Μαζική Πνευμονική Εμβολή

και Δεξιά Καρδιακή Ανεπάρκεια

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Πανεπιστημιακή Καρδιολογική Κλινική

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Diagnosis and Management of Acute Pulmonary Embolism

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

Task Force Members:

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

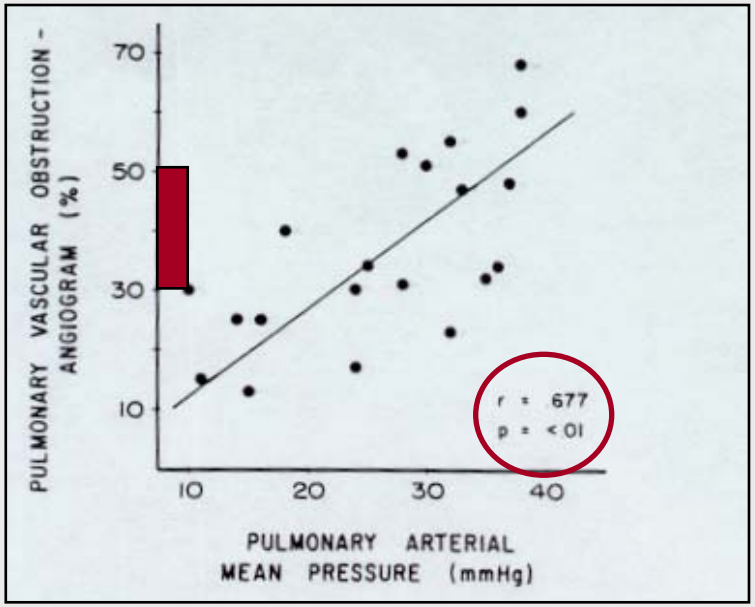
and Adam Torbicki, *Warsaw, Poland*

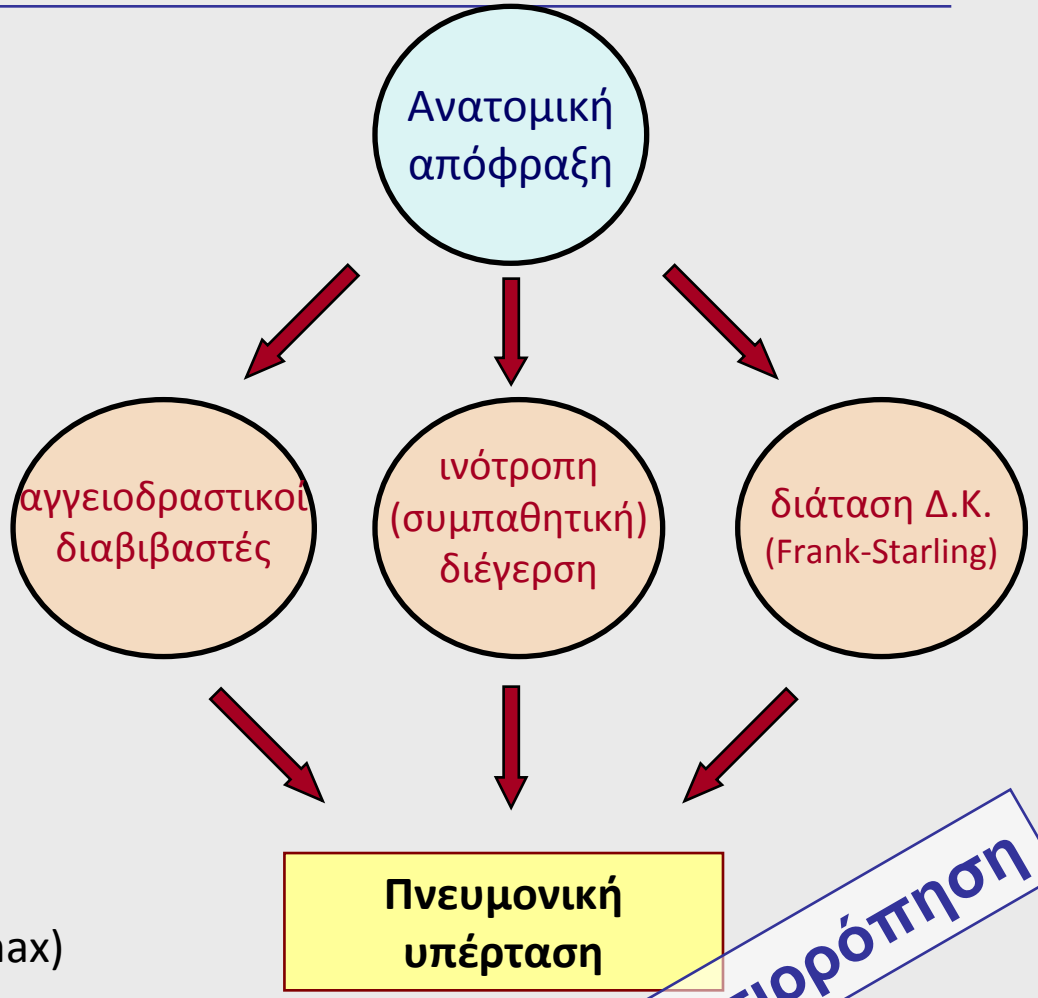
«Ανομοιογενής» ομάδα ασθενών
⇒ έμφαση στη **βαρύτητα** της πνευμονικής εμβολής

Study	Mortality
British Thoracic Society (GB), *Lancet* 1992	**1%**
PIOPED (US), *N Engl J Med* 1992	**2.5%**
MAPPET Registry (D), *JACC & Circulation* 1997	**20%**
JA Heit (DK), *Arch Intern Med* 1999	**28%**
ICOPER Registry, *Lancet* 1999	**17%**
M Nakamura (JP), *Clin Cardiol* 2001	**14%**

Τι καθορίζει τη «βαρύτητα» της πνευμονικής εμβολής ;

Παθοφυσιολογία της βαριάς πνευμονικής εμβολής



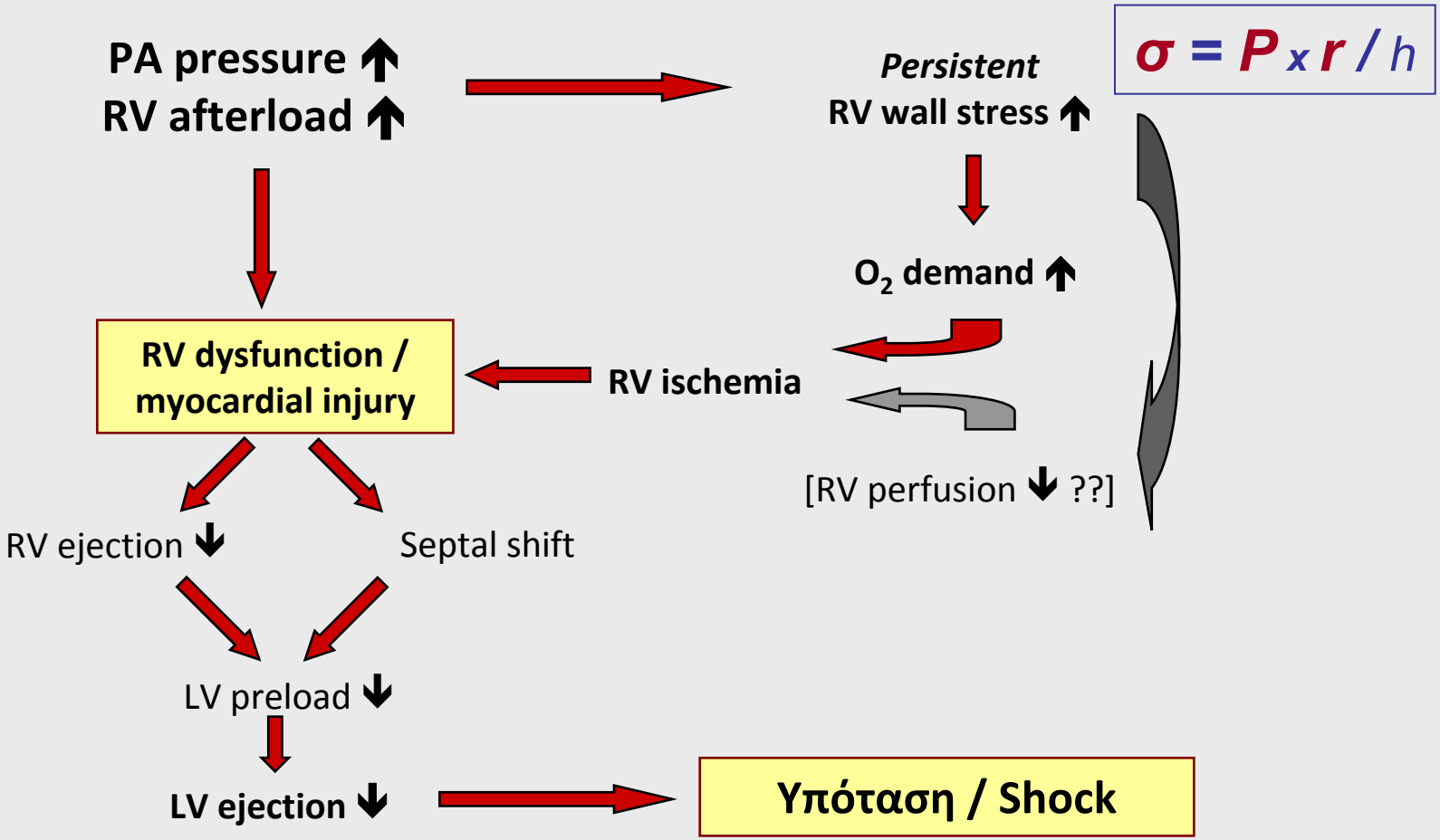


- **Οριο αύξησης της πίεσης:** 40 mmHg (mean), 60-70 mmHg (max)

RL Miller. Chest 1998;113:665-670
KM McIntyre und AA Sasahara. Am J Cardiol 1971;28:288-294

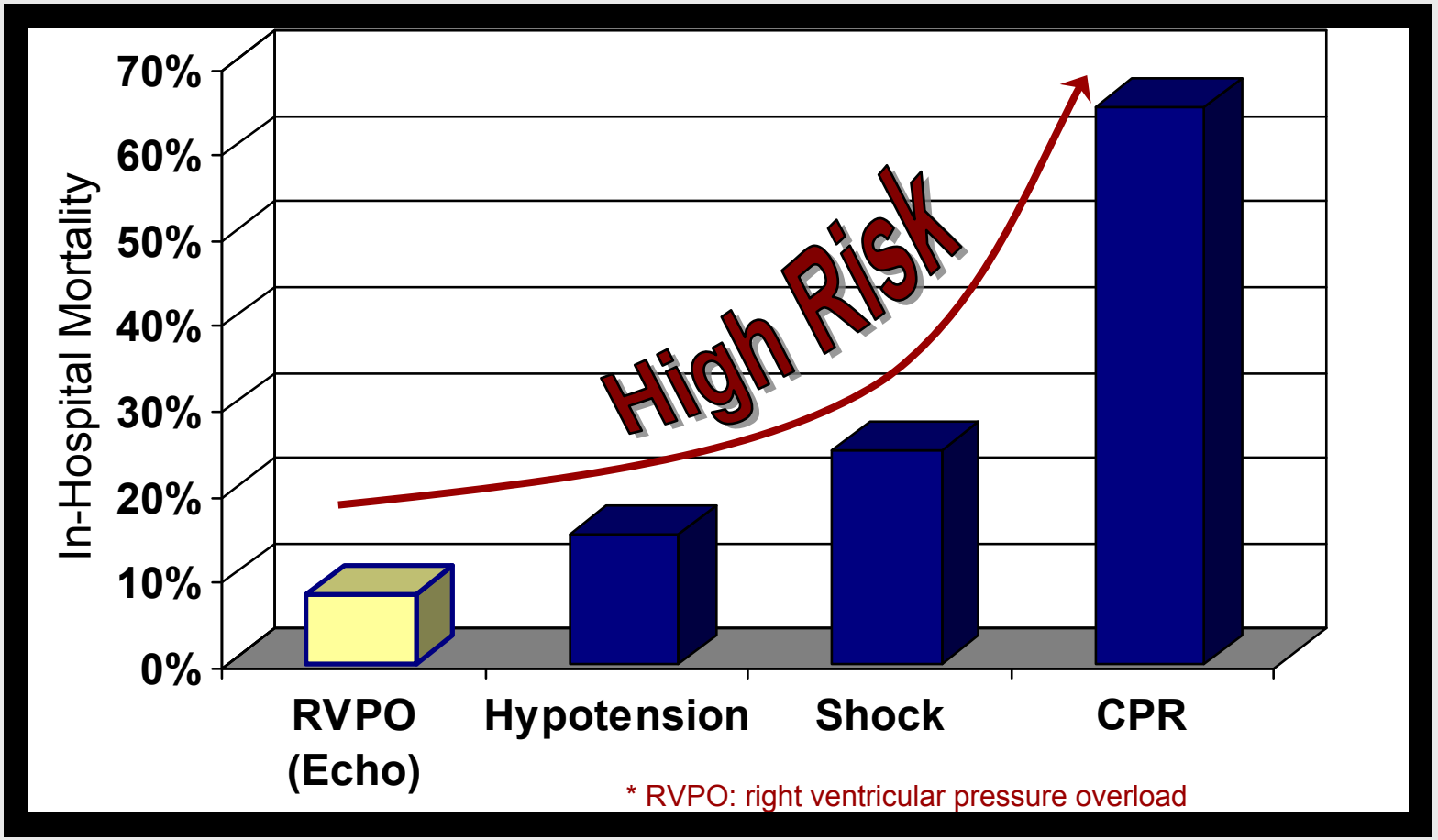
YM Smulders. Cardiovasc Res 2000;48:23-33
A Torbicki. Eur Heart J 2008;29:2276-2315

Ο φαύλος κύκλος της ανεπάρκειας της Δ.Κ.



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

Αιμοδυναμική αστάθεια και έκβαση Π.Ε.

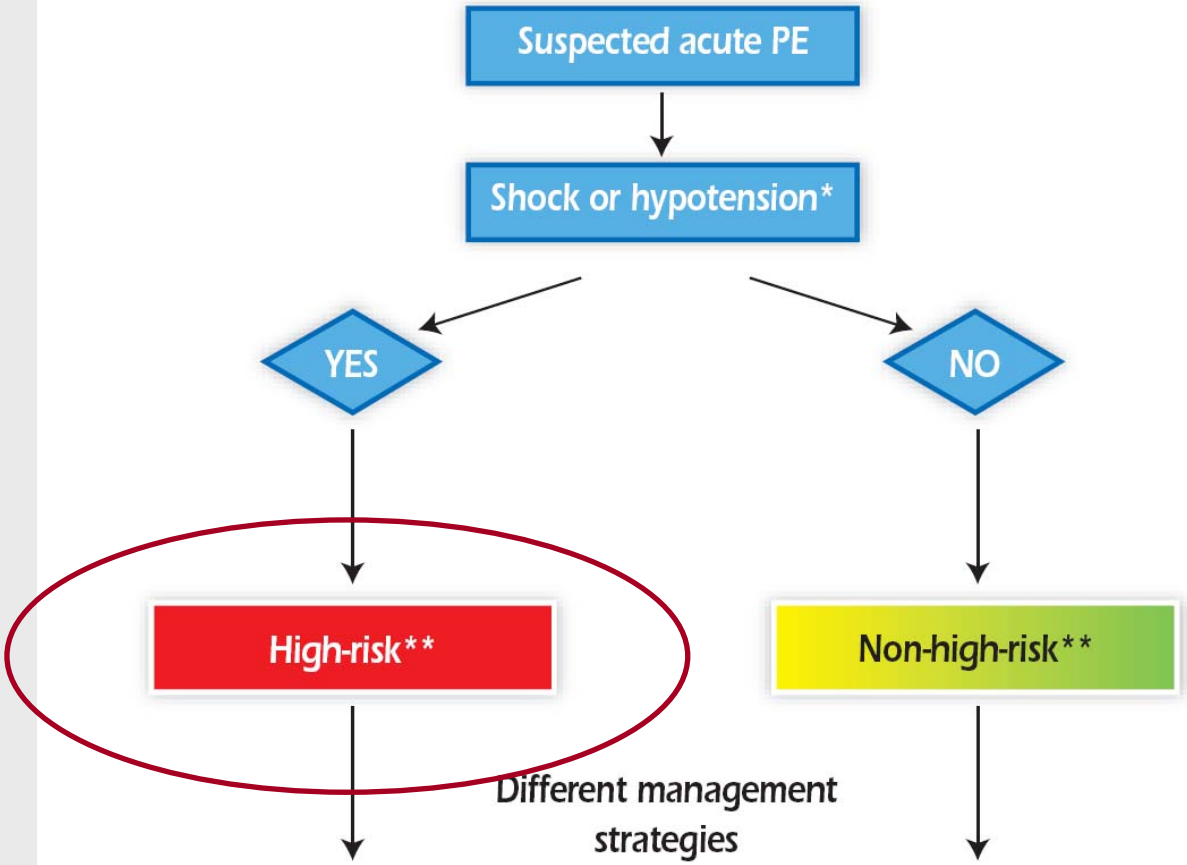


W Kasper. J Am Coll Cardiol 1997;30:1165-1171

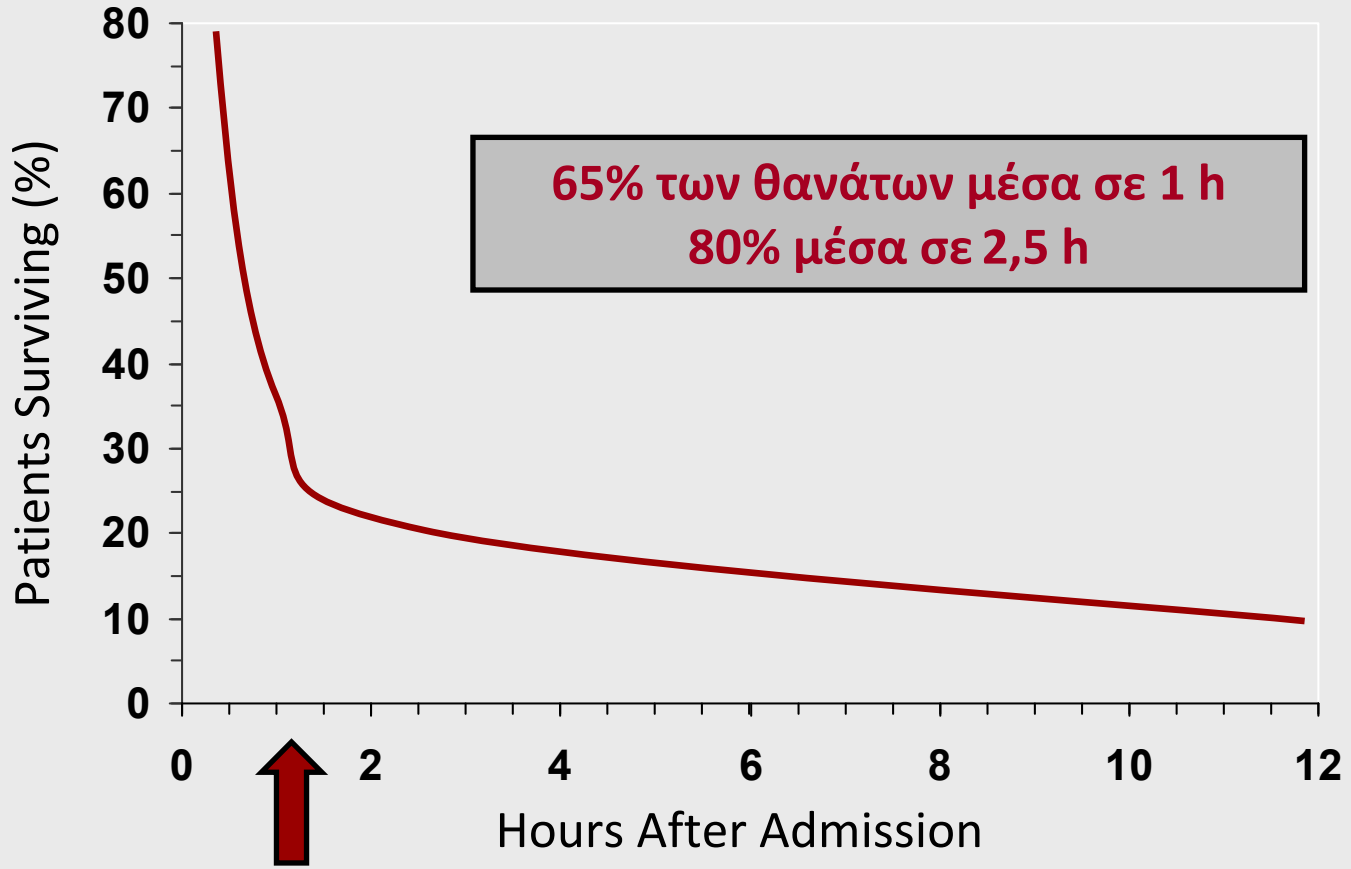
Η διαστρωμάτωση κινδύνου αρχίζει με την υποψία Π.Ε.

Recommendations	Class [a]	Level [b]
▪ Initial risk stratification of suspected and/or confirmed PE based on the presence of shock and hypotension is recommended to distinguish between patients with high and non-high risk of PE related early mortality	I	B

Υποτασικοί ασθενείς «υψηλού» κινδύνου



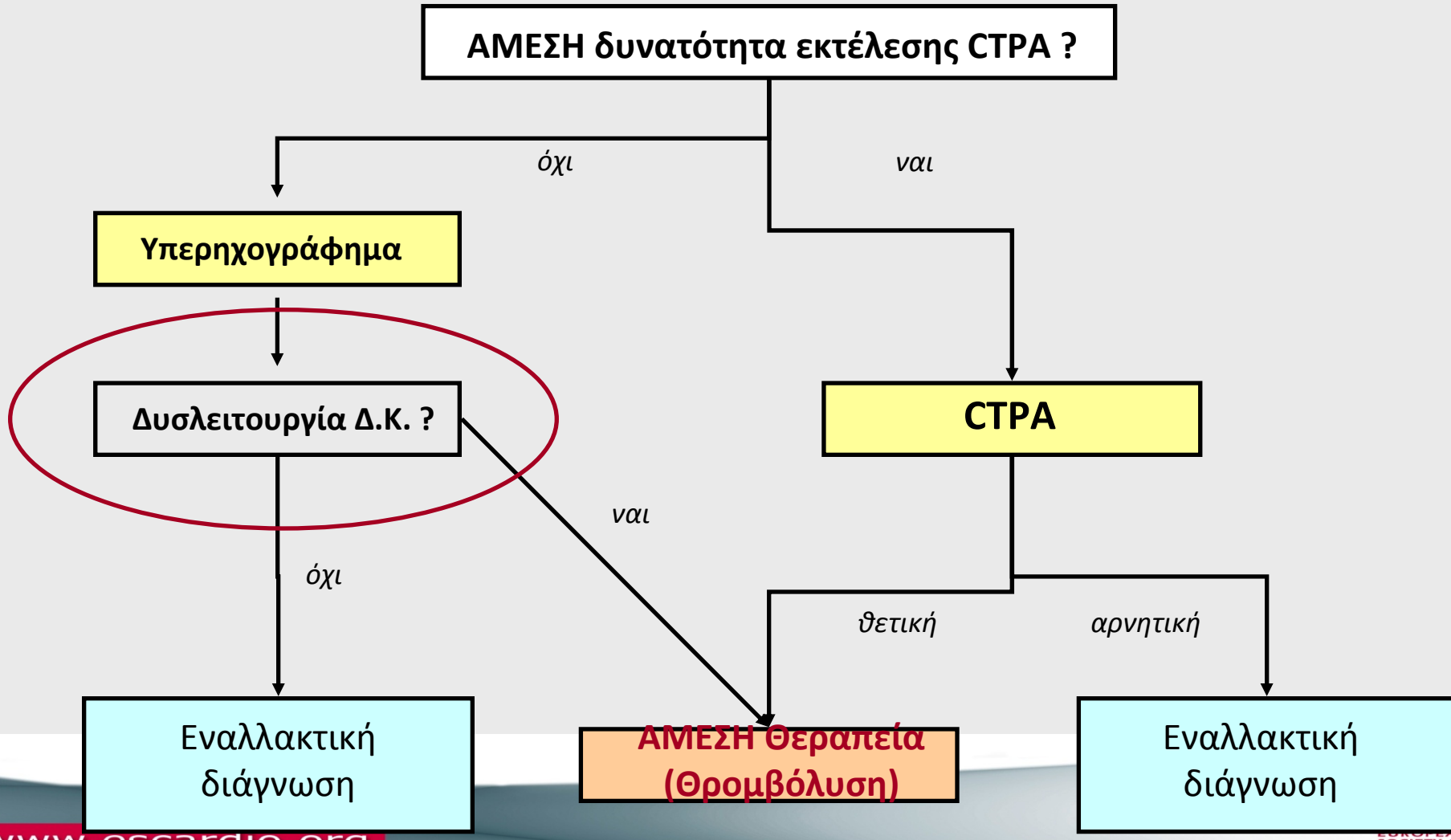
Υψηλός κίνδυνος σε αιμοδυναμική αστάθεια



PD Stein. Chest 1995;108:978-981

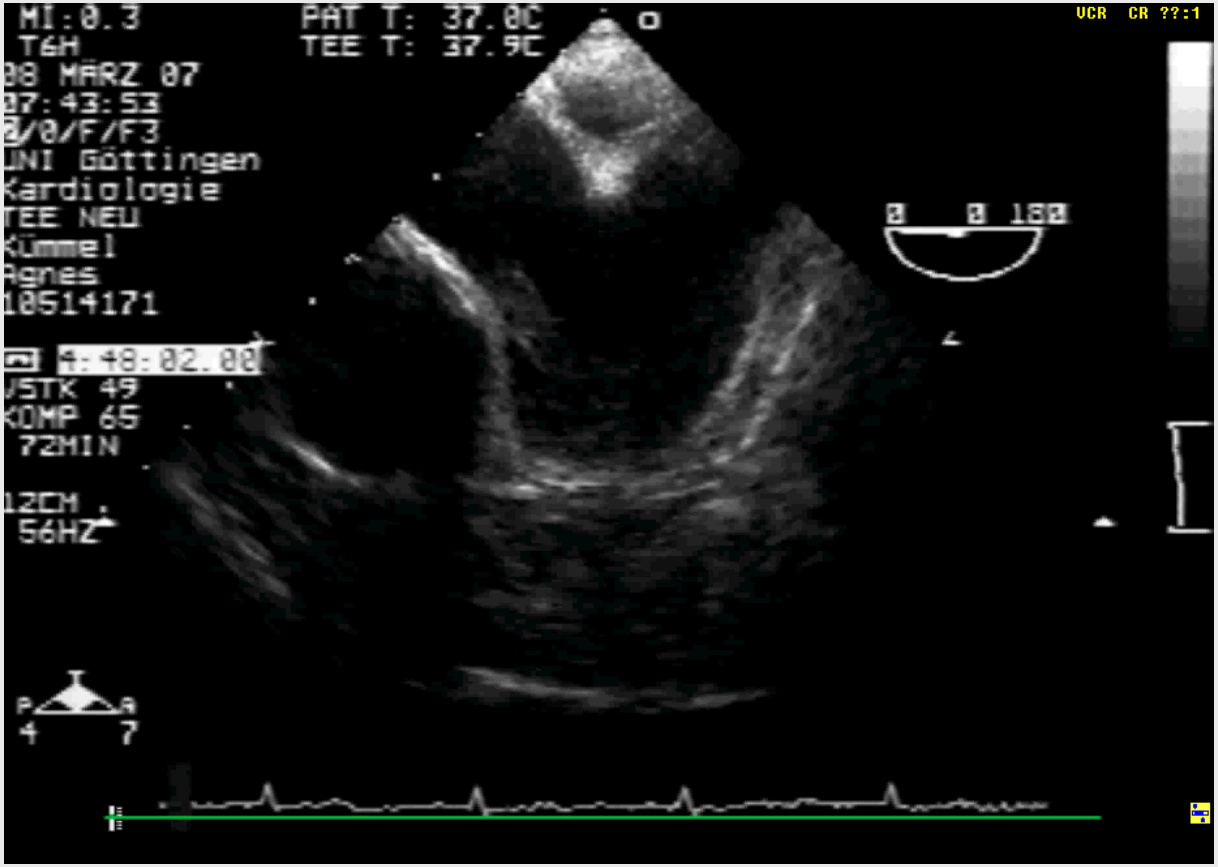
High-risk PE

Αλγόριθμος διάγνωσης Π.Ε. υψηλού κινδύνου



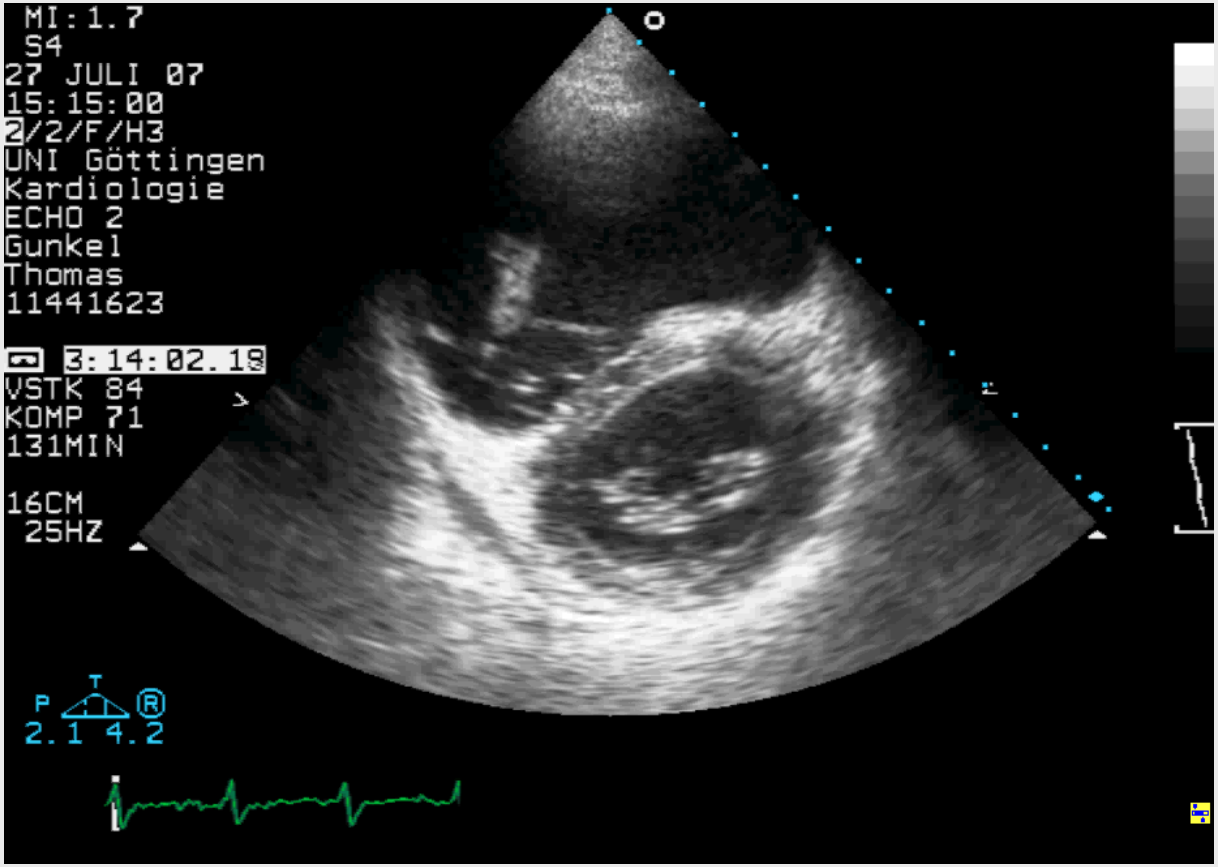
High-risk PE

Echo in PE (TEE): Thrombus Detection



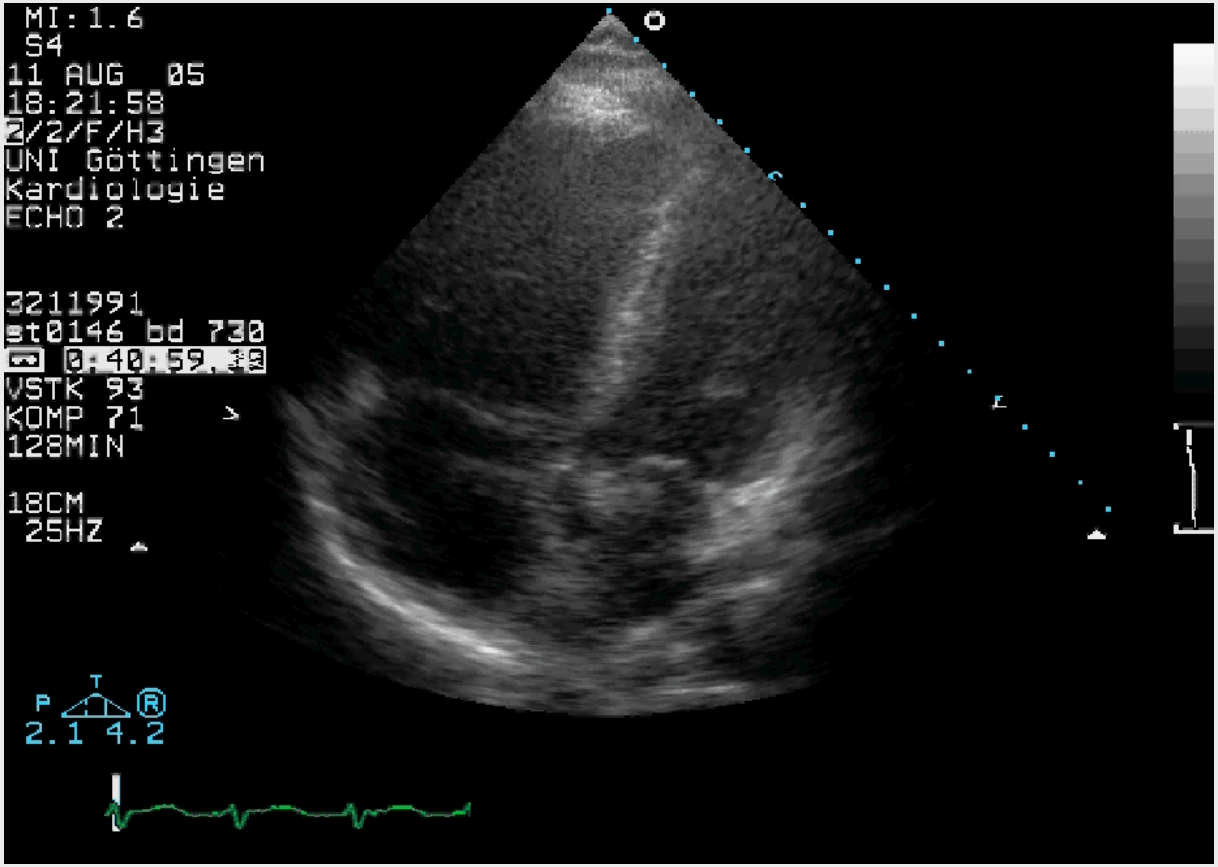
High-risk PE

Echo in PE (TTE): Thrombus Detection



High-risk PE

Echo in PE (TTE): RV Dysfunction



High-risk PE

Recommendations	Class [a]	Level [b]
✓ ▪ Anticoagulation with UFH should be initiated without delay in patients with high-risk PE	I	A
✓ ▪ Systemic hypotension should be corrected to prevent progression of RV failure and death due to PE	I	C
✓ ▪ Vasopressive drugs are recommended for hypotensive patients with PE	I	C
✓ ▪ Dobutamine and dopamine may be used in patients with PE, low cardiac output and normal blood pressure	IIa	B
✓ ▪ Aggressive fluid challenge is not recommended	III	B
✓ ▪ Oxygen should be administered to patients with hypoxaemia	I	C

Thrombolysis, Surgery,
***or* Catheter-Based Treatment !**

Κλασική ηπαρίνη (UFH) σε υψηλού κινδύνου ΠΕ

(και σε νεφρική ανεπάρκεια, υψηλό κίνδυνο αιμορραγίας)

Start: 80 U/kg as bolus, 18 U/kg/h infusion rate

Maintain: Infusion Rate Based on aPTT	
aPTT	**Dose change**
<35 sec (<1.2-fold elevated)	80 U as bolus, infusion rate ▲ by 4.0 U/h
35-45 sec (1.2-1.5-fold)	40 IE U as bolus, infusion rate ▲ by 2.0 U/h
46-70 sec (1.5-2.3-fold)	No change
71-90 sec (2.3-3.0-fold)	Infusion rate ▼ by 2.0 U/h
>90 sec (>3.0-fold)	Stop infusion for 1 hour, then continue with infusion rate ▼ by 3.0 U/h

Raschke RA. Ann Intern Med 1993; 119:874-81

High-risk PE

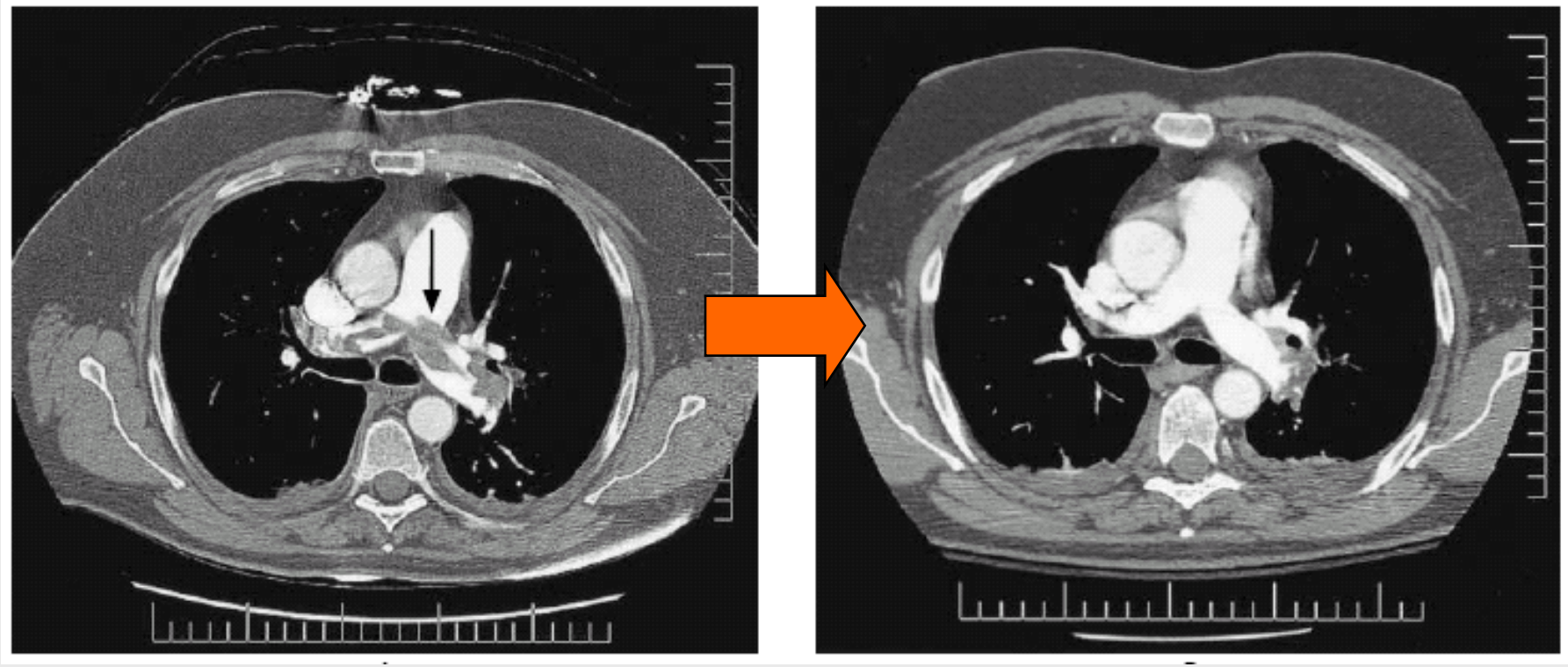
Αμεση θεραπεία σε αιμοδυναμική αστάθεια

Recommendation	Class	Level
Θρομβολυτική θεραπεία για τους ασθενείς με **υψηλού κινδύνου ΠΕ** που παρουσιάζονται με εμμένουσα υπόταση ή καρδιογενές shock	**I** (1)	**A** (B)
Χειρουργική εμβολεκτομή είναι εναλλακτική λύση ΑΝ η θρομβόλυση ανενδείκνυται απόλυτα ή έχει αποτύχει	**I** (2)	**C** (C)
Διακαθετηριακή αναρρόφηση/τεμαχισμός του θρόμβου είναι ίσως εναλλακτική λύση ΑΝ η θρομβόλυση ανενδείκνυται απόλυτα ή έχει αποτύχει	**IIb** (2)	**C** (C)

Overview of Randomised Trials 1972-2002

Study	Year	N	Groups	PE-Diagnosis	FU (d)	End points
UPET	**1973**	**160**	UK (82) Heparin (78)	PA, LS	14	angio, haemo
Marini	1988	30	UK (20) Heparin (10)	PA, LS	7	LS
Tibbutt	1974	30	SK (13) Heparin (17)	PA	3	Angio
Ly	1978	25	SK (14) Heparin (11)	PA	10	Angio
J-Sanchez	1995	8	SK (4) Heparin (4)	PA	3	LS
PIOPED	1990	13	rtPA (9) Heparin (4)	PA, LS	7	Haemo
Levine	1990	58	rtPA (33) Heparin (25)	PA, LS	10	LS
PAIMS-2	1992	36	rtPA (20) Heparin (16)	PA	7	angio, haemo
Goldhaber	**1993**	**101**	rtPA (46) Heparin (55)	PA, LS, **echo**	14	**echo**
MAPPET-3	**2002**	**256**	rtPA (118) Heparin (138)	PA, LS, **echo**	30	**clinical**

Thrombolysis Highly Effective



NP Fam. N Engl J Med 2002; Vol. 347, No. 15

Risks of Thrombolysis

Study	Design	Thrombolytic	Bleeding (Thrombolysis Group) Major	Intracranial / fatal
UPET 1973	P, R	UK (vs. heparin)	37/82	1/82
USPET 1974	P, R	UK vs. SK (no heparin group)	32/113 12/54	0/113 0/54
Levine 1990	P, R	rtPA (vs. heparin)	0/33	0/33
PAIMS-2 1992	P, R	rtPA (vs. heparin)	4/20	2/20
Meyer 1992	P, R	rtPA vs. UK (no heparin group)	7/34 8/29	1/34 1/29
Sors 1994	P, R	2 rtPA regimens (no heparin group)	0/53	0/53
Kanter 1997	Meta analysis (5 studies)	rtPA vs. UK (no heparin group)	----	6/312
MAPPET 2002	P, R	rtPA (vs. heparin)	1/118	0/118
Overall			**101/536 (19%)**	**11/536 (2.0%)**

High-risk PE

Thrombolysis for High-Risk PE: Meta-Analysis

Studies That Included Patients With High-Risk-PE

S Wan. Circulation 2004;110:744-749

End point	Thrombolysis n / N	Heparin n / N	OR (95% CI)
PE Recurrence or Death	**12/128 (9.4%)**	**24/126 (19%)**	**0.45 (0.22-0.92)**
PE Recurrence	5/128 (3.9%)	9/126 (7.1%)	0.61 (0.23-1.62)
Death	8/128 (6.2%)	16/126 (12.7%)	0.47 (0.20-1.10)
Major Bleeding	28/128 (21.9%)	15/126 (11.9%)	1.98 (1.00-3.92)

High-risk PE

Θρομβολυτικά σχήματα

Streptokinase	250,000 U over 30 min followed by 100,000 U/h over **12-24 h** Accelerated: 1.5 Mio. U over **2 h**
Urokinase	4,400 U/kg KG over 10 min, followed by 4,400 U/kg/h over **12-24 h** Accelerated: 3 Mio. U over **2 h**
Alteplase	100 mg over **2 h** Accelerated: 0.6 mg/kg over **15 min**
Reteplase	Two bolus injections (10 U each) with 30 min-interval (off-label)

High-risk PE

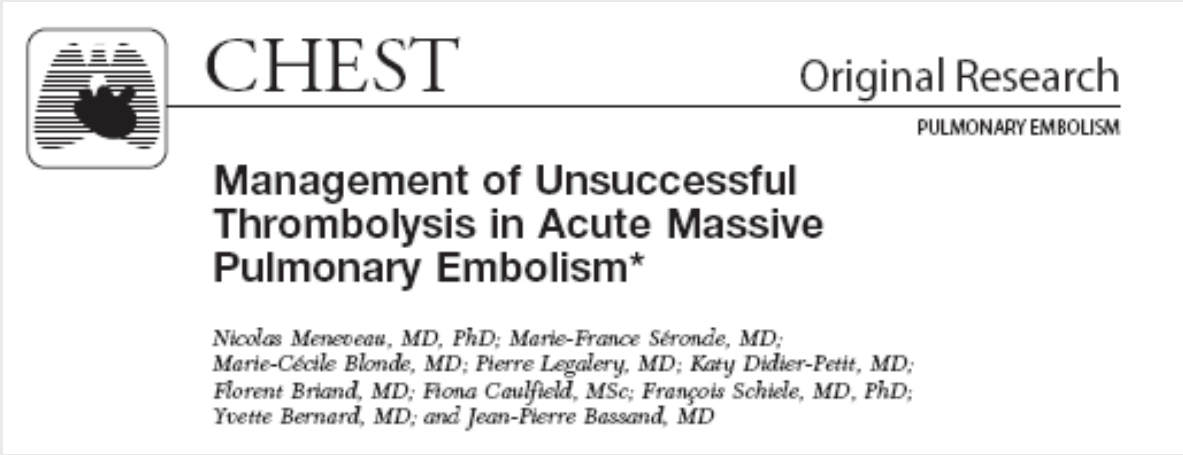
Contra-indications to thrombolytic therapy

Absolute contra-indications*:

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

"Lysis Failure": An Unlikely Event

Incidence: 8% of thrombolysed patients, based on clinical and echo criteria



CHEST Original Research

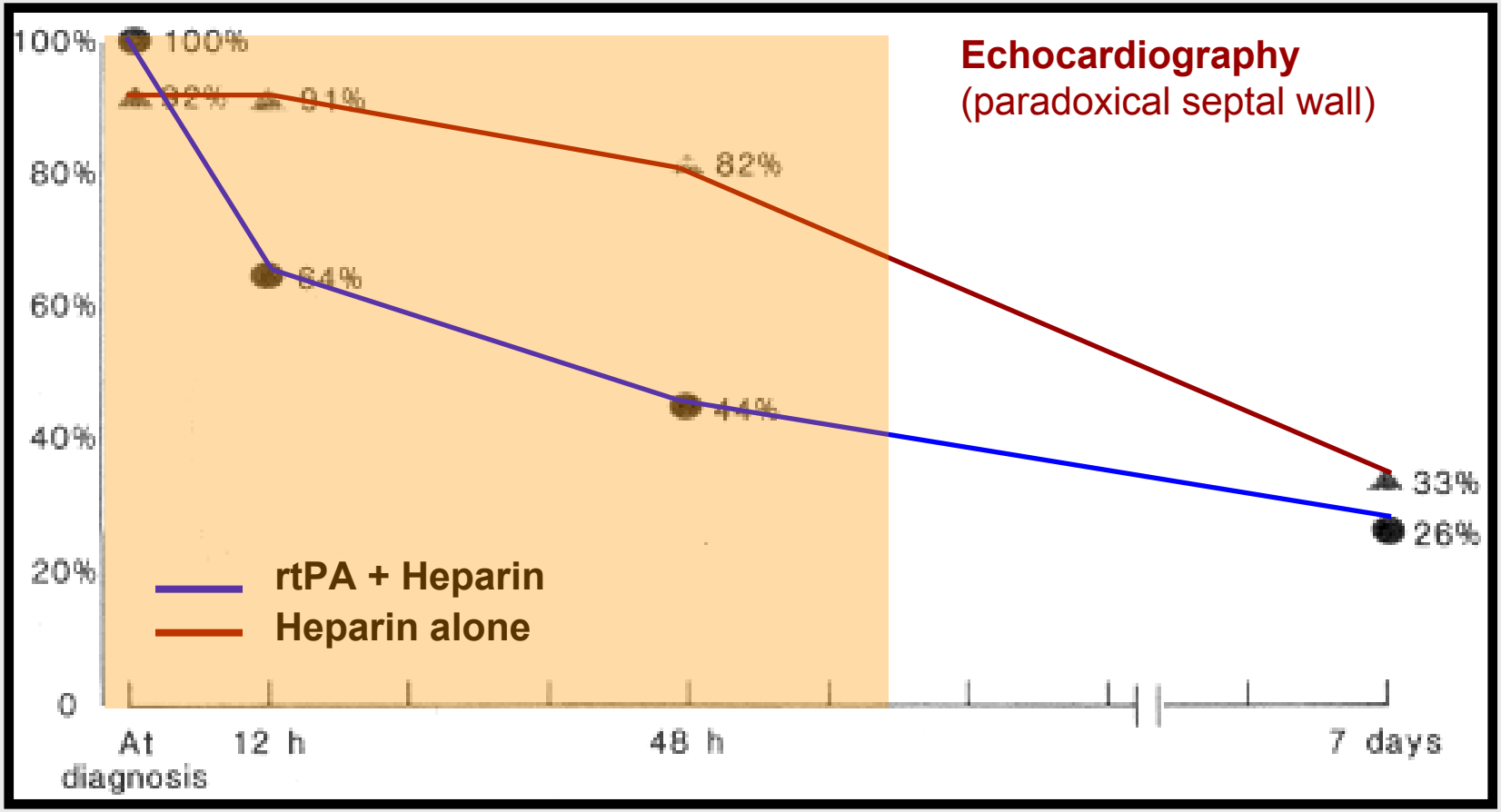
PULMONARY EMBOLISM

Management of Unsuccessful Thrombolysis in Acute Massive Pulmonary Embolism*

Nicolas Meneveau, MD, PhD; Marie-France Séronde, MD; Marie-Cécile Blonde, MD; Pierre Legalery, MD; Katy Didier-Petit, MD; Florent Briand, MD; Fiona Caulfield, MSc; François Schiele, MD, PhD; Yvette Bernard, MD; and Jean-Pierre Bassand, MD

N Meneveau. Chest 2006;129:1043-1050

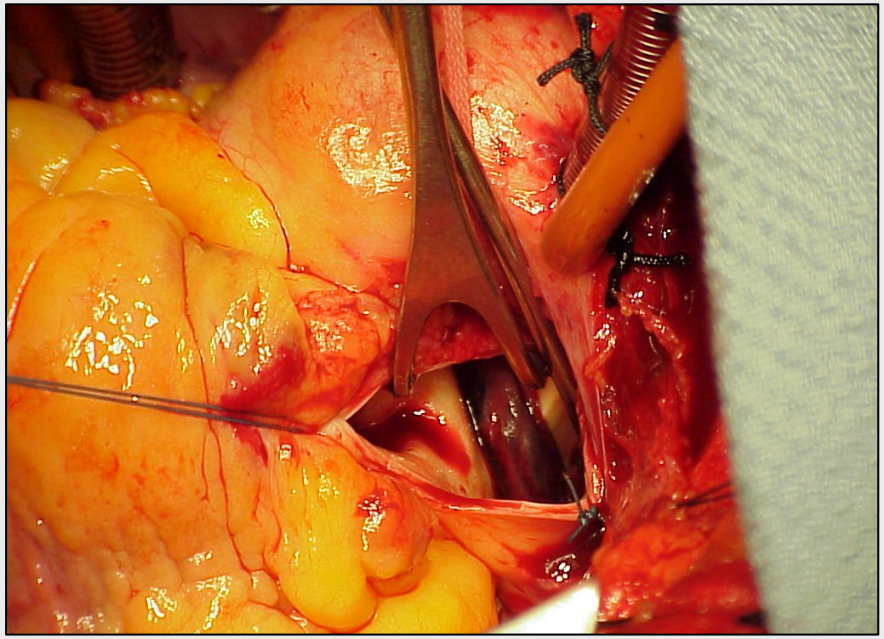
Rapid Resolution of RV Dysfunction

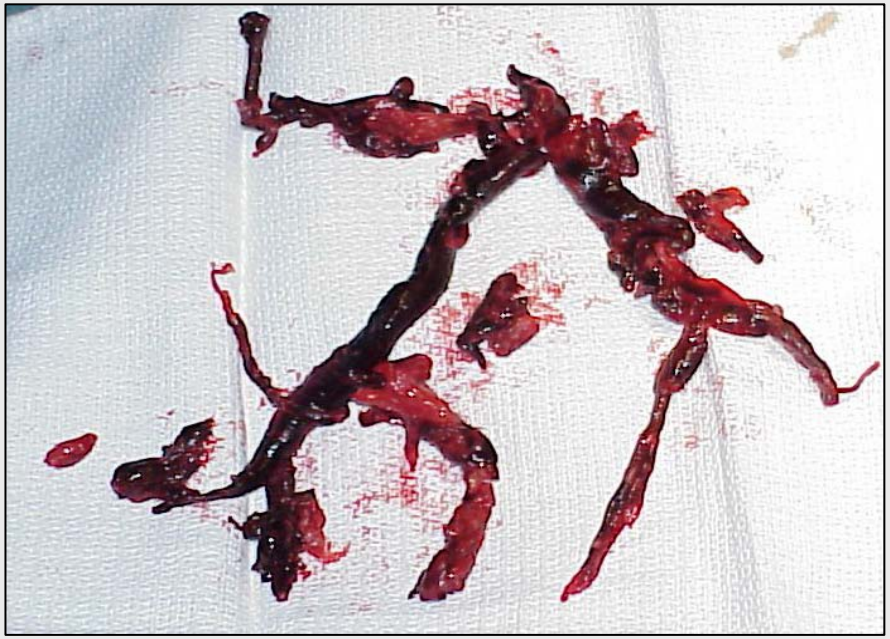


S Konstantinides, Am J Cardiol 1998;82:966-970

High-risk PE

Alternative: Surgical Embolectomy





L Aklog. In: Management of Pulmonary Embolism. Humana Press 2007

Surgical Embolectomy for Massive PE

Author	Country	Publication date	Time period	Patients	Operations/y	Deaths	Surgical mortality
Aklog	USA	2001	1999-2001	29	14,5	3	10%
Doerge	Germany	1999	1979-1998	41	2,2	12	29%
Ullman	Germany	1999	1989-1997	40	5,0	14	35%
Jakob	Germany	1995	1988-1994	25	3,6	6	24%
Gulba	Germany	1994	1988-1993	13	2,6	3	23%
Stulz	Switzerland	1994	1968-1992	50	1,9	23	46%
Laas, Schmid	Germany	1993	1975-1992	34	2,0	15	44%
Bauer	Switzerland	1991	1978-1990	44	3,7	9	20%
Kieny	France	1991	1970-1989	134	7,1	21	16%
Meyer	France	1991	1968-1988	96	4,8	36	38%
Clarke	England	1986	1960-1985	55	2,2	24	44%
De Weese	USA	1976	1961-1975	11	0,8	7	64%
Gesamt				**837**	**2,9**	**261**	**31%**

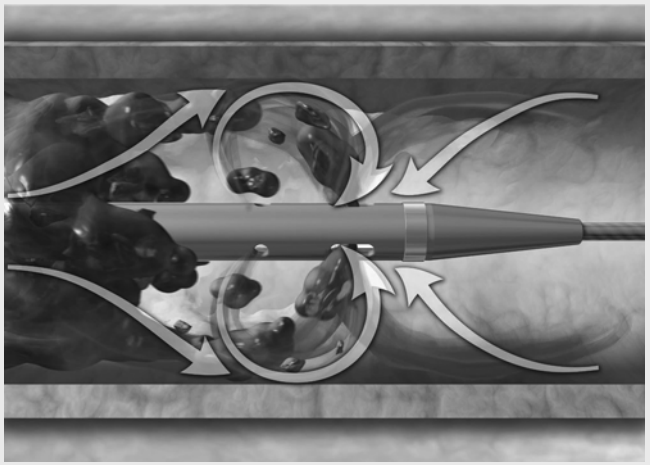
L Aklog, Kapitel in „Management of Pulmonary Embolism“. Humana Press 2007

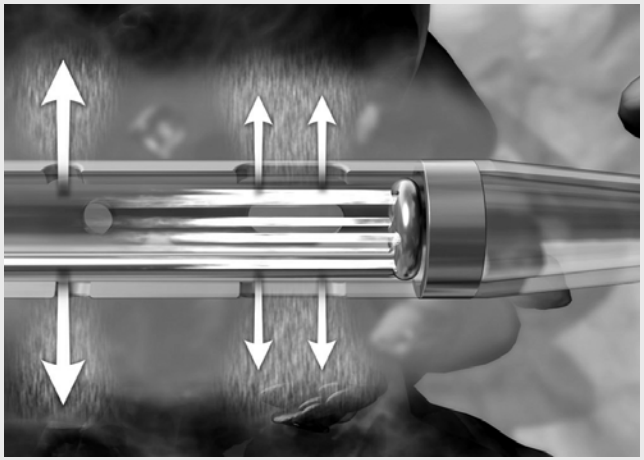
High-risk PE

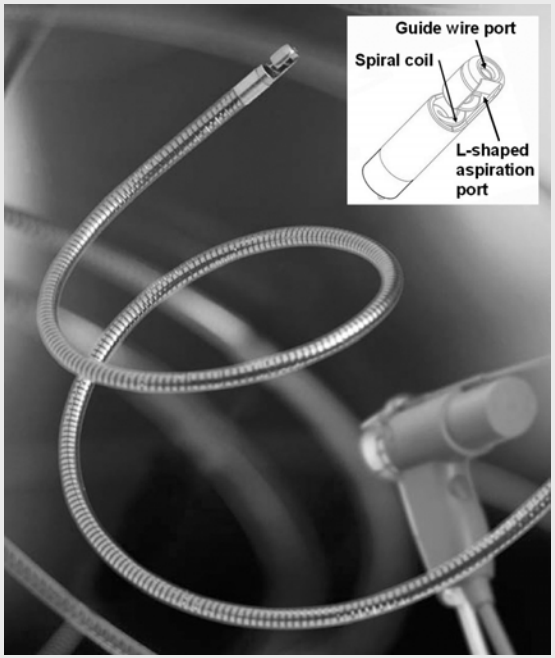
Alternative: Catheter-Based Therapy

N Kucher. In: Management of Pulmonary Embolism. Humana Press 2007

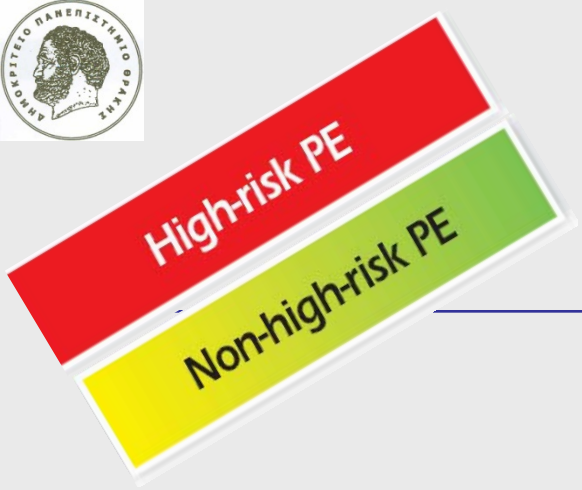
AngioJet Xpeedior, Possis, MN







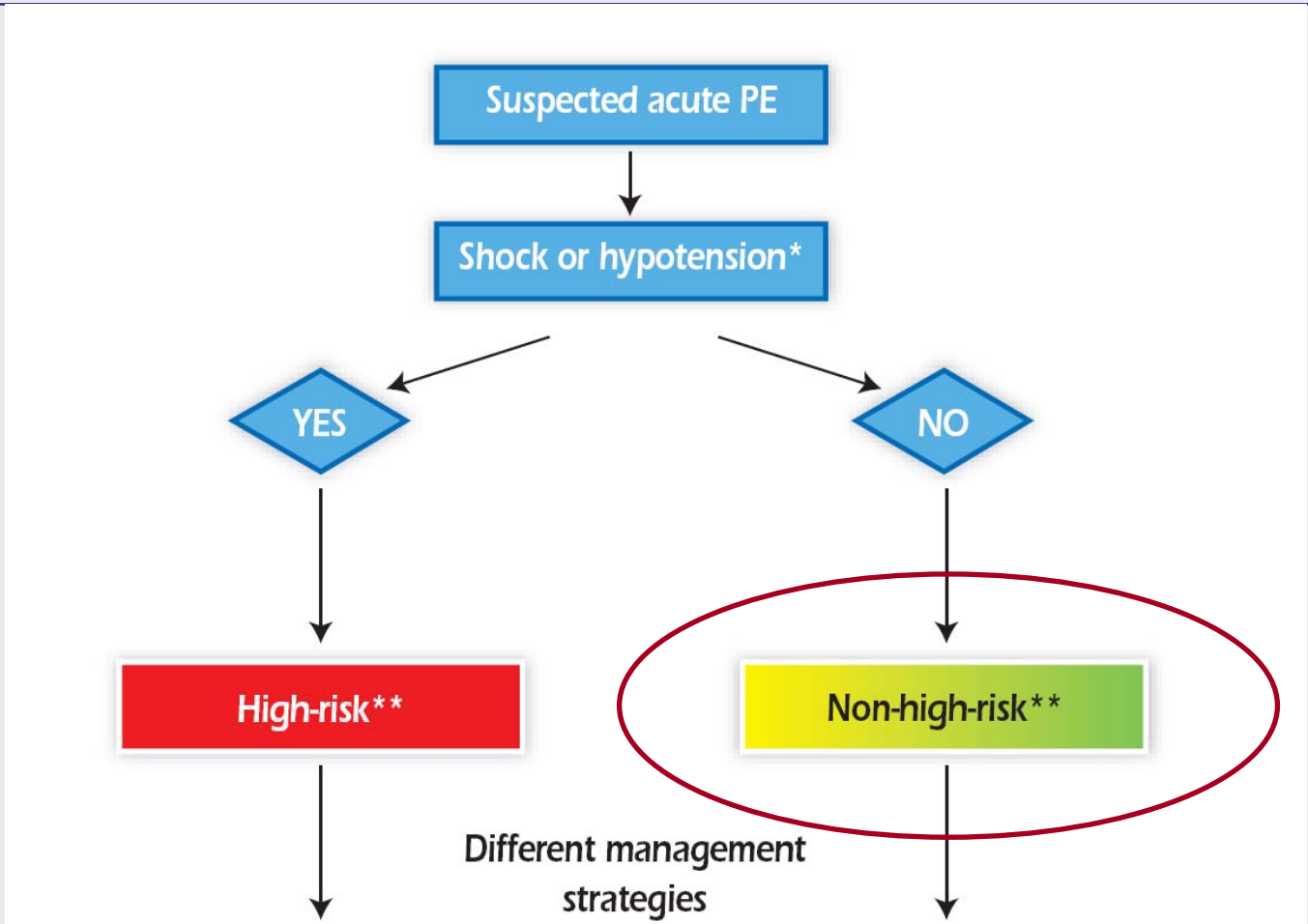
Aspirex, Straub, CH



Vena Cava Filters

Recommendation	Class	Level
✓ IVC filters may be used when there are absolute contraindications to anticoagulation and a high risk of recurrence	**IIb**	**B**
✓ The routine use of IVC filters in patients with PE is **not** recommended	**III**	**B**

Νορμοτασικοί ασθενείς «μη υψηλού» κινδύνου



Non-high-risk PE

Treatment Recommendations

Recommendation	Class	Level
Anticoagulation should be initiated without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is still ongoing	I (1)	C (C)
LMWH or fondaparinux recommended form of initial treatment for most patients	**I (1)**	**A (A)**
Routine use of thrombolysis (afterload reduction) in non–high-risk PE patients is not recommended (1B); **may be used in selected patients**	**IIb**	**B**

Thrombolysis in Non-High-Risk PE

No Clinical Benefit (?)

Studies That *Excluded* Patients With Massive PE

Outcome	Thrombolysis n / N	Heparin n / N	OR (95% CI)
Recurrent PE or Death	**13/246 (5.3%)**	**12/248 (4.8%)**	**1.07 (0.50-2.30)**
Recurrent PE	5/246 (2.0%)	7/248 (2.8%)	0.76 (0.28-2.08)
Death	8/246 (3.3%)	6/248 (2.4%)	1.16 (0.44-3.05)
Major Bleeding	6/246 (2.4%)	8/248 (3.2%)	0.67 (0.24-1.86)

S Wan. Circulation. 2004;110:744-749

Non-high-risk PE

Need For Further Risk Stratification ?

Recommendation	Class	Level
In non-high-risk PE patients, further stratification to an intermediate or low-risk PE subgroup based on the presence of of RV dysfunction and myocardial injury should be considered	IIa	B

Acute Pulmonary Embolism:

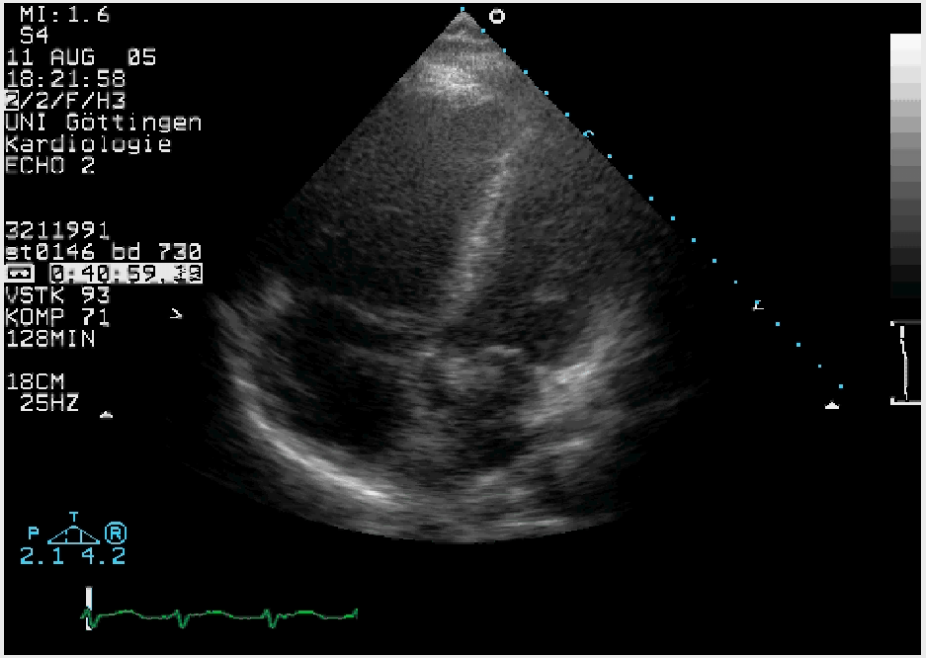
How to Detect RV Dysfunction ?

Early Markers of RV Dysfunction

- ECG
- Right heart catheterization
- Echocardiography
- CT scan
- Biomarkers

NF Voelkel. Circulation 2006;114:1883-1891

Imaging of RV Dysfunction (echo)



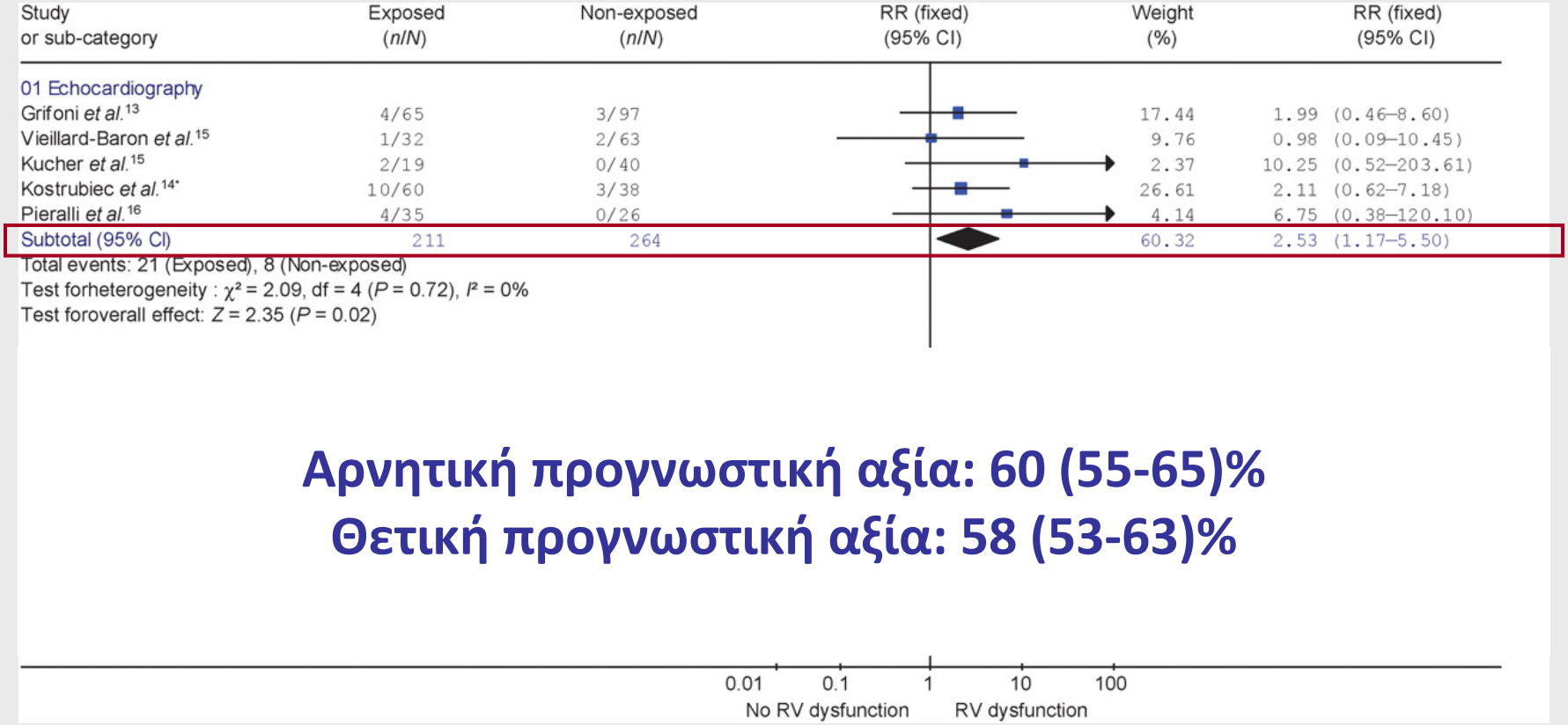
Echo criteria:

non-standardized; various combinations and thresholds

- RV dilatation (RV>LV, or RVEDD >30 mm)
- RV free wall hypokinesia
- Paradoxical septal wall
- Pulmonary hypertension (RV-RA gradient >30 mm Hg, or pulm acceleration time <80 ms)

Υπερηχογραφικά ευρήματα σε νορμοτασικούς: μετα-ανάλυση

Relative risk of in-hospital death

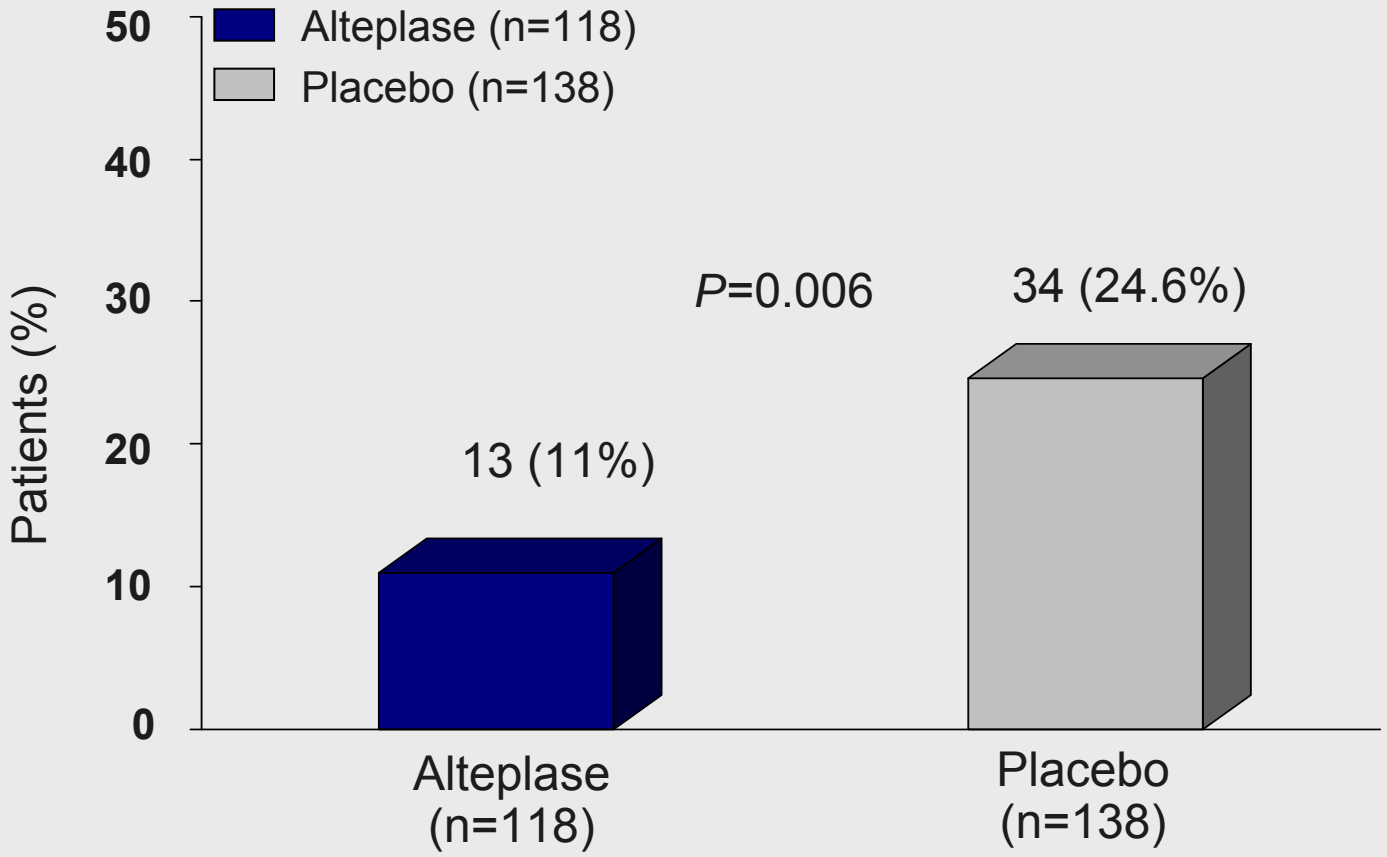


Αρνητική προγνωστική αξία: 60 (55-65)%

Θετική προγνωστική αξία: 58 (53-63)%

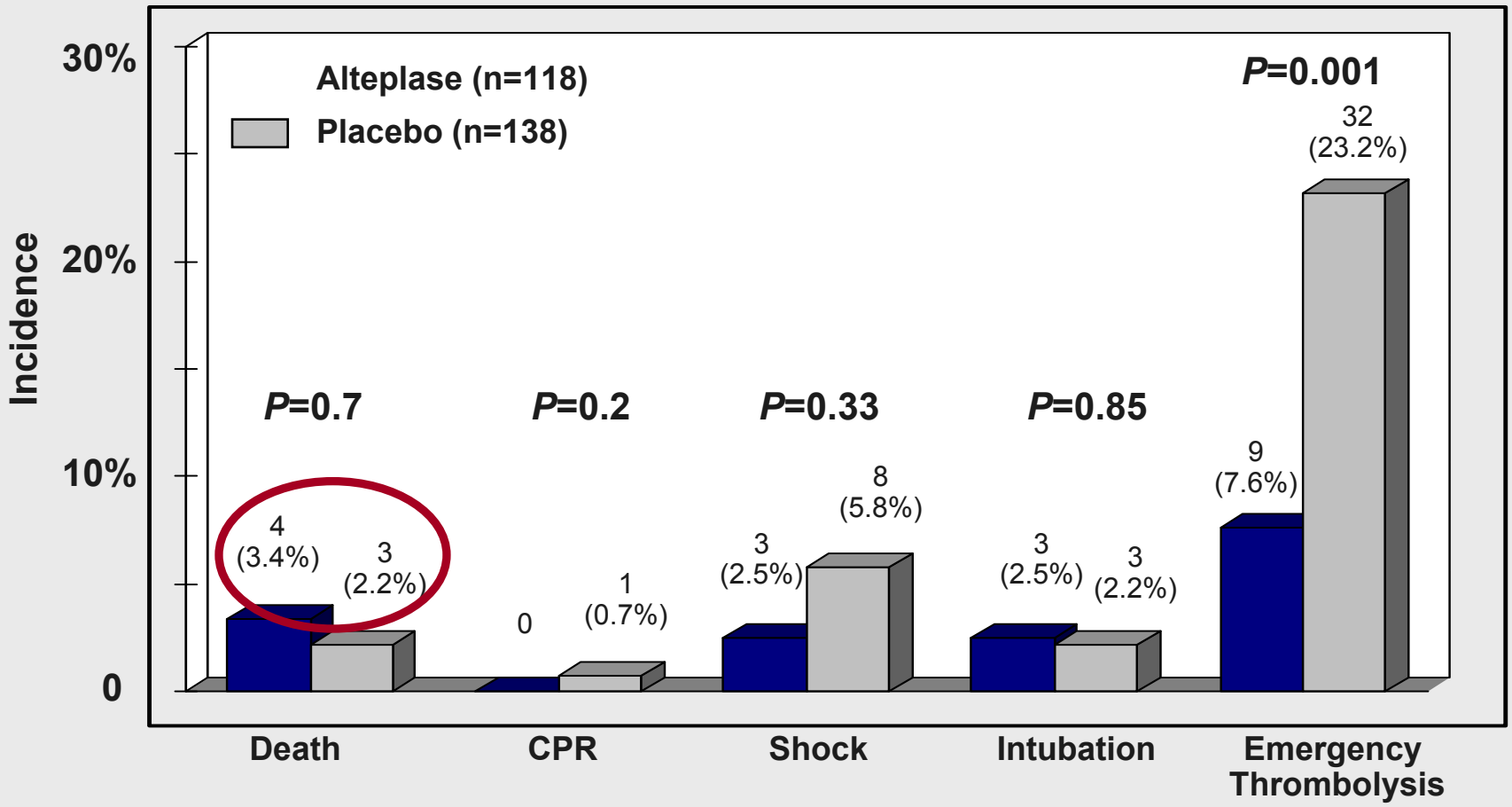
O Sanchez. Eur Heart J 2008;29:1569-1577

RV Dysfunction in Normotensive PE: Therapeutic Implications ?



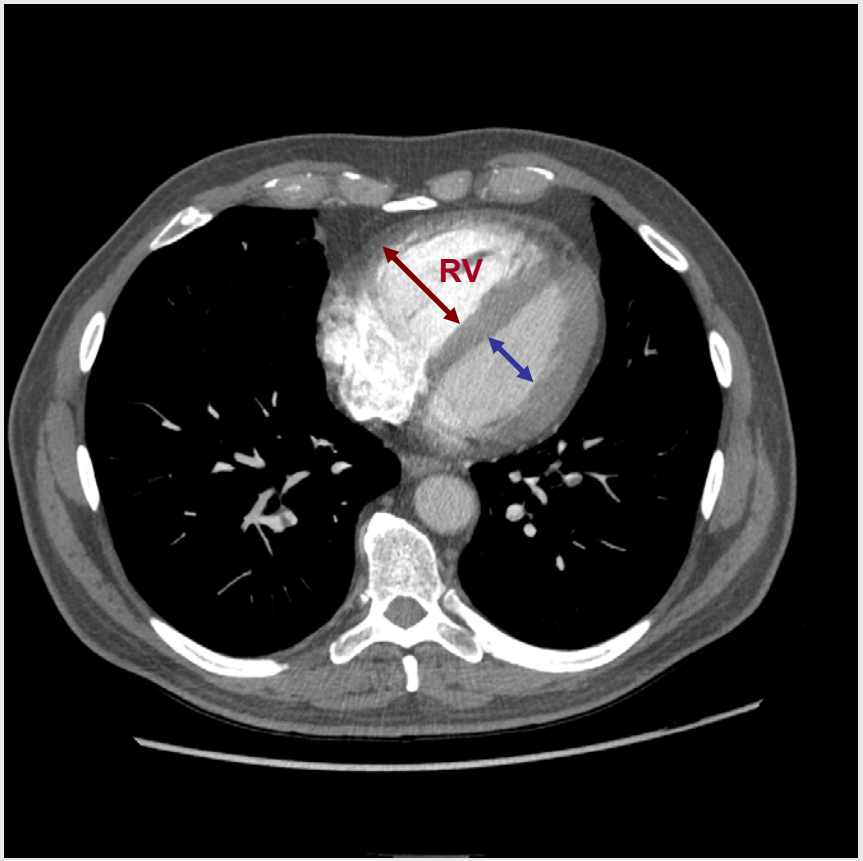
S. Konstantinides. N Engl J Med 2002;347:1143

RV Dysfunction in Normotensive PE: Therapeutic Implications ?



N Engl J Med 2002;347:1143

Ευρήματα από την αξονική τομογραφία

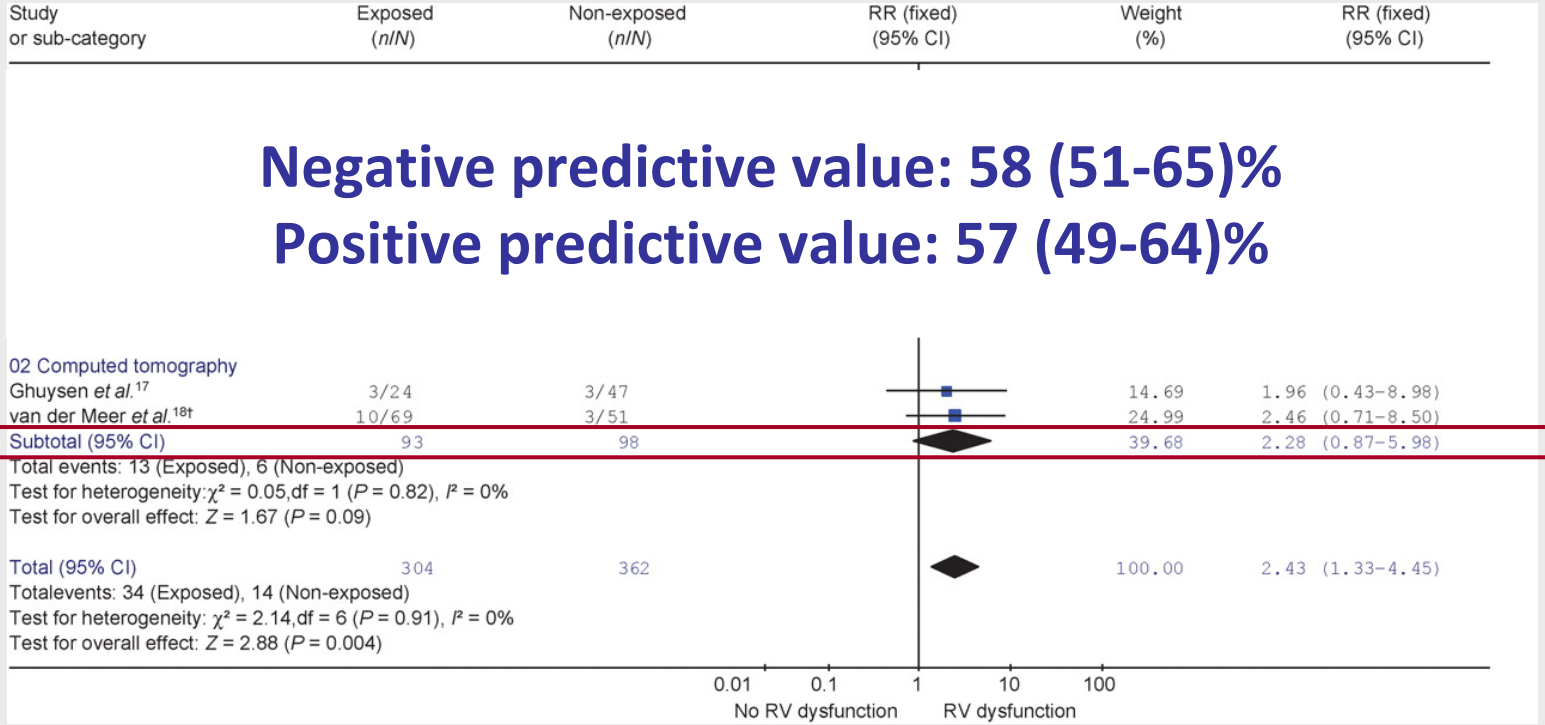


CT Criteria:

retrospectively tested

- RV dilatation, RV:LV >1.0 (or RV:LV >1.5)
- [Leftward septal bulging]
- [Pulmonary arterial obstruction indexes (Bankier, Qanadli, Mastora)]

RV Dysfunction (CT) in Patients Without Schock

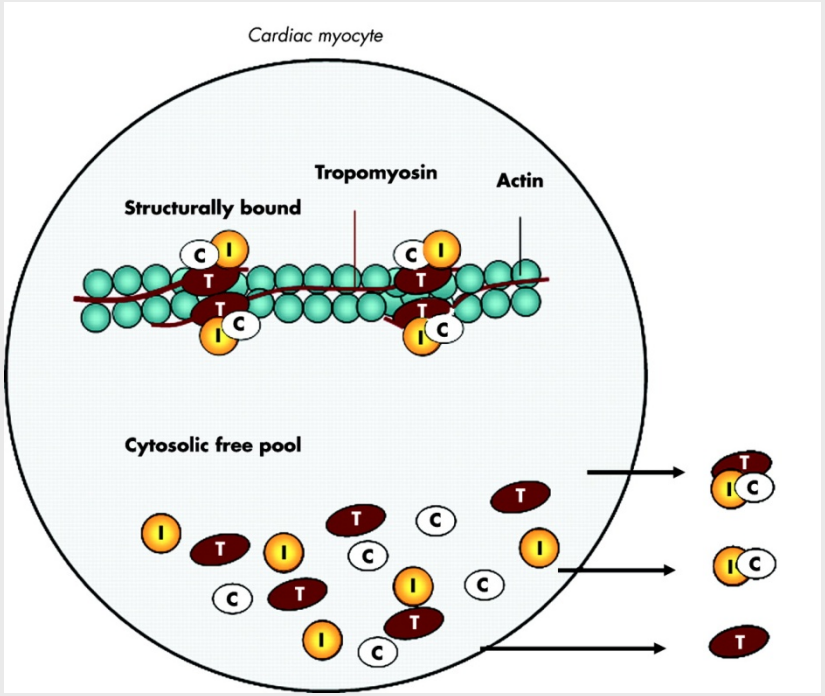


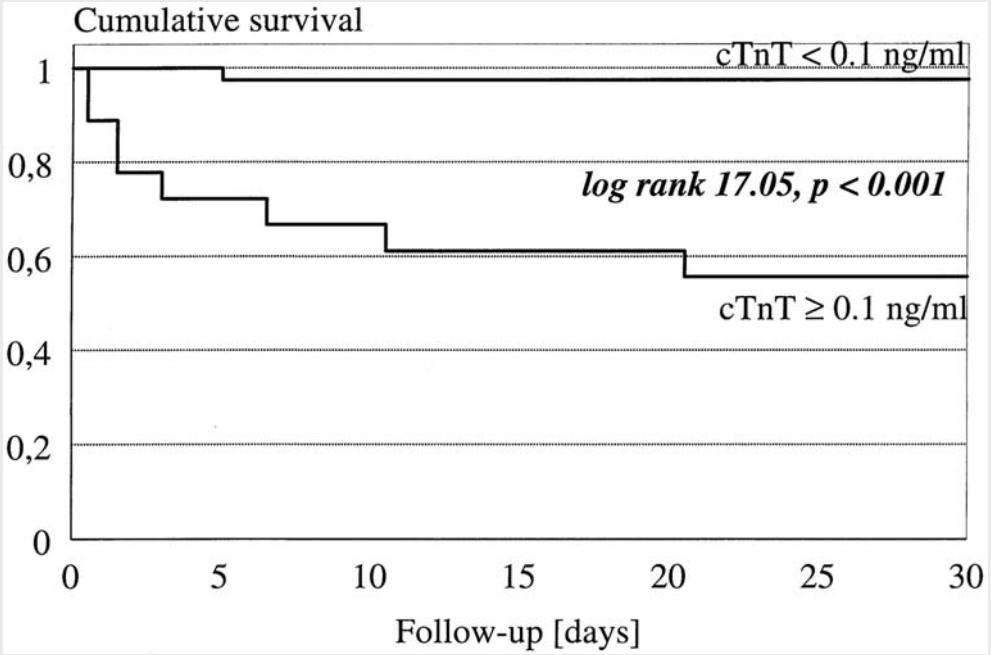
O Sanchez. Eur Heart J 2008;29:1569-1577

Εργαστηριακοί βιοδείκτες: Τροπονίνες

bound and circulating troponin

Troponin T: independent predictor
of 30-day mortality
in 56 (unselected) patients with PE



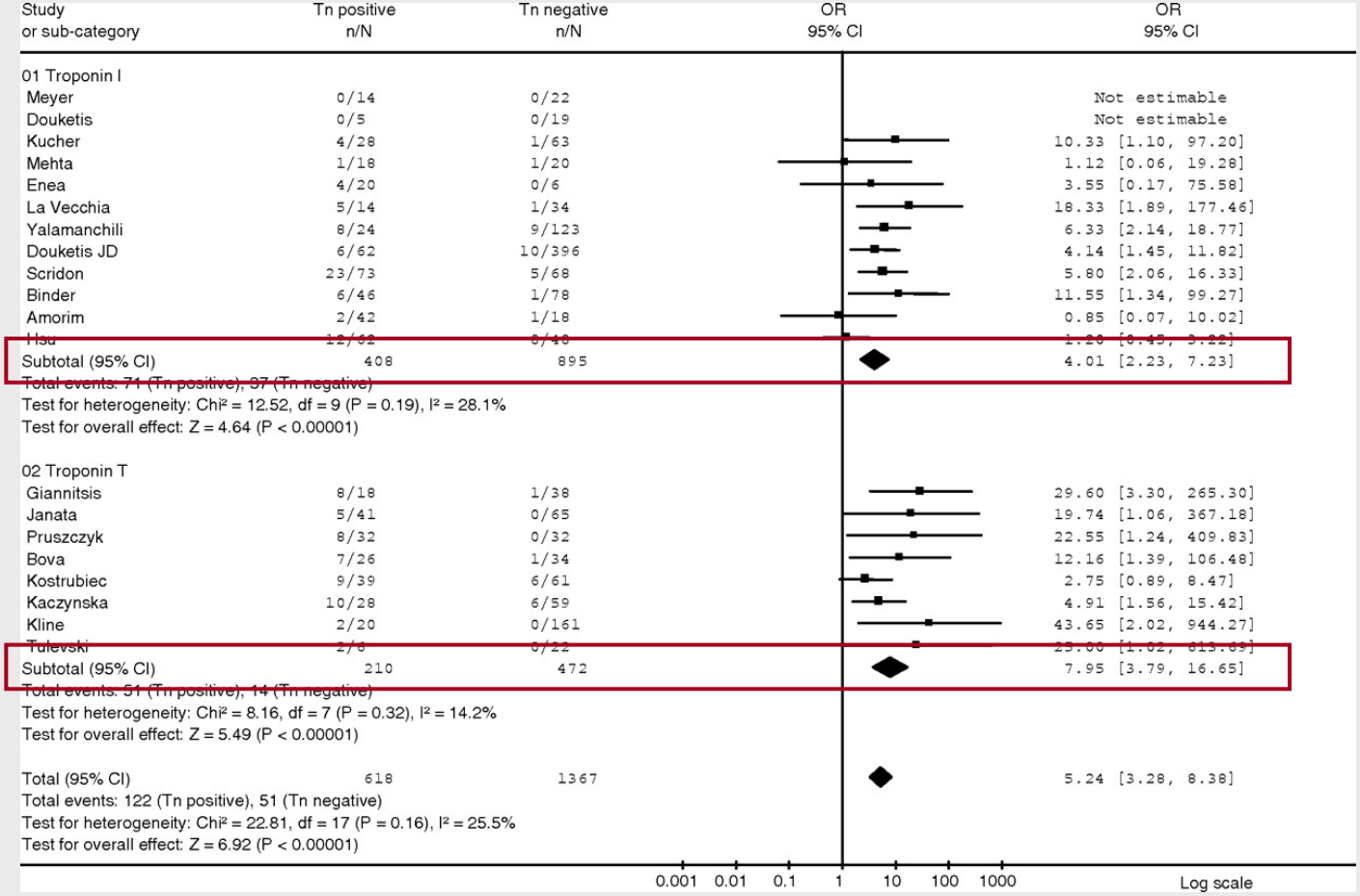


S Korff. Heart 2006;92:987-993

E Giannitsis. Circulation 2000;102:211-217

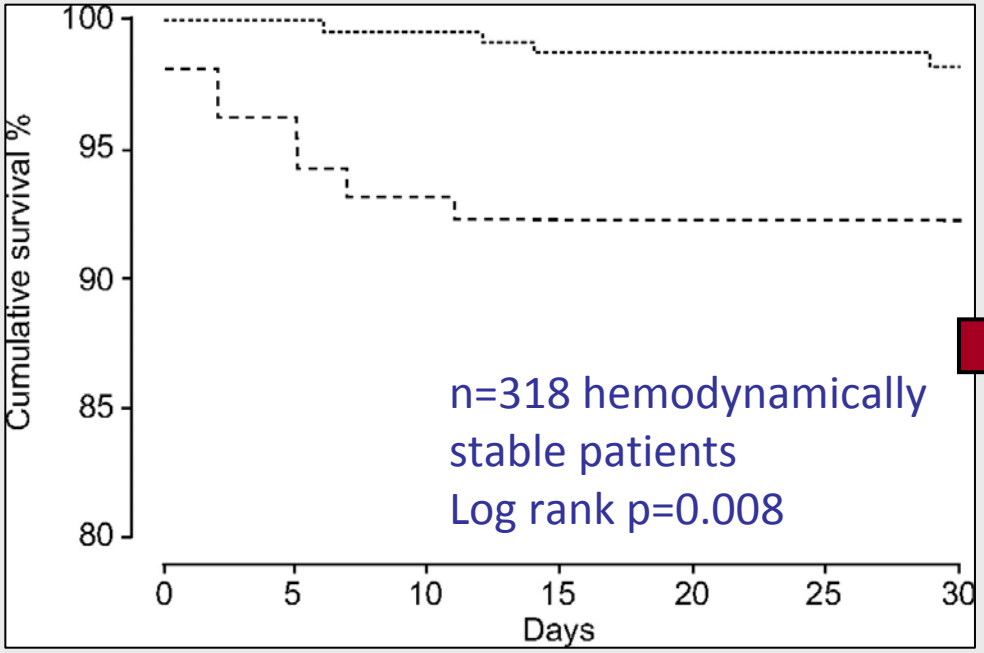
Τροπονίνες και θνητότητα: Μετα-ανάλυση

Data from 20 studies (4 retrospective); n=1,985 pts (1998-2006): **Troponin ↑ in 31%**



C Becattini. Circulation 2007;116:427-433

Τροπονίνες και θνητότητα: Νορμοτασικοί ασθενείς



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

D Jimenez. Eur Respir J 2008;31:847

Meta analysis:

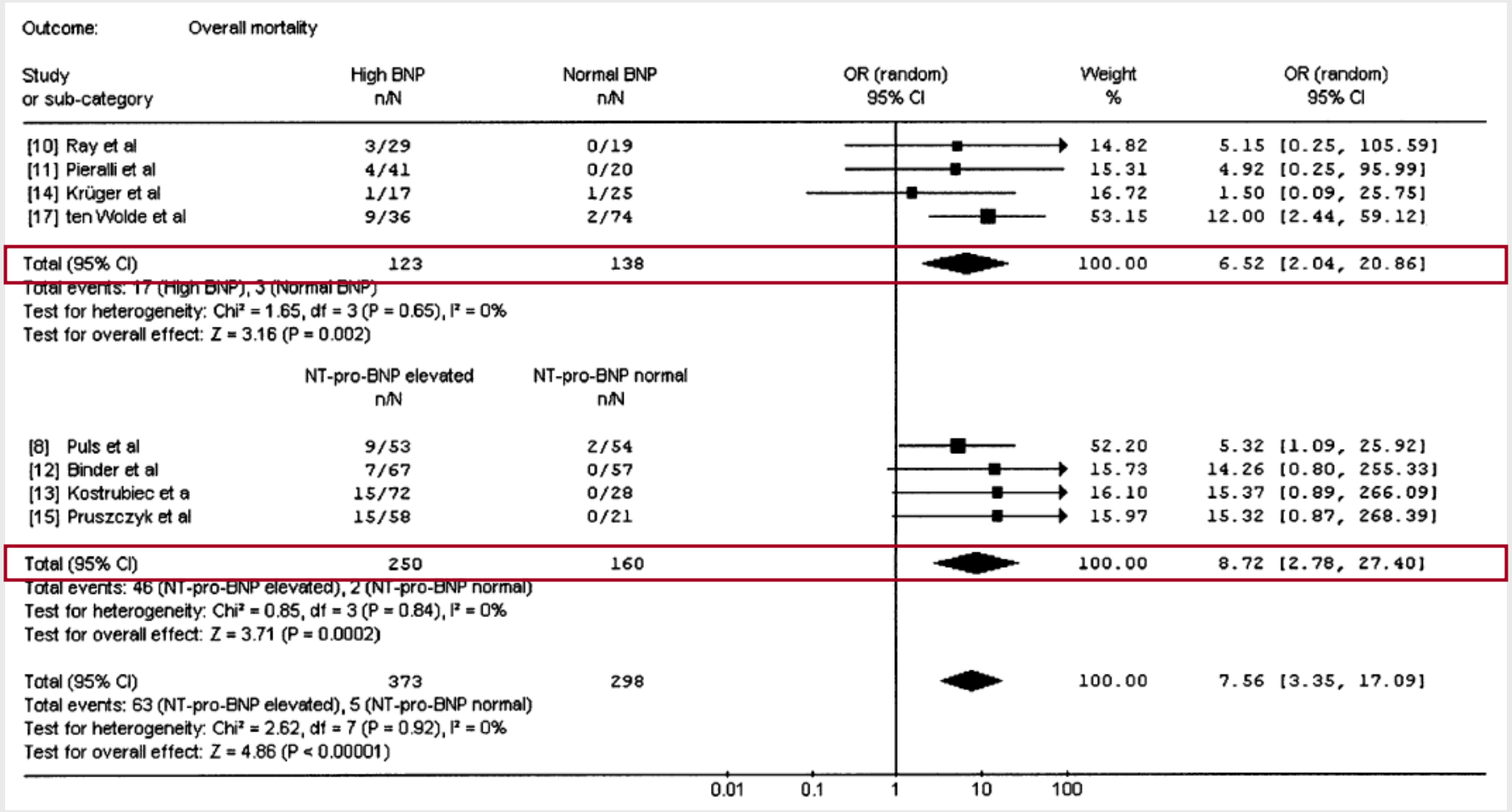
- 9 studies
- 1366 patients with symptomatic PE
- Pts **normotensive** at diagnosis

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

D Jimenez. Chest 2009; 136:974-982

Meta-analysis of Natriuretic Peptides

Data from 13 studies; n=1,132 pts: **BNP/NT-proBNP ↑ in 51%**



FA Klok. Am J Respir Crit Care Med 2008;178:425-430

Acute Pulmonary Embolism and Pulmonary Hypertension: RV Dysfunction - Evolving Concepts and Outlook

1) Συνδυασμοί βιοδεικτών
2) Νέοι βιοδείκτες μυοκαρδιακής νέκρωσης (υψηλού κινδύνου)
3) Ολοκληρωμένοι βιοδείκτες ΔΚ δυσλειτουργίας και νέκρωσης

Non-high-risk PE

1) Συνδυασμοί βιοδεικτών

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

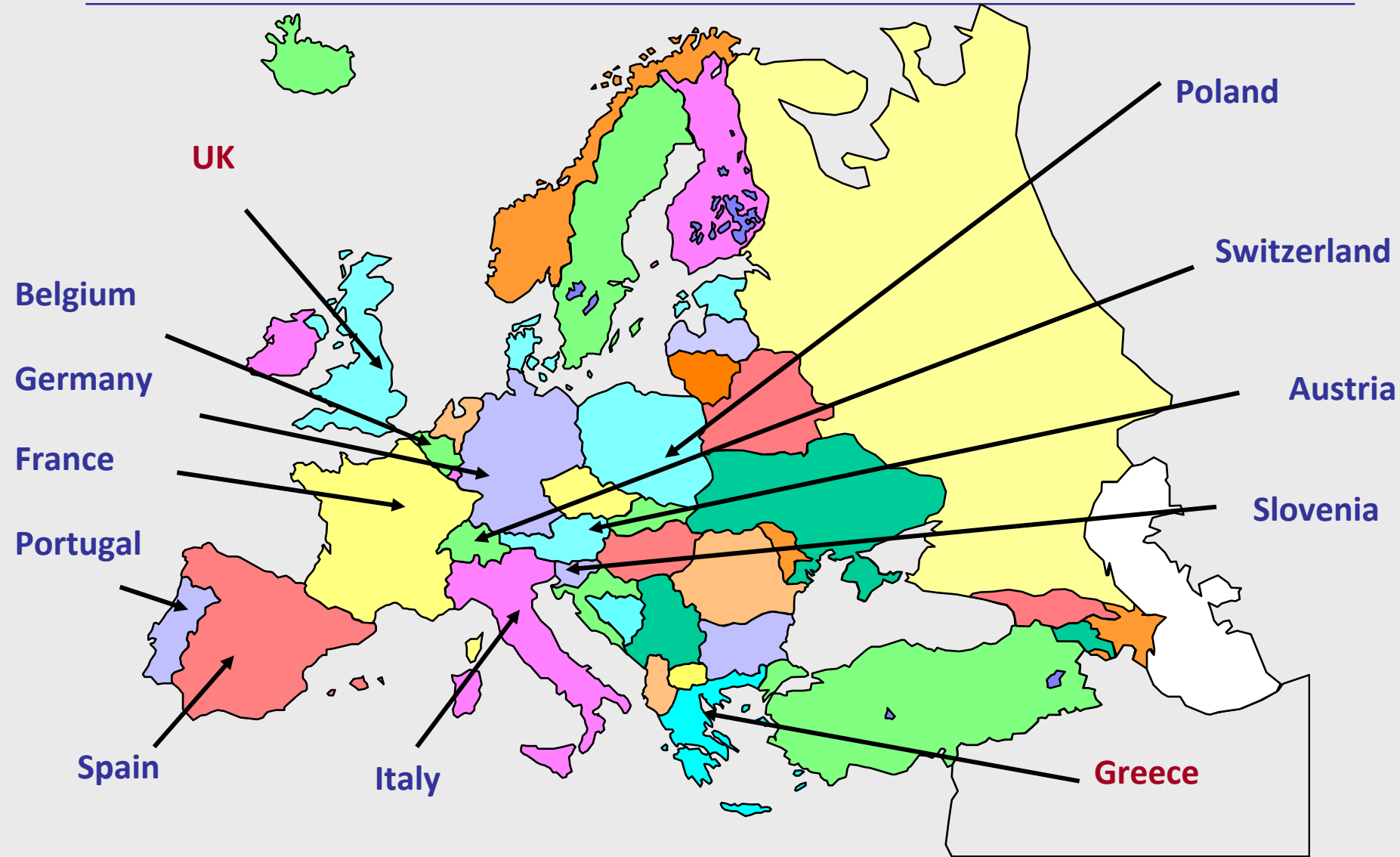
1) Συνδυασμοί βιοδεικτών

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

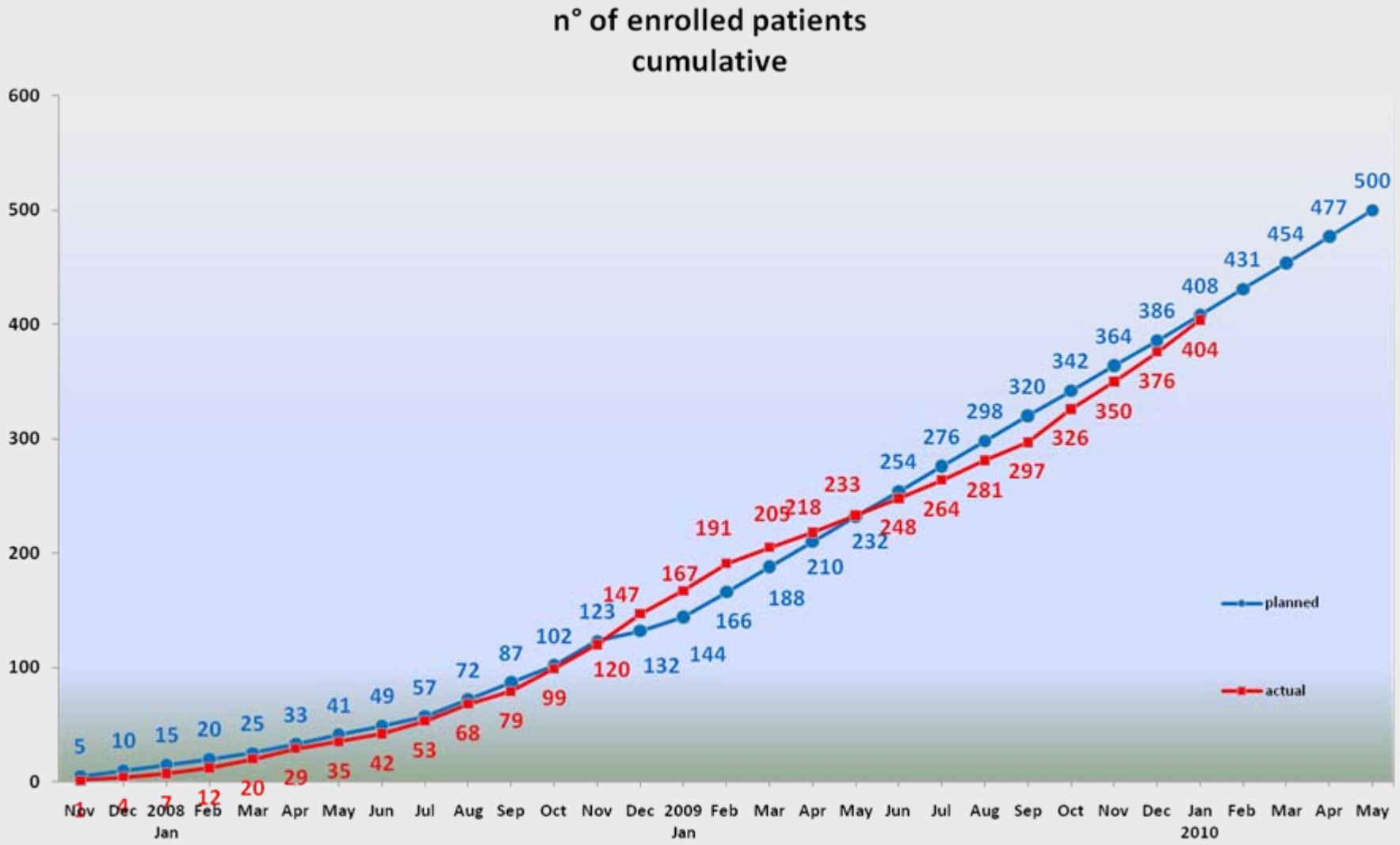
~ 15% όλων των ασθενών με Π.Ε.

L Binder. Circulation 2005;112:1573-1579

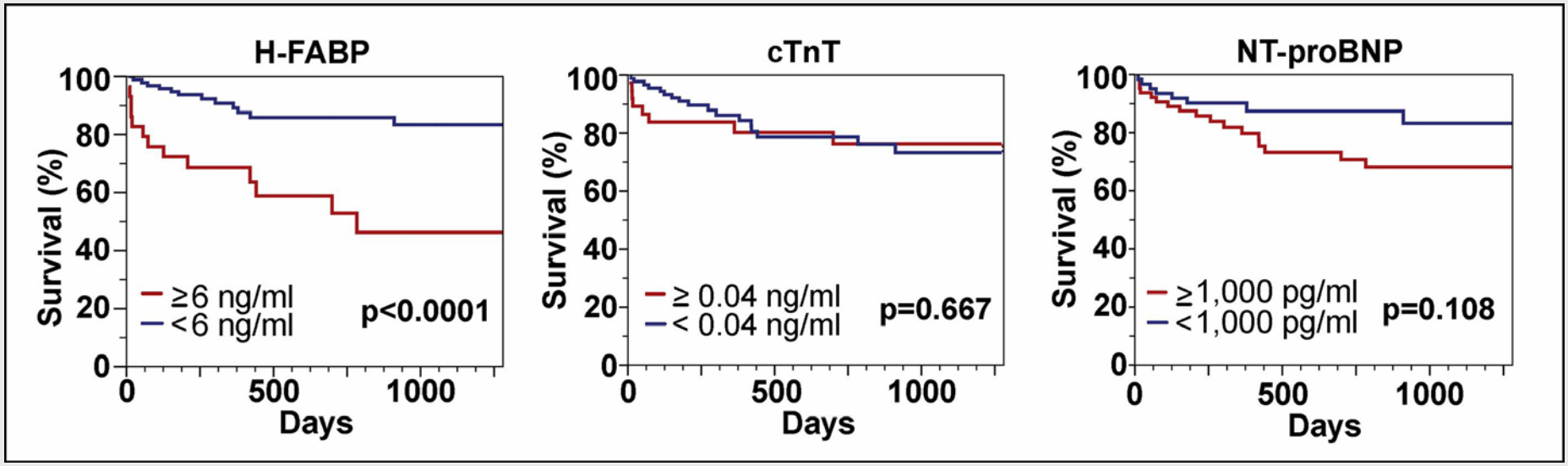
RV Dysfunction (Echo) + Injury (Troponin):
⇒ an International Randomized Thrombolysis Trial



PEITHO Status (as of January 31, 2010)



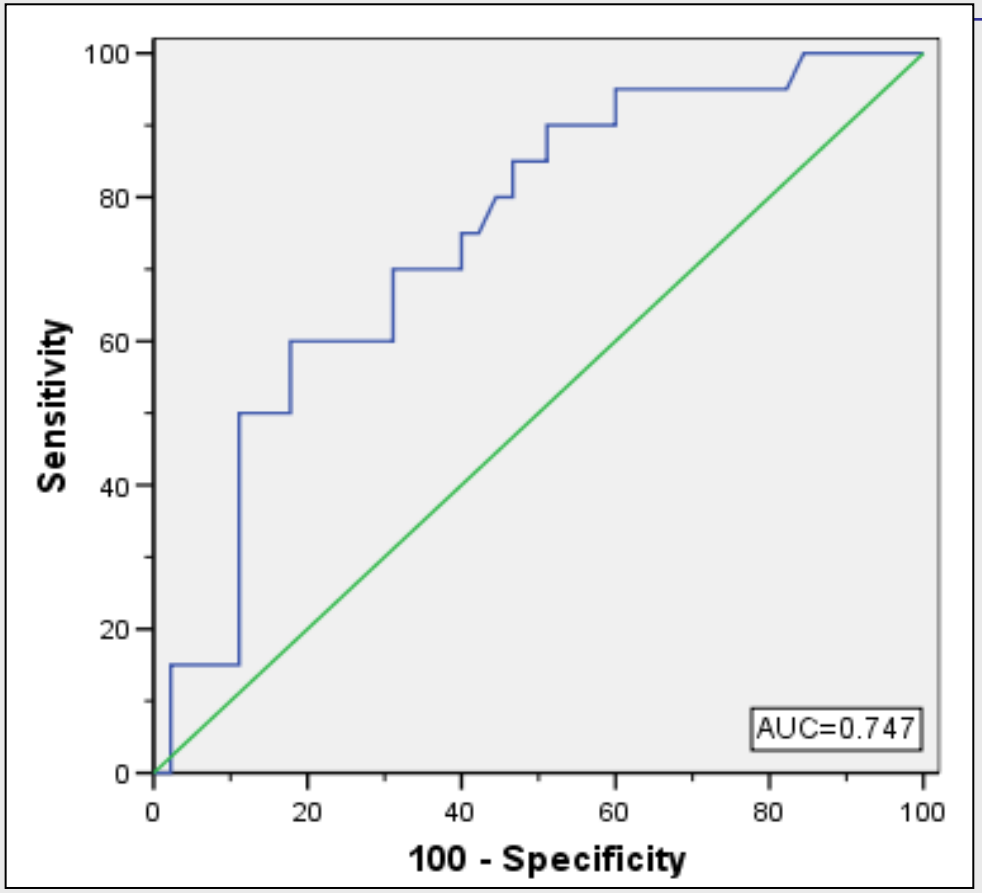
2) Νέοι βιοδείκτες υψηλού κινδύνου: H-FABP



H-FABP in normotensive PE	Sensitivity	Specificity	NPV	PPV
H-FABP ≥6 ng/l (23% of patients)	0.89	0.82	0.99	0.28

M Puls. Eur Heart J 2007;28:224-229
C Dellas. J Am Coll Cardiol 2010; in press

CTEPH: Prognostic Value of H-FABP



Cut-off level: 4 ng/mL

Sensitivity: 0.55

Specifity: 0.82

Patients with a H-FABP ≥4 ng/mL had a **4.26**-fold higher risk for reaching the primary endpoint.

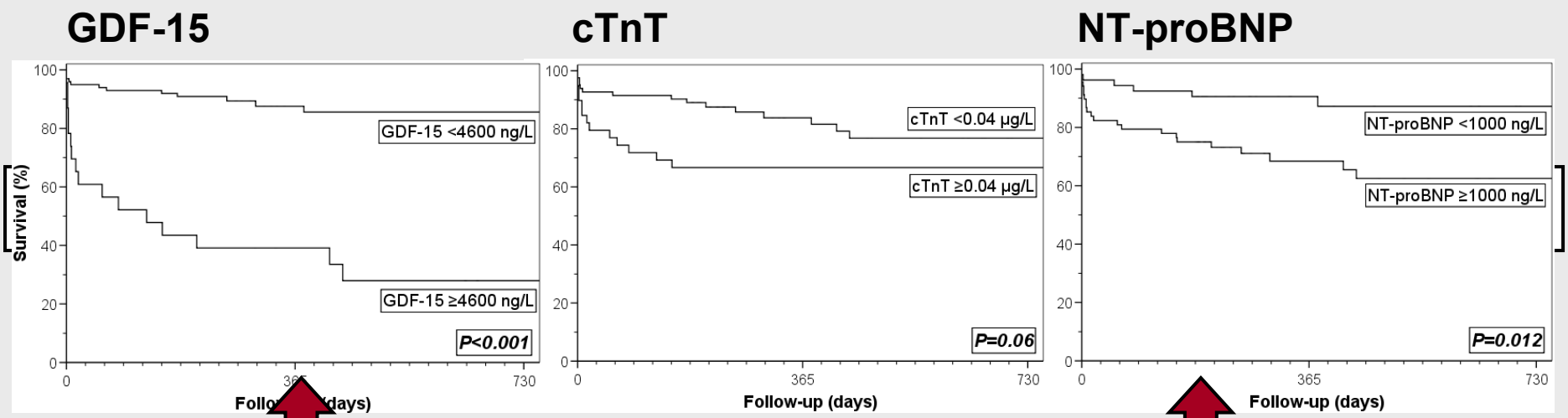
Prognostic Value of cardiac troponin T:

Only 2 (3%) patients had detectable cardiac troponin T

- both died within 20 days

M. Lankeit. Eur Resp J 2008;31:1024

3) «Ολοκληρωμένοι» βιοδείκτες: GDF-15



Πιθανά πλεονεκτήματα του ολοκληρωμένου δείκτη έναντι της τροπονίνης

Ανώτερος του NT-proBNP

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

Νορμοτασικός ασθενής με ΠΕ και ΔΚ δυσλειτουργία (intermediate risk):

Ποια είναι η στρατηγική το 2010 ?

1. Εισαγωγή σε CCU ή ΜΕΘ
2. ΧΜΒ ηπαρίνη αρκεί στις περισσότερες περιπτώσεις – watchful waiting
3. Πρωτογενής θρομβόλυση στις εξής περιπτώσεις:
   a) Ελαττωμένα καρδιοπνευμονικά αποθέματα
   b) Σοβαρή συννοσηρότητα
   c) patent foramen ovale με R→L Shunt
4. **Συμμετοχή σε τυχαιοποιημένη μελέτη !!**

Διαστρωμάτωση κινδύνου στην Π.Ε.: 2010

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