FIBRINOLISIS EN LA TROMBOEMBOLIA DE PULMÓN AGUDA SINTOMÁTICA: SÍ

Dr. D. Jiménez
Servicio de Neumología
Unidad de Enfermedad Tromboembólica
Hospital Ramón y Cajal

Mallorca, Mayo 2009

Summary

- Thrombolytic therapy is indicated in patients with massive PE, as shown by shock and/or hypotension.
- Most contraindications for thrombolytic therapy in massive PE are relative.
- Thrombolytic therapy should be based on objective diagnostic tests.
- The use of thrombolytic therapy in patients with

European Heart Journal (2000) **21**, 1301–1336
doi:10.1053/euhj.2000.2250, available online at http://www.idealibrary.com on IDEAL®

Task Force Report

Guidelines on diagnosis and management of acute pulmonary embolism[1]

Massive PE

- CTPA or echocardiog
- Thrombolysis is the fir diac arrest is immi-
  nent [B]; a 50 mg bol
- Invasive approaches and expertise are
  readily available. [C]

4.3.1. All PE patients should undergo rapid risk stratification (Grade 1C). **For patients with evidence of hemodynamic compromise, we recommend use of thrombolytic therapy unless there are major contraindications owing to bleeding risk** (Grade 1B). **Thrombolysis in these patients should not be delayed because irreversible cardiogenic shock may ensue. In selected high-risk patients without hypotension who are judged to have a low risk of bleeding, we suggest administration of thrombolytic therapy** (Grade 2B).

tion of thrombolytic therapy (Grade 2B). For patients who are hemodynamically unstable, we suggest use of thrombolytic therapy (Grade 2B).

Thrombolytic therapy for venous thromboembolism: Current clinical practice

- 84% en los 2 últimos años
- 99% si hipotensión
- 83% si hipoxemia y TEP extensa
- 62% si submasiva

Stashenko GJ. J Hosp Med 2009

“The principal difficulty in your case”, remarked Holmes, in his didactic fashion, “lay in the fact of there being too much evidence. What was vital was overlaid and hidden by what was irrelevant”.

Memoirs of Sherlock Holmes. The naval treaty,
Arthur Conan Doyle, 1893.

¿De verdad crees que no hay que fibrinolisar a los pacientes?

David, Manel me obligó a hacerlo. Tú (casi) siempre llevas razón.
La fibrinolisis es lo mejor para el paciente con TEP.

Índice

- Fundamento para la trombolisis
- TEP masiva
- TEP submasiva

Trombolisis versus heparina

- La fibrinolisis LISA el coágulo al facilitar el paso de plasminógeno a plasmina
- La heparina NO LISA el coágulo; impide su propagación y facilita la fibrinolisis endógena del organismo

Kearon C. Thromb Haemost 1999

¿De qué fallecen los pacientes con TEP?

- MAPPET[1]: 10% in-hospital death; 94% due to PE
- ICOPER[2]: 11% 2-weeks death; 45% due to PE
- PIOPED[3]: 10% PE-related deaths; 90% within two weeks of diagnosis
- RIETE[4]: 61% of early deaths due to PE

[1]Konstantinides S. Circulation 1997
[2]Goldhaber SZ. Lancet 1999
[3]Carson JL. N Engl J Med 1992
[4]Conget F. Thromb Haemost 2008

¿Por qué fallecen los pacientes con TEP?

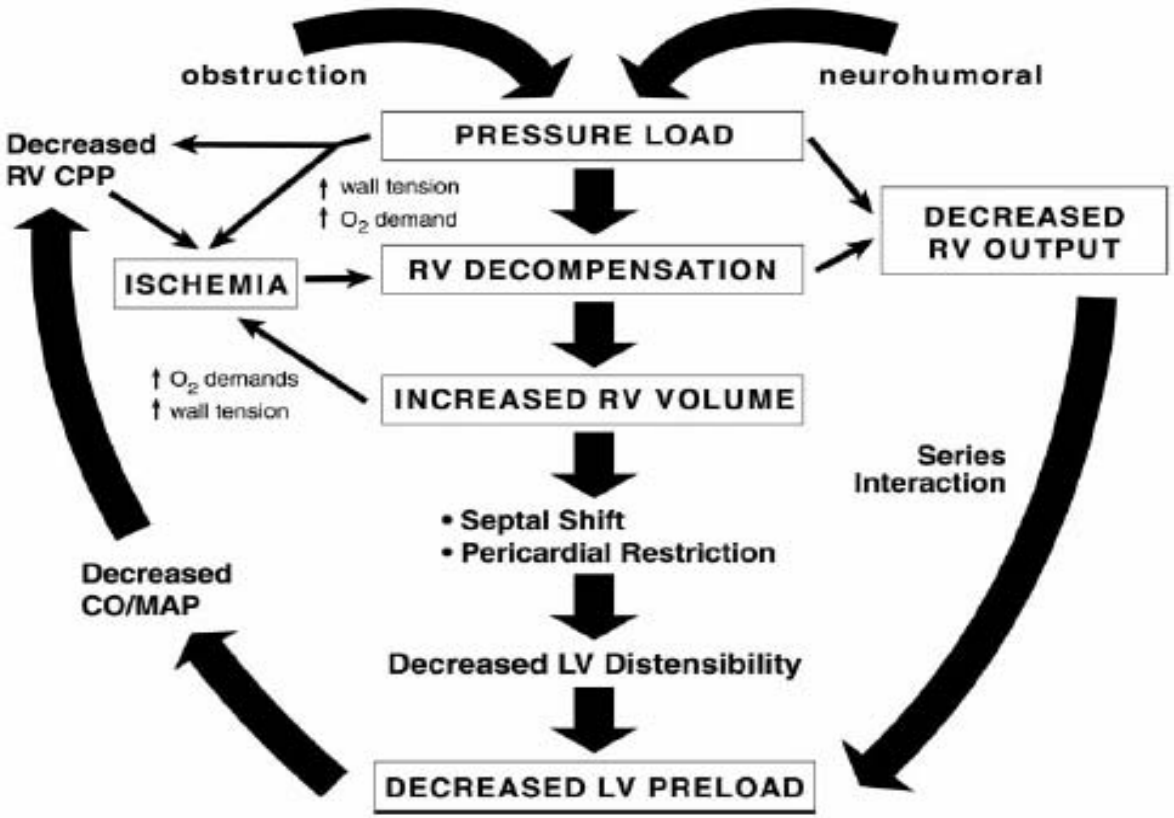


FIGURE 4. Pathophysiologic cycle of MPE.

Wood KE. Chest 2002

¿Cuándo fallecen los pacientes con TEP?

La mayoría de los casos mortales de TEP se producen en las primera horas[1, 2, 3]

[1]Stein P. Chest 1995
[2]Donaldson GA. N Engl J Med 1967
[3]Tibbut DA. BMJ 1974

Mortalidad de la TEP inestable

- Pacientes inestables hemodinámicamente: desde hipotensión a parada cardiaca
- UPET[1]: 36% vs 5%
- Alpert et al[2]: 25% vs 5%
- ICOPER[3]: 58.3% vs 15.1%

[1]UPET trial. JAMA 1970
[2] Alpert JS. JAMA 1976
[3]Goldhaber SZ. Lancet 1999

Risk Factors for Mortality after PE in the ICOPER: a Multivariate Analysis of 815 patients

Variable	**Hazard Ratio** (95% CI)
Age > 70 yrs	1.6 (1.1-2.3)
Cancer	2.3 (1.5-3.5)
Clinical CHF	2.4 (1.5-3.7)
SBP < 90mmHg	2.9 (1.7-5)
COPD	1.8 (1.2-2.7)
RR > 20 breath/min	2.0 (1.2-3.2)
RV Hypokinesis	2.0 (1.3-2.9)

Goldhaber SZ et al Lancet 1999;353: 1386-1389

Predictores de muerte en los pacientes con TEP

	Short-term dead, N = 36	*Long-term dead, N = 106*	*Alive, N = 1196*
Clinical characteristics[a],			
Age > 65 years	28 (78%)	77 (73%)	778 (65%)
Male	15 (42%)	43 (41%)	569 (48%)
Risk factors for VTE,			
Surgery	3 (8%)	10 (9%)	140 (12%)
Immobility for ≥ 4 days[†‡]	14 (39%)	30 (28%)	214 (18%)
Cancer[‡γ]	9 (25%)	56 (53%)	195 (16%)
Previous VTE	2 (6%)	12 (11%)	191 (16%)
Underlying disease,			
Chronic lung disease	3 (8%)	12 (11%)	130 (11%)
Heart failure[‡]	2 (6%)	14 (13%)	71 (6%)
Clinical presentation at admission,			
Syncope[‡]	7 (19%)	9 (8%)	216 (18%)
Chest pain[†‡]	8 (22%)	39 (37%)	596 (50%)
Dyspnea	29 (81%)	88 (83%)	945 (79%)
Heart rate ≥ 110 bpm	14 (39%)	30 (28%)	261 (22%)
Systolic BP < 100 mm Hg[†]	8 (22%)	13 (12%)	87 (7%)
Arterial oxyhemoglobin saturation (SaO_2) < 90%[†]	16 (44%)	29 (27%)	238 (20%)
ECG,			
SI-QIII pattern[‡]	4 (11%)	5 (5%)	150 (13%)
Complete/incomplete RBBB	6 (17%)	22 (21%)	207 (17%)
Inverted T waves in V_1 through V_3	5 (14%)	14 (13%)	219 (18%)
Laboratory findings,			
cTnI > 0.1ng mL^{-1}	7 (19%)	18 (17%)	157 (13%)

Conget F. Thromb Haemost 2008

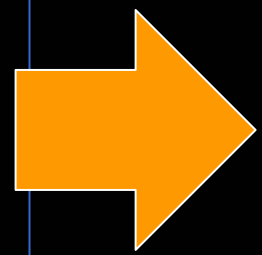
Trombolíticos versus heparina

Tiempo desde el diagnóstico	Uroquinasa	Heparina
24 h	24.1%	8.3%
2 semanas	55.4%	56.2%
1 año	78.8%	77.2%

UPET trial. JAMA 1970

Razones para considerar la fibrinolisis en la TEP

- Mejoría precoz de la perfusión, hemodinamia, intercambio gaseoso y función del ventrículo derecho
- Revierte la disfunción del Vd (aguda y subaguda)
- Eliminación del trombo, y disminución del riesgo de recurrencia
- Eliminación del trombo, y disminución del riesgo de hipertensión arterial pulmonar tromboembólica crónica



DISMINUCIÓN DE LA MORTALIDAD

Revisión sistemática

ORIGINAL INVESTIGATION

Thrombolysis vs Heparin in the Treatment of Pulmonary Embolism

A Clinical Outcome–Based Meta-analysis

Giancarlo Agnelli, MD; Cecilia Becattini, MD; Timo Kirschstein, MD

Revisión sistemática

- Muerte: RR 0.9 (95% CI: 0.57-1.32)
- Recurrencia: RR 0.6 (95% CI 0.29-1.15)
- Sangrado: RR 1.49 (95% CI 0.85-2.81)
- Muerte y recurrencia: RR 0.55 (95% CI 0.33-0.96)

Revisión sistemática

Journal of the American College of Cardiology
© 2002 by the American College of Cardiology Foundation
Published by Elsevier Science Inc.

Vol. 40, No. 9, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)02381-1

Pulmonary Embolism

Thrombolytic Therapy of Pulmonary Embolism

A Meta-Analysis

Gabriel Thabut, MD,* Dominique Thabut, MD,† Robert P. Myers, MD,† Brigitte Bernard-Chabert, MD,† Rolana Marrash-Chahla, MD,* Hervé Mal, MD,* Michel Fournier, MD*

Clichy and Paris, France

OBJECTIVES We sought to assess the efficacy and safety of thrombolytic therapy in patients with an acute

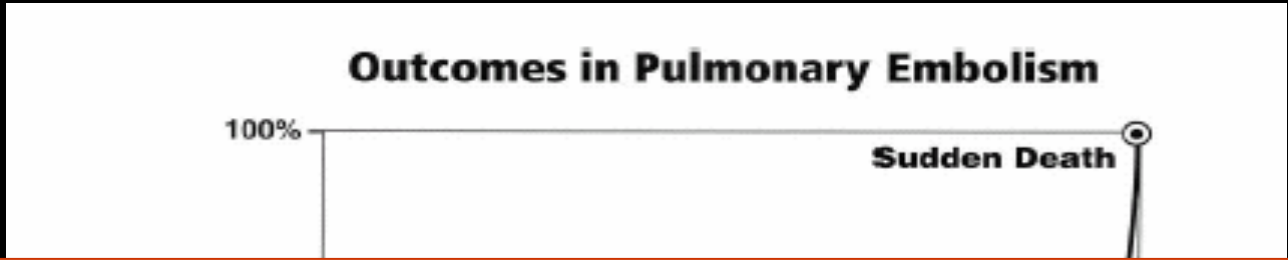
Revisión sistemática

- Muerte: RR 0.63 (95% CI: 0.32-1.23)
- Recurrencia: RR 0.59 (95% CI 0.30-1.18)
- Sangrado: RR 1.76 (95% CI 1.04-2.98)

Revisión sistemática

- Trabajos no diseñados para evaluar mortalidad
- Número pequeño de pacientes
- Catéteres centrales en los pacientes
- Protocolos de fibrinolisis antiguos*
- ¿TEP masiva?

¿A qué llamamos TEP masiva?



SÓLO UNA MINORÍA DE LOS PACIENTES CON TEP ANATÓMICA MASIVA

PRESENTAN INESTABILIDAD HEMODINÁMICA

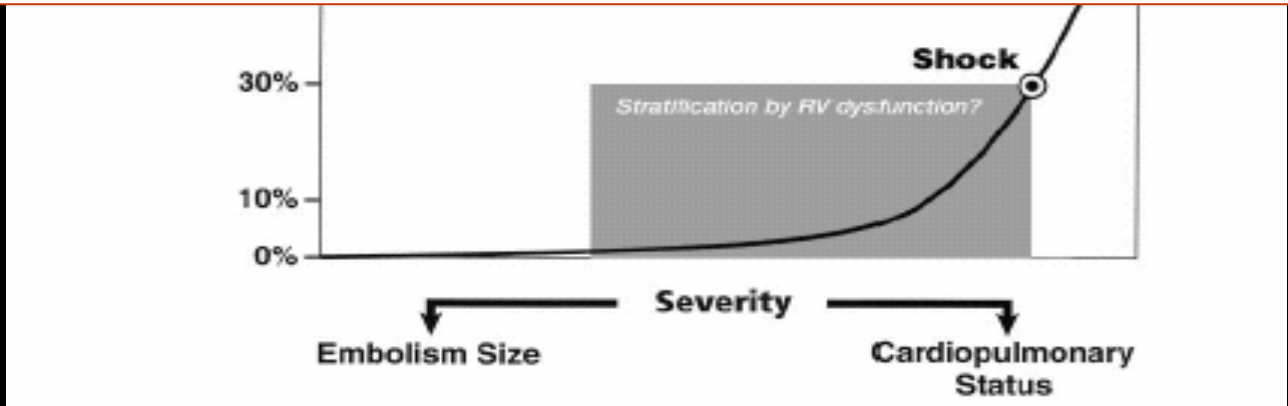


FIGURE 1. The relationship of severity and mortality in patients with MPE.

Wood KE. Chest 2002

Revisión sistemática

Thrombolysis Compared With Heparin for the Initial Treatment of Pulmonary Embolism

A Meta-Analysis of the Randomized Controlled Trials

Susan Wan; Daniel J. Quinlan, MBBS; Giancarlo Agnelli, MD; John W. Eikelboom, MBBS

Wan S. Circulation 2004

Revisión sistemática

Trial, Year	Eligibility	n	Randomized Treatment		Subsequent Anticoagulation		Follow-Up*
			Thrombolysis	Heparin	Thrombolysis	Heparin	
UPET trial, 1973	Acute PE,† symptoms ≤5 days	160	Urokinase 12 hours	Heparin	Heparin, warfarin	Heparin, warfarin	14 days
Tibbutt et al, 1974	Acute life-threatening PE†	30	Streptokinase‡ 72 hours	Heparin‡	Warfarin (started at 60 hours)	Warfarin (started at 60 hours)	72 hours
Ly et al, 1978	Acute major PE†, symptoms <5 days	25§	Streptokinase 72 hours	Heparin (7 days)	Warfarin, heparin if TCT <2× control	Heparin, warfarin	10 days
Dotter et al, 1979	Acute PE†	31	Streptokinase 18–72 hours	Heparin (5 days)	Heparin, warfarin	Heparin, warfarin	In hospital
Marini et al, 1988	Acute PE, symptoms ≤7 days	30	Urokinase, 12 hours or 3 days	Heparin (7 days)	Warfarin	Heparin, warfarin	7 days
Levine et al, 1990	Acute PE, symptoms ≤14 days	58	tPA 2 minutes	Heparin	Heparin, warfarin	Heparin, warfarin	10 days
PIOPED, 1990	Acute PE, symptoms ≤7 days	13	tPA 40 to 90 minutes	Heparin	Heparin, warfarin	Heparin, warfarin	7 days
Dalla-Volta et al, 1992	Acute PE, symptoms ≤10 days	36	tPA 2 hours	Heparin	Heparin, warfarin	Heparin, warfarin	30 days
Goldhaber et al, 1993	Acute PE, symptoms ≤14 days	101	tPA 2 hours	Heparin	Heparin, warfarin	Heparin, warfarin	In hospital or 14 days
Jerjes-Sanchez et al, 1995	Acute massive PE,† symptoms ≤14 days	8	Streptokinase 2 hours	Heparin	Heparin, warfarin	Heparin, warfarin	In hospital
Konstantinides et al, 2002	Acute PE, symptoms ≤4 days	256	tPA 2 hours	Heparin	Heparin, warfarin	Heparin, warfarin	In hospital or 30 days

Revisión sistemática

- Sangrado menor: RR 2.63 (95% CI 1.53-4.54)
- Sangrado mayor: RR 1.42 (95% CI 0.81-2.46)
- Muerte o recurrencia*: RR 0.45 (95% CI 0.22-0.92)

Subgroup analyses in the 5 trials that included patients with major PE

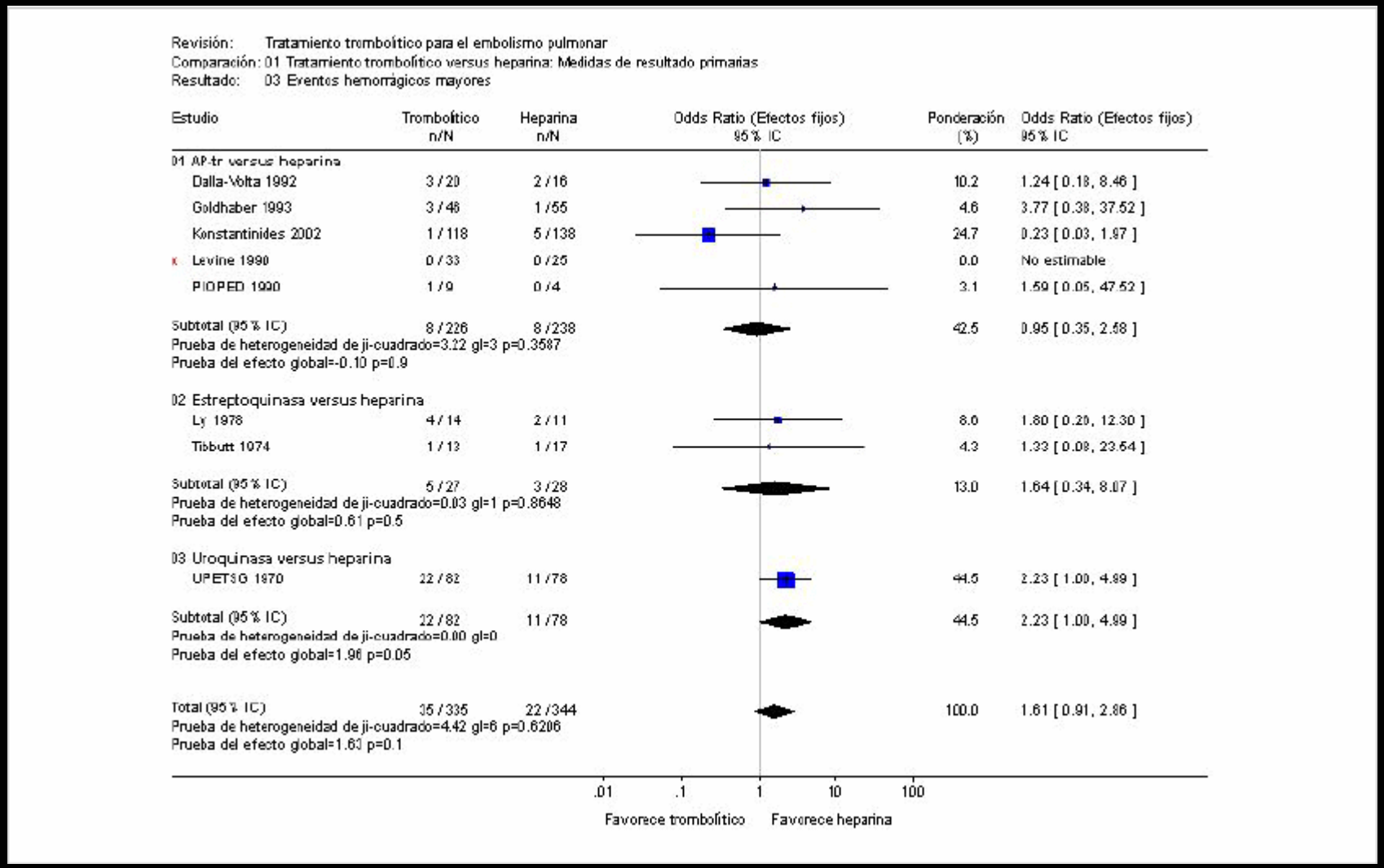
Revisión sistemática

THE COCHRANE COLLABORATION®

Tratamiento trombolítico para el embolismo pulmonar

Dong B, Jirong Y, Liu G, Wang Q, Wu T

Revisión sistemática



Analysis of 312 patients who received lytic Rx in 5 clinical trials (t-PA and UK)

Thrombolytic Regiments:

- T-PA 50-90 mg 47 pts
- T-PA 100 mg 138 pts
- T-PA 0.6 mg/kg bolus 59 pts
- UK 2000u/lb/hr x 24 hrs 23 pts
- UK 3 million U/2 hrs 45 pts

Risk Factors for Bleeding

- **Age >70** y led to **x 4** bleeding risk compared to those < 50 y/o
- Increased **BMI > 30** leads to **x 2** increased bleeding risk compared to <25
- **Catheterization** leads to **x 5** bleeding risk compared to no catheterization

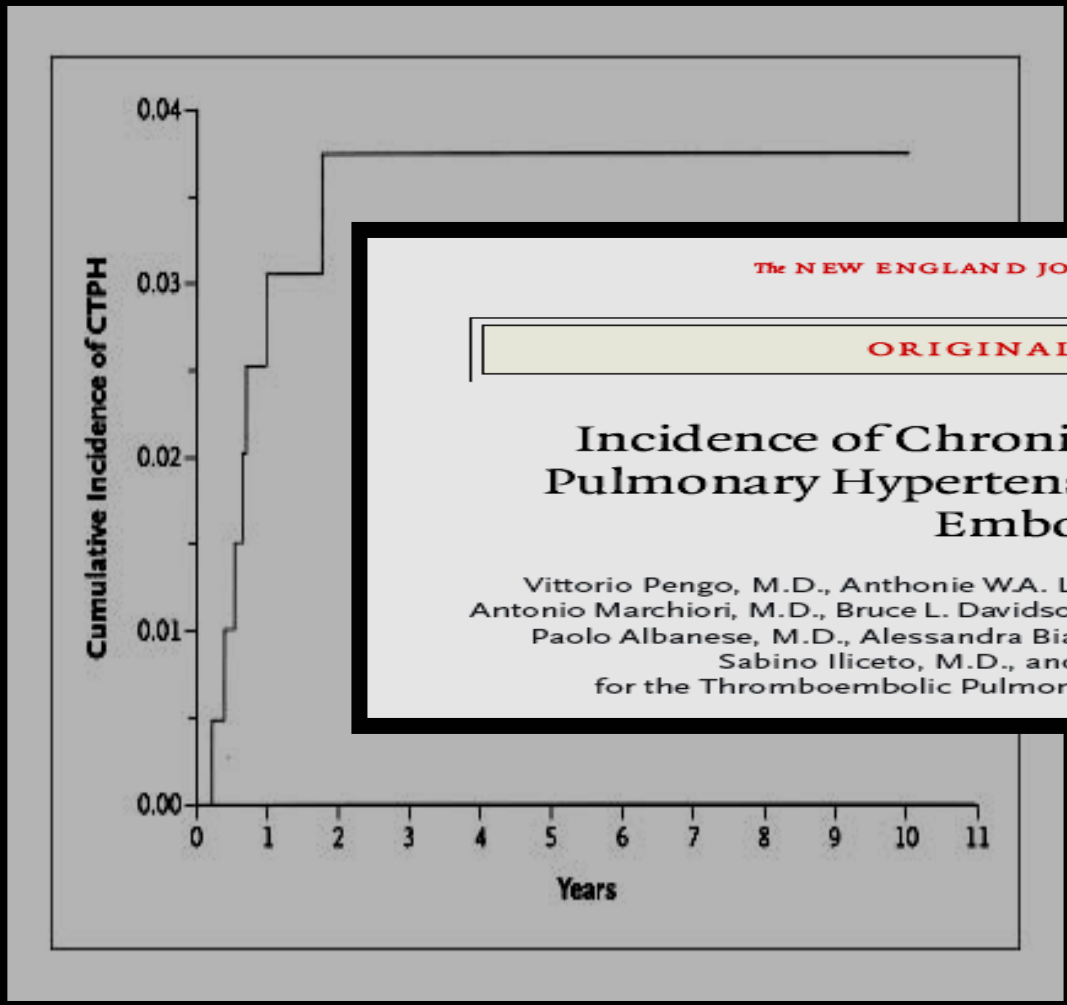
Mikkola KM. Am Heart J 1997

THROMBOLYSIS COMPLICATIONS

- Major bleeding frequency after noninvasive diagnosis= 4.2%
- Major bleeding frequency after invasive diagnosis= 14%
- ***Fewer complications would occur with noninvasive management***

Stein P. *Ann Intern Med* 1994

Incidence of Symptomatic CTPH after a First, Symptomatic, Properly Treated PE



VTE is a CHRONIC disease

The NEW ENGLAND JOURNAL of MEDICINE

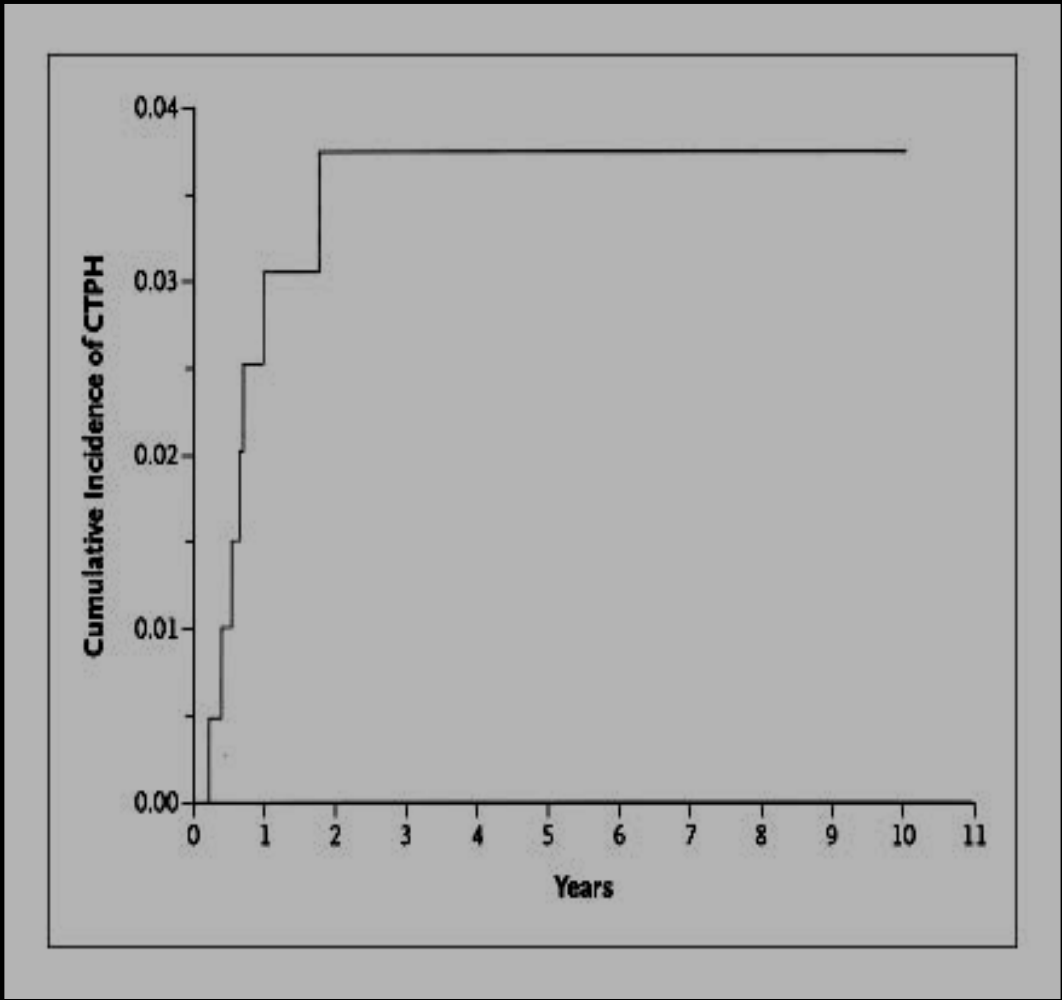
ORIGINAL ARTICLE

Incidence of Chronic Thromboembolic Pulmonary Hypertension after Pulmonary Embolism

Vittorio Pengo, M.D., Anthonie W.A. Lensing, M.D., Martin H. Prins, M.D., Antonio Marchiori, M.D., Bruce L. Davidson, M.D., M.P.H., Francesca Tiozzo, M.D., Paolo Albanese, M.D., Alessandra Biasiolo, D.Sci., Cinzia Pegoraro, M.D., Sabino Iliceto, M.D., and Paolo Prandoni, M.D., for the Thromboembolic Pulmonary Hypertension Study Group*

Pengo, V. et al. N Engl J Med 2004;350:2257-2264

Incidence of Symptomatic CTPH after a First, Symptomatic, Properly Treated PE

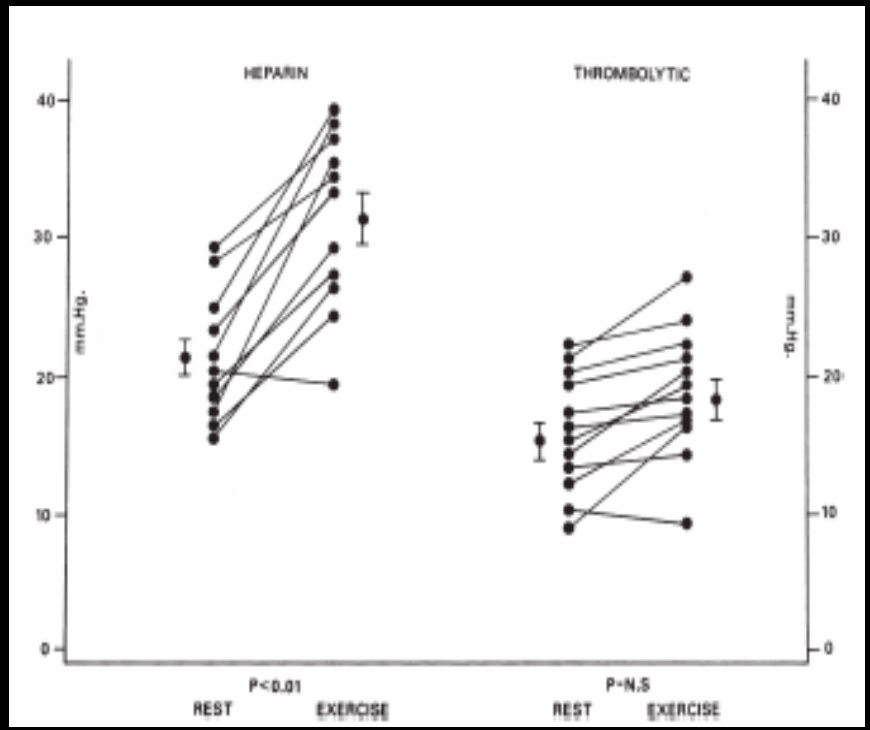


- Only those who developed "unexplained persistent dyspnea" had echo
- S PA pressure ≥ 40 mmHg and mean PA pressure ≥ 25 mmHg
- We know: 5 yr survival when S PA pressure > 40 is 30%, 10% w S PA pressure > 50 mmHg

Pengo, V. et al. N Engl J Med 2004;350:2257-2264

HAP tromboembólica crónica

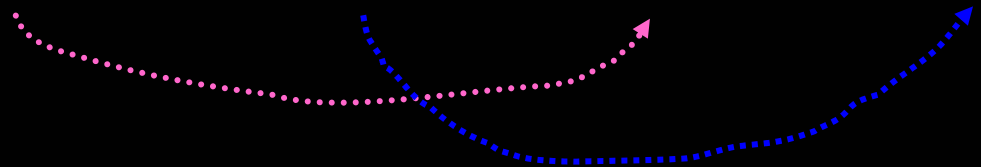
- Seguimiento 40 pacientes durante 7 años
- Diferencias significativas en disnea, recurrencia VTE, y parámetros hemodinámicos en el grupo de tratamiento trombolítico



Sharma GV. Vasc Med 2000

Long-Term Hemodynamic Benefit of lytic Rx in Patients With PE

	Thrombolysis (n = 12)		Heparin (n = 11)	
	Rest	Exercise	Rest	Exercise
Pulmonary artery pressure	17	19	22*	32
Pulmonary vascular resistance	171	179	351**	437



*P < .05
**P < .02

TEP submasiva

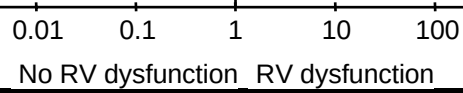
¿Hay pacientes con TEP submasiva y mayor riesgo de fallecer?

Hospital mortality and echocardiogarphy

Review: A systematic review of prognostic studies in patients with non severe pulmonary embolism
Comparison: 01 Right ventricular dysfunction assessed by echocardiography or CT
Outcome: 01 Mortality

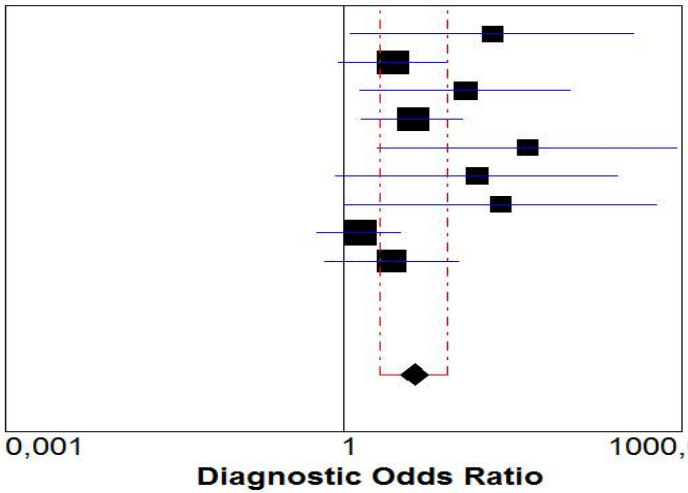
Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Grifoni	4/65	3/97		11.78	1.99 [0.46, 8.60]
Vieillard-Baron	1/32	2/63		5.90	0.98 [0.09, 10.45]
Kucher, Hess	2/19	0/40		3.97	10.25 [0.52, 203.61]
Ghuysen	3/24	3/47		11.21	1.96 [0.43, 8.98]
Kucher	65/405	59/630		28.66	1.71 [1.23, 2.38]
Sukhija	19/46	6/126		19.95	8.67 [3.69, 20.36]
van	10/69	3/51		14.30	2.46 [0.71, 8.50]
Pieralli	4/35	0/26		4.24	6.75 [0.38, 120.10]
Total (95% CI)	695	1080		100.00	2.84 [1.50, 5.37]

Total events: 108 (Treatment), 76 (Control)
Test for heterogeneity: $Chi^2 = 14.29$, df = 7 (P = 0.05), $I^2 = 51.0\%$
Test for overall effect: Z = 3.21 (P = 0.001)



Sanchez O. Eur Heart J 2008

Short-term mortality and troponin



	Diagnostic OR (95% CI)
Pruszczyk (32). 2003	21,00 (1,16 - 381,49)
Kostrubiec (33). 2005	2,75 (0,89 - 8,47)
Bova (34). 2005	12,16 (1,39 - 106,48)
Douketis (35). 2005	4,14 (1,45 - 11,82)
Kline (36). 2006	43,65 (2,02 - 944,28)
Logeart (37). 2006	15,38 (0,85 - 278,65)
Tulevski (38). 2007	25,00 (1,02 - 613,69)
Jiménez (39). 2007	1,40 (0,58 - 3,34)
Gallota (40). 2007	2,71 (0,68 - 10,76)

Random Effects Model
Pooled Diagnostic Odds Ratio = 4,26 (2,13 to 8,50)
Cochran-Q = 12,64; df = 8 (p = 0,1248)
Inconsistency (I-square) = 36,7 %
Tau-squared = 0,3614

Jiménez D. Chest 2009

The MAPPET Registry

1001 patients from 204 participating German centers 9/1993-12/1994.

PE with RV dysfunction and/or Pulmonary HTN

In-Hospital Event	Thrombolysis (n = 169)	Heparin (n = 550)	*P* Value
Death	4.7%	11.0%	.016
Death from PE	4.1%	10.0%	
Recurrent PE	7.7%	19.0%	<.001
Major bleeding	22.0%	7.8%	<.001
Intracranial bleed	1.2%	0.4%	

The Management and Prognosis of Pulmonary Embolism Registry (MAPPET)
Konstantinides et al. *Circulation.* 1997;96:882–888.

THROMBOLYSIS STABLE MAJOR PE

Characteristic	Odds Ratio	95% Confidence Interval	*P*
Thrombolytic treatment	0.46	0.21-1.00	.051

ONLY INDEPENDENT PREDICTOR OF SURVIVAL (719 PATIENTS)

Konstantinides S. *Circulation* 1997

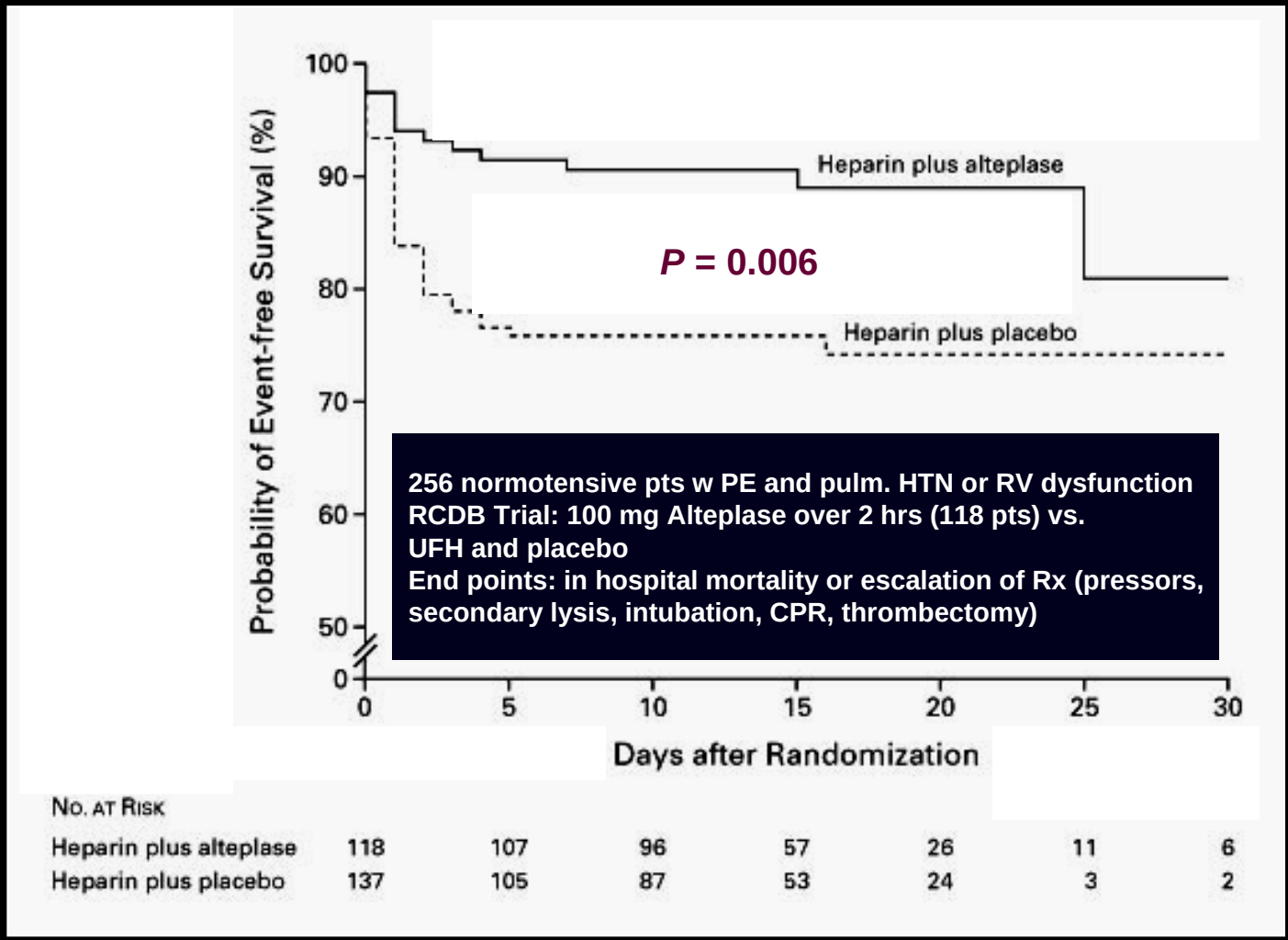
Thrombolysis in submassive PE

HEPARIN PLUS ALTEPLASE COMPARED WITH HEPARIN ALONE IN PATIENTS WITH SUBMASSIVE PULMONARY EMBOLISM

STAVROS KONSTANTINIDES, M.D., ANNETTE GEIBEL, M.D., GERHARD HEUSEL, PH.D., FRITZ HEINRICH, M.D., AND WOLFGANG KASPER, M.D., FOR THE MANAGEMENT STRATEGIES AND PROGNOSIS OF PULMONARY EMBOLISM-3 TRIAL INVESTIGATORS*

Konstantinides S. N Engl J Med 2002

Kaplan-Meier Estimates of the Probability of Event-free Survival among Patients with Acute Submassive Pulmonary Embolism, According to Treatment with Heparin plus Alteplase or Heparin plus Placebo



Konstantinides, S. et al. N Engl J Med 2002;347:1143-1150

TABLE 2. IN-HOSPITAL CLINICAL EVENTS.*

EVENT	HEPARIN PLUS ALTEPLASE (N=118)	HEPARIN PLUS PLACEBO (N=138)	P VALUE†
	no. (%)		
Primary end point	13 (11.0)	34 (24.6)	0.006
Death from all causes	4 (3.4)	3 (2.2)	0.71
Escalation of treatment	12 (10.2)	34 (24.6)	0.004
Catecholamine infusion (for persistent hypotension or shock)	3 (2.5)	8 (5.8)	0.33
Secondary thrombolysis	9 (7.6)	32 (23.2)	0.001
Endotracheal intubation	3 (2.5)	3 (2.2)	0.85
Cardiopulmonary resuscitation	0	1 (0.7)	1.0
Embolectomy or thrombus fragmentation	0	1 (0.7)	1.0
Secondary end points			
Recurrent pulmonary embolism‡	4 (3.4)	4 (2.9)	0.89
Major bleeding§	1 (0.8)	5 (3.6)	0.29
Fatal bleeding	0	1 (0.7)	1.0
Hemorrhagic stroke¶	0	0	—
Ischemic stroke¶	0	1 (0.7)	1.0

*The numbers shown are based on calculations for the intention-to-treat population.

†P values were calculated with the use of Fisher's exact test (two-sided).

‡Recurrence of pulmonary embolism had to be confirmed by ventilation–perfusion lung scanning, spiral computed tomography, or pulmonary angiography.

§Major bleeding was defined as fatal bleeding, hemorrhagic stroke, or a drop in the hemoglobin concentration by at least 4 g per deciliter, with or without the need for red-cell transfusion.

¶Hemorrhagic or ischemic stroke had to be confirmed by computed tomography or magnetic resonance imaging.

Konstantinides S. N Engl J Med 2002

Transthoracic echocardiography plus cardiac biomarkers

Event	Complicated in-hospital course, OR (95% CI)	P
TnT negative, echo negative	-	-
TnT positive, echo negative	3.70 (0.76-18.18)	0.107
TnT negative, echo positive	5.56 (0.97-31.99)	0.055
TnT positive, echo positive	10.00 (2.14-46.80)	0.004

Binder L. Circulation 2005

PEITHO: Pulmonary EmbolIsm THrOmbolysis Study

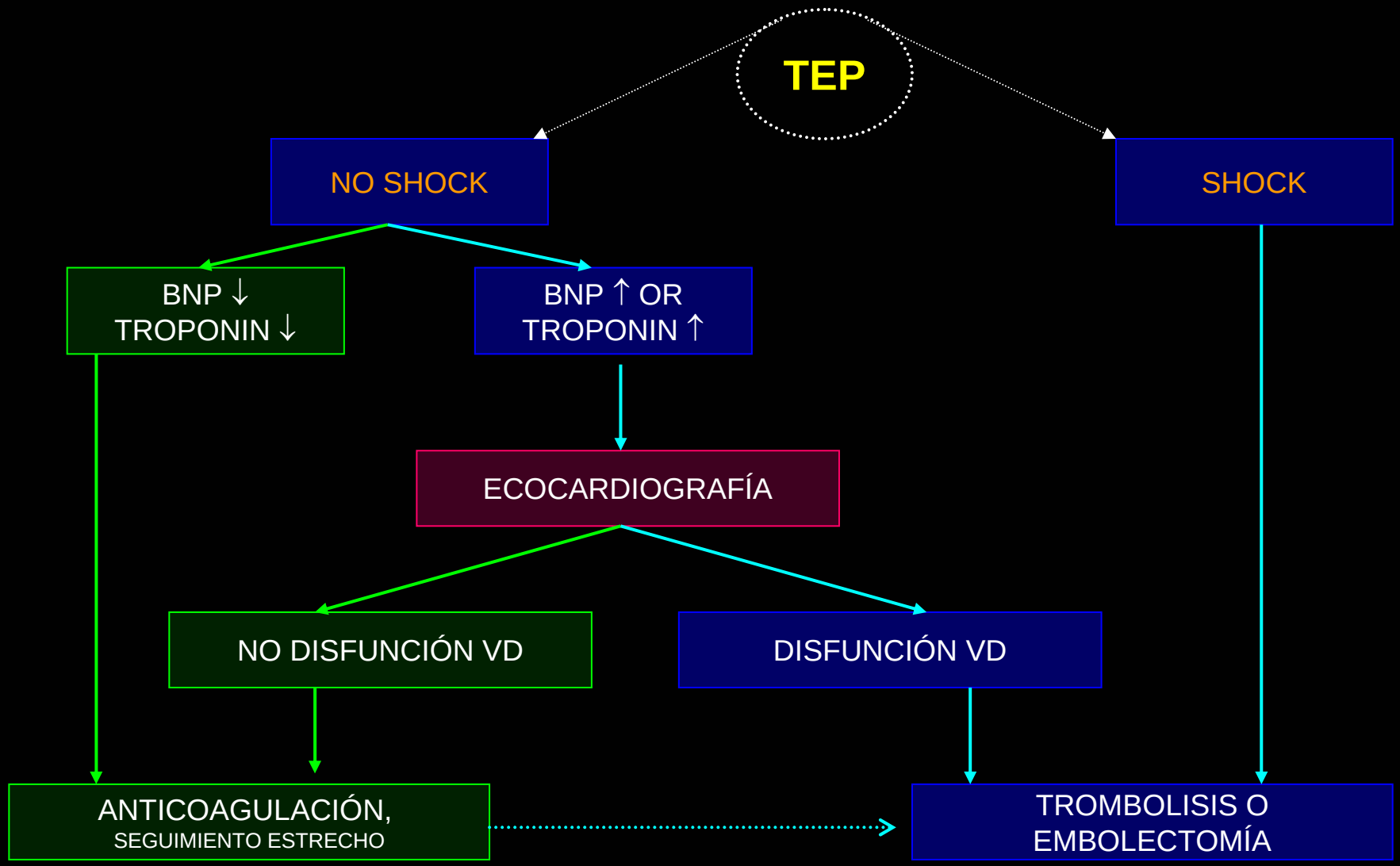
A prospective, randomized, double-blind, placebo-controlled, international, multicenter, parallel-group comparison trial evaluating the efficacy and safety of single i.v. bolus tenecteplase as compared with standard treatment in normotensive patients with acute pulmonary embolism and with echographic and laboratory evidence of right ventricular dysfunction.

Study Features

- Phase III
- Prospective
- Randomized (1:1)
- Double-Blind
- Placebo-controlled
- Multicentre/International

- **Name of finished product:** **Metalyse®**
- **Name of active ingredient:** **Tenecteplase**

Algoritmo de tratamiento de la TEP



Se lo recomiendo al Doctor y le hago un favor,
la fibrinolisis es lo mejor

La heparina no deshace el “clot”
y el riesgo del paciente será “a lot”

Si el paciente está hipotenso, yo no me lo pienso
Una dosis de urokinasa, y se irá vivo a casa

En el paciente inestable deshaz el
coágulo del pecho,
si no es bastante probable que “al hoyo” vaya
derecho

El riesgo de hemorragia me importa poco,
ni siquiera la del “coco”

Cuando al paciente con TEP hay que salvar
la fibrinolisis has de usar

DJC