GESTIONE DEL PAZIENTE CON TROMBOEMBOLISMO VENOSO (VTE)

Dr. S. Grifoni – Centro di Riferimento Regionale per la Diagnosi ed il Trattamento dell'Embolia Polmonare

Dip. Emergenza Urgenza- Careggi - Firenze

Prima descrizione clinica (Helie, 1837):

Caso clinico inerente una signora di 65 anni, di professione lavandaia, di bassa statura e sovrappeso; deceduta dopo un episodio di improvvisa dispnea e cianosi del volto, circa due settimane dopo la distorsione di un arto inferiore; all'autopsia venne rilevato un "*cuore ingrandito con coaguli rossi ben organizzati nel ventricolo destro e nell'arteria polmonare*".

Tromboembolismo venoso: epidemiologia

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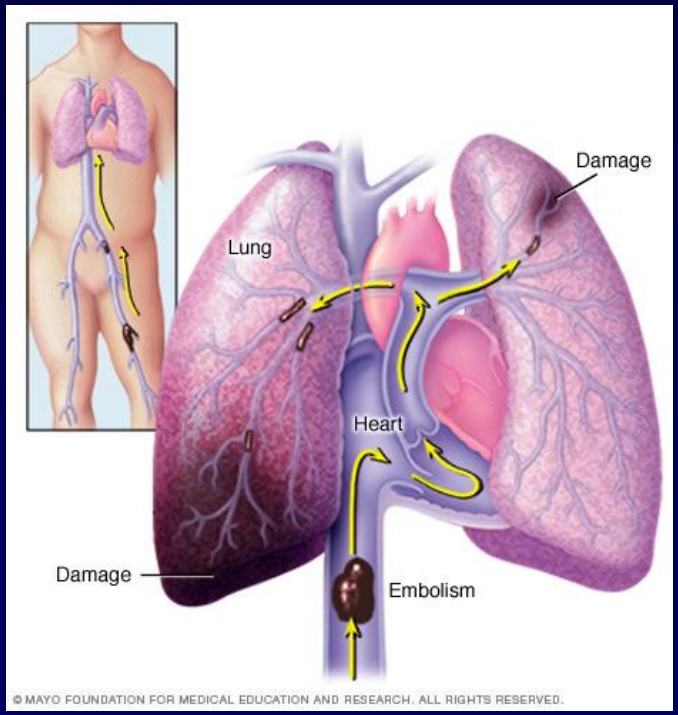
- Il tromboembolismo venoso è la terza più comune malattia cardiovascolare dopo la coronaropatia e lo stroke

- Il tromboembolismo venoso può presentarsi come **trombosi venosa profonda (DVT), embolia polmonare (PE) o ambedue:**

  più del 50% di pazienti con trombosi venosa profonda ha evidenza di embolia polmonare silente

  -più del 70% di pazienti con embolia polmonare ha una trombosi venosa profonda

- I pazienti con VTE e fattori di rischio permamenti rimangono ad alta probabilità di sviluppare recidive negli anni a seguire



Tromboembolismo venoso: fattori di rischio

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Fattori di rischio iatrogeni	Secondari ad altre malattie	Secondari ad altre malattie e situazioni fisiologiche
Chirurgia maggiore	Trombofilie congenite	Iperomocisteinemia
Trattamento con estrogeni	Neoplasie (> ematologiche)	Vene varicose
Trombocitopenia indotta da eparina	Traumi	Età maggiore di 40 anni
Cateteri venosi centrali	Immobilità	Puerperio
	Stroke	Gravidanza
	Insufficienza cardiaca	Viaggi prolungati
	Infarto miocardico	
	Obesità	
	Sindrome nefrosica	
	IBD	

Tromboembolismo venoso: prognosi a breve termine

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-il 3% delle embolie polmonari esordisce come morte improvvisa

-10% di pazienti con embolia polmonare sintomatica muore entro la prima ora

-oltre il 15% dei pazienti con embolia polmonare complicata da instabilità emodinamica muore entro un mese

- <10% dei pazienti deceduti precocemente riceve una corretta diagnosi prima del decesso

-il 30% delle DVT non diagnosticate si complica con una embolia polmonare sintomatica

Kearon C. *Circulation* 2003; Ribeiro A, et al. *Circulation* 1999;
Heit JA, et al. *Arch Intern Med* 1999; Cohen AT, et al. *Thromb Haemost* 2007
ESC Guidelines, 2014

Tromboembolismo venoso: prognosi a lungo termine

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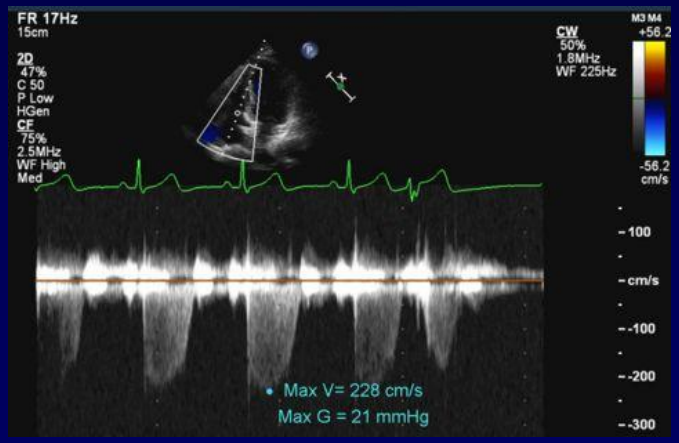
- RECIDIVE

  Il 30% dei pazienti con VTE ha ricorrenti episodi di tromboembolismo venoso

- SINDROME POST-TROMBOTICA
  - Complicanza tardiva della DVT
  - Incidenza del 20-25% a 2 anni

- IPERTENSIONE POLMONARE CRONICA
  - Incidenza del 4% a 4 anni

- Ulcerazioni venose



Prandoni P, et al. A*nn Intern Med* 1996; Ginsberg JS. *Arch Intern Med* 2004;164:

Pengo V, et al; for T Pul Hyp Study Group. *N Engl J Med* 2004;350 2257.

Tromboembolismo venoso: prognosi a lungo termine

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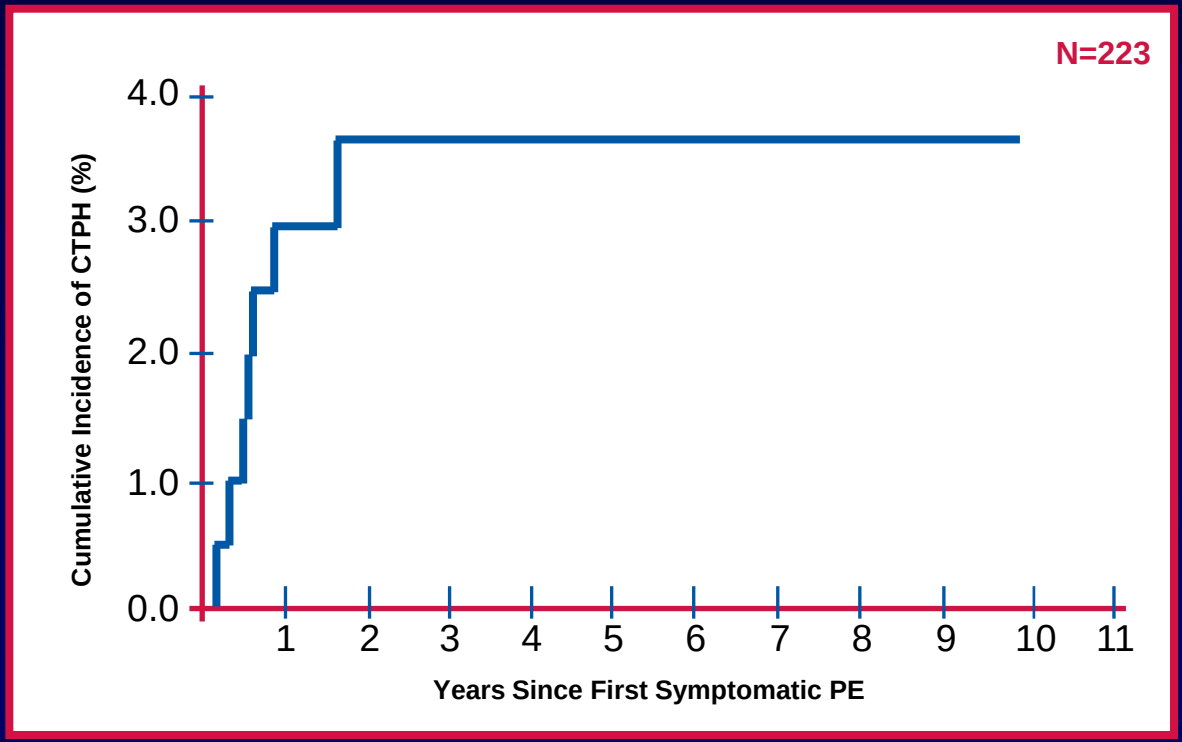
- Incidenza cumulativa di ipertensione polmonare sintomatica in pazienti con embolia polmonare acuta
  - 1.0% a 6 mesi
  - 3.1% a 1 anno
  - 3.8% a 2 anni



Pengo V et al; for Thr Pul Hypertension Study Group. *N Engl J Med* 2004;350:2257-2264.

Tromboembolismo venoso: obiettivi della terapia

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Goals terapeutici nella fase acuta:

Impedire la propagazione

e l'embolizzazione del trombo

(anticoagulazione, filtri cavali)

Ridurre le resistenze polmonari (post-carico ventricolare destro)

(trombolisi, anticoagulazione, embolectomia)

Goals terapeutici a lungo termine

Prevenire complicanze e recidive

Una appropriata terapia anticoagulante riduce
di 3 volte la ricorrenza di VTE
Il trattamento a lungo termine è necessario per i pazienti con
fattori di rischio permanenti

Tromboembolismo venoso: Approccio Clinico

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CRITERIO DOMINANTE

- Paz. emodinamicamente instabile — ***TEMPO***
- Paz. normoteso, dispnoico — ***Stratificazione Prognostica***
- Paz. eupnoico, dolore toracico parietale, sospetta DVT — ***Accuratezza Diagnostica***

Tromboembolismo venoso: fisiopatologia

Dr. S. Grifoni

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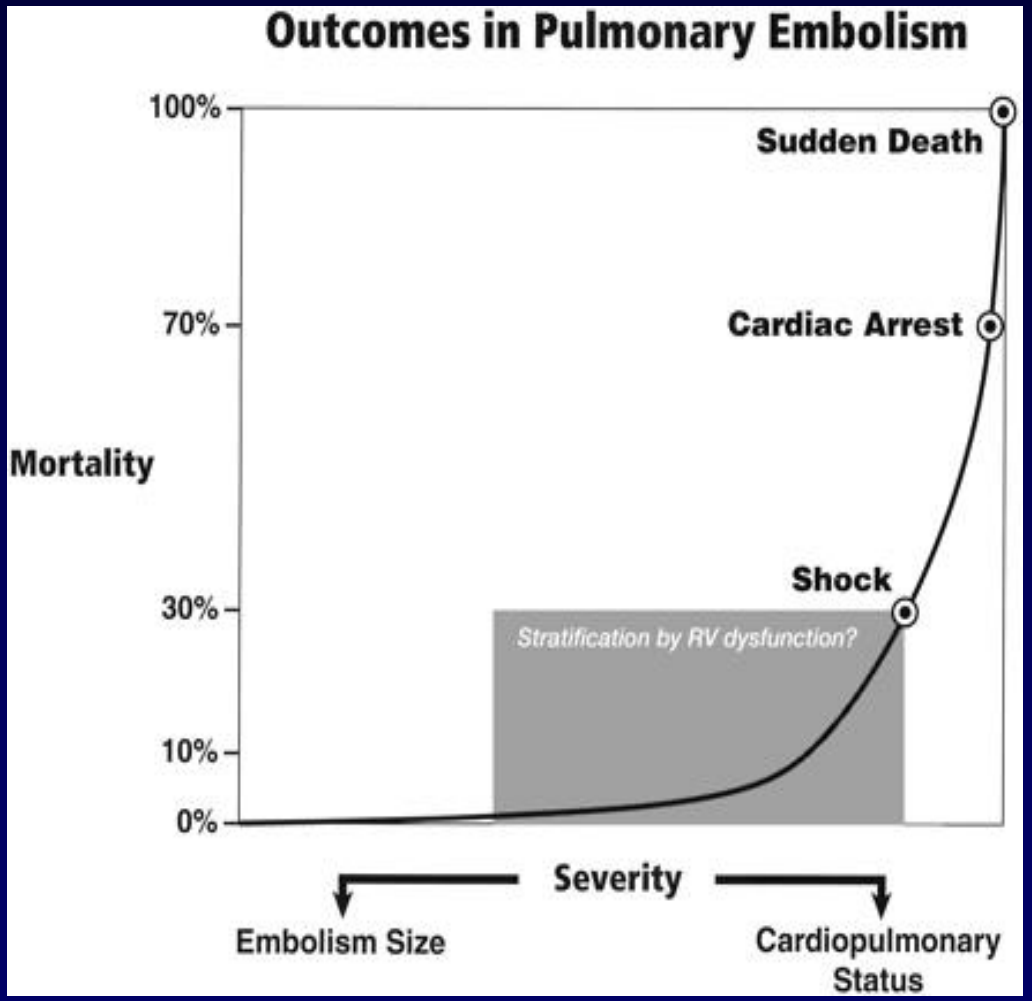

Wood KE, Chest 2002

Tromboembolismo venoso: fisiopatologia

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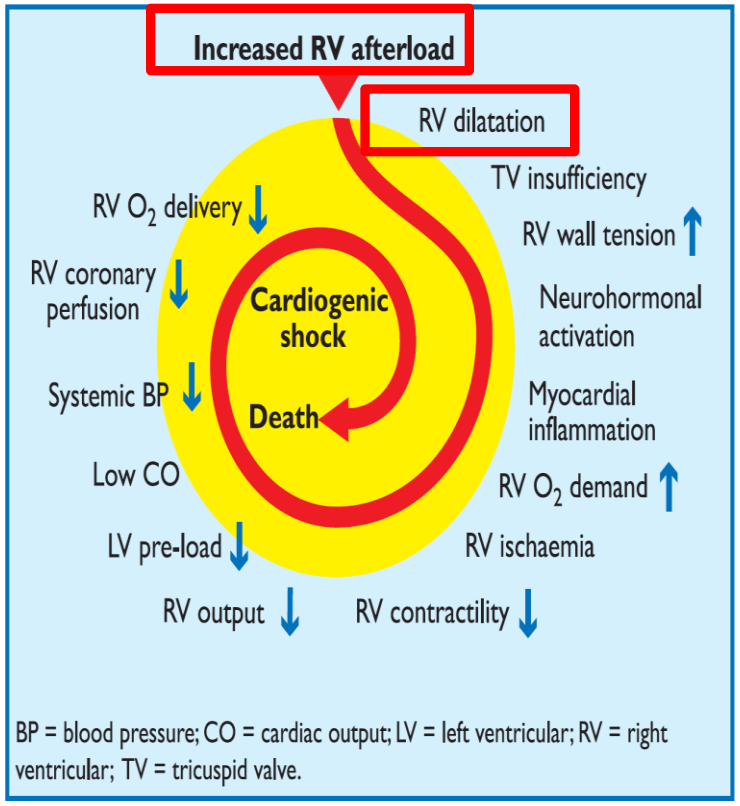
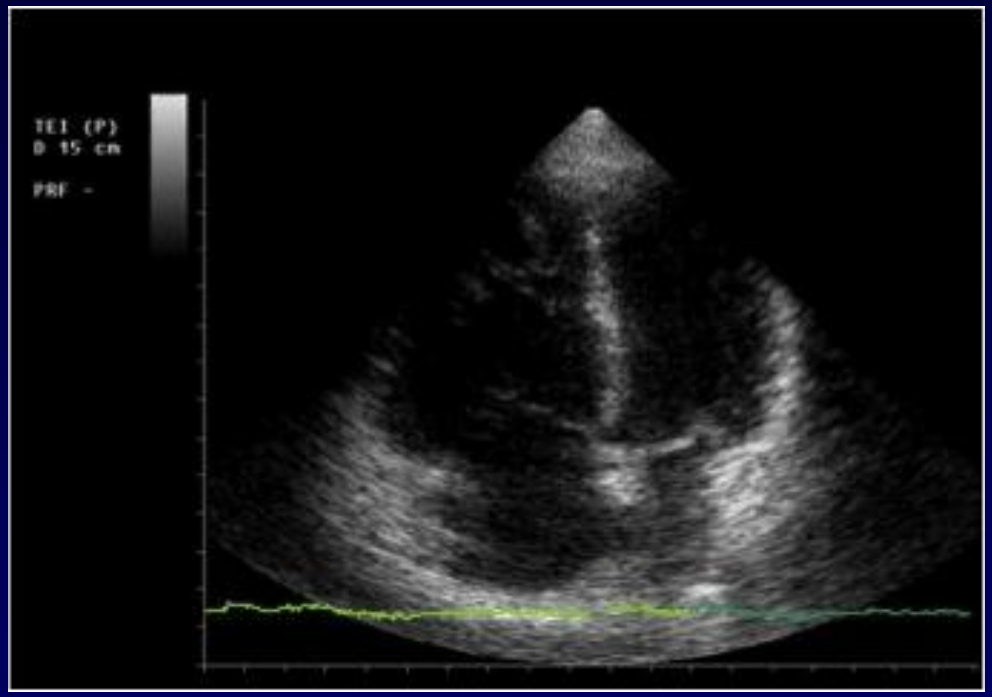


Figure 1 Key factors contributing to haemodynamic collapse in acute pulmonary embolism



La DISFUNZIONE VENTRICOLARE DESTRA risulta il meccanismo fisiopatologico maggiormente implicato nella prognosi del paziente: il riconoscimento di tale quadro permette un corretto inquadramento prognostico e terapeutico del paziente

Tromboembolismo venoso: Arresto Cardiaco

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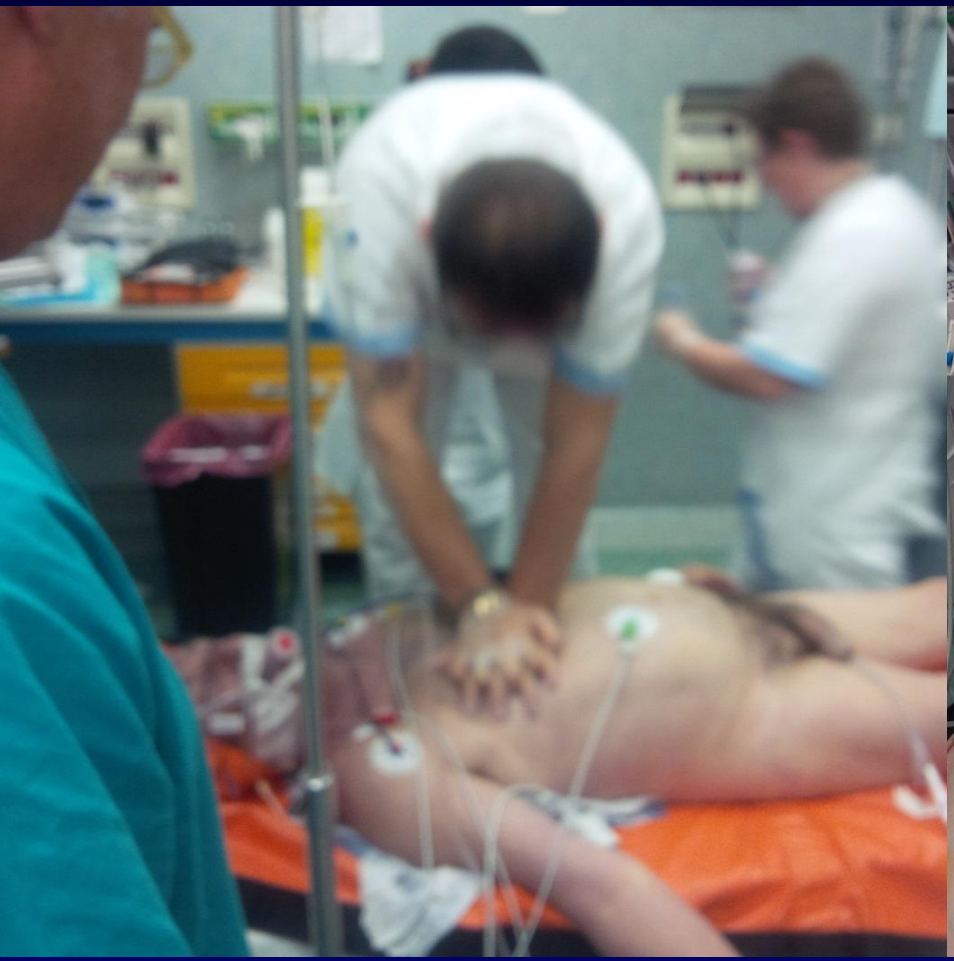

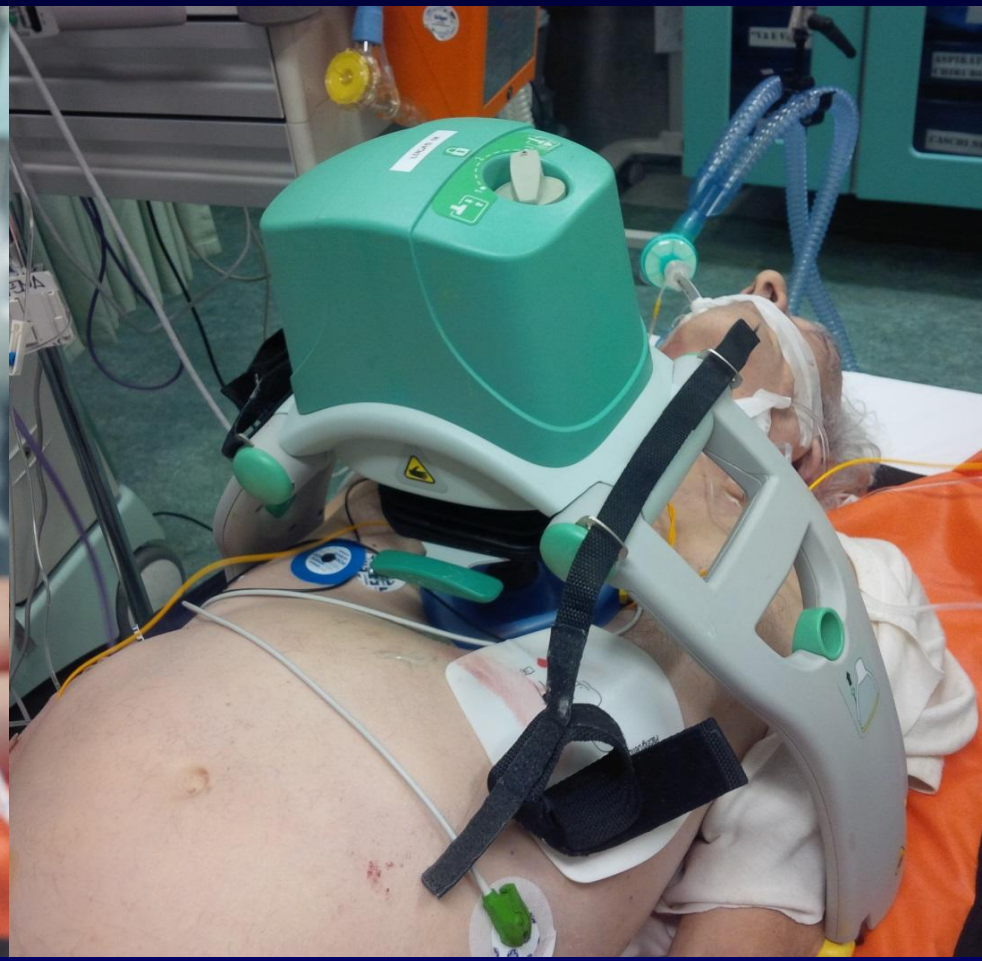

VTE: algoritmo diagnostico-terapeutico

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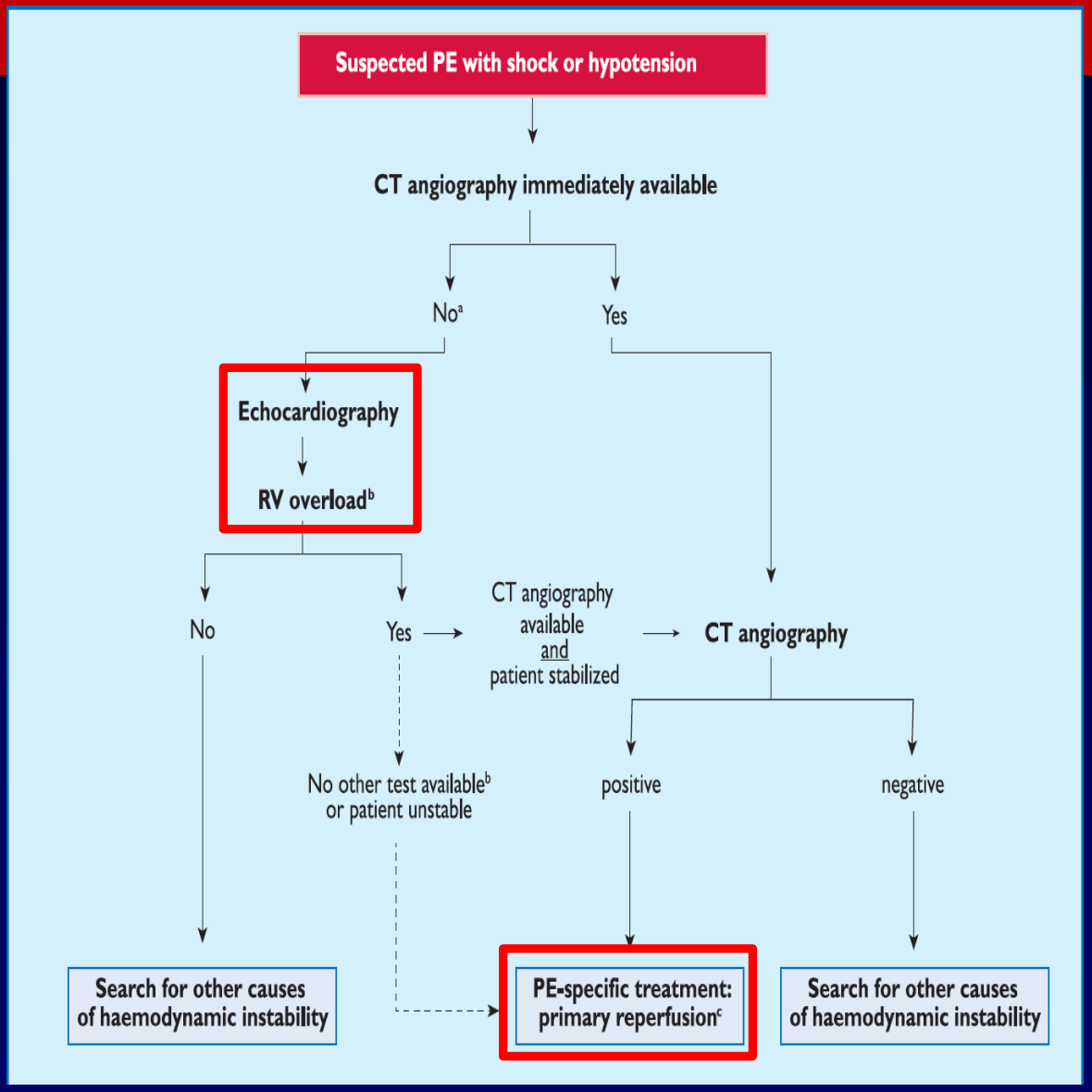

Nel paziente **con instabilità emodinamica**, le cui condizioni cliniche non permettano l'esecuzione di una AngioTC, sono indicati esami mirati *bed-side* (ecocardiogramma transtoracico, CUS, eventuale TEE).

Il rilievo di ecocardiografico di disfunzione ventricolare destra in tali pazienti è sufficiente per avviare una **terapia di riperfusione** (trombolisi, trattamento endovascolare od embolectomia chirurgica).

ESC Guidelines, 2014

Trombolisi sistemica: realtà italiana

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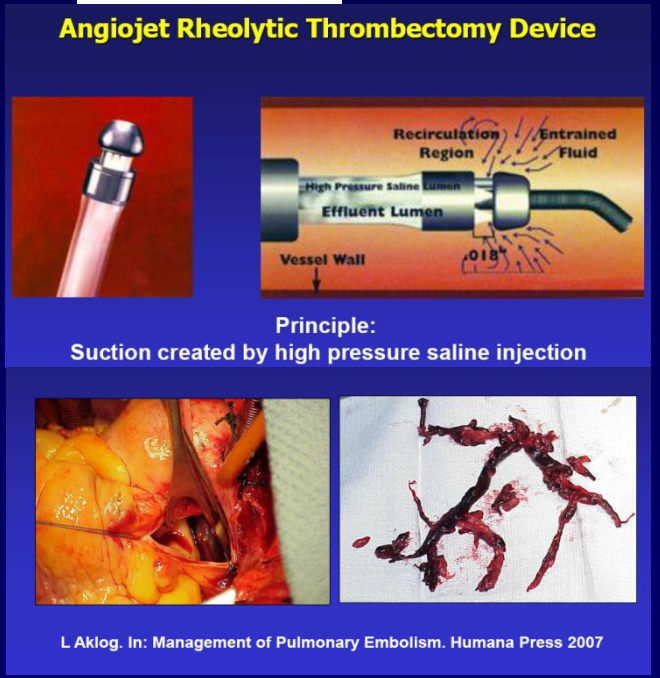
Registro italiano IPER
(1716 pazienti, 47 ospedali, 4 anni):

-pazienti sottoposti a trombolisi : 10.8%
-% di pazienti ad alto rischio sottoposti a trombolisi: 41%

-14 pazienti (0.8%) sottoposti a trombectomia percutanea
-2 pazienti ad embolectomia chirurgica
-attuale possibilità di ECMO come «bridge-therapy»

-in 64 pazienti (3.7%) impianto di filtro cavale



Trombolisi sistemica: evidenze

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Web Table 4 Contraindications to thrombolytic therapy (adapted from ref. 312)

Absolute contraindications:[a]

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke in the preceding 6 months
- Central nervous system damage or neoplasms
- Recent major trauma/surgery/head injury in the preceding 3 weeks
- Gastrointestinal bleeding within the last month
- Known bleeding risk

Relative contraindications

- Transient ischaemic attack in the preceding 6 months
- Oral anticoagulant therapy
- Pregnancy, or within one week postpartum
- Non-compressible puncture site
- Traumatic resuscitation
- Refractory hypertension (systolic blood pressure >180 mm Hg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer

[a]Absolute contraindications to thrombolysis might become relative in a patient with immediately life-threatening high-risk PE.

Incidenza di sanguinamenti intracranici: **1-2%**

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Trombolisi sistemica: evidenze

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CHEST

Original Research

THROMBOEMBOLISM

Efficacy and Safety of Low Dose Recombinant Tissue-Type Plasminogen Activator for the Treatment of Acute Pulmonary Thromboembolism

A Randomized, Multicenter, Controlled Trial

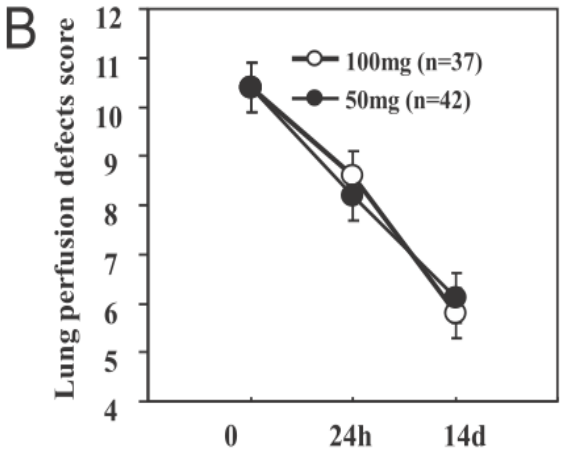

Table 3—*Comparison of Adverse Events During the First 14 d After Treatment, Comparing Two Treatments for PTE*

Adverse Events	rt-PA 100 mg (n = 48)	rt-PA 50 mg (n = 55)	*P*
Death	3 (6)	1 (2)	.472
Due to PTE	2 (4)	1 (2)	…
Due to bleeding	1 (2)	0 (0)	…
Bleeding complications	17 (32)	11 (17)	.054
Major bleeding	5 (10)	2 (3)	.288
Fatal bleeding	1 (2)	0 (0)	…
Others	4 (8)	2 (3)	…
Minor bleeding	12 (22)	9 (14)	.214
Recurrent PTE	2 (4)	1 (2)	.858
Fatal	0 (0)	0 (0)	…
Nonfatal	2 (4)	1 (2)	…

Data presented are number (%) of patients. Others = other major bleeding without death. See Table 1 for expansion of abbreviations.

Wang C et al Chest 2010

VTE: stratificazione prognostica

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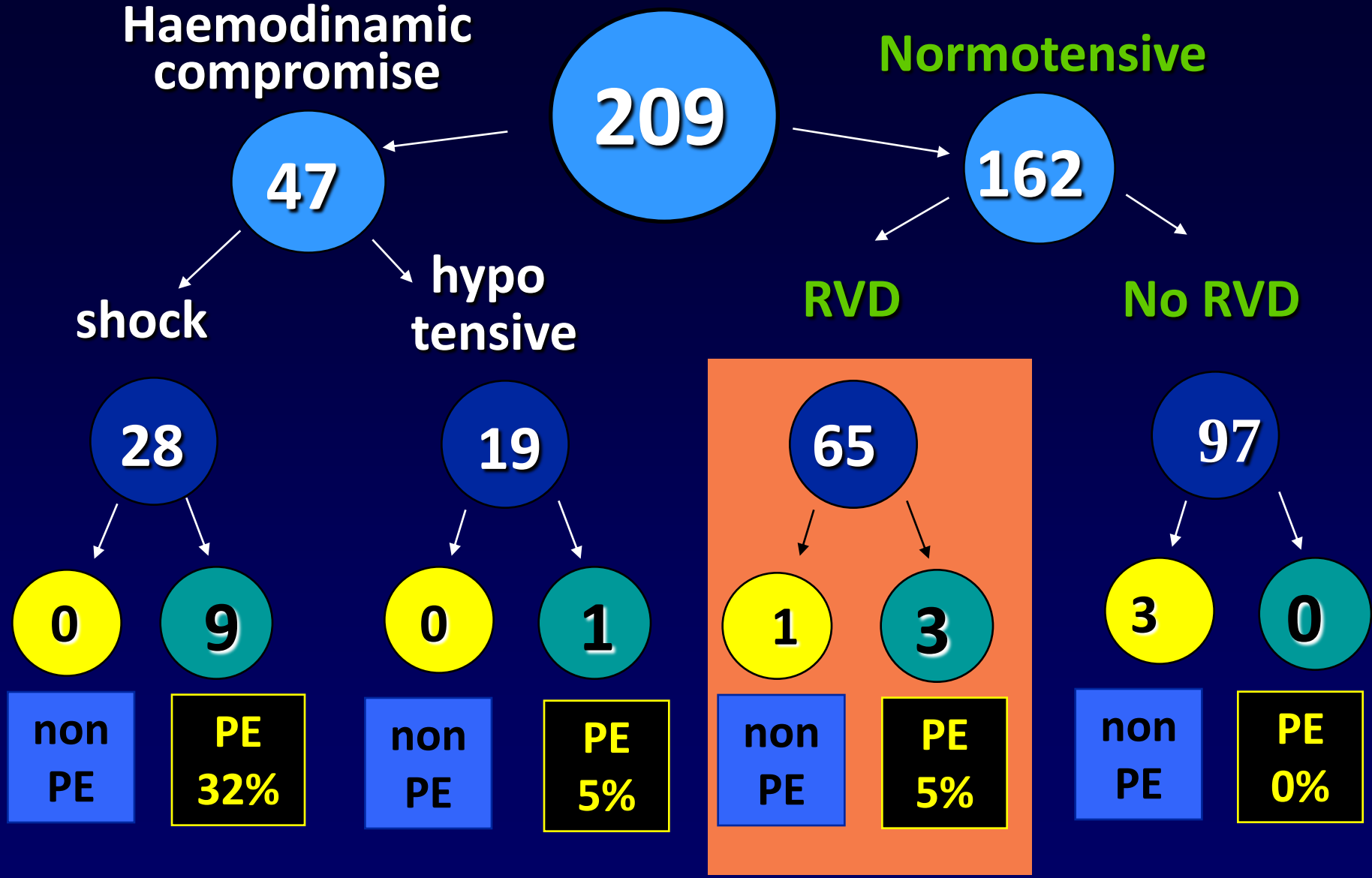
Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V or sPESI ≥I[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High >15%		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	–	+	Both positive	
	Intermediate–low	–	+	Either one (or none) positive[e]	
Low <1%		–	–	Assessment optional; if assessed, both negative[e]	

La stratificazione prognostica è strettamente correlata alla presenza dei fattori di rischio associati ad una elevata mortalità in acuto, in primis la presenza di shock / ipotensione
e l'evidenza ecografica / bioumorale (incremento di troponina e BNP) di disfunzione ventricolare destra.
Tali reperti vengono integrati nella stratificazione di rischio da altri fattori clinico-anamnestici, valutabili attraverso il PESI (*Pulmonary embolism severity index*), un punteggio confermatosi ad elevata accuratezza prognostica a 30 giorni.

IN-HOSPITAL MORTALITY (1995-97)

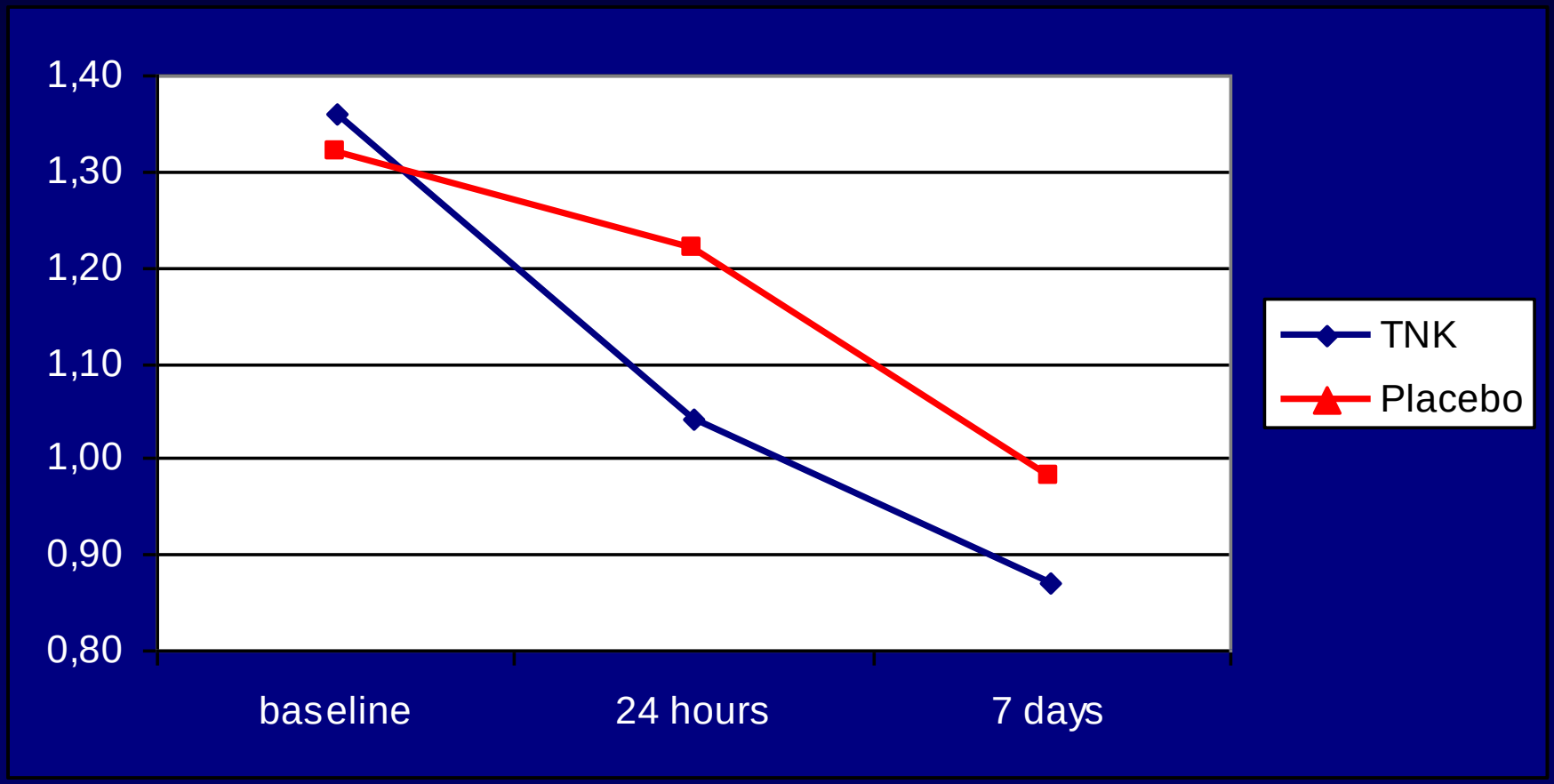


Grifoni et al. Circulation, 2000

TNK in normotensive PE patients

R/L end-diastolic dimension ratio :

Time course



Agnelli G et al 2007

Trombolisi nei pazienti a rischio intermedio

S. Grifoni

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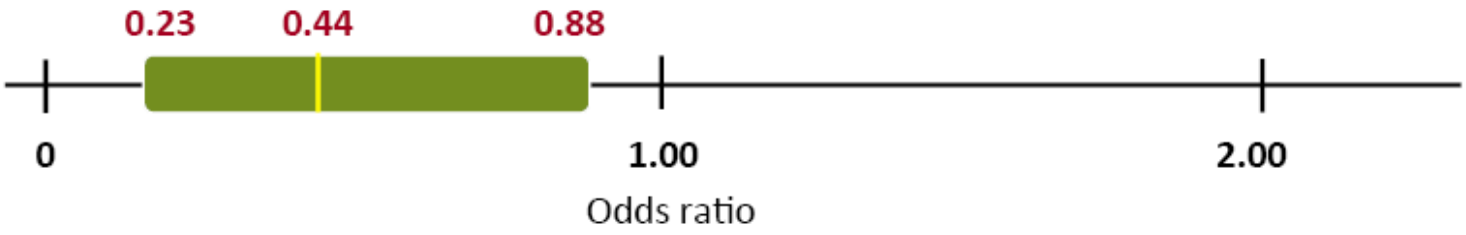
PEITHO: Primary efficacy outcome

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality or hemodynamic collapse within 7 days of randomization	13	(2.6)	28	(5.6)	0.015



Kostantinides et al, NEJM 2014

Trombolisi nei pazienti a rischio intermedio

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PEITHO: Safety outcomes (2)

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All strokes by day 7	12	(2.4)	1	(0.2)	0.003
Hemorrhagic	10		1		
Ischemic	2		0		
Serious adverse events (SAE)	29	(5.7)	39	(7.8)	0.19

Kostantinides et al, NEJM 2014

Trombolisi nei pazienti a rischio intermedio

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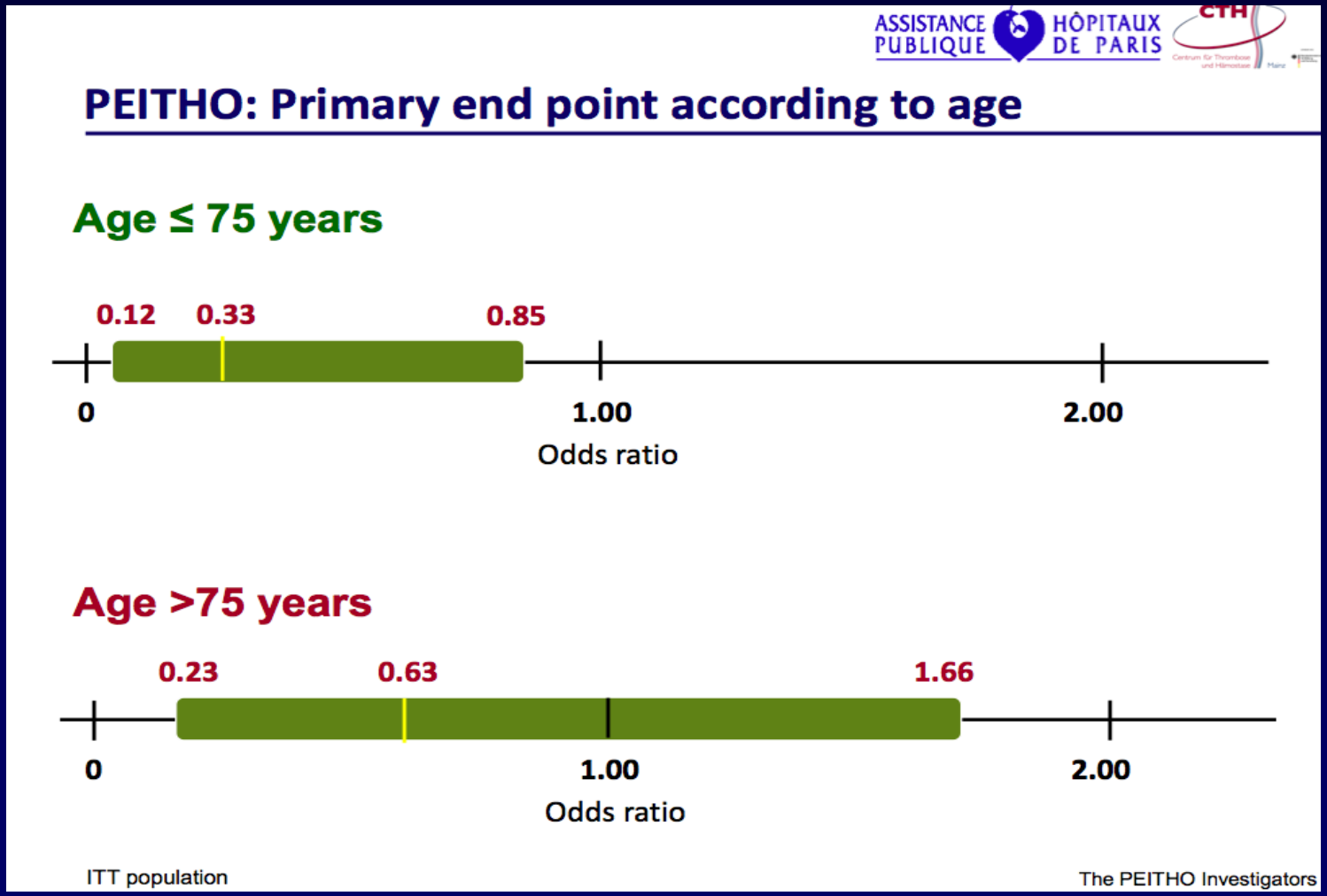

Kostantinides et al, NEJM 2014

Trombolisi nei pazienti a rischio intermedio

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Moderate Pulmonary Embolism Treated With Thrombolysis (from the "MOPETT" Trial)

Mohsen Sharifi, MD[a,b,*], Curt Bay, PhD[b], Laura Skrocki, DO[a], Farnoosh Rahimi, MD[a], and Mahshid Mehdipour, DMD[a,b], "MOPETT" Investigators

Table 2
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.

Am J Card 2013

Trombolisi nei pazienti a rischio intermedio

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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	—

Data are presented as mean ± SD or n (%).

Am J Card 2013

Pazienti a rischio intermedio: proposta di trattamento

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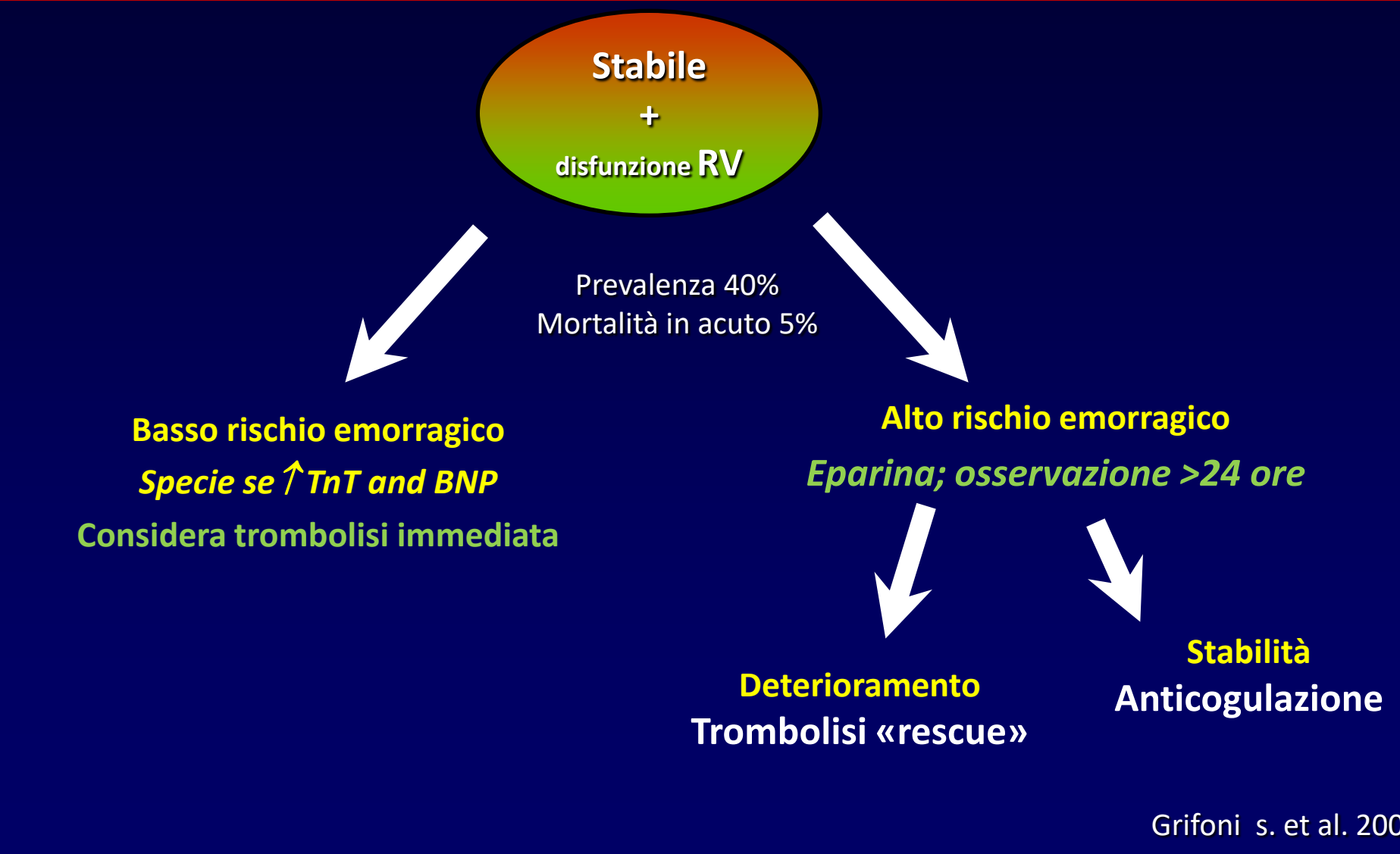

Grifoni s. et al. 2002

Pazienti a rischio intermedio: markers prognostici

S. Grifoni

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Limiti dei marker di disfunzione ventricolare destra

- Non esistono studi di confronto fra *scores* clinici, biomarkers ed *imaging* che abbiano identificato il miglior indicatore prognostico
- Sono stati utilizzati nei vari studi *cut-off* differenti per i vari biomarkers
- Nessun test ha dimostrato un potere predittivo positivo che possa guidare nella scelta della trombolisi

Pazienti a rischio intermedio:

quali altri markers prognostici?

S. Grifoni

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ORIGINAL ARTICLE

Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate

Simone Vanni,[1] David Jiménez,[2] Peiman Nazerian,[1] Fulvio Morello,[3] Michele Parisi,[4] Elena Daghini,[5] Mauro Pratesi,[5] Raquel López,[6] Pedro Bedate,[7] José Luis Lobo,[8] Luis Jara-Palomares,[9] Ana K Portillo,[2] Stefano Grifoni[1]

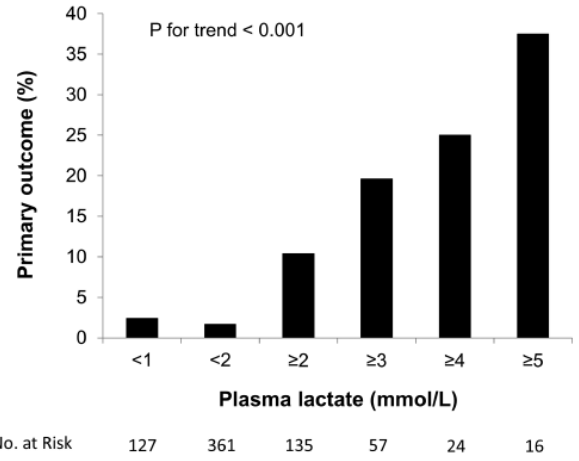

Figure 2 Frequency of the primary outcome according to baseline lactate levels.

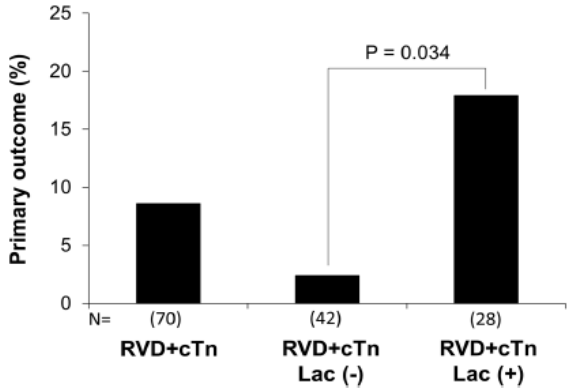

Figure 3 Escalation of PE-related complication rates depending on lactate levels in combination with echocardiography and troponin. cTn, elevated cardiac troponin; Lac (+), lactate ≥2 mmol/L; Lac (–), lactate <2 mmol/L; RVD, right ventricular dysfunction.

Thorax, 2015

Pazienti a rischio intermedio:

quali altri markers prognostici?

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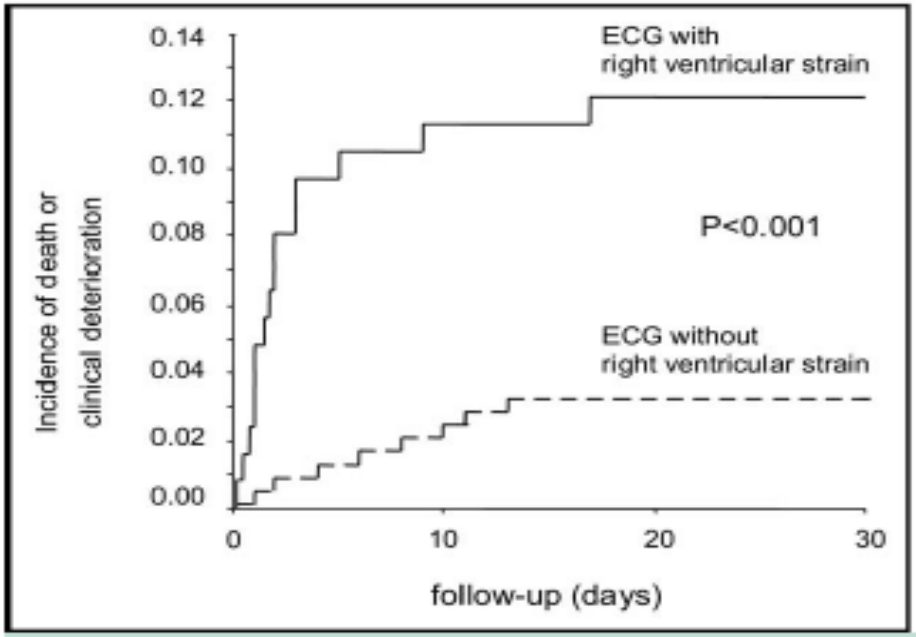

Figure 1 In-hospital follow-up of patients with first episode of acute pulmonary embolism and normal blood pressure based on ECG pattern at presentation. ECG = electrocardiography.

-S1 Q3 T 3

-BBdx

-Onde T negative in V1-V4

Prognostic value of ECG among patients with acute pulmonary embolism and normal blood pressure.
Vanni S, Polidori G, Vergara R, Pepe G, Nazerian P, Moroni F, Daviddi F, Grifoni S.
Am J Med. 2009 Mar;122(3):257

Pazienti a rischio intermedio:

quali altri markers prognostici?

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Carlo Bova[1], Olivier Sanchez[2,3], Paolo Prandoni[4], Mareike Lankeit[5], Stavros Konstantinides[5], Simone Vanni[6] and David Jiménez[7]

TABLE 5 Risk score

Predictor	Points
SBP 90–100 mmHg	2
Elevated cardiac troponin	2
RVD (echocardiogram or CT scan)	2
Heart rate ⩾110 beats per min	1

Points are assigned for each variable of the scoring system to obtain a total point score (range 0–7). SBP: systolic blood pressure; RVD: right ventricular dysfunction; CT: computed tomography.

Eur Resp J, 2014

Pazienti a rischio intermedio:

quali altri markers prognostici?

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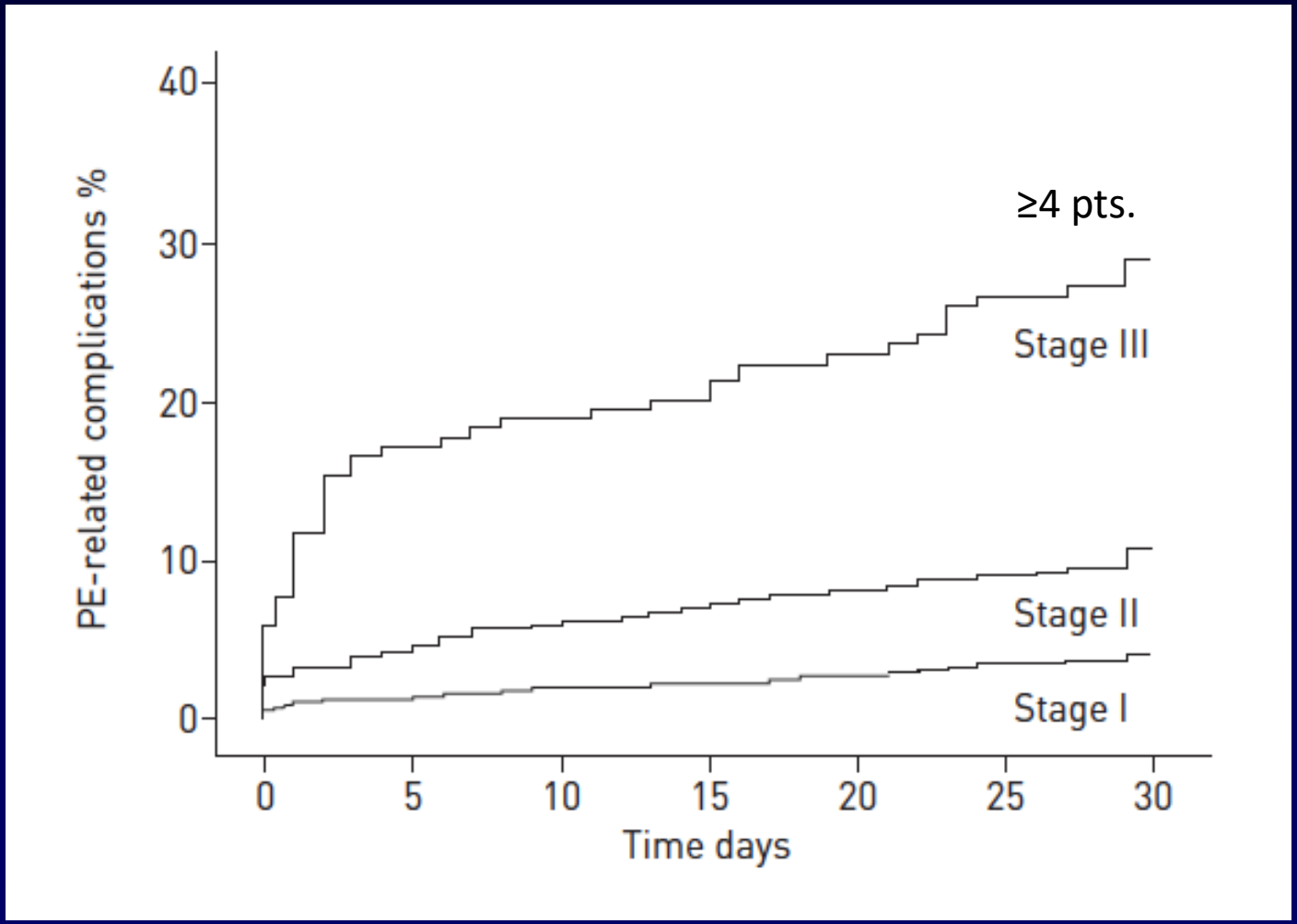

Eur Resp J, 2014

Edoxaban:

studio HOKUSAI-VTE

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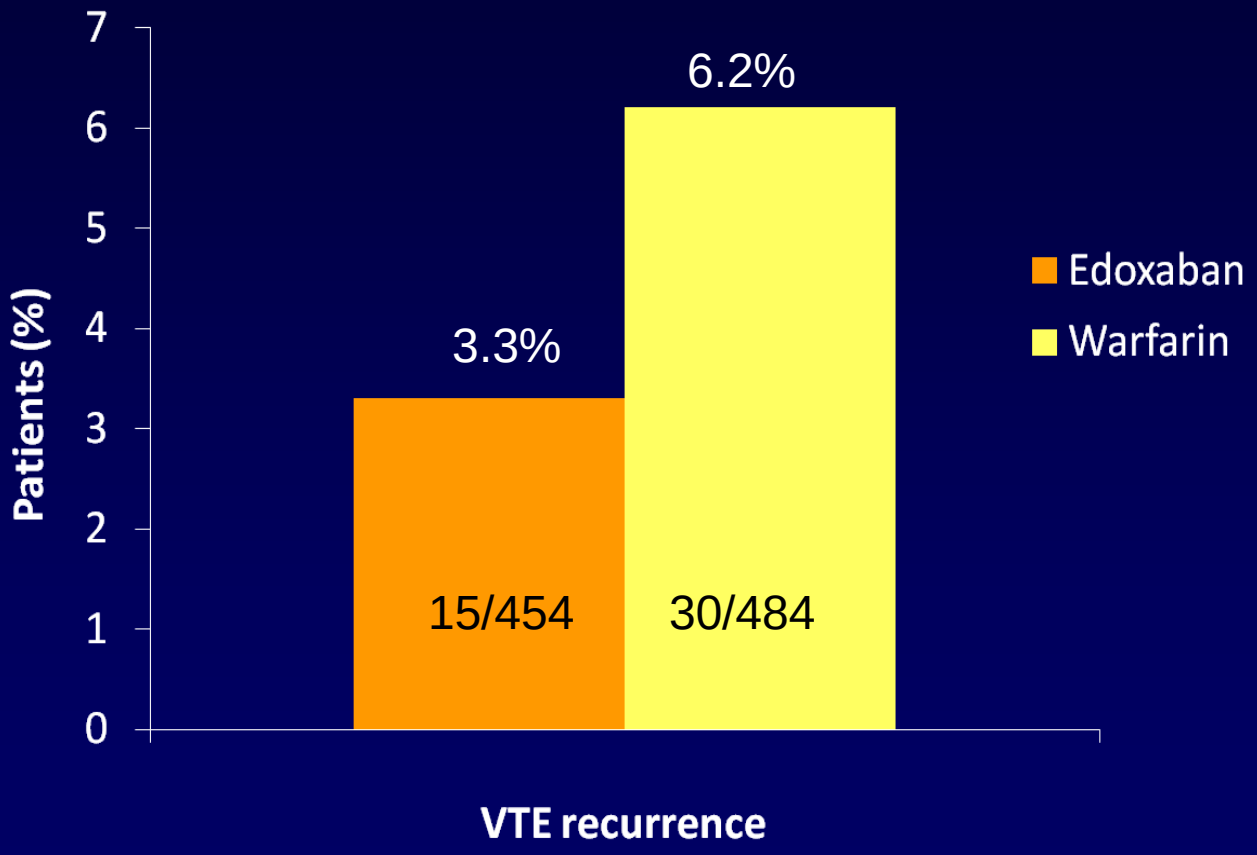


In PE patients with NT-proBNP levels ≥500 pg/mL
recurrent VTE occurred in 15 of 454 patients (3.3%) who received edoxaban
and in 30 of 484 patients (6.2%) given warfarin (HR 0.52 [0.28-0.98])

I NAO: EDOXABAN

EDOXABAN

-**efficacia sovrapponibile** al trattamento tradizionale con WARFARIN in termini di recidiva di malattia tromboembolica venosa (RR 0.89; IC 95%: 0.70-1.13)

-**ridotta incidenza di sanguinamenti**, maggiori o clinicamente rilevanti (RR 0.81; IC 95%: 0.71-0.94)

Edoxaban	Hokusai-VTE[298]	Double-blind, double-dummy	LMWH/edoxaban (60 mg o.d.; 30 mg o.d. if creatinine clearance 30–50 ml/min or body weight <60 kg) vs. UFH or LMWH/warfarin	Variable, 3–12 months	8240 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 3.2% under edoxaban vs. 3.5% under warfarin	Major or CRNM bleeding: 8.5% under edoxaban vs. 10.3% under warfarin

I NAO: DABIGATRAN

S. Grifoni

Dip. Emergenza Urgenza- Careggi - Firenze

DABIGATRAN

-**efficacia sovrapponibile** al trattamento tradizionale con WARFARIN in termini di recidiva di malattia tromboembolica venosa, nei risultati congiunti di due trial clinici della durata di 6 mesi (HR 1.09; IC 95%: 0.76-1.57)

-**incidenza sovrapponibile di sanguinamenti maggiori** (HR 0.73; IC 95%: 0.48-1.11) ridotta incidenza di sanguinamenti di qualsiasi entità

Drug	Trial	Design	Treatments and dosage	Duration	Patients	Efficacy outcome (results)	Safety outcome (results)
Dabigatran	RE-COVER[293]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2539 patients with acute VTE	Recurrent VTE or fatal PE: 2.4% under dabigatran vs. 2.1% under warfarin	Major bleeding: 1.6% under dabigatran vs. 1.9% under warfarin
	RE-COVER II[294]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2589 patients with acute VTE	Recurrent VTE or fatal PE: 2.3% under dabigatran vs. 2.2% under warfarin	Major bleeding: 15 patients under dabigatran vs. 22 patients under warfarin

I NAO: RIVAROXABAN

S. Grifoni

Dip. Emergenza Urgenza- Careggi - Firenze

RIVAROXABAN

-**efficacia sovrapponibile** al trattamento tradizionale con WARFARIN in termini di recidiva di tromboembolia
(HR 1.12; IC 95%: 0.75-1.68)
-sovrapponibile incidenza di sanguinamenti di rilevanza clinica; **ridotta incidenza di sanguinamenti maggiori**
(1.1% vs 2.2.%; HR 0.49; IC 95%: 0.31-0.79);

Rivaroxaban	EINSTEIN-DVT[295]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	3449 patients with acute DVT	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 3.0% under warfarin	Major or CRNM bleeding 8.1% under rivaroxaban vs. 8.1% under warfarin
	EINSTEIN-PE[296]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	4832 patients with acute PE	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 1.8% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs. 11.4% under warfarin

I NAO: APIXABAN

S. Grifoni

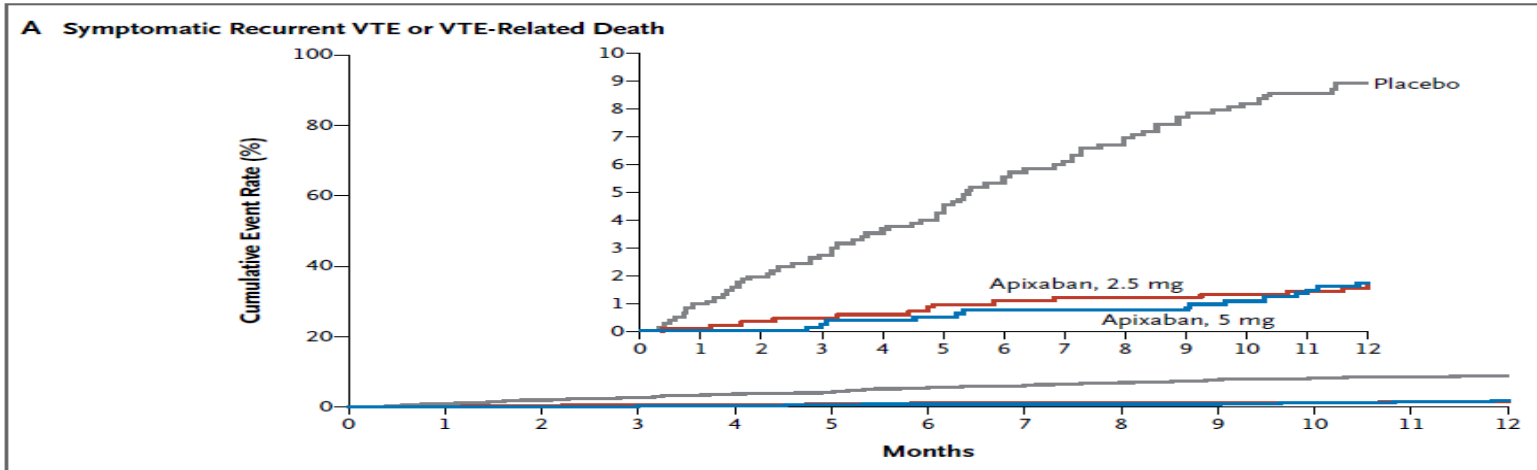
Dip. Emergenza Urgenza- Careggi - Firenze

APIXABAN

-**efficacia sovrapponibile** al trattamento tradizionale con WARFARIN in termini di recidiva di malattia tromboembolica venosa (RR 0.84; IC 95%: 0.60-1.18)

-**ridotta incidenza di sanguinamenti**, sia maggiori che clinicamente rilevanti (RR 0.44; IC 95%: 0.36-0.55)

Apixaban	AMPLIFY[297]	Double-blind, double-dummy	Apixaban (10 mg b.i.d. for 7 days, then 5 mg b.i.d.) vs. enoxaparin/warfarin	6 months	5395 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 2.3% under apixaban vs. 2.7% under warfarin	Major bleeding: 0.6% under apixaban vs. 1.8% under warfarin



NAO

Tutti i NAO sono risultati **non inferiori al warfarin** in termini di recidiva di tromboembolia, ed **in alcuni casi** più sicuri in termini di sanguinamenti maggiori o clinicamente rilevanti.

In un gruppo selezionato di pazienti a rischio intermedio,
Edoxaban si è dimostrato superiore

Il loro utilizzo in alternativa al WARFARIN è di conseguenza preso in considerazione nelle linee guida ESC 2014 (Classe I, Liv. evidenza B)

NAO: limiti attuali

-Non vi è dimostrazione di una maggiore efficacia della terapia anticoagulante tradizionale nel prevenire recidive di TEP; inoltre, non vi sono tuttora studi di confronto definitivi tra i vari NAO

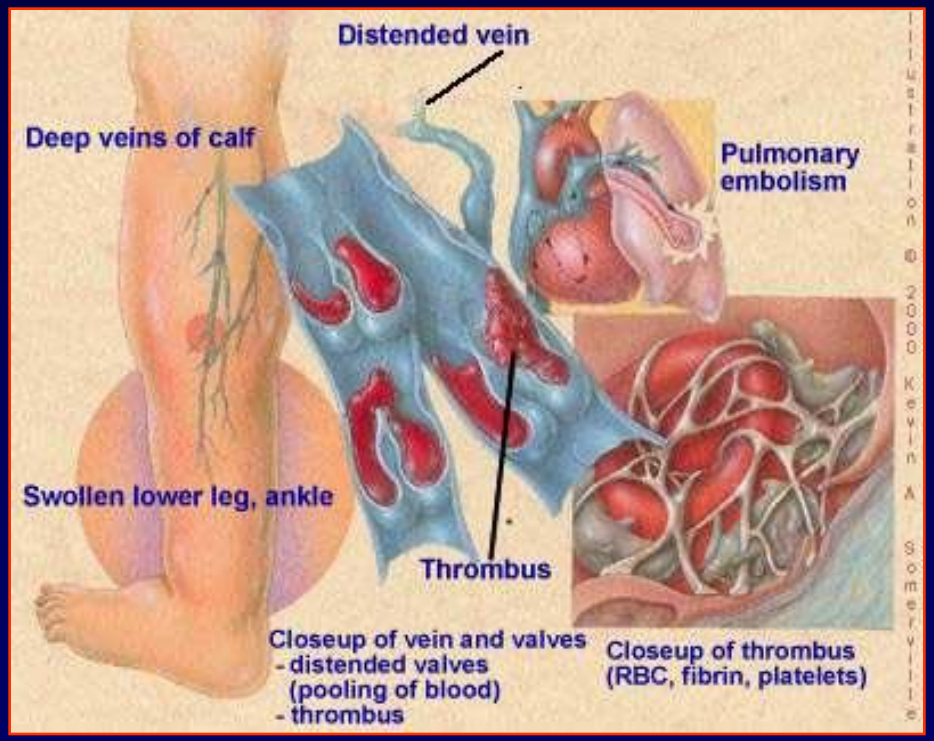
-ridotta esperienza clinica su pazienti >80 anni e con comorbidità significative (nefro- ed epatopatie) o politerapie concomitanti

-ridotta esperienza inerente i tempi di avvio di tale terapia nei pazienti potenzialmente evolutivi (rischio intermedio): studio PEITHO-2

-più complesso approccio agli eventi emorragici, sia per la difficoltà a valutare l'assetto coagulativo che per l'assenza di un efficace antidoto universale (dabigatran ed idarucizumab)

GESTIONE DEL PAZIENTE CON TROMBOEMBOLISMO VENOSO (VTE)

Dip. Emergenza Urgenza- Careggi - Firenze



Ultima riflessione :

“Il nostro corpo è una macchina per vivere.
E’ organizzato a questo scopo e questa è la sua natura
Fate si che la vita prosegua in esso”

Lev Tolstoi

ALTRE DIAPOSITIVE

Conclusioni

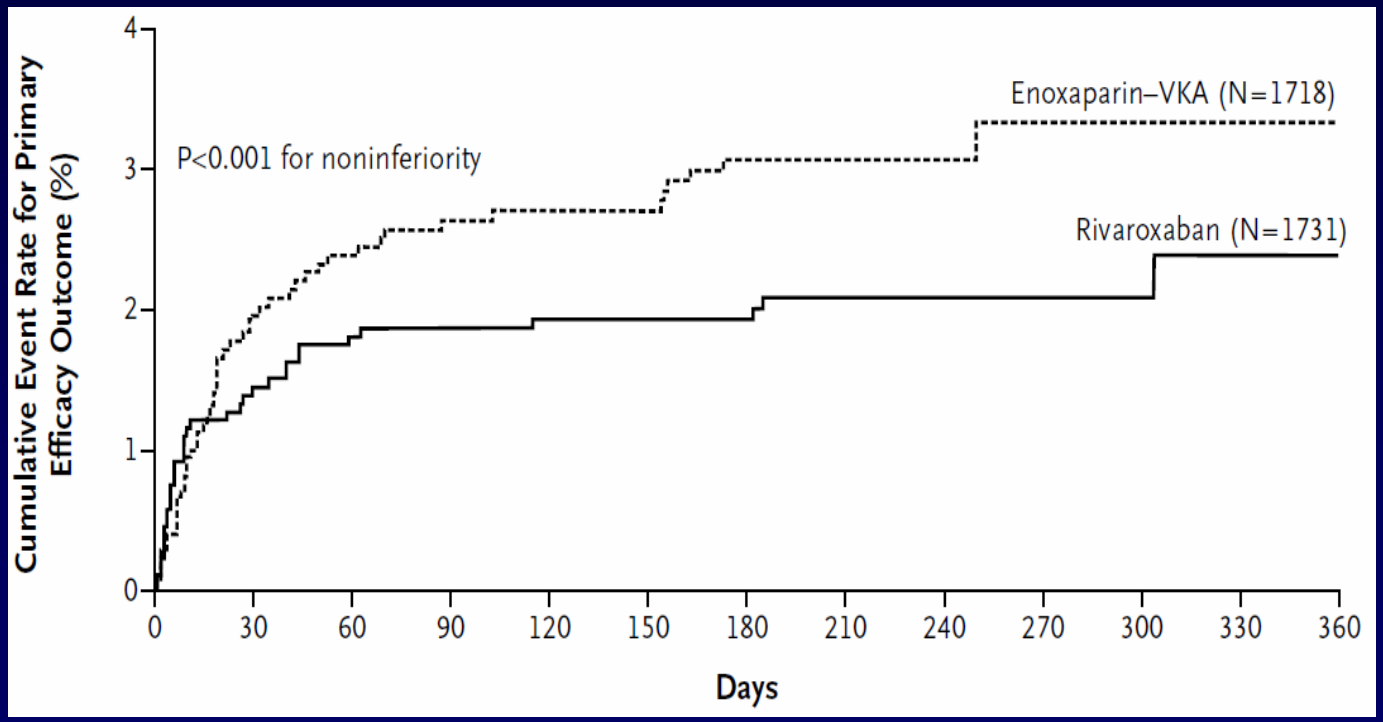
- Trials nel trattamento del tromboembolismo venoso

  Rivaroxaban apixaban hanno mostrato efficacia sovrapponibile alla terapia tradizionale ma con importante riduzione delle emorragie maggiori maggiori HR 0,49
- Negli studi extension ridotta incidenza di tromboembolismo venoso con aumento dell'incidenza di emorragie maggiori per Rivaroxaban e dabigatran (non apixaban) rispetto al placebo
- Edoxaban Sottogruppo di pazienti (n=938) con embolia polmonare ed associato incremento di NTproBNP riduzione delle recidive

Rivaroxaban for acute VTE

The EINSTEIN-DVT trial

Treatment	Recurrent VTE
Rivaroxaban	2.1%
Standard treatment	3.0%



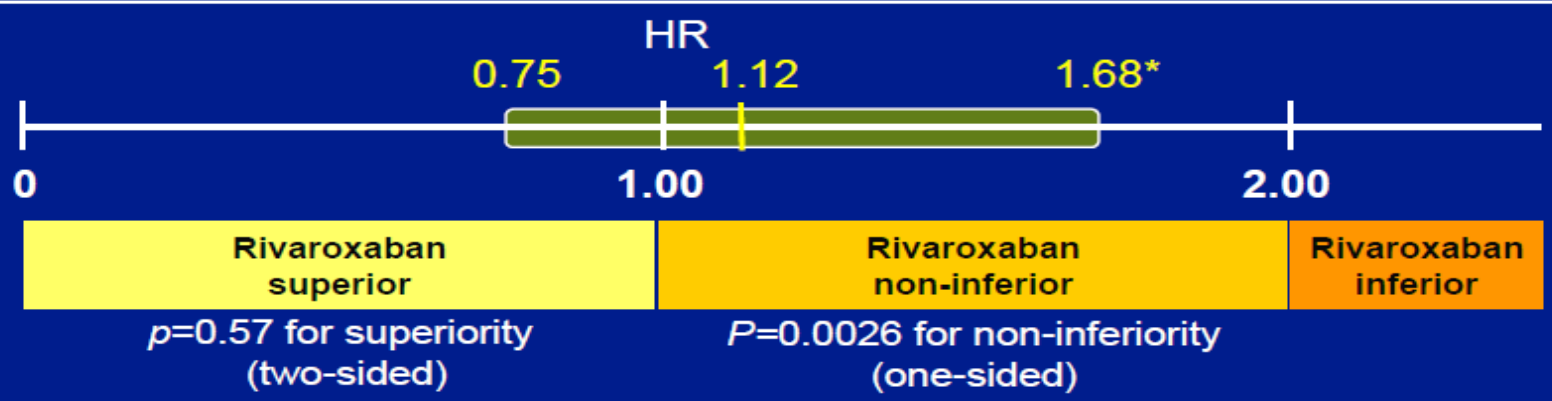
Conclusion: rivaroxaban is as effective and safe as standard treatment for acute DVT

NEJM 2010; 363: 2499

EINSTEIN-PE

EINSTEIN PE: primary efficacy outcome analysis

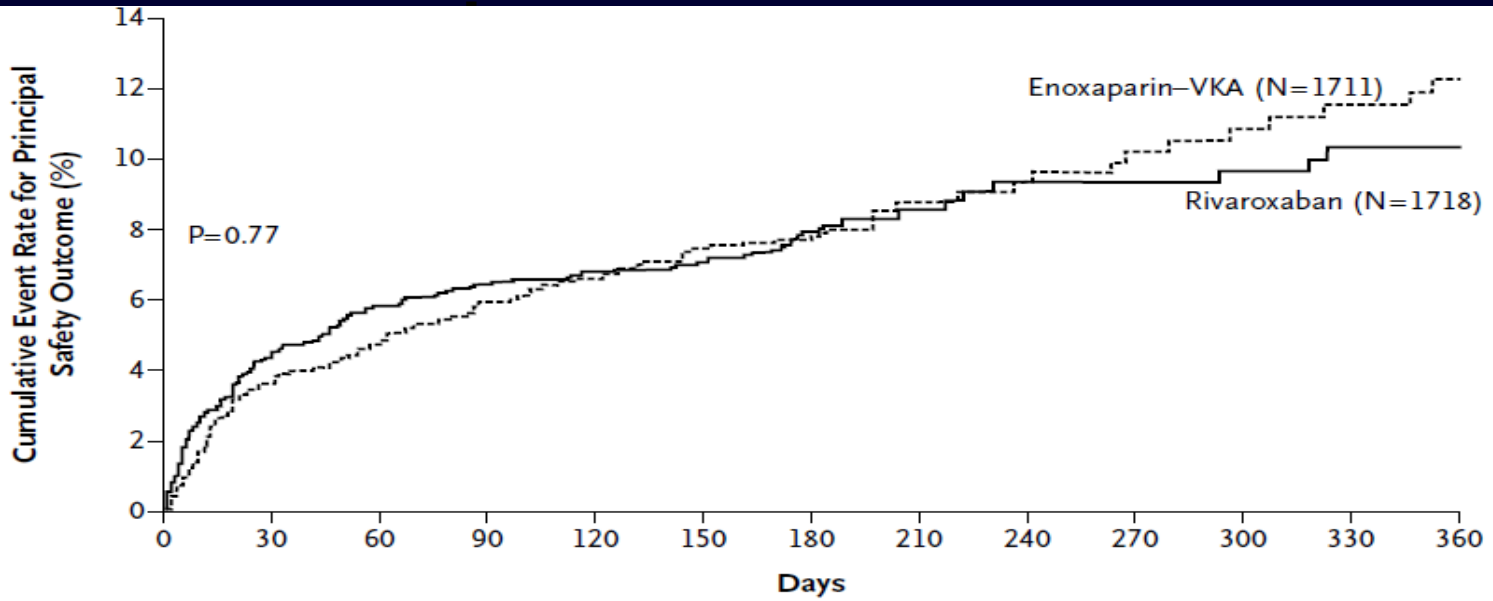
	Rivaroxaban (N=2419)		Enoxaparin/VKA (N=2413)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**50**	**(2.1)**	**44**	**(1.8)**
Recurrent DVT	18	(0.7)	17	(0.7)
Recurrent DVT + PE	0		2	(<0.1)
Non-fatal PE	22	(0.9)	19	(0.8)
Fatal PE/unexplained death where PE cannot be ruled out	10	(0.4)	6	(0.2)



*Potential relative risk increase <68.4%; absolute risk difference 0.24% (–0.5 to 1.02)

NEJM 2012;366:1287-97

EINSTEIN; end-point di



No. at Risk													
Rivaroxaban	1718	1585	1538	1382	1317	1297	715	355	338	304	278	265	140
Enoxaparin–VKA	1711	1554	1503	1340	1263	1238	619	338	321	287	268	249	118

Figure 3. Kaplan–Meier Cumulative Event Rates for the Principal Safety Outcome in the Acute DVT Study.
VKA denotes vitamin K antagonist.

In conclusion, oral rivaroxaban, at a dose of 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily thereafter, without the need for laboratory monitoring, may provide an effective, safe, single-drug approach to the initial and continued treatment of venous thrombosis.

NEJM 2010;263;2499-2510

EINSTEIN PE: conclusions

- In patients with acute symptomatic PE with or without DVT, rivaroxaban showed:
  - Non-inferiority to LMWH/VKA for efficacy: HR=1.12 (0.75–1.69); $p_{\text{non-inferiority}}$ =0.0026 for non-inferiority margin of 2.0
  - Similar findings for principal safety outcome: HR=0.90 (0.76–1.07); *p=0.23*
  - Superiority for major bleeding: HR=0.49 (0.31–0.79) *p*=0.0032
  - Consistent efficacy and safety results irrespective of age, body weight, gender, kidney function and cancer
  - No evidence for liver toxicity

NEJM 2012;366:1287-97

EINSTEIN-Extension: Rivaroxaban in the long-term prevention of recurrent, symptomatic VTE

Patients completed 6 - 12 months of anticoagulant treatment for acute episode of VTE.

Rivaroxaban (direct oral factor Xa inhibitor) 20mg OD vs placebo

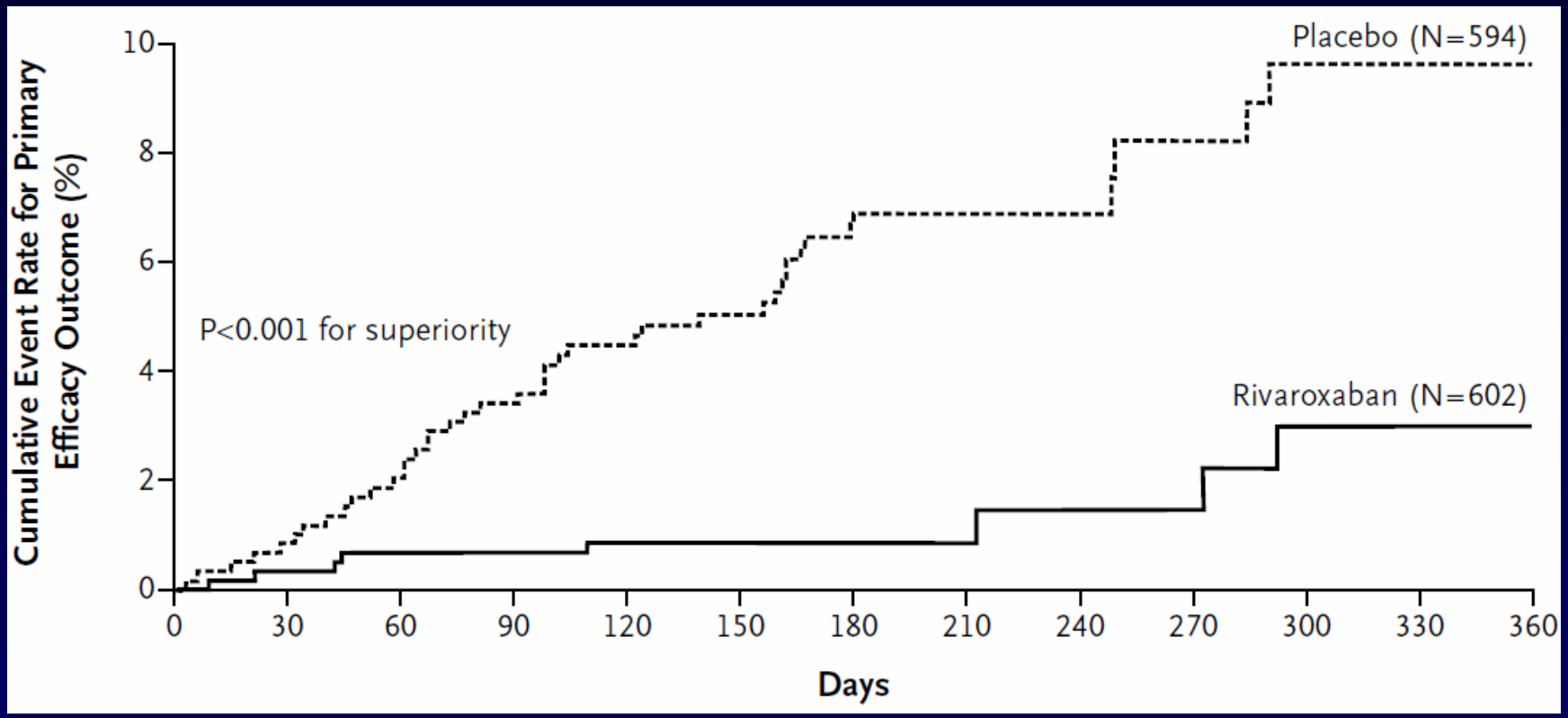
N = 1197

Primary efficacy outcome: symptomatic recurrent VTE (composite of recurrent DVT, non-fatal PE, and fatal PE).

Principal safety outcome: Major bleeding

NEJM 2010; 363: 2499

Rivaroxaban to prevent recurrent VTE
The EINSTEIN-Extension trial



Rivaroxaban prevented 34 recurrent events at a cost of 4 major bleeding events

1 recurrence prevented per 15 patients treated; 1 major bleed per 139 patients treated

NEJM 2010; 363: 2499

EINSTEIN-Extension Results

N = 1197	Rivaroxaban 20mg/OD n(%)	Placebo n (%)	*P*- value
Symptomatic recurrent VTE events*	8 (1.3%)	42 (7.1%)	*P*< 0.0001
Major bleeding	4 (0.7%)	0	*P*=0.106
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)	
Deaths	1 (0.2%)	2 (0.3%)	
ALT 3xULN/total bilirubin >2xULN.	0	0	

*Hazard ratio, 0.18; 95 % CI, 0.09 – 0.39
NNT = 15
NNH = 139

Conclusion: Fixed dose of 20 mg of rivaroxaban once-daily is associated with an 82% relative risk reduction in the recurrence of VTE in patients who had completed a 6 -12 months of anticoagulant therapy for their index event. The mean duration of therapy was 190 days in both groups.

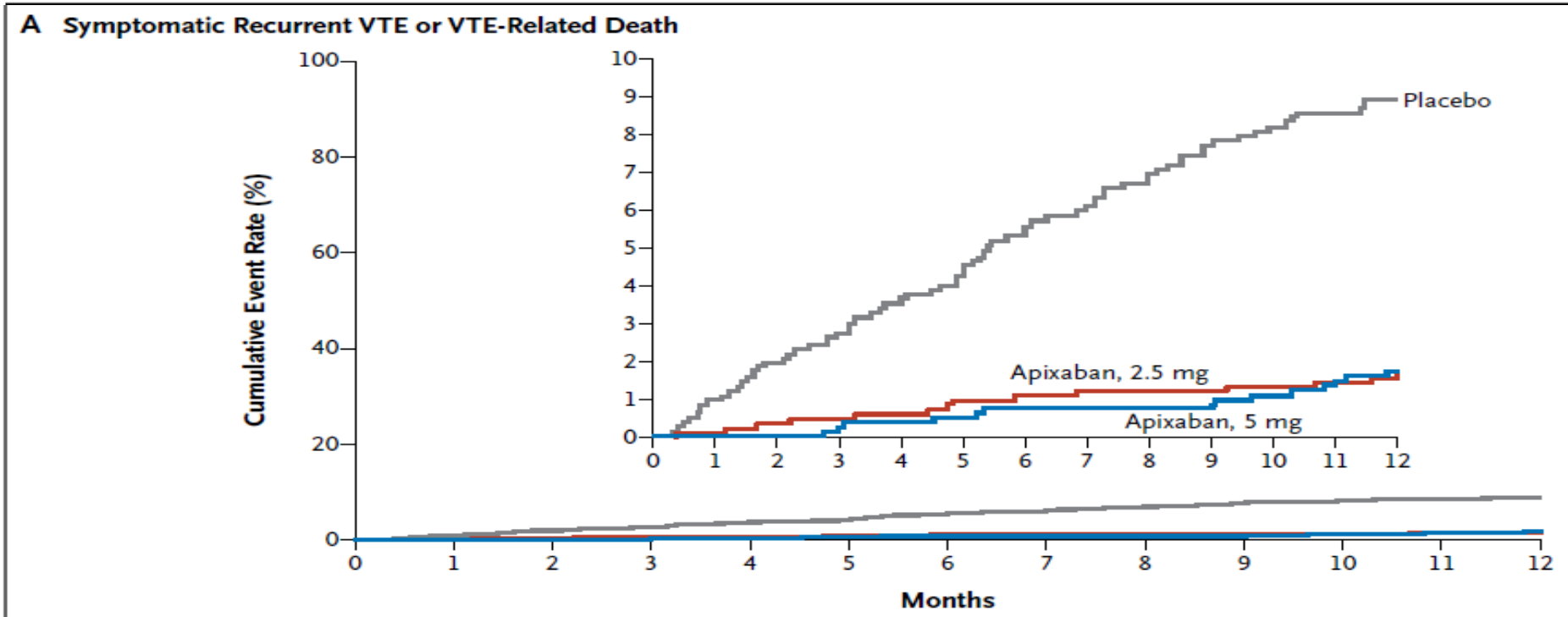
NNT: Number needed to treat
NNH: Number needed to harm

ULN = Upper limit of normal
ALT = Alanine aminotransferase

Buller, American Society of Hematology New Orleans, 2009.

AMPLYFY-Extension Results

Trial	Treatments	Patients	Trials design and methods
extended apixaban vs placebo			
AMPLIFY-EXT , 2012 [NCT00633893] n=2430 follow-up: 12 mo	Extended Treatment with apixaban 5 or 2.5 mg twice daily 12 months versus placebo	patients who have completed their intended treatment for deep vein thrombosis or pulmonary embolism	Parallel groups double blind



No. at Risk					
Apixaban, 2.5 mg	840	836	825	818	533
Apixaban, 5 mg	813	807	799	791	513
Placebo	826	796	768	743	471

NEJM 2013 368:699-708

Limiti dei marker di disfunzione ventricolare destra

- Non esistono studi di confronto fra score clinici, biomarkers ed imaging che abbiano identificato il miglior indicatore prognostico
- Sono state utilizzati nei vari studi cut-off differenti per i vari biomarkers
- Nessun test ha dimostrato un potere predittivo positivo che possa guidare nella scelta del trattamento trombolitico

Limiti del trattamento fibrinolitico secondo Peitho

- Trattamento salvavita nella fase acuta
- Non differenze su RVD a lungo termine

Limiti di NAO nel TEV

Uso diffuso del Warfarin

Bilancio tra costi ed efficacia

Non antidoti

Difficile assessment per quanto riguarda la compliance dei pazienti

Non esistono studi scientifici di confronto tra i diversi farmaci

Difficoltà ad interpretare la non inferiorità dei risultati

Difficile aderenza dei pazienti ad assumere i farmaci due volte al giorno

- Eur H J 2014 kostantinides
- Peitho meyer N E J med 2014
- Pesi semplificato post hoc analisis
- Einstein DVT e Xalia
- Enstein pe clot regression following acute pe 2013 J Tromb and Emostasis
- Kearon chest 2016 su ep e trattamento

Mortalità; PESI e sPESI

Table 3. Thirty-Day Mortality Within Risk Strata Derived From the Original and the Simplified PESI in the Derivation and Validation Cohorts

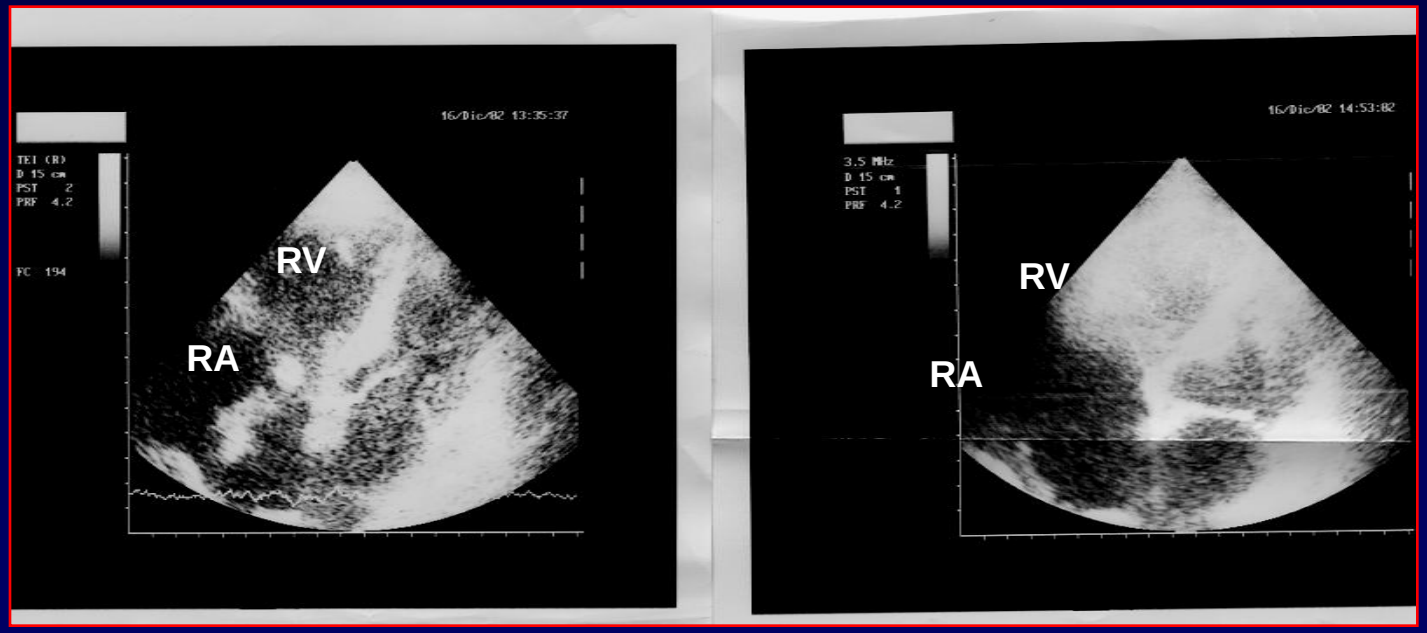
PESI Risk Categories	Original PESI Derivation Cohort, % (95% CI)		Simplified PESI Derivation Study Cohort, % (95% CI)		Simplified PESI Validation (RIETE) Cohort, % (95% CI)	
	Patients (n=10 354)	Deaths[a] (n=953)	Patients (n=995)	Deaths (n=78)	Patients (n=7106)	Deaths (n=434)
Original						
I	19.4 (18.7-20.2)	1.1 (0.7-1.7)	14.3 (12.1-16.4)[b]	2.1 (0.2-4.5)		
II	21.5 (20.7-22.3)	3.1 (2.5-4.0)	22.0 (19.4-24.6)	2.7 (0.6-4.9)		
III	21.7 (20.9-22.5)	6.5 (5.5-7.6)	27.7 (25.0-30.5)[b]	5.4 (2.8-8.1)		
IV	16.4 (15.7-17.1)	10.4 (9.0-11.9)	21.5 (18.9-24.1)[b]	10.3 (6.2-14.3)		
V	21.0 (20.3-21.8)	24.5 (22.7-26.9)	14.5 (12.3-16.7)[b]	22.2 (15.4-29.0)		
Low[d]	40.9 (40.0-41.8)	2.1 (1.7-2.6)	36.3 (33.3-39.3)[c]	2.5 (0.9-4.1)		
High[d]	59.1 (58.1-60.0)	14.0 (13.1-14.9)	63.7 (60.7-66.7)	10.9 (8.5-13.3)		
Simplified						
Low			30.7 (27.8-33.5)	1.0 (0.0-2.1)	36.1 (35.0-37.3)[e]	1.1 (0.7-1.5)
High			69.3 (66.5-72.2)	10.9 (8.5-13.2)	63.9 (62.7-65.0)	8.9 (8.1-9.8)

Abbreviations: CI, confidence interval; PESI, Pulmonary Embolism Severity Index; RIETE, Registro Informatizado de la Enfermedad Tromboembólica.
[a] Per risk stratum.
[b] For comparison between the original and the simplified PESI derivation samples, $P < .001$.
[c] For comparison between the original and the simplified PESI derivation samples, $P < .01$.
[d] Original PESI class I and II categories are classified as low risk, and classes III through V are classified as high risk.
[e] For comparison between the simplified PESI derivation sample and the simplified PESI validation sample, $P < .001$.

Jimenez D Arc Int Med 2010

CLINICAL SCORE + ECOCARDIOGRAMMA
In pazienti con EP MASSIVA (n=32),

- ✓ Sensibilità 97%
- ✓ Valore predittivo negativo 98%



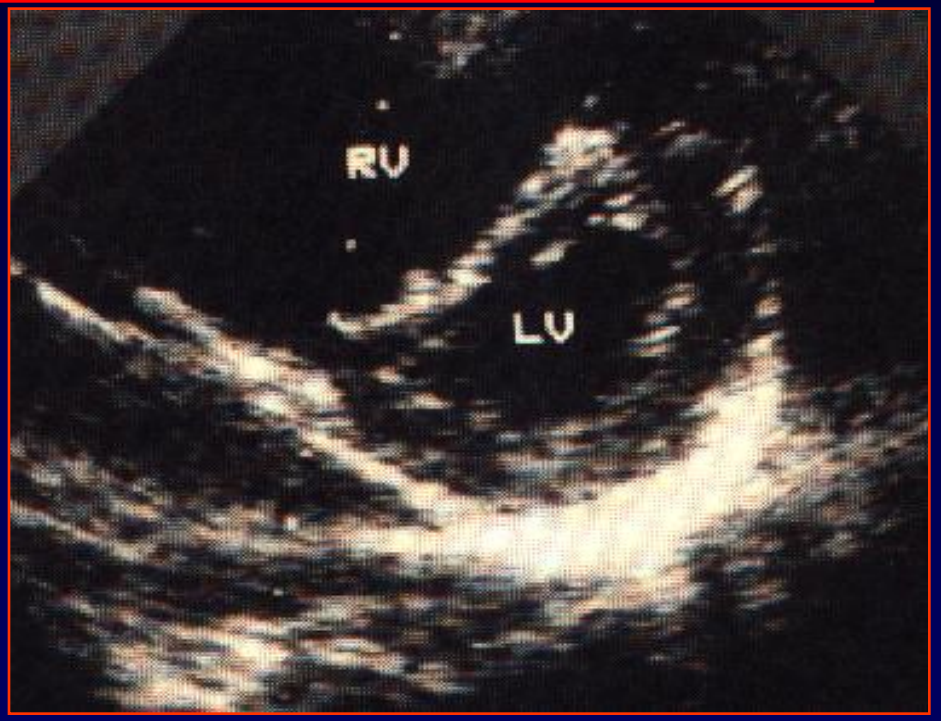
Ingresso Post-rTPA

Grifoni S et al, Am J Cardiol 1998

Emergency Dept.- Careggi - Florence

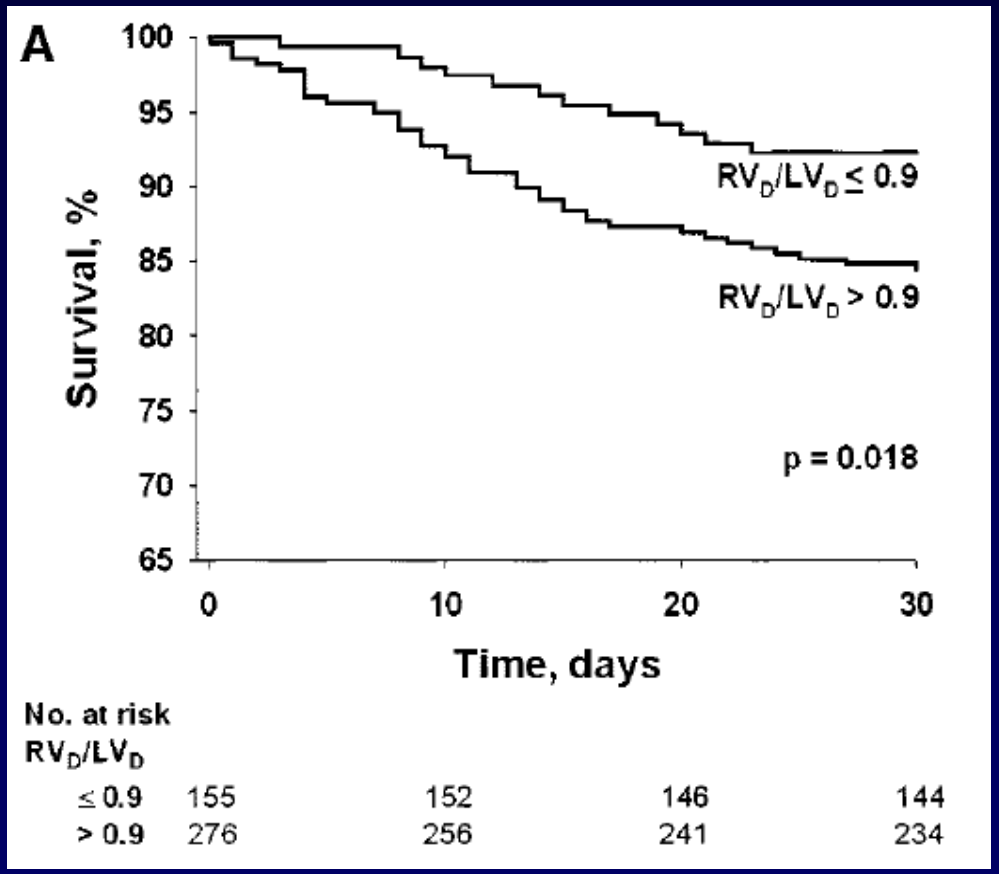
SEGNI ECOCARDIOGRAFICI DI SOVRACCARICO EMODINAMICO ACUTO DEL VENTRICOLO DESTRO

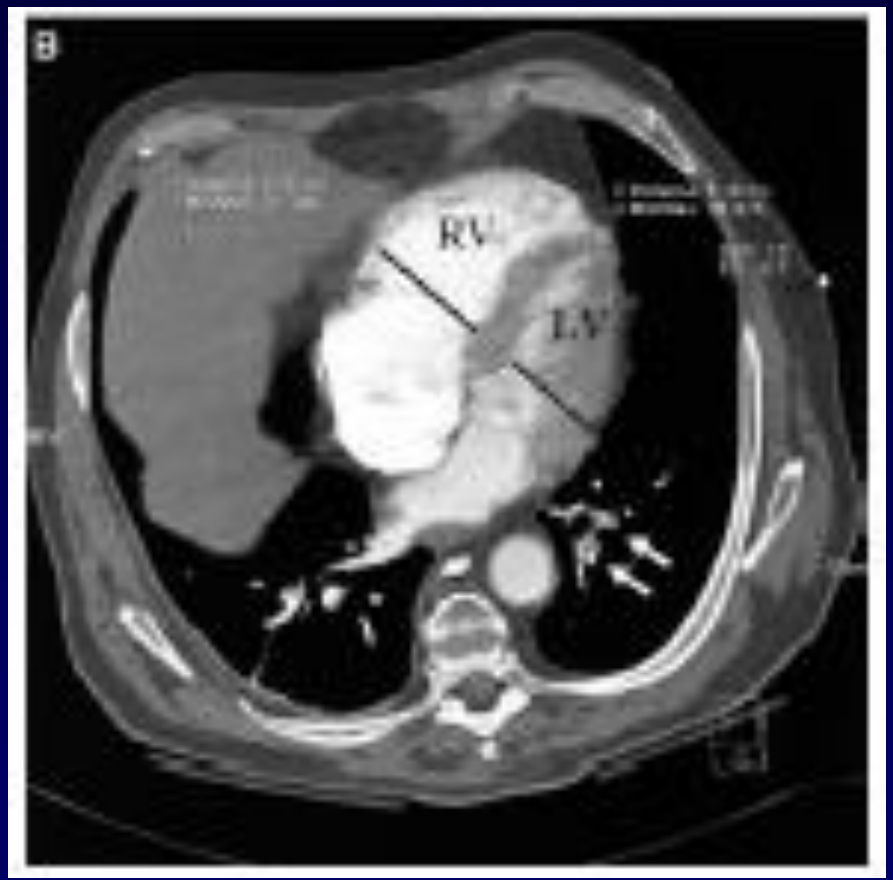
- Almeno 1 dei seguenti
  - Dilatazione VDX (RVED>30 mm or RVED/LVED >1)
  - Movimento paradosso del setto IV
  - Ipertensione polmonare (VD-AD > 30 mm Hg)
- In assenza di aumento dello spessore VDX (≤6mm)



S Grifoni et al Am J Cardiol 1998
S Grifoni et al Circulation 2000
S Grifoni et al Arch Intern Med 2006

Right ventricular enlargment on CT scan





Schoepf UJ et al Circulation 2004

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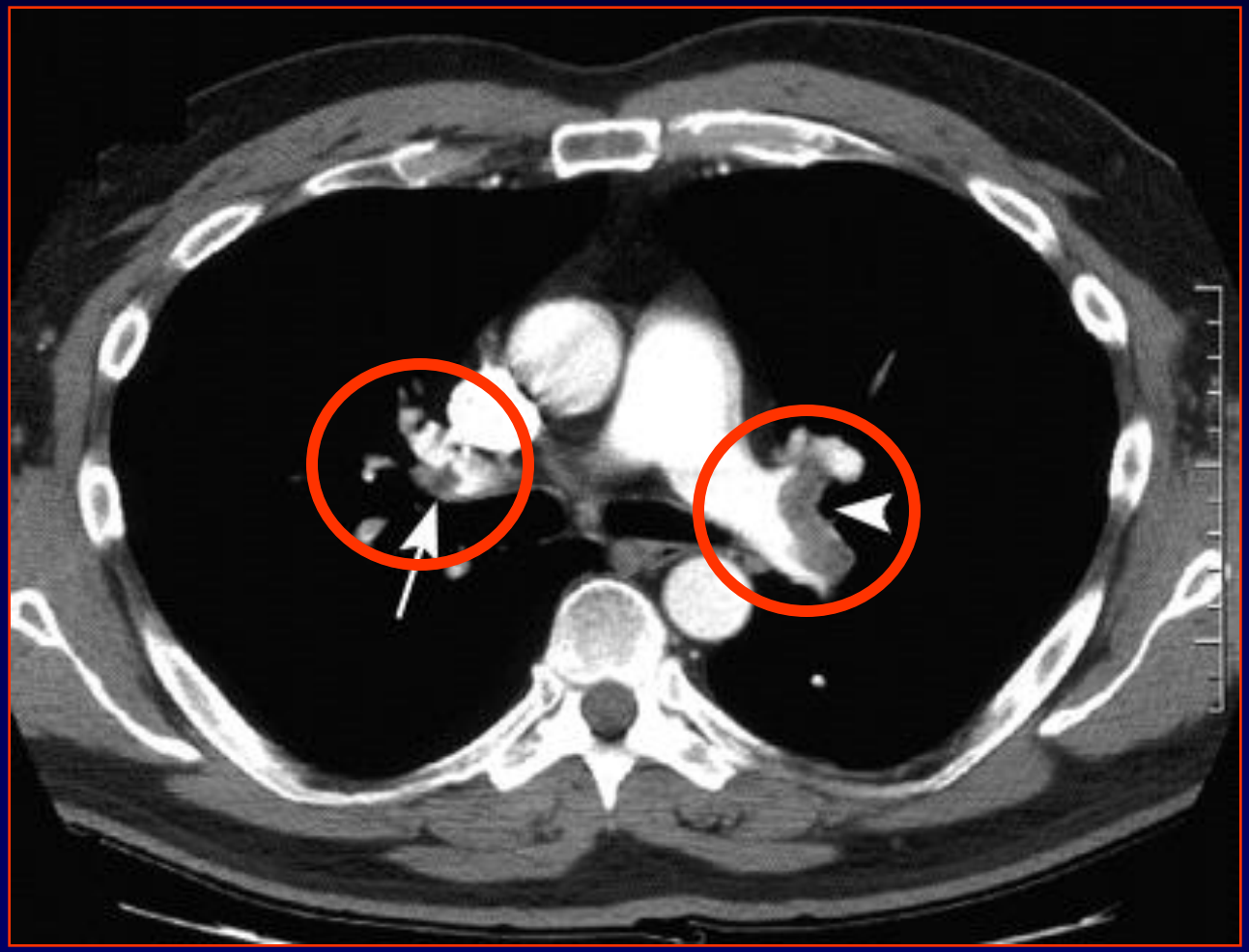
SPIRAL CT



ACCURACY OF A PRELIMINARY DIAGNOSIS OF PULMONARY EMBOLISM BASED ON CLINICAL SCORE AND CARDIAC AND VENOUS ULTRASOUND EXAMINATION

	CLINICAL SCORE, CARDIAC AND VENOUS ULTRASOUND	*ECHOCARD.*
■ sensitivity	92%	51%
■ specificity	66%	87%
■ positive predictive value	75%	82%
■ negative predictive value	88%	60%
■ total accuracy	80%	67%

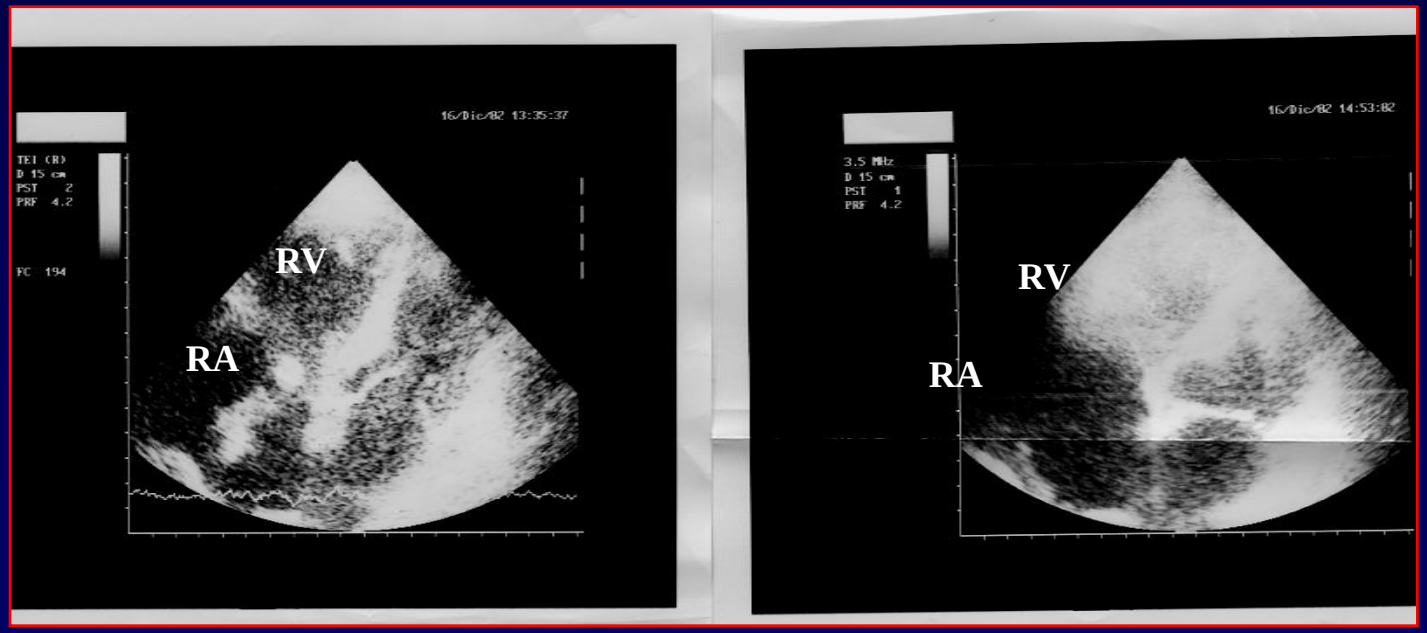
Grifoni S et al, Am J Cardiol 1998

Conclusioni

- Profilassi tromboembolica in chirurgia ortopedica :
- maggiore efficacia del rivaroxaban correlata ad un maggior rischio di sanguinamento
- Non differenze significative nell' efficacia e nella sicurezza tra i nuovi anticoagulanti
- Profilassi tromboembolica in medicina
- Il trattamento prolungato (28 gg) con NAO è più efficace del trattamento con Enoxaparina (6-14 gg)
- Tuttavia,associato ad aumento di emorragie maggiori sia nel trattamento a breve che lungo periodo
-

CLINICAL SCORE + ECOCARDIOGRAMMA
In pazienti con EP MASSIVA (n=32),

- ✓ Sensibilità 97%
- ✓ Valore predittivo negativo 98%



Ingresso Post-rTPA

Grifoni S et al, Am J Cardiol 1998

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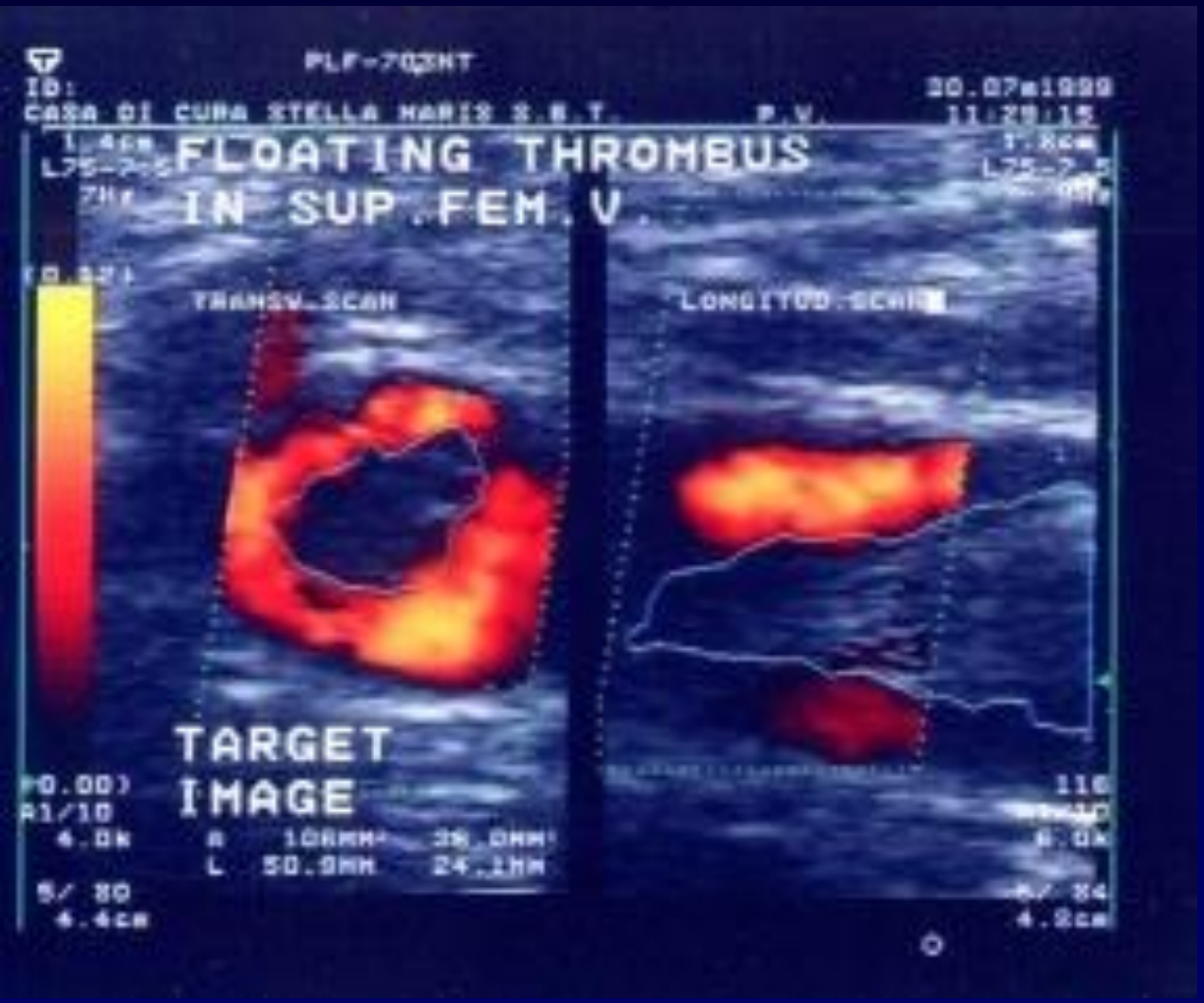
Ecocolordoppler vene arti inferiori



- Presenza di TVP flottante minacciosa
- Necessari posizionamento di filtro cavale ed eventuale trombolisi

Esami utili nell'indirizzare il sospetto diagnostico

Ecocolordoppler venoso in DEA

- Sensibilità: 96,3%
- Specificità: 100%
- Valore predittivo negativo: 98,6%

NB !!!!

Positività del test nei pazienti con EP <50%

Magazzini S et al 2003

Prognostication in EP

- To rule out adverse prognosis?
  - Biomarkers (natriuretic peptides, Troponin)
- To rule in aggressive treatment?
  - Echocardiography/TC plus
    - Biomarkers
    - ECG
    - Lactate

RVD on admission and outcome in patients with Pulmonary Embolism

- **RVD persistence appears to be common**
- **Echocardiography should be repeated before discharge**
- **Selected patients with RVD persistence may require evaluation for surgical thrombectomy**
- **Can we prevent RVD persistence with more aggressive initial treatment ?**

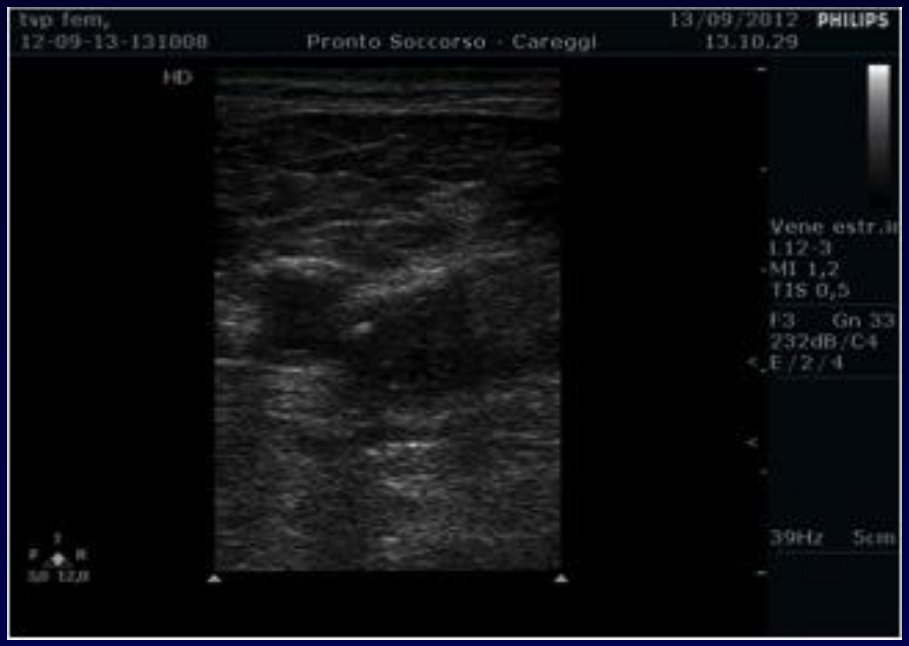
Terapia dei pazienti con EP

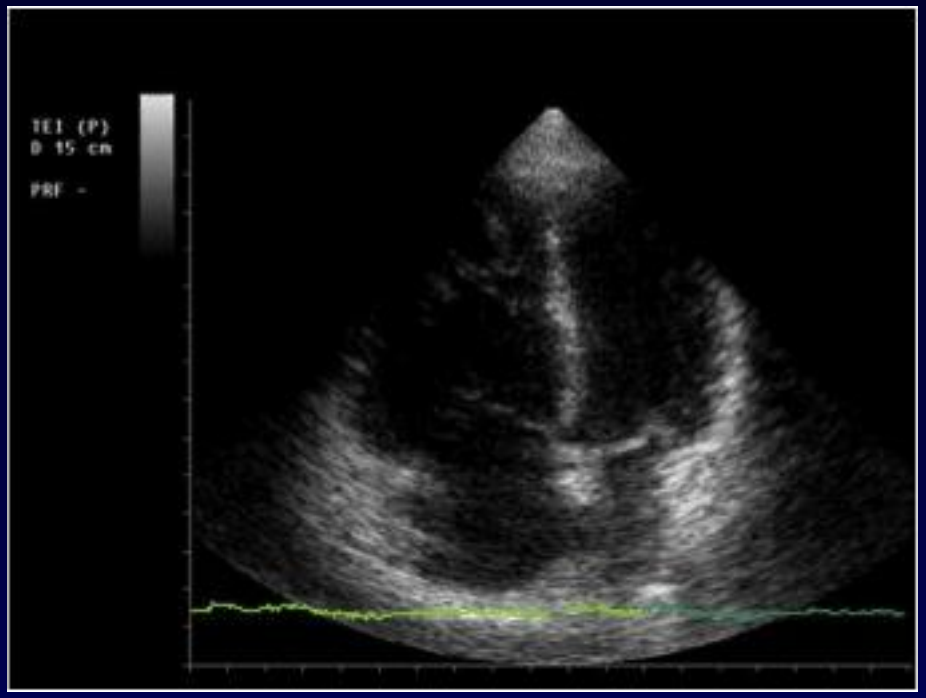
INDICAZIONI TERAPEUTICHE NOTE DA TEMPO

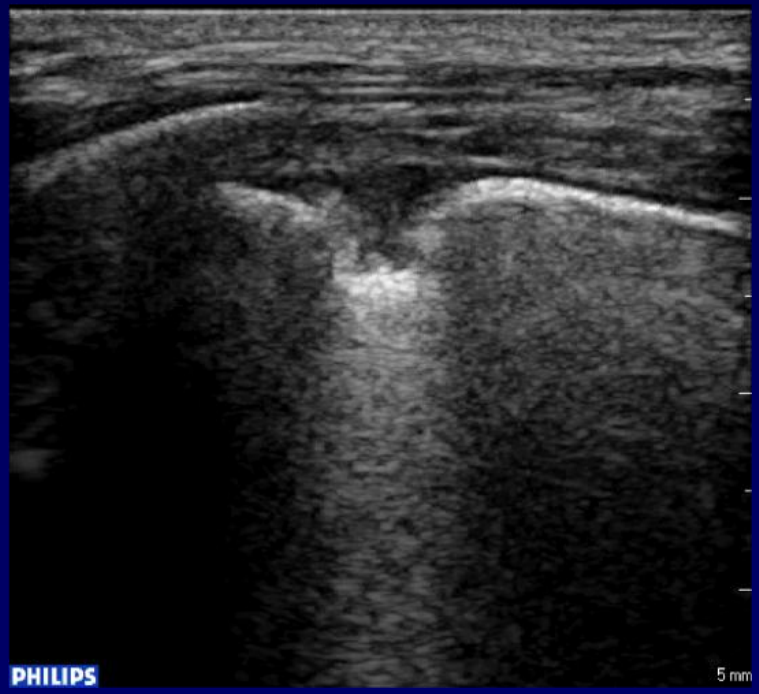
- L'Eparina è meglio del placebo
- I trombolitici riducono la mortalità dei pazienti in shock

PROBLEMI ANCORA APERTI

- La strategia di gestione ottimale
- Ampliamento dell'utilizzo dei trombolitici







MULTIORGAN US POSITIVE FOR PE IF ONE OR MORE OF THE FOLLOWING WERE DETECTED:

- **Deep vein thrombosis**
- **Right ventricular dilatation or thrombi in right cavities**
- **One or more subpleural infarct**

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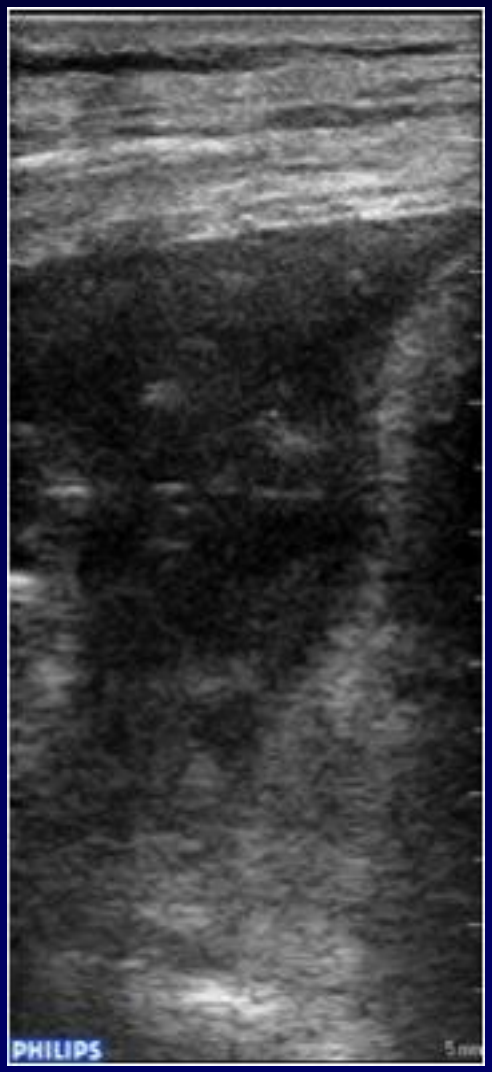
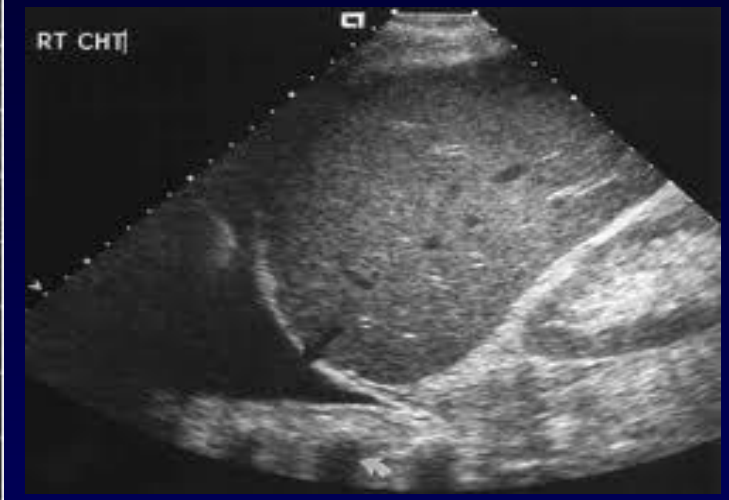
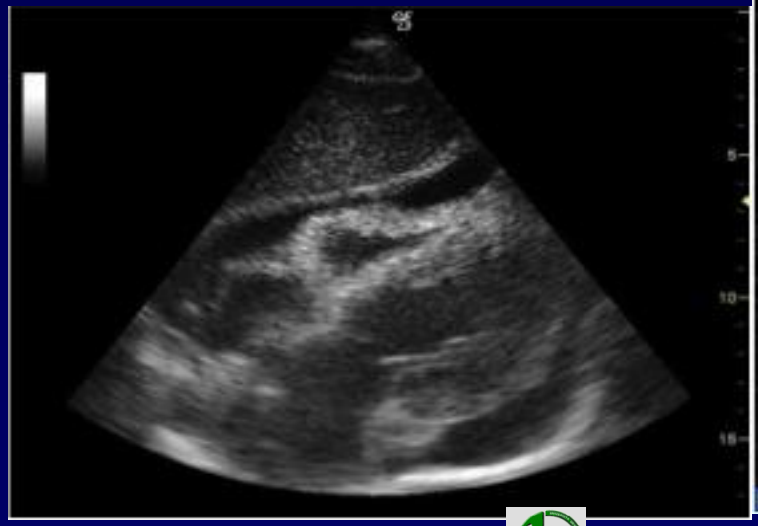
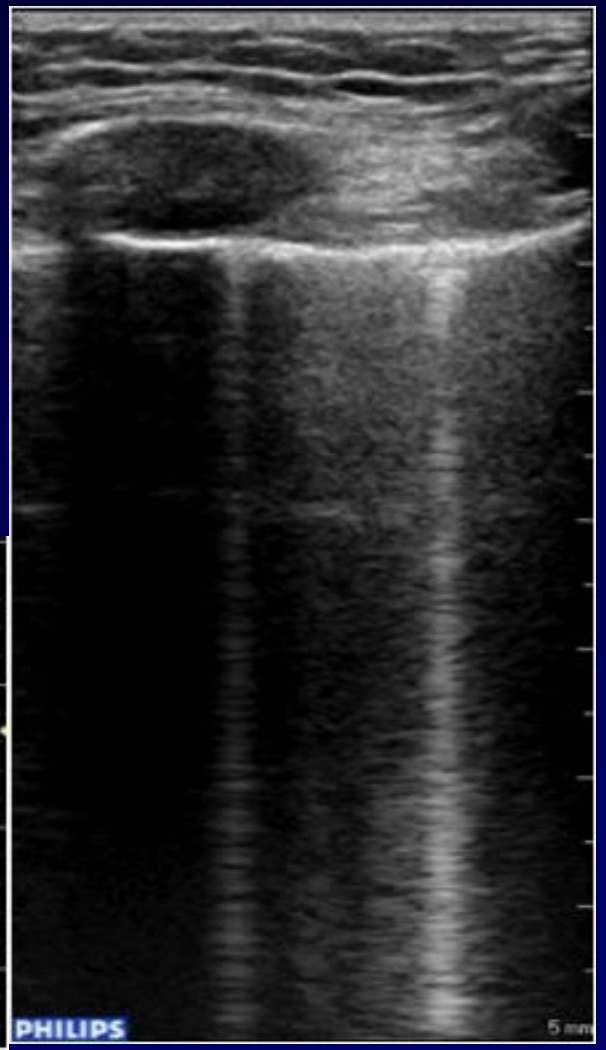
Alternative US diagnosis in patients with negative multiorgan US







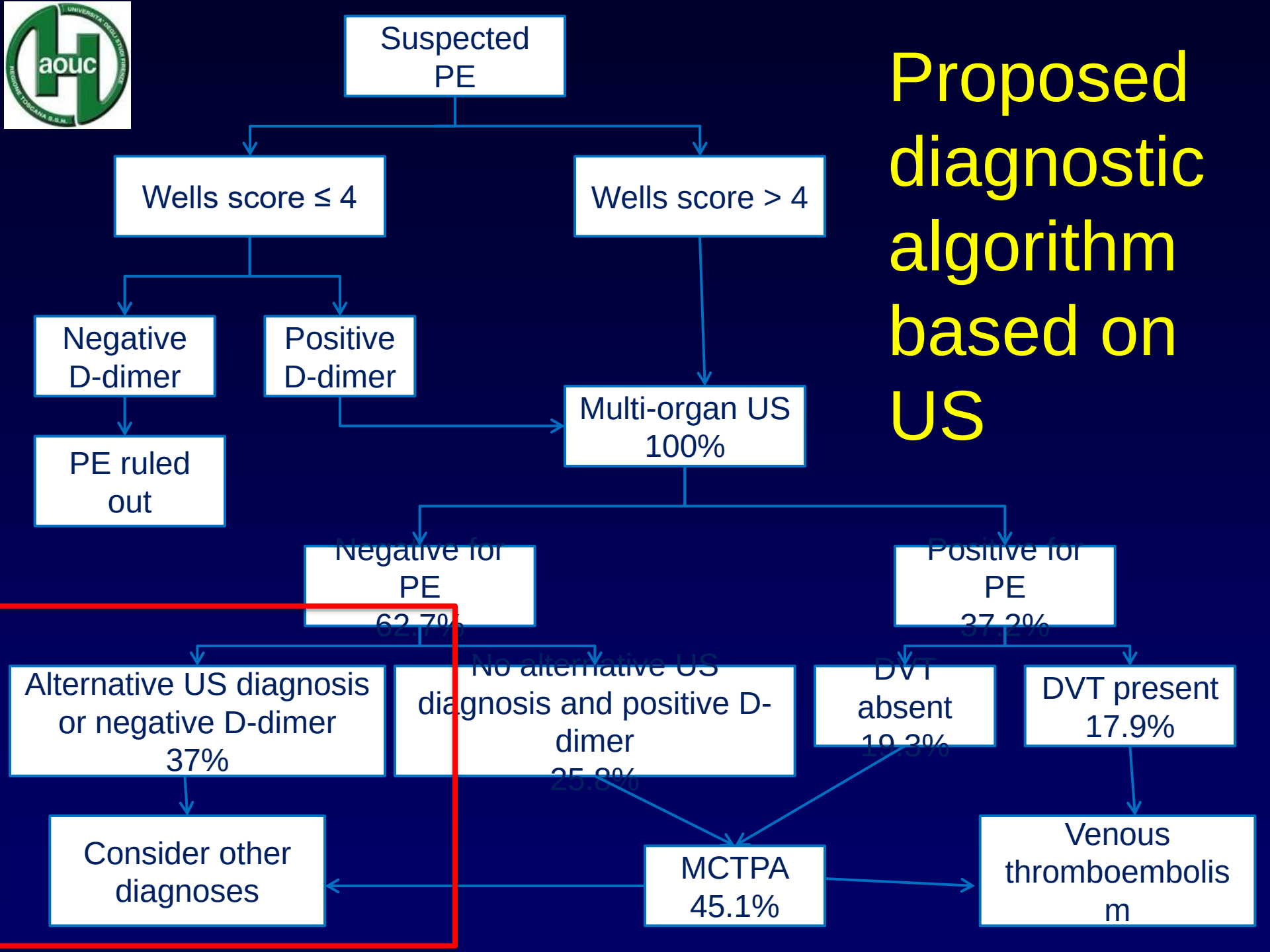


Emergency Dept.- Careggi - Florence

Accuracy of point-of-care multiorgan ultrasonography for the diagnosis of pulmonary embolism

	Sens % (95% CI)	Spec % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Multiorgan US	90% (82.8-94.9)	86.2% (81.3-90.3)	74.4% (66.1-81.6)	95.1% (91.4-97.5)
Negative multiorgan US plus alternative	100% (96.7-100)	42.9% (36.7-49.3)	43.8% (37.6-50.2)	100% (96.5-100)

Proposed diagnostic algorithm based on US



Ultrasonographic Wells Score

Adapted with permission from

Clinical feature	Points	Patient score
Leg veins CUS positive for DVT g swelling and pain with palpation of the deep veins)	3	
Subpleural infarct or the absence of an alternative diagnosis *	3	
Heart rate > 100 beats per minute	1.5	
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5	
Previous DVT/PE	1.5	
Haemoptysis	1	
Malignancy (on treatment, treated in the last 6 months, or palliative)	1	
Clinical probability simplified scores		
PE *likely*	More than 4 points	
PE *unlikely*	4 points or less	

CHEST

Original Research

THROMBOEMBOLISM

Efficacy and Safety of Low Dose Recombinant Tissue-Type Plasminogen Activator for the Treatment of Acute Pulmonary Thromboembolism

A Randomized, Multicenter, Controlled Trial

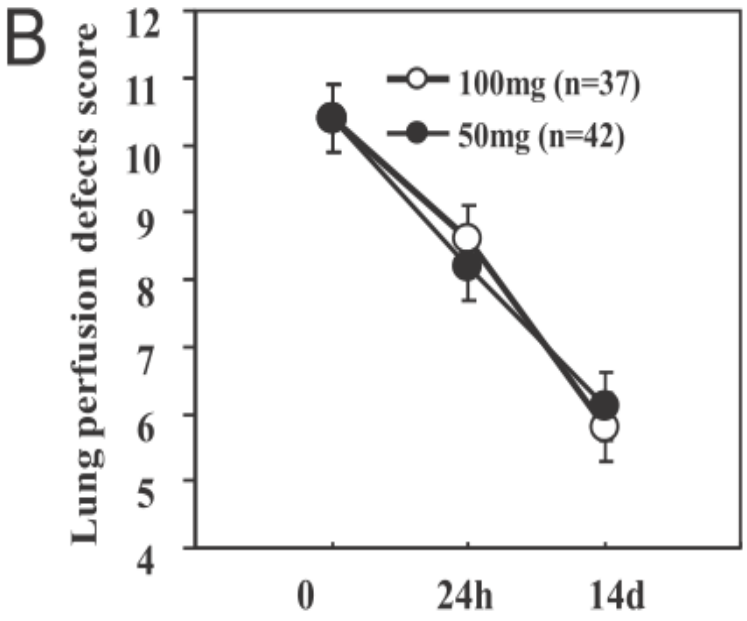


Table 3—*Comparison of Adverse Events During the First 14 d After Treatment, Comparing Two Treatments for PTE*

Adverse Events	rt-PA 100 mg (n = 48)	rt-PA 50 mg (n = 55)	*P*
Death	3 (6)	1 (2)	.472
Due to PTE	2 (4)	1 (2)	…
Due to bleeding	1 (2)	0 (0)	…
Bleeding complications	17 (32)	11 (17)	.054
Major bleeding	5 (10)	2 (3)	.288
Fatal bleeding	1 (2)	0 (0)	…
Others	4 (8)	2 (3)	…
Minor bleeding	12 (22)	9 (14)	.214
Recurrent PTE	2 (4)	1 (2)	.858
Fatal	0 (0)	0 (0)	…
Nonfatal	2 (4)	1 (2)	…

Data presented are number (%) of patients. Others = other major bleeding without death. See Table 1 for expansion of abbreviations.

Wang C et al Chest 2010

Moderate Pulmonary Embolism Treated With Thrombolysis (from the "MOPETT" Trial)

Mohsen Sharifi, MD[a,b,*], Curt Bay, PhD[b], Laura Skrocki, DO[a], Farnoosh Rahimi, MD[a], and Mahshid Mehdipour, DMD[a,b], "MOPETT" Investigators

Table 2
Primary end points at 28 ± 5 mo of follow-up

Variable
Pulmonary h
Pulmonary h recurrent p embolism

* Pulmona

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	—

Data are presented as mean ± SD or n (%).

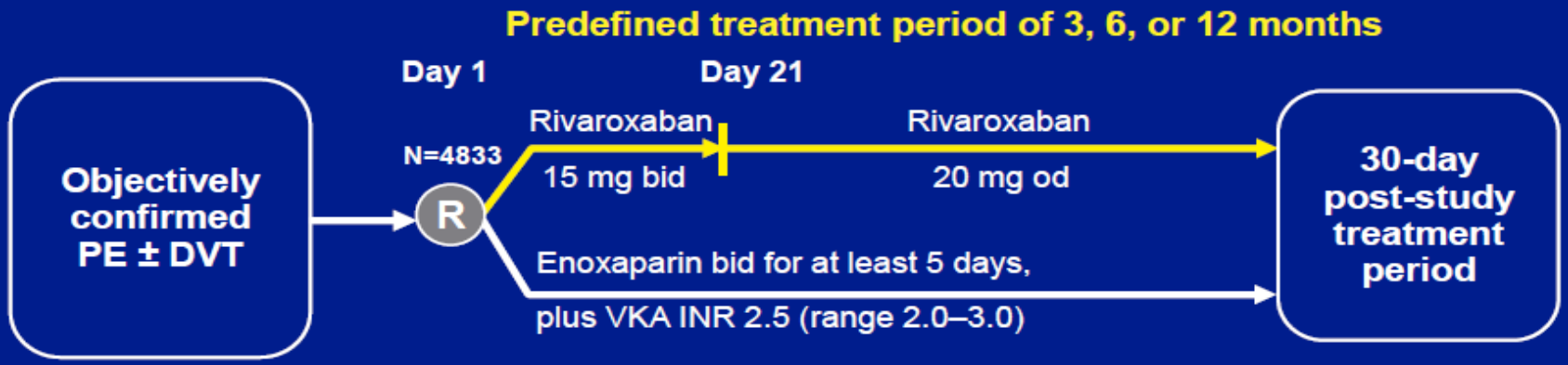
Am J Cardiol 2013

EINSTEIN-PE

EINSTEIN PE: study design

Randomized, open-label, event-driven, non-inferiority study

- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry
- 88 primary efficacy outcomes needed
- Non-inferiority margin: 2.0

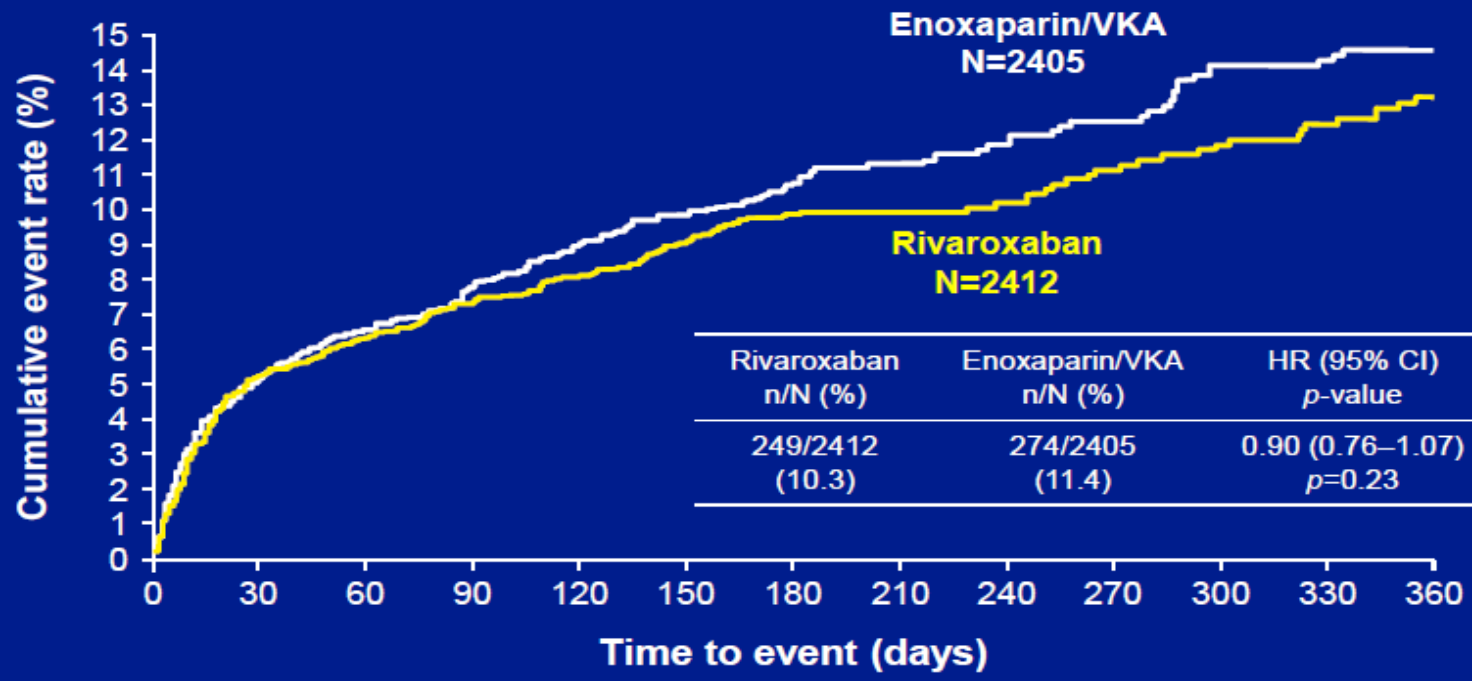


- Primary efficacy outcome: first recurrent VTE
- Principal safety outcome: first major or non-major clinically relevant bleeding

NEJM 2012;366:1287-97

EINSTEIN-PE

EINSTEIN PE: principal safety outcome – major or non-major clinically relevant bleeding



Rivaroxaban n/N (%)	Enoxaparin/VKA n/N (%)	HR (95% CI) *p*-value
249/2412 (10.3)	274/2405 (11.4)	0.90 (0.76–1.07) *p*=0.23

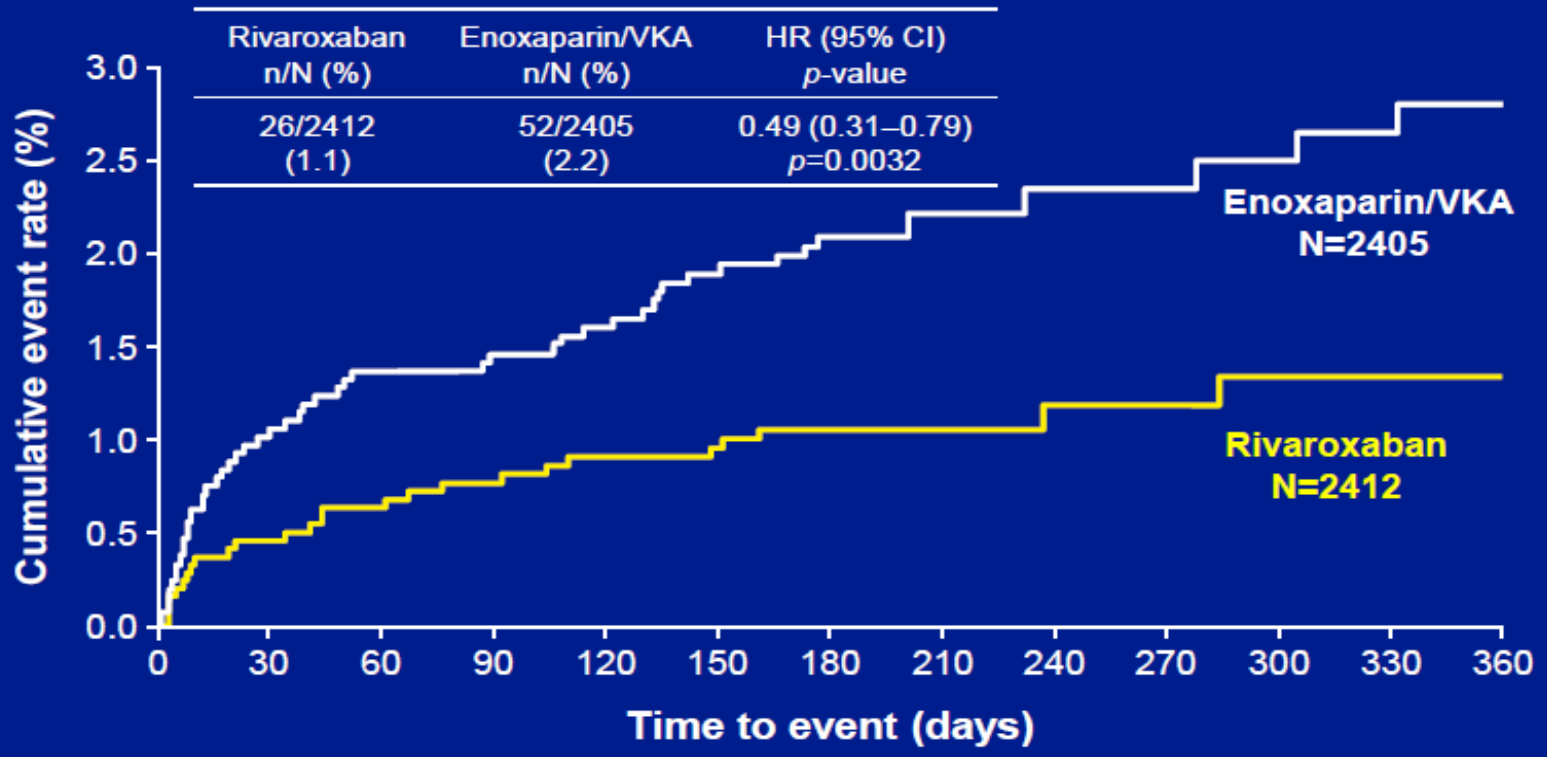
Number of patients at risk													
Rivaroxaban	2412	2183	2133	2024	1953	1913	1211	696	671	632	600	588	313
Enoxaparin/VKA	2405	2184	2115	1990	1923	1887	1092	687	660	620	589	574	251

Safety population

NEJM 2012;366:1287-97

EINSTEIN-PE

EINSTEIN PE: major bleeding

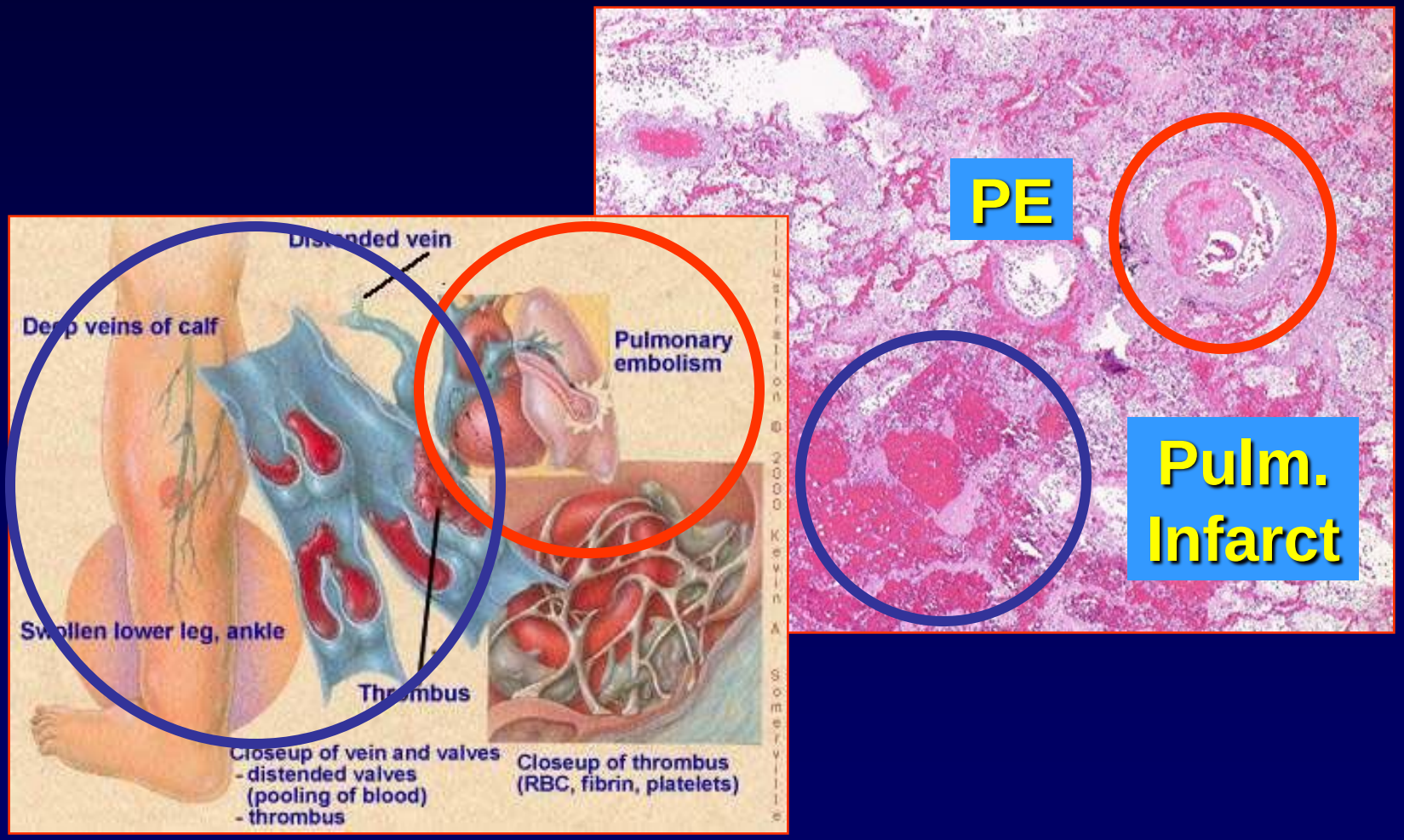


Number of patients at risk													
Rivaroxaban	2412	2281	2248	2156	2091	2063	1317	761	735	700	669	659	350
Enoxaparin/VKA	2405	2270	2224	2116	2063	2036	1176	746	719	680	658	642	278

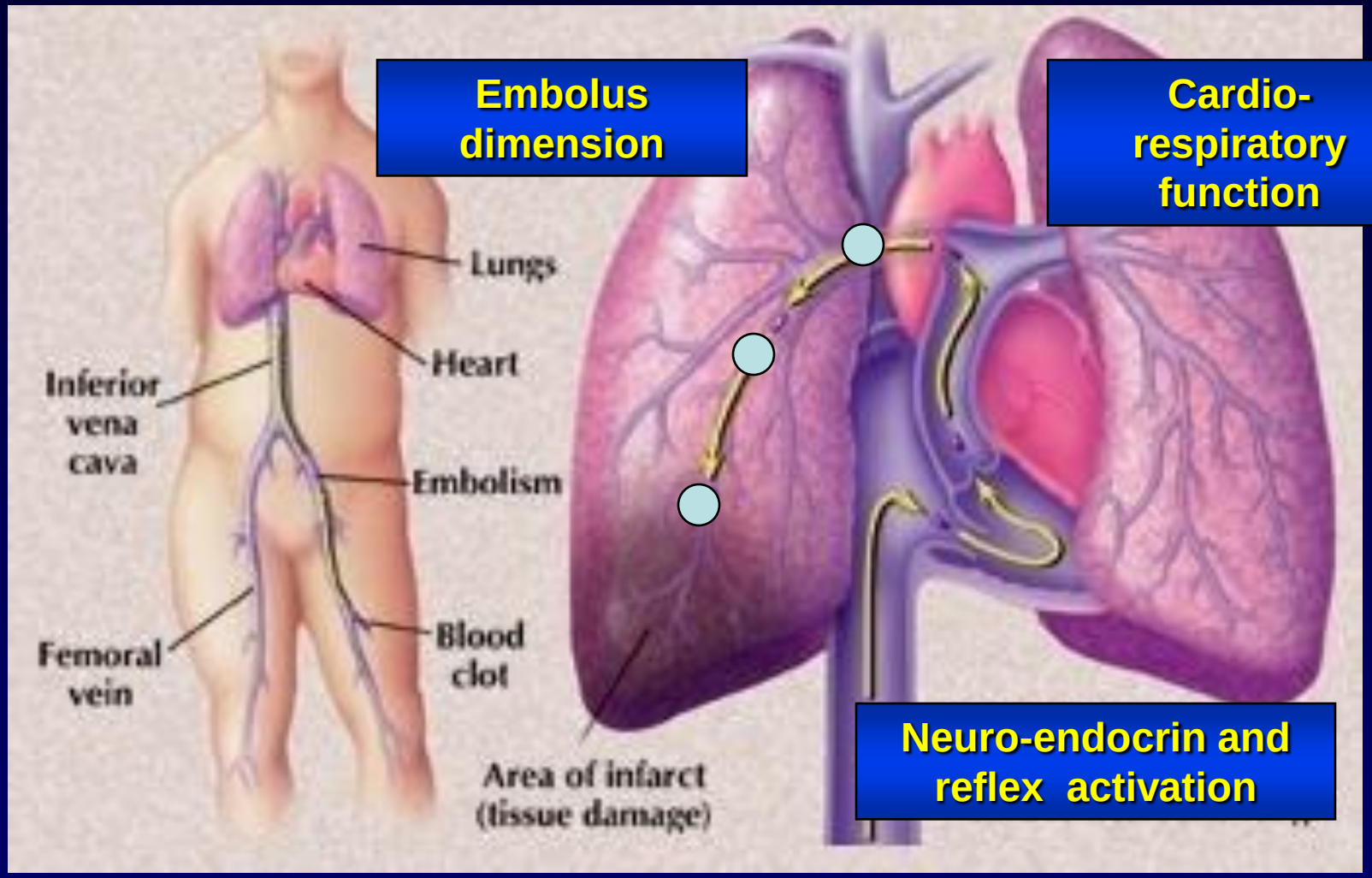
Safety population

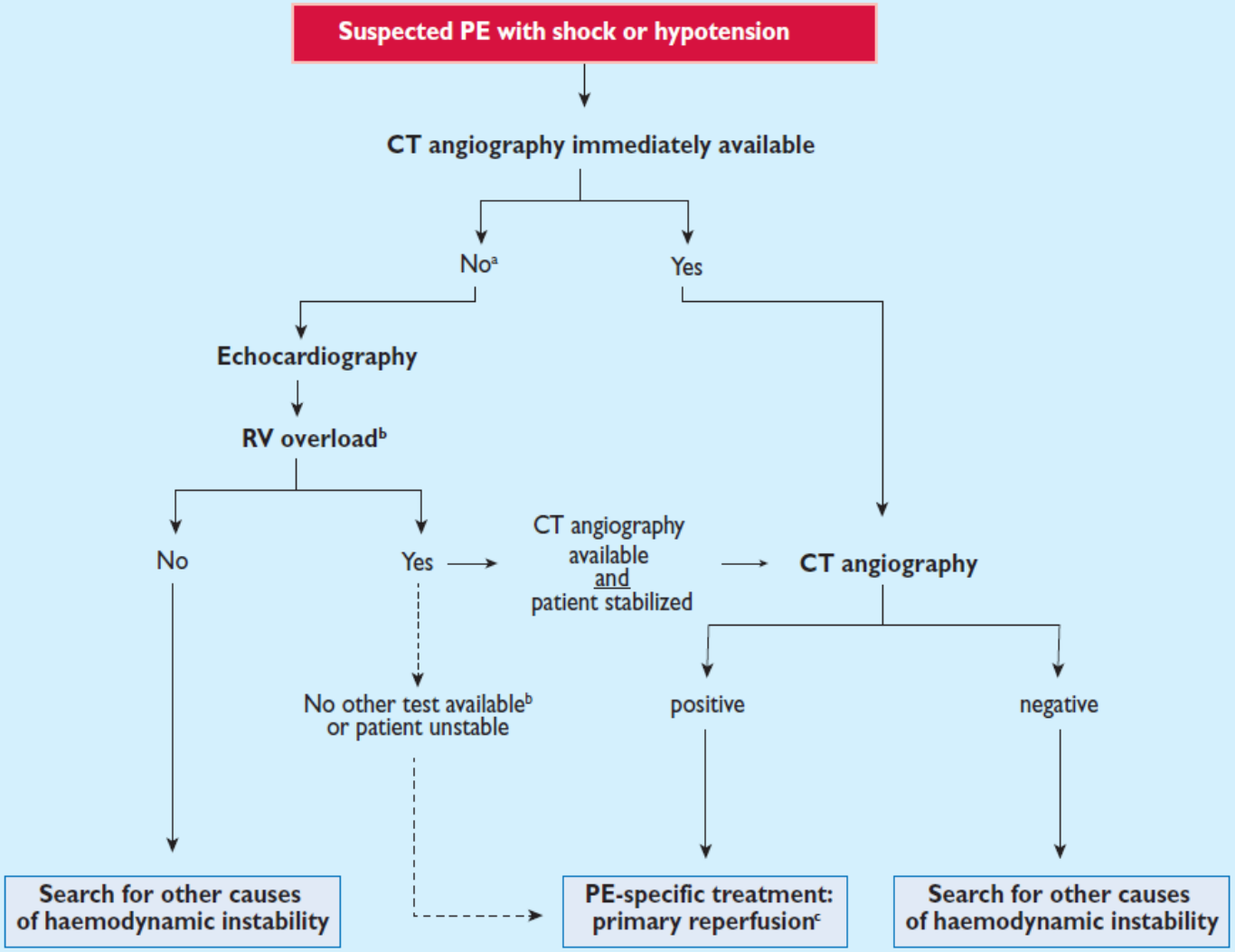
NEJM 2012;366:1287-97

Acute pulmonary thromboembolic disease can present with a wide spectrum of clinical signs and symptoms



Hemodynamics response to PE



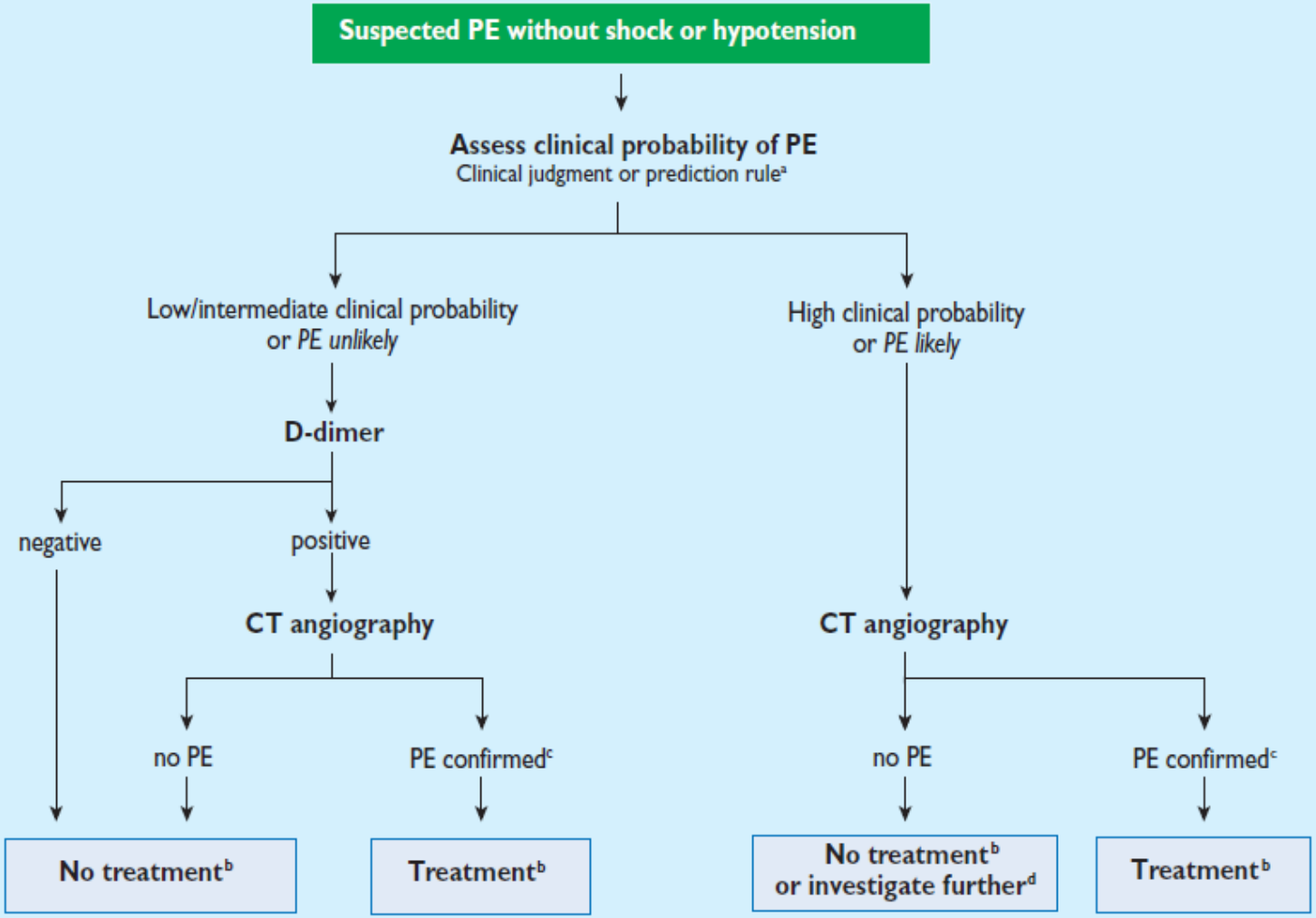


CT = computed tomographic; PE = pulmonary embolism; RV = right ventricular.

[a]Includes the cases in which the patient's condition is so critical that it only allows bedside diagnostic tests.

[b]Apart from the diagnosis of RV dysfunction, bedside transthoracic echocardiography may, in some cases, directly confirm PE by visualizing mobile thrombi in the right heart chambers. Ancillary bedside imaging tests include transoesophageal echocardiography, which may detect emboli in the pulmonary artery and its main branches, and bilateral compression venous ultrasonography, which may confirm deep vein thrombosis and thus be of help in emergency management decisions.

[c]Thrombolysis; alternatively, surgical embolectomy or catheter-directed treatment (Section 5).



CT = computed tomographic; PE = pulmonary embolism.

[a]Two alternative classification schemes may be used for clinical probability assessment, i.e. a three-level scheme (clinical probability defined as low, intermediate, or high) or a two-level scheme (PE unlikely or PE likely). When using a moderately sensitive assay, D-dimer measurement should be restricted to patients with low clinical probability or a PE-unlikely classification, while highly sensitive assays may also be used in patients with intermediate clinical probability of PE. Note that plasma D-dimer measurement is of limited use in suspected PE occurring in hospitalized patients.

[b]Treatment refers to anticoagulation treatment for PE.

[c]CT angiogram is considered to be diagnostic of PE if it shows PE at the segmental or more proximal level.

[d]In case of a negative CT angiogram in patients with high clinical probability, further investigation may be considered before withholding PE-specific treatment.

PE without shock/Hypotension

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V or sPESI ≥1[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	–	+	Both positive	
	Intermediate–low	–	+	Either one (or none) positive[e]	
Low		–	–	Assessment optional; if assessed, both negative[e]	

Embolia polmonare. DEFINIZIONE

Ostruzione acuta completa o parziale di uno o più rami dell'arteria polmonare, nella maggior parte dei casi provocata da materiale embolico di origine extrapolmonare, più raramente da fenomeni di trombosi locale

Trombo-embolica 95% dei casi

Non trombotica 5% dei casi

- EP gassosa
- EP grassosa
- EP solida da corpi estranei
- EP di liquido amniotico

Presentazione clinica

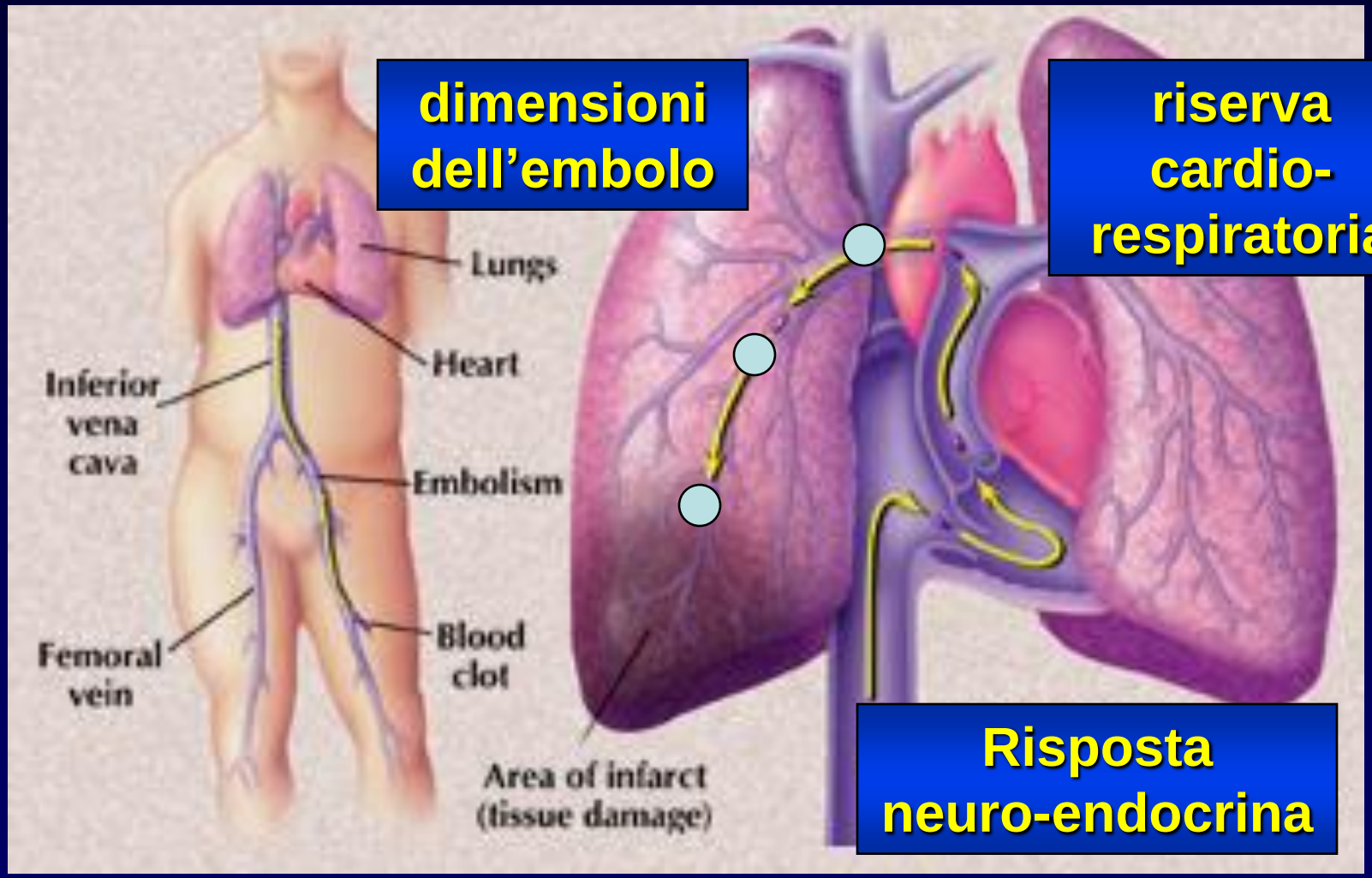
Con compromissione emodinamica

- Prevalenza 15%
- Mortalità per EP in acuto 32%

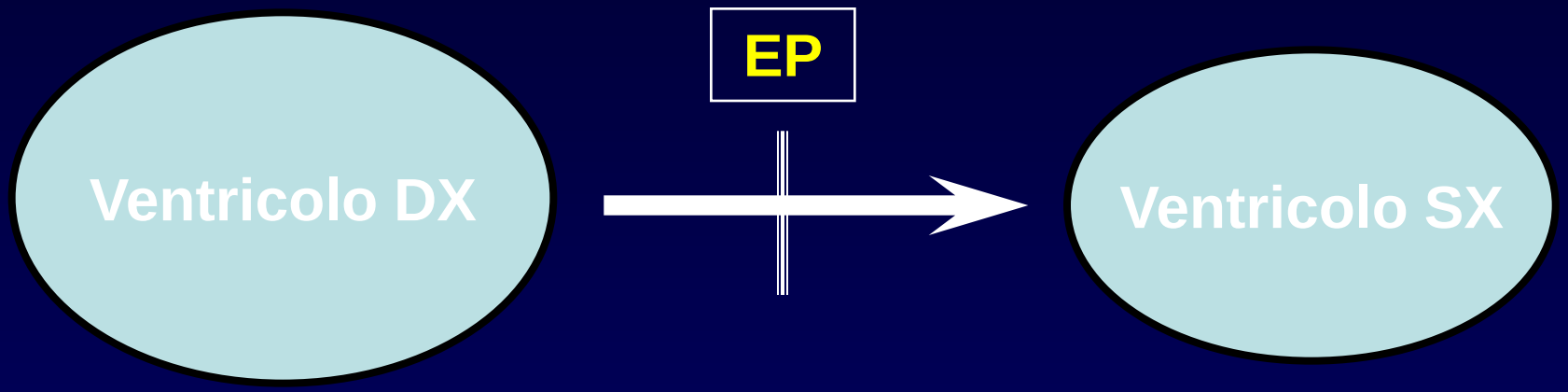
Senza compromissione emodinamica

- Prevalenza 45%
- Mortalità per EP in acuto 0%

DETERMINANTI DELLA ESPRESSIONE CLINICA DELLA EP

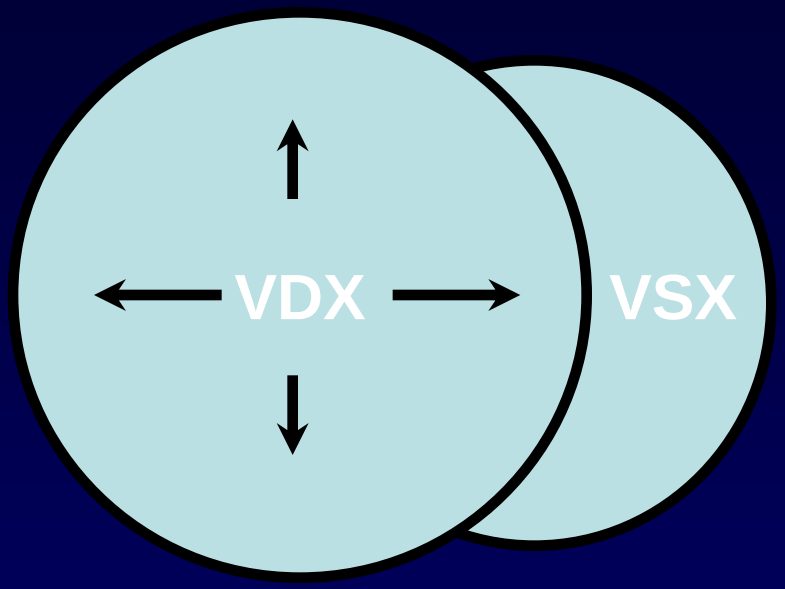


FISIOPATOLOGIA DELL' EP
alterazioni emodinamiche



- ↑ Resistenze Polmonari
- ↓ CO Vdx
- ↓ Riempimento Vsx
- ↓ CO Vsx

FISIOPATOLOGIA DELL' EP
alterazioni emodinamiche



↑ **Pressione telediastolica Vdx (Setto paradosso)**

↓ **Compliance Vsx**

↓ **CO Vsx**

FISIOPATOLOGIA DELL' EP
alterazioni emodinamiche

Perché il Vdx si scompensa (RVD)?

- ✓ Incapacità del Vdx di far fronte ad una mPAP > 40 mmHg } ↑ BNP

- ✓ Ischemia-necrosi Vdx
  - ↑ del consumo miocardico di O2
  - ↓ della press. di perf. coronarica

  } ↑ cTn

Embolia polmonare

Procedimento diagnostico

Quali pazienti sono a rischio di EP?

- Immobilizzazione (degenza, ictus, viaggi)
- Recente chirurgia/Traumi (arti inferiori, pelvici)
- Precedenti TVP e/o Embolia polmonare
- Cancro
- Obesità
- Ustioni
- CVC
- Contracettivi orali, Gravidanza, postpartum
- Coagulopatie: APC-R, mutazione gene PT, Proteina C, proteina S, AT III.

Segni e Sintomi

Dispnea (improvvisa)	82%
Tachipnea (>20/min)	60%
Dolore toracico	49%
FC >100/min	40%
Tosse	20%
Sincope	14%
Emottisi	7%

ICOPER Lancet, 1999

Esami utili nell'indirizzare il sospetto diagnostico

ECG: NORMALE < 20% dei casi

Nelle massive:
- S1Q3T3
- Inversione delle onde T V1-V3
- RBBB

} 80%

Fibrillazione/flutter atriale 0-5%

Wood KE Chest 2002

Esami utili nell'indirizzare il sospetto diagnostico

RX torace: UTILE per escludere altre diagnosi
Normale nel 20-30 % dei casi
Westermark
Hampton

EGA: IPOSSIEMIA – ipocapnia
normale $P(A\text{-}a)O_2$ nel 14%

DDimero: potere predittivo negativo 99,6%
(ELISA) in DEA. (*Dunn KL, JACC 2002*)

Wood KE Chest 2002

ECHOCARDIOGRAPHIC SIGNS OF ACUTE RIGHT VENTRICULAR STRAIN

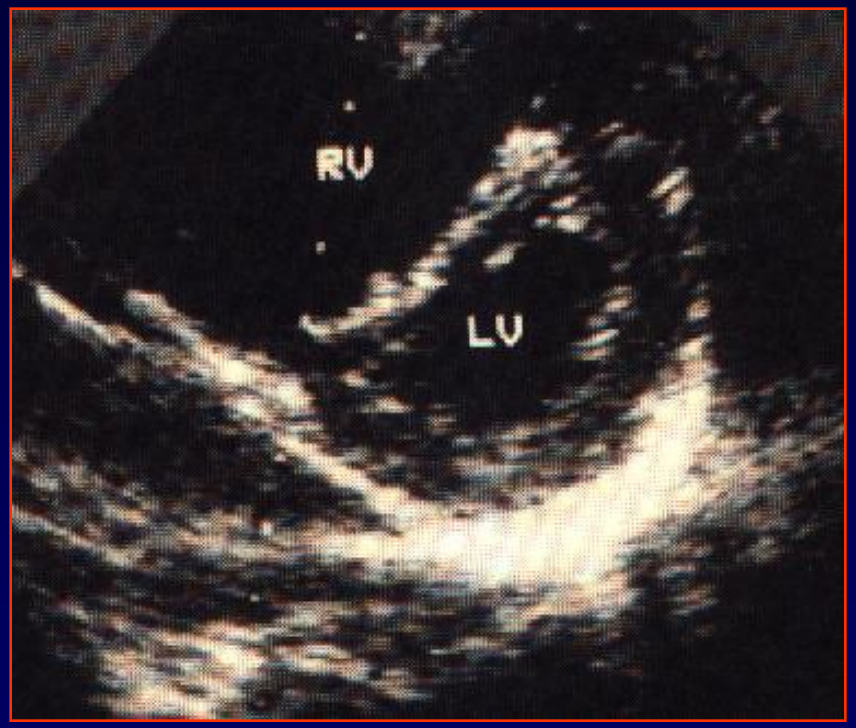
Right ventricular hypokinesis and dilatation

Systolic flattening of interventricular septum

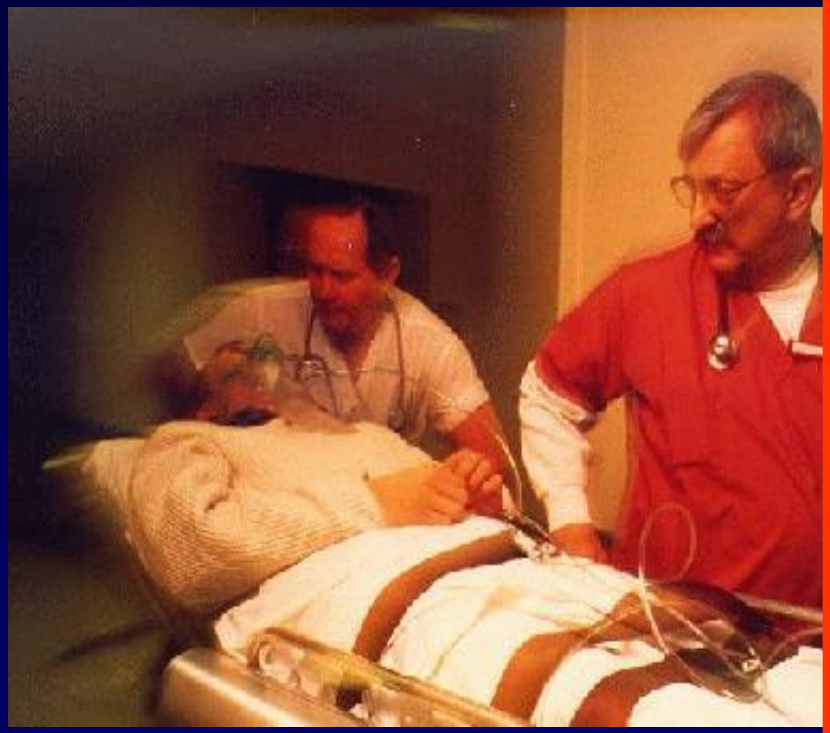
Doppler evidence of pulmonary hypertension

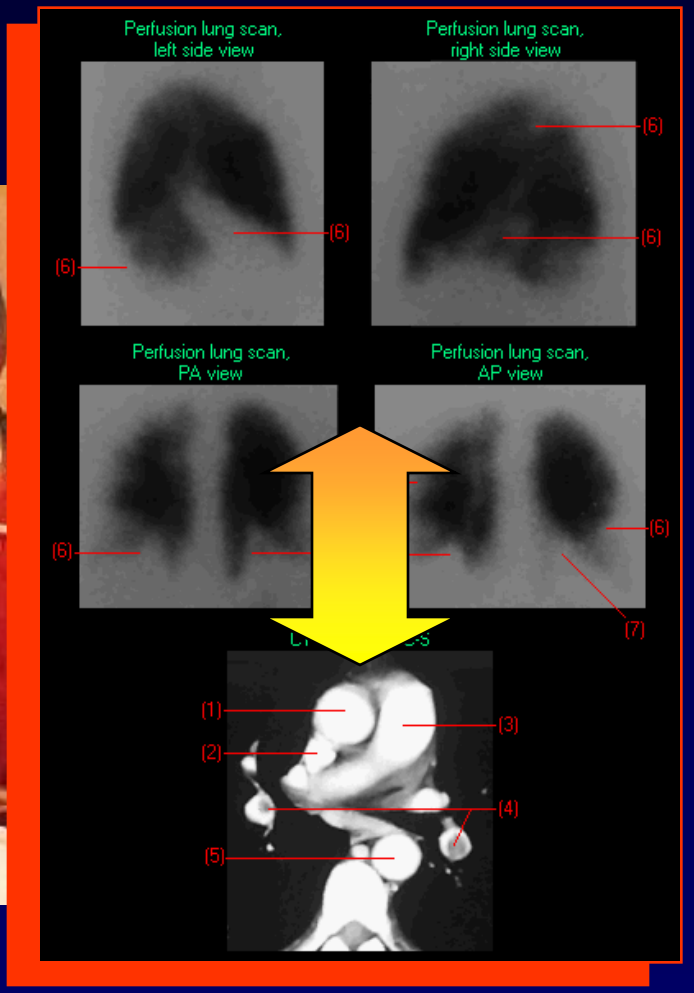
Distention of inf.Vena Cava

In absence of right ventricular wall hypertrophy



SCINTIGRAFIA contro TC SPIRALE nel DEA





Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial.

- Randomized, single blinded, non inferiority trial
- 1417 pz wih suspected pulmonary embolism
- main outcome: PE or TVP in patient with normal imaging test
- CTPA is not inferior to V(dot)Q to ruling out EP
- More pz were diagnosed with PE using CTPA

JAMA 2007

MODERN INDICATIONS FOR LUNG SCAN

NORMOTENSIVE PATIENTS WITH

SUSPICION OF PE DESPITE :

- **NON-DIAGNOSTIC CT SCAN**
- **NEGATIVE VENOUS 2D DOPPLER SCAN**

Grifoni S. et al. 2002

LUNG SCAN: LIMITATIONS

- Nuclear Medicine units not available in most hospitals.
- Lung scans not usually available 24h/24.
- Long time gap from suspicion to diagnosis (increased risk in patients with hemodynamic instability)

Indici prognostici clinici

- Età
- Comorbidità
  - Neoplasie
  - Insufficienza cardiaca
  - BPCO
- Parametri clinici
  - FC > 110/min
  - Pressione sistolica <100 mmHg
  - Sincope
  - Frequenza respiratoria > 30/min
  - Ipotermia
  - Alterazione del sensorio
  - Sat 02 <90%

Modificata da Aujeski, Eur Heart J 2006

Presentazione clinica

Con compromissione emodinamica

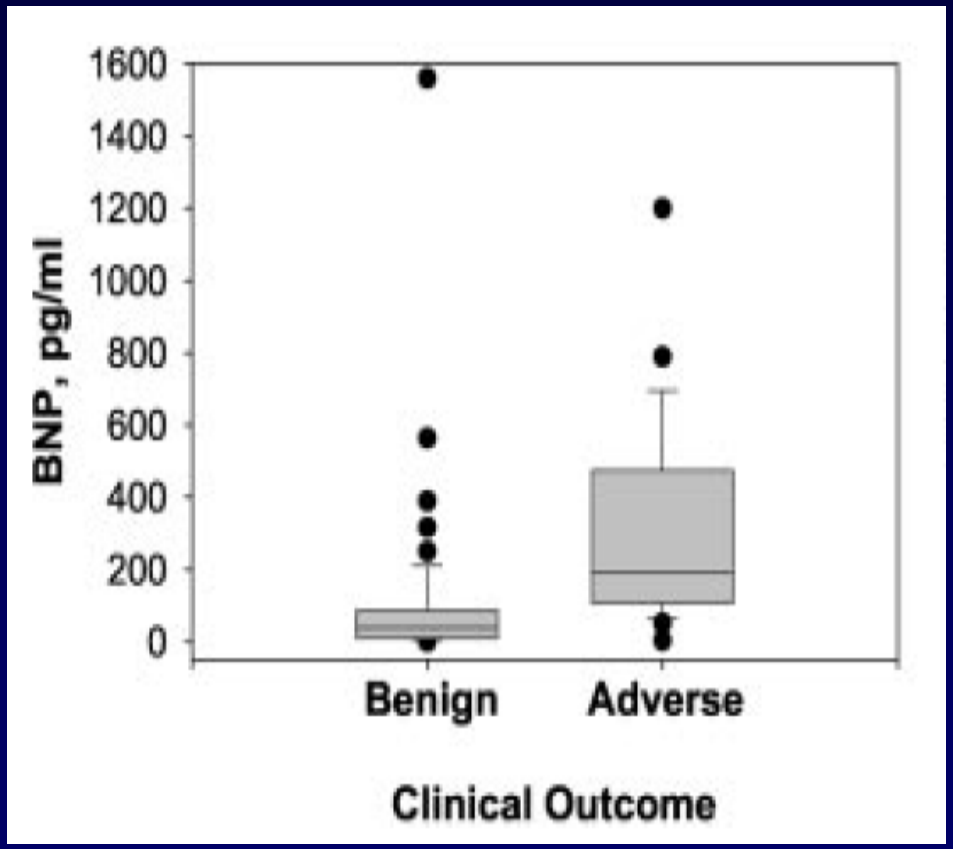
- Prevalenza 15%
- Mortalità per EP in acuto 32%

Senza compromissione emodinamica

- Prevalenza 45%
- Mortalità per EP in acuto 0%

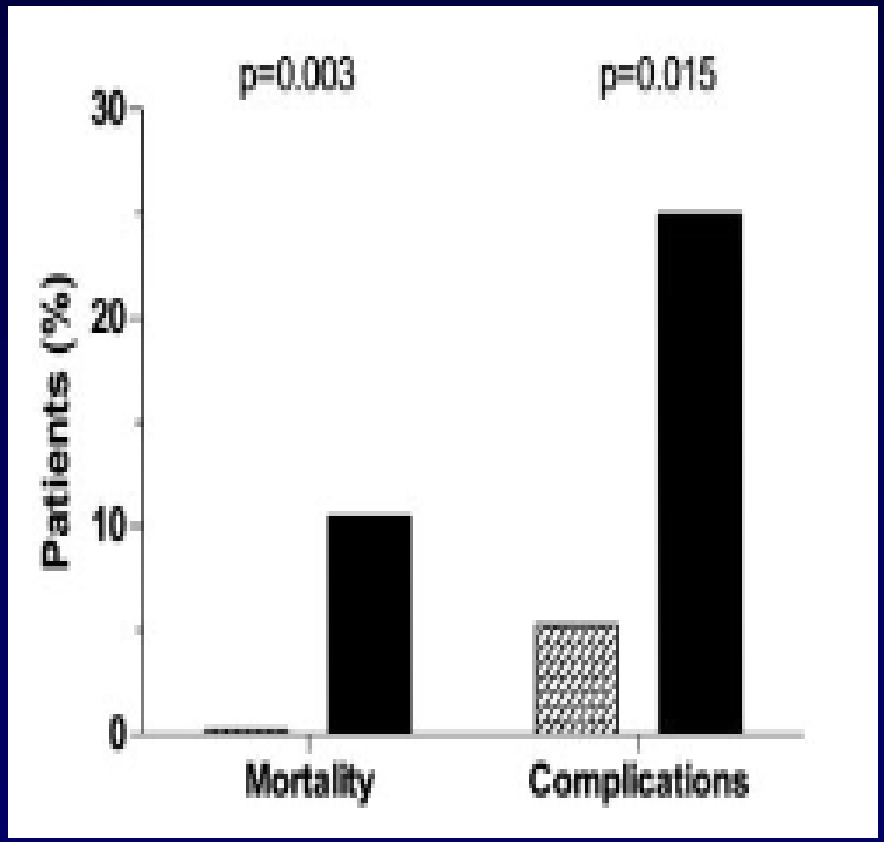
Brain natriuretic peptides

BNP >50 pg/ml sens 95%



Kucher et al Circulation 2003

NTproBNP >1000 sens 95%



Binder L et al Circulation 2005

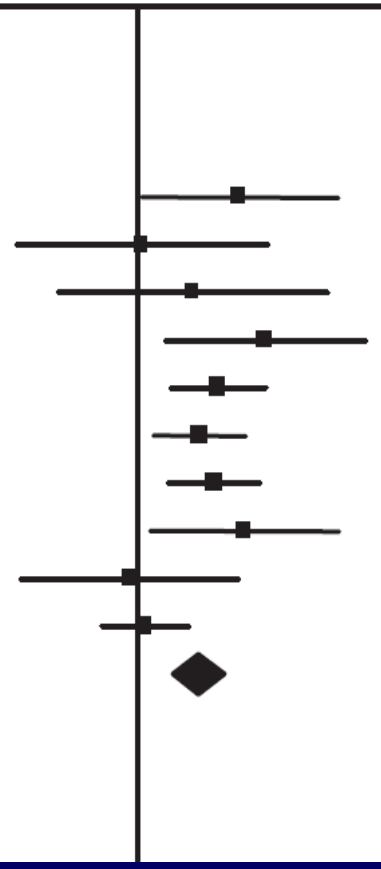
Troponin I and in hospital death

Study or sub-category	Tn positive n/N	Tn negative n/N	OR 95% CI
01 Troponin I			
Meyer	0/14	0/22	
Douketis	0/5	0/19	
Kucher	4/28	1/63	
Mehta	1/18	1/20	
Enea	4/20	0/6	
La Vecchia	5/14	1/34	
Yalamanchili	8/24	9/123	
Douketis JD	6/62	10/396	
Scridon	23/73	5/68	
Binder	6/46	1/78	
Amorim	2/42	1/18	
Hsu	12/62	8/48	
Subtotal (95% CI)	408	895	

Total events: 71 (Tn positive), 37 (Tn negative)

Test for heterogeneity: $Chi^2 = 12.52$, df = 9 (P = 0.19), $I^2 = 28.1\%$

Test for overall effect: Z = 4.64 (P < 0.00001)



Positive and negative predictive values of Troponins and natriuretic peptides

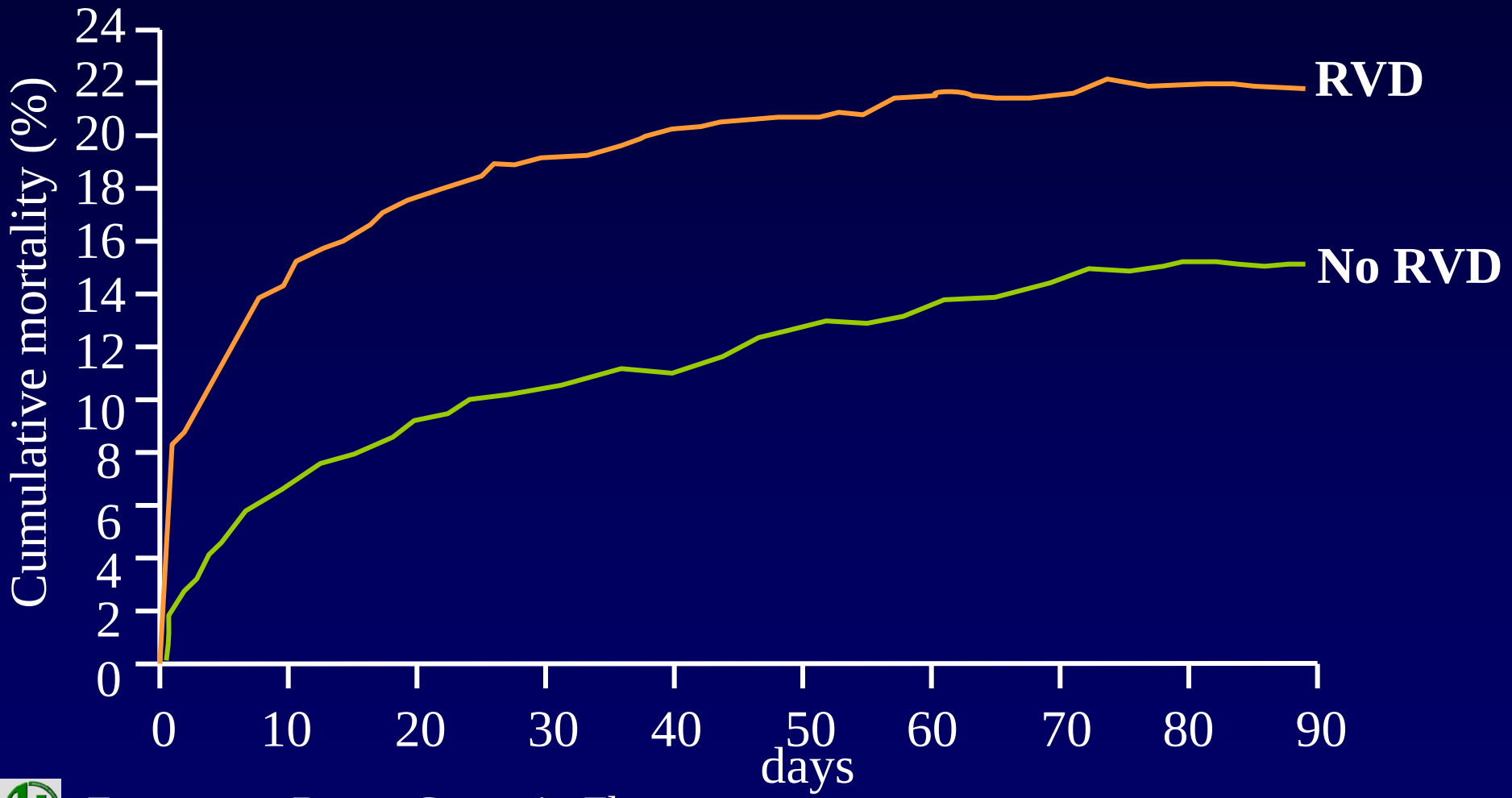
Accuracy of Cardiac Biomarkers for the Prediction of In-Hospital Death in Pulmonary Embolism

Reference	n	Biomarker	Cut-Off Level	Test +, %	NPV, %	PPV, %
Konstantinides et al[11]	106	cTnI	0.07 ng/mL	41	98	14
Konstantinides et al[11]	106	cTnT	0.04 ng/mL	37	97	12
Giannitsis et al[12]	56	cTnT	0.10 ng/mL	32	97	44
Janata et al[24]	106	cTnT	0.09 ng/mL	11	99	34
Pruszczyk et al[13]	64	cTnT	0.01 ng/mL	50	100	25
ten Wolde et al[25]	110	BNP	21.7 pmol/L	33	99	17
Kucher et al[18]	73	NT-proBNP	500 pg/mL	58	100	12
Kucher et al[17]	73	BNP	50 pg/mL	58	100	12
Pruszczyk et al[26]	79	NT-proBNP	153 to 334* pg/mL	66	100	23

NPV indicates negative predictive value; PPV, positive predictive value.
*Age and gender adjusted cut-off levels according to the manufacturer.

Kucher and Goldhaber Circulation 2003

Baseline RV hypokinesis is a predictor of mortality in unselected patients with PE



ICOPER ,Lancet 1999

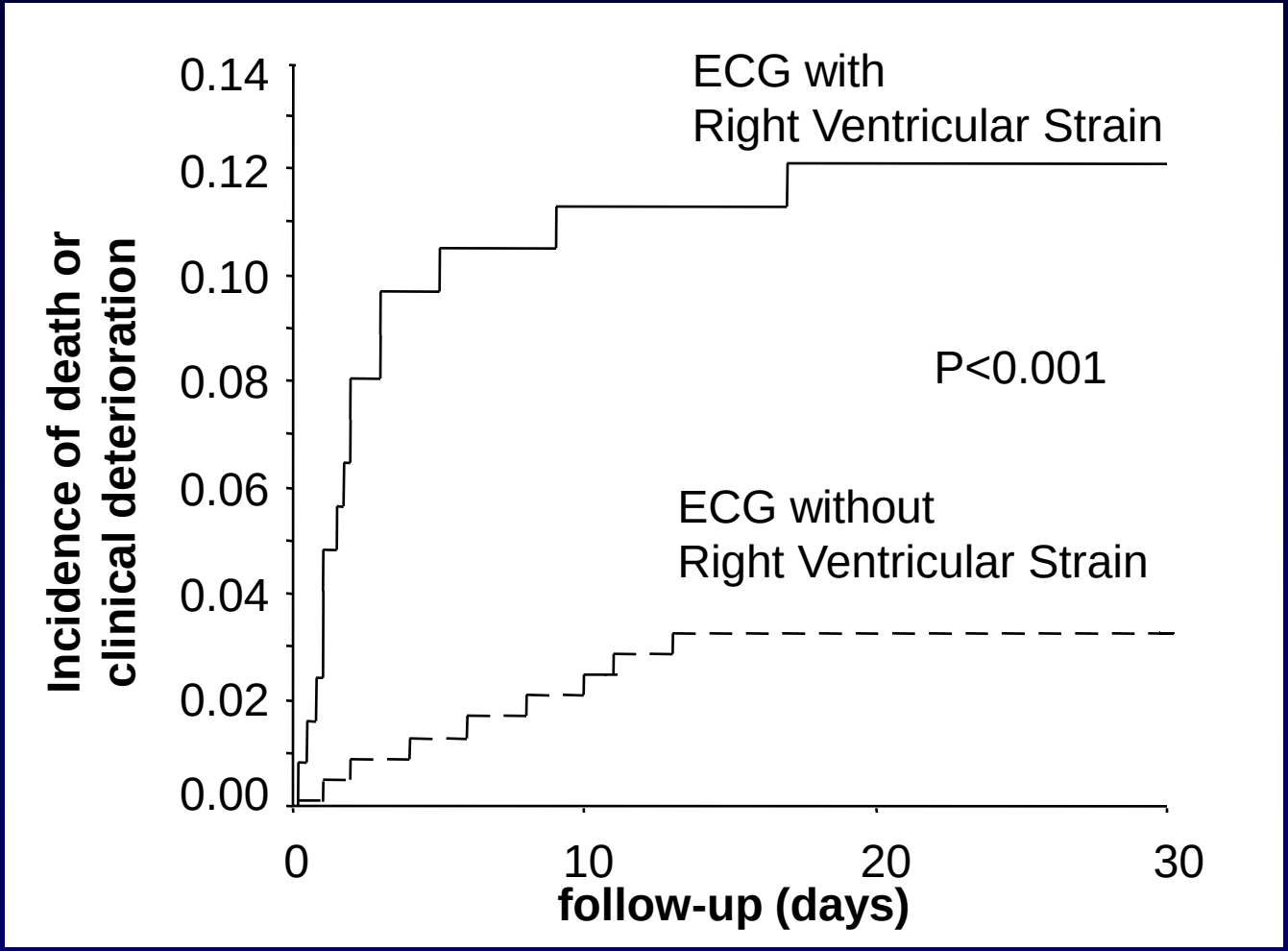
Combined strategies

TABLE 3. Combination of NT-proBNP or Cardiac Troponin T With Echocardiography for Definition of Risk Groups in Patients With Acute PE

Event	Complicated In-Hospital Course, OR (95% CI)	*P*
NT-proBNP combined with echocardiography		
Group 1: NT-proBNP <1000 pg/mL	. . .	
Group 2: NT-proBNP >1000, echo negative*	3.28 (0.60–18.02)	0.172
Group 3: Echo positive*†	12.16 (2.45–60.29)	0.002
Cardiac troponin T combined with echocardiography		
Group 1: TnT negative,‡ echo negative*	. . .	
Group 2: TnT positive,‡ echo negative*	3.70 (0.76–18.18)	0.107
Group 3: TnT negative,‡ echo positive*	5.56 (0.97–31.99)	0.055
Group 4: TnT positive,‡ echo positive*	10.00 (2.14–46.80)	0.004

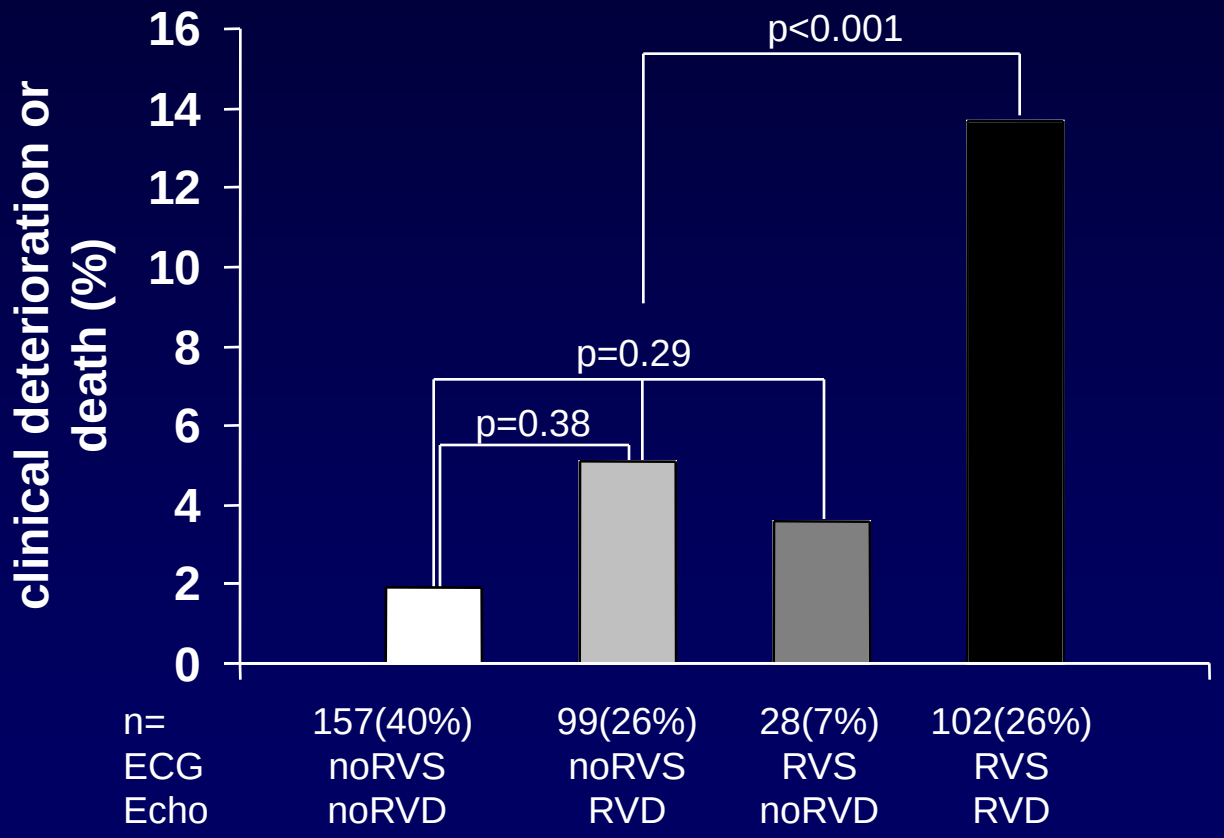
Binder et al *Circulation* 2005

ECG in normotensive PE



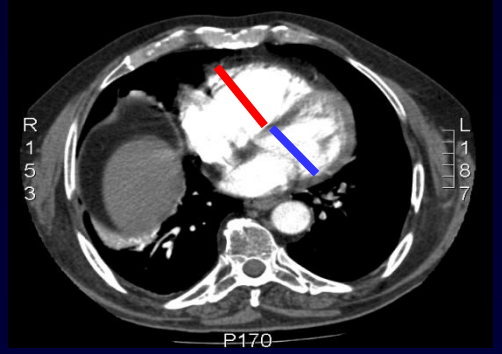
Vanni et al Am J Med 2008 in press

Combined strategies ECG+Echo

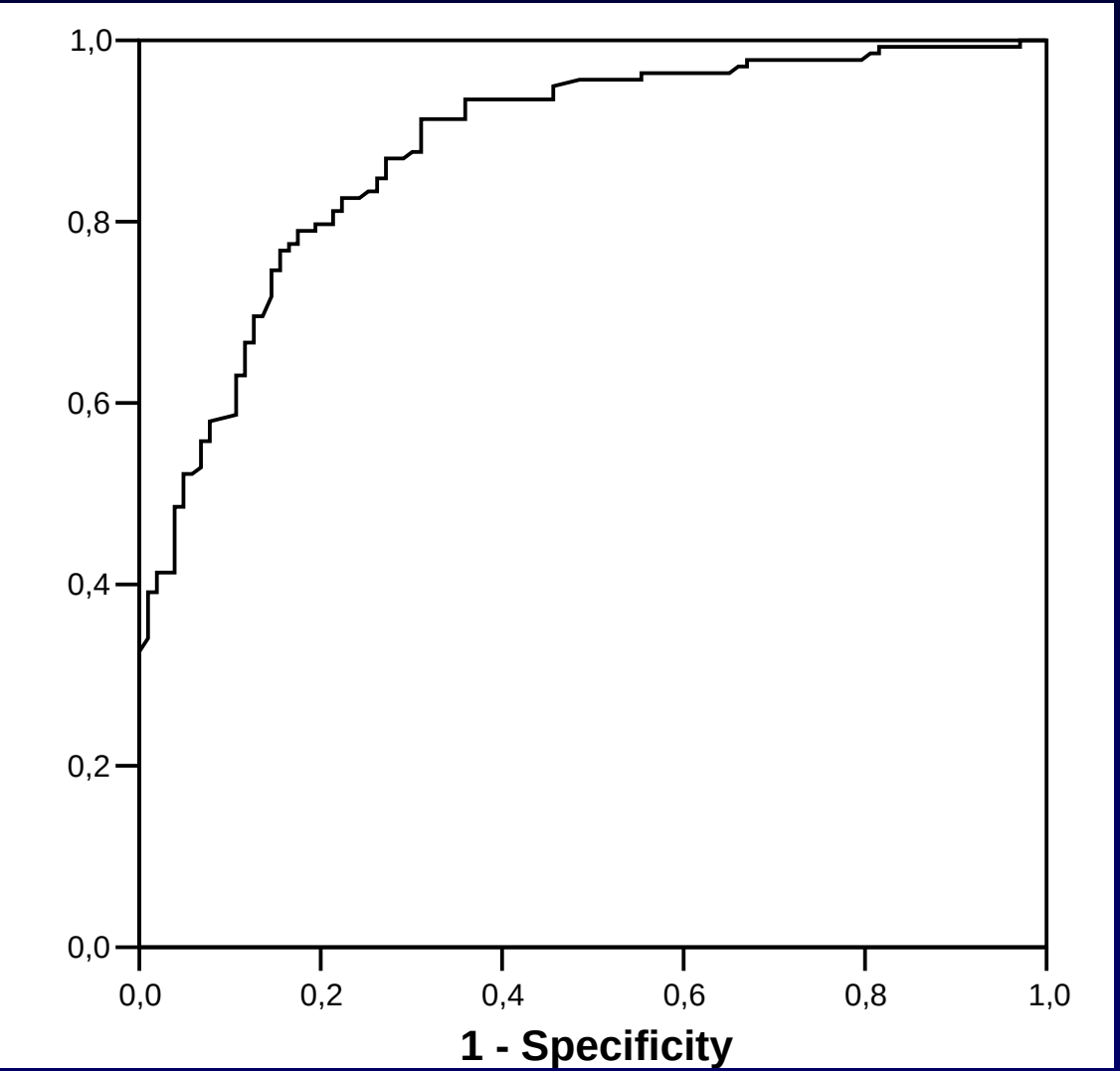


Vanni et al Am J Med 2008 in press

Accuracy: RVD at CT vs Echo

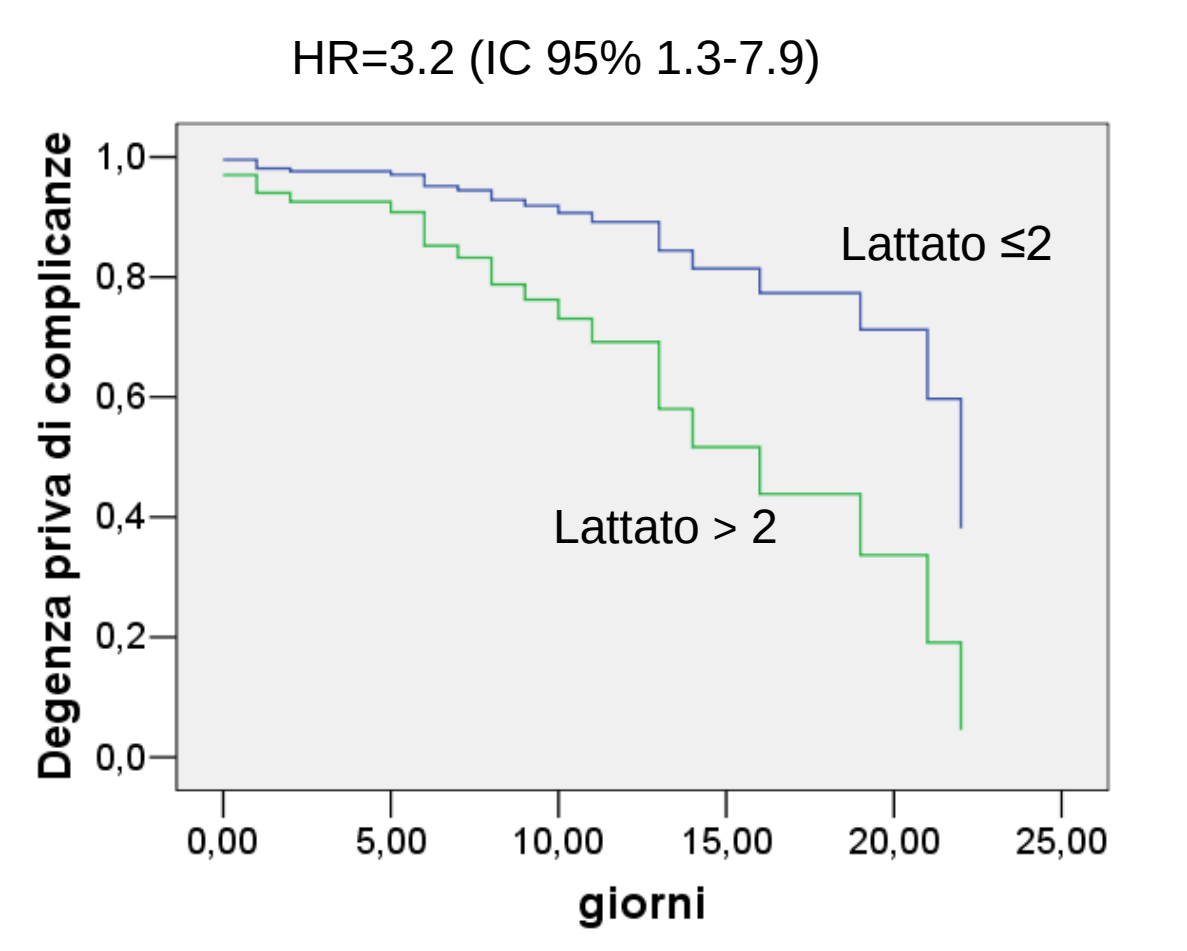


AUC 0.88 (95% CI 0.84-0.92)



Becattini C et al 2008

Il lattato nei pazienti con EP normotesi



Vanni et al abstract Simeu 2008

Prognostication in EP

- To rule out adverse prognosis?
  - Biomarkers (natriuretic peptides, Troponin)
- To rule in aggressive treatment?
  - Echocardiography/TC plus
    - Biomarkers
    - ECG
    - Lactate

Terapia trombolitica

Table 13 Approved thrombolytic regimens for pulmonary embolism

Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h
	Accelerated regimen: 1.5 million IU over 2 h
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24 h
	Accelerated regimen: 3 million IU over 2 h
rtPA	100 mg over 2 h
	or 0.6 mg/kg over 15 min (maximum dose 50 mg)

rtPA = recombinant tissue plasminogen activator.

ESC guidelines Eur Heart J 2008

Efficacia e sicurezza degli agenti trombolitici

- UK, SK e rt-PA sembrano essere ugualmente efficaci e sicuri

- L'infusione di rt-PA in 2 ore risulta più rapida nella lisi del trombo quando confrontata con i regimi di infusione di 12 o 24 ore della UK e SK

Arcasoy SM et al., Chest 1999

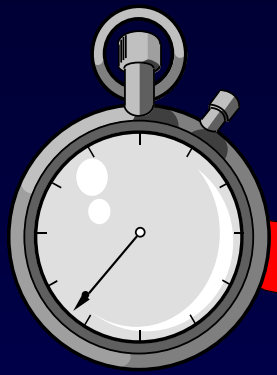
Rischio emorragico della terapia trombolitica

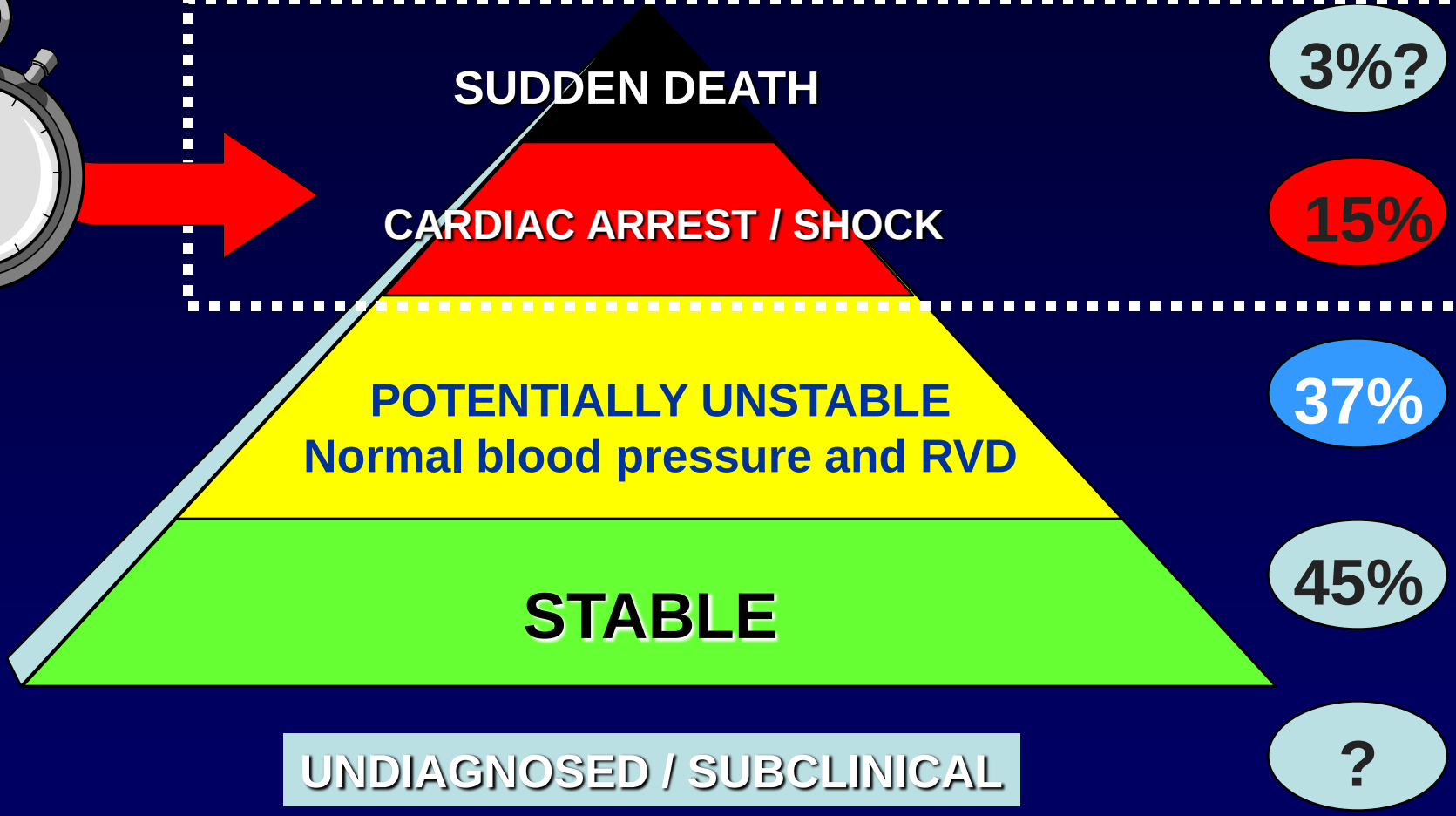
- Rischio emorragico superiore all'eparina (6.3% vs 1,8%)
- Rischio clinicamente rilevante di emorragie intracraniche (2-3.5%)

Arcasoy SM et al. Chest, 1999

Clinical presentation in patients with PE

204 consecutive cases





Grifoni S et al., Circulation 2000

Trombi nelle sezioni dx

- La presenza di trombi nelle sezioni dx è associata ad aumento della mortalità
- La terapia con sola eparinica è insufficiente anche nei pz che clinicamente sembrano stabili
- La fibrinolisi e l' embolectomia chirurgica sono le terapie di scelta

Gestione dell' ACR nei pazienti con Embolia polmonare

•Nei pazienti in arresto cardiaco dovuto a presunta o diagnosticata embolia polmonare è ragionevole somministrare fibrinolitici (IIA)

• Successo terapeutico di embolectomia chirurgica o embolectomia percutanea meccanica nei pazienti in ACR con o senza pretrattamento con fibrinolisi

AHA guidelines for cardiopulmonary resuscitation; Circulation 2010

Embolectomia chirurgica

Si tratta di una tecnica chirurgica complessa, gravata da elevato tasso di mortalità (20-50%).

CONSIDERA (in extremis)

- EP massiva non rispondente alla terapia medica massimale per >1 ora
- Arresto cardiaco
- Controindicazione o fallimento della fibrinolisi

Embolectomia chirurgica

- Può essere un' opzione anche nei pz con Pa normale , in presenza di embolia polmonare estesa e grave disfunzione ventricolare dx
- In centri di III° livello la sopravvivenza ad 1 mese aumenta fino all'89%

Aklog et al Circulation 2002;105:1416-19

Angiojet nell' embolia polmonare massiva

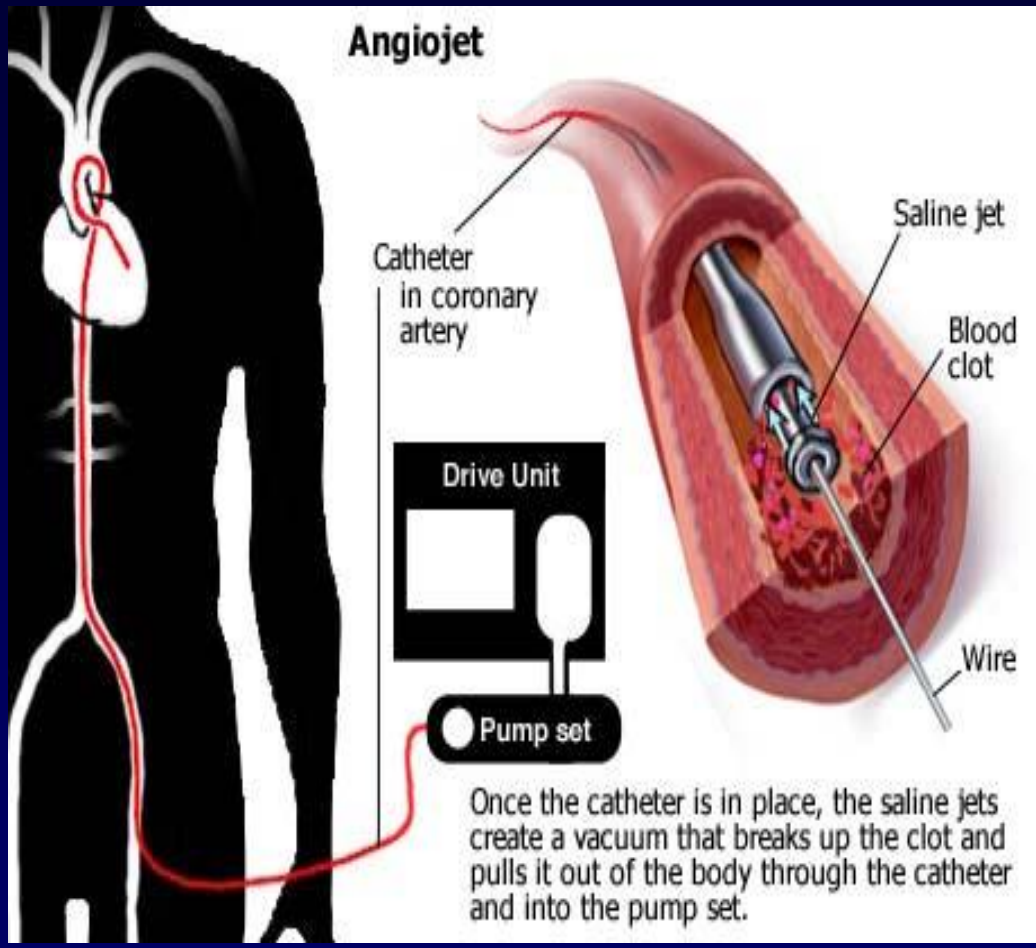
- Una meta-analisi ha mostrato un successo di tale metodica nell' 86,5% dei pazienti, non trattati con precedente fibrinolisi

- In centri con esperienza l' angiojet può essere considerato un trattamento di prima scelta nei pz con embolia polmonare massiva

Kuo et alJ Vasc Interv Radiology 2009

Angiojet Rheolytic Thrombectomy System

- Rapida rivascolarizzazione con riduzione della PAP
- Eseguibile anche in pz. ad elevato rischio chirurgico
- Da considerare nel pz ad alto rischio in caso di fallimento o controindicazione della fibrinolisi



E.C.L.S nell' embolia polmonare massiva

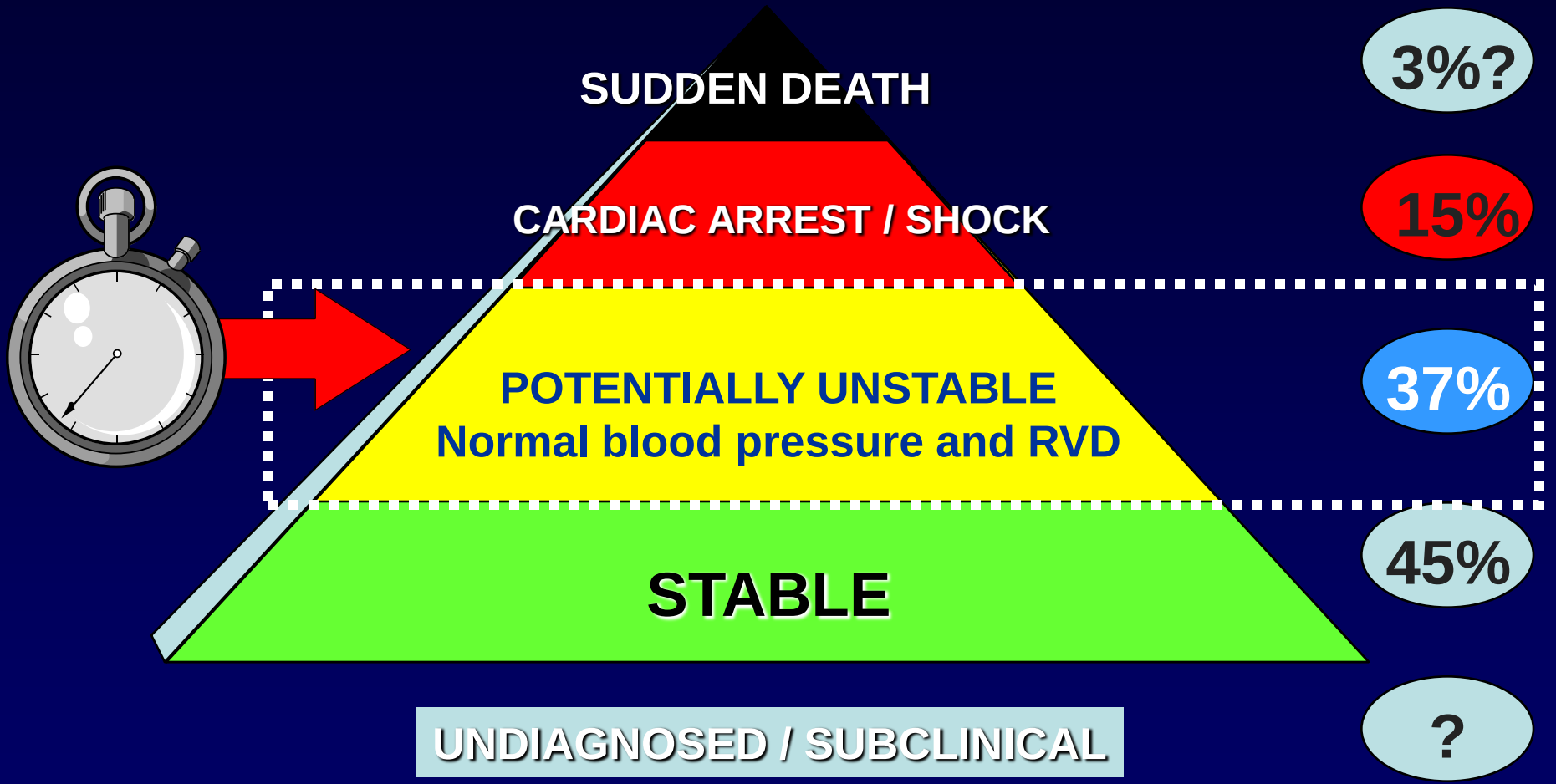
- **In uno studio di 21 pz (terapia con vasoattivi, ipossici e con acidosi) trattati con ECLS la sopravvivenza è stata del 62%**

- **L' ECLS può essere un'opportunità per migliorare la prognosi di una condizione altrimenti quasi sempre fatale**

J Trauma 2007 62;570-576

Clinical presentation in patients with PE

204 consecutive cases



Grifoni S et al., Circulation 2000

Stratificazione prognostica

PE-related early MORTALITY RISK		RISK MARKERS			Potential treatment implications
		CLINICAL (shock or hypotension)	RV dysfunction	Myocardial injury	
HIGH >15%		+	(+)[a]	(+)[a]	Thrombolysis or embolectomy
NON HIGH	Inter mediate 3–15%	–	+	+	Hospital admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

ESC guidelines Eur Heart J 2008

Thrombolysis in PE with Echo-RVD without shock (256 pts)

In-hospital events	Heparin plus alteplase (118)	Heparin (138)	p
Death	3.4%	2.2%	0.71
Escalation of treatment	10.2%	24.6%	0.004
Secondary thrombolysis	7.6%	23.2%	
PE recurrences	3.4%	2.9%	0.89
Major bleeding	0.8%	3.6%	0.29
Hemorragic stroke	0	0	

(Konstantinides S et al. NEJM 2002)

Conclusioni

- La terapia con alteplase ed eparina migliora il decorso dei pz con embolia polmonare sub-massiva (ipertensione polmonare e disfunzione del ventricolo destro)
- Indicazione ad estendere l' uso dei fibrinolitici, assicurandosi del basso rischio di complicanze emorragiche

Konstantinides S et al. NEJM 2002

Studio TIPES

MULTICENTRICO RANDOMIZZATO, CONTROLLATO, DOPPIO CIECO (n=180)

TNK-tPA bolo e.v. + Eparina UFH e.v.

VS

Eparina UFH e.v.

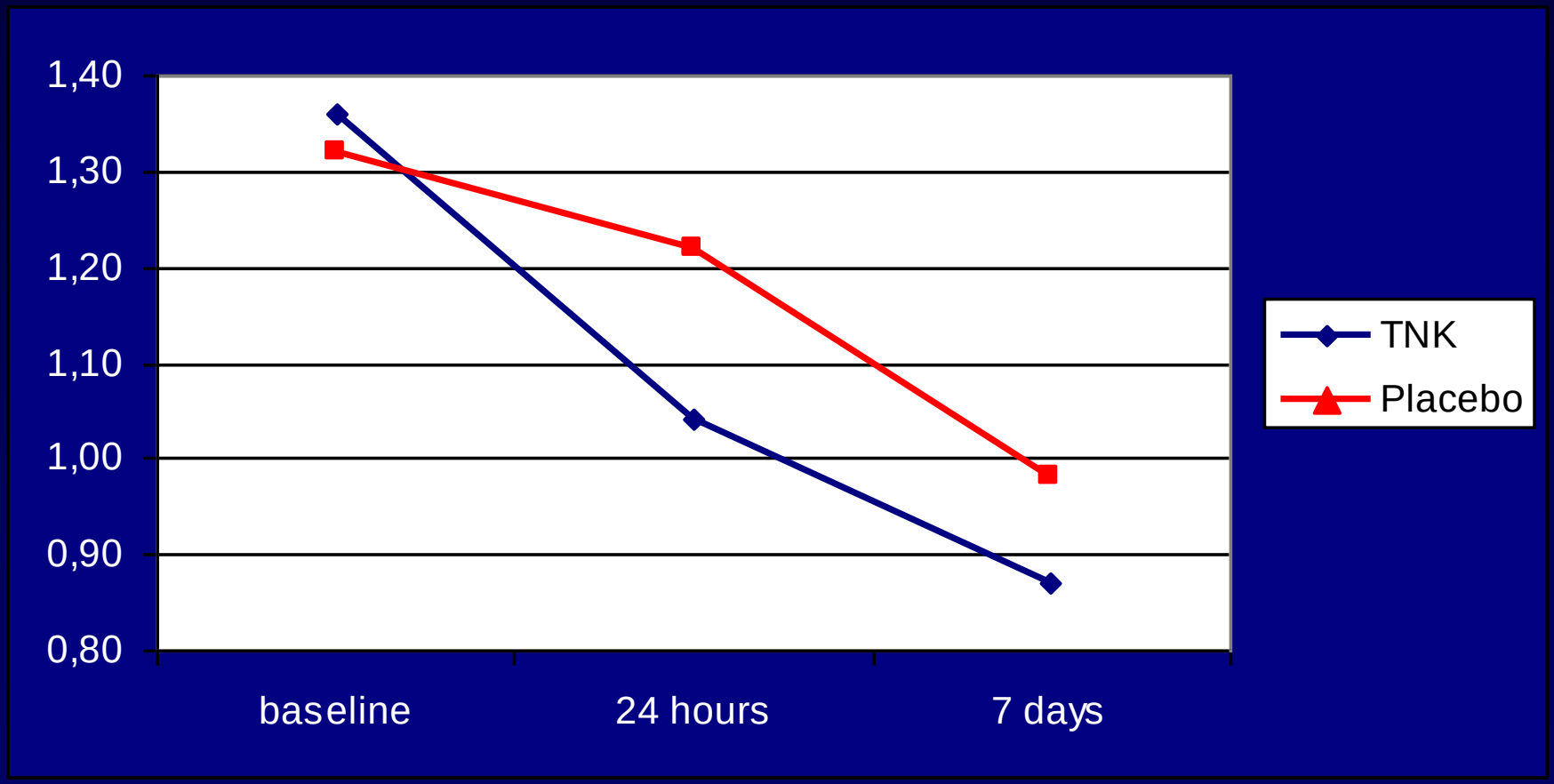
CRITERI DI INCLUSIONE:

- 18-80 ANNI
- EP SINTOMATICA
- PA ≥ 100 mmHg
- RVD +

TNK in normotensive PE patients

R/L end-diastolic dimension ratio :

Time course



Agnelli G et al 2007

Conclusioni

- E’ il primo studio sull’ uso del TNK nell’ embolia polmonare
- Dimostrazione della riduzione della RVD a 24 ore
- Necessità di verificare che questo effetto benefico sia associato ad un miglioramento prognostico

Agnelli G et al Thromb Res. 2010 Mar;125

Studio PEiTHO

MULTICENTRICO RANDOMIZZATO, CONTROLLATO, DOPPIO CIECO (circa 1000 pz) Europeo

rtPA bolo e.v.
+
Eparina UFH e.v.

VS

Eparina UFH e.v.

CRITERI DI INCLUSIONE:

- 18-80 ANNI
- EP SINTOMATICA
- PA ≥ 100 mmHg
- RVD + Troponina o BNP elevati

Endpoints:

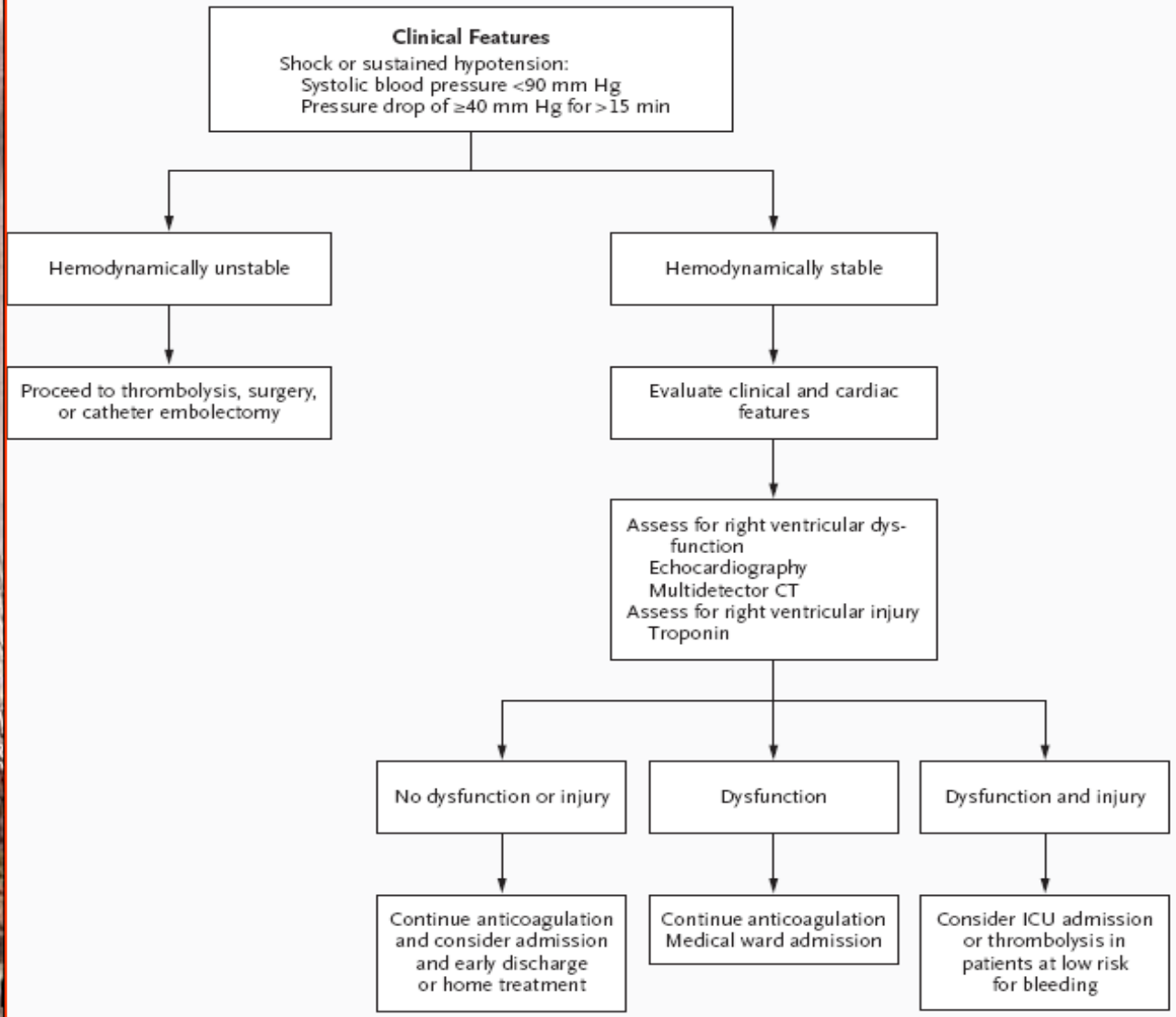
- Mortalità per EP
- Recidiva
- Shock

RVD on admission and outcome in patients with Pulmonary Embolism

- **RVD persistence appears to be common**
- **Echocardiography should be repeated before discharge**
- **Selected patients with RVD persistence may require evaluation for surgical thrombectomy**
- **Can we prevent RVD persistence with more aggressive initial treatment ?**

Pazienti con embolia polmonare e disfunzione ventricolare destra

- "Routine use of thrombolyses in non-high risk patient is not recommended, but may be considered in selected patients with intermediate risk PE and after a thorough consideration of conditions increasing the risk of bleeding."
- *Guidelines on diagnosis and management of acute PE, Eur Heart J, 2008*

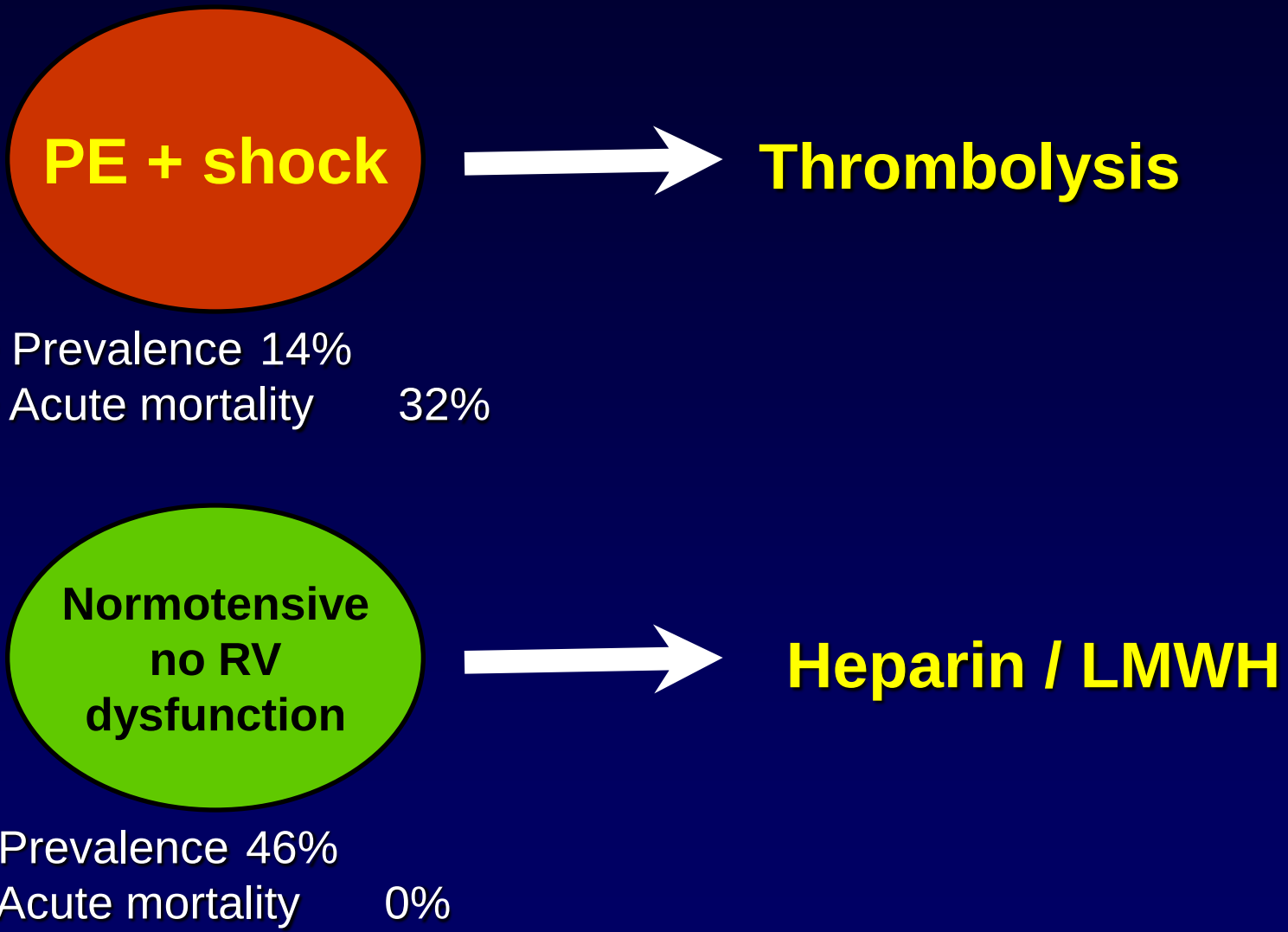


gure 2. Clinical Management of Confirmed Acute Pulmonary Embolism.

U denotes intensive care unit.

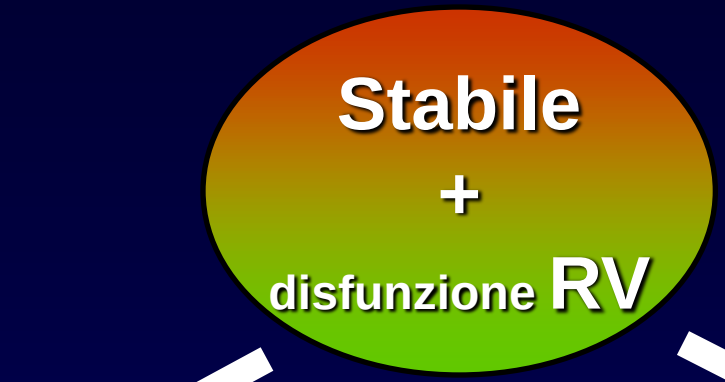
Agnelli N Eng J Med 2010

Evidence-based treatment strategy for PE



Emergency Dept.- Careggi - Florence

Evidence-based treatment strategy for PE



Prevalenza 40%
mortalità Acuta 5%

Basso rischio emorragico

Specie se ↑ TnT and BNP

Considera trombolisi immediata

Alto rischio emorragico

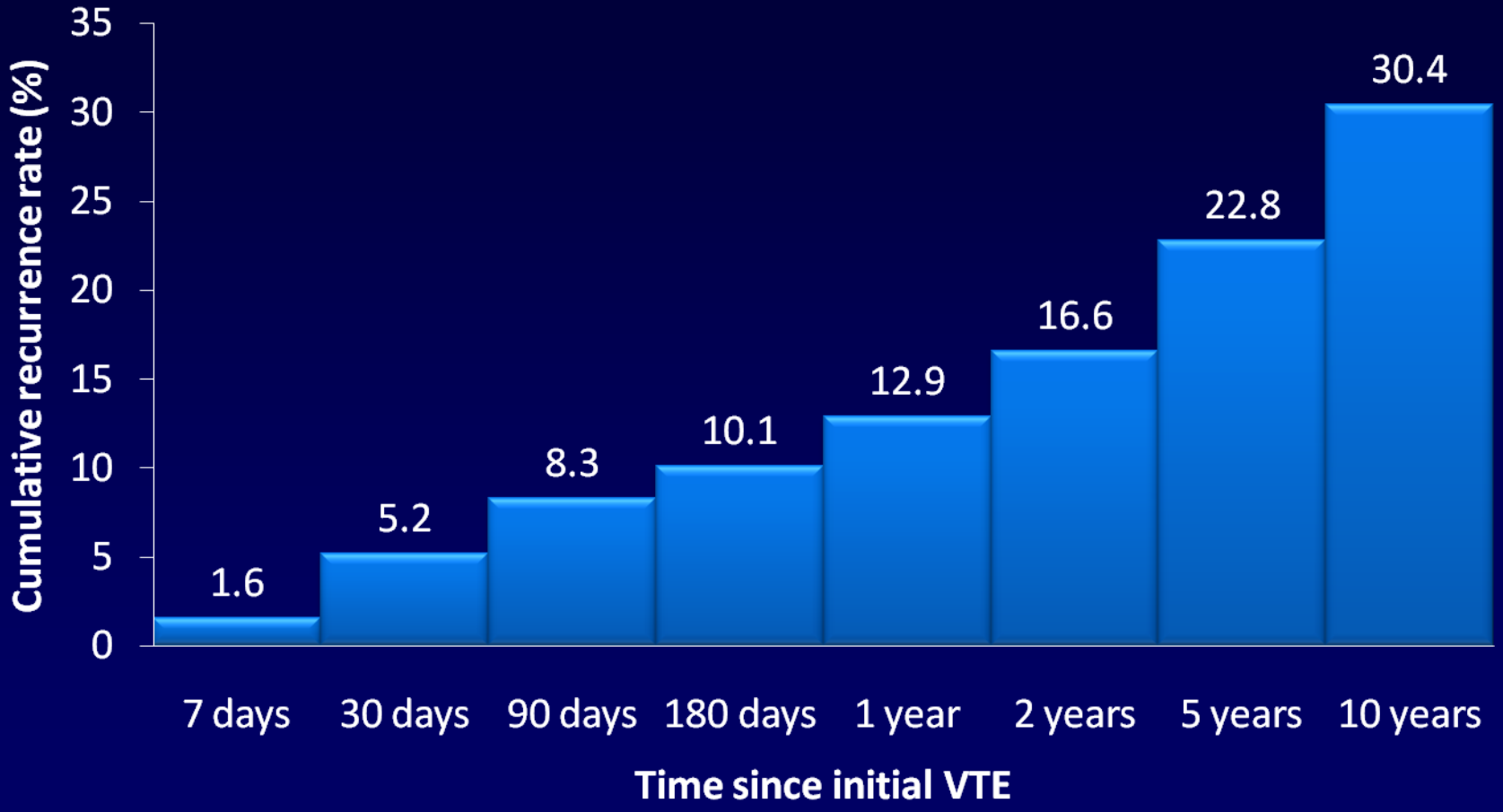
eparina - Osserve >24 ore

Deterioramento
"rescue" trombolisi

Stabile
Continua eparina

Grifoni s. et al. 2002

Recurrent VTE – long term perspective



DVT=deep vein thrombosis; VTE=venous thromboembolism

Heit JA, et al. *Arch Intern Med* 2000;160:761-768.

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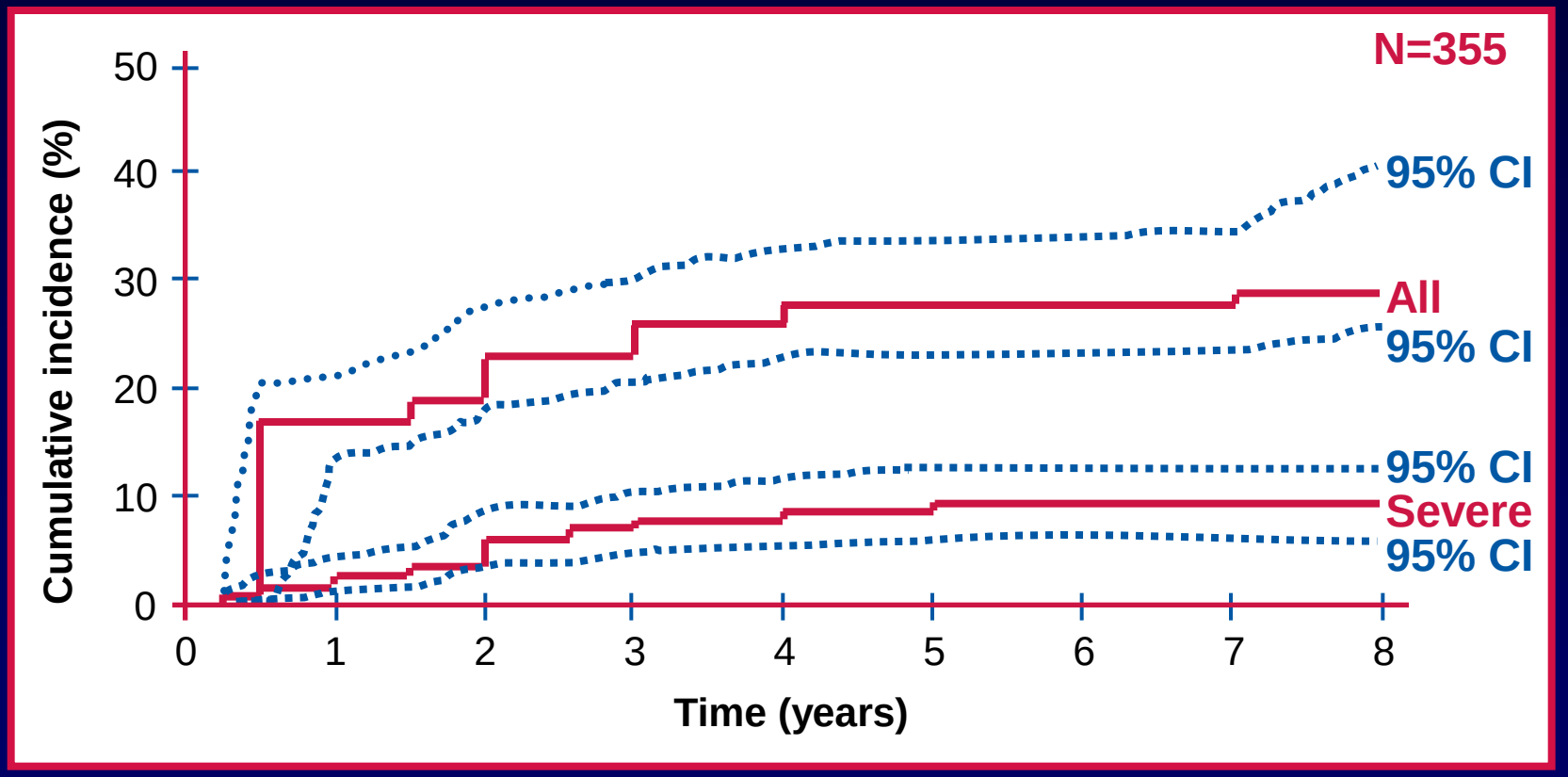
Cumulative Incidence of Post-thrombotic Syndrome

Cumulative incidence of all PTS and severe PTS, after first episode of symptomatic DVT



Prandoni P et al. *Ann Intern Med.* 1996;125:1-7.

Dimensioni del problema

Incidenza:

- **60.000/anno Italia (~0,1%)**
- **Intraospedaliera: 0,2-0,4%**
- **Aumenta con l'età**
- **Non differenze uomo donna (> 50 anni)**

Dimensioni del problema

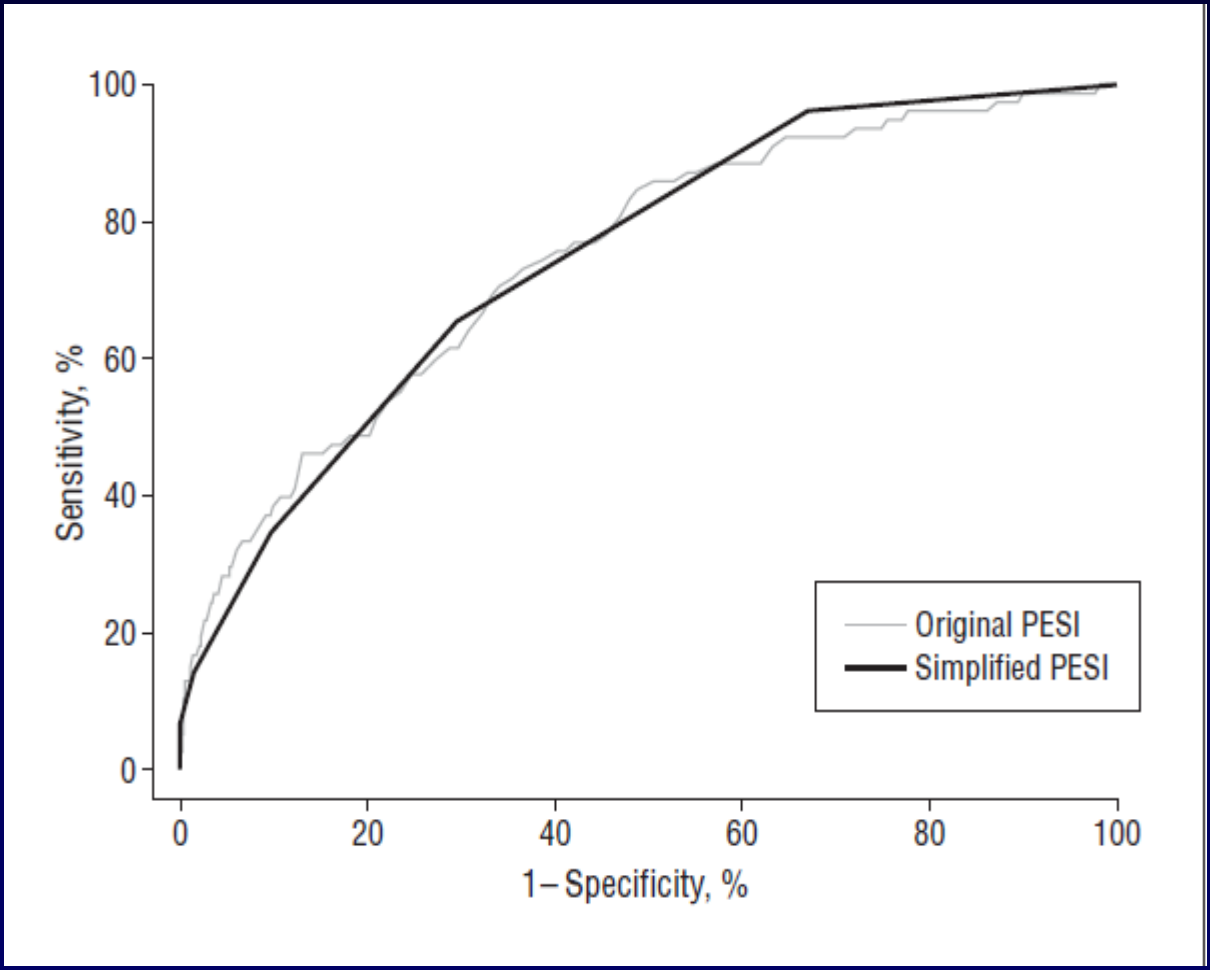
- **Mortalità: 30% se non riconosciuta**

  Mortalità intraospedaliera: 7%

  Mortalità a tre mesi (Icoper): 17%

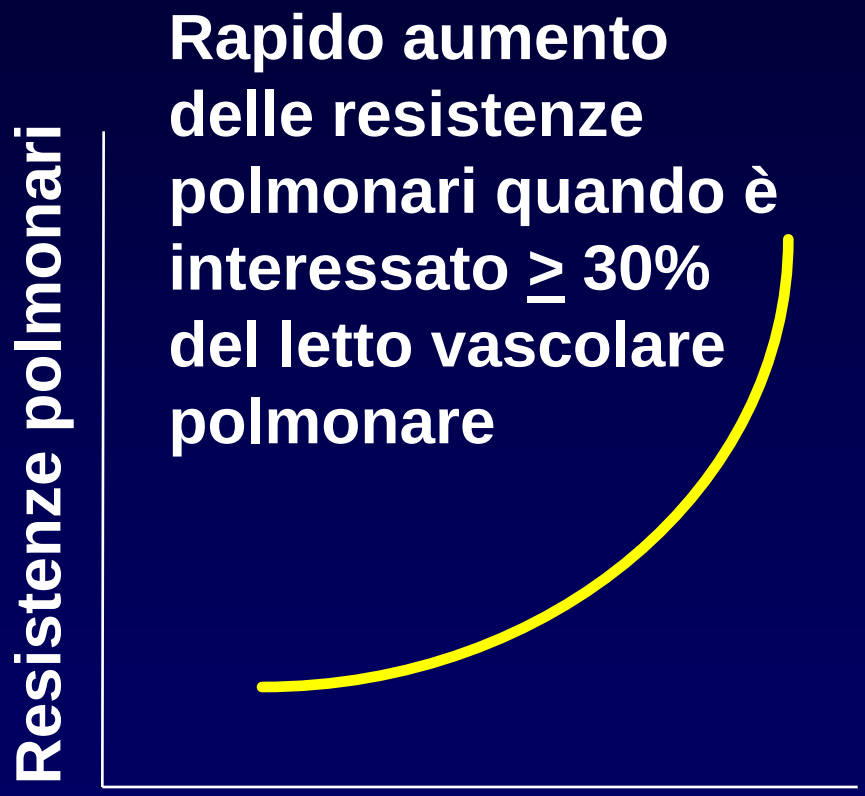
- **Ipertensione polmonare persistente: 20%**

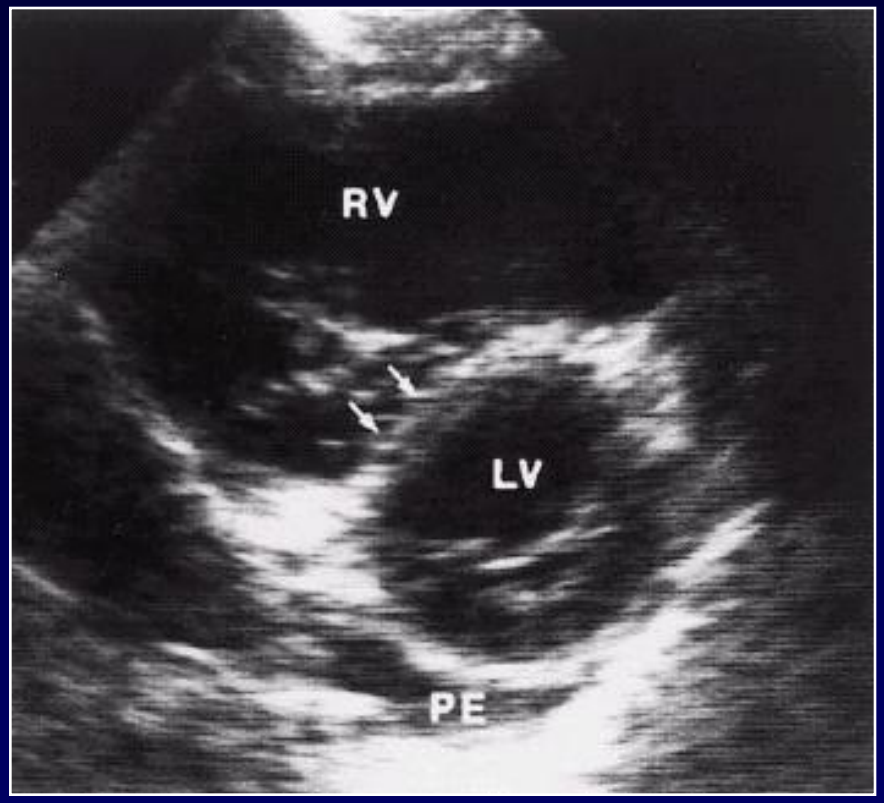
Stratificazione prognostica clinica.



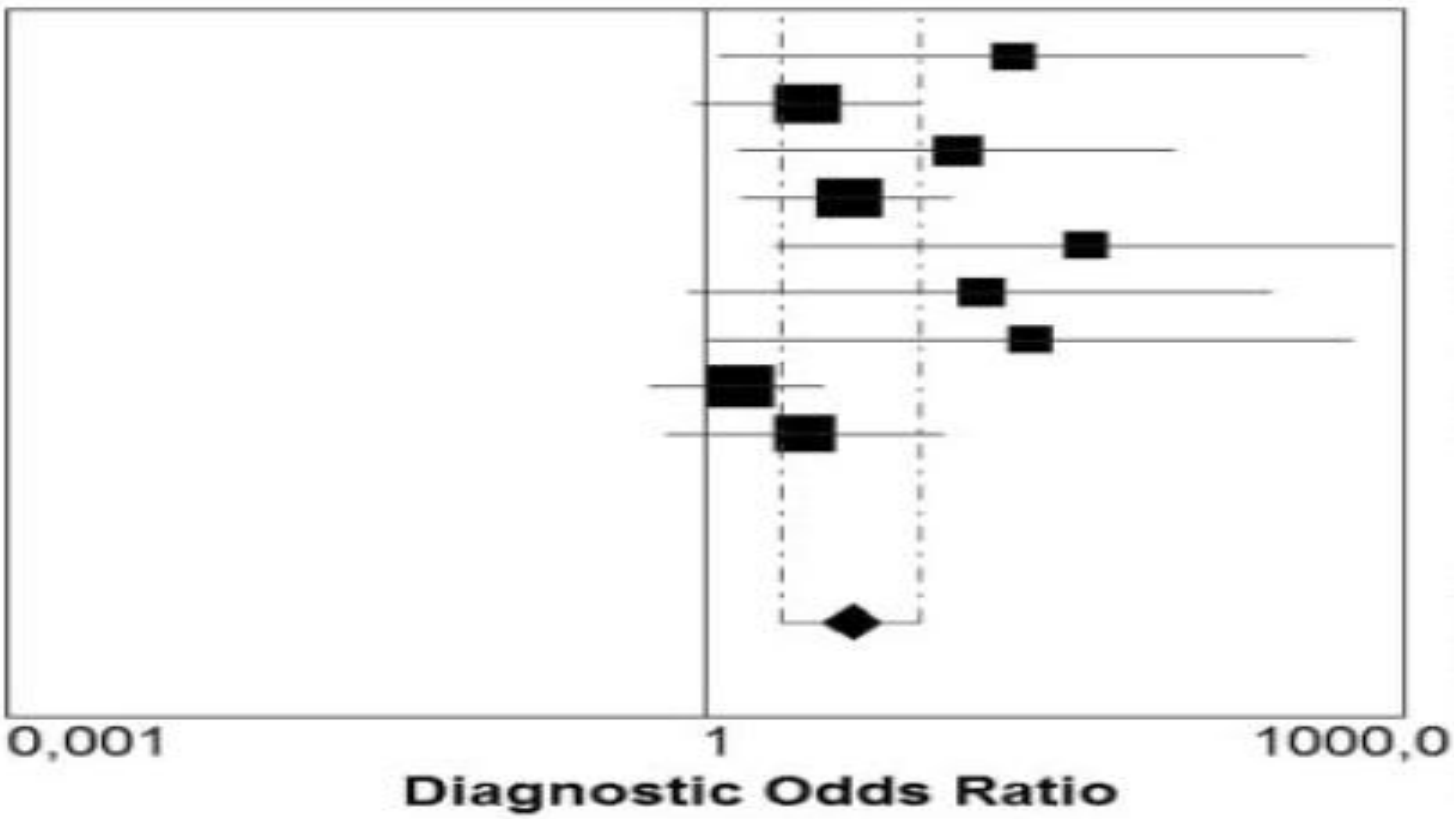
Jimenez D Arc Int Med 2010

FISIOPATOLOGIA DELL' EP
alterazioni emodinamiche





Tpn e mortalità nei normotesi



Jimenez et sl Chest 2009

Post-thrombotic Syndrome

- Chronic, potentially disabling
- Cumulative incidence of PTS is 29% after 8 years[1]
- Any sign of PTS is seen in 56.3% of patients at 10 years[2]
- Long-term medical costs of treating this late complication add an estimated 75% to the costs of treating the primary DVT[3]

DVT=deep vein thrombosis; PTS=post-thrombotic syndrome

1. Prandoni P et al. *Ann Intern Med.* 1996;125:1-7; 2. Schulman S, et al. *J Thromb Haemost* 2006;4:734-742; 2. Bergqvist D, et al. *Ann Intern Med* 1997;126:454-457.

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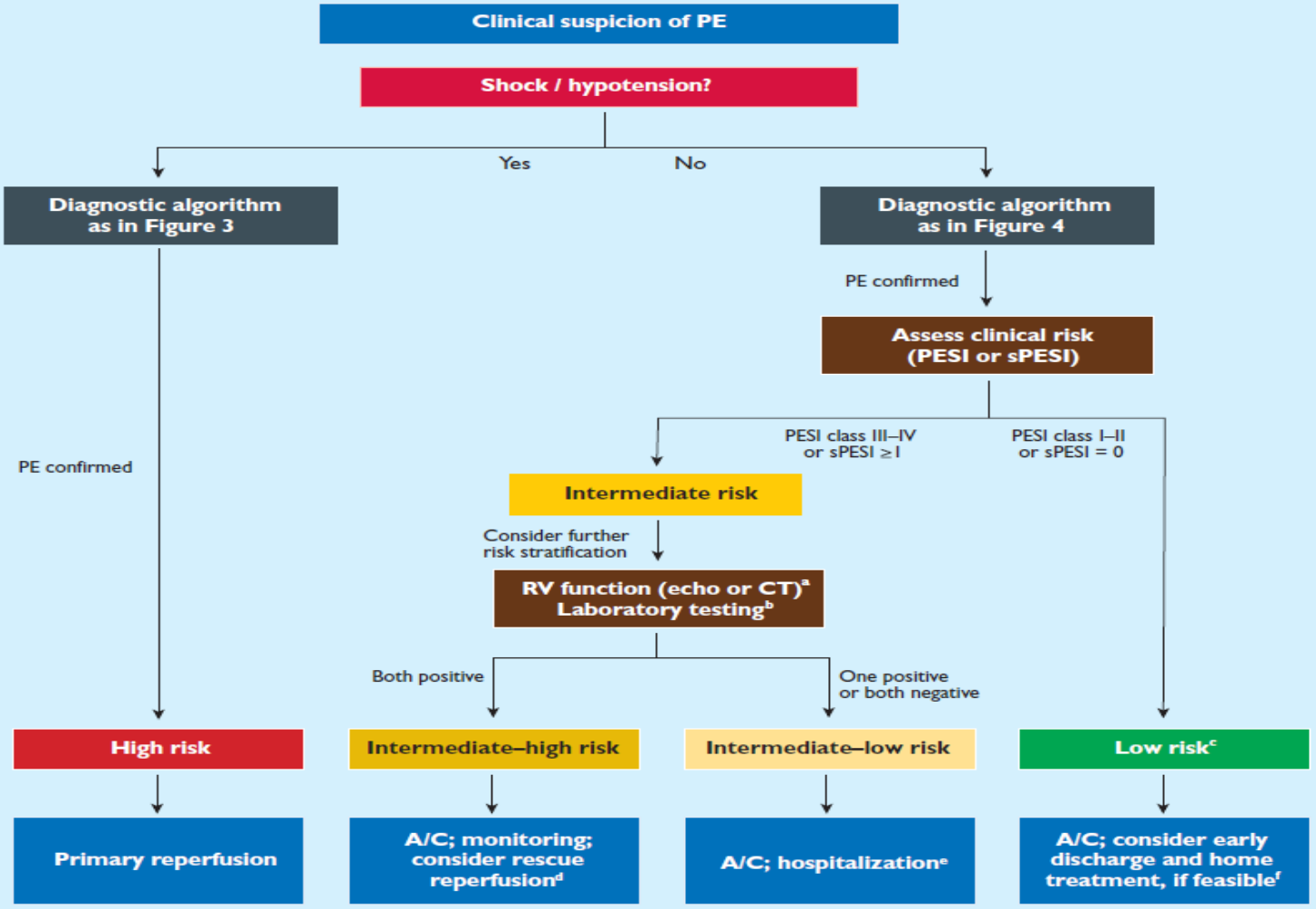
Presentazione dell'EP nel DEA: TRE PARADIGMI

	CRITERIO DOMINANTE
➢ Paz in SHOCK	*TEMPO*
➢ Paz normoteso, dispnoico	*Stratificazione Prognostica*
➢ Paz eupnoico, dolore toracico parietale, sospetta TVP	*Accuratezza Diagnostica*



A/C = anticoagulation; CT = computed tomographic pulmonary angiography; PE = pulmonary embolism; PESI = pulmonary embolism severity index; RV = right ventricular; sPESI = simplified pulmonary embolism severity index.

[a]If echocardiography has already been performed during diagnostic work-up for PE and detected RV dysfunction, or if the CT already performed for diagnostic work-up has shown RV enlargement (RV/LV (left ventricular) ratio ≥0.9), a cardiac troponin test should be performed except for cases in which primary reperfusion is not a therapeutic option (e.g. due to severe comorbidity or limited life expectancy of the patient).

[b]Markers of myocardial injury (e.g. elevated cardiac troponin I or T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma). If a laboratory test for a cardiac biomarker has already been performed during initial diagnostic work-up (e.g. in the chest pain unit) and was positive, then an echocardiogram should be considered to assess RV function, or RV size should be (re)assessed on CT.

[c]Patients in the PESI Class I–II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also to be classified into the intermediate–low risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index. These patients are probably not candidates for home treatment.

[d]Thrombolysis, if (and as soon as) clinical signs of haemodynamic decompensation appear; surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative options to systemic thrombolysis, particularly if the bleeding risk is high.

[e]Monitoring should be considered for patients with confirmed PE and a positive troponin test, even if there is no evidence of RV dysfunction on echocardiography or CT.

[f]The simplified version of the PESI has not been validated in prospective home treatment trials; inclusion criteria other than the PESI were used in two single-armed (non-randomized) management studies.

Stratificazione prognostica clinica. PESI

Predictors	Score
• Age	Years
• Male sex	+10
• Cancer	+30
• Heart failure	+10
• COPD	+10
• HR ≥ 110 bpm	+20
• SBP < 100 mmHg	+30
• RR ≥ 30	+20
• BT < 36 °C	+20
• Delirium	+60
• SaO_2 < 90%	+20
Total_____	

Low risk
≤65 class I, mortality 0.7%
66–85 class II, mortality 1.2%

High risk
86–105 class III, mortality 4.8%
106–125 class IV, mortality 13.6%
>125 class V, mortality 25%

 Aujeski et al Int J Med 2007

Stratificazione prognostica clinica.
sPESI

Table II. Simplified pulmonary embolism severity index.

Variable	Points
Age >80 years	1
History of cancer	1
History of chronic cardiopulmonary disease	1
Pulse ≥110 beats/min	1
Systolic blood pressure <100 mmHg	1
Arterial oxyhemoglobin saturation (SaO_2) <90%	1

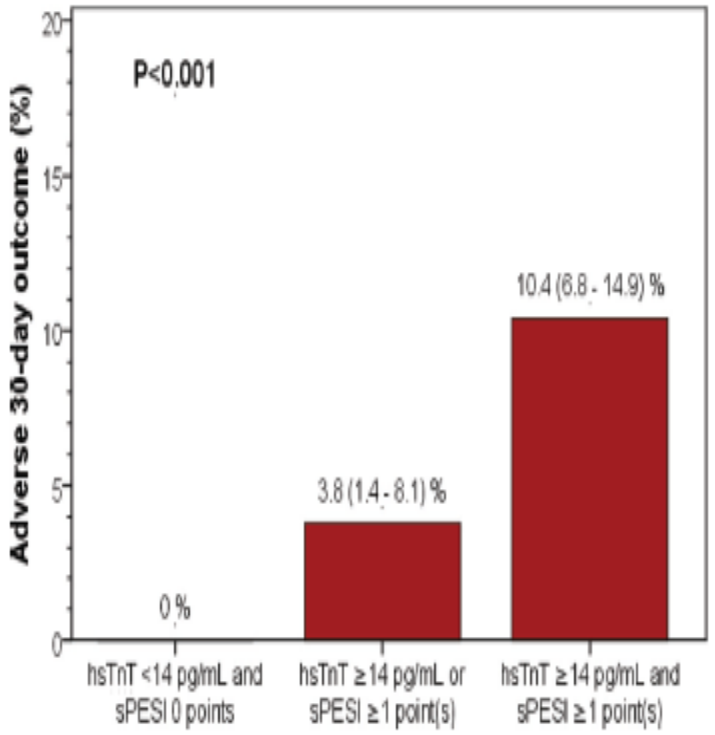
A total point score for a given patient is obtained by summing the points. The score corresponds with the following risk classes: 0, low risk; ≥1, high risk.

Troponina ultrasensibile e sPESI nei normotesi

Table 3. Value of hsTnT and the sPESI, Alone and in Combination, for Predicting an Adverse 30-Day Outcome after Acute Pulmonary Embolism

	Sensitivity	Specificity	PPV	NPV
hsTnT ≥14 pg/mL	0.87	0.42	0.09	0.98
sPESI ≥1 point(s)	0.94	0.40	0.09	0.99
hsTnT ≥14 pg/mL *and* sPESI ≥1 point(s)	1.00	0.26	0.08	1.00

PPV indicates positive predictive value; NPV, negative predictive value; hsTnT, high-sensitivity troponin T; and sPESI, simplified Pulmonary Embolism Severity Index.



Lankeit et al Circulation 2011

CHEST

Original Research

THROMBOEMBOLISM

Efficacy and Safety of Low Dose Recombinant Tissue-Type Plasminogen Activator for the Treatment of Acute Pulmonary Thromboembolism

A Randomized, Multicenter, Controlled Trial

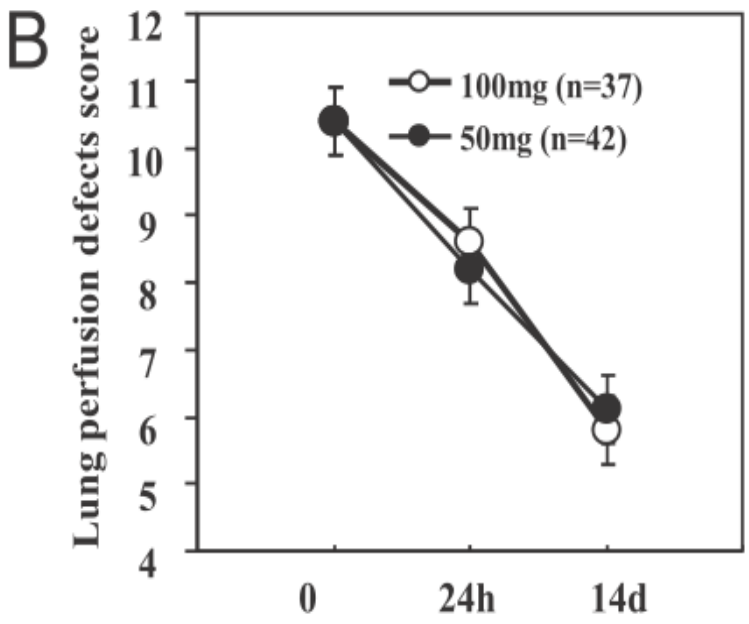


Table 3—*Comparison of Adverse Events During the First 14 d After Treatment, Comparing Two Treatments for PTE*

Adverse Events	rt-PA 100 mg (n = 48)	rt-PA 50 mg (n = 55)	*P*
Death	3 (6)	1 (2)	.472
Due to PTE	2 (4)	1 (2)	…
Due to bleeding	1 (2)	0 (0)	…
Bleeding complications	17 (32)	11 (17)	.054
Major bleeding	5 (10)	2 (3)	.288
Fatal bleeding	1 (2)	0 (0)	…
Others	4 (8)	2 (3)	…
Minor bleeding	12 (22)	9 (14)	.214
Recurrent PTE	2 (4)	1 (2)	.858
Fatal	0 (0)	0 (0)	…
Nonfatal	2 (4)	1 (2)	…

Data presented are number (%) of patients. Others = other major bleeding without death. See Table 1 for expansion of abbreviations.

Wang C et al Chest 2010