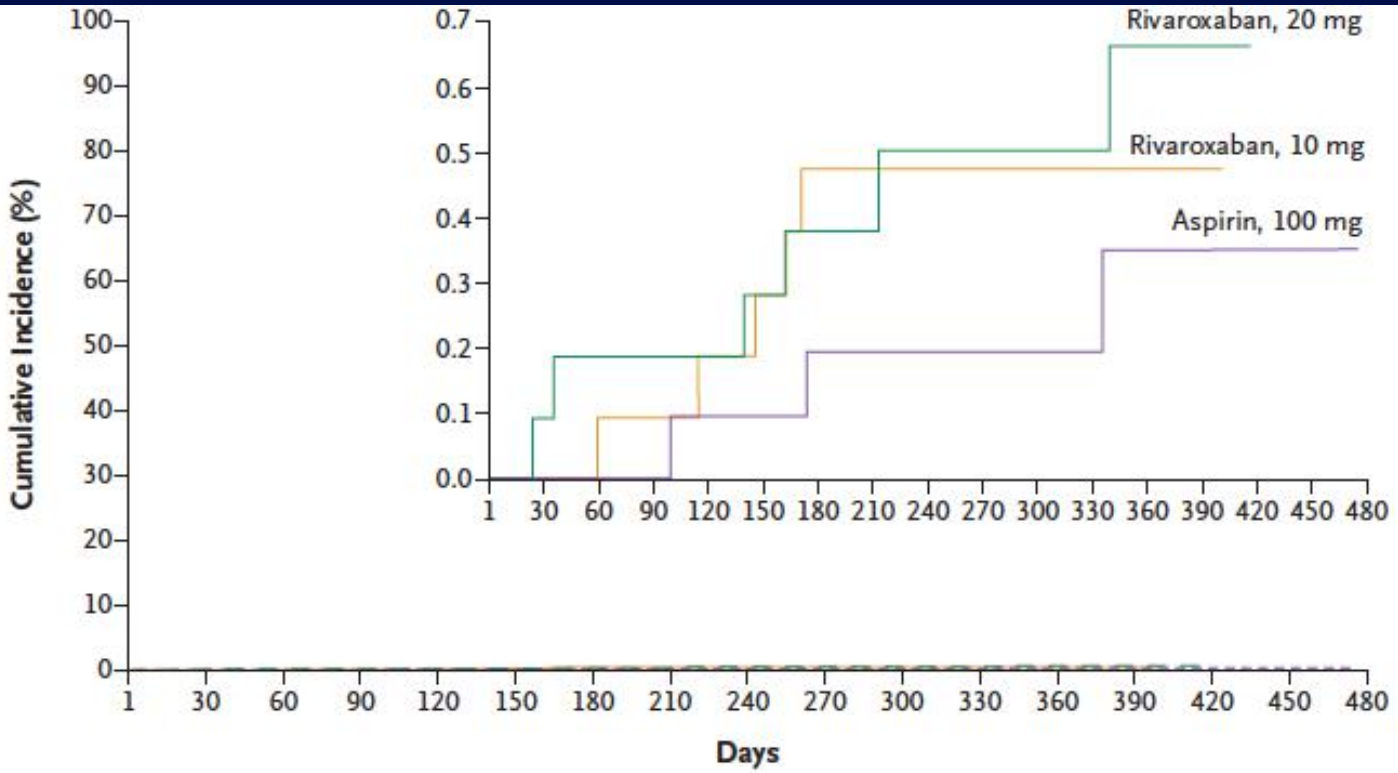
VTE recurrence



No. at Risk

Rivaroxaban, 20 mg	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban, 10 mg	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspirin, 100 mg	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

Major Bleeding



No. at Risk

Rivaroxaban, 20 mg	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449	10	0	0	0
Rivaroxaban, 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin, 100 mg	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

Conclusioni

- Il trattamento dell'embolia polmonare acuta va impostata in relazione alla gravità del quadro clinico:
  - Fibrinolisi nei pazienti con instabilità emodinamica (frammentazione con catetere nei pazienti con rischio emorragico)
  - Anticoagulanti nei pazienti a rischio basso o intermedio basso
  - Anticoagulanti/Fibrinolitici(?) nei pazienti a rischio intermediio alto
- Gli anticoagulanti diretti (DOAC) rappresentano un valida alternativa terapeutica rispetto EBPM/Dicumarolico (riduzione emorragie maggiori !)
- Il "single-drug approach" (testata con il Rivaroxaban e Apixaban) è una semplificazione della terapia permettendo una dimissione precoce del paziente a basso rischio
- L'utilizzo di un DOAC riduce il tempo di ospedalizzazione (XALIA Riva 5 gg vs Warf 7.7)
- Il basso rischio emorragico rende i NAO una prospettiva interessante per il trattamento a lungo termine come profilassi di TEV nei pazienti ad alto rischio di recidive

E’ razionale una strategia terapeutica guidata dal d-dimero per stratificare il rischio di recidive di TEV e continuare la TAO ?

D-dimero & rischio di ricorrenza TEV

Study, Year (Reference)	Patients, *n*			Age, *y*		Body Mass Index, *kg/m²*	
	Analyzed	Men	Women	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
Palareti et al, 2003 (18)	292	147	145	66.9 (15.6)	71.0 (21.0–90.0)	–	–
Eichinger et al, 2003 (19)	422	194	228	49.8 (17.2)	50.6 (14.7–85.6)	27.2 (4.9)	26.6 (17.4–47.5)
Palareti et al, 2006 (17)	497	259	238	61.3 (15.8)	64.6 (18.7–84.3)	–	–
Shrivastava et al, 2006 (16)	110	60	50	54.1 (12.2)	52.5 (31.0–80.0)	32.3 (7.7)	30.7 (20.4–61.0)
Tait et al, 2007 (22)	131	63	68	57.2 (15.0)	60.5 (21.5–89.0)	28.5 (6.4)	28.0 (7.3–52.6)
Baglin et al, 2008 (21)	197	113	84	62.6 (17.7)	65.4 (0–95.0)	26.8 (7.2)	25.8 (0–57.0)
Poli et al, 2008 (20)	169	99	70	61.3 (15.6)	63.0 (14.0–92.0)	–	–
Pooled data	1818	935	883	58.9 (17.1)	61.6 (0–95.0)	28.1 (6.3)	27.2 (0–61.0)*

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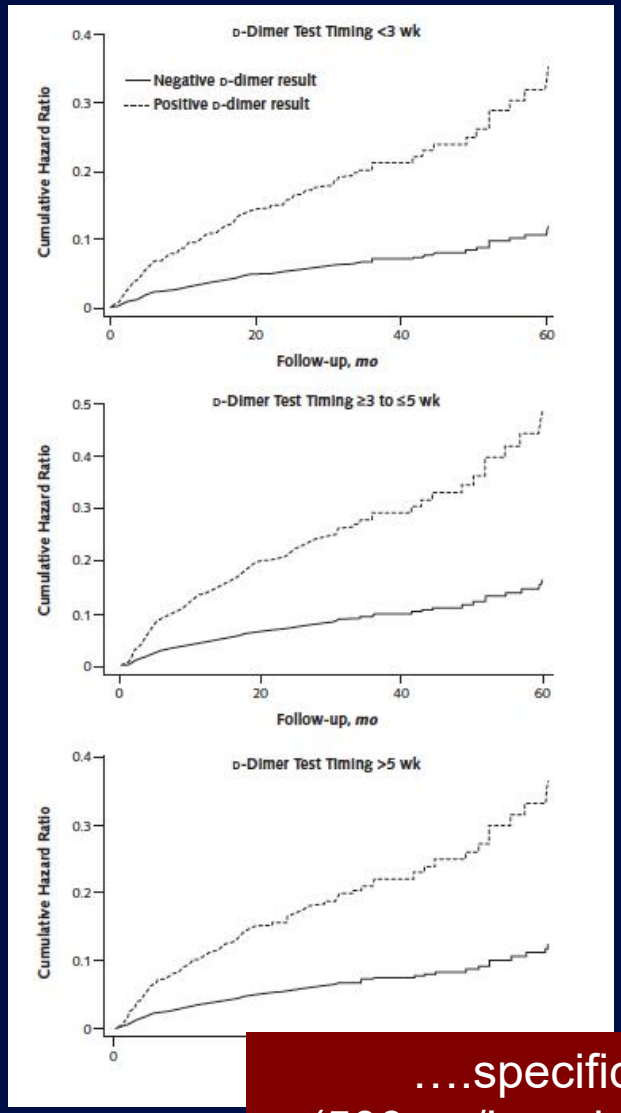
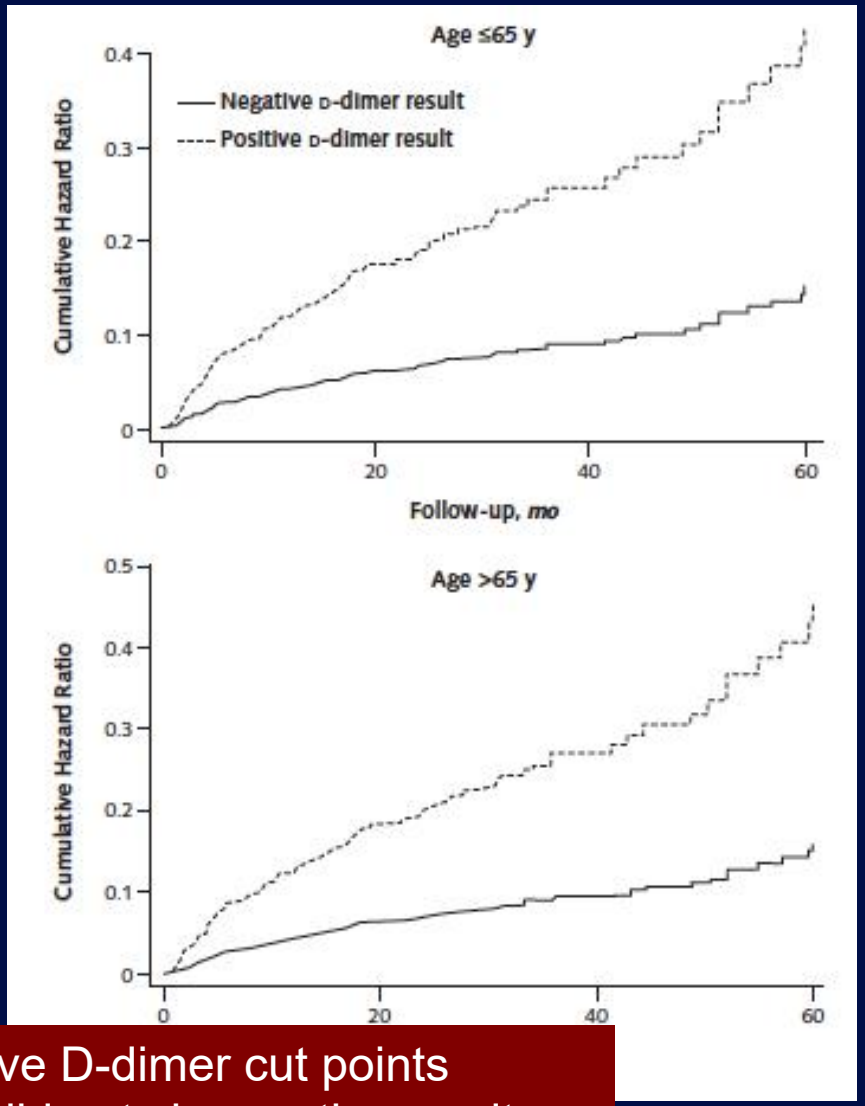
Douketis J. Ann Intern Med. 2010;153:523-531

D-dimero & rischio di ricorrenza TEV





….specific quantitative D-dimer cut points
(500 µg/L and 250 µg/L) did not change the results.

Douketis J. Ann Intern Med. 2010;153:523-531

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Conclusioni

- Gli anticoagulanti diretti rappresentano un valida alternativa terapeutica nel trattamento dell'embolia polmonare acuta (riduzione emorragie maggiori !)
- Il "single-drug approach" (testata con il Rivaroxaban e Apixaban) rappresenta una semplificazione della terapia permettendo una dimissione precoce del paziente a basso rischio
- L'utilizzo di un NOAC riduce il tempo di ospedalizzazione (XALIA Riva 5 gg vs Warf 7.7)
- Il basso rischio emorragico rende i NAO una prospettiva interessante per il trattamento a lungo termine come profilassi di TEV nei pazienti ad alto rischio di recidive

- incidence rates of major bleeding events are alsoconsistent with those reported in the long-running RIETE registry (3.3% per year in XALIA and 2.6% per year in RIETE)
- In patients treated with a vitamin K antagonist, the mean time in therapeutic range was 56.2% (SD 38.2).
- Hospital admission for venous thromboembolism; Rivaroxaban 29% vs 46% VKA
- Duration of hospital stay was Rivaroxaban 5.0 days (SE 0.07) vs VKA 7.7 days (SE 0.04)

Early discharge and home treatment		
Patients with acute low-risk PE should be considered for early discharge and continuation of treatment at home if proper outpatient care and anticoagulant treatment can be provided.	IIa	B

Extended anticoagulation

Recommendations for duration of anticoagulation after pulmonary embolism	Class[a]	Level[b]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.	IIa	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B

In extended anticoagulation risk-benefit ratio should be reassessed at regular interval

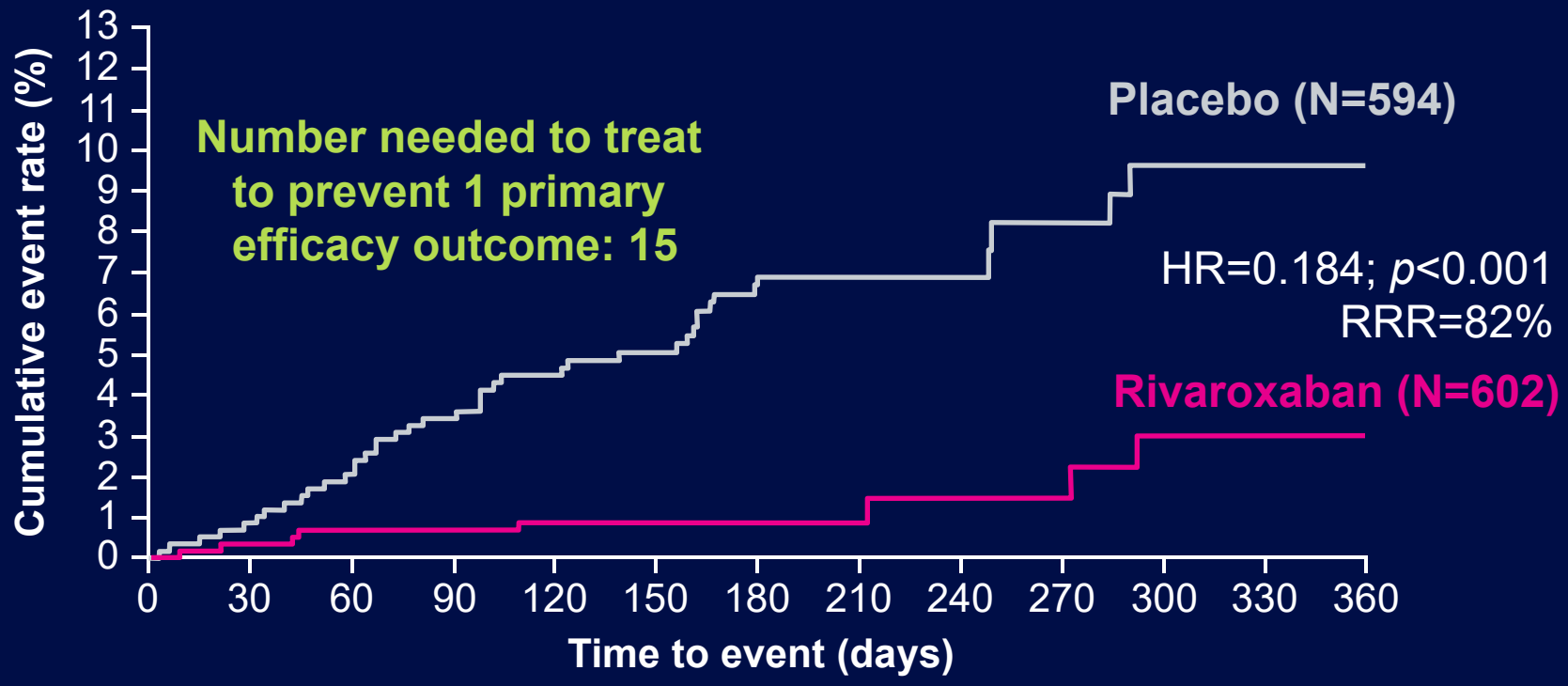
Prevention of recurrent DVT and PE
NOAC trial designs

Trial	Study Drug	Comparator	Tx Before Randomisation	Number of Patients*	Length of Tx (months)
RE-SONATE[1]	Dabigatran 150 mg twice-daily	Placebo	6–18 months of VKA or dabigatran	1343	6
EINSTEIN-EXT[2]	Rivaroxaban 20 mg once-daily	Placebo	6 or 12 months of VKA or rivaroxaban	1196	6 or 12
AMPLIFY-EXT[3]	Apixaban 2.5 mg or 5 mg twice-daily*	Placebo	6–12 months of standard therapy or apixaban	2482	12
RE-MEDY[1]	Dabigatran 150 mg twice-daily	Warfarin	3–12 months of VKA or dabigatran	2856	6-36

**Only apixaban 2.5 mg twice-daily is licensed for prevention of recurrent DVT / PE*

1. Schulman et al. *N Engl J Med. 2013;368:709–718*The EINSTEIN Investigators. *N Engl J Med.* 2010;363:2499–2510.
2. Bauersachs et al. *N Engl J Med.* 2010;363:2499–2510
3. Agnelli et al. *N Engl J Med. 2013;368:699–708*

EINSTEIN Extension: recurrence of VTE



Number of subjects at risk													
Rivaroxaban	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	555	522	468	444	164	138	133	110	93	85

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EINSTEIN Investigators. *N Engl J Med* 2010

EINSTEIN Extension: primary efficacy outcome and individual components

	Rivaroxaban (n=602)		Placebo (n=594)	
	n	(%)	n	(%)
Symptomatic recurrent VTE*	**8**	**(1.3)#**	**42**	**(7.1)**
Recurrent DVT	5	(0.8)	31	(5.2)
Non-fatal PE	2	(0.3)	13	(2.2)
Fatal PE	0		1	(0.2)
Unexplained death (where PE cannot be excluded)	1	(0.2)	0	

ITT population; *Some patients experienced more than one event; #$p<0.001$

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

Anticoagulation and Thrombolysis

- Unfractionated heparin infusion should be stopped during administration of streptokinase or urokinase; it can be continued during rtPA infusion. In patients receiving LMWH or fondaparinux at the time that thrombolysis is initiated, infusion of UFH should be delayed until 12 hours after the last LMWH injection (given twice daily), or until 24 hours after the last LMWH or fondaparinux injection (given once daily). Given the bleeding risks associated with thrombolysis and the possibility that it may become necessary to immediately discontinue or reverse the anticoagulant effect of heparin, it appears reasonable to continue anticoagulation with UFH for several hours after the end of thrombolytic treatment before switching to LMWH or fondaparinux.

Risk stratification in intermediate PE

Variable	Original PESI	Simplified PESI
Age 1 per year		
Age > 80 years	NA	1
Male sex	10	
Cancer	30	1
Heart Failure	10	1
Chronic lung disease	10	1
Arterial oxygen saturation <90%	20	1
Heart rate ≥ 110/min	20	1
Respiratory rate ≥ 30/min	20	
Temperature < 36ºC	20	
Systolic blood pressure < 100 mm Hg	30	1
Altered mental status	60	
Risk class		
Low class	< 106 points	0 points
High risk	≥ 106 points	≥ 1 point

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Jimenez D. Arch Intern Med 2010;170:1383-9.

Rivaroxaban nel paziente con Insufficienza Renale

Indicazione	IR lieve (CrCl 50-80 ml/min)	IR moderata (CrCl 30-49 ml/min)
Prevenzione dell'ictus in pazienti con FANV	20 mg OD	15 mg OD
Trattamento della TVP e prevenzione delle recidive di TEV	15 mg BID per 21 gg + 20 mg OD	15 mg BID per 21 gg + 20 mg OD* NB: riduzione a 15 mg OD solo se il rischio di sanguinamento supera il rischio trombotico

IR grave (CrCl 30-15ml/min): USO con CAUTELA
SPAF: 15 mg od; DVT: 15 mg BID per 21 gg + 20 mg OD*
Rivaroxaban è controindicato se ClCr <15 ml/min

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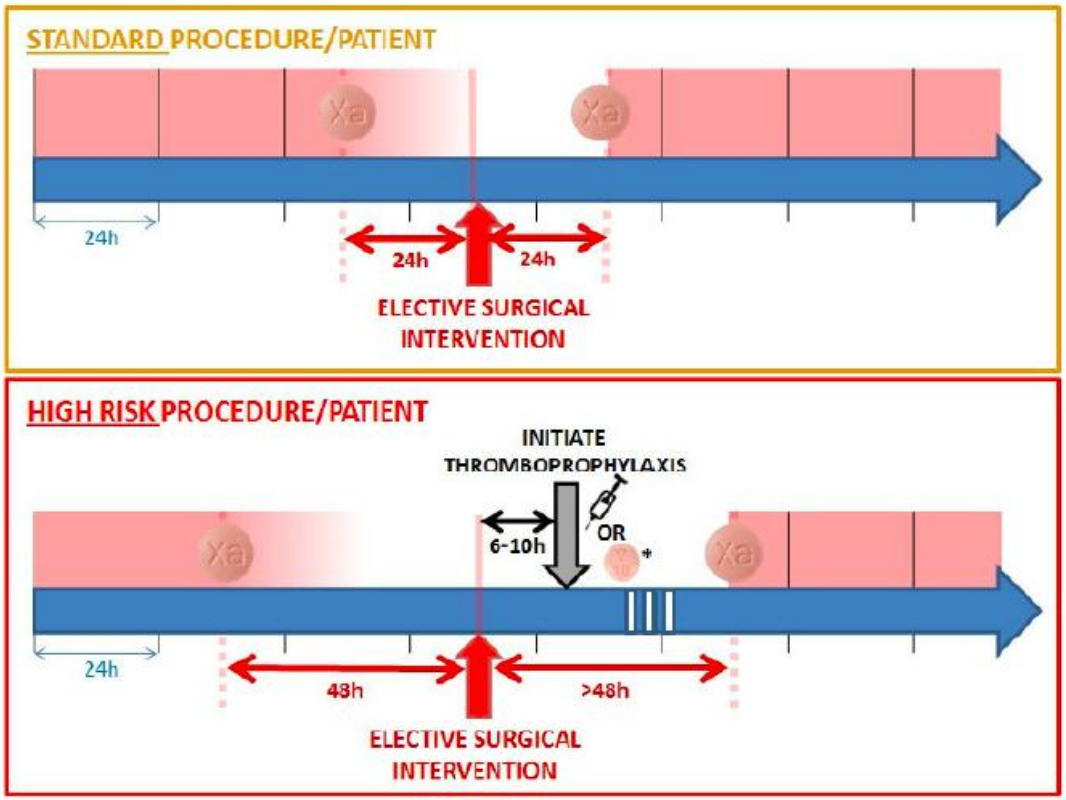
RCP Xarelto

Recommendations for duration of anticoagulation after pulmonary embolism	Class[a]	Level[b]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.	IIa	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B

Management of NOAC and surgical procedures

Table 10 Classification of elective surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulation
Dental interventions
Extraction of 1 to 3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Ophthalmology
Cataract or glaucoma intervention
Endoscopy without surgery
Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .)
Interventions with low bleeding risk
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture)
Angiography
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with high bleeding risk
Complex left-sided ablation (pulmonary vein isolation; VT ablation)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy

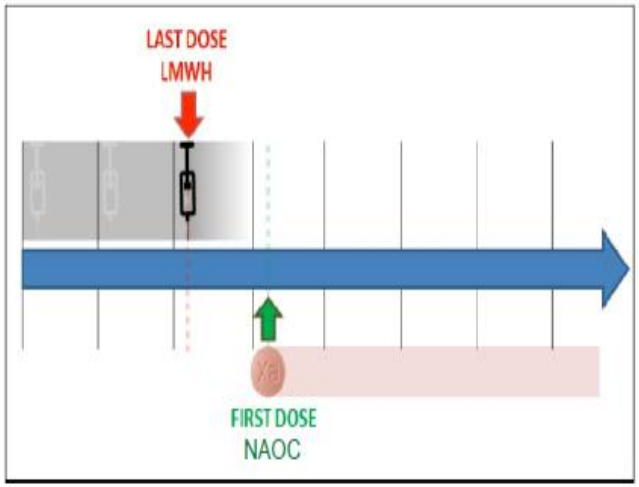


Heidbuchel H, et al. *Eur Heart J* 2013; 15: 625-651

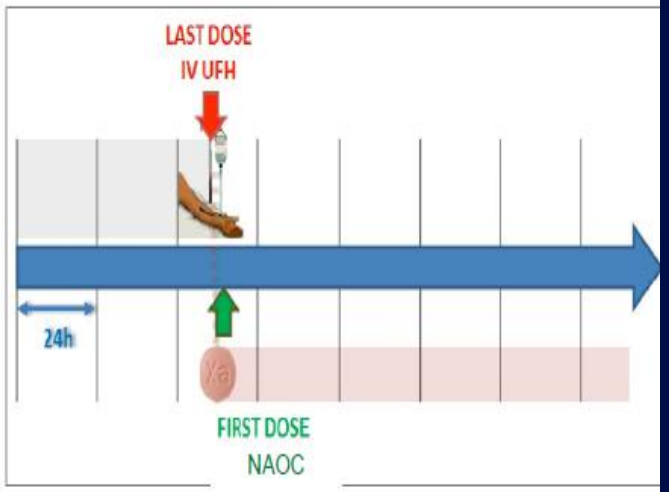
Switch eparine - anticoagulanti orali

Schema con nuovi anticoagulanti orali

Switch tra anticoagulanti parenterali e nuovi OAC



Iniziare NAOC 0-2 ore prima della dose successiva di LMWH



Iniziare NAOC al momento della sospensione dell'eparina ev

Heidbuchel H, et al. *Eur Heart J* 2013; 15: 625-651

Switch eparine - anticoagulanti orali

Chirurgia e nuovi anticoagulanti orali

Table 10 Classification of elective surgical interventions according to bleeding risk

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Cataract or glaucoma intervention
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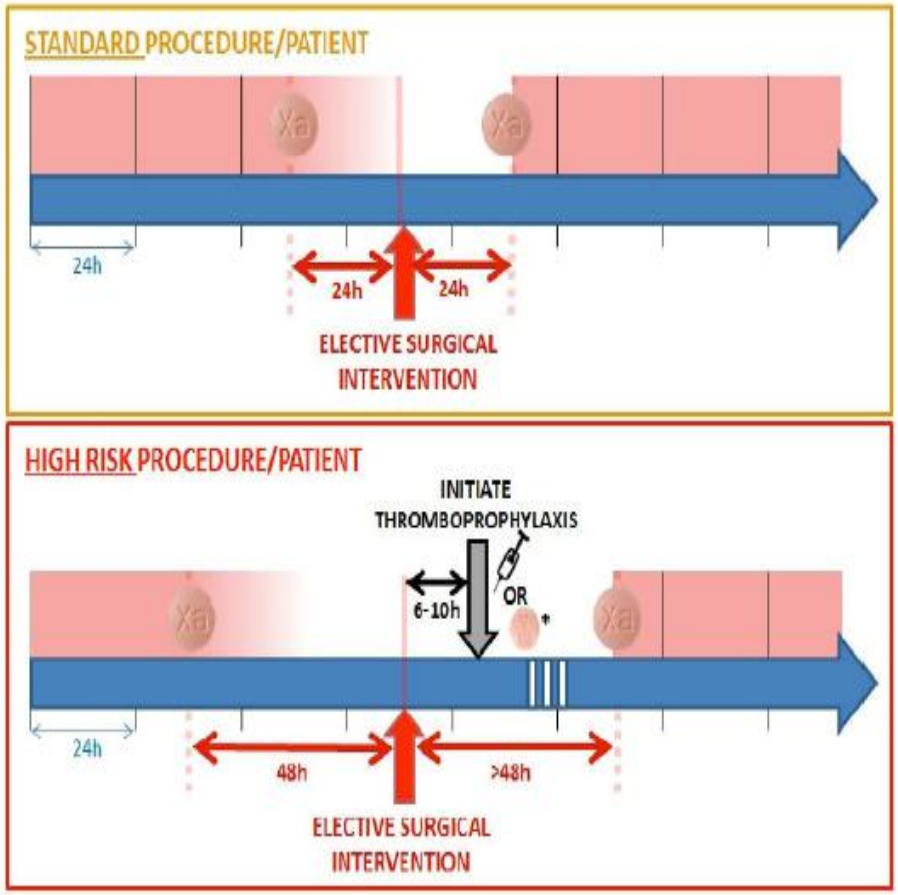
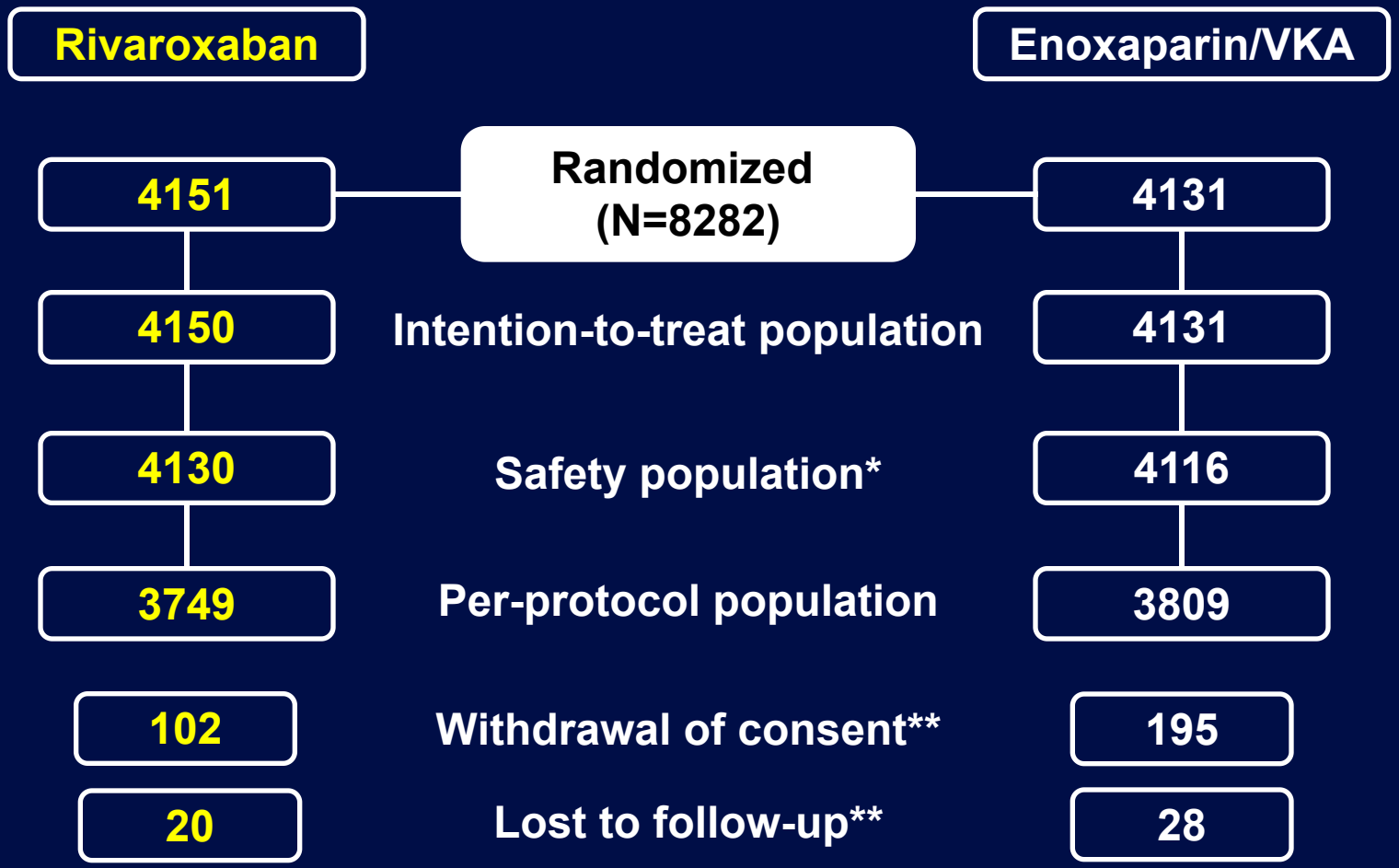
Thoracic surgery
Abdominal surgery
Major orthopedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy



Heidbuchel H, et al. *Eur Heart J* 2013; 15: 625-651

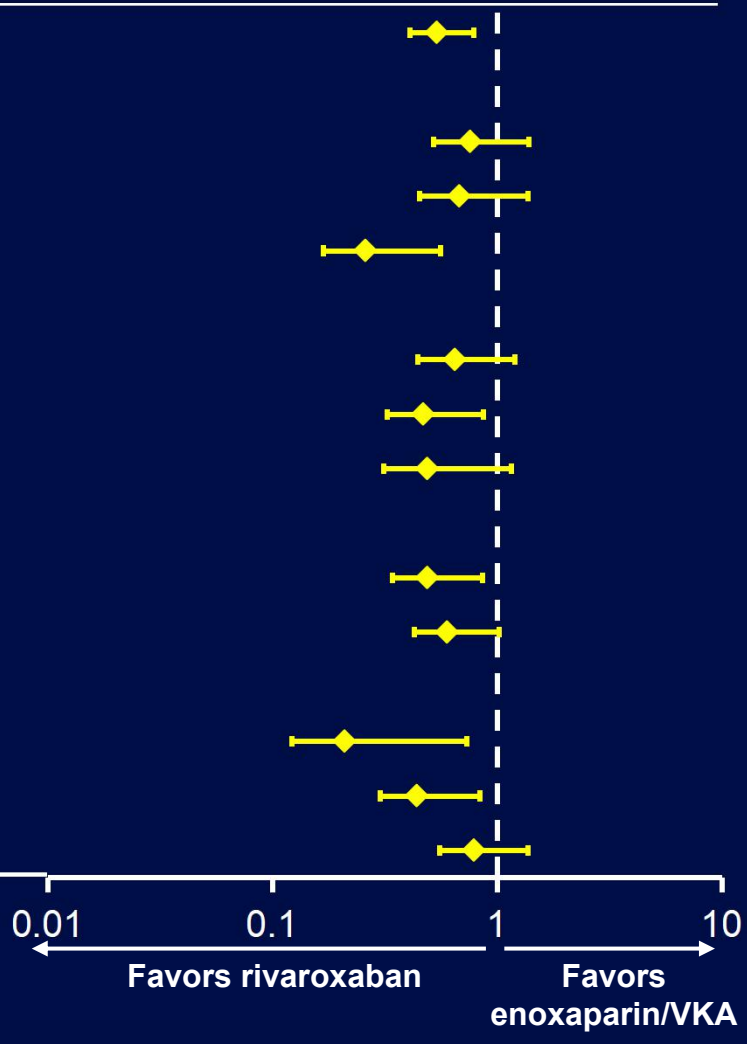
EINSTEIN DVT and EINSTEIN PE pooled analysis



*As treated; **Discontinuation of study medications

EINSTEIN DVT and EINSTEIN PE pooled analysis: major bleeding by subgroup

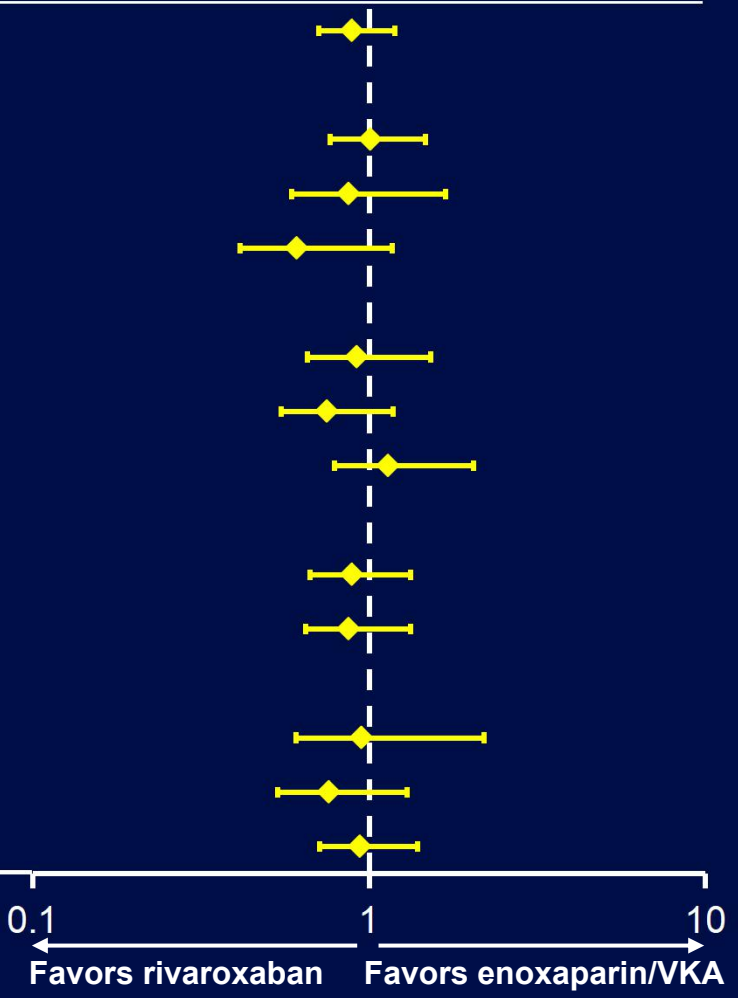
	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	%	n/N	%	
Overall	40/4130	1.0	72/4116	1.7	
Age, years					
<65	19/2592	0.7	24/2579	0.9	
65–75	13/883	1.5	20/913	2.2	
>75	8/655	1.2	28/624	4.5	
Body weight, kg					
≤70	17/1141	1.5	25/1140	2.2	
>70–90	15/1811	0.8	32/1824	1.8	
>90	8/1171	0.7	15/1151	1.3	
Gender					
Male	18/2294	0.8	35/2206	1.6	
Female	22/1836	1.2	37/1910	1.9	
Creatinine clearance, ml/min					
<50	3/329	0.9	13/320	4.1	
50–<80	14/1024	1.4	30/993	3.0	
≥80	23/2739	0.8	29/2776	1.0	



Safety population

EINSTEIN DVT and EINSTEIN PE pooled analysis: primary efficacy outcome by subgroup

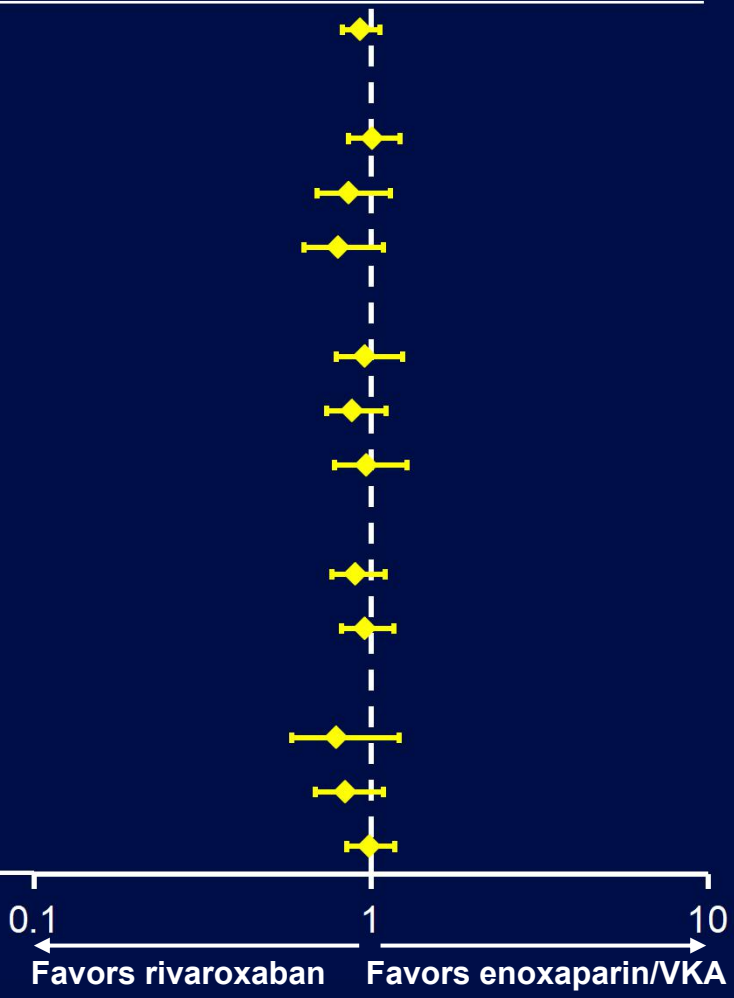
	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	%	n/N	%	
Overall	86/4131	2.1	95/4150	2.3	
Age, years					
<65	55/2606	2.1	53/2590	2.0	
65–75	16/888	1.8	19/914	2.1	
>75	15/656	2.3	23/627	3.7	
Body weight, kg					
≤70	29/1147	2.5	31/1145	2.7	
>70–90	33/1821	1.8	43/1826	2.4	
>90	24/1174	2.0	21/1158	1.8	
Gender					
Male	42/2302	1.8	45/2214	2.0	
Female	44/1848	2.4	50/1917	2.6	
Creatinine clearance, ml/min					
<50	11/332	3.3	11/322	3.4	
50–<80	24/1030	2.3	30/992	3.0	
≥80	49/2748	1.8	52/2787	1.9	



ITT population

EINSTEIN DVT and EINSTEIN PE pooled analysis: principal safety outcome by subgroup

	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	%	n/N	%	
Overall	388/4130	9.4	412/4116	10.0	
Age, years					
<65	218/2592	8.4	215/2579	8.3	
65–75	93/883	10.5	110/913	12.0	
>75	77/655	11.8	87/624	13.9	
Body weight, kg					
≤70	119/1141	10.4	121/1140	10.6	
>70–90	169/1811	9.3	191/1824	10.5	
>90	99/1171	8.5	100/1151	8.7	
Gender					
Male	192/2294	8.4	203/2206	9.2	
Female	196/1836	10.7	209/1910	10.9	
Creatinine clearance, ml/min					
<50	39/329	11.9	44/320	13.8	
50–<80	109/1024	10.6	122/993	12.3	
≥80	238/2739	8.7	245/2776	8.8	



Safety population

EINSTEIN DVT and EINSTEIN PE pooled analysis: key secondary and other outcomes

Outcome	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	%	n/N	%	
Net clinical benefit*	134/4150	3.2	169/4131	4.1	0.77 (0.61–0.97)
Total mortality	104/4130	2.5	103/4116	2.5	
Cerebrovascular events	9/4130	0.2	12/4116	0.3	
Acute coronary syndrome	19/4150	0.5	16/4131	0.4	
Systemic embolism	8/4150	0.2	5/4131	0.1	
ALT >3× ULN and bilirubin >2× ULN	7/4120	0.2	8/4102	0.2	

*Primary efficacy outcome plus major bleeding

EINSTEIN DVT and EINSTEIN PE pooled analysis: patient disposition

	Rivaroxaban (N=4150)		Enoxaparin/VKA (N=4131)	
Prerandomization/initial treatment, n (%)	3503	(84.4)	4120	(99.7)
Median duration, days (range)	2.0	(1.0–37.0)	8.0	(1.0–336)
Mean treatment duration, days	207		203	
Compliance with study medication, n (%)				
<50%	82	(2.0)	93	(2.3)
≥50% to <80%	147	(3.5)	179	(4.3)
≥80%	3860	(93.0)	3838	(92.9)
Hospitalization, % (median, days)	73	(6)	75	(7)
Intensive care unit	11	(4)	10	(4)

ITT population

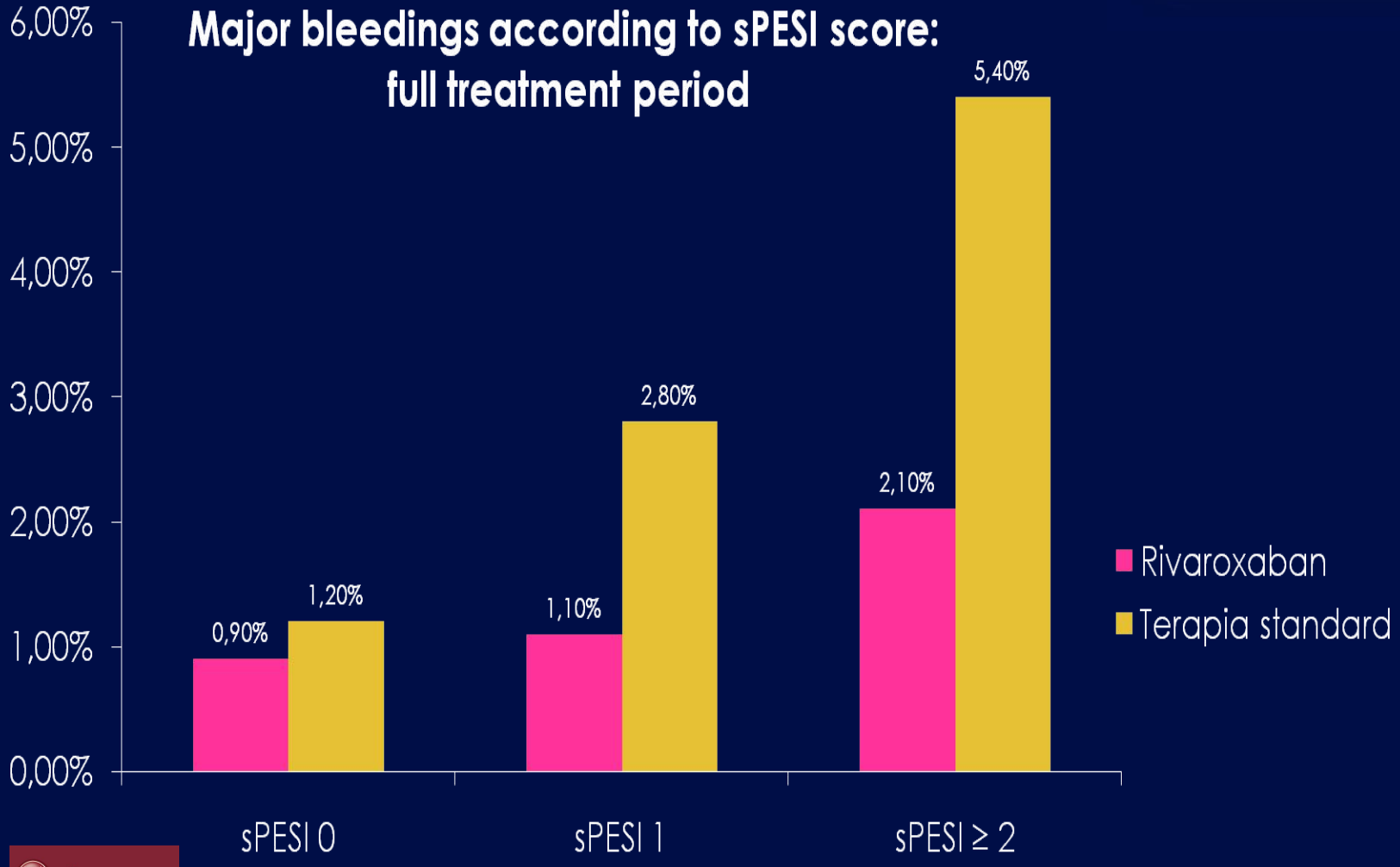
Academic Emergency Medicine
Official Journal of the Society for Academic Emergency Medicine

ORIGINAL CONTRIBUTION

Treatment of Pulmonary Embolism With Rivaroxaban: Outcomes by Simplified Pulmonary Embolism Severity Index Score from a Post Hoc Analysis of the EINSTEIN PE Study

Gregory J. Fermann, MD, Petra M. G. Erkens, PhD, Martin H. Prins, MD, Philip S. Wells, MD, Akos F. Pap, MSc, and Anthonie W. A. Lensing, MD

Major bleedings according to sPESI score: full treatment period



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A: ≤ 7 days

PESI Score	Outcome	Rivaroxaban (*n* = 2,419) *n/N* (%)	Standard Therapy* (*n* = 2,412) *n/N* (%)
0	Recurrent VTE	5/1,256 (0.4)	4/1,333 (0.3)
	Fatal PE	0/1,256 (0.0)	1/1,333 (<0.1)
	All-cause mortality	0/1,256 (0.0)	1/1,333 (<0.1)
	Major bleeding†	4/1,254 (0.3)	3/1,329 (0.2)
1	Recurrent VTE	2/919 (0.2)	3/856 (0.4)
	Fatal PE	0/919 (0.0)	1/856 (0.1)
	All-cause mortality	1/919 (0.1)	1/856 (0.1)
	Major bleeding†	0/916 (0.0)	5/853 (0.6)
≥2	Recurrent VTE	4/244 (1.6)	3/223 (1.3)
	Fatal PE	1/244 (0.4)	2/223 (0.9)
	All-cause mortality	3/244 (1.2)	4/223 (1.8)
	Major bleeding†	2/242 (0.8)	3/222 (1.4)

B: ≤ 14 days

PESI Score	Outcome	Rivaroxaban (*n* = 2,419) *n/N* (%)	Standard Therapy* (*n* = 2,412) *n/N* (%)
0	Recurrent VTE	7/1,256 (0.6)	7/1,333 (0.5)
	Fatal PE	0/1,256 (0.0)	2/1,333 (0.2)
	All-cause mortality	0/1,256 (0.0)	2/1,333 (0.2)
	Major bleeding†	6/1,254 (0.5)	6/1,329 (0.5)
1	Recurrent VTE	6/919 (0.7)	6/856 (0.7)
	Fatal PE	1/919 (0.1)	1/856 (0.1)
	All-cause mortality	2/919 (0.2)	2/856 (0.2)
	Major bleeding†	1/916 (0.1)	8/853 (0.9)
≥2	Recurrent VTE	4/244 (1.6)	5/223 (2.2)
	Fatal PE	1/244 (0.4)	2/223 (0.9)
	All-cause mortality	4/244 (1.6)	5/223 (2.2)
	Major bleeding†	2/242 (0.8)	4/222 (1.8)

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