Δυσλειτουργία της Δεξιάς Κοιλίας στην Πνευμονική Εμβολή και Πνευμονική Υπέρταση

Προγνωστική σημασία και συνέπειες για τη θεραπεία

Σταύρος Β. Κωνσταντινίδης, MD, FESC
Δημοκρίτειο Πανεπιστήμιο Θράκης
Πανεπιστημιακή Καρδιολογική Κλινική
www.cardioalex.gr

Clinical and Epidemiological Relevance of Venous Thromboembolism

- *Annual incidence of VTE in the US: 350,000-600,000*
- *Annual mortality: 100,000*
- *More deaths than from breast cancer, AIDS, car accidents*

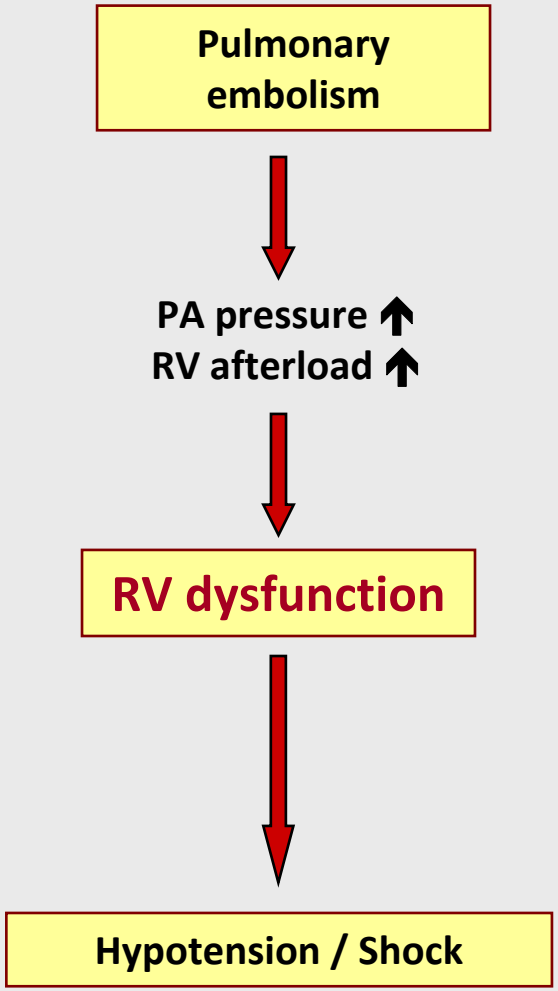
Acute Pulmonary Embolism and Pulmonary Hypertension:

Pathophysiology of RV Dysfunction

Pulmonary Embolism: Heterogeneous Patient Population

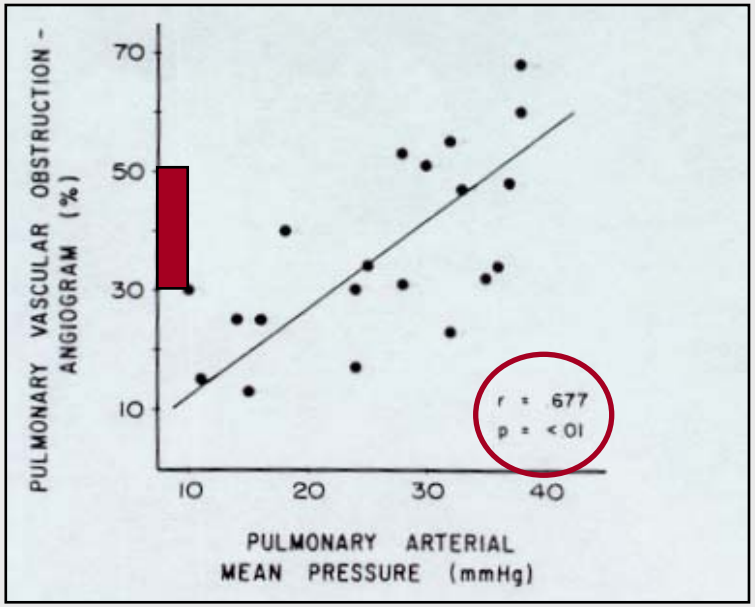
Study	Mortality
British Thoracic Society (GB), *Lancet* 1992	**1%**
PIOPED (US), *N Engl J Med* 1992	**2.5%**
MAPPET Registry (D), *JACC & Circulation* 1997	**20%**
JA Heit (DK), *Arch Intern Med* 1999	**28%**
ICOPER Registry, *Lancet* 1999	**17%**
M Nakamura (JP), *Clin Cardiol* 2001	**14%**

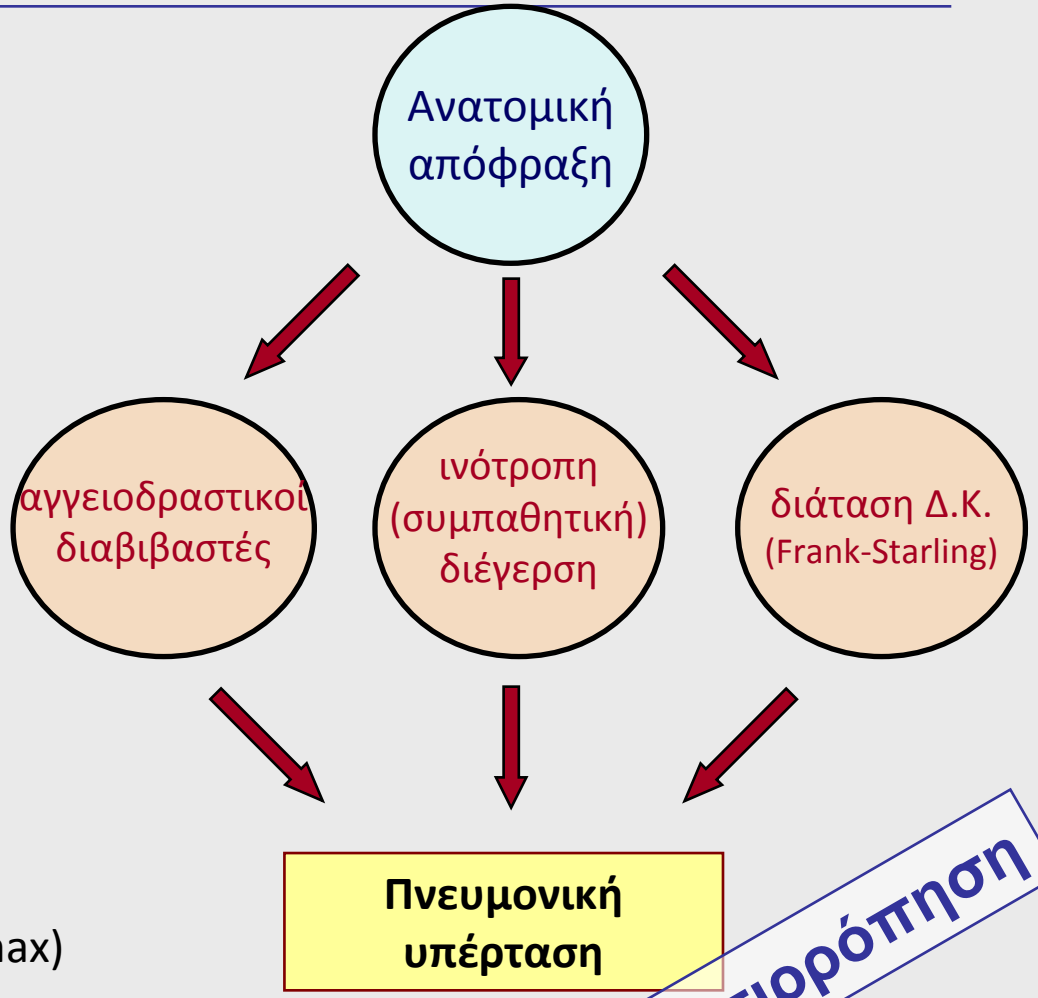
Right Ventricular Dysfunction Is the Crucial Event



The NHLBI Working Group on Right Heart Failure. Circulation 2006;114:1883-1891
HJ Bogaard. Chest 2009;135:794-804

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

Contribution of Pulmonary Vasoconstrictors

- Thromboxane A2
- Serotonin
- [Endothelin]
- [Hypoxic pulmonary vasoconstriction]

→ **Platelet activation !**

T Chung. J Thromb Haemost 2007;5:918-924

Circulation 2002;106:1748-1749

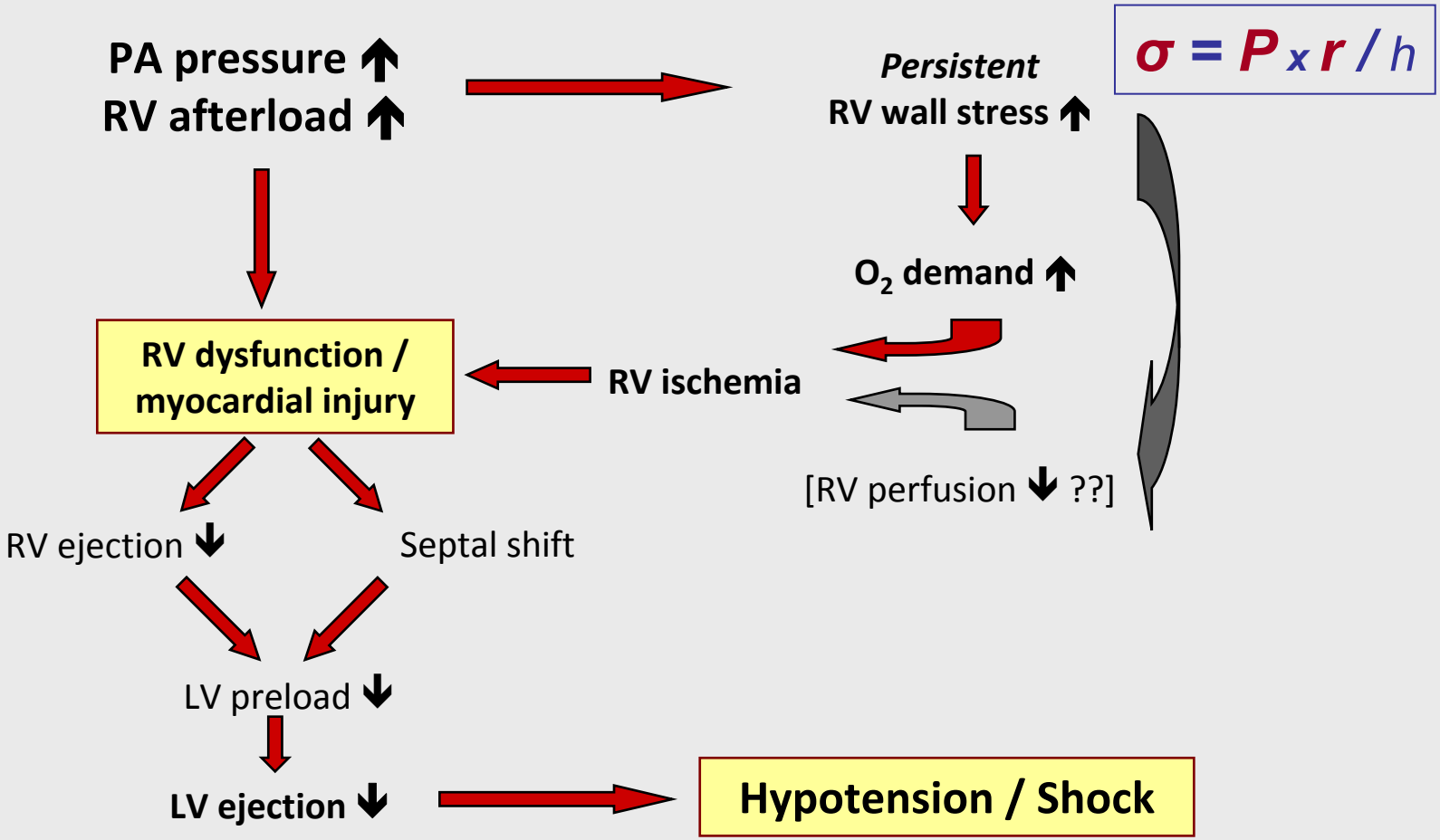
Editorial

Acute Pulmonary Embolism
Don't Ignore the Platelet

Piotr Sobieszczyk, MD; Michael C. Fishbein, MD; Samuel Z. Goldhaber, MD

YM Smulders. Cardiovasc Res 2000;48:23-33

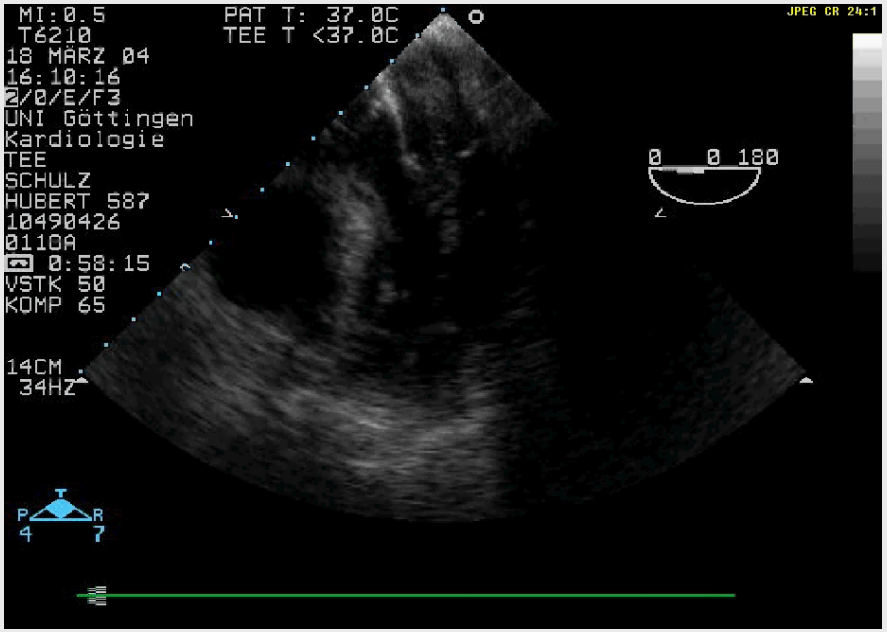
Failed Compensation:
The Vicious Circle of Acute RV Dysfunction

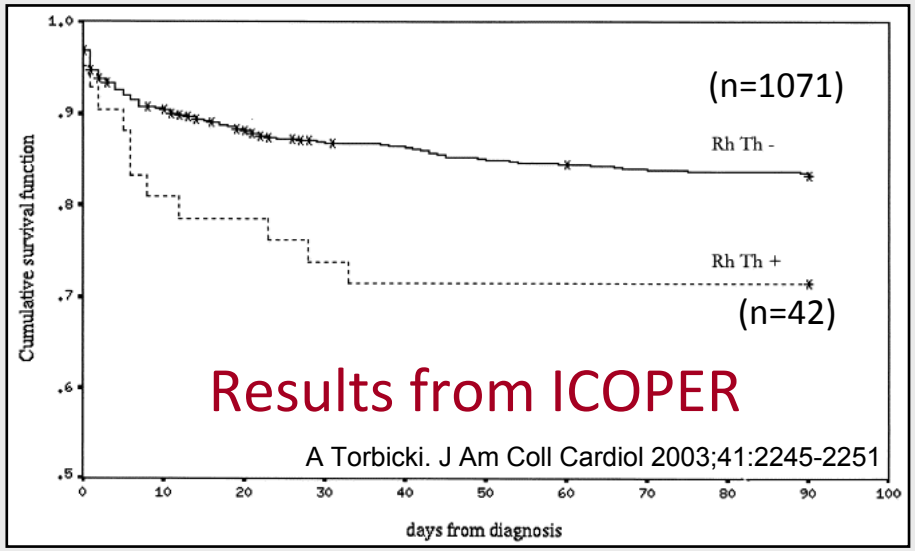


C Greyson. Cardiovasc Res 1997; Am J Physiol Heart Circ Physiol 2000
Schmitto JD. Eur J Cardiothorac Surg 2009

Further Determinants of Adverse Outcome: Massive PE Recurrence

Large thrombus in transit *plus* impending paradoxical embolism

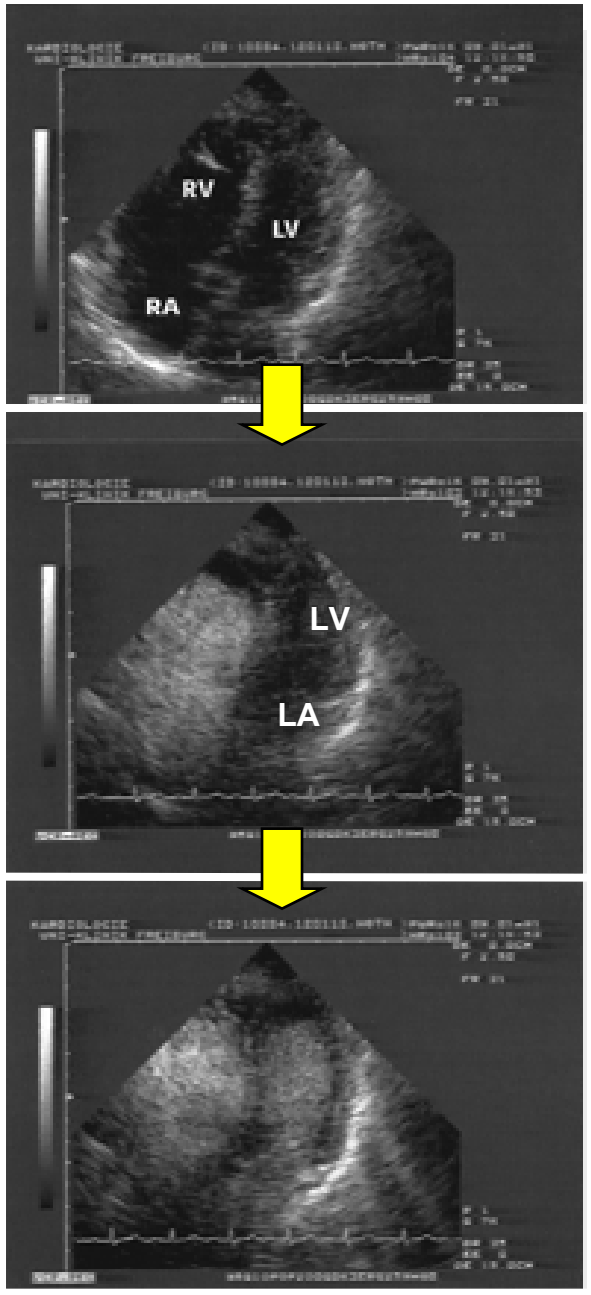




PS Rose. Chest 2002;121:806-814

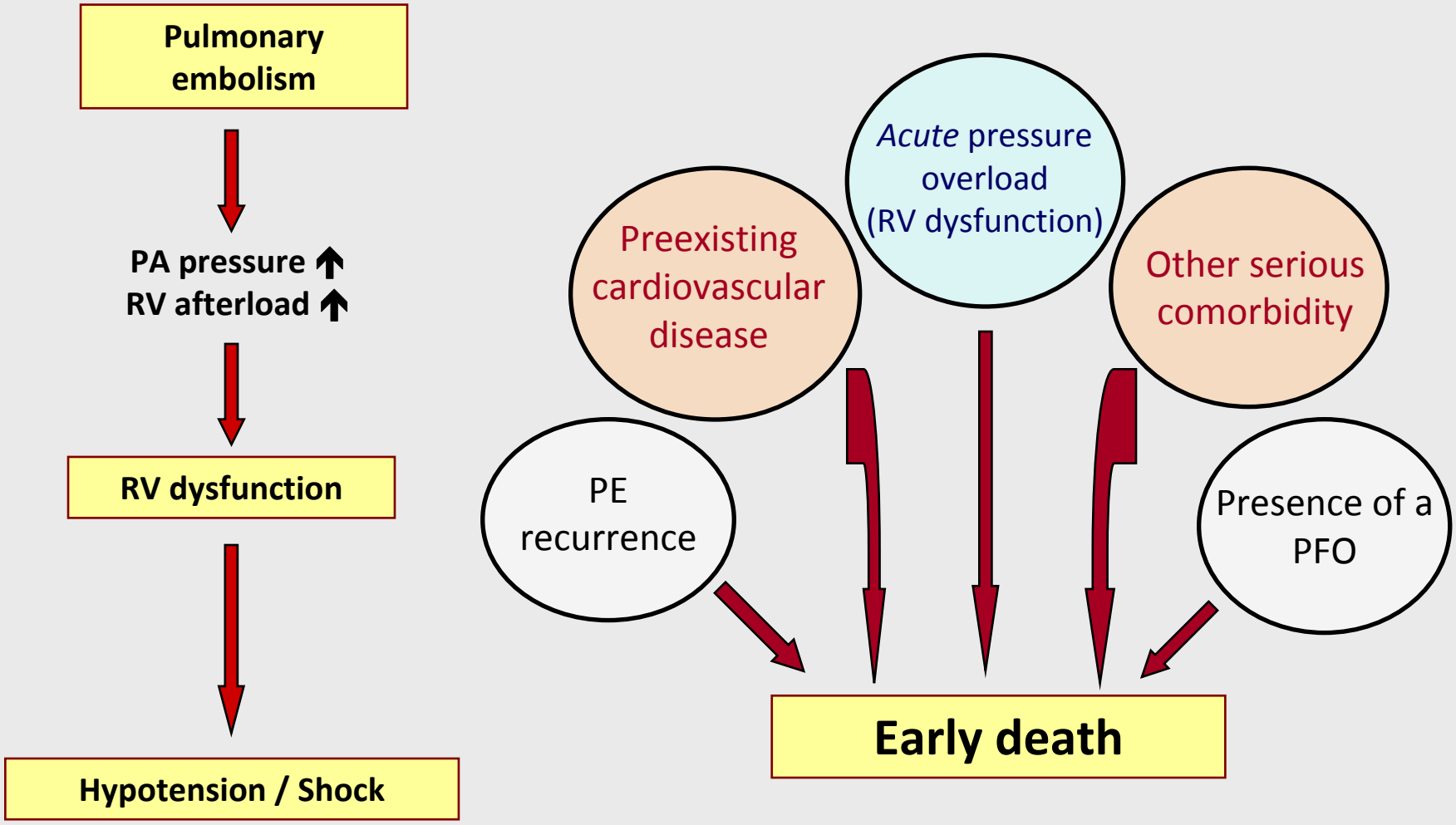
Further Determinants of Outcome: PFO With R→L Shunt

n=139 pts	**Mortality** OR (95%CI)	**Complicated course** OR (95% CI)
Patent foramen ovale	11.4 (2.9-44.5) *P*<0.001	5.2 (2.3-11.7) *P*<0.001
Arterial hypotension / shock	26.3 (5.8-120) *P*<0.001	7.6 (2.1-27.3) *P*<0.002

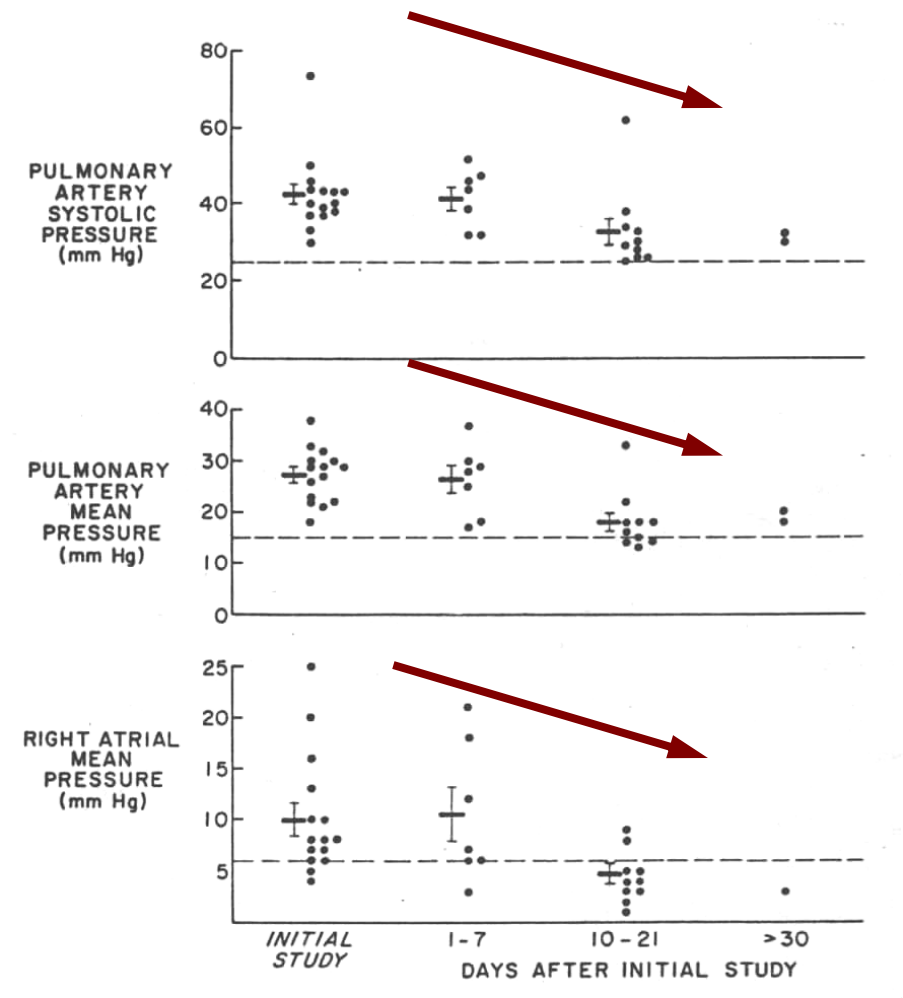


S Konstantinides. Circulation 1998;97:1946-1951

Failed Compensation: Determinants of an Adverse Outcome in Acute PE

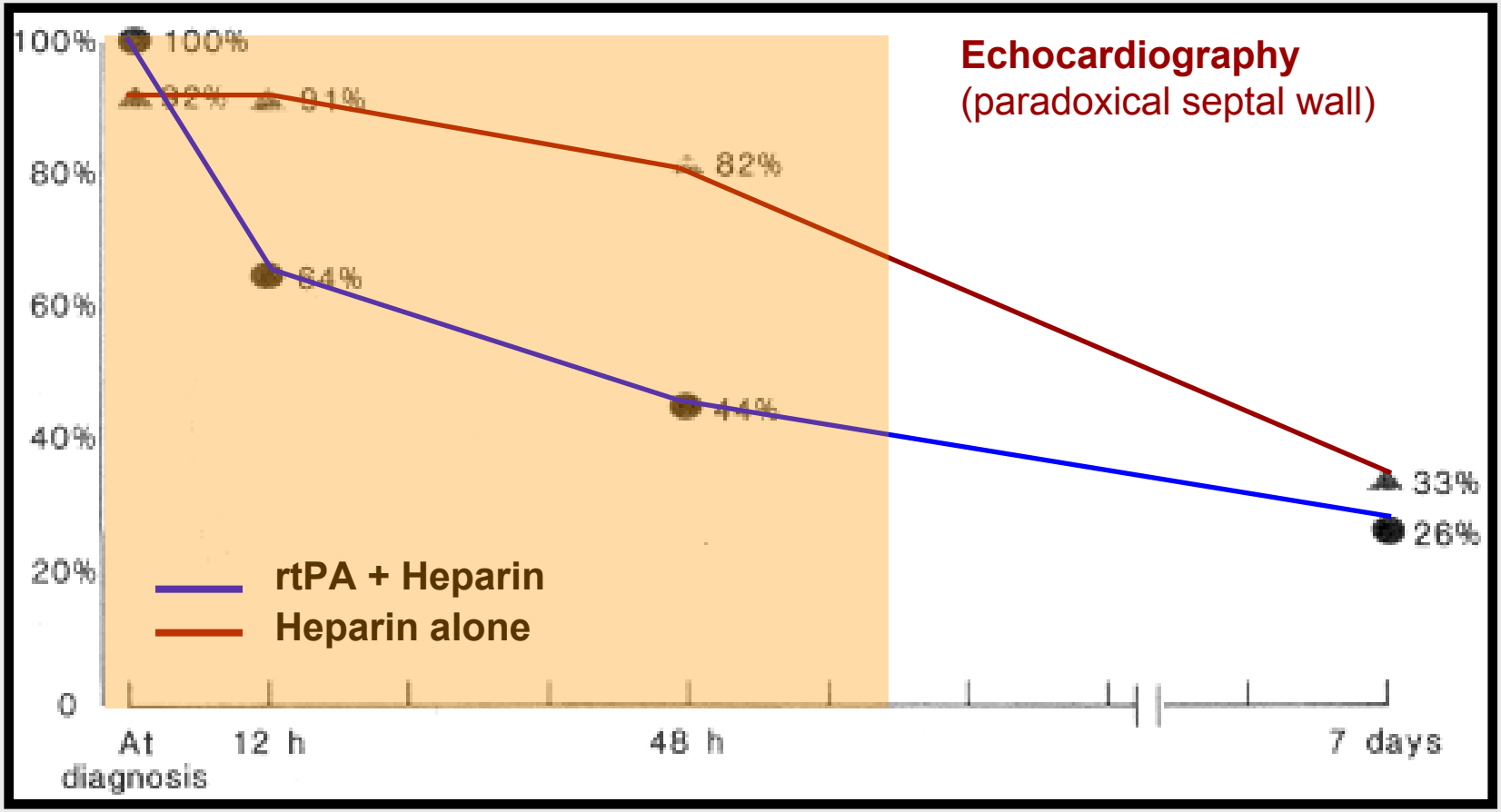


Successful Compensation: Resolution of Pressure Overload in Survivors



JE Dalen. N Engl J Med 1969;280:1194-1199

Successful Compensation: Resolution of RV Dysfunction in Survivors

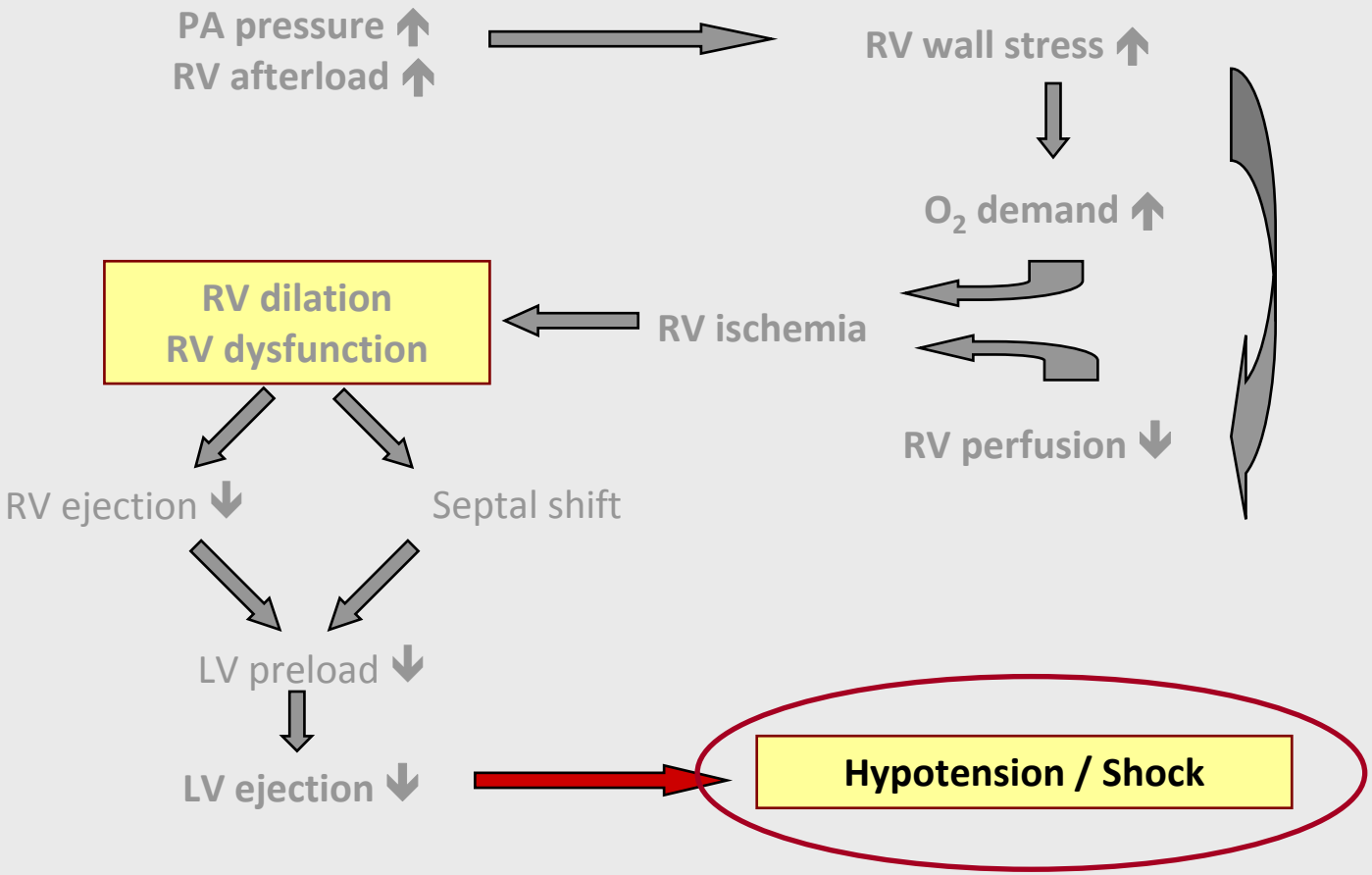


S Konstantinides, Am J Cardiol 1998;82:966-970

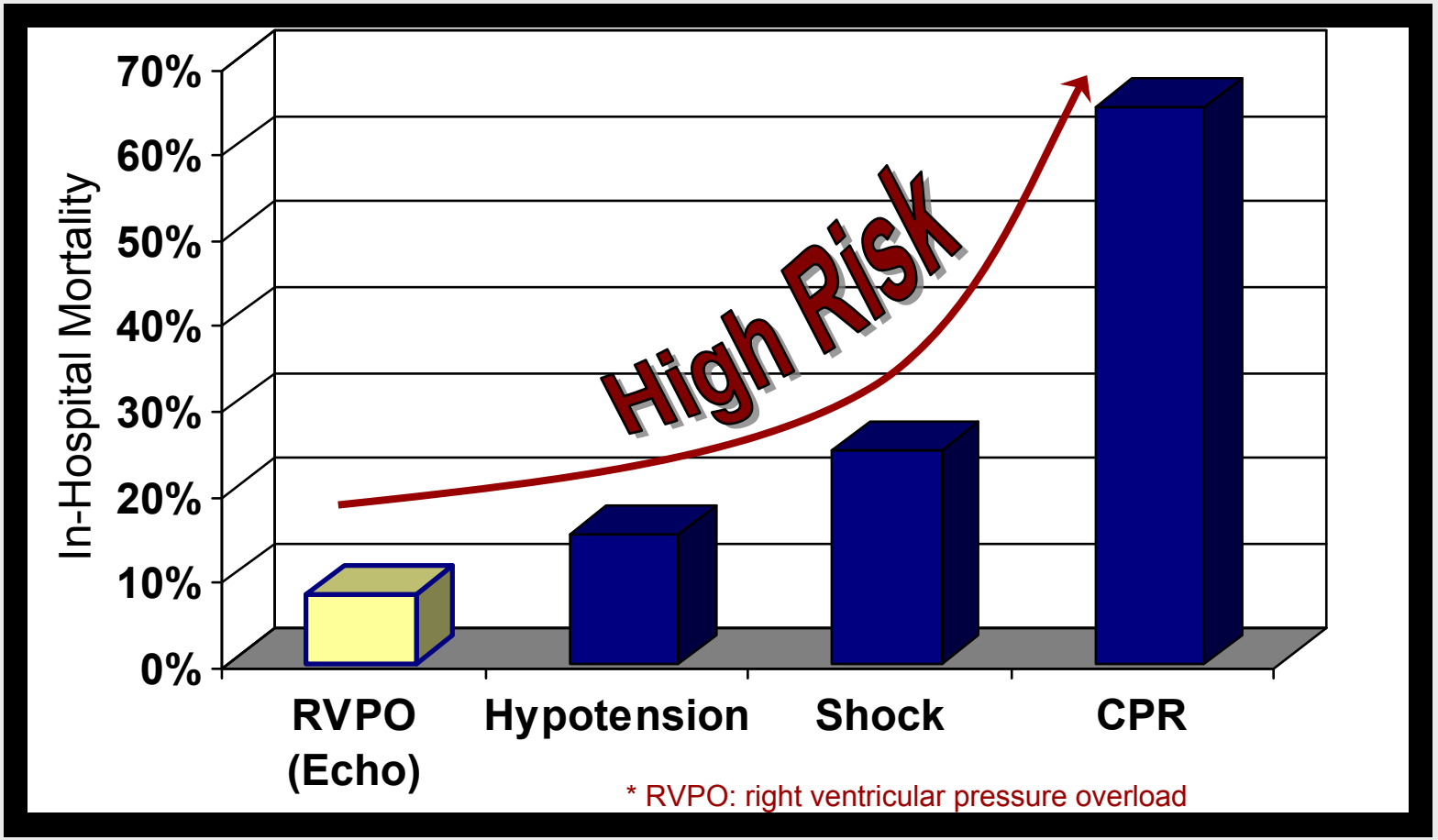
Acute Pulmonary Embolism:

How to Detect RV Dysfunction ?

Clinical Diagnosis of RV Failure

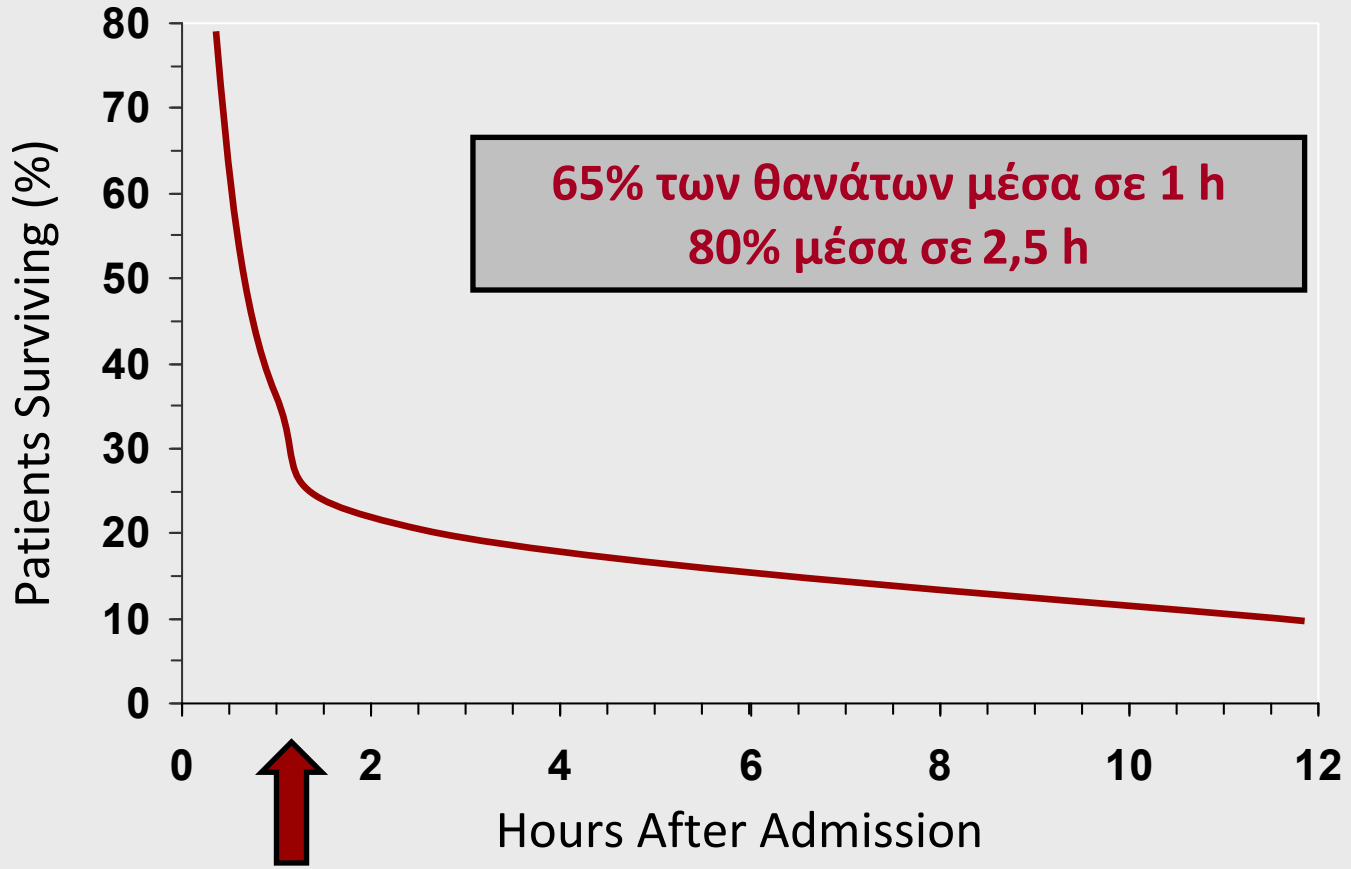


Αιμοδυναμική αστάθεια και έκβαση Π.Ε.



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

Υψηλός κίνδυνος σε αιμοδυναμική αστάθεια



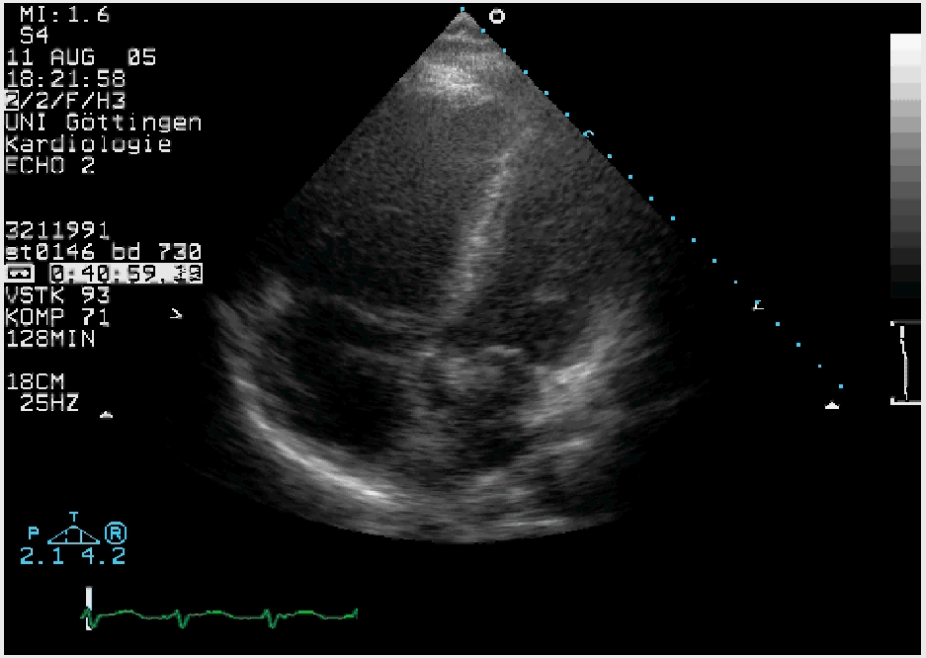
PD Stein. Chest 1995;108:978-981

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)



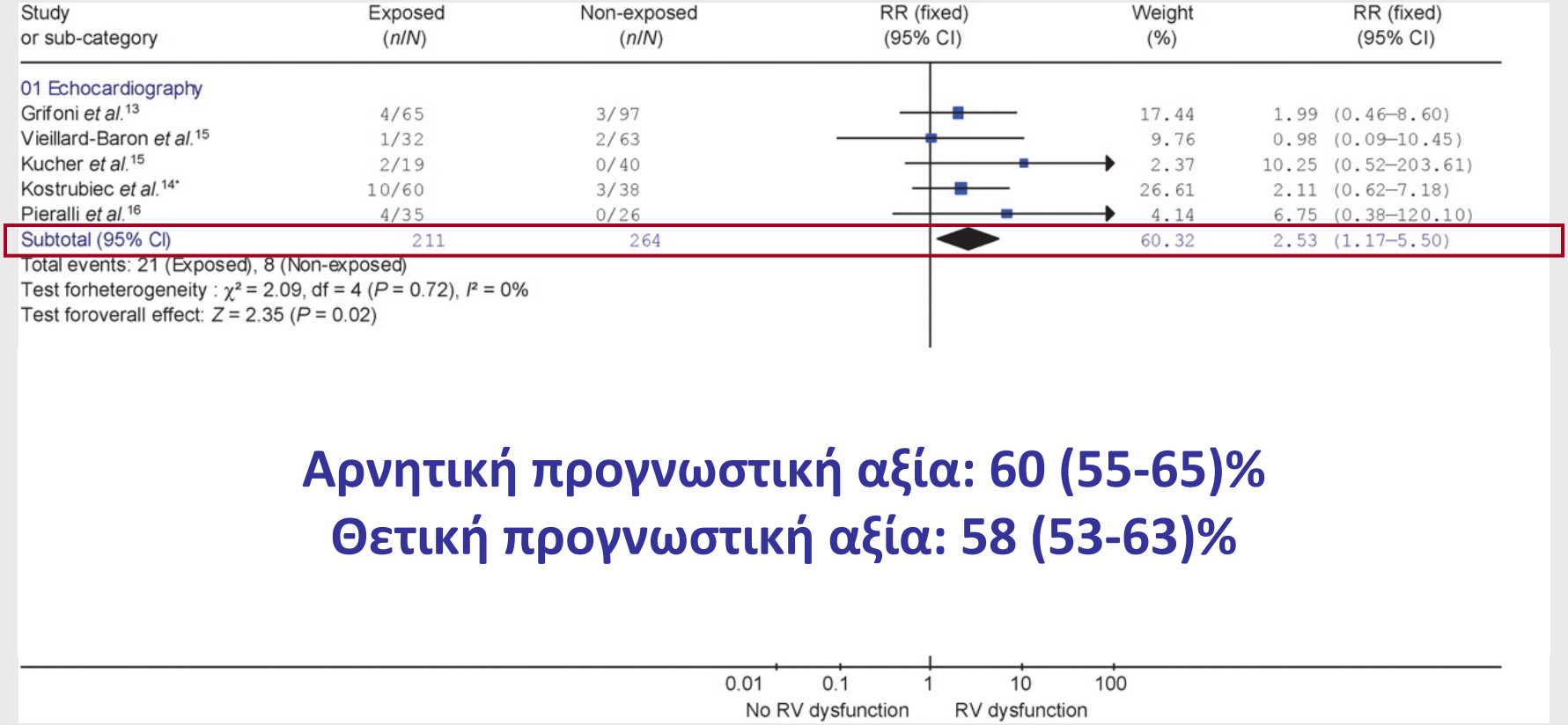
Echo criteria:

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

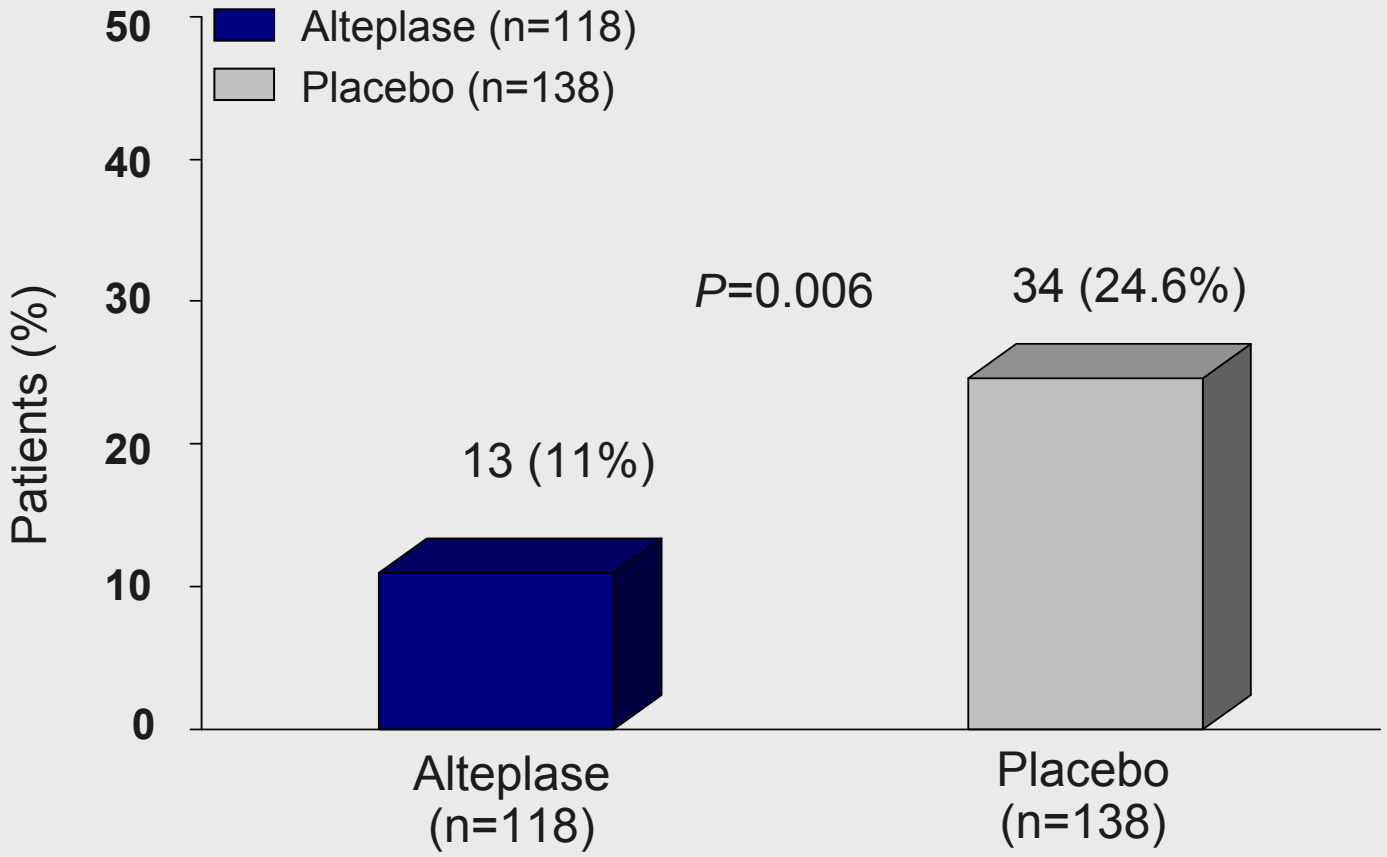


Αρνητική προγνωστική αξία: 60 (55-65)%

Θετική προγνωστική αξία: 58 (53-63)%

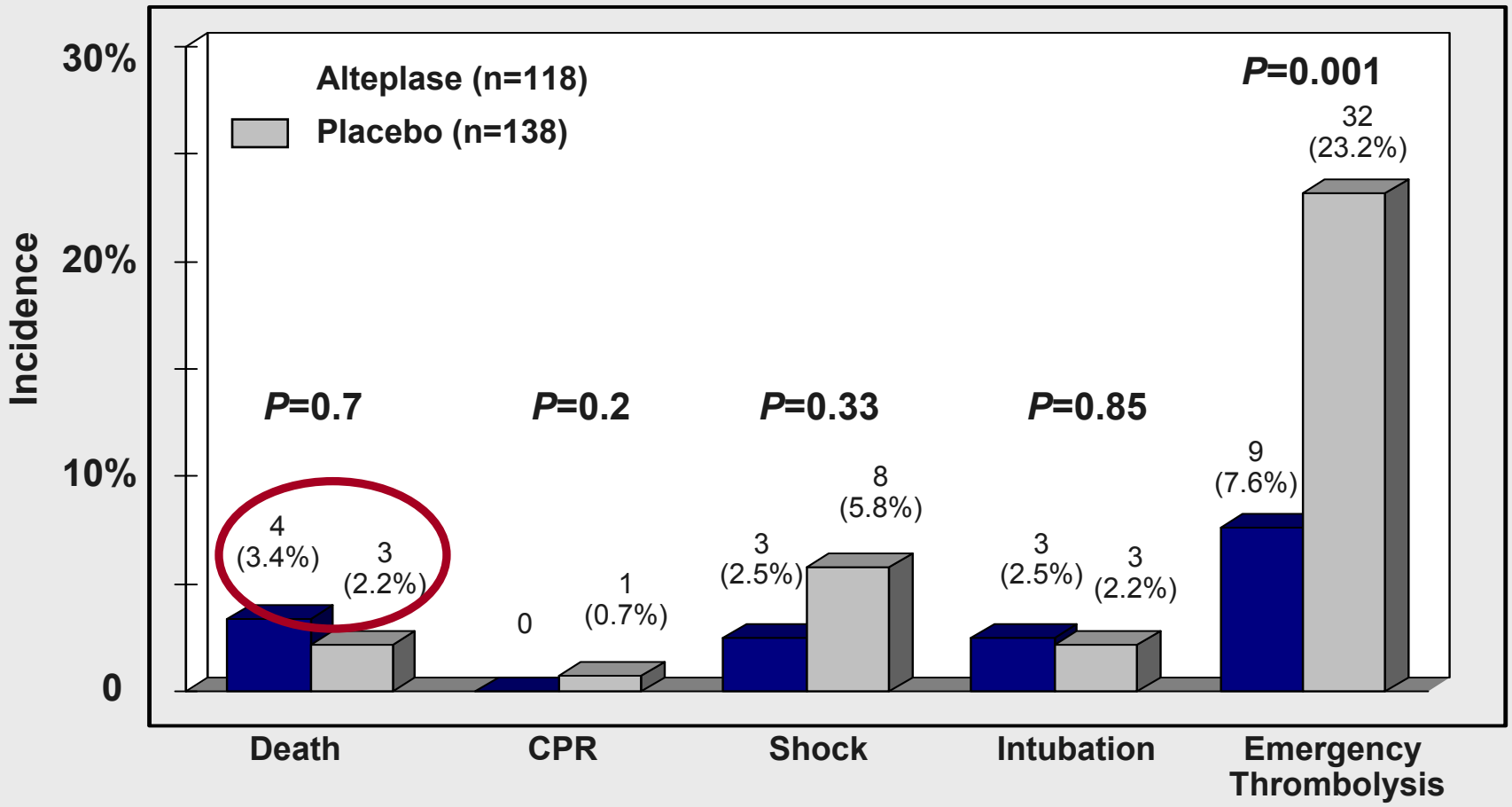
O Sanchez. Eur Heart J 2008;29:1569-1577

RV Dysfunction in Normotensive PE: Therapeutic Implications ?



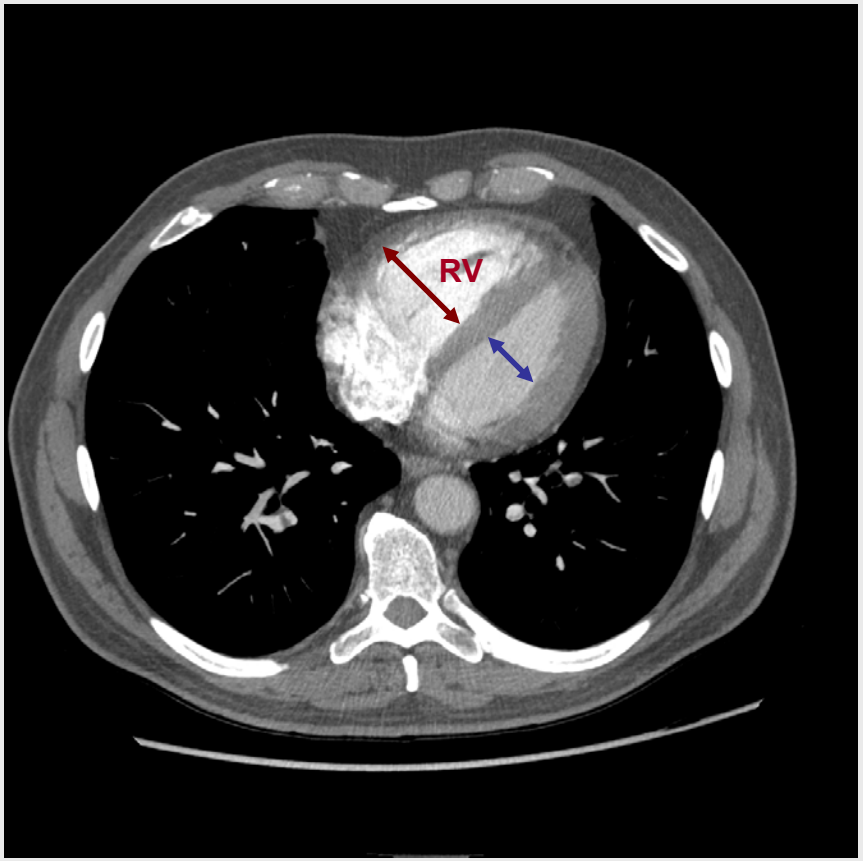
S. Konstantinides. N Engl J Med 2002;347:1143

RV Dysfunction in Normotensive PE: Therapeutic Implications ?



N Engl J Med 2002;347:1143

Ευρήματα από την αξονική τομογραφία

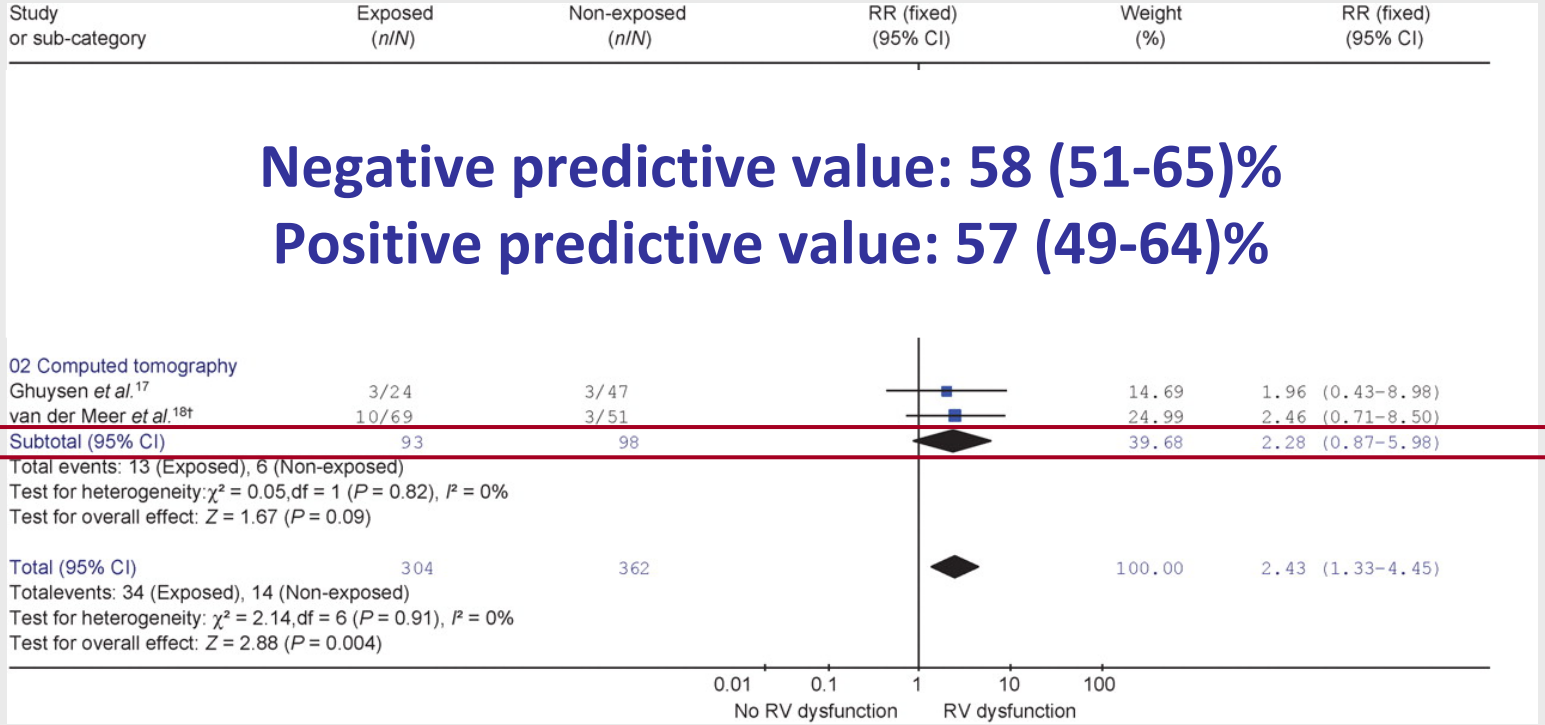


CT Criteria:

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

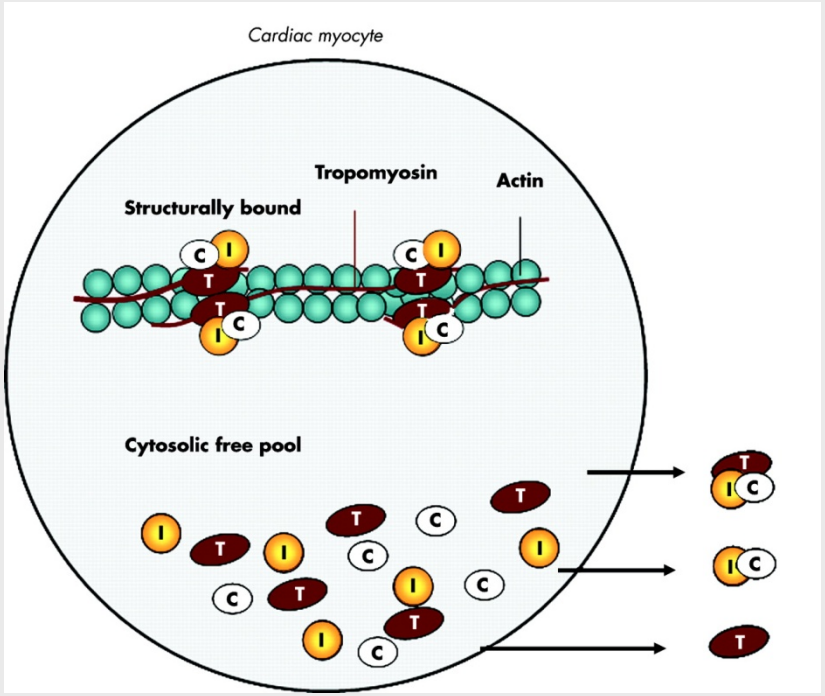


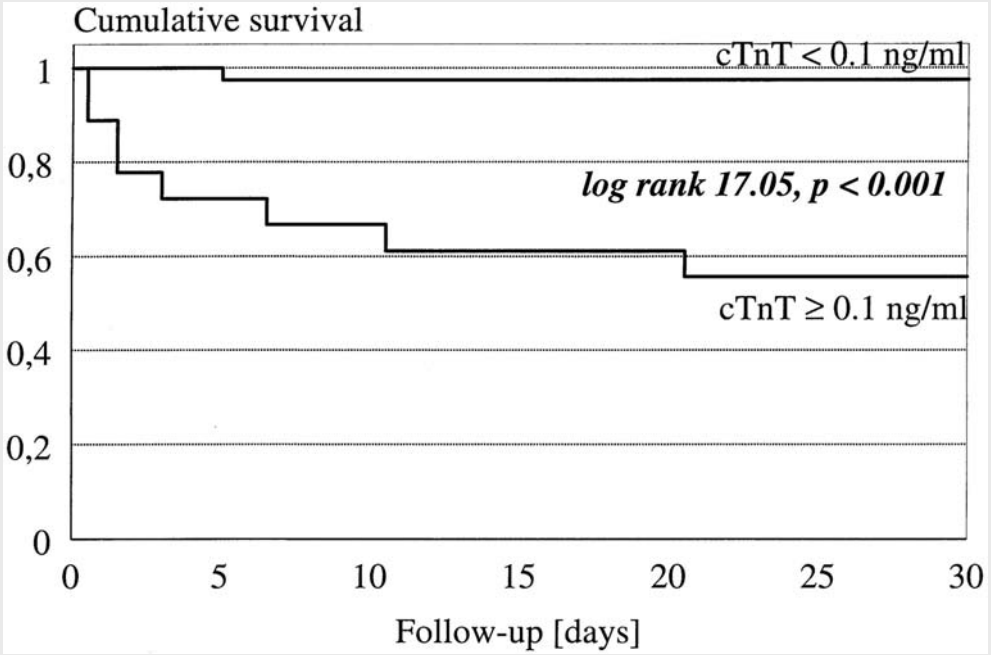
O Sanchez. Eur Heart J 2008;29:1569-1577

Εργαστηριακοί βιοδείκτες: Τροπονίνες

bound and circulating troponin

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



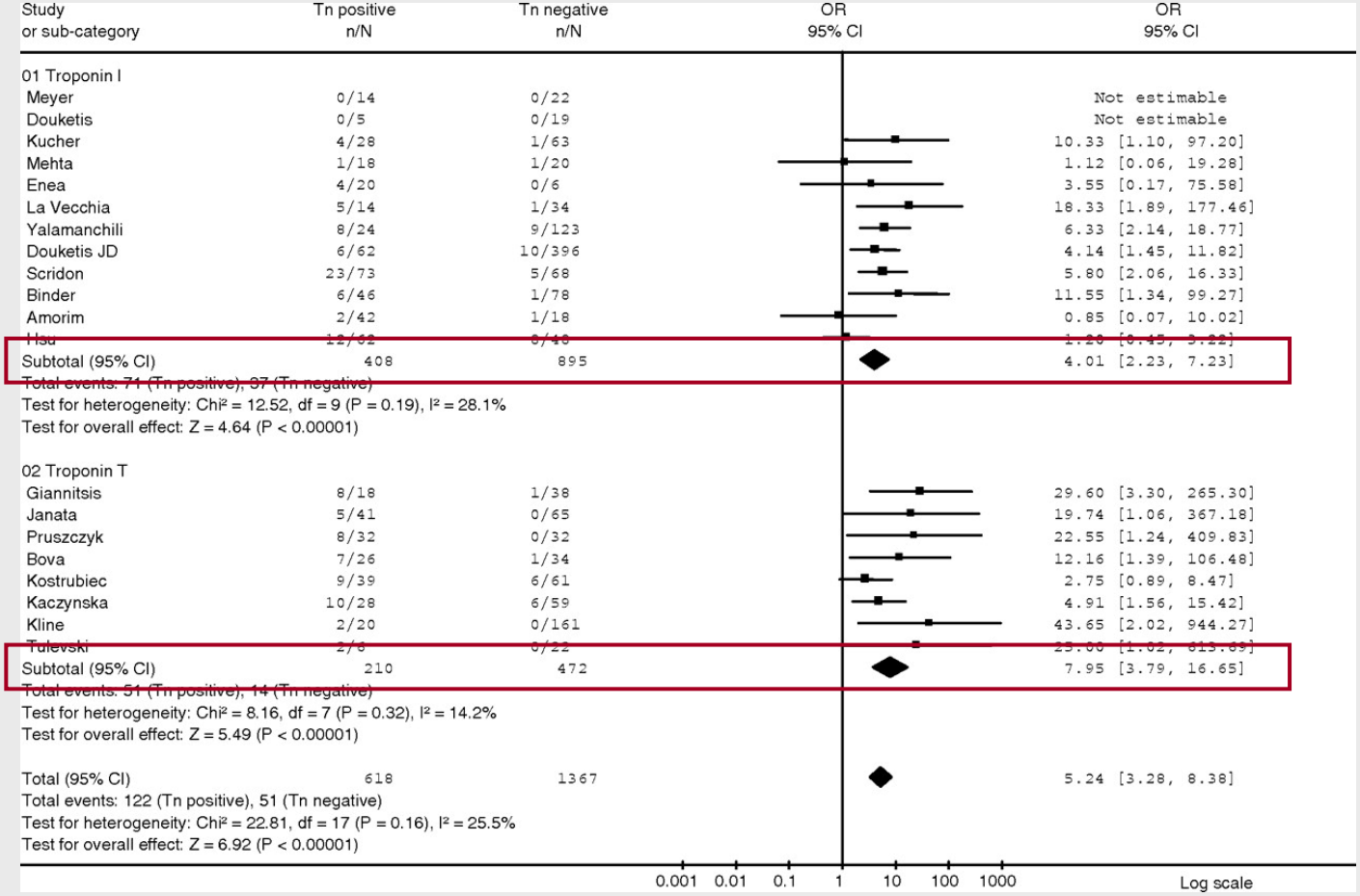


S Korff. Heart 2006;92:987-993

E Giannitsis. Circulation 2000;102:211-217

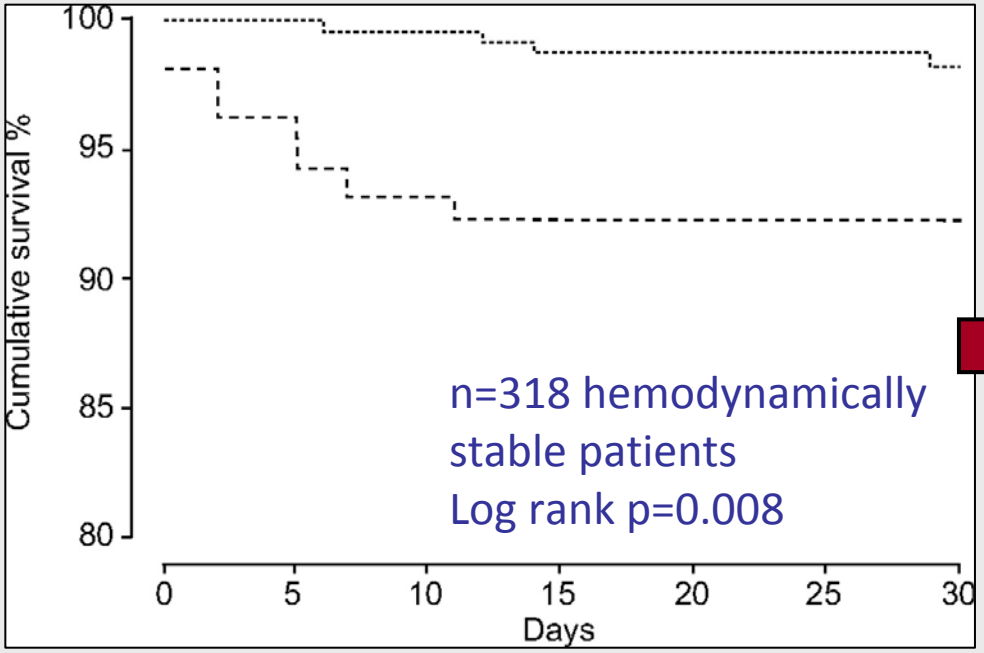
Τροπονίνες και θνητότητα: Μετα-ανάλυση

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:

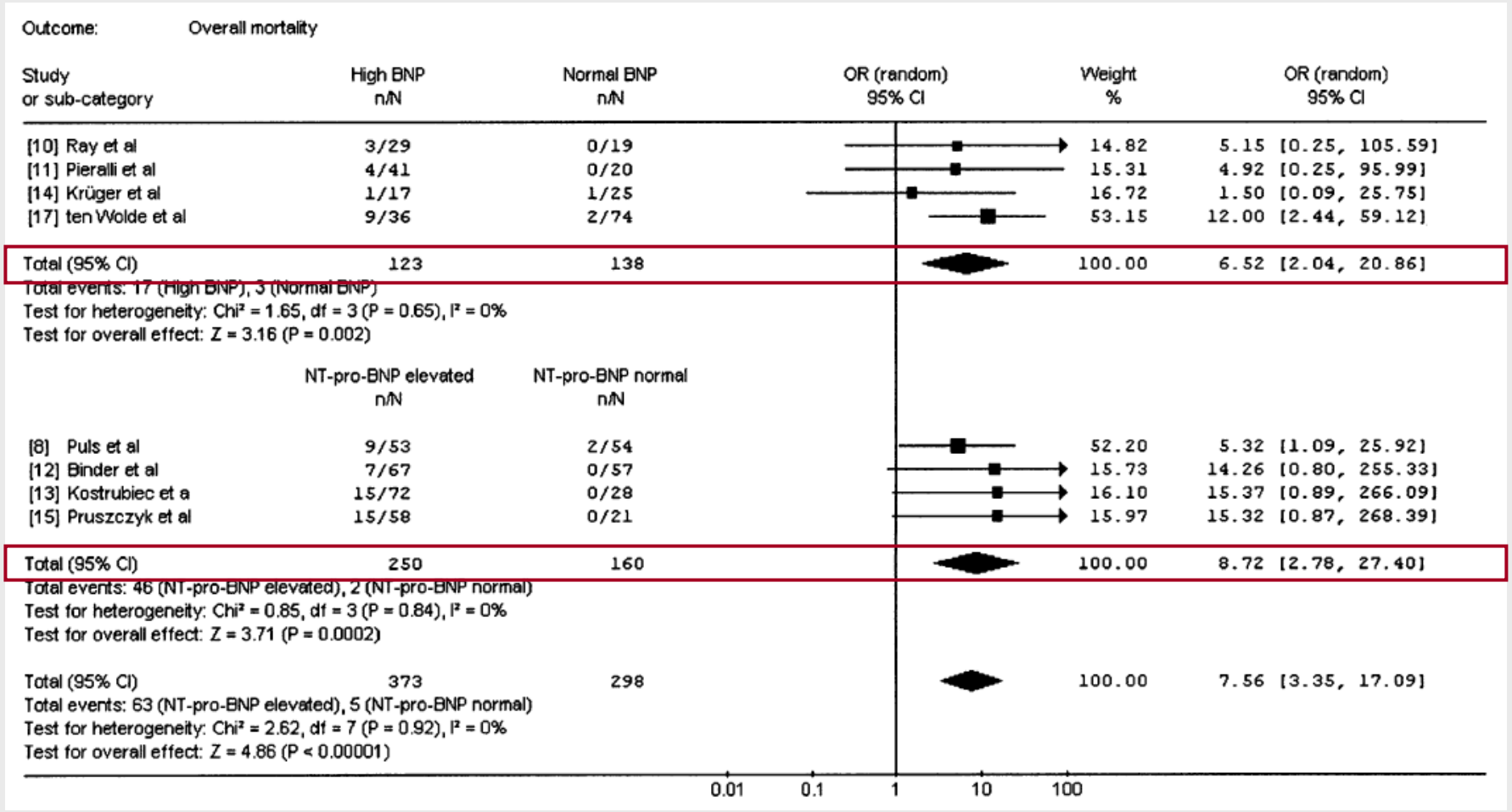
- 9 studies
- 1366 patients with symptomatic PE
- Pts **normotensive** at diagnosis

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

RV Dysfunction 2010: Pitfalls and Limitations

- Echo and CT criteria poorly standardized; reporting of confounding factors heterogeneous;
- Biomarker studies mostly included patients with hypotension and shock; prognostic effect not adjusted for confounding variables;
- Cutoff values, particularly for BNP/NT-proBNP, controversial;
- Troponins or natriuretic peptides alone have a low positive predictive value in PE.

Ισχύει για **όλους** τους σημερινούς δείκτες

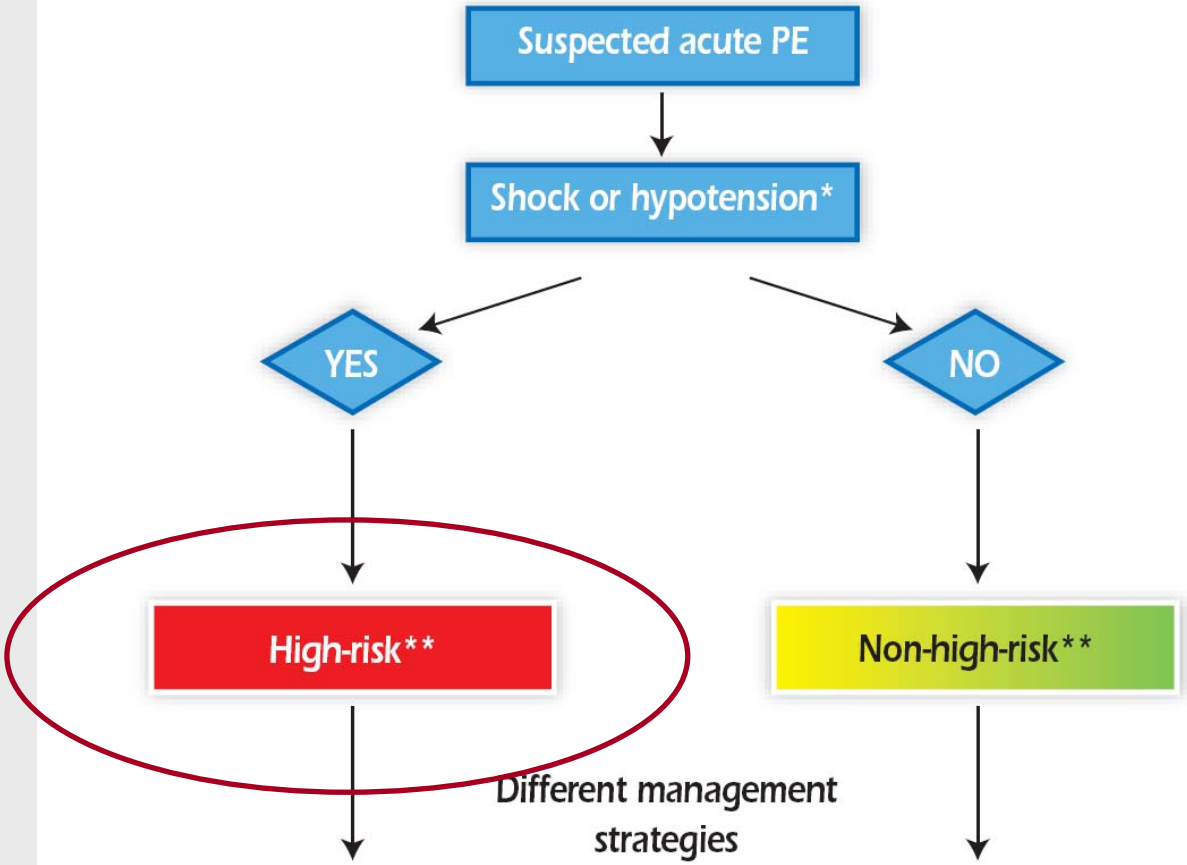
Conclusions: High concer ients with pulmonary embolism at higher hospital course and death from those with low BNP level Increased BNP or NT–pro-BNP concentrations alone, however, do not justify more invasive treatment regimens.

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

Acute Pulmonary Embolism and Pulmonary Hypertension:

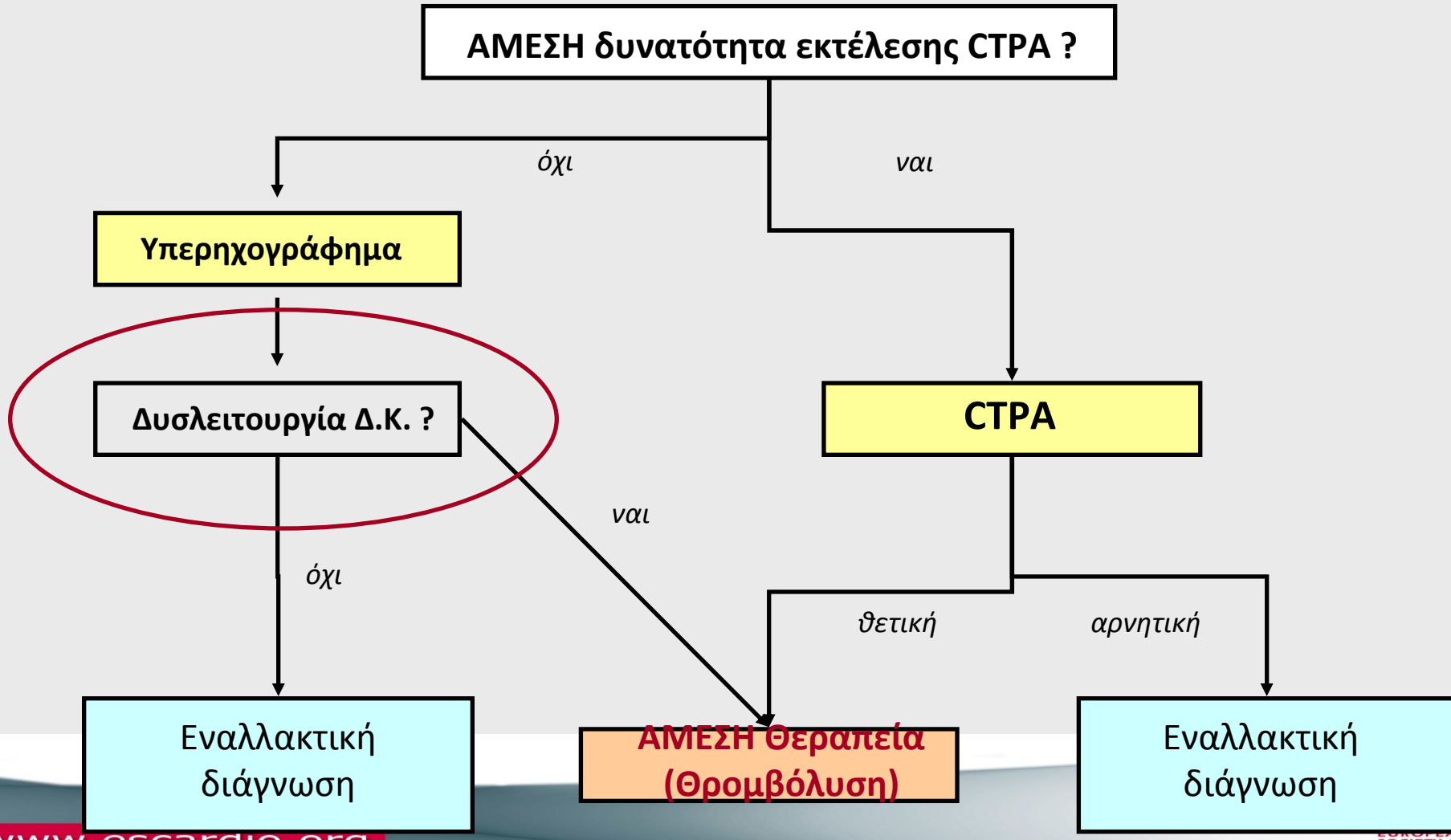
RV Dysfunction in Current Guidelines

Υποτασικοί ασθενείς «υψηλού» κινδύνου



High-risk PE

Αλγόριθμος διάγνωσης Π.Ε. υψηλού κινδύνου



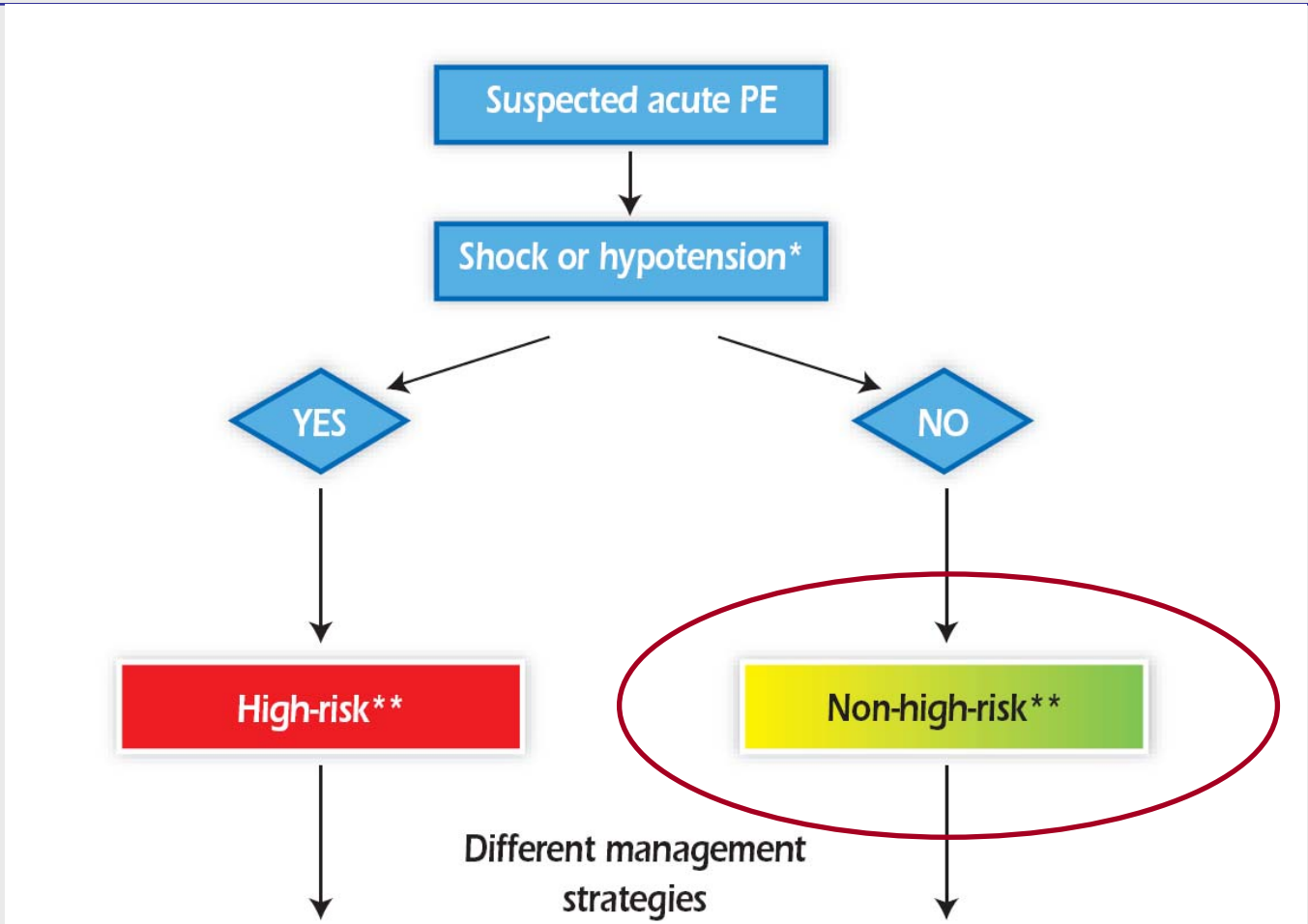
High-risk PE

Emergency Treatment of RV Dysfunction

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

Afterload reduction (+inotropic support, moderate fluid replacement)

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**

Πνευμονική αρτηριακή υπέρταση
Ελεγχος αποτελεσματικότητας θεραπείας

	At baseline (prior to therapy)	**Στόχοι: «σταθερή και ικανοποιητική» κατάσταση**	nical g
Clinical assessment WHO-FC ECG	✓	Κλινική απουσία ανεπάρκειας Δ.Κ., FC I-II	
6MWT[b]	✓	>400 m	
Cardio-pulmonary exercise testing[b]	✓	Peak VO2 >15 ml/kg/min	
BNP/NT-proBNP	✓	(Σχεδόν) φυσιολογικά επίπεδα	
Echocardiography	✓	ΟΧΙ περικαρδ. υγρό, TAPSE>2 cm	
RHC	✓[c]	RAP <8 cm, CI >2,5 ml/min/m^2	

[a]Intervals should to be adjusted to individual patients needs.
[b]Usually one of the two exercise tests is performed.
[c]Is recommended (*Table 11A*).
[d]Should be performed (*Table 11A*).
BNP = brain natriuretic peptide; ECG= electrocardiogram; RHC = right heart catheterization; 6MWT = 6-minute walking test; WHO-FC =WHO functional class.

ESC/ERS Guidelines. Eur Heart Journal 2009;30:2493

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]

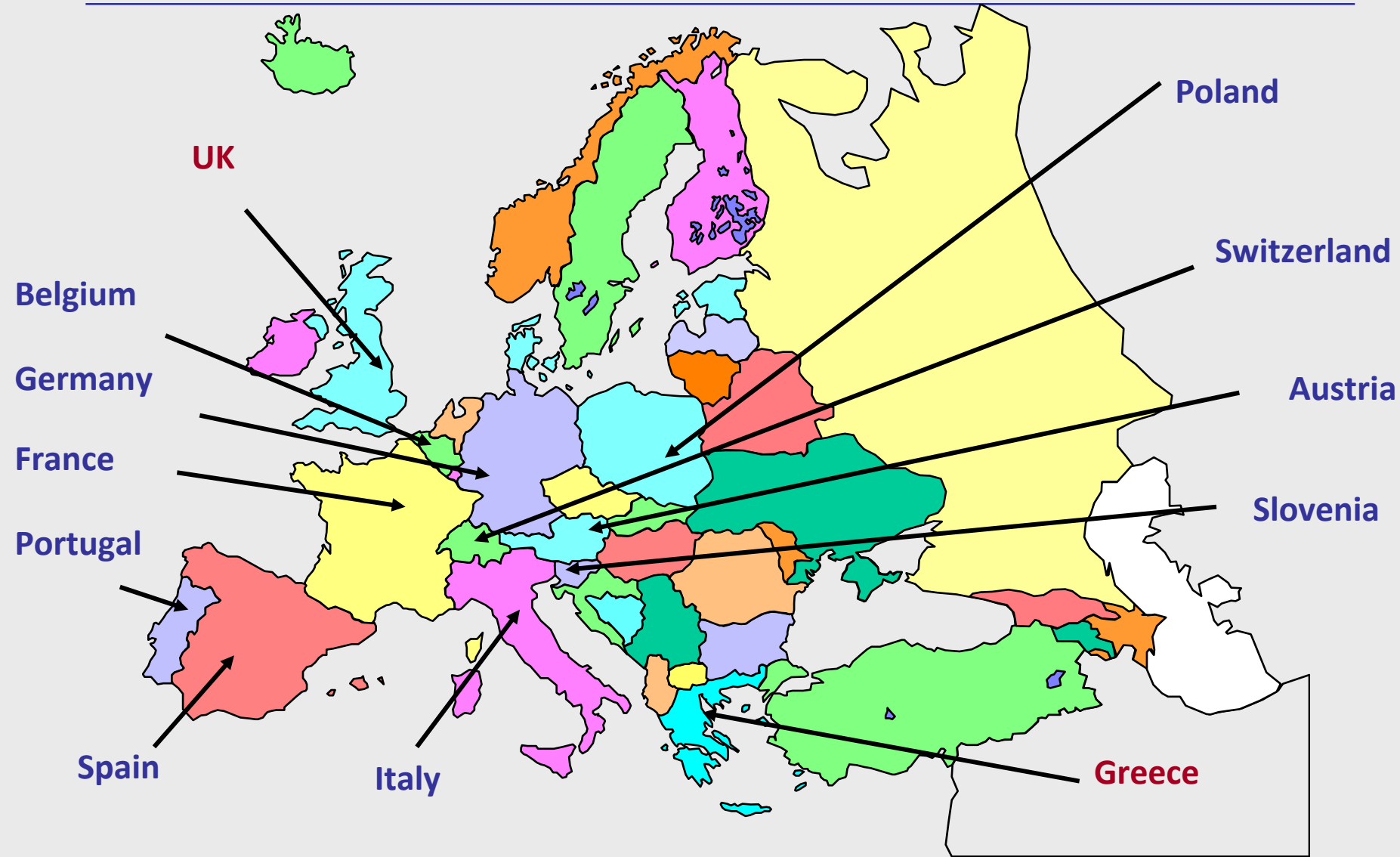
1) Συνδυασμοί βιοδεικτών

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**

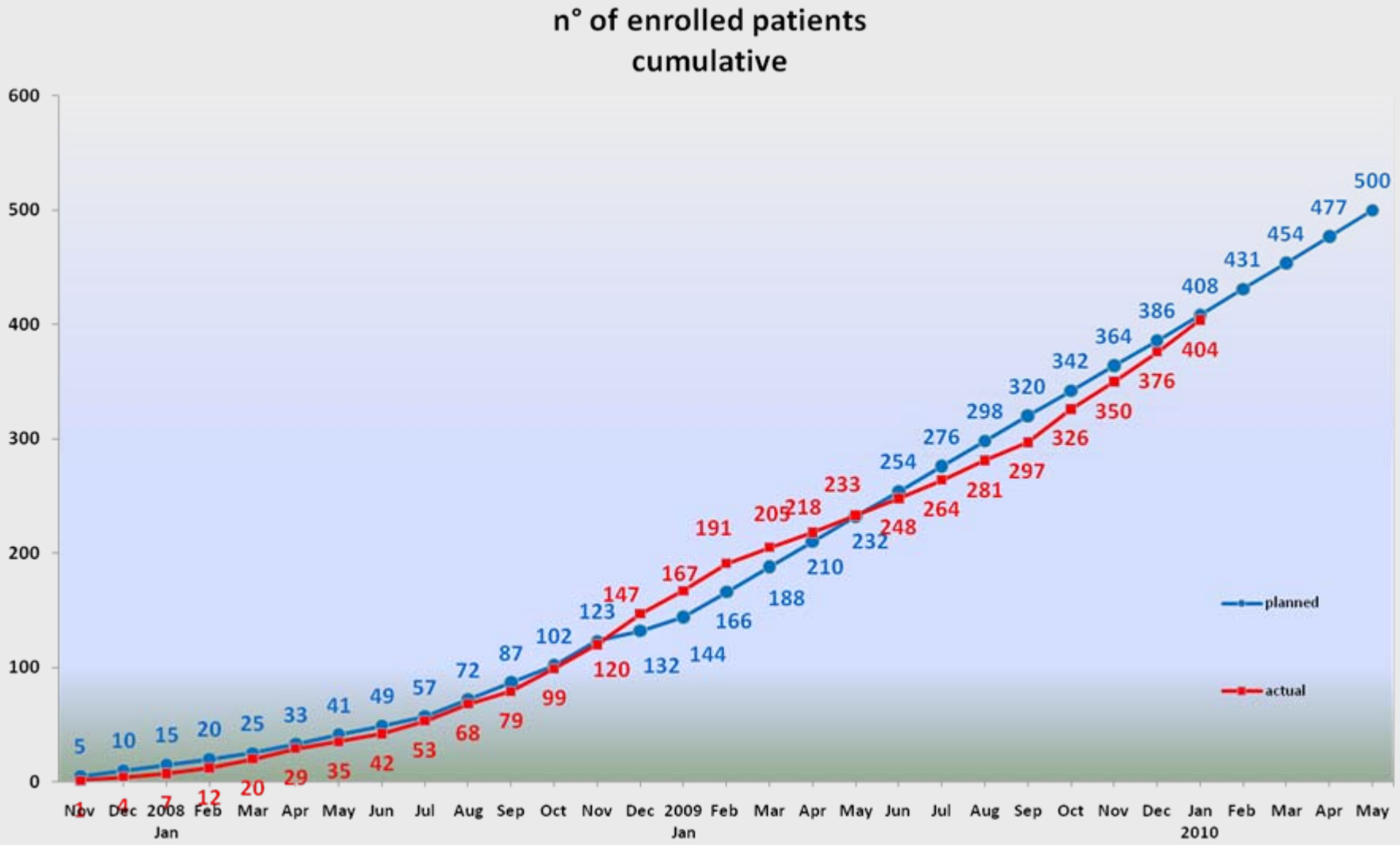
~ 15% όλων των ασθενών με Π.Ε.

L Binder. Circulation 2005;112:1573-1579

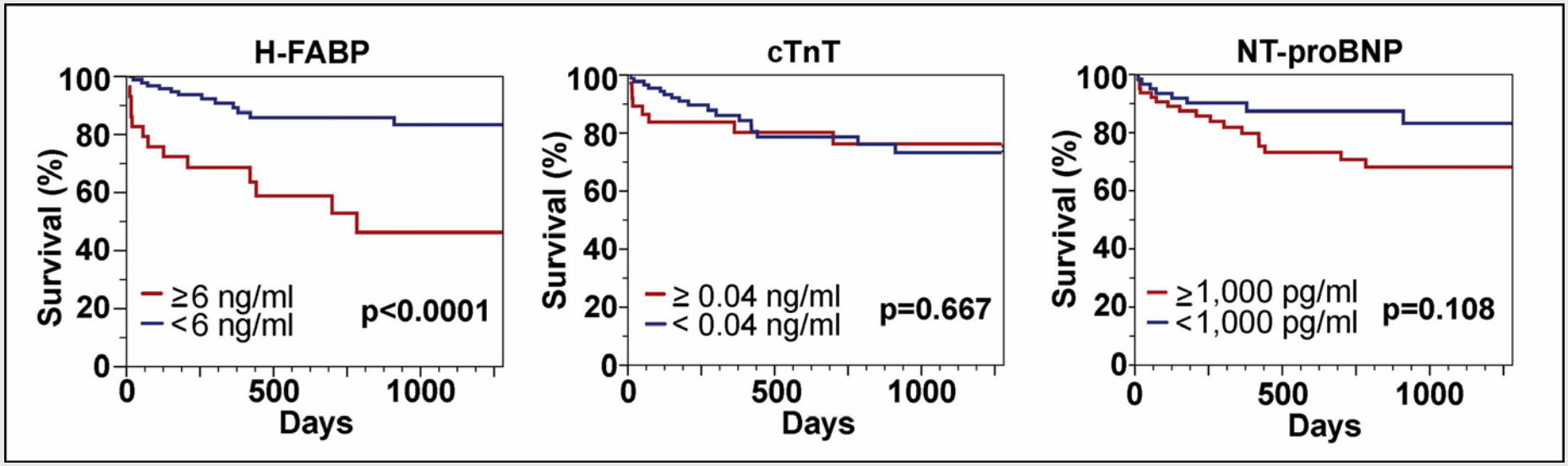
RV Dysfunction (Echo) + Injury (Troponin):
⇒ an International Randomized Thrombolysis Trial



PEITHO Status (as of January 31, 2010)



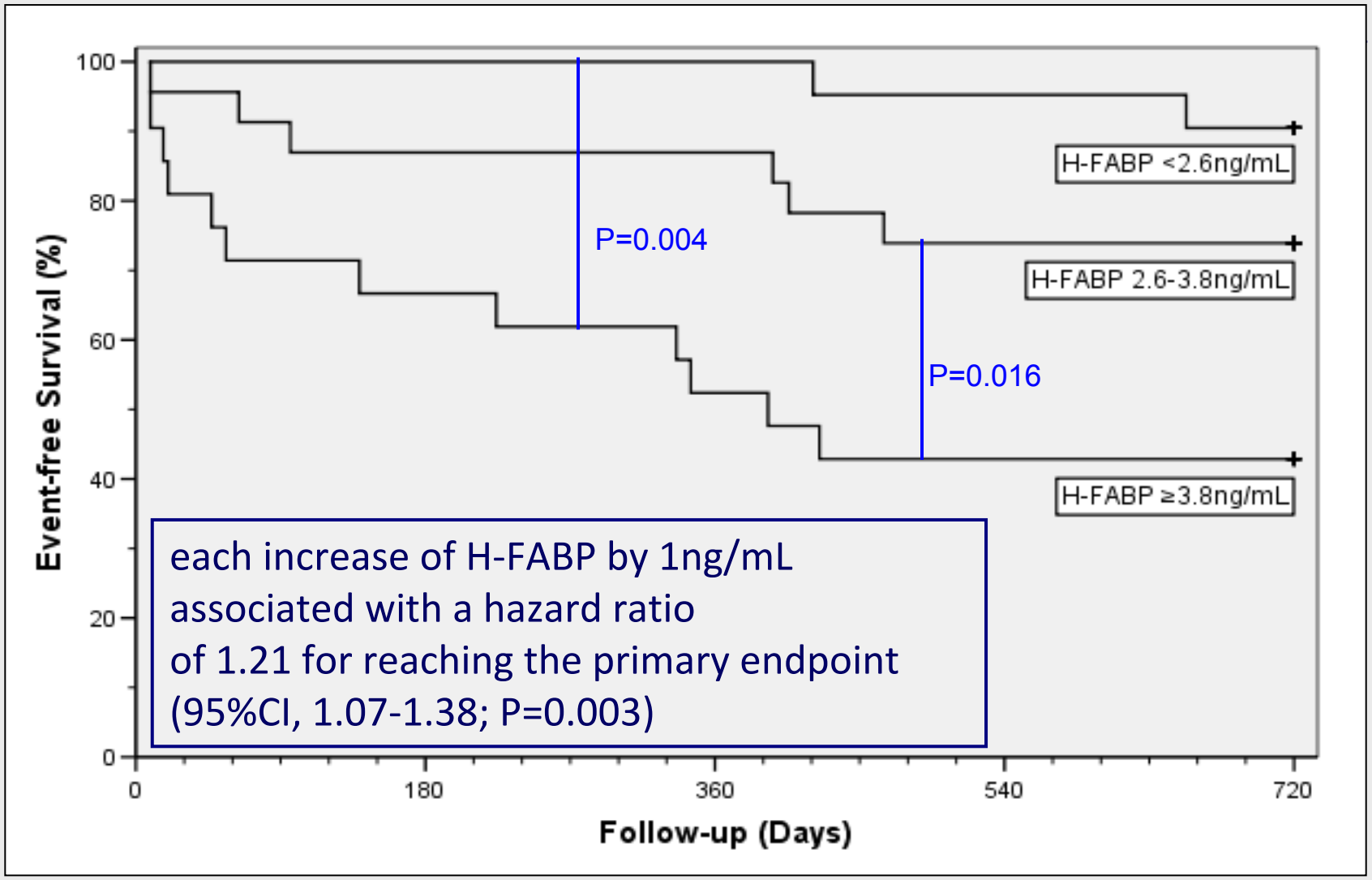
2) Νέοι βιοδείκτες υψηλού κινδύνου: H-FABP



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

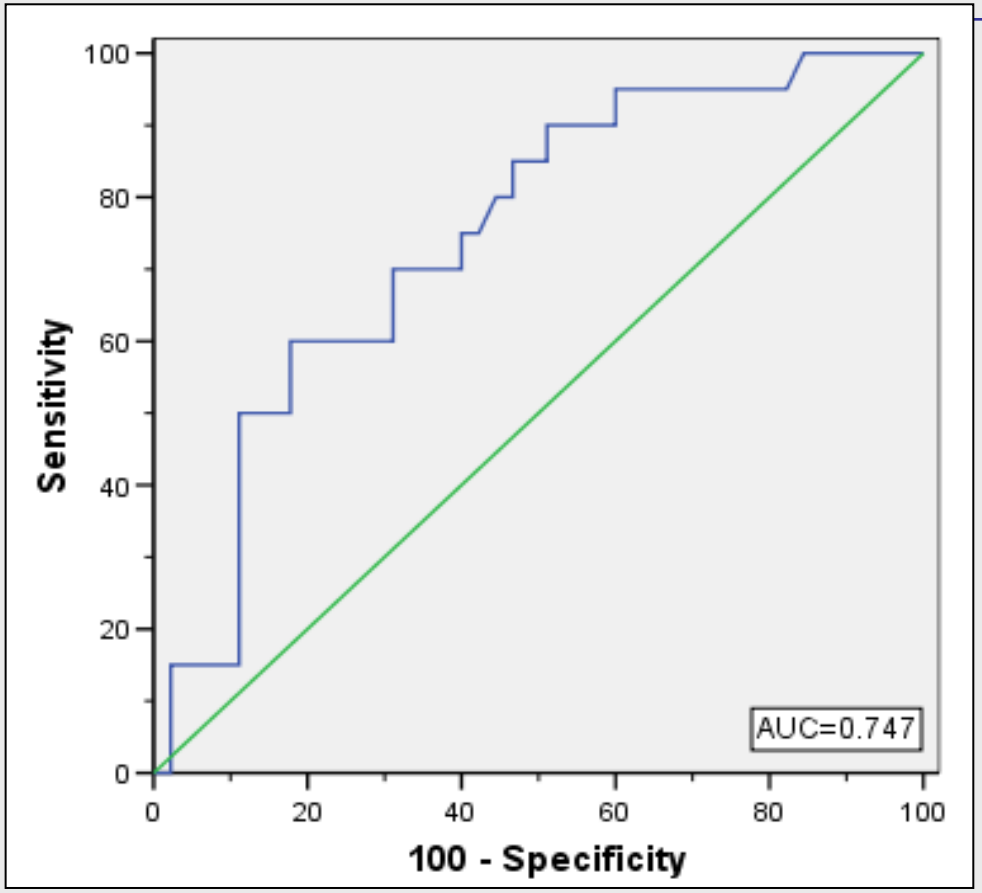
M Puls. Eur Heart J 2007;28:224-229
C Dellas. J Am Coll Cardiol 2010; in press

CTEPH: Survival According to H-FABP Tertiles



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

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.

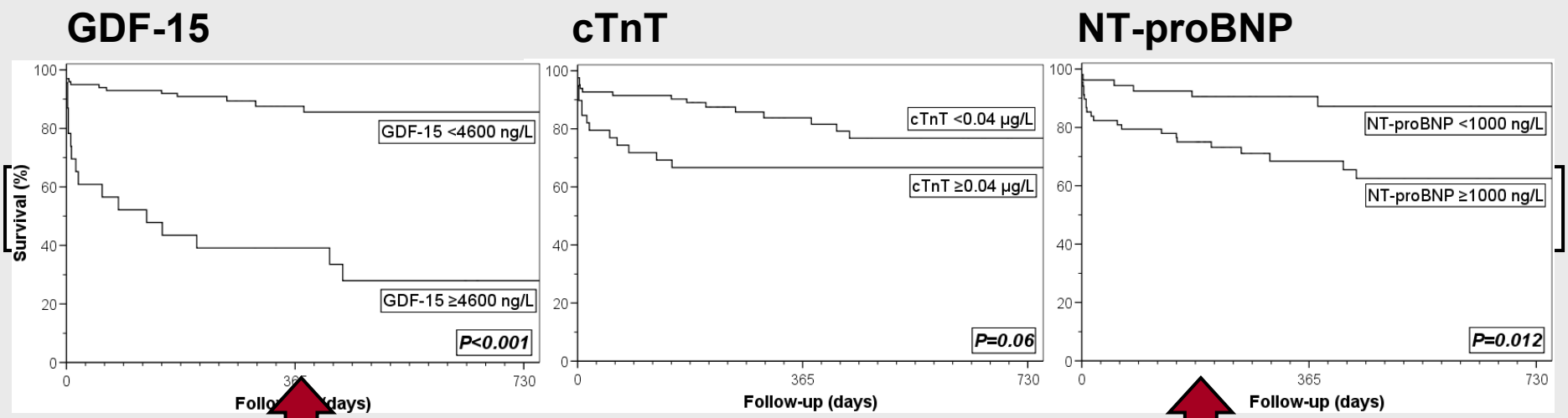
Prognostic Value of cardiac troponin T:

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

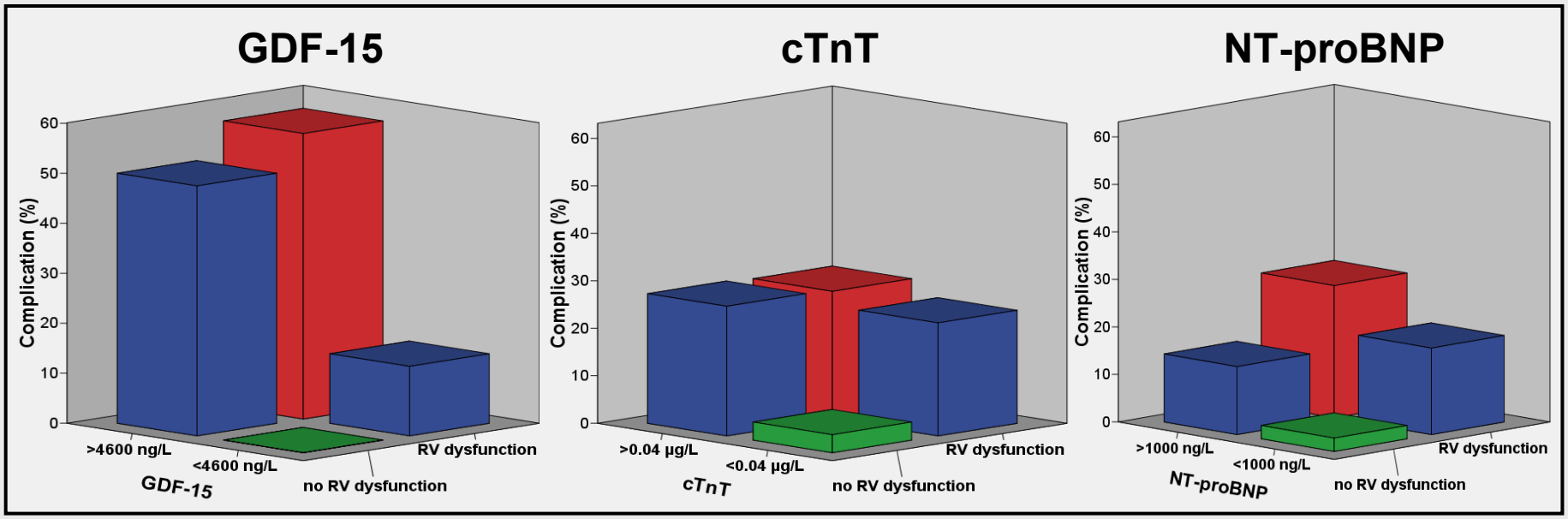


Πιθανά πλεονεκτήματα του ολοκληρωμένου δείκτη έναντι της τροπονίνης

Ανώτερος του NT-proBNP

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

Echo Imaging Combined With GDF-15



	OR	95% CI	*P* Value
RV dysfunction	4.1	1.3 – 12.7	0.014
RV dysfunction *and* GDF-15 ≥4600 ng/L	15.9	4.0 – 64.0	<0.001
RV dysfunction *and* cTnT ≥0.04 µg/L	3.0	1.0 – 8.8	0.052
RV dysfunction *and* NT-proBNP ≥1000 ng/L	3.7	1.3 – 10.9	0.015

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Σύνοψη και Συμπεράσματα

- Η δεξιά κοιλιακή δυσλειτουργία αποτελεί καθοριστικό προγνωστικό παράγοντα στην πνευμονική εμβολή (και στη χρόνια πνευμονική υπέρταση).
- Κανένας απο τους σήμερα διαθέσιμους απεικονιστικούς (υπέρηχο, CT) ή βιοχημικούς (τροπονίνες, νατριουρητικά πεπτίδια) βιοδείκτες δεν είναι *από μόνος του* αρκετός για να καθορίσει τη θεραπεία.
- Νέες εξεταζόμενες στρατηγικές περιλαμβάνουν το συνδυασμό υπαρχόντων βιοδεικτών, νέους βιοδείκτες μυοκαρδιακής νέκρωσης και ολοκληρωμένους βιοδείκτες μυοκαρδιακής νέκρωσης και δυσλειτουργίας.

Global Biomarkers: Growth-Differentiation Factor-15

- Member of the TGF-β cytokine family

  (Bootcov, PNAS 1997)
- Not expressed in the myocardium under normal conditions
- Cardiac expression occurs in response to pressure overload and/or ischemia

  (Kempf, Circ Res. 2006; Xu, Circ Res. 2006)
- Elevation of GDF-15 levels shown to predict high risk in patients with NSTEMI or heart failure

  (Wollert, Circulation 2007; Wollert, Circulation 2007; Kempf, JACC 2007)