Management of Venous Thromboembolism

State of the Art 2011

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Venous Thromboembolism: Epidemiological Relevance

Author / Country	Incidence per year
E Oger (France), *Thromb Haemost* 2000	**1.83/1,000 population**
MD Silverstein (MN, USA), *Arch Intern Med* 1998	**1.22/1,000 population**
AW Tsai (USA), *Arch Intern Med* 2002	**1.45/1,000 population**

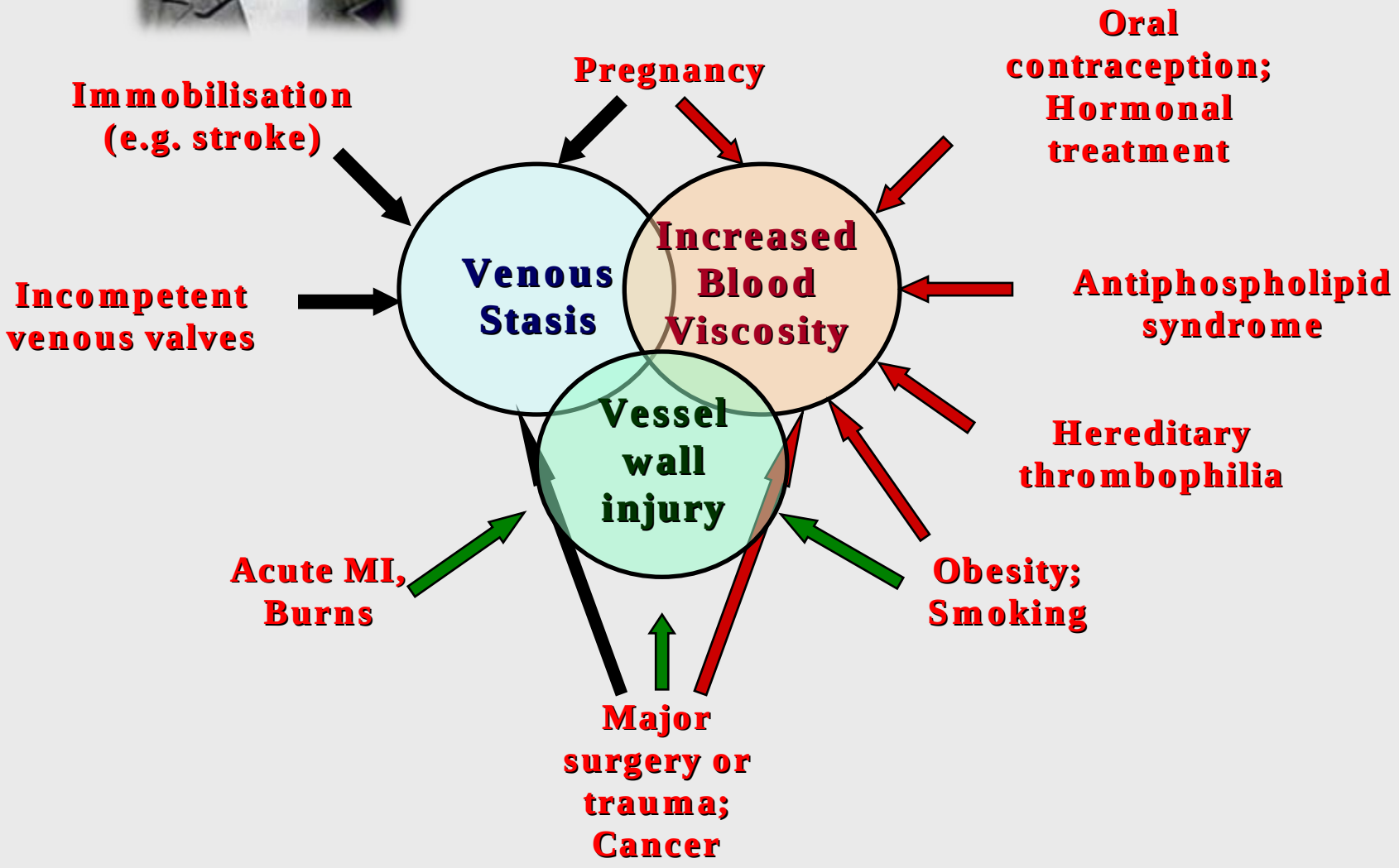
European Union (population approx. 400 million):

- **approx. 500,000 *confirmed* VTE cases p.a.; 300,000 DVT**
- **plus 900,000 *missed* (undiagnosed) VTE cases p.a.**
- **total of 1.5 million VTE cases p.a.; 1.000,000 DVT cases**

Pathogenesis of Deep Venous Thrombosis: Predisposing Factors

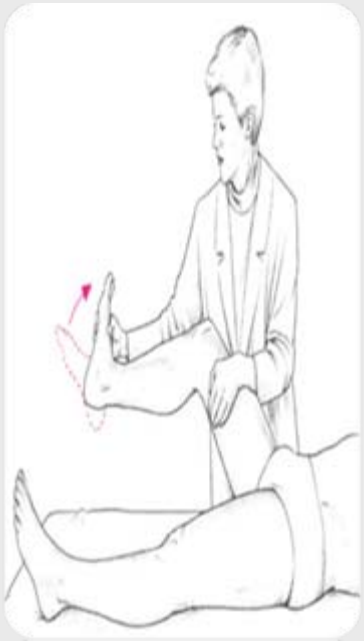
Acquired	Genetic / Hereditary	Other*
Age (80x)	Antithrombin deficiency	Hyperhomocysteinaemia
Previous DVT or PE	Protein C deficiency	High F VIII levels
Surgery / Trauma / Air travel	Protein S deficiency	High F XI levels
Obesity, cancer (10-15%)	Factor V_{Leiden}	High F IX levels
Hormonal treatment	Factor II G20210A	High F VII levels
Pregnancy / Lactation		
Indwelling central venous catheter		
Antiphospholipid syndrome		
Heparin-induced thrombocytopaenia		* Possible genetic regulation

Virchow`s Triad



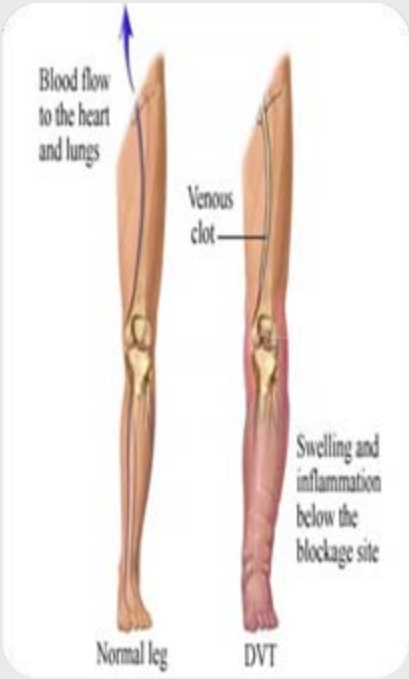
Clinical presentation

50% of patients who have VTE do not present with any symptoms



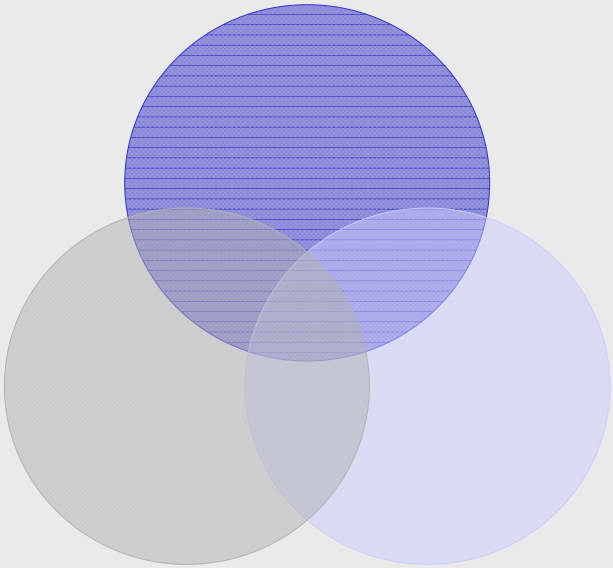
Classic symptoms associated with DVT include :

- **leg swelling,**
- **pain upon palpation in the calf or thigh,**
- **Homans sign (calf pain with dorsiflexion of the foot)**



Objective testing for DVT

Pre-test Clinical Probability



Test Selection

Test Interpretation

"Sensitivity of certain diagnostic tests is affected by the location of the thrombus"

Risk of suspected DVT

Before laboratory examinations....

Table 1 Clinical model for predicting pretest probability for deep vein thrombosis

- Risk factor category
  - Major
    - Active cancer*
    - Paralysis, paresis, or recent immobilization of lower extremities
    - Bedridden >3 days and/or major surgery within previous 4 wk
    - Localized tenderness of deep venous system†
    - Swelling of thigh and calf confirmed by measurement
    - Calf swelling showing >3 cm difference vs. nonsymptomatic calf‡
    - Strong family history of DVT (≥2 first-degree relatives with history of DVT)
  - Minor
    - History of trauma to affected leg (within ≥60 days)
    - Pitting edema in symptomatic leg
    - Dilated nonvaricose veins in symptomatic leg
    - Hospitalization within previous 6 mo
- Stratification (clinical probability)
  - High
    - No alternative diagnosis *plus*
      - ≥3 major risk factors *or*
      - ≥2 major and ≥2 minor risk factors
  - Moderate
    - All combinations not specifically designated high or low
  - Low
    - No alternative diagnosis *plus*
      - 1 major and ≥1 minor risk factor *or*
      - ≥2 minor risk factors
    - Alternative diagnosis *plus*
      - 1 major and ≥2 minor risk factors *or*
      - ≥3 minor risk factors

Risk of suspected DVT

Table 1. Wells Prediction Rule for Deep Venous Thrombosis: Clinical Evaluation Table for Predicting Pretest Probability of Deep Vein Thrombosis

Clinical Characteristic	Score
Active cancer (treatment ongoing, within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis at least as likely as deep venous thrombosis	-2

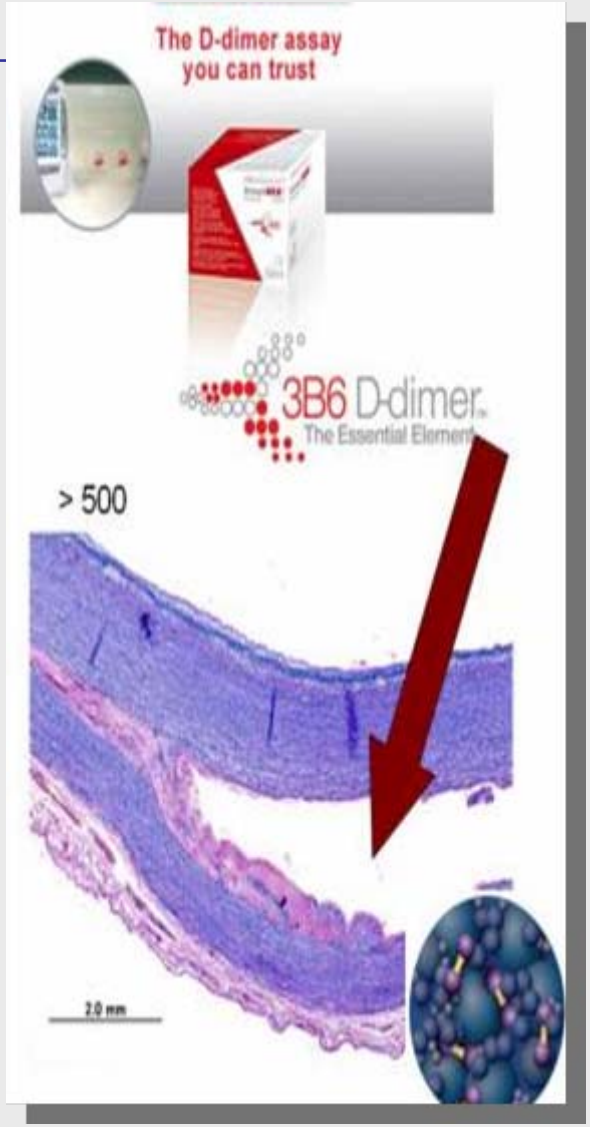
Note: A score of 3 or higher indicates a high probability of deep vein thrombosis; 1 or 2, a moderate probability; and 0 or lower, a low probability. In patients with symptoms in both legs, the more symptomatic leg is used.

D-dimers

Heim et al, meta-analysis :included 23 studies

Sensitivity of the assay was less than 90%,

Insufficiently sensitive to "rule out" a diagnosis of DVT



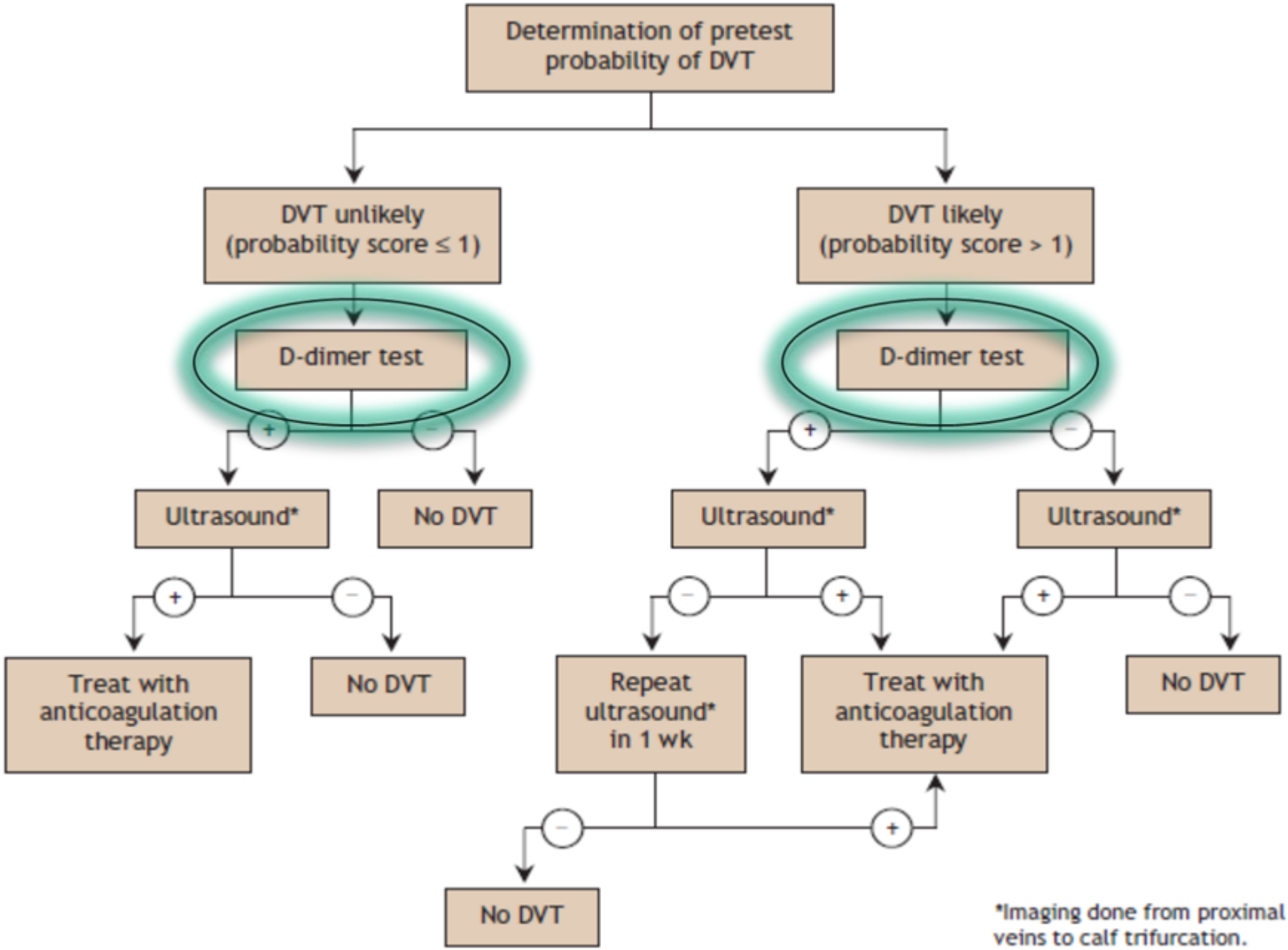
The performance of the assays was affected by

- the prevalence of DVT in the population,
- the choice of reference test (best for venography)
- location of thrombus (best above the knee)

D-dimers

Stein et al, Meta-analysis : 78 studies

Sensitivities of 95% (95% CI, 91%-9%) and 96% (95% CI, 90%-100%)


Determination of pretest probability of DVT
DVT unlikely (probability score ≤ 1)
DVT likely (probability score > 1)
D-dimer test
D-dimer test
+
−
+
−
Ultrasound*
No DVT
Ultrasound*
Ultrasound*
+
−
−
+
+
−
Treat with anticoagulation therapy
No DVT
Repeat ultrasound* in 1 wk
Treat with anticoagulation therapy
No DVT
−
+
No DVT
*Imaging done from proximal veins to calf trifurcation.

Criticism of the algorithm

1. Pregnant women were not included in these studies.

2... the utility of the D-dimer test in patients admitted to hospital who often have other comorbidities (e.g., infection, postoperative symptoms) is lower since the D-dimer assay rarely yields negative results.

3. No D-dimer assay should be used to exclude DVT in patients who have high pretest probability.

4. Finally, if DVT is not a diagnostic possibility, a D-dimer test should not be done.

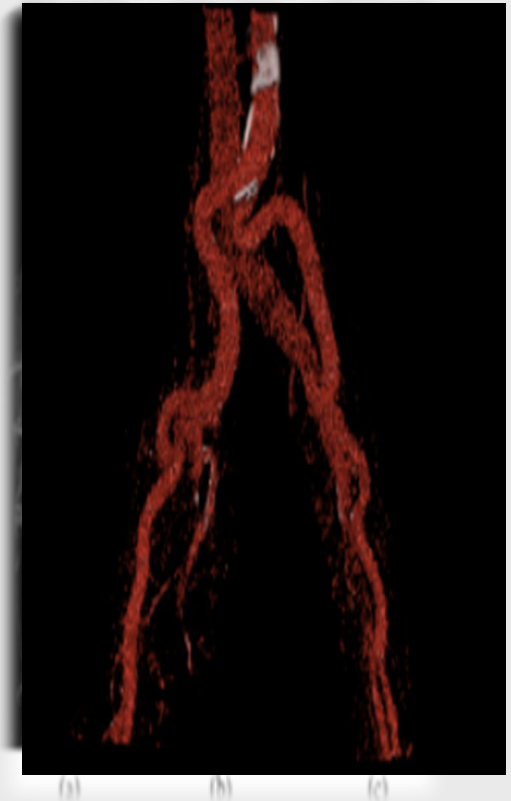
Imaging modalities for DVT

Contrast venography imaging

Although it remains the "gold standard" for confirmatory diagnosis of DVT (100% specific and 100% sensitive)

Complications :from contrast imaging / invasive modality

Contraindicated : in patients with renal insufficiency and lack of accuracy in recurring cases of suspected DVT



Imaging modalities for DVT

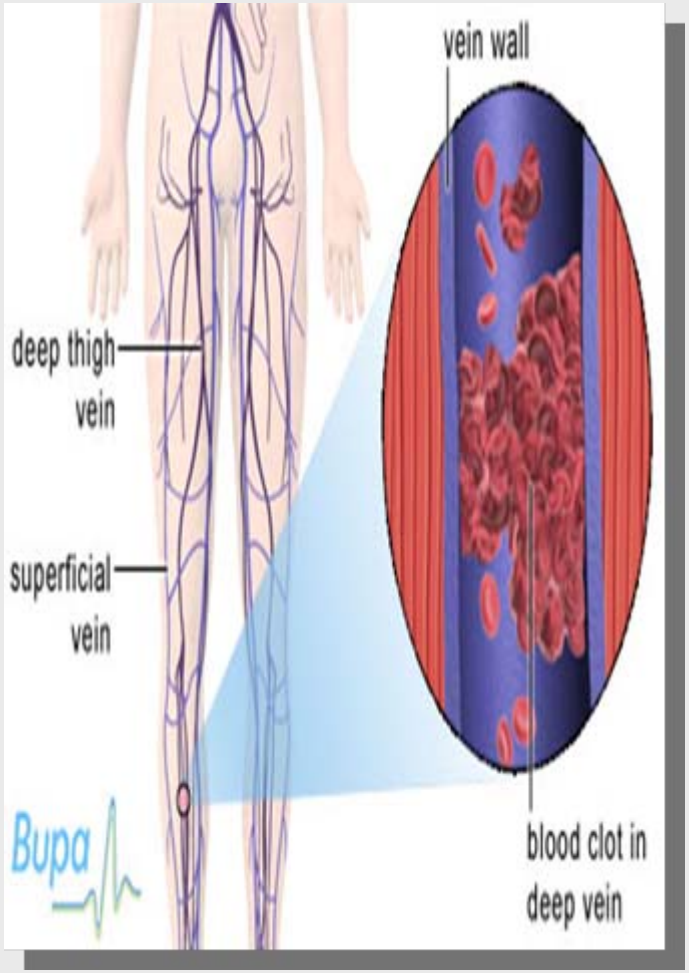
Compression ultrasound / Doppler – Triplex tracings

Indications : acute symptomatic proximal DVT, as well as DVT of the upper extremities

- The demonstration of venous noncompressibility is the *major diagnostic* criterion for venous thrombosis.

- Is not specific or sensitive for the detection of DVT in patients with *asymptomatic proximal* DVT or in patients *with symptomatic or asymptomatic DVT of the calf,*

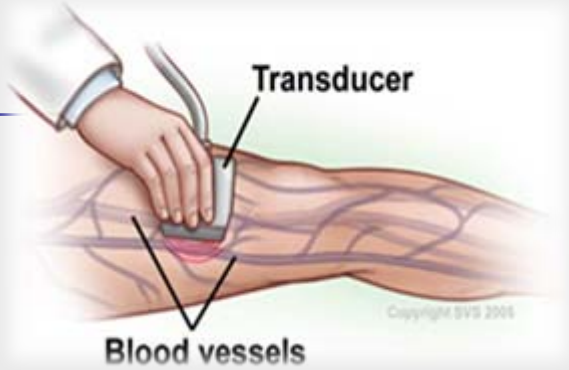
- It demonstrates limited accuracy in cases of chronic DVT, in patients who are obese or who have edema

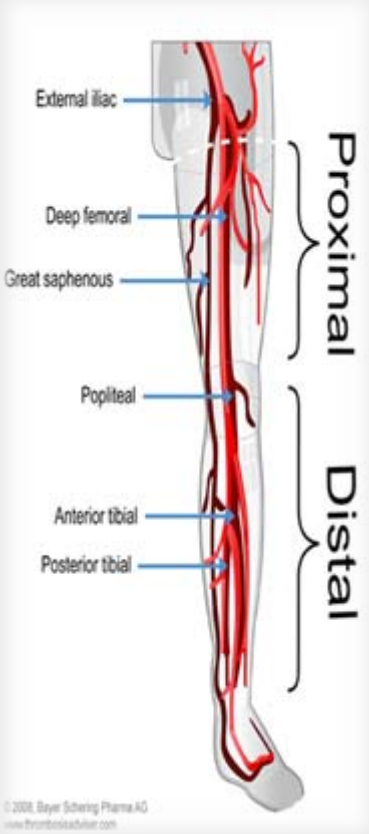


Imaging modalities for DVT

Ultrasound: sensitivity/specificity

For the diagnosis of *symptomatic thrombosis in the proximal veins of the lower extremity :*
sensitivities of 89% to 96% and specificities of 94% to 99%





For detection of thrombi in *proximal veins in asymptomatic patients :*
high specificity was maintained, but sensitivity was lower.

For *calf vein (distal) thrombosis in symptomatic patients :*
sensitivity of 73%-93% and specificity of 75%- 99%.

For asymptomatic patients, sensitivities for detecting calf vein thrombosis were consistently around 50%

Imaging modalities for DVT

Ultrasound – Recurrent thrombosis

- Diagnosing DVT in patients who have previously had DVT in the symptomatic leg (recurrent DVT) is still a subject of debate.

- The biggest concern with this patient population is false-positive ultrasound results.

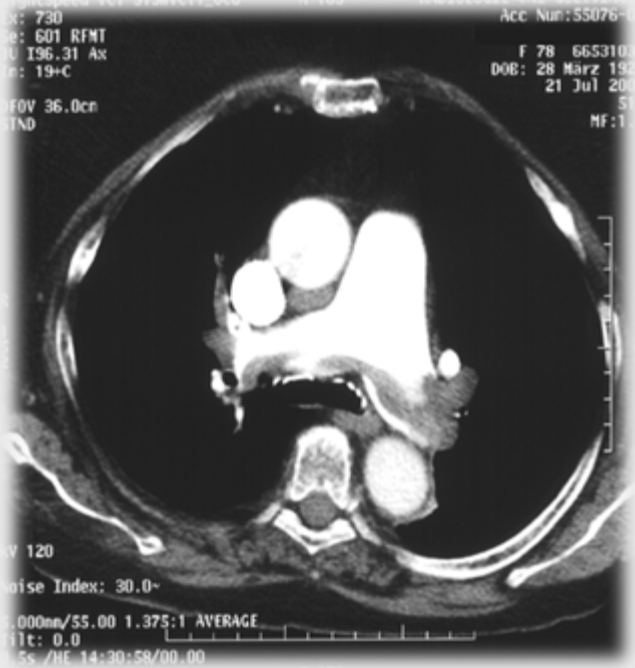
- It is helpful to recognize that *acute DVT* is usually occlusive, not echogenic, and it tends to be continuous.

« If the US reveals thrombosis that is echogenic, nonocclusive or discontinuous, then chronic DVT should be considered»

Management of DVT

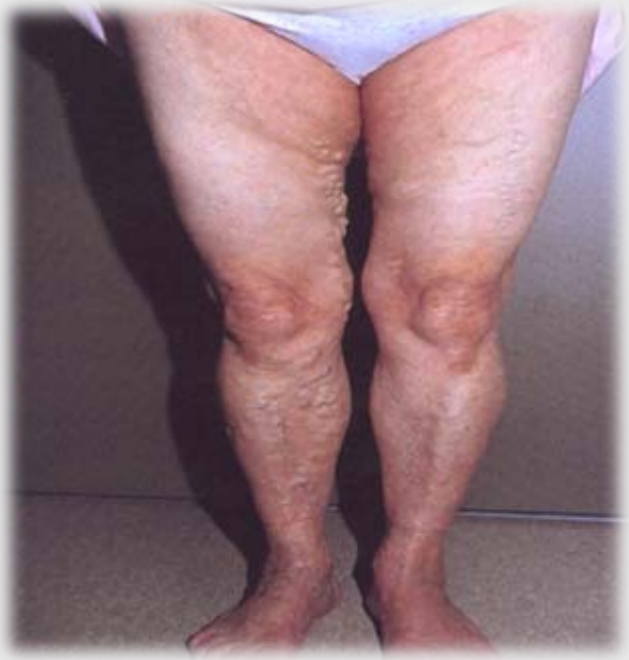
Aims

Prevent VTE
(acute and recurrent PE)



50% of pts with DVT

Prevent post-thrombotic sdr



25% of pts within 5 yrs

Treatment of DVT (and Venous Thromboembolism)

- **Initial heparin anticoagulation**
- **Thrombolysis**
- **Supportive measures**
- **Oral anticoagulation with VKA**
- **Novel oral anticoagulants**

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
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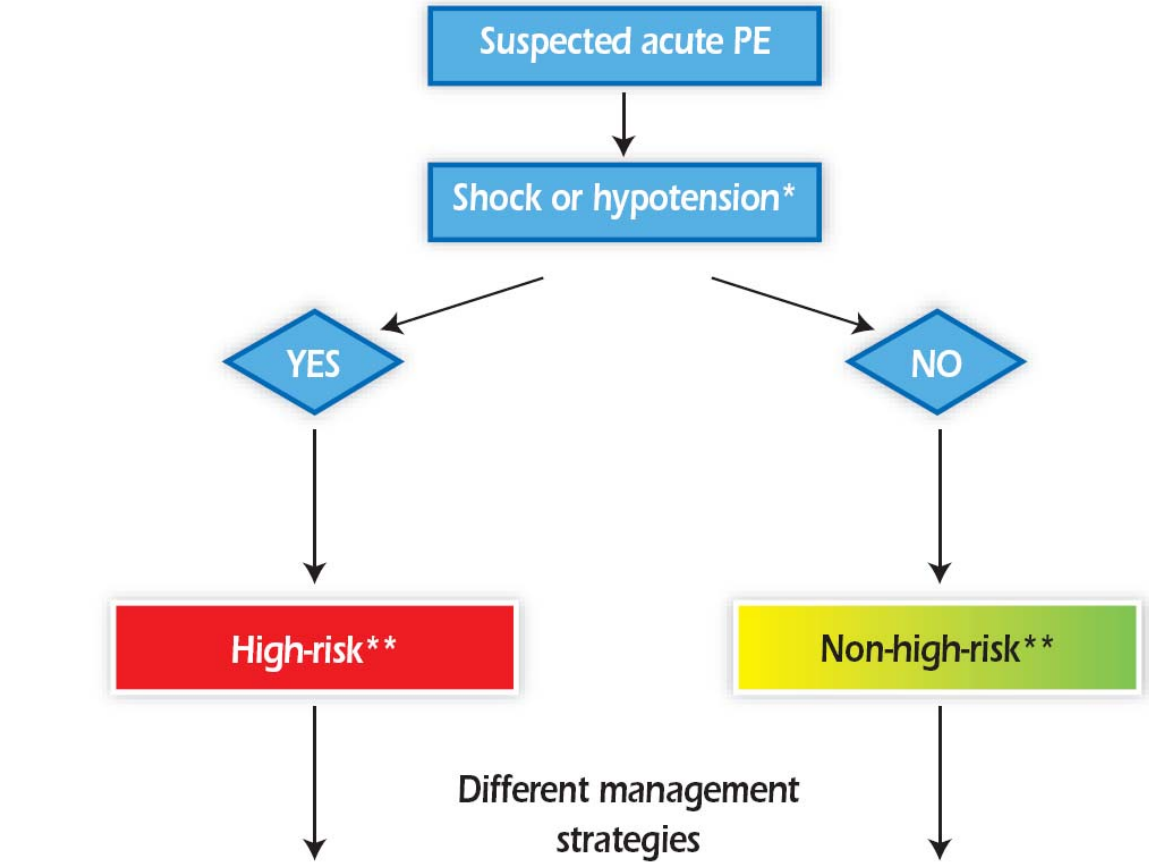
- Eckhard Mayer, Mainz, Germany
- Martine Remy-Jardin, Lille, France
- Jean-Pierre Bassand, Besançon, France

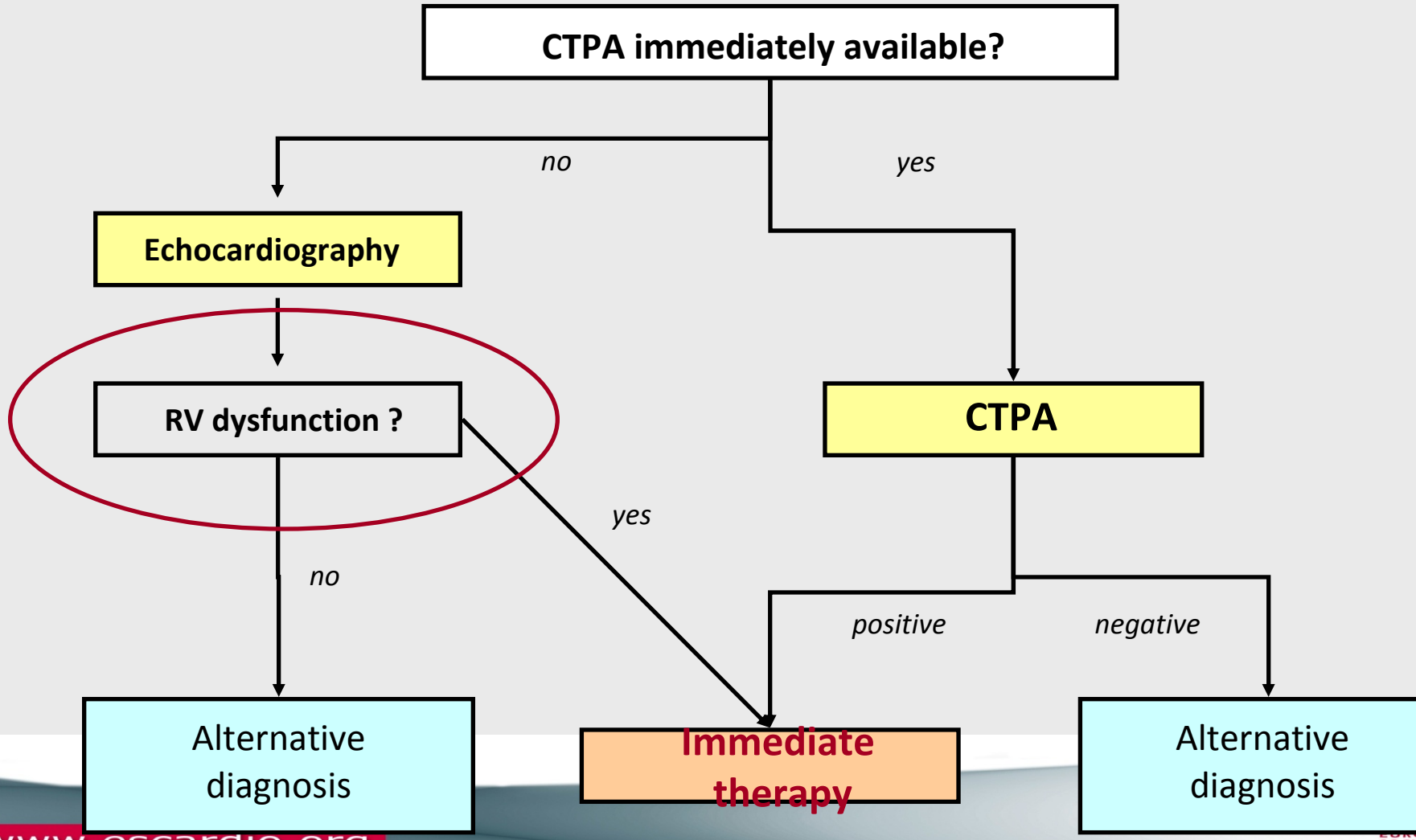
and Adam Torbicki, *Warsaw, Poland*

Risk stratification based on hemodynamic status



High-risk PE

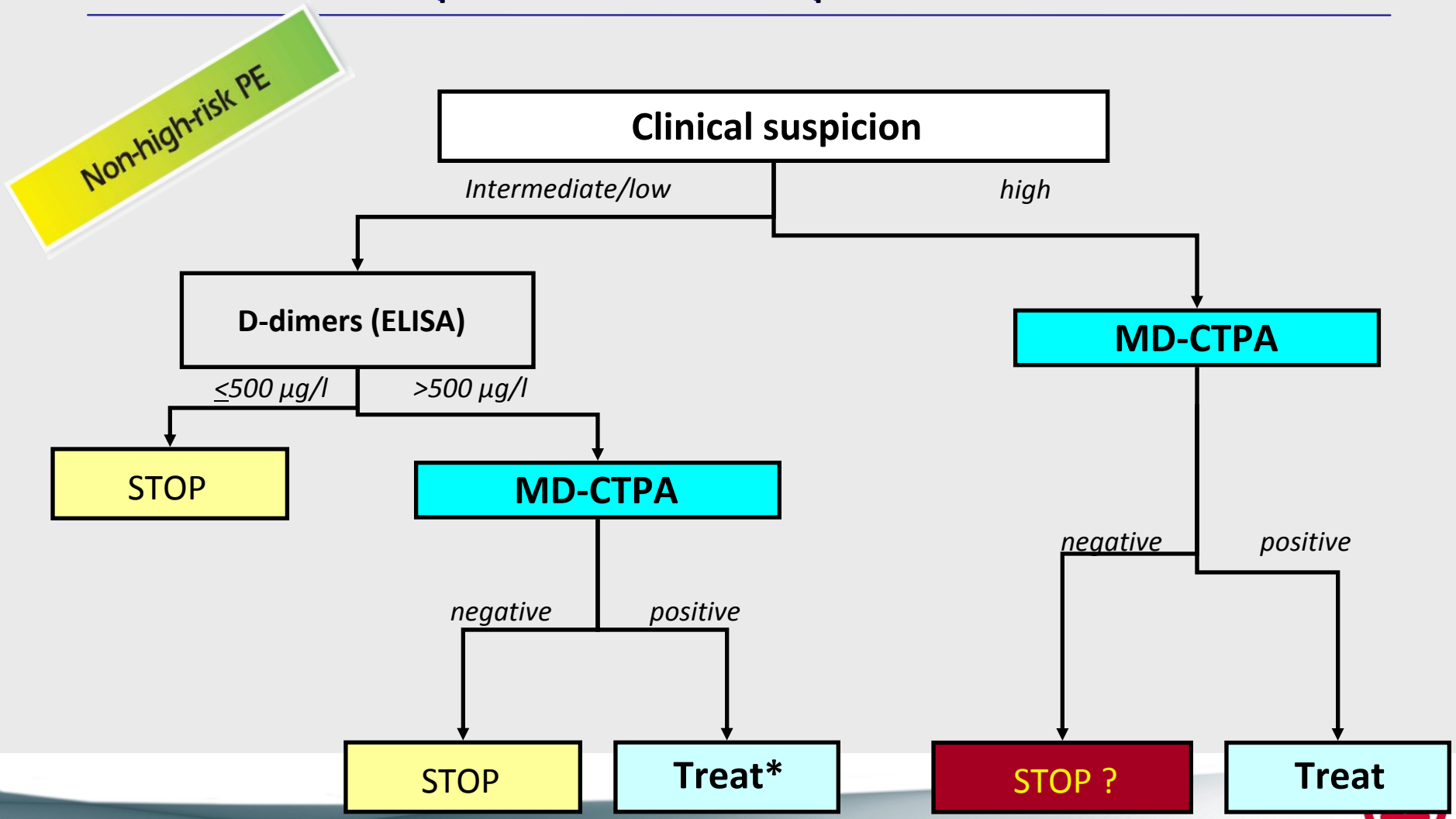
Diagnostic algorithm for the high-risk patient



ESC recommendations

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 normotensive, non-high-risk patient with suspected PE



* If multiple subsegmental defects

Non-high-risk PE

ESC recommendations

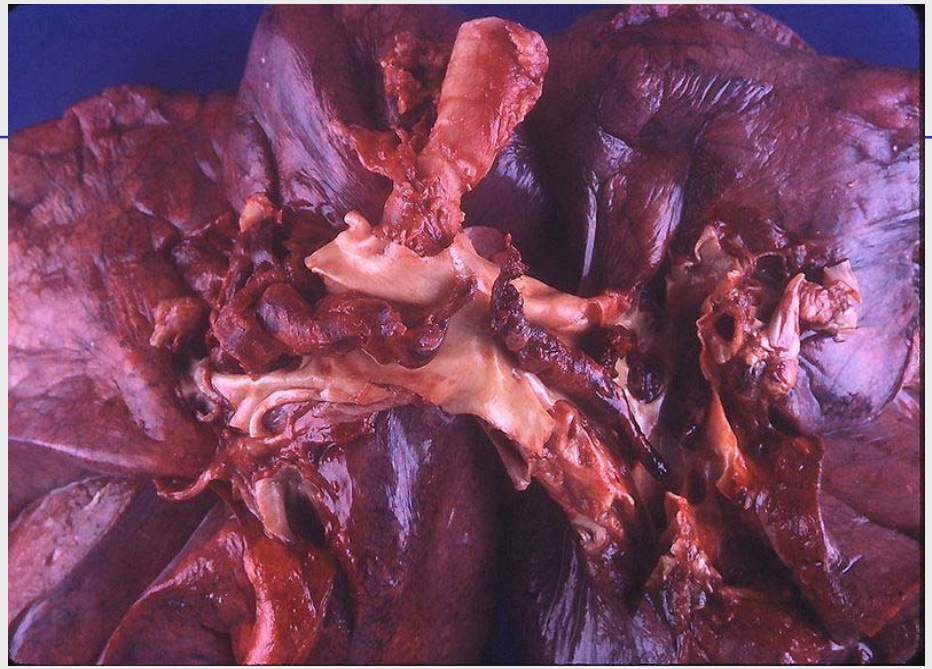
Recommendation	Class	Level
Anticoagulation should be initiated without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is still ongoing	I (1)	C (C)
LMW heparin or fondaparinux for most patients	I (1)	A (A)
Thrombolysis generally NOT recommended (1B) – may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

Secondary VTE prophylaxis - 2008

Recommendations	Class [a]	Level [b]
▪ For patients with PE secondary to a transient (reversible) risk factor, treatment with a VKA is recommended for 3 months	I	A
▪ For patients with unprovoked PE, treatment with a VKA is recommended for at least 3 months	I	A
▪ Patients with a first episode of unprovoked PE and low bleeding risk, and in whom stable anticoagulation can be achieved, may be considered for long-term oral anticoagulation	IIb	B
▪ For patients with a second episode of unprovoked PE, long-term treatment is recommended	I	A
▪ In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals	I	C
▪ For patients with PE and cancer, LMWH should be considered for the first 3 to 6 months after this period, anticoagulant therapy with VKA or LMWH should be continued indefinitely, or until the cancer is considered cured	IIa I	B C
▪ In patients with PE, the dose of VKA should be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) regardless of treatment duration	I	A

Q1

What is new 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.

Which is the « best » score ?

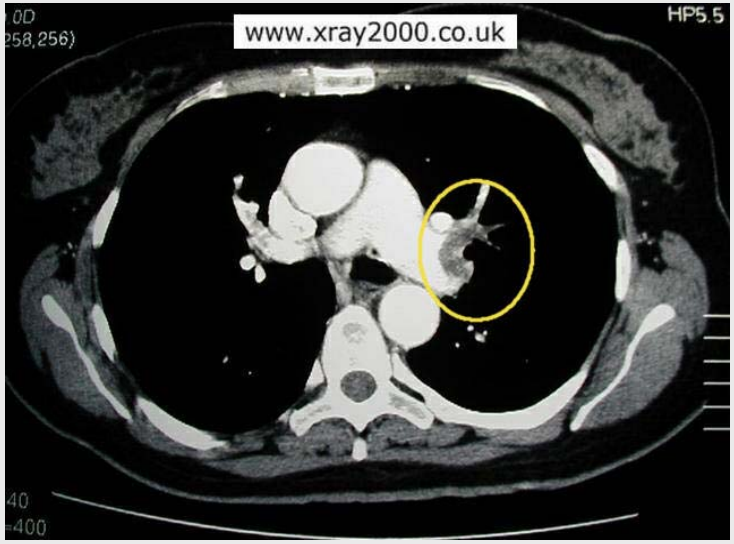
- Similar accuracy
- Prevalence of PE in suspected patients
  - > 20%: revised Geneva score
  - < 20%: any score
- Setting
  - Outpatients, emergency ward: all scores
  - Inpatients: Wells score

Ceriani E et al., J Thromb Haemost 2010;8:957-970

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

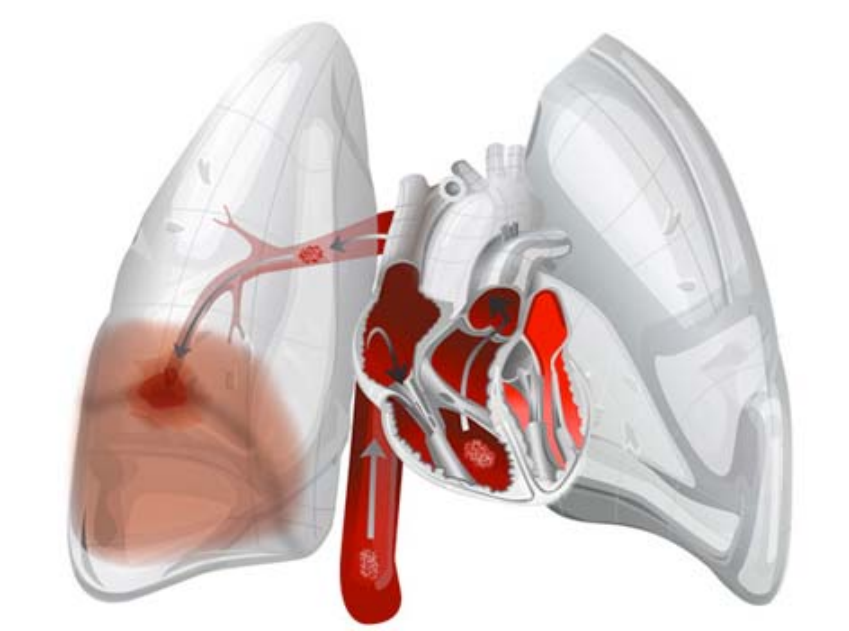


- Multicenter US study including 371 consecutive patients(susp A.PE)
- **MR angiography technically inadequate in 25% (11 to 52%)**
- Performance of technically adequate tests:
  - **Sensitivity 78%, specificity 99%(MRA)**
  - **Sensitivity 92%,specificity 96%(MRA+MRV)**

Ann Intern Med. 2010;152:434-443

Q2

Progress in the management of **intermediate-risk** patients ?



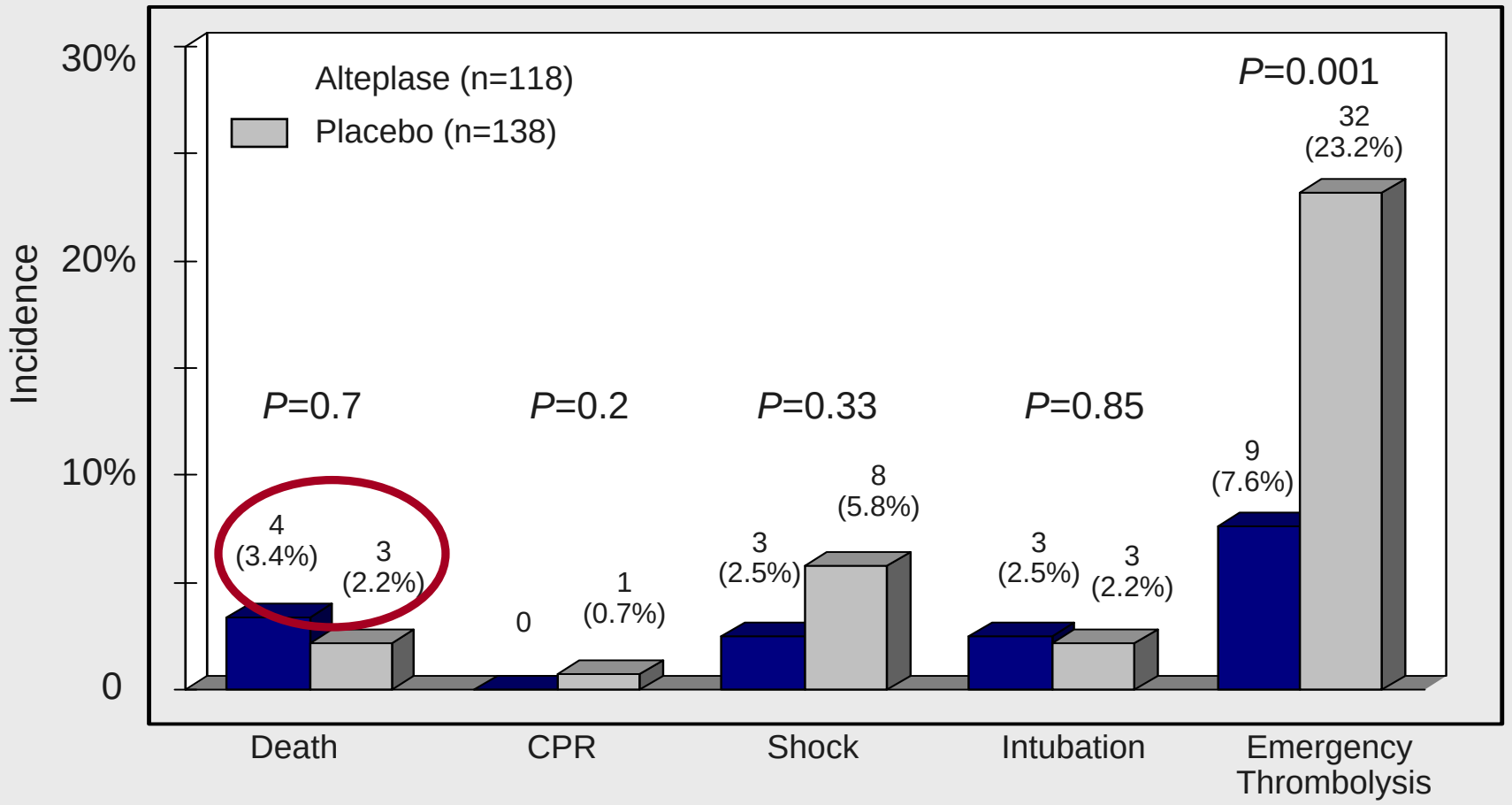
High – low- intermediate risk (?)

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

Identifying patients at intermediate risk

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]

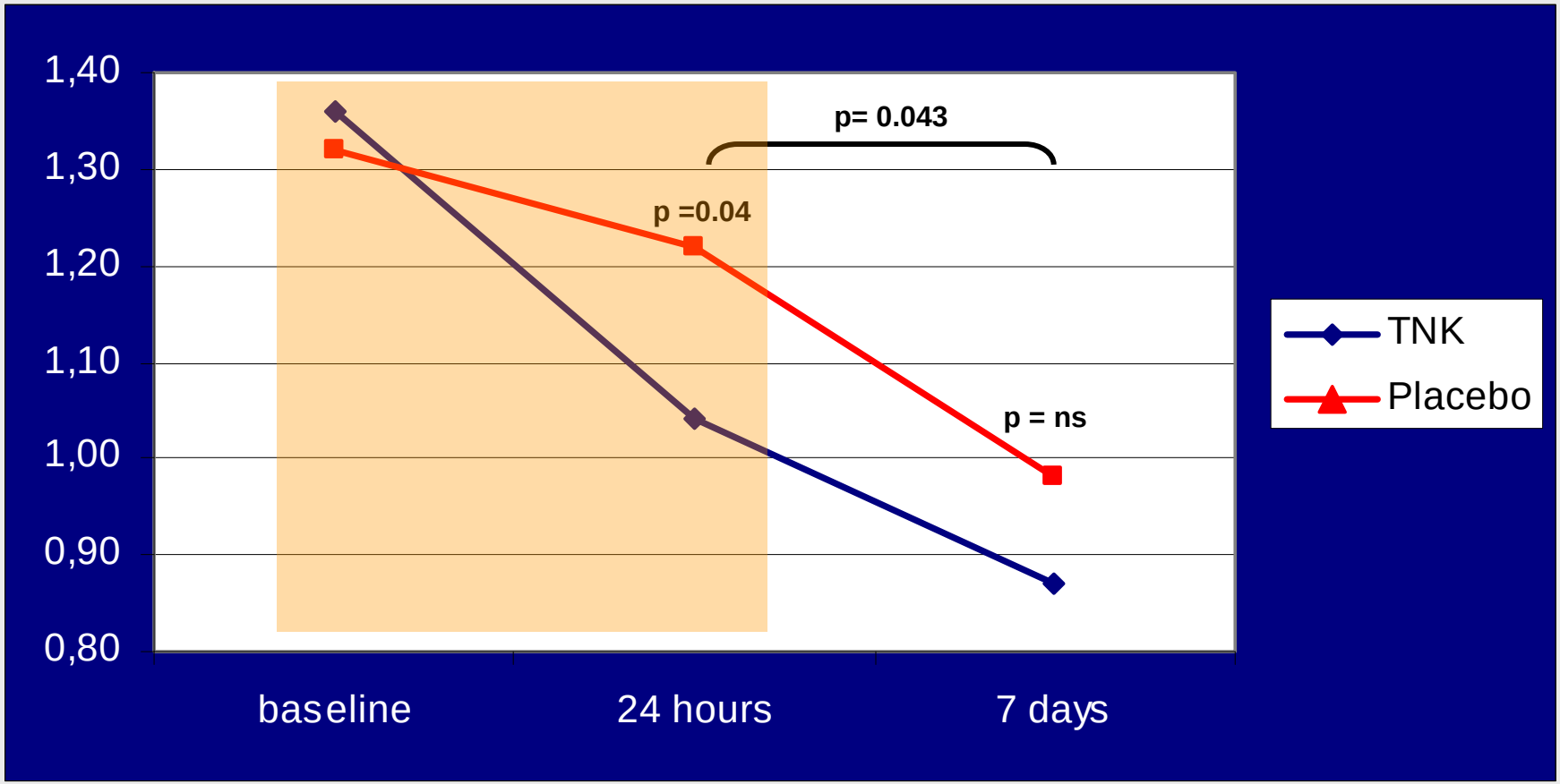
1 RV dysfunction on Echo in normotensive PE patients: Therapeutic implications ?



S. Konstantinides. N Engl J Med 2002;347:1143

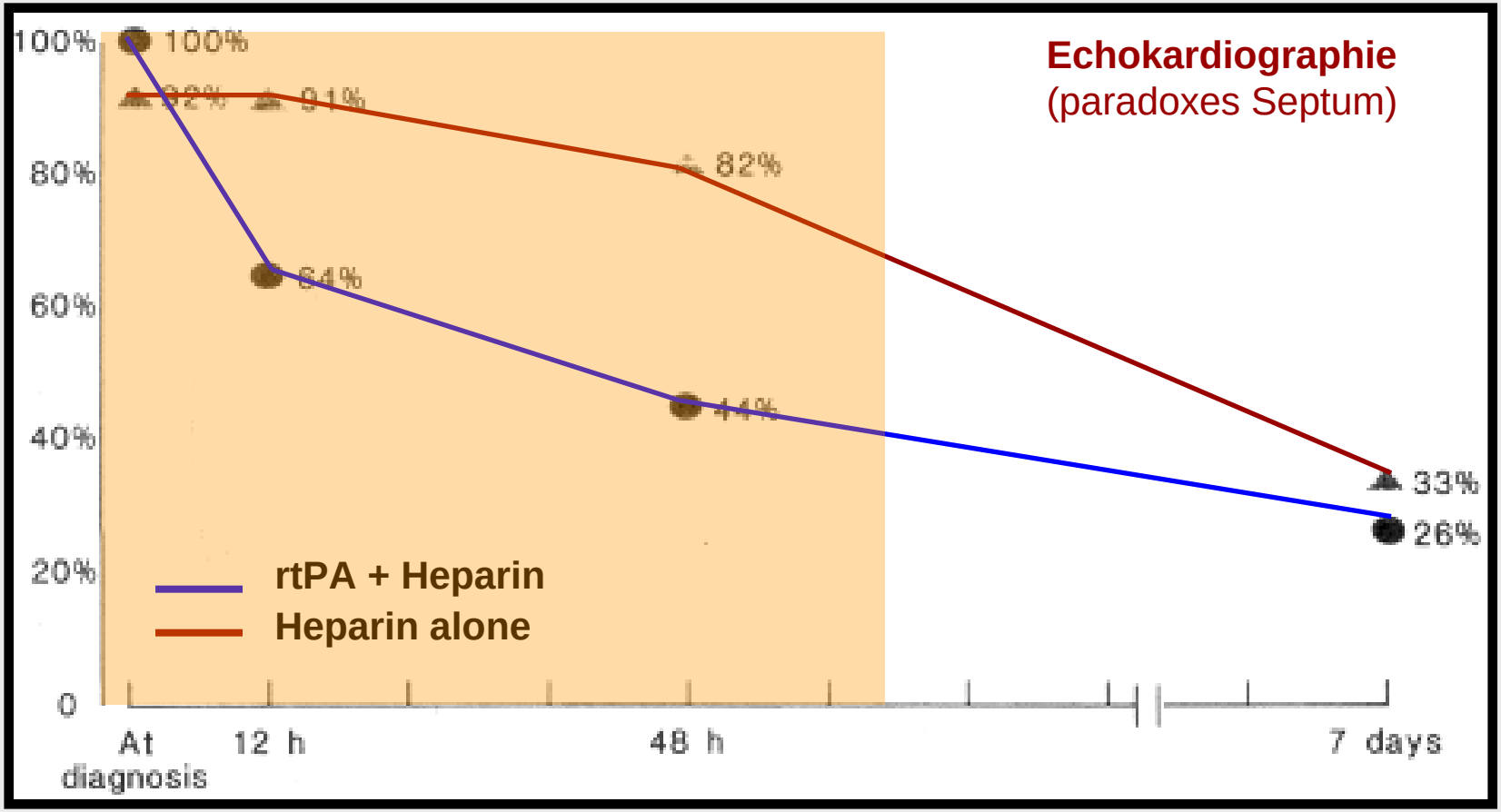
TIPES study (Tenecteplase): Results

Impact on RVEDD/LVEDD ratio (echo)



C Becattini et al. Thromb Res 2009

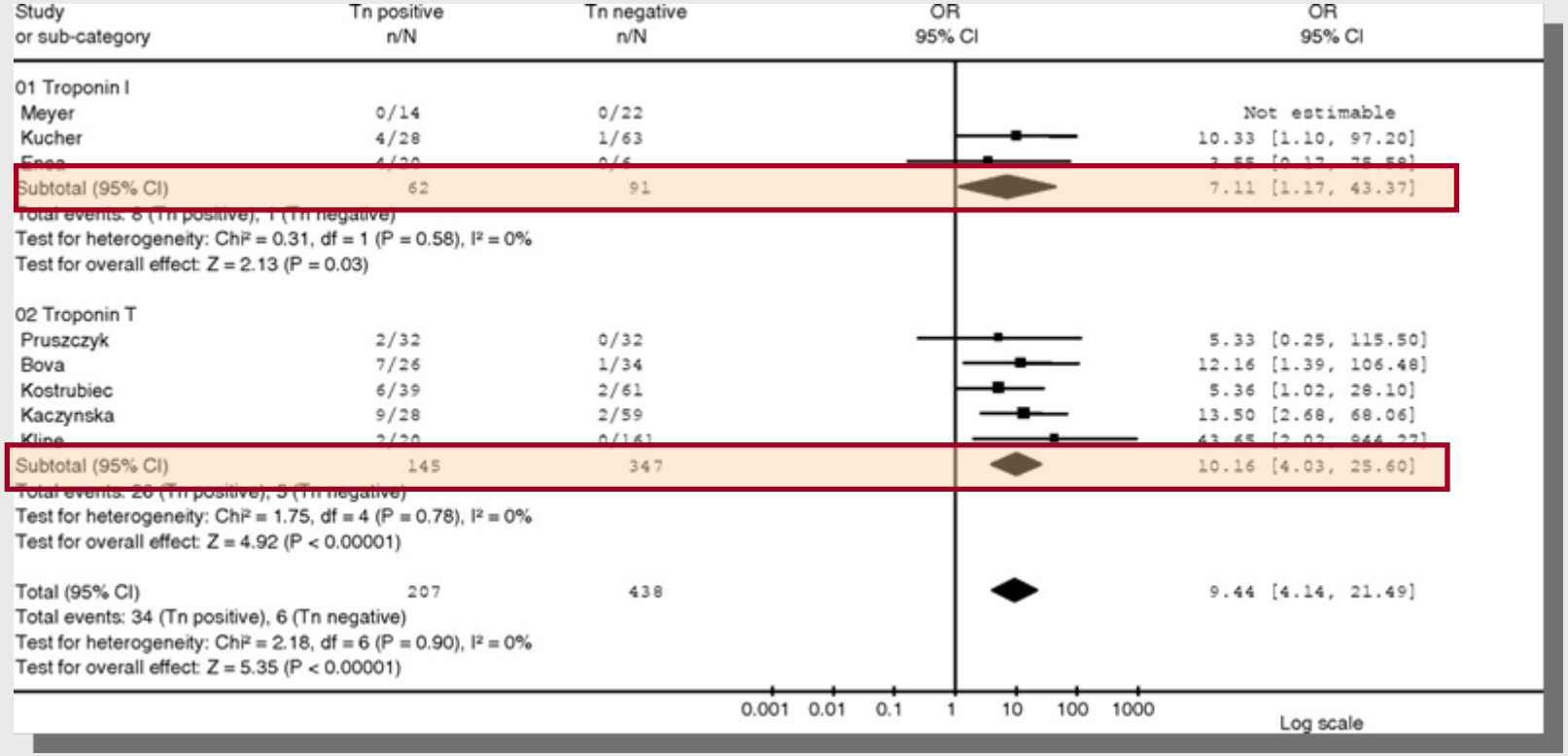
…like alteplase 12 years ago



S Konstantinides, Am J Cardiol 1998;82:966-970

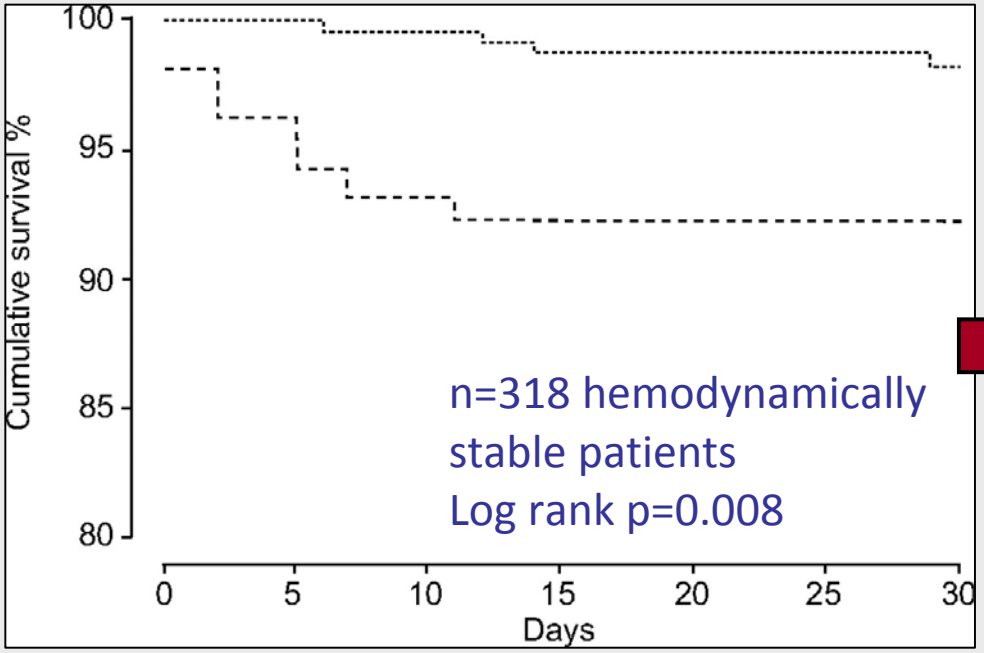
2 Myocardial injury on troponin test in PE patients: Meta-analysis: PE-related mortality

Data from 20 studies (4 retrospective), n=1985 patients (1998-2006)



C Becattini. Circulation 2007;116:427-433

Myocardial injury **on troponin test** in normotensive PE patients: Therapeutic implications ?



but…
cardiac troponin (I) NOT an indepenedent predictor of overall mortality

D Jimenez. Eur Respir J 2008;31:847

Meta analysis:

- 9 studies
- 1366 patients with symptomatic PE
- Pts normotensive at diagnosis

cardiac troponin levels did NOT adequately distinguish between high risk and low risk

D Jimenez. Chest 2009; 136:974-982

3 The „next“ strategy: Biomarkers *combined* with imaging ?

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]

Biomarkers combined with RV imaging:
Early evidence - 2005

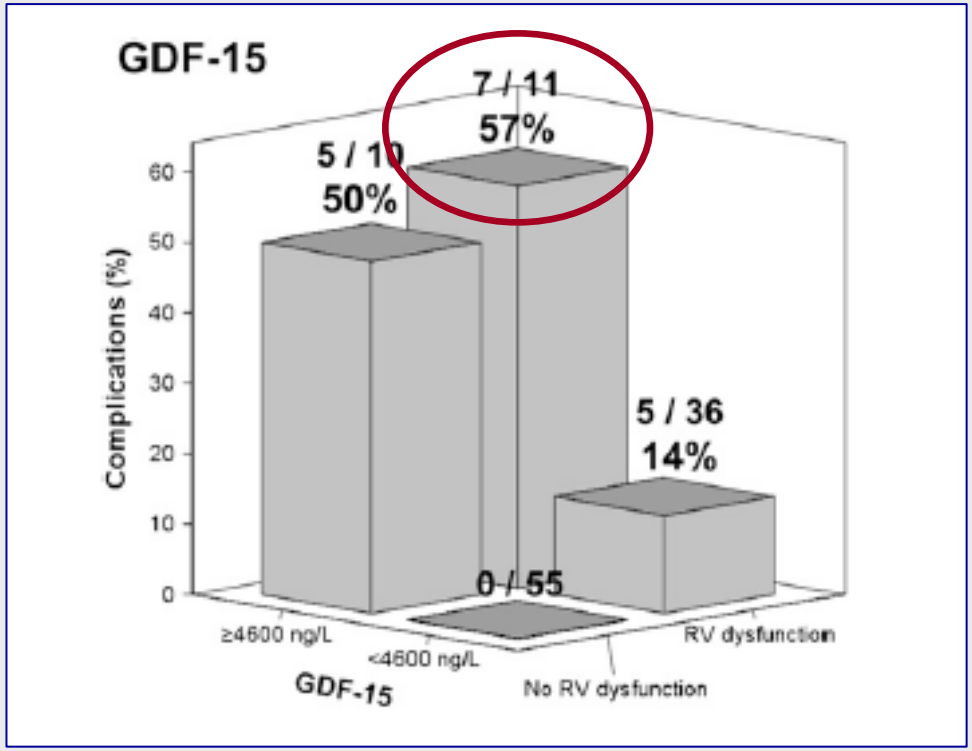
Patient group	Complication risk (OR, 95% CI)
Troponin T-negative (<0.04 ng/ml)	-------
Troponin-positive, echo-negative	3.70 (0.76-18.18) =0.107
Troponin-negative, echo-positive	(0.97-32) *P*=0.055
***Both* troponin- and echo-positive**	**10.00 (2.14-46.80)** ***P*=0.004**

~ 15% of all PE patients

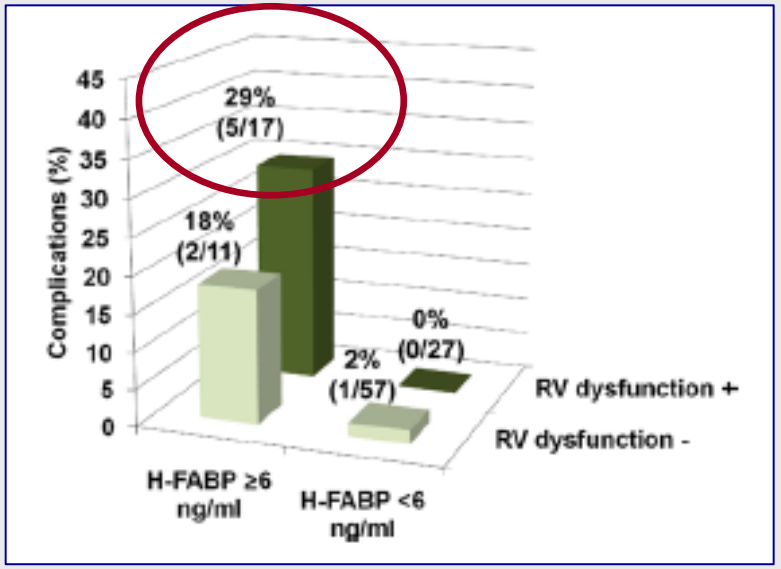
L Binder, S Konstantinides. Circulation 2005;112:1573-1579

RV dysfunction (Echo) *plus* myocardial injury (biomarkers): Evidence of additive prognostic value

Echo + GDF-15



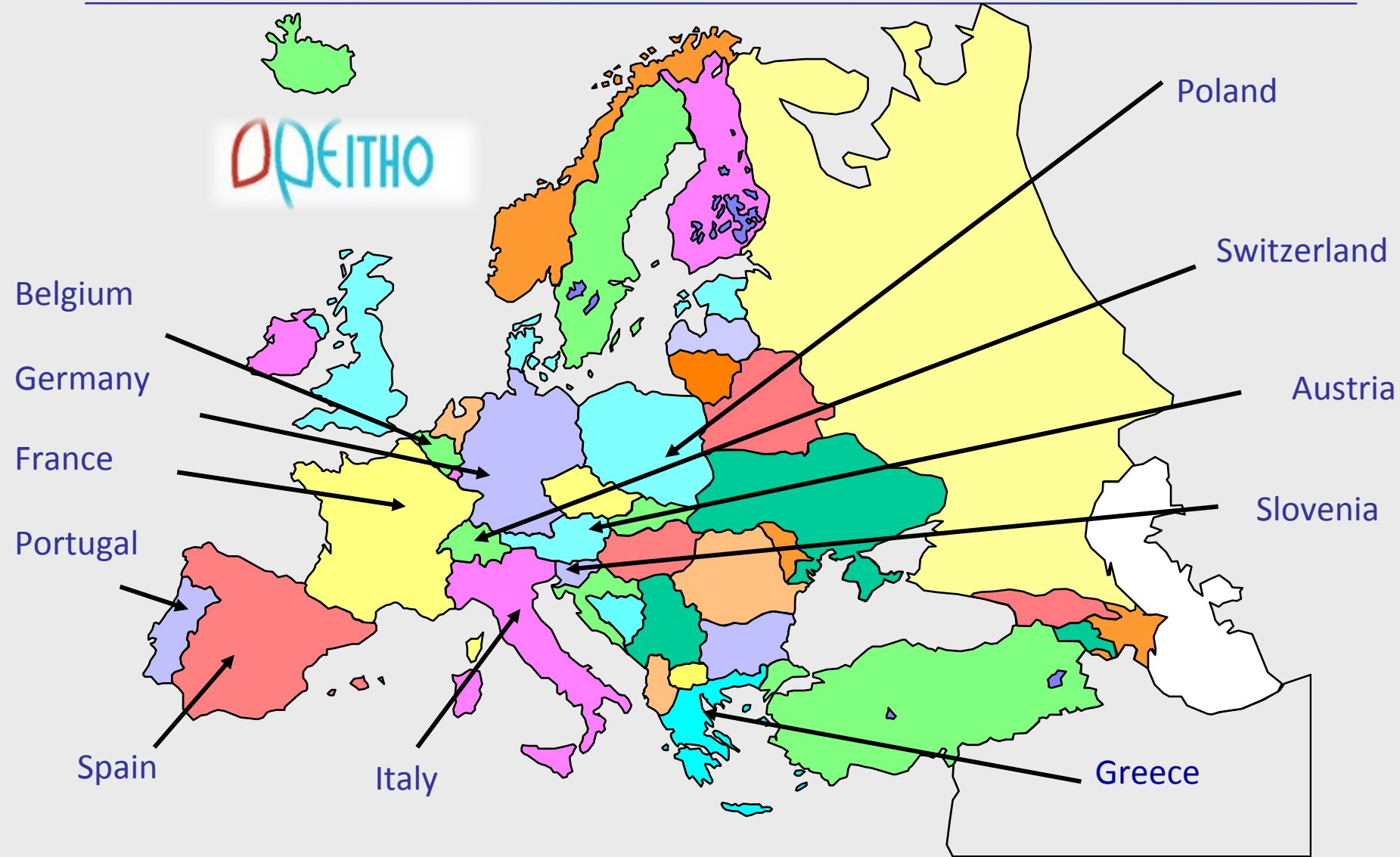
Echo + H-FABP



M Lankeit. Am J Respir Crit Care Med 2008;177:1018-1025

C Dellas. J Am Coll Cardiol 2010;55:2150

RV dysfunction (Echo/CT) + myocardial injury (troponin):
⇒ International randomized thrombolysis study



Global Coordinators

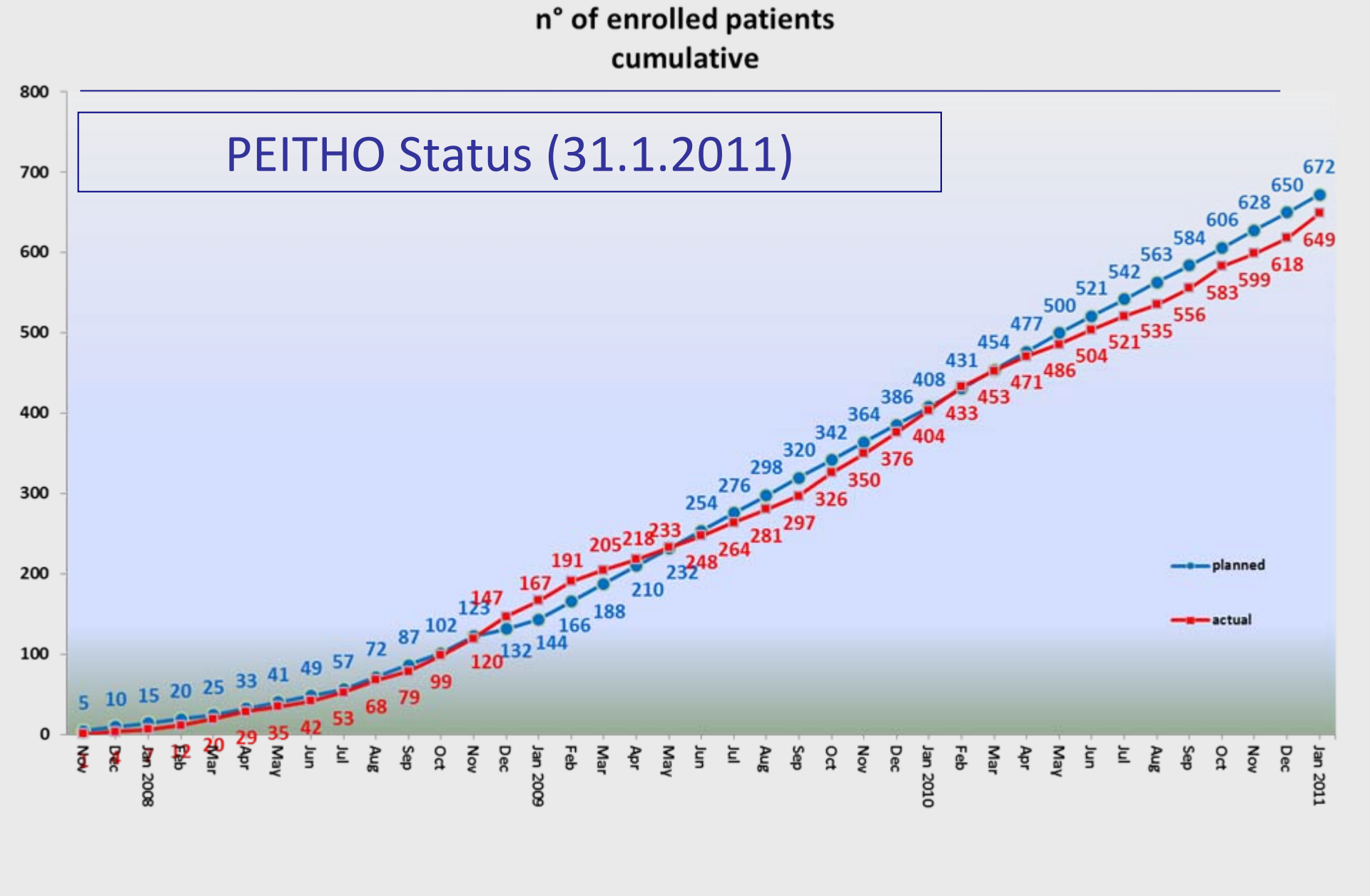
Stavros Kostantinides

Guy Meyer

National Coordinators

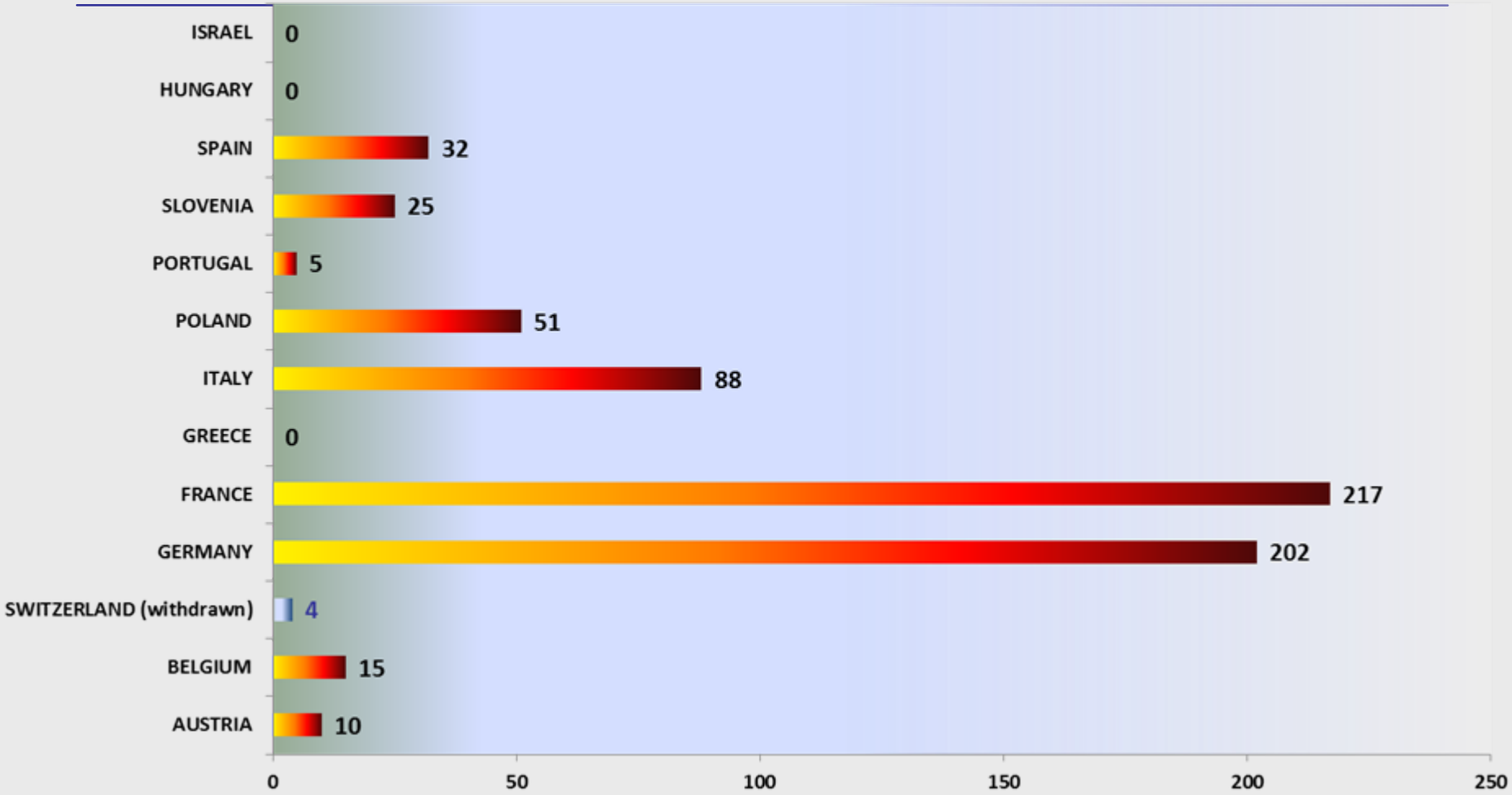
David Jimenez	(Spain)
Piotr Prusczcyk	(Poland)
Nazzareno Galiè	(Italy)
Annette Geibel	(Germany)
Nicolas Meneveau	(France)
Ana Franca	(Portugal)
Matija Kozak	(Slovenia)
Nils Kucher	(Switzerland)
Irene Lang	(Austria)
Stavros Kostantinides	(Greece)
Franck Verschuren	(Belgium)
Jaquelina Ota	(Brazil)
Carlos Jerjes Sánchez Díaz	(Mexico)
Benjamin Brenner	(Israel)
Istvan Sarosi	(Hungary)
Zhi-Cheng Jing	(China)
A. Petris / G. Tatu-Chitoiu	(Romania)

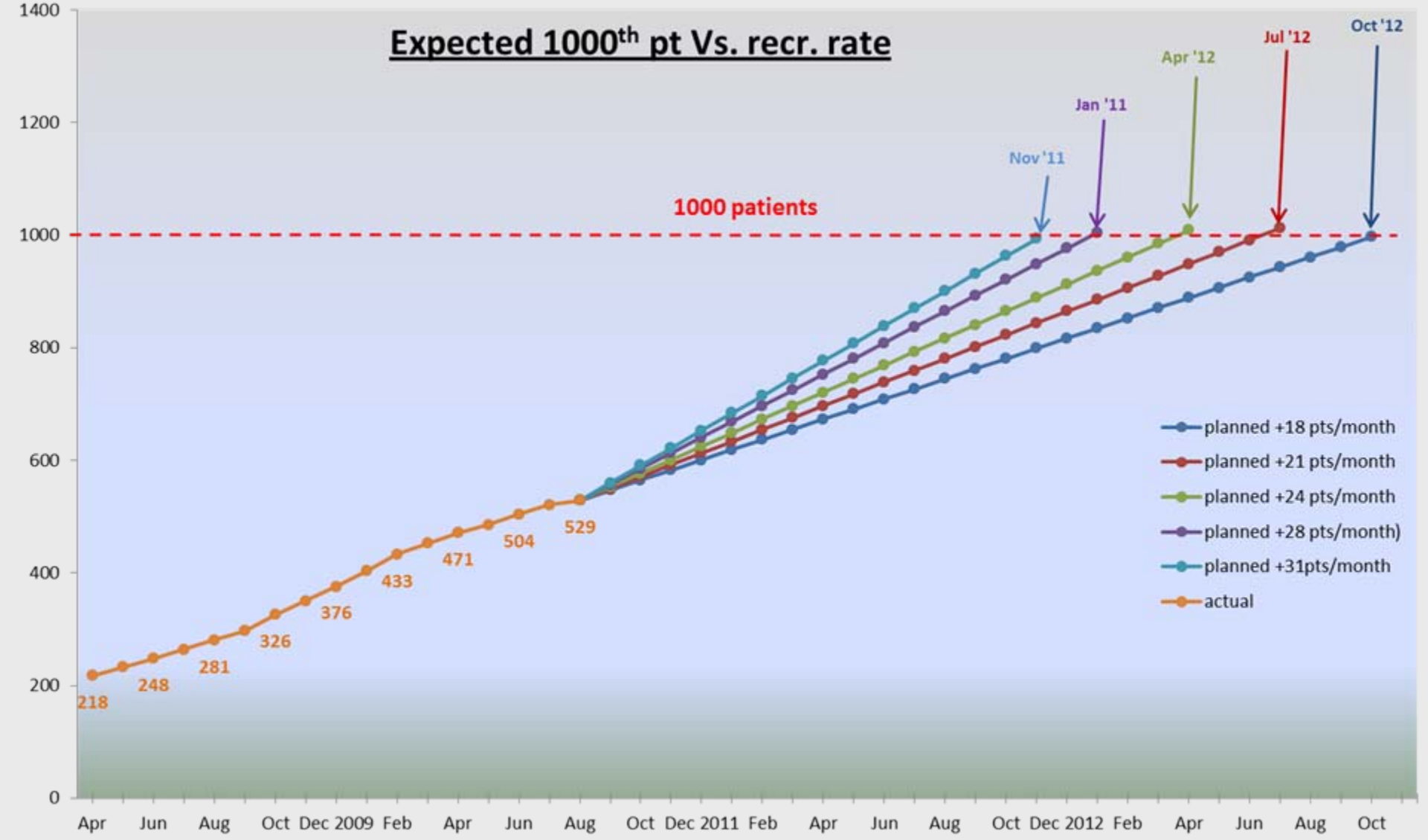
PEITHO 2011 - a GLOBAL study: 18 countries, 3 continents


n° of enrolled patients
cumulative
PEITHO Status (31.1.2011)
800
700
600
500
400
300
200
100
0
planned
actual
5 10 15 20 25 33 41 49 57 72 87 102 123 147 167 191 205 218 233 254 276 298 320 342 364 386 408 431 454 477 500 521 542 563 584 606 628 650 672
5 10 15 20 20 29 35 42 53 68 79 99 120 132 144 166 188 210 232 248 264 281 297 326 350 376 404 433 453 471 486 504 521 535 556 583 599 618 649
Nov Dec Jan 2008 Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan 2009 Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan 2010 Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan 2011

Total recruitment per country

number of randomised patients




Expected 1000th pt Vs. recr. rate
1400
1200
1000
800
600
400
200
0
1000 patients
Nov '11
Jan '11
Apr '12
Jul '12
Oct '12
218
248
281
326
376
433
471
504
529
planned +18 pts/month
planned +21 pts/month
planned +24 pts/month
planned +28 pts/month)
planned +31pts/month
actual
Apr
Jun
Aug
Oct
Dec 2009
Feb
Apr
Jun
Aug
Oct
Dec 2011
Feb
Apr
Jun
Aug
Oct
Dec 2012
Feb
Apr
Jun
Aug
Oct

Q3

Progress in the management of **low-risk** patients ?

High – intermediate – low risk (?)

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

Home treatment of low-risk PE ?

~ 20% more realistic ??

"Ou ent is **safe** in hemodynamically stable patients w 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 out of hospital treatment as inconvenient and have no increase in anxiety scores".

Excluded (199/352 patients):

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

MJ Agterof. J Thromb Haemost H 2010 [epub ahead of press]

Low risk: simplified PESI score

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

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

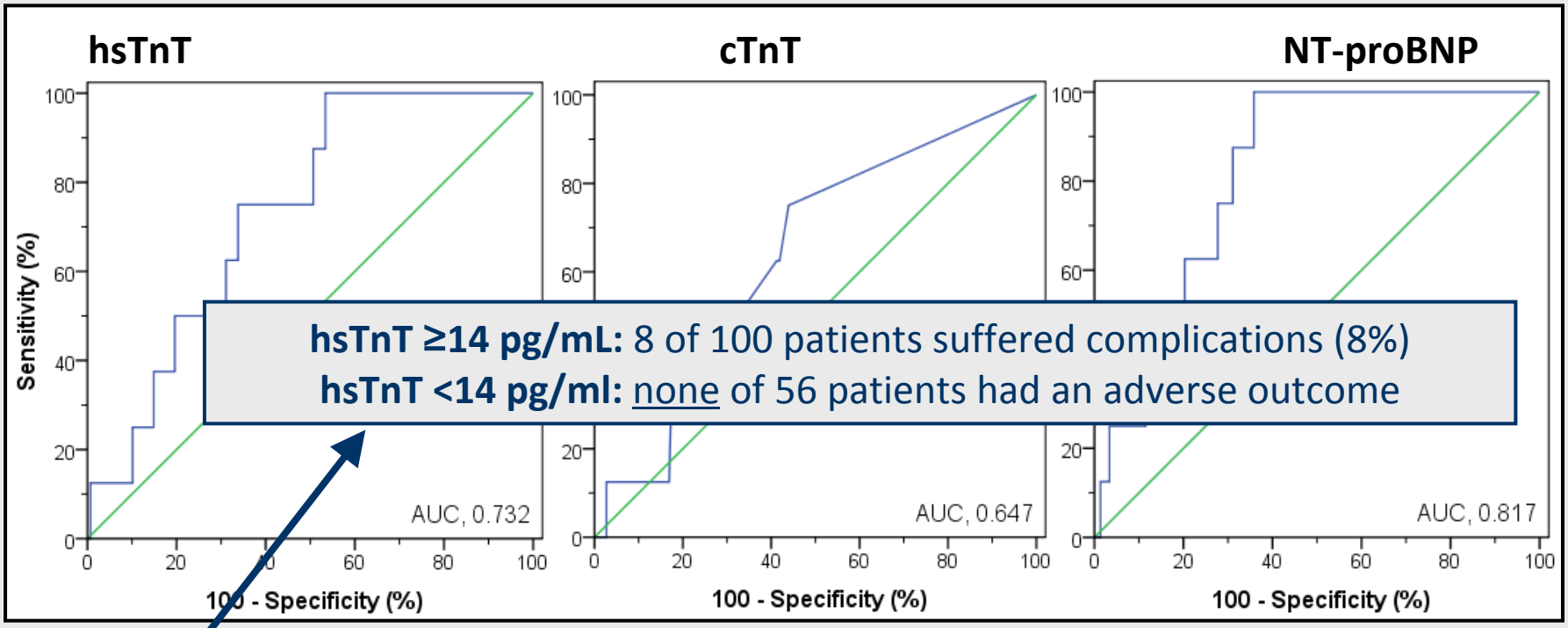
Derivation:
995 patients prospectively included in single-center registry
30-day mortality
- **Low-risk 1.0% (0.0-2.1)**
- High-risk 10.9% (8.5-13.2)

Validation:
7106 patients retrospectively analysed in RIETE registry
30-day mortality
- **Low-risk 1.1% (0.7-1.5)**
- High-risk 8.9% (8.1-9.8)

Low-risk, 0 points (30 to 36% of patients)
High-risk, 1 or more points

D Jiménez. Arch Intern Med. 2010;170:1383-1389

Low risk: highly sensitive troponin (hsTnT) assay



	Sensitivity	Specificity	PPV	NPV
hsTnT ≥14 pg/mL (n=100)	1.00	0.38	0.08	1.00
cTnT ≥0.03 ng/mL (n=52)	0.50	0.68	0.08	0.96
NT-proBNP ≥1000 pg/mL (n=78)	1.00	0.53	0.10	1.00

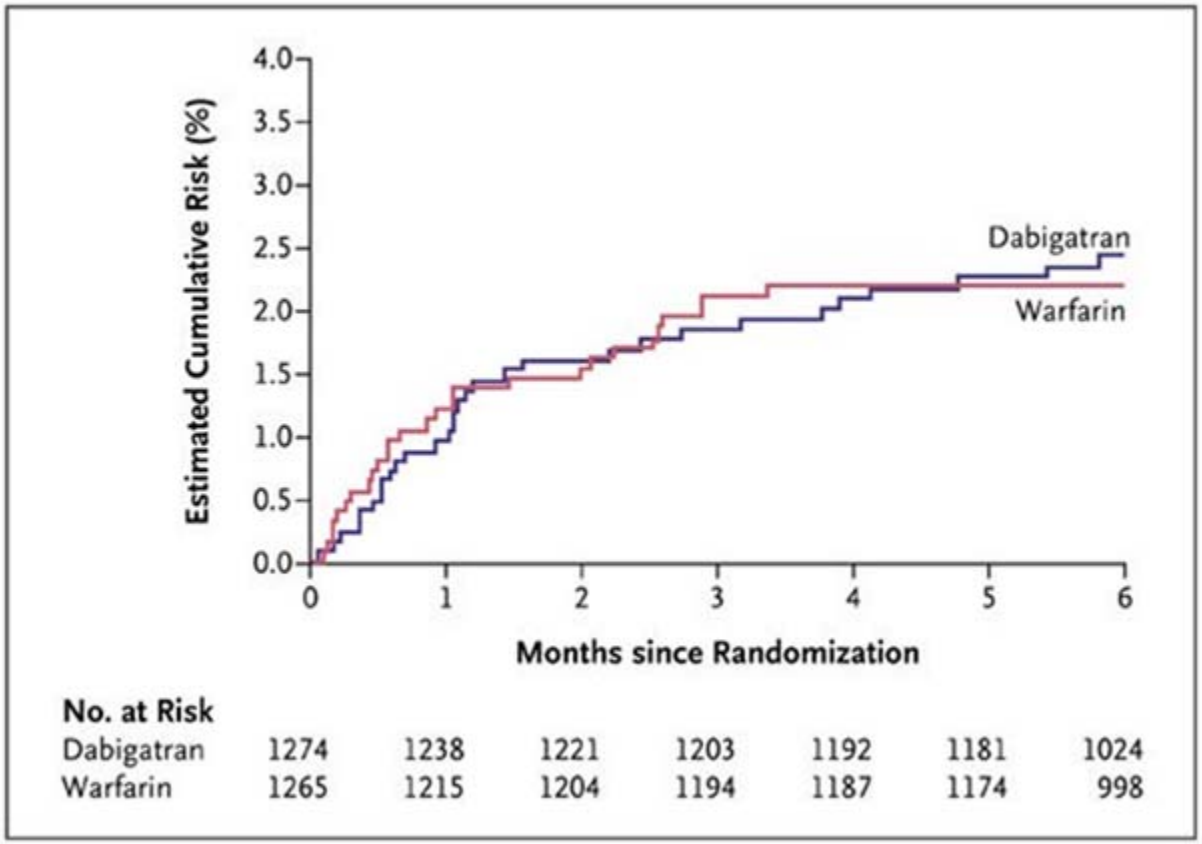
M. Lankeit, S Konstantinides. Eur Heart H 2010 (FastTrack publication)

Q4

Progress in **anticoagulation** and secondary VTE prophylaxis

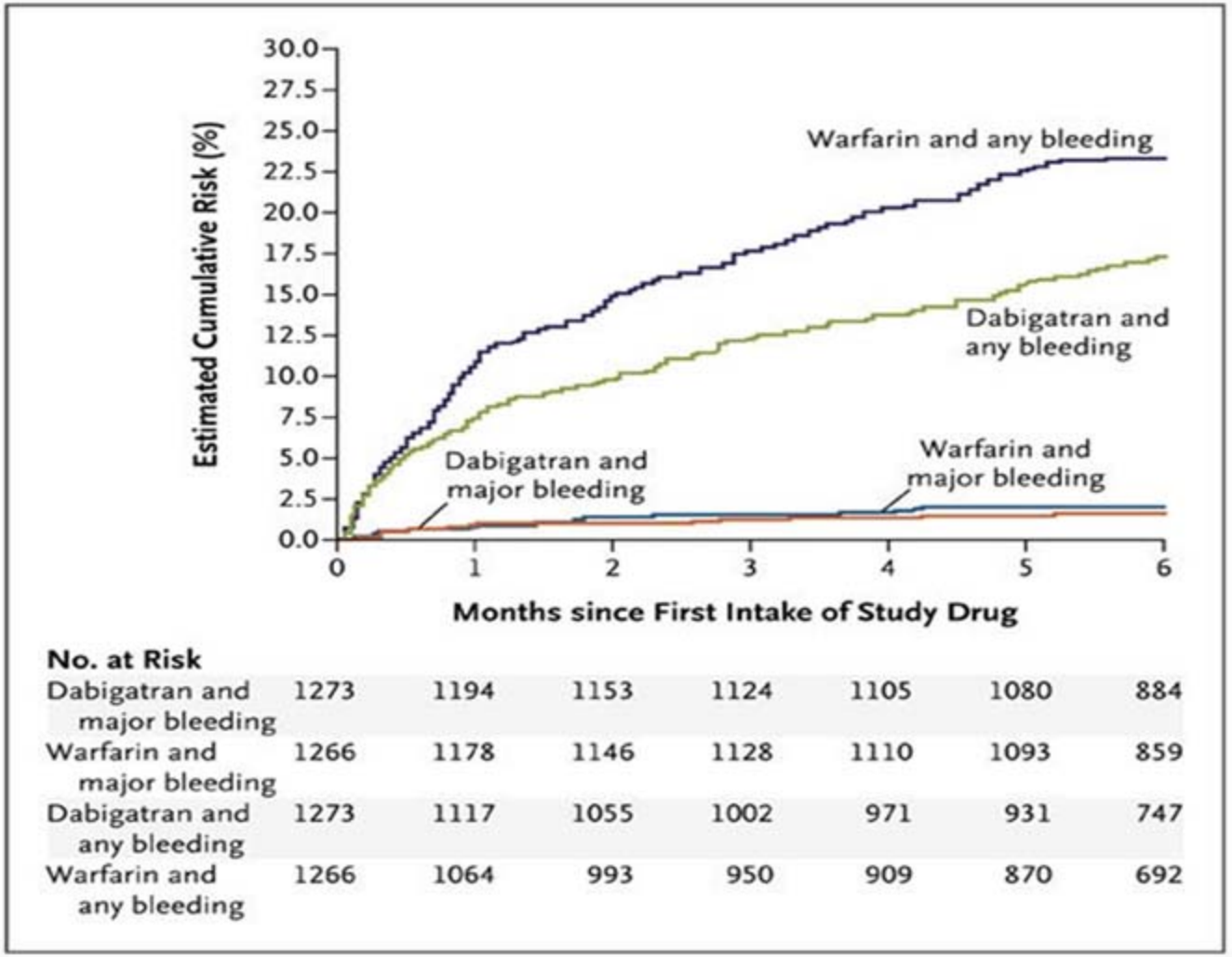
Dabigatran after acute VTE: RE-COVER

- 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
- Non-inferiority study



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

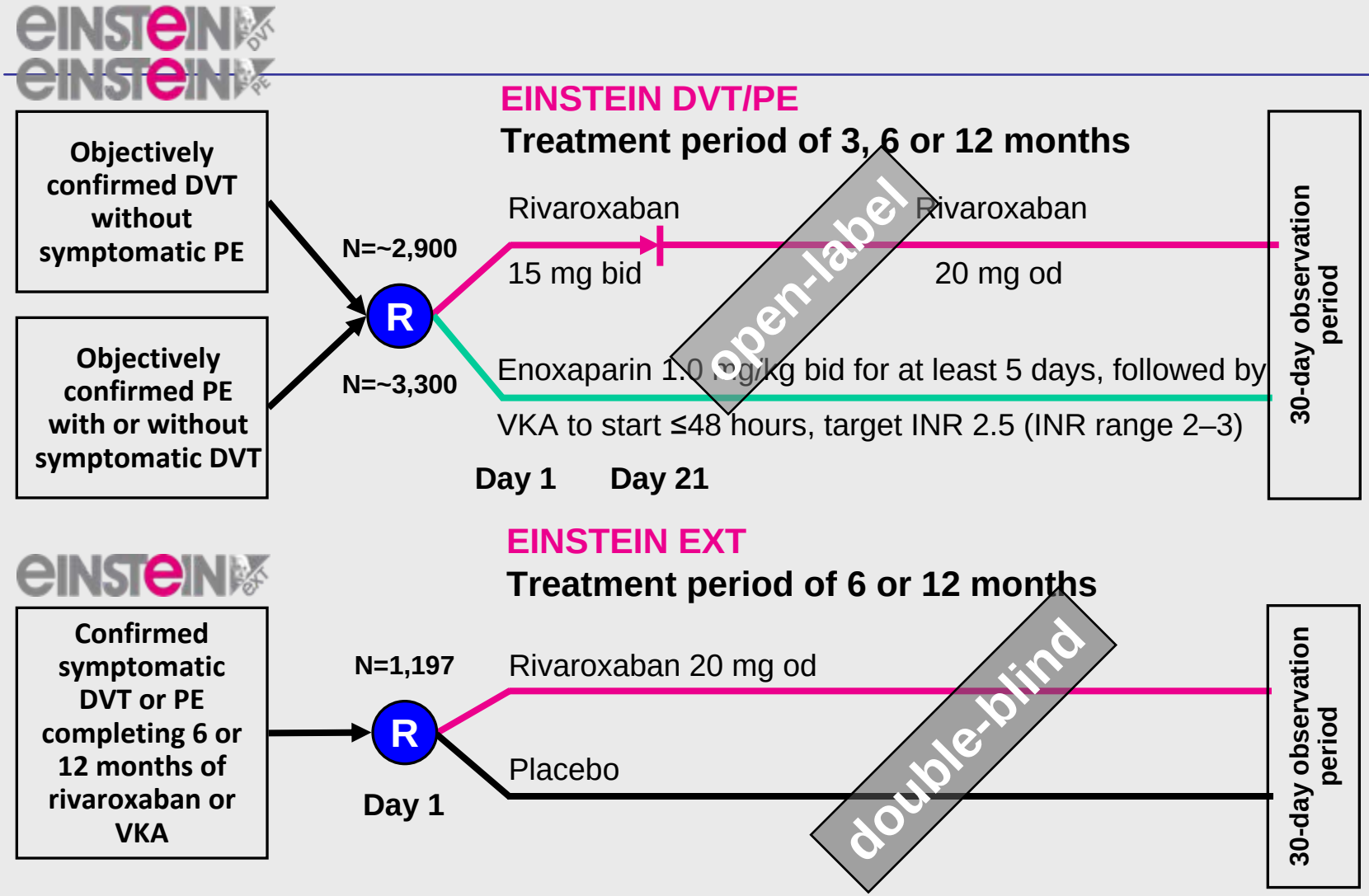
Dabigatran after acute PE: RECOVER



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

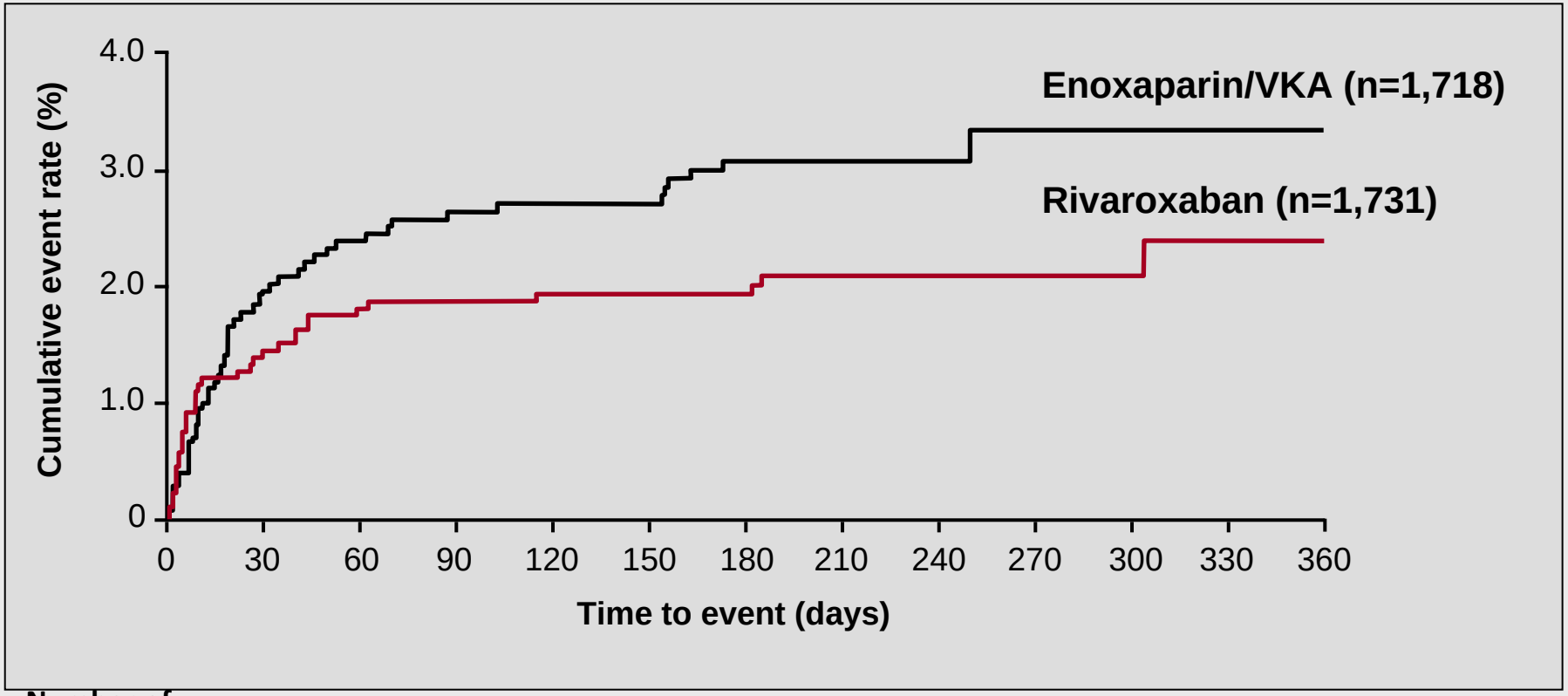
Schulman S et al. N Engl J Med 2009;361:2342-2352

EINSTEIN – Phase III: study design



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

Primary efficacy outcome: time to first event



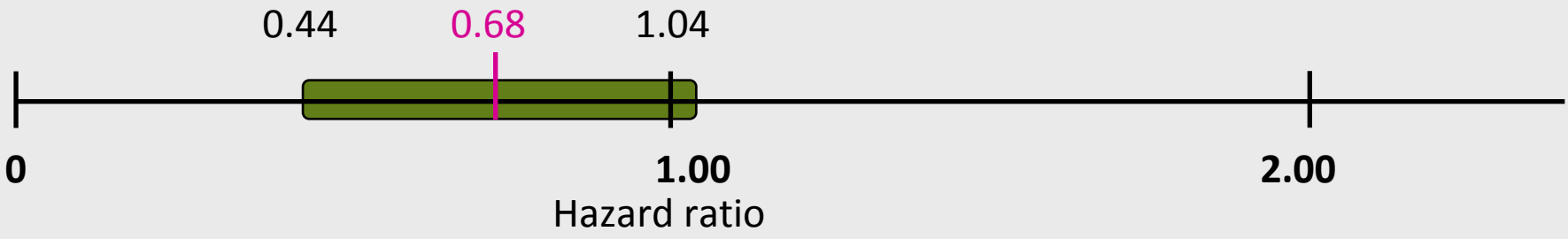
Number of subjects at risk

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 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%)



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

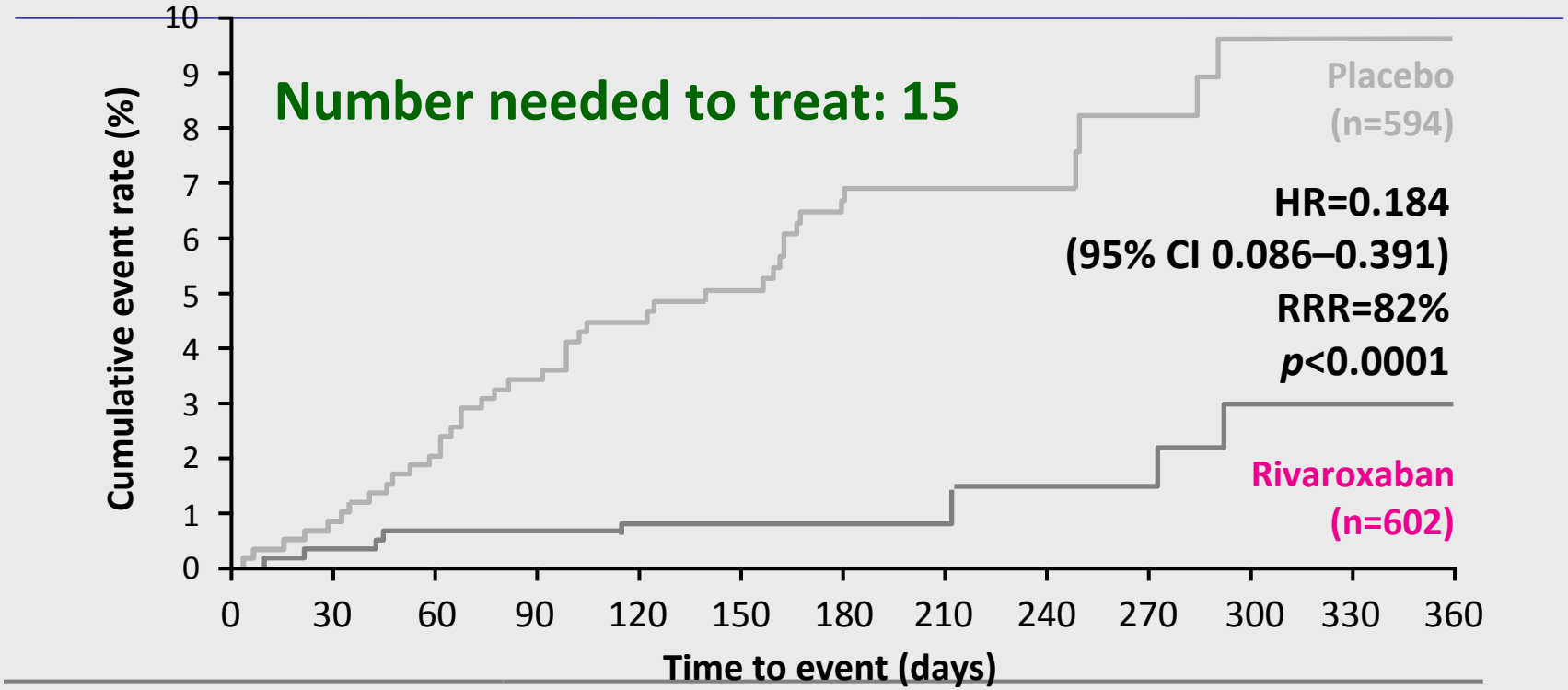
Primary safety outcome analysis

	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

Efficacy end points

	Placebo (n=594)		Rivaroxaban (n=602)	
Symptonatic VTE recurrence*	42	(7.1%)	8	(1.3%)
Recurrent DVT	31	(5.2%)	5	(0.8%)
Non-fatal PE	13	(2.2%)	2	(0.3%)
Fatal PE	1	(0.2%)	0	
Cause of death unclear (LE nicht auszuschließen)	0		1	(0.2%)

ITT population; *some patients experienced more than one event

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

Safety end points (major bleeding)

	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%)

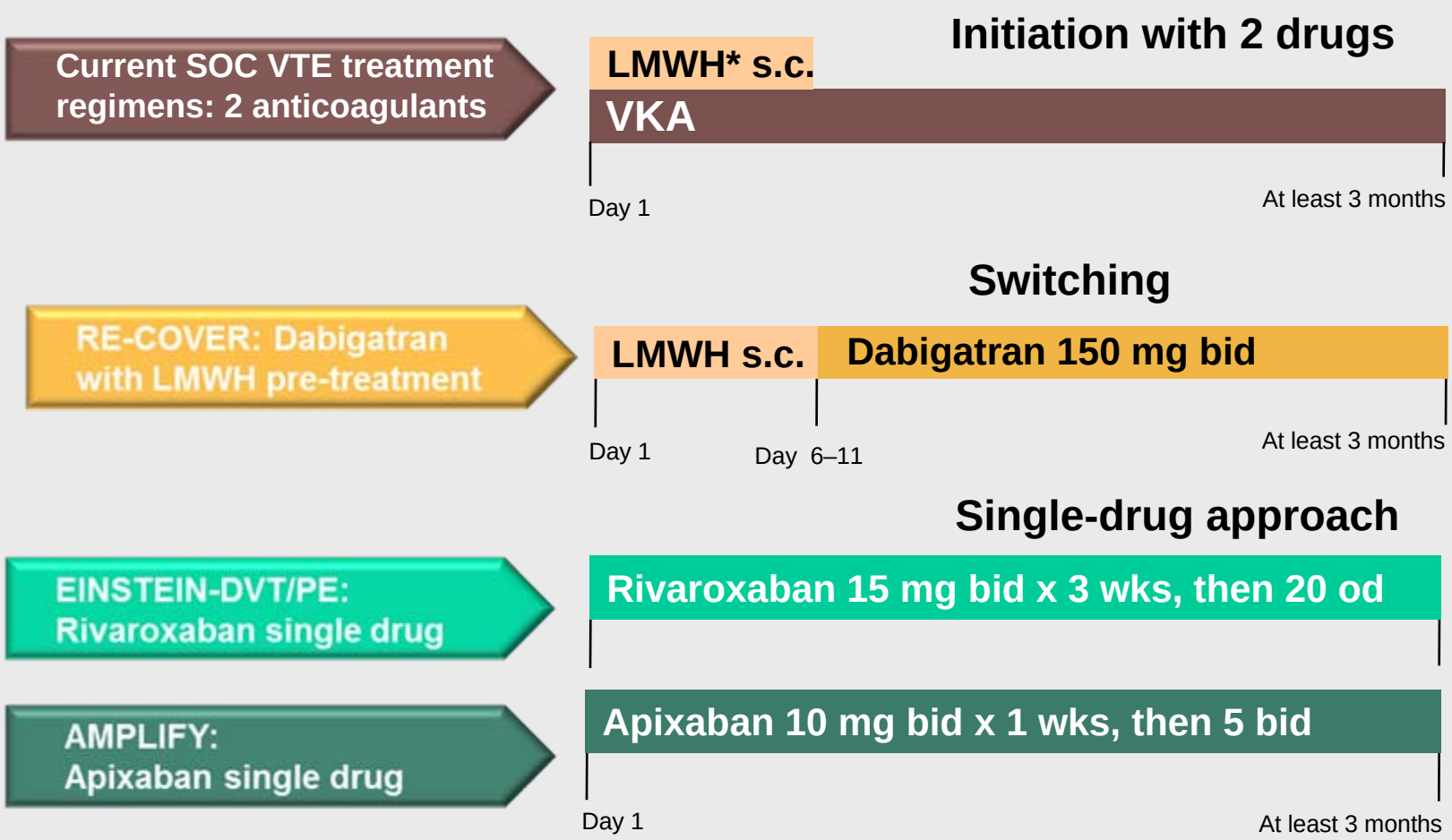
- **Number needed to harm: approximately 139**

*p=0.11

Safety population

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

New oral anticoagulants:
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.