Νεότερα Δεδομένα στην Αντιμετώπιση της Πνευμονικής Εμβολής

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What do the ESC Guidelines (2008) say ?

September 2008

Diagnosis and Management of Acute Pulmonary Embolism

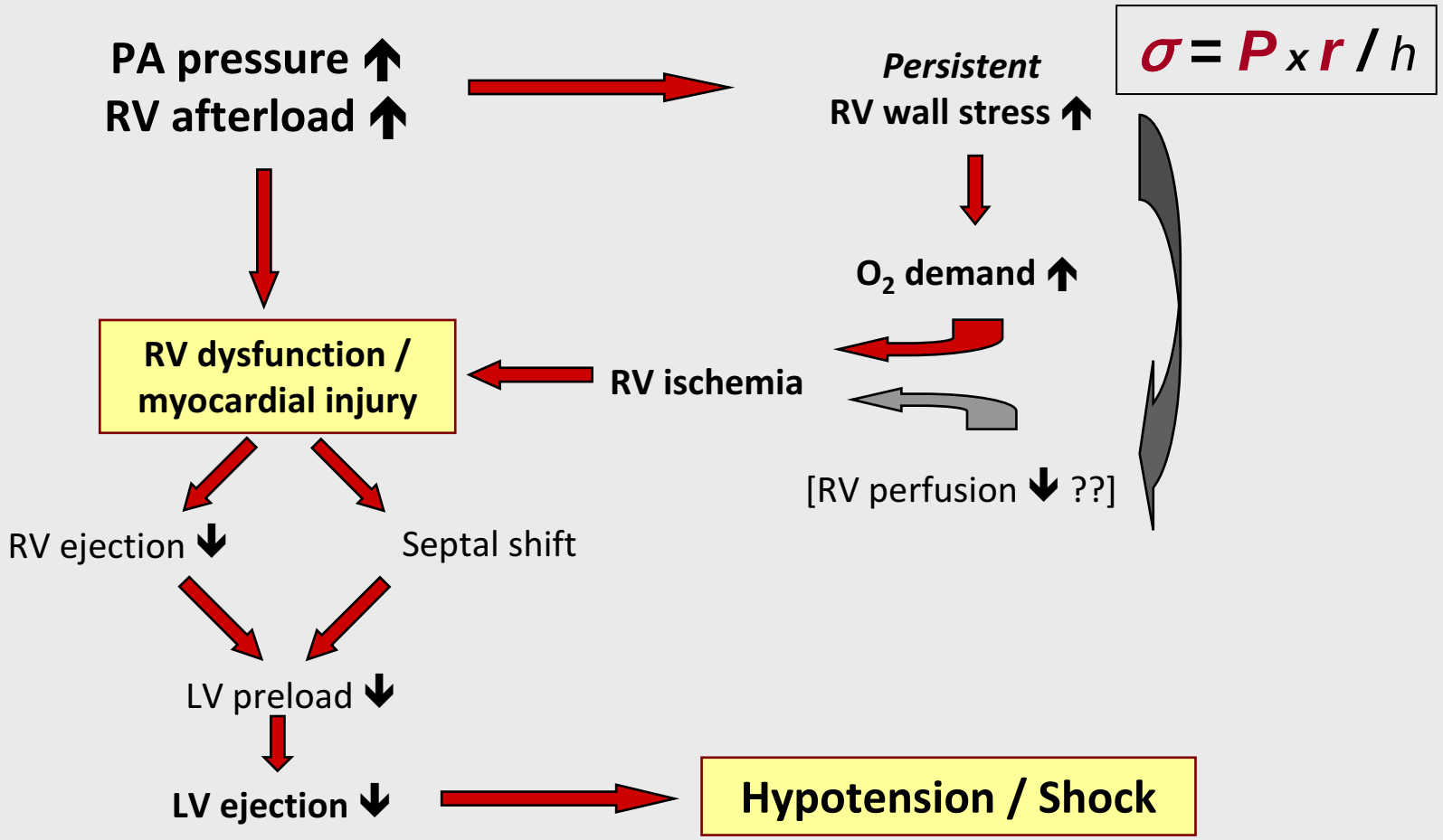
The Task Force on Acute Pulmonary Embolism of the European Society of Cardiology

Task Force Members:

- Arnaud Perrier, Geneva, Switzerland
- Stavros Konstantinides, Goettingen, Germany
- Giancarlo Agnelli, Perugia, Italy
- Nazzareno Galiè, Bologna, Italy
- Piotr Pruszczyk, Warsaw, Poland
- Frank Bengel, Baltimore, USA
- Adrian J.B. Brady, Glasgow, UK
- Daniel Ferreira, Charneca De Caparica, Portugal
- Uwe Janssens, Eschweiler, Germany
- Walter Klepetko, Vienna, Austria
- Eckhard Mayer, Mainz, Germany
- Martine Remy-Jardin, Lille, France
- Jean-Pierre Bassand, Besançon, France

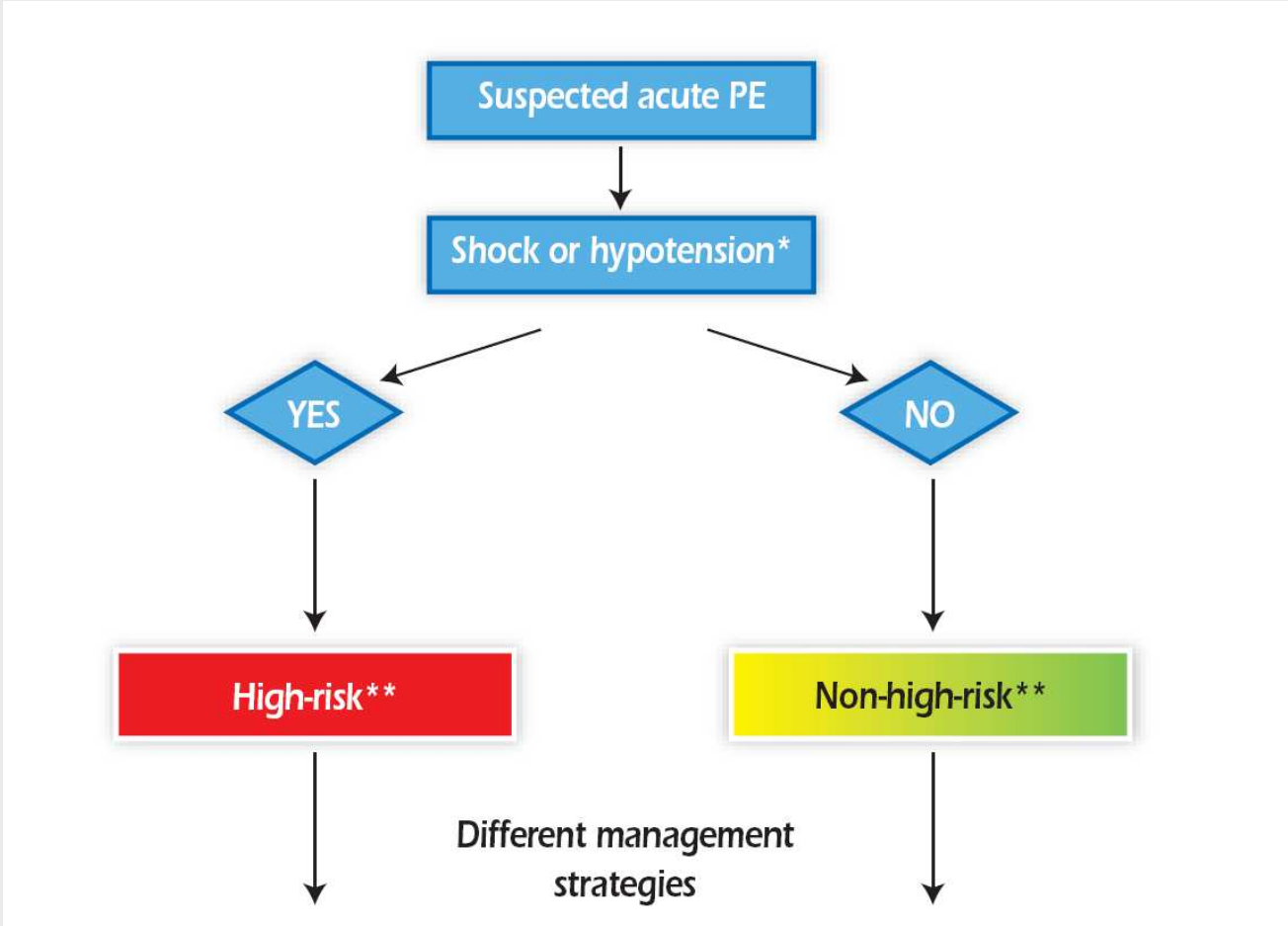
and Adam Torbicki, *Warsaw, Poland*

The vicious circle of right ventricular dysfunction

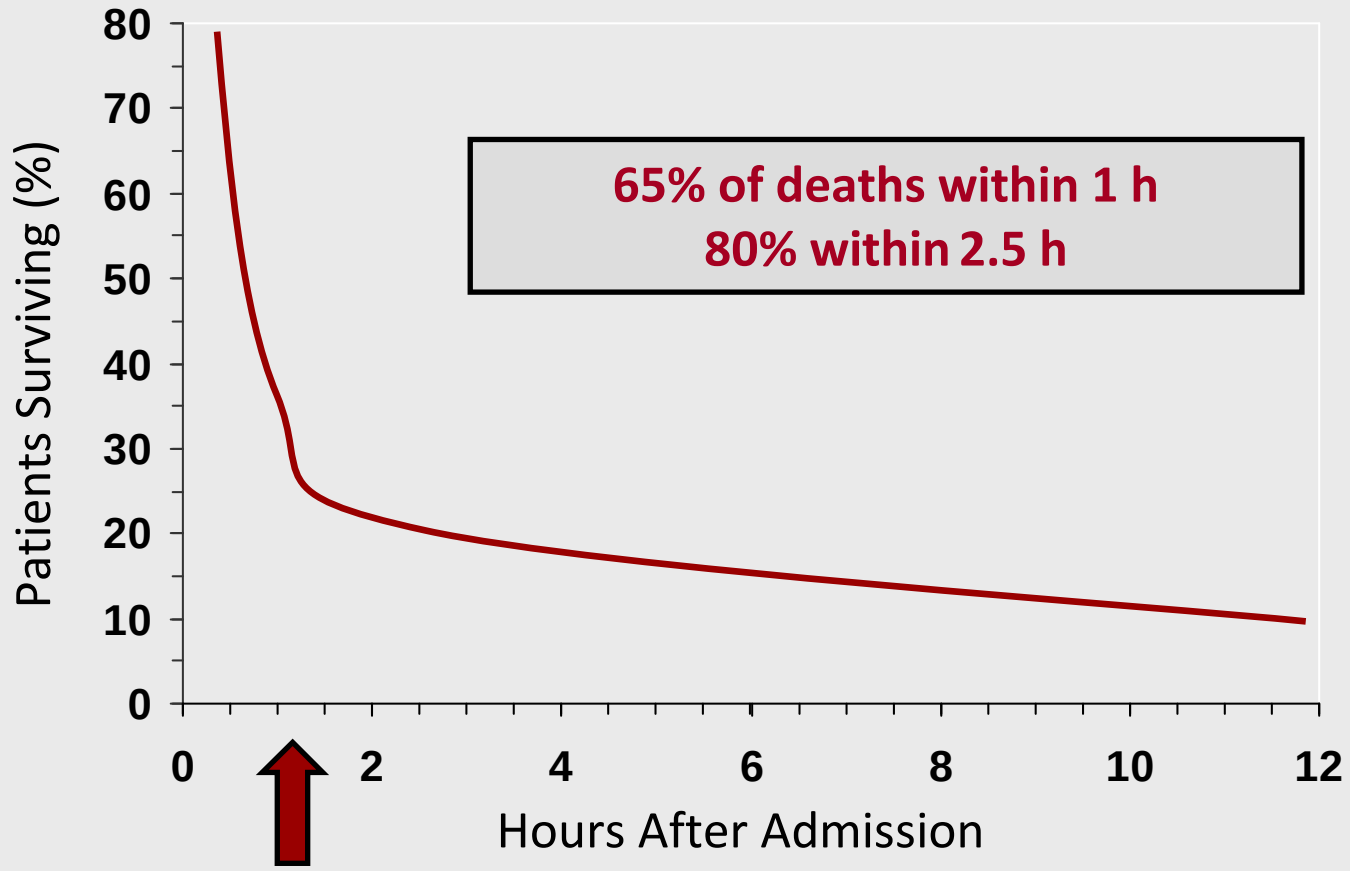


C Greyson. Cardiovasc Res 1997; Am J Physiol Heart Circ Physiol 2000
Schmitto JD. Eur J Cardiothorac Surg 2009

Initial risk stratification based on hemodynamic status



High risk of early death in hemodynamic instability



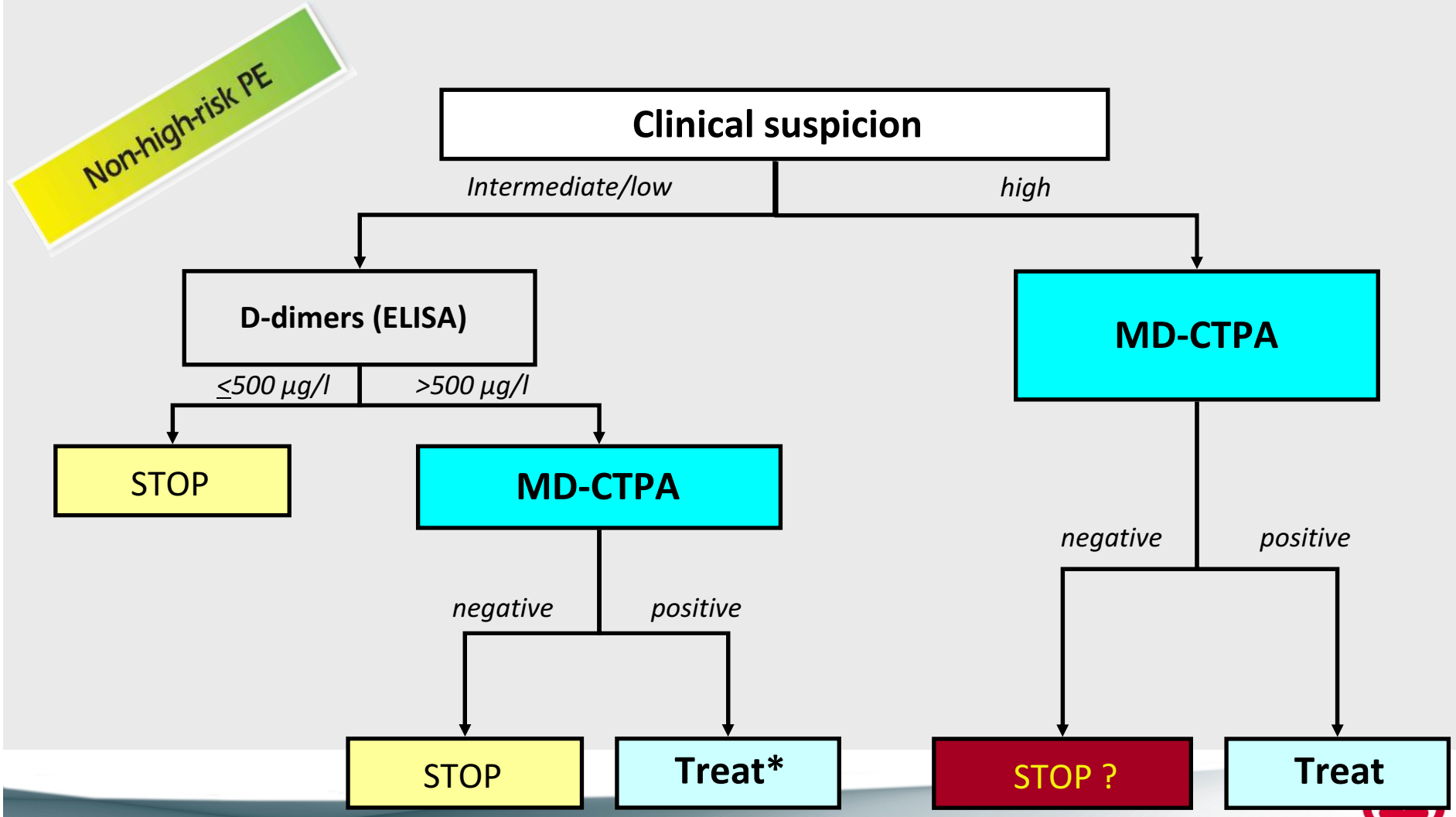
PD Stein. Chest 1995;108:978-981

Initial treatment: ESC recommendations

High-risk PE

Recommendation	Class	Level
Thrombolytic therapy should be used in patients with high-risk PE presenting with cardiogenic shock and/or persistent arterial hypotension	I (1)	A (B)
Surgical pulmonary embolectomy is a therapeutic alternative if thrombolysis is absolutely contraindicated or has failed	I (2)	C (C)
Catheter embolectomy or fragmentation of proximal pulmonary arterial clots may be an alternative to surgical treatment when thrombolysis absolutely contraindicated or has failed	IIb (2)	C (C)

Diagnostic algorithm for the **non-high-risk** patient



Initial treatment: ESC recommendations

Non-high-risk PE

Recommendation	Class	Level
Anticoagulation should be initiated without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is still ongoing	I (1)	C (C)
LMW heparin or fondaparinux for most patients	I (1)	A (A)
Thrombolysis generally NOT recommended (1B) – may be considered in **selected cases**	IIb	B

Low molecular-weight heparins approved for PE

Substance	Brand name	Dose (s.c.)	Interval
Certoparin	Mono-Embolex (Novartis)	8.000 U	q24 h
Dalteparin	Fragmin (Pharmacia/Pfizer)	200 U/kg	q24 h
Enoxaparin LE	**Clexane (Sanofi-Aventis)**	**1,0 mg/kg (1,5 mg/kg**	**q12 h q24 h)**
Nadroparin	Fraxiparin (Glaxo) Fraxodi (Glaxo)	85 U/kg 171 U/kg	q12 h q24 h
Tinzaparin LE	**Innohep (Leo)**	**175 U/kg**	**q24 h**
Fondaparinux LE	**Arixtra (Glaxo)**	**7,5 mg (if BW <50 kg: 5 mg; if >100 kg: 10 mg)**	**q24 h**

2

What is new (2008-2011) in pulmonary embolism **diagnosis** ?

Simplified scores of clinical probability

Wells score	
Previous DVT or PE	+ 1
Immobilization or surgery (< 4 weeks)	+ 1
Cancer	+ 1
Alternative diagnosis less probable	+ 1
Hemoptysis	+ 1
Heart rate > 100/min	+ 1
Clinical signs of DVT*	+ 1

**limb edema and pain on palpation of deep veins*

- **PE unlikely: 0 to 1; PE likely: 2 or more**

Revised Geneva score	
Age > 65 years	+1
Previous DVT or PE	+1
Surgery or fracture (< 1 month)	+1
Cancer	+1
Unilateral lower limb pain	+1
Hemoptysis	+1
Heart rate	+1
75 to 94 beats per minute	+1
≥ 95 beats per minute	+1
Clinical signs of DVT*	+1

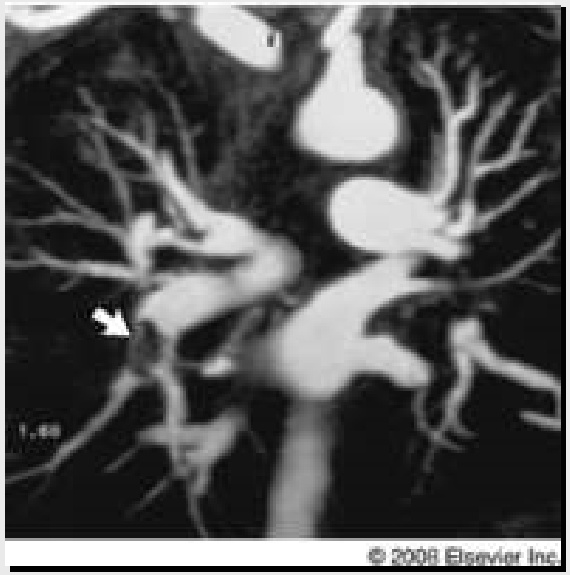
- **Low 0 to 1; intermediate 2 to 4; high 5 or more**
- **PE unlikely: 0 to 2; PE likely: 3 or more**

Thromb Haemost 2009;101:197–200; Arch Intern Med 2008;168:2131-6.

MRI in PE diagnosis: the PIOPED III study

Table 3. **Results of MRA and Combined MRA and MRV, by Reference Test**

Test Result	Reference Test Result, *n*		Total, *n*
	Positive for PE	Negative for PE	
MRA result			
Positive	59	2	61
Negative	17	201	218
Technically inadequate	28	64	92
Total	104	267	371



- Multicenter US study including 371 consecutive patients
- MR angiography technically inadequate in 25% (11 to 52%)
- Performance of technically adequate tests:
  - Sensitivity 78%, specificity 99%

Ann Intern Med. 2010;152:434-443

3

Is there progress in the management of **intermediate-risk** patients ?

Management of acute PE

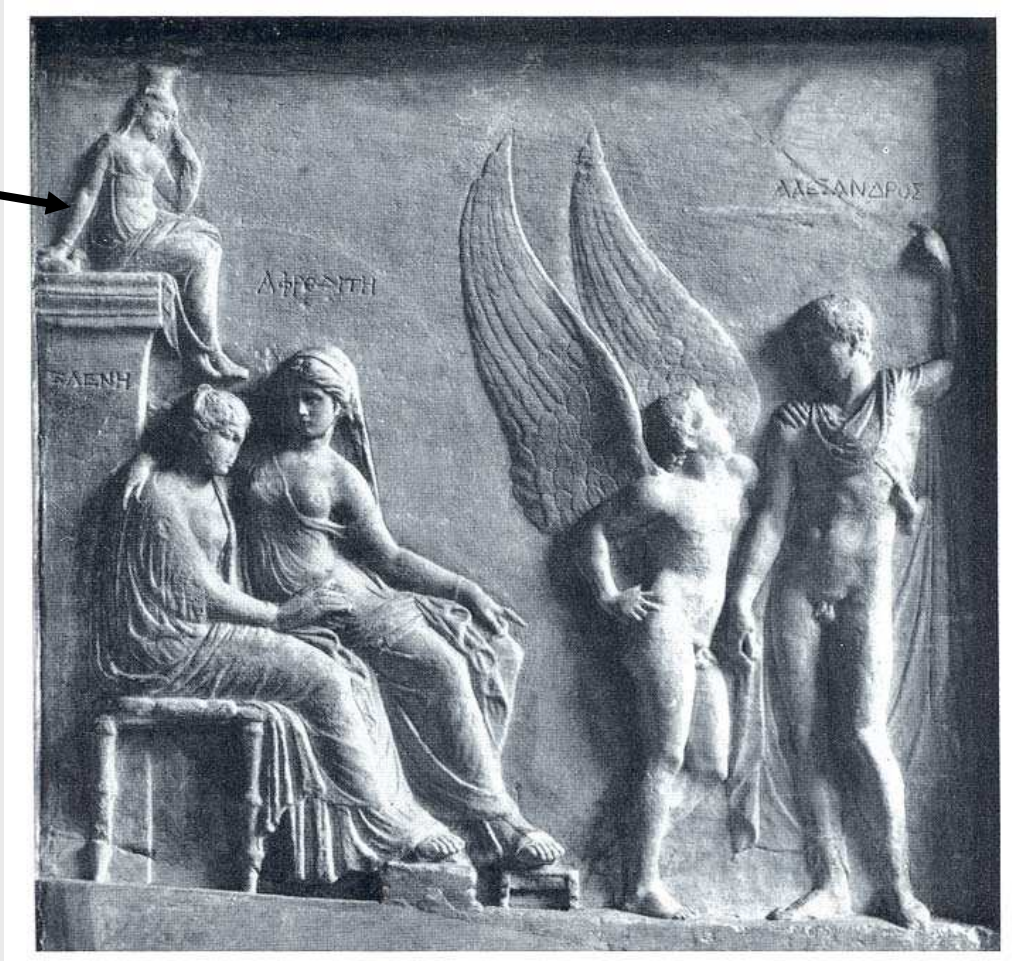
PE-related early MORTALITY RISK		RISK MARKERS: CLINICAL (Shock or hypotension)	RISK MARKERS: RV Dysfunction	RISK MARKERS: Myocardial injury	Potential treatment implications
HIGH > 15%		+	(+)*	(+)*	Thrombolysis or Embolectomy
NON HIGH	Intermediate 3 - 15%	–	+	+	Hospital Admission
			+	– ?	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

Is there room for **thrombolysis** in Intermediate-Risk PE?

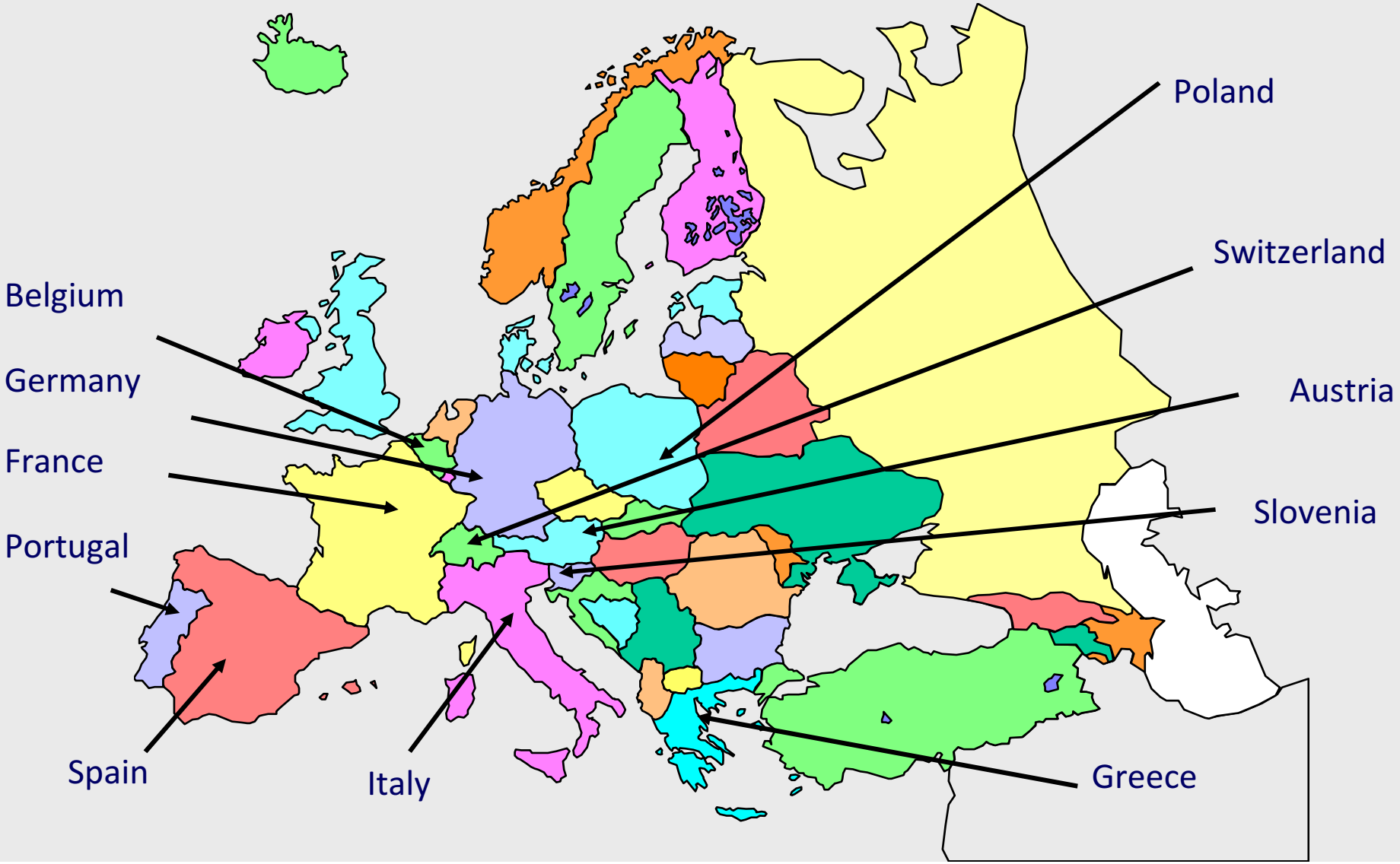
The Pulmonary Embolism International Thrombolysis Trial (PEITHO)

PEITHO - The Goddess of Persuasion

Πειθώ



PEITHO - International randomized thrombolysis trial



PEITHO - objectives

Primary

to investigate the clinical benefits (efficacy) of thrombolysis (tenecteplase) over placebo *in normotensive patients with acute intermediate-risk PE* (both treatment arms receive standard heparin anticoagulation)

Secondary

to assess the *safety* of tenecteplase in patients with intermediate-risk PE

PEITHO - Inclusion criteria (1)

1. Age ≥ 18 years
2. Acute PE confirmed by:

ù

   a) lung scan, ***or***
   b) spiral CT, ***or***
   c) pulmonary angiogram

3. **RV dysfunction *plus* myocardial injury**:
   a) echocardiography ***or*** CT

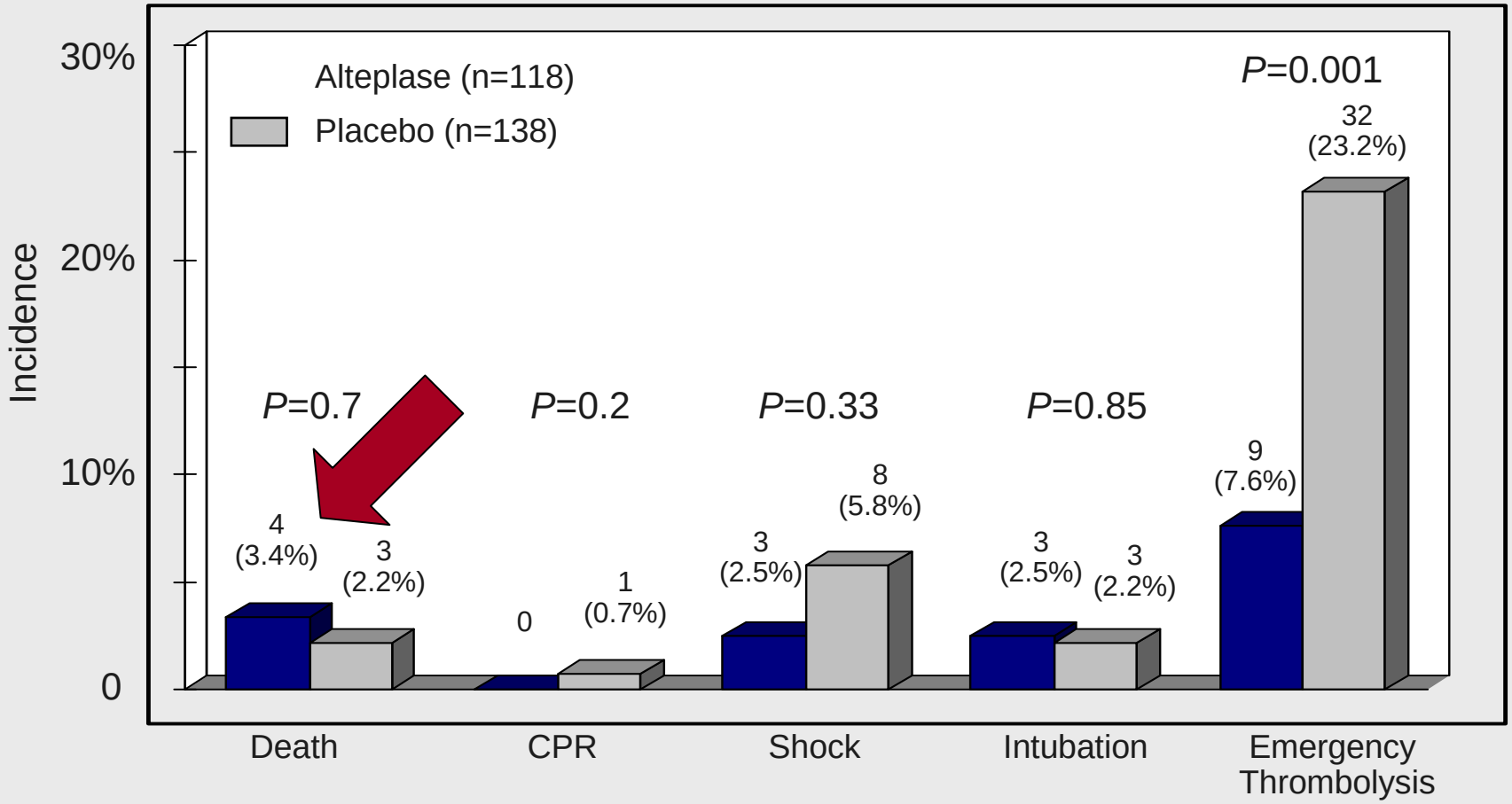
   PLUS

   b) troponin I ***or*** T positive

Differences between PEITHO and previous trials (1)

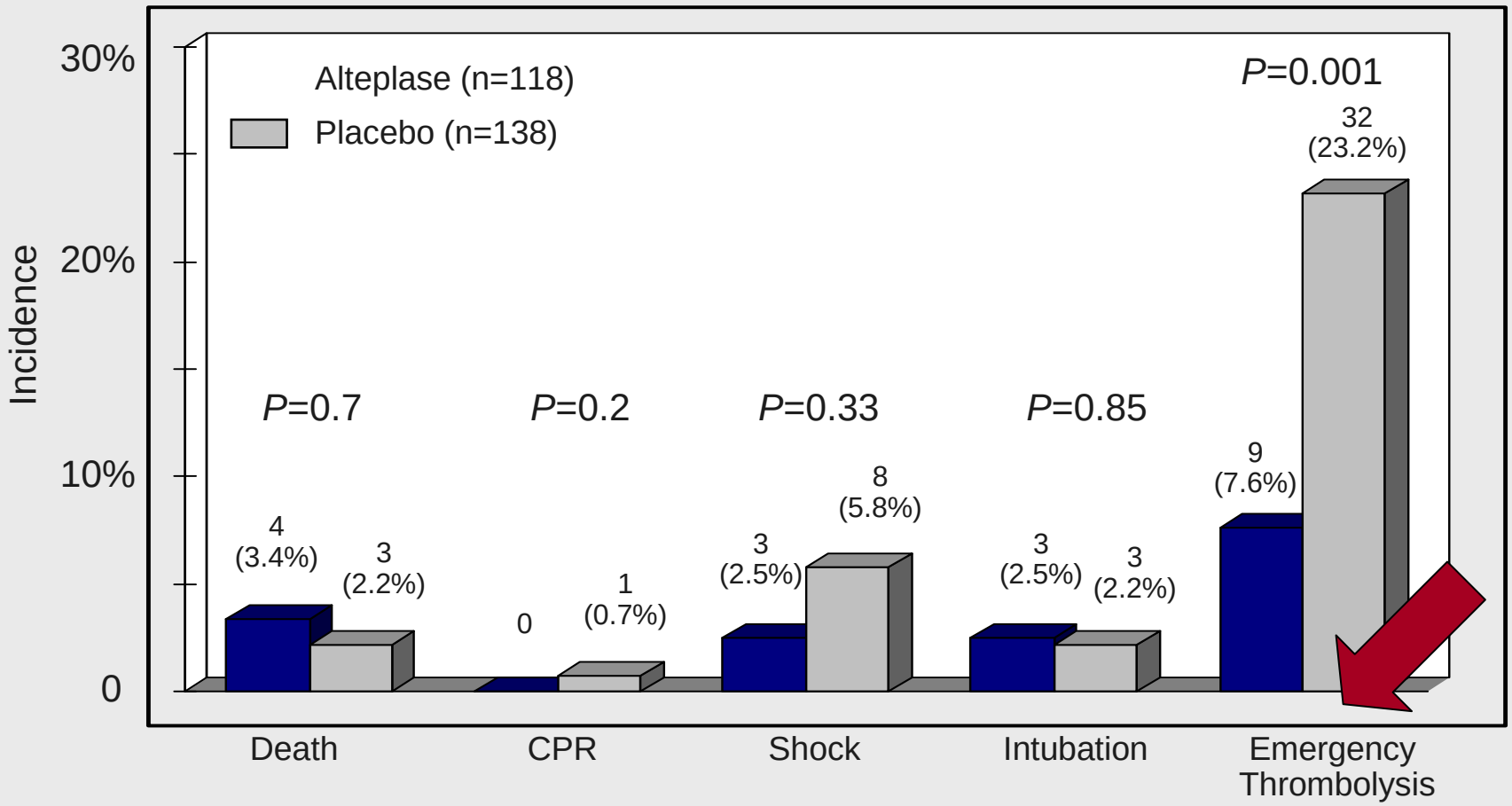
Parameter	Tests / Findings
RV Dysfunction +	RV dilatation, hypokinesis or pressure overload on echocardiography RV dilatation on spiral CT [BNP or NT-proBNP elevation] [↑ right heart pressures at RHC]
Myocardial injury	Cardiac troponin T or I positive [H-FABP] [Myoglobin]

Differences between PEITHO and previous trials (1)



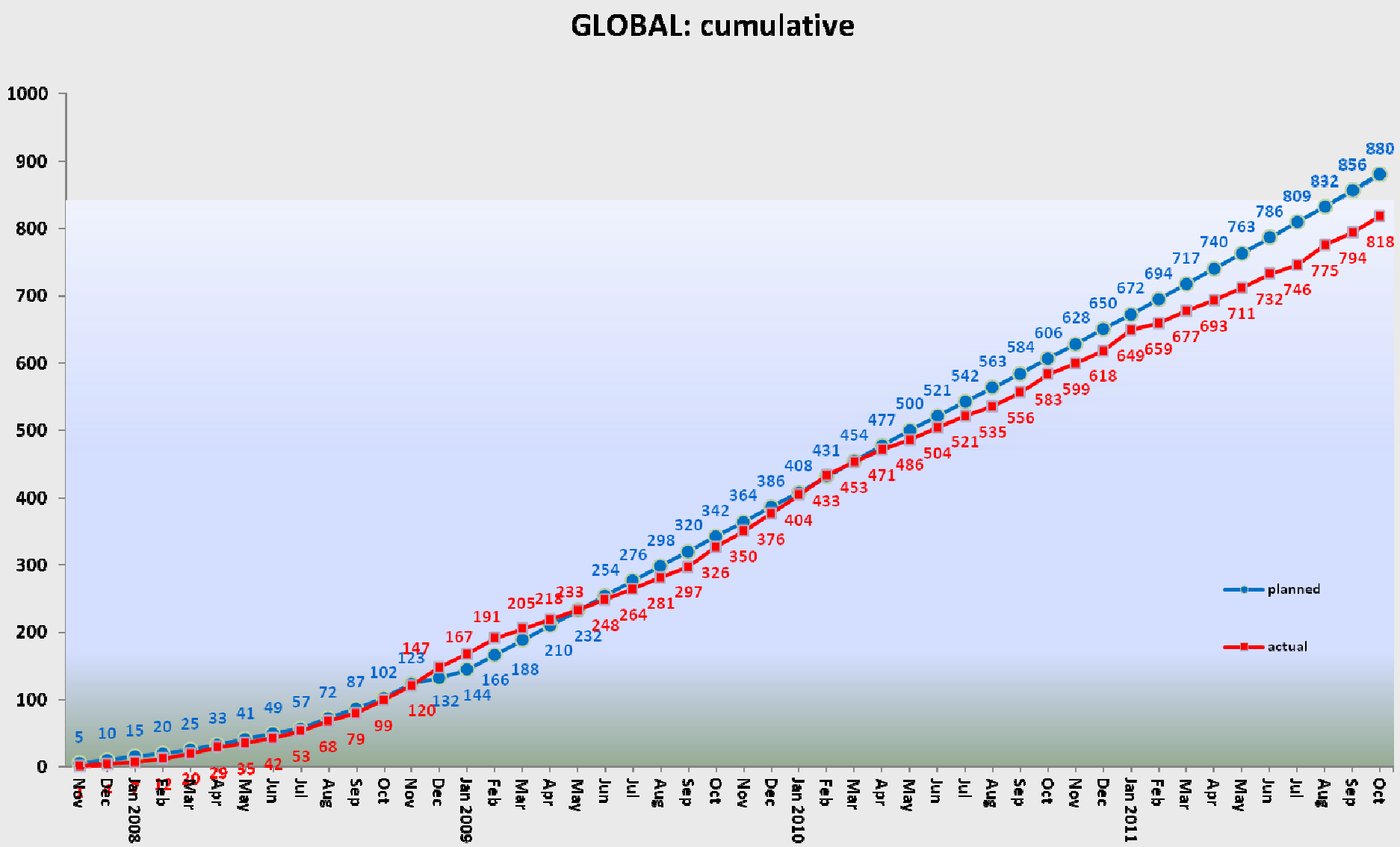
N Engl J Med 2002;347:1143

Differences between PEITHO and previous trials (2)



N Engl J Med 2002;347:1143

PEITHO Status (October 31, 2011)



Management of intermediate-risk PE: the future ??

PE-related early MORTALITY RISK		RISK MARKERS: CLINICAL (Shock or hypotension)	RISK MARKERS: RV Dysfunction	RISK MARKERS: Myocardial injury	Potential treatment implications
HIGH > 15%		+	(+)*	(+)*	Thrombolysis or Embolectomy
NON HIGH	Intermediate 3 - 15%	–	+	+	Thrombolysis?
			+	–	Hospital Admission
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

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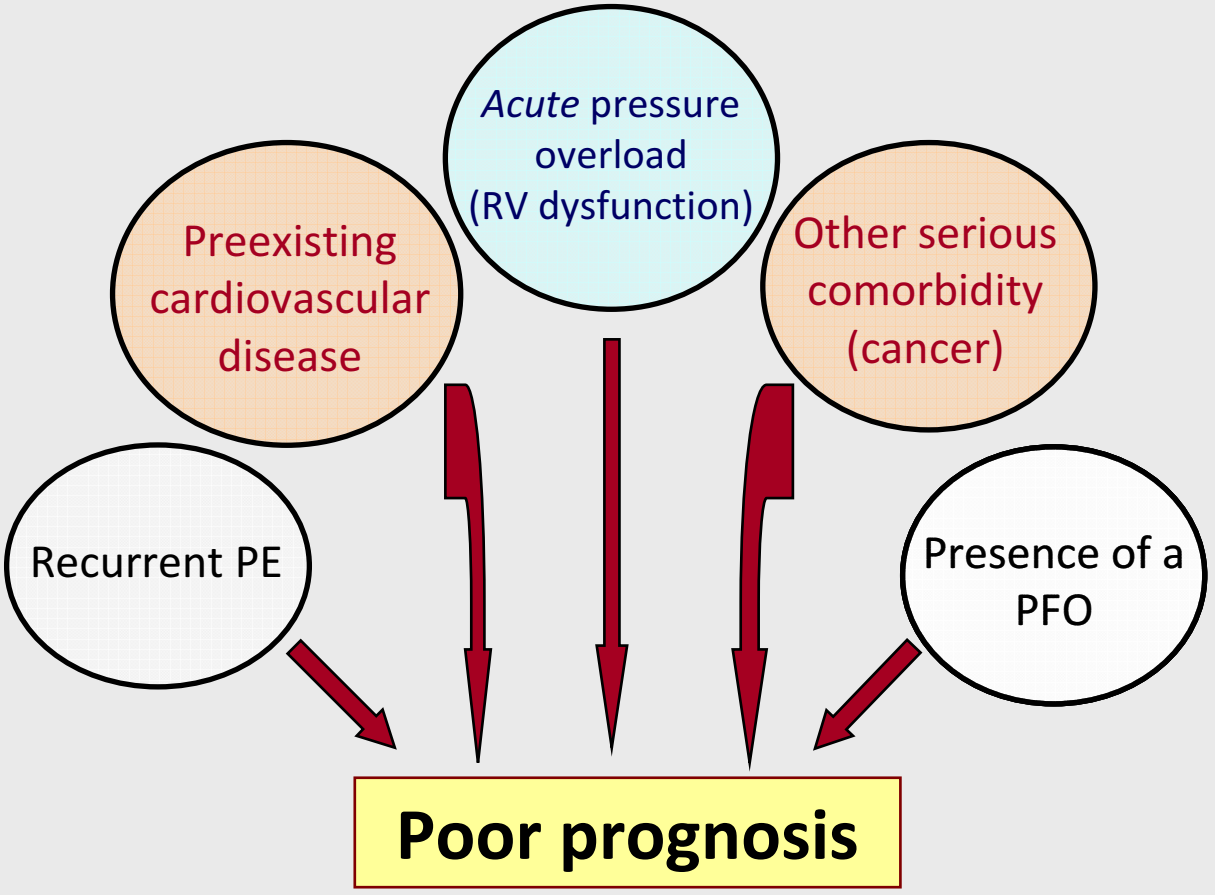
Which patients with **low-risk PE** are candidates for early discharge and home treatment ?

Management of acute PE

PE-related early MORTALITY RISK		RISK MARKERS			Potential treatment implications
		CLINICAL (Shock or hypotension)	RV Dysfunction	Myocardial injury	
HIGH > 15%		+	(+)*	(+)*	Thrombolysis or Embolectomy
NON HIGH	Inter mediate 3 - 15%	–	+	+	Hospital Admission
			+	–	
			–	+	
	Low <1%	–	–	– ?	Early discharge or home treatment

Determinants of an adverse early outcome



Who *could* be sent home ?

- No haemodynamic instability / shock
- No acute right heart failure
- No preexisting cardiac / respiratory failure
- No serious comorbidity (gastrointestinal tract, kidneys, blood; cancer)
- Low risk of early recurrence

- No other indications for hospitalisation (e.g. pain)
- Low bleeding risk with anticoagulants
- Treatment feasible, support at home well organised, patient compliance guaranteed

Home treatment of low-risk PE

Multicenter prospective management study: 352 pts screened
Primary endpoint: 10-day mortality related to PE or the treatment

Excluded (199/352 patients):

- Concomitant disease ➔ need for hospitalisation
- Renal failure
- Pain necessitating analgesics
- Active bleeding or high bleeding risk
- Poor compliance or support at home

- "Out of hospital treatment is safe in haemodynamically stable patients with PE with low (< 500 pg mL−1) NT-proBNP levels. Approximately 45% of patients with PE can be treated in an outpatient setting. Patients do not consider treatment as inconvenient and have no increase in anxiety scores".

MJ Agterof. J Thromb Haemost 2010;8:1235

Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial

	Outpatient group	Inpatient group	Difference in percentages ($\%_{outpatient}-\%_{inpatient}$)	Upper 95% CL for difference	p value*
Primary analysis outcomes within 90 days†					
Recurrent VTE	1 (0·6%)‡	0	0·6%	2·7%	0·011
Major bleeding	3 (1·8%)	0	1·8%	4·5%	0·086
Intramuscular	2 (1·2%)	0	1·2%	3·6%	0·031
Menometrorrhagia	1 (0·6%)	0	0·6%	2·7%	0·011
Overall mortality	1 (0·6%)§	1 (0·6%)¶	0%	2·1%	0·005

D Aujesky. Lancet 2011; 378: 41–48

D Jiménez. Arch Intern Med 2010;170:1383

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

Help from clinical risk scores

- No haemodynamic instability / shock
- No acute right heart failure
- No preexisting cardiac / respiratory failure
- No serious comorbidity (gastrointestinal tract, kidneys, blood; cancer)
- Low risk of early recurrence

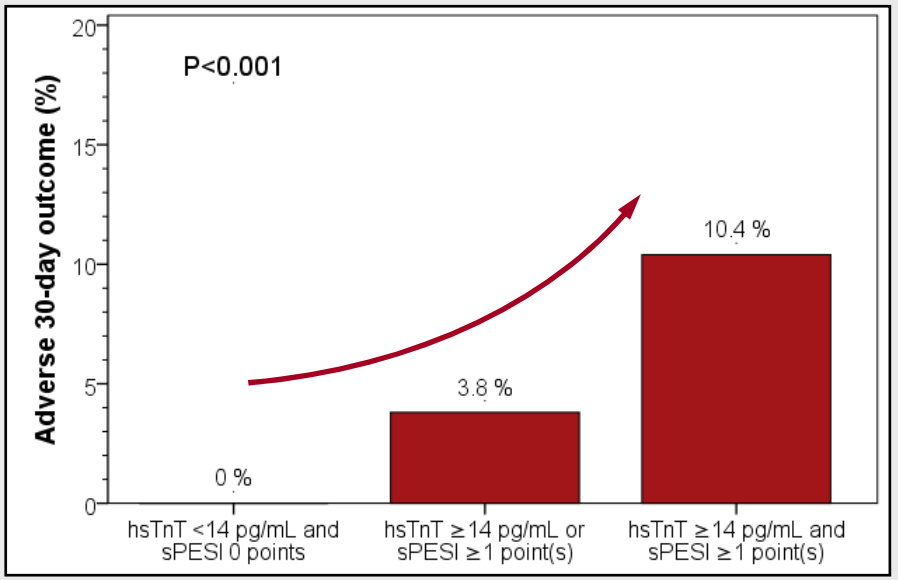
- No other indications for hospitalisation (e.g. pain)
- Low bleeding risk with anticoagulants
- Treatment feasible, support at home well organised, patient compliance guaranteed

Progress with the high sensitivity troponin T assay

Adverse 30-day outcome	AUC	95% CI	Sens.	Spec.	PPV	NPV
hsTnT ≥14 pg/ml	0.73	0.65-0.82	0.87	0.42	0.09	0.98
sPESI ≥1 point(s)	0.67	0.59-0.75	0.94	0.40	0.09	0.99
hsTnT ≥14 pg/ml *and* sPESI ≥1 point(s)	**0.69**	**0.60-0.77**	**1.00**	**0.26**	**0.08**	**1.00**

Of 214 patients (41%) with **hsTnT <14 pg/ml**, four (1.9%) had an adverse outcome (none PE-related).

Of 198 patients (38%) with **sPESI of 0**, two (1.0%) had an adverse outcome; none of them died due to the initial PE event.



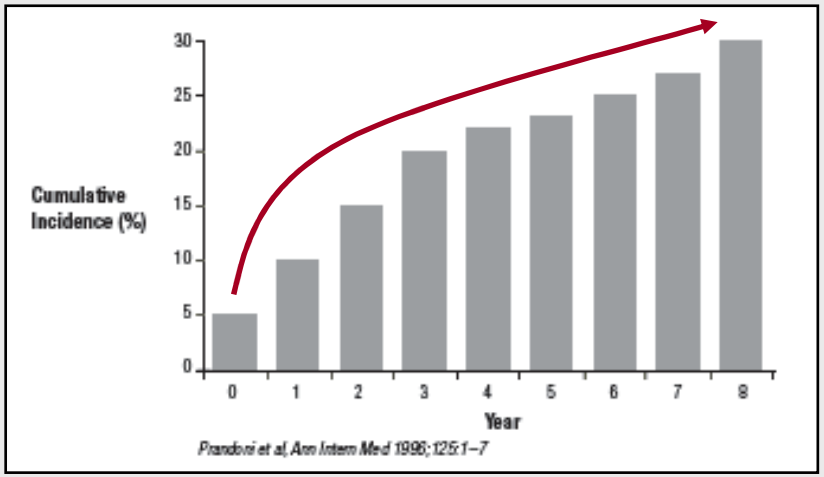
M Lankeit et al. Circulation 2011; Epub ahead of print

5

Progress in **anticoagulation** and secondary VTE prophylaxis

Rationale for long-term secondary prophylaxis

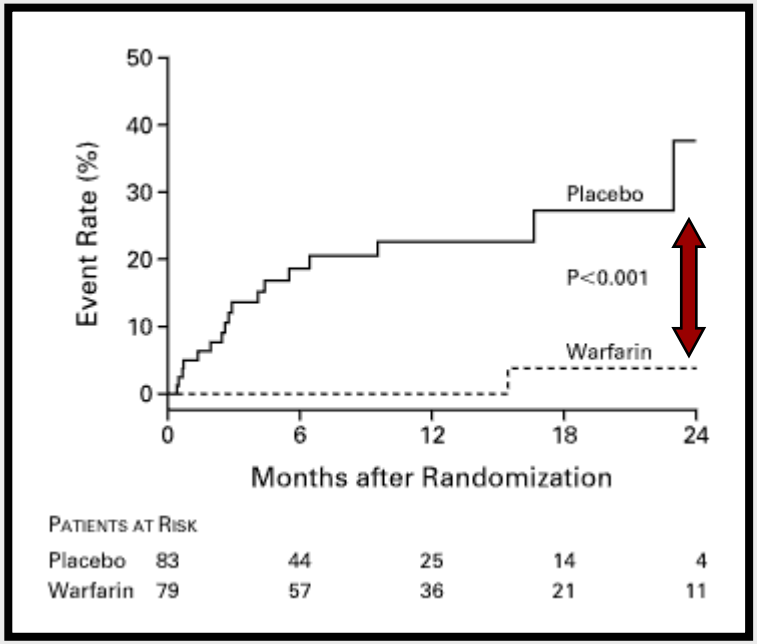
	Cumulative Incidence		Survival rate
	Recurrent DVT	Post thrombotic syndrome	
2 years	17%	25%	80%
5 years	24%	30%	74%
8 years	30%	30%	69%



Prandoni P, et al. Ann Intern Med 1996;125:1-7
Prandoni P, et al. Haematologica 1997; 82: 423-428

Long-term secondary prophylaxis

Highly effective, BUT…



Recurrence reduced by 90%

***Major bleeding*: 3,8% / year**

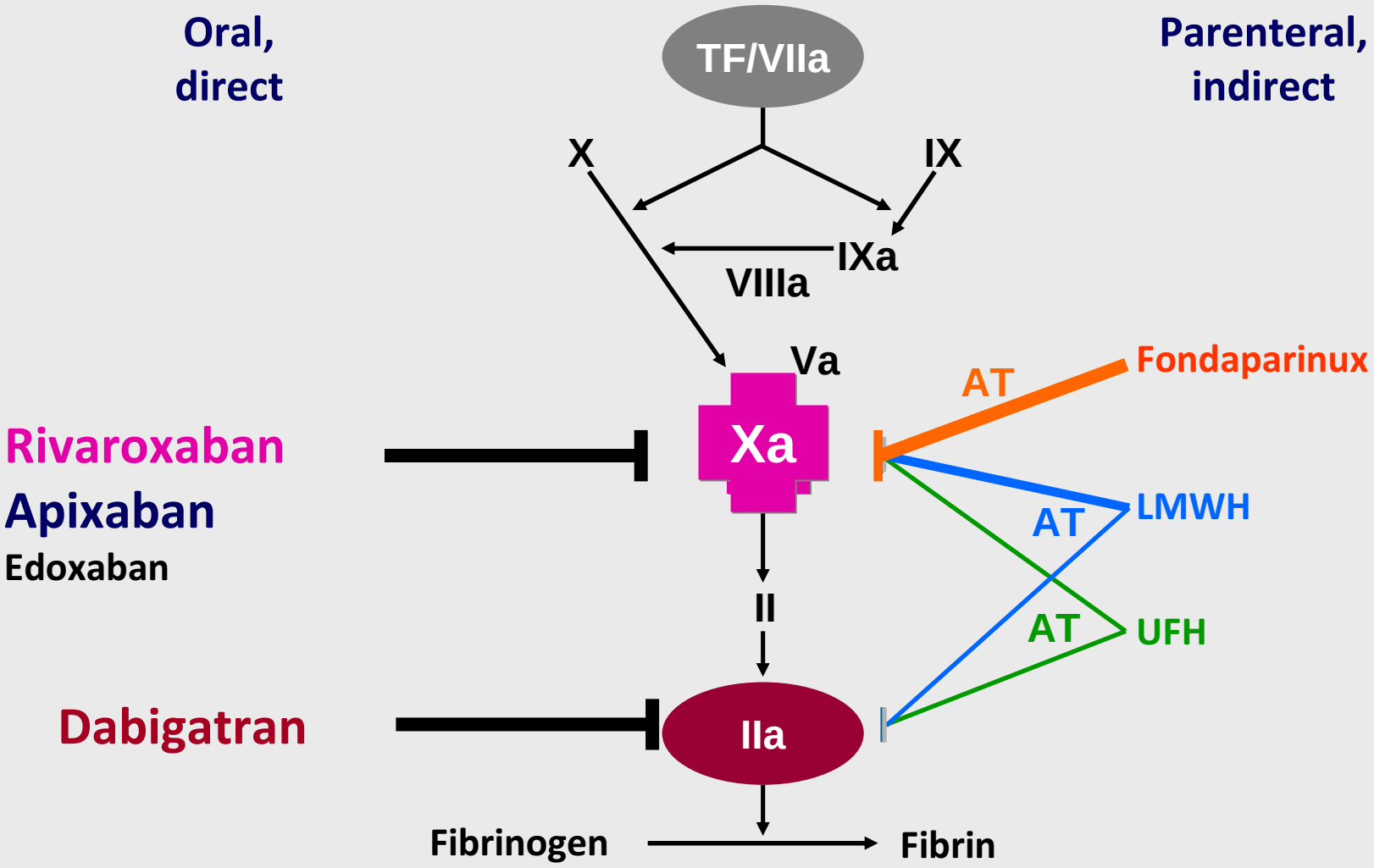
Study discontinued after 2 years

C Kearon. N Engl J Med 1999;340:910-907

Duration of OAC after VTE: a compromise

Recommendation		
First event, transient risk factor: **VKA for 3 months**	I	A
„Idiopathic“/“unprovoked“ event: **VKA for at least 3 months**	I	A
Idiopathic event, low bleeding risk, stable anticoagulation: consider long-term treatment	IIb	B
In PE with cancer, **LMWH for 3-6 months**;	IIa	B
then long-term therapy with VKA or LMWH	I	C

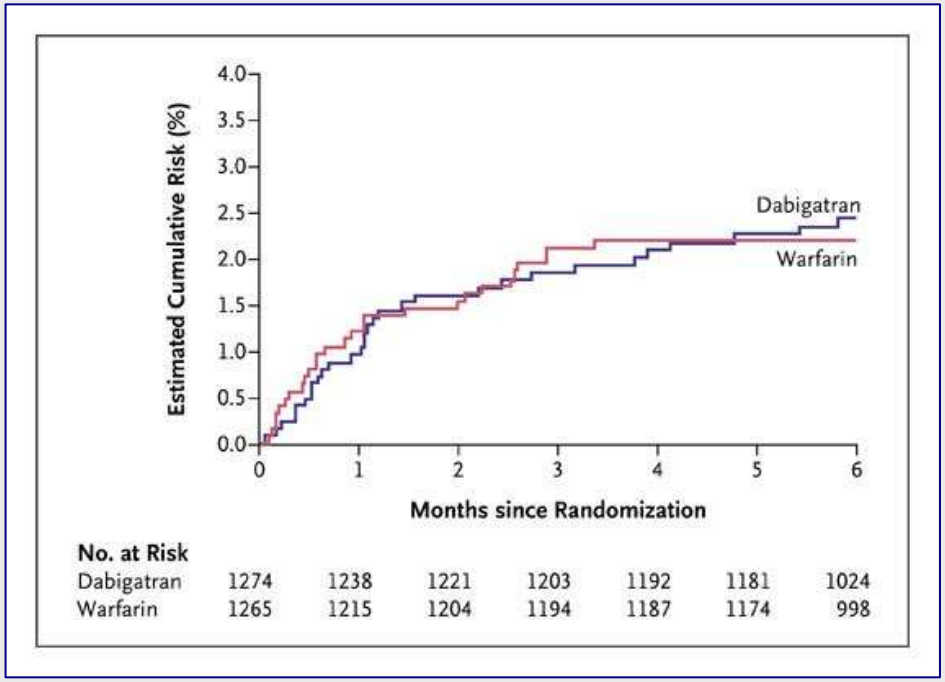
Established and new anticoagulants



Dabigatran after acute DVT/PE: RECOVER

1724 patients, symptomatic DVT or PE

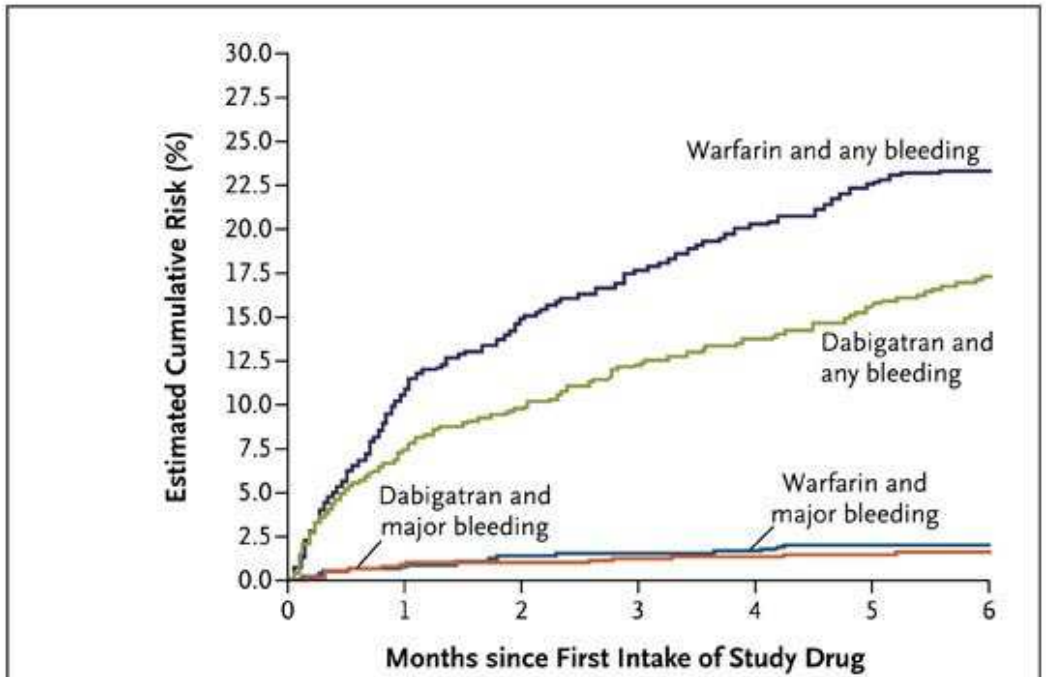
- **Initial parenteral anticoagulation (LMWH) for 9 (8-11) days**
- Double-blind: dabigatran 150 mg x 2 /d vs. warfarin @ INR 2.0-3.0
- FU 6 months



Events	Dabigatran (n=1,274)		Warfarin (n=1,265)		Hazard ratios and confidence intervals
Recurrent VTE or related death*	30	**(2.4%)**	27	**(2.1%)**	Risk difference = 0.4%; 95% CI –0.8 to 1.5 *p*<0.001 for **prespecified non-inferiority**

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

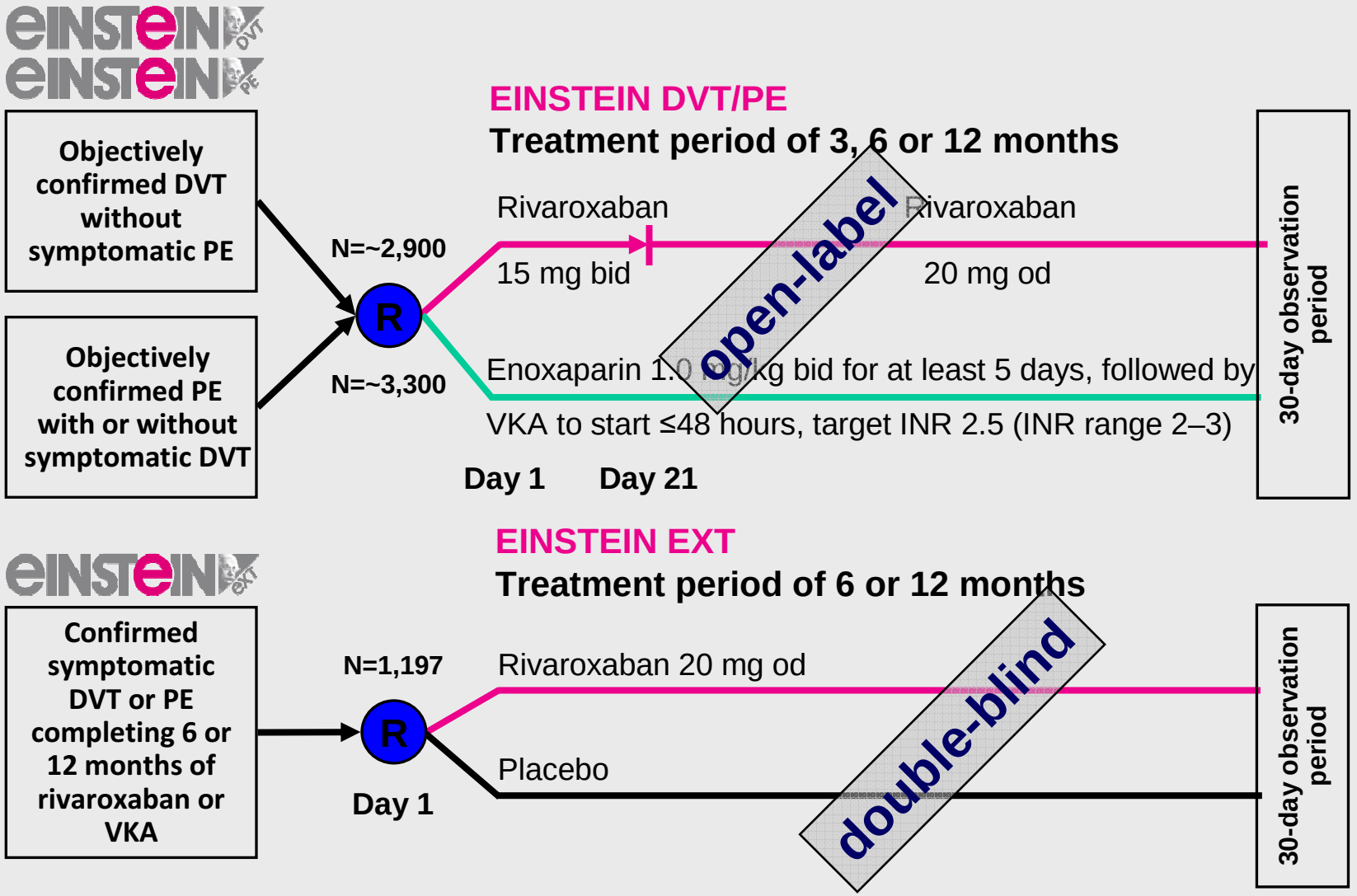
Dabigatran after acute DVT/PE: RECOVER



No. at Risk							
Dabigatran and major bleeding	1273	1194	1153	1124	1105	1080	884
Warfarin and major bleeding	1266	1178	1146	1128	1110	1093	859
Dabigatran and any bleeding	1273	1117	1055	1002	971	931	747
Warfarin and any bleeding	1266	1064	993	950	909	870	692

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

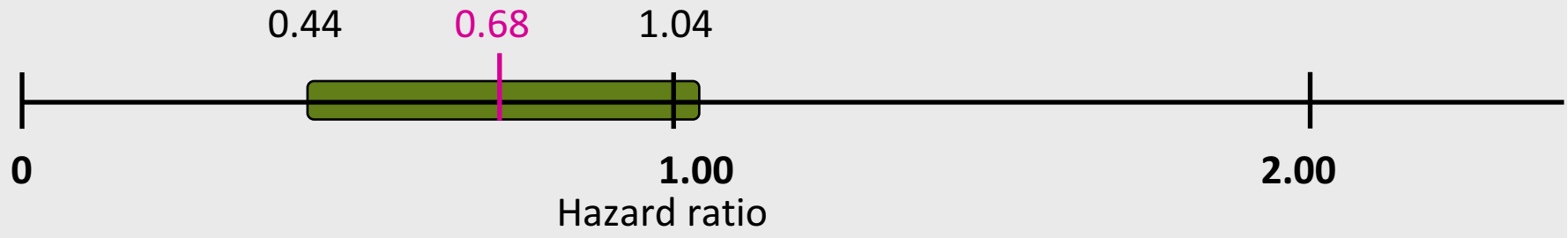
Rivaroxaban after VTE: EINSTEIN



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

EINSTEIN: Primary efficacy outcome analysis

	Rivaroxaban (n=1,731)		Enoxaparin/VKA (n=1,718)	
First symptomatic recurrent VTE	**36**	**(2.1%)**	**51**	**(3.0%)**
Recurrent DVT	14	(0.8%)	28	(1.6%)
Recurrent DVT + PE	1	(<0.1%)	0	(0)
Non-fatal PE	20	(1.2%)	18	(1.0%)
Fatal PE/unexplained death (PE could not be ruled out)	4	(0.2%)	6	(0.3%)



Rivaroxaban superior | **Rivaroxaban non-inferior** | **Rivaroxaban inferior**

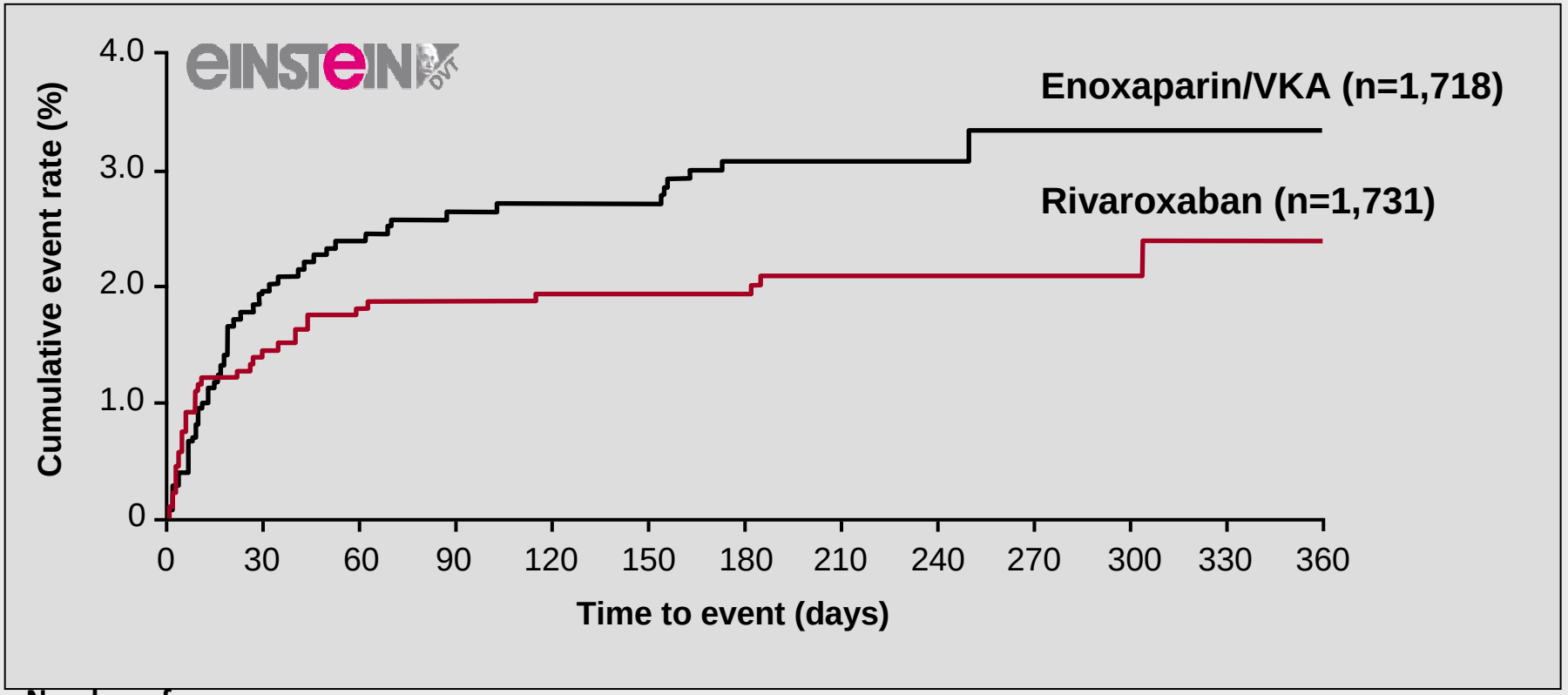
p=0.076 for superiority (two-sided)

p<0.0001 for non-inferiority (one-sided)

ITT population

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

Primary efficacy outcome: time to first event



Number of subjects at risk

Rivaroxaban	1,731	1,668	1,648	1,621	1,424	1,412	1,220	400	369	363	345	309	266
Enox/VKA	1,718	1,616	1,581	1,553	1,368	1,358	1,186	380	362	337	325	297	264

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

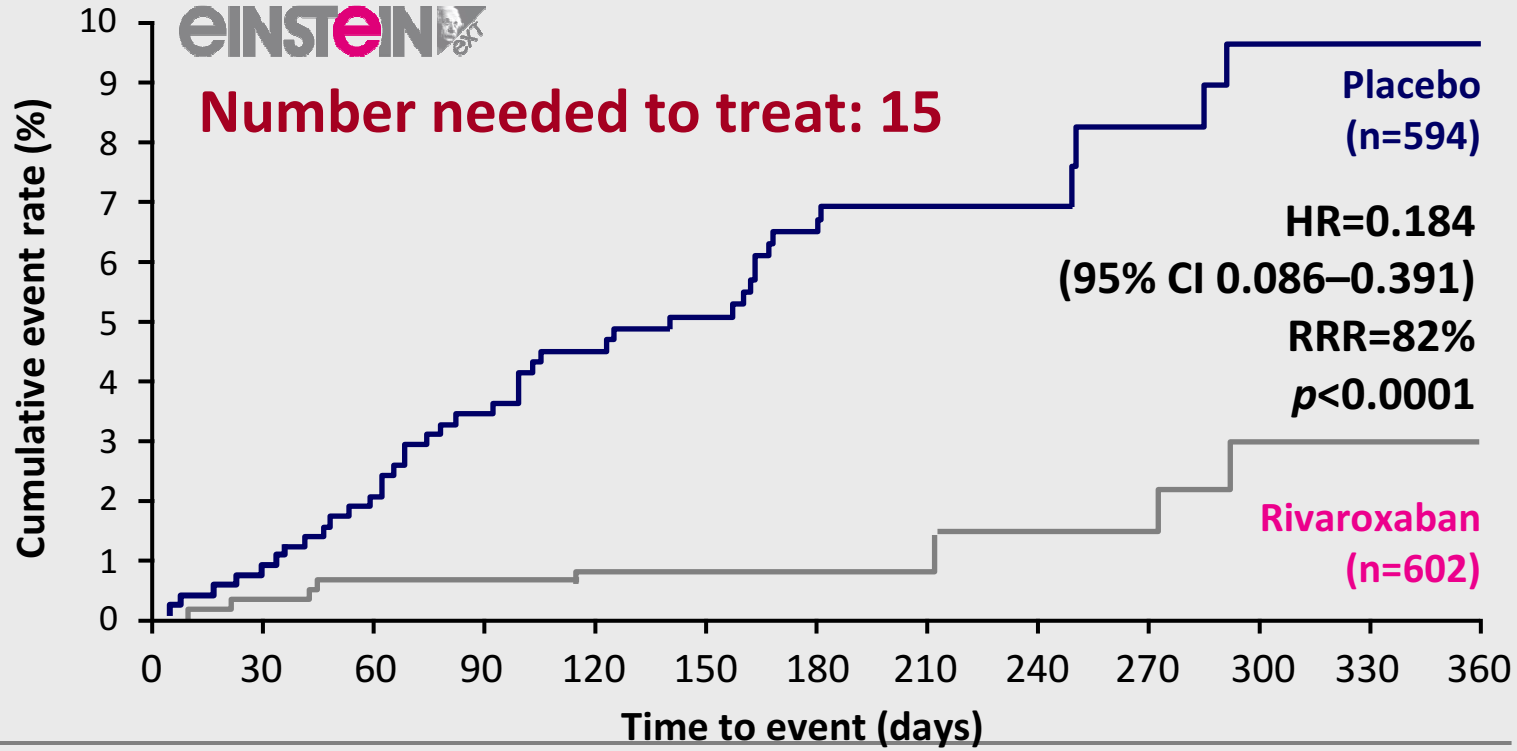
Primary safety outcome analysis

EINSTEIN DVT	Rivaroxaban (n=1,718)		Enox/VKA (n=1,711)		HR (95% CI)
	n	(%)	n	(%)	*p* value
First major or clinically relevant non-major bleeding	**139**	**(8.1)**	**138**	**(8.1)**	**0.97 (0.76–1.22) *p*=0.77**
Major bleeding	**14**	**(0.8)**	**20**	**(1.2)**	
Contributing to death	1	(<0.1)	5	(0.3)	
In a critical site	3	(0.2)	3	(0.2)	
Associated with fall in Hb ≥2 g/dl and/or transfusion of ≥2 units	10	(0.6)	12	(0.7)	
Clinically relevant non-major bleeding	126	(7.3)	119	(7.0)	

Safety population

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

Efficacy end points (time to first event)



Number of subjects at risk													
Rivaroxaban	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	554	521	467	444	164	138	133	110	93	85

ITT population; CI, confidence interval; HR, hazard ratio; RRR, relative risk reduction

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

Long-term treatment - Safety end points

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

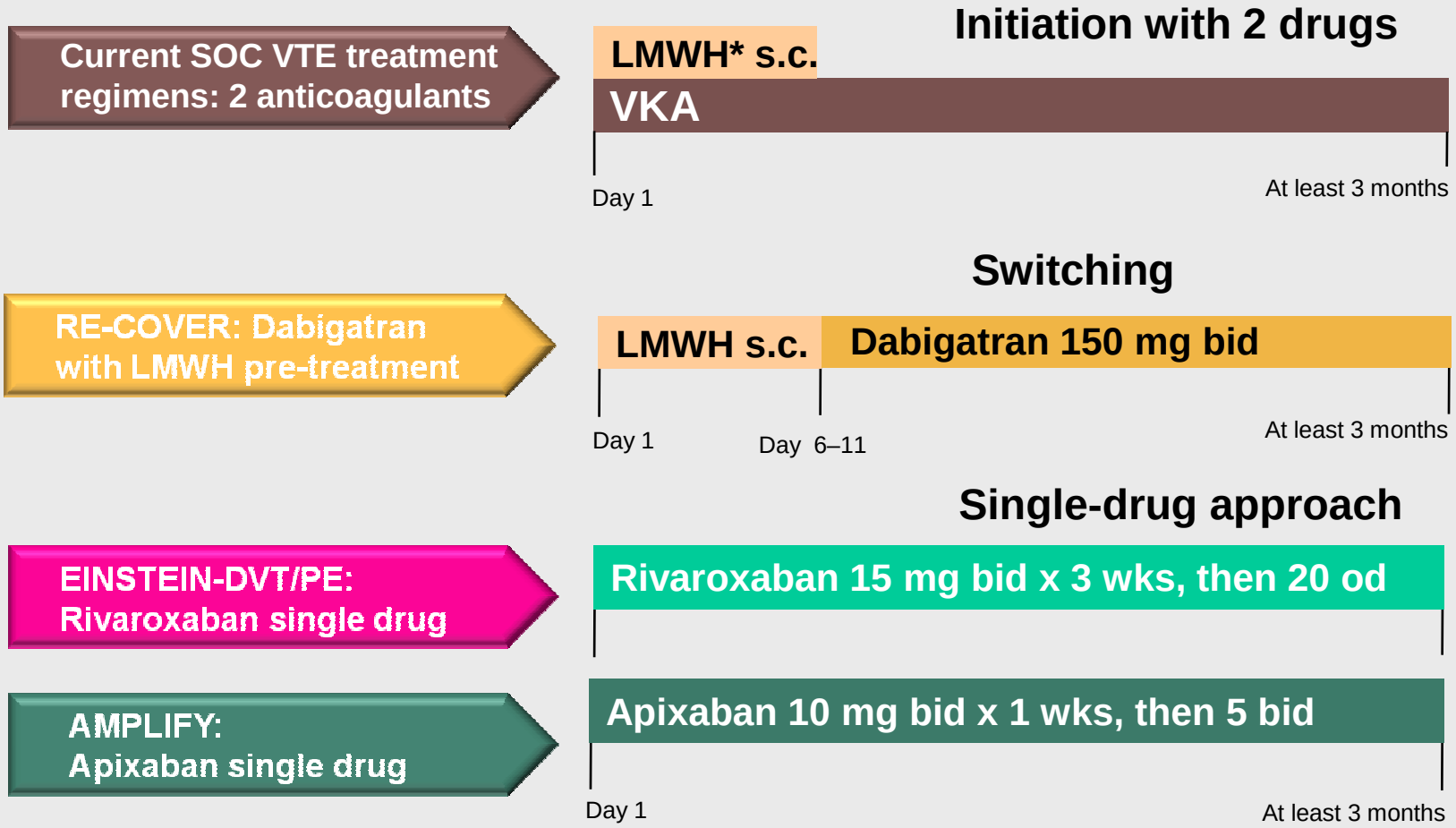
- **Number needed to harm: approximately 139**

*p=0.11

Safety population

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

Evolving anticoagulation concepts for VTE



*Or UFH or fondaparinux

Summary and Conclusions

- Consensus exists regarding the need for thrombolysis (or surgery/intervention) in **high-risk (massive)** PE.
- Most normotensive patients with (non-high-risk) PE can be treated with low molecular-weight heparins.
- The optimal definition and management of **intermediate-risk** PE remain controversial; PEITHO (LPO expected early 2012) hopes to find out whether patients with RV dysfunction and myocardial injury need early thrombolysis.
- Ongoing studies may identify candidates for early discharge and home treatment among patients with **low-risk** PE.
- **New oral anticoagulants** may soon radically change VTE prophylaxis and treatment.

Overview: Characteristics of the new OAC

Parameter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Oral bioavailability	~6.5%	~80%	~66%	~50%
Prodrug	Yes	No	No	No
Half-life (h)	**12–14**	**5–13**	**8–15**	**9–11**
t_{max} (h)	**1.5**	**2–4**	**1.5–3.5**	**1.5**
Renal clearance	**80%**	**33%**	**25%**	**35%**
Potential drug interactions	Rifampicin, quinidine, amiodarone, P-gp inhibitors	CYP3A4, P-gp inhibitors	CYP3A4 inhibitors	CYP3A4, P--gp inhibitors

CYP3A4, cytochrome P450 3A4; P-gp, P-glycoprotein; t_{max}, time to reach maximum plasma concentration

Eriksson et al, 2011; Mavrakanas et al, 2011; Kreutz, 2011