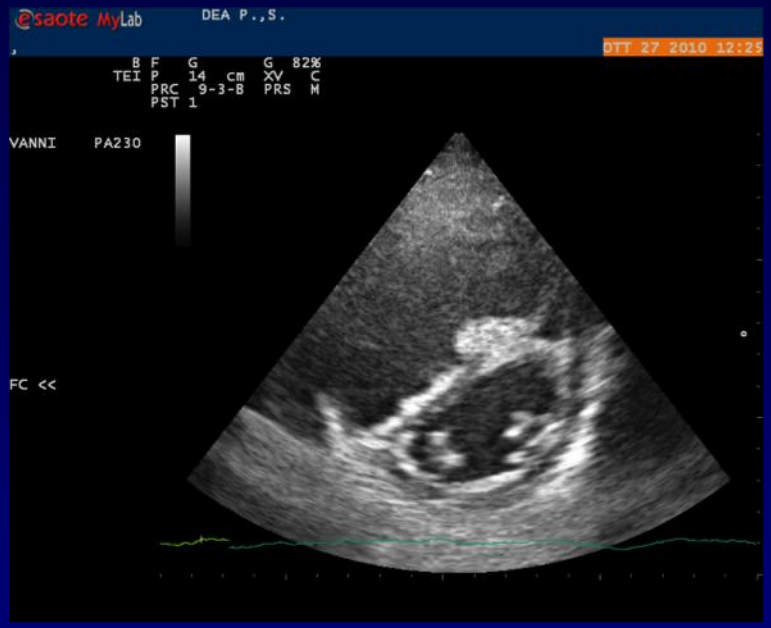
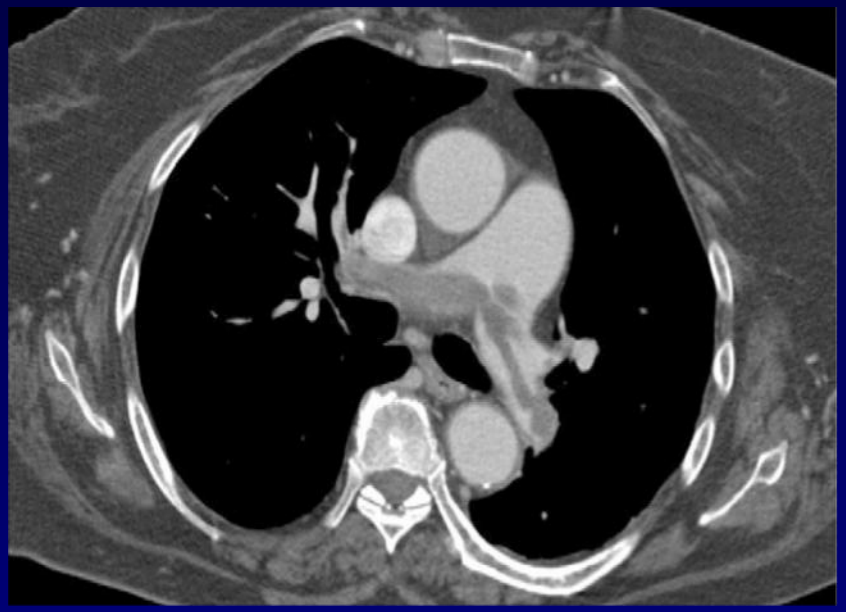
L’embolia polmonare ad alto rischio, dalla diagnosi alla terapia riperfusiva.





Centro di riferimento regione toscana per la diagnosi e la terapia della tromboembolia polmonare

Dip Emergenza Urgenza- Careggi - Firenze

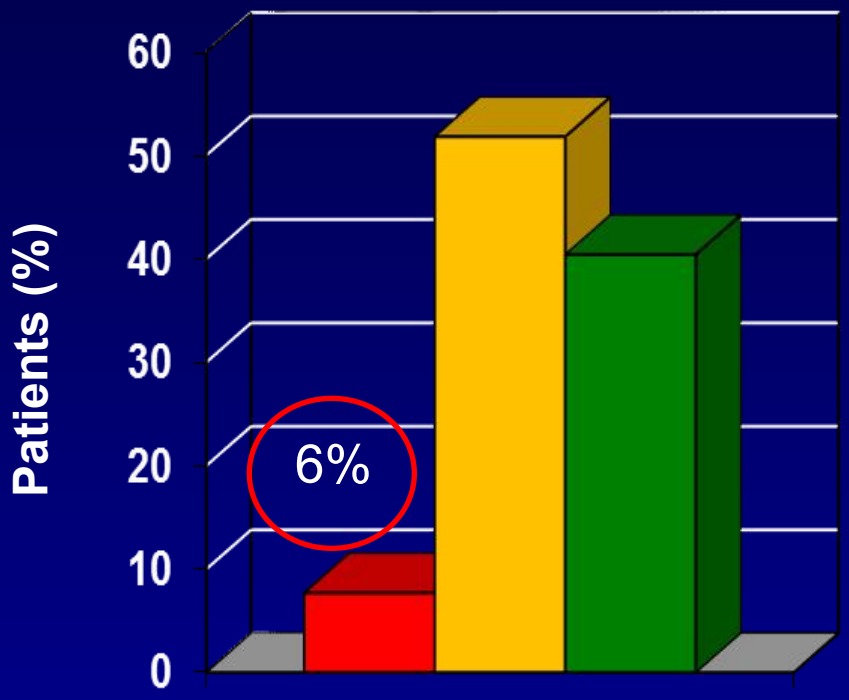
SOC Medicina d’Urgenza - Empoli

High risk patients who are they?

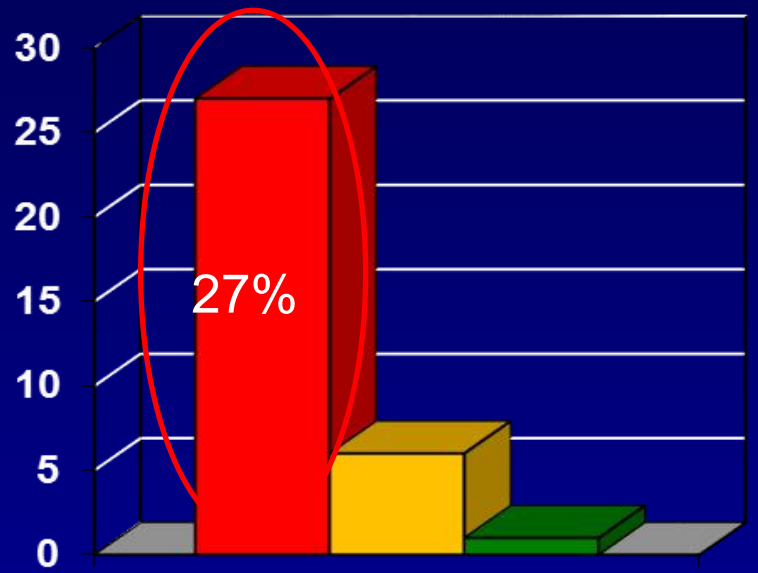
- Cardiac arrest
- Shock
- Severe Hypotension: sBP < 90 mmHg lasting more than 15 min
  - Not due to a cause other than PE (sepsis, hypovolemia, arrythmia).

Prevalence and mortality of high risk patients

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



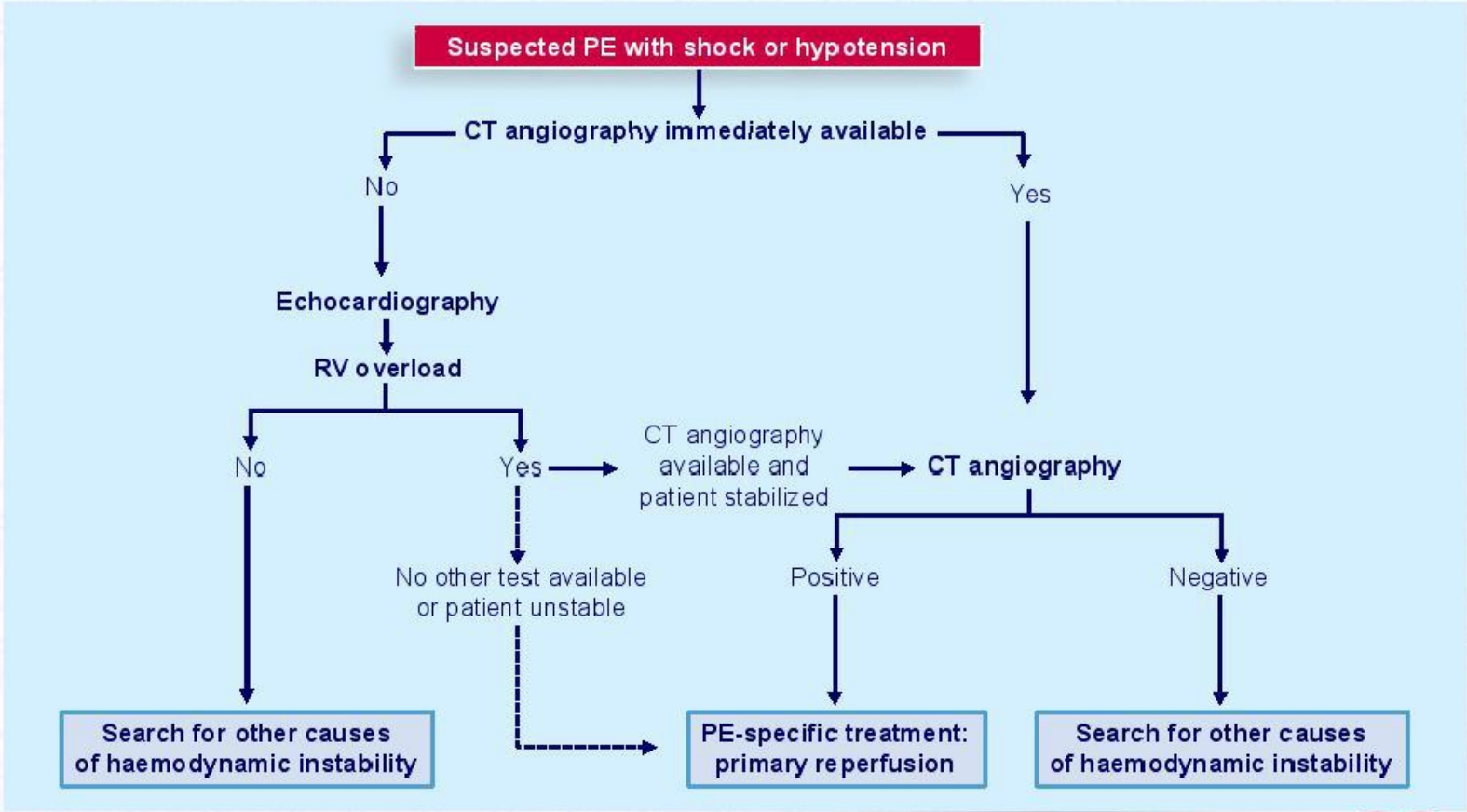
PE related death



Vanni S, Nazerian P, Pepe G, Baioni M, Risso M, Grifoni G, Viviani G, Grifoni S. J Thromb Haemost. 2011

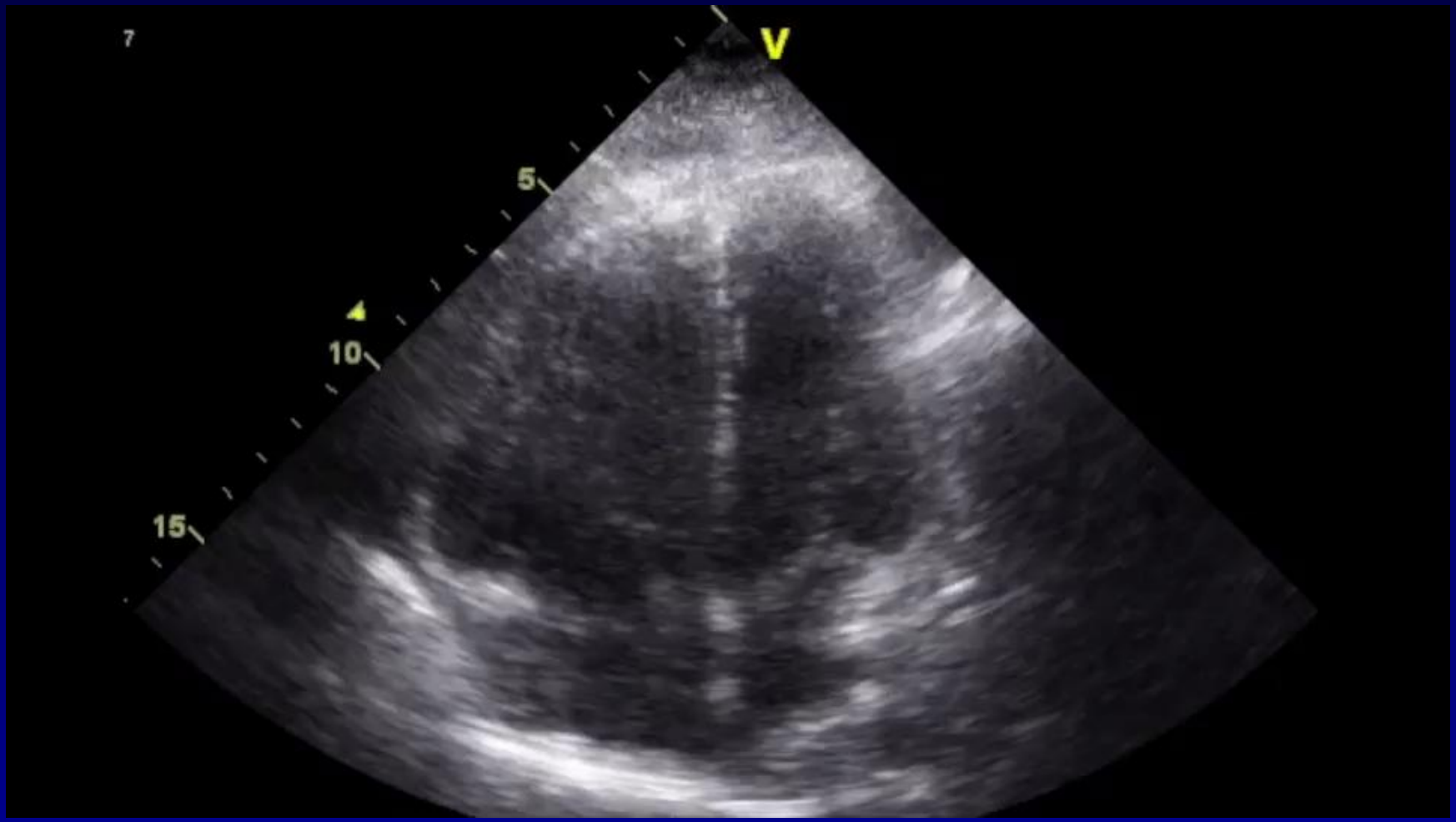
Shock patients: Diagnosis

Diagnostic algorithm: high-risk PE

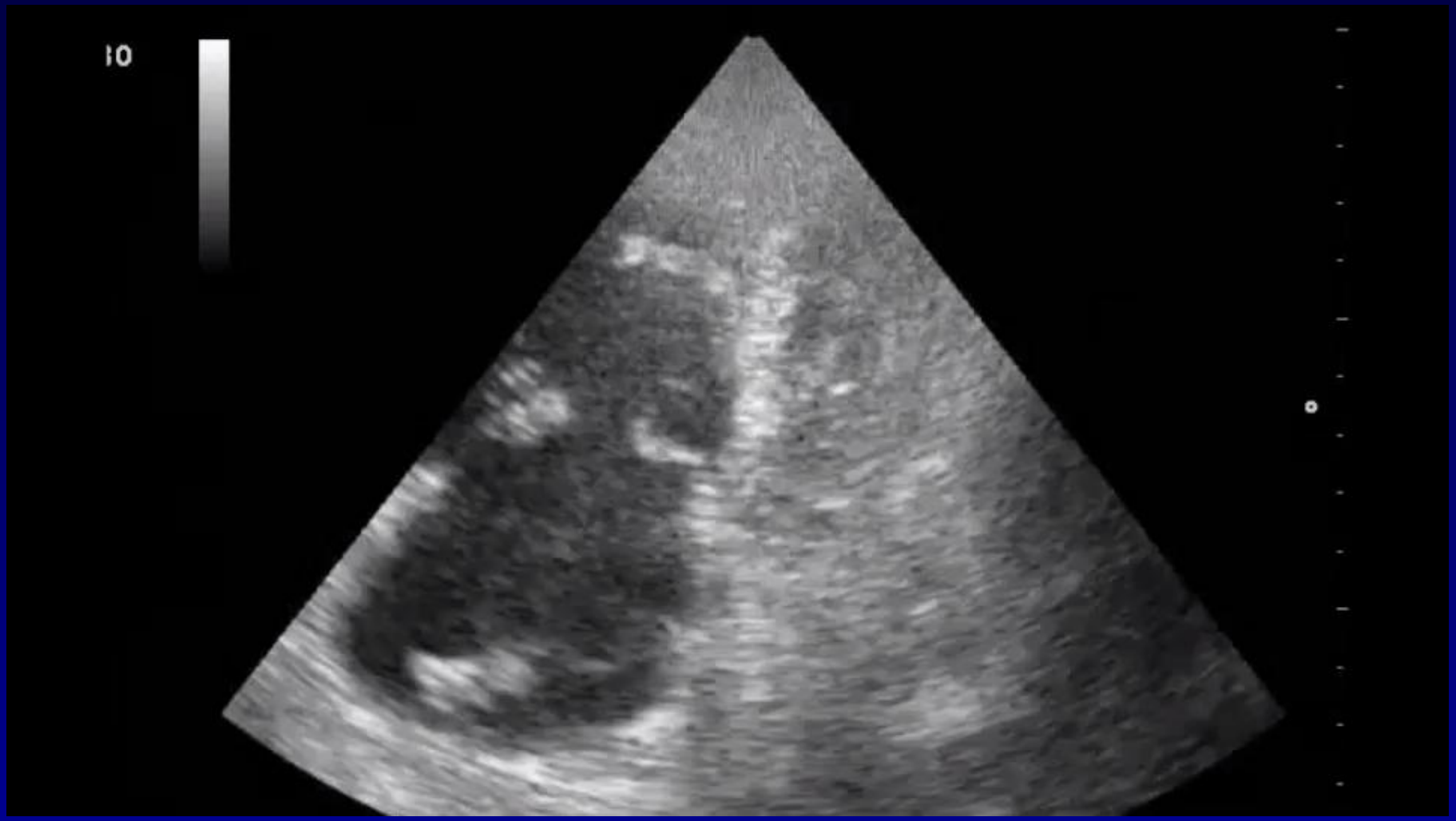


European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Shock patients: Diagnosis



Shock patients: Diagnosis



Prevalence and mortality of high risk patients

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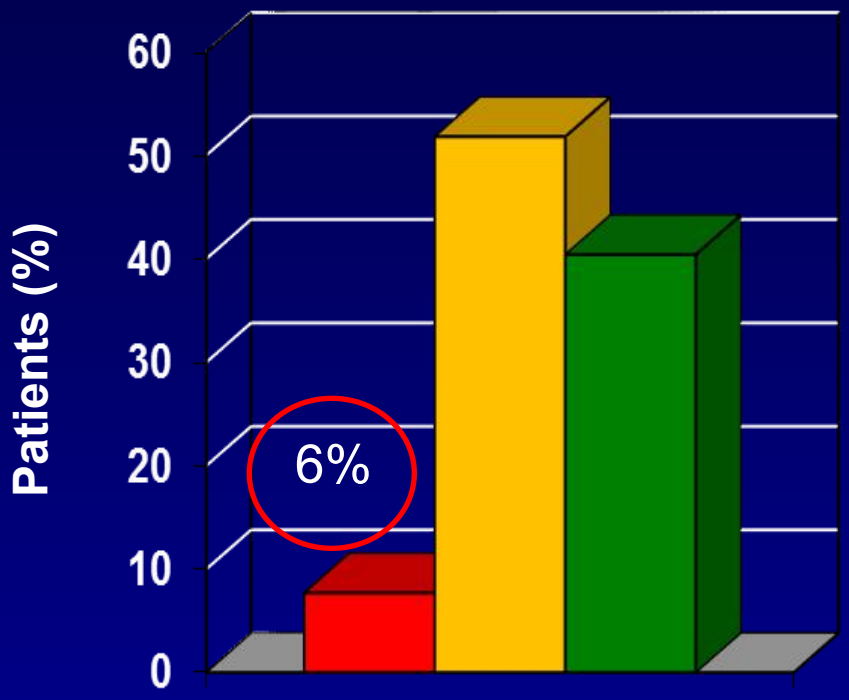
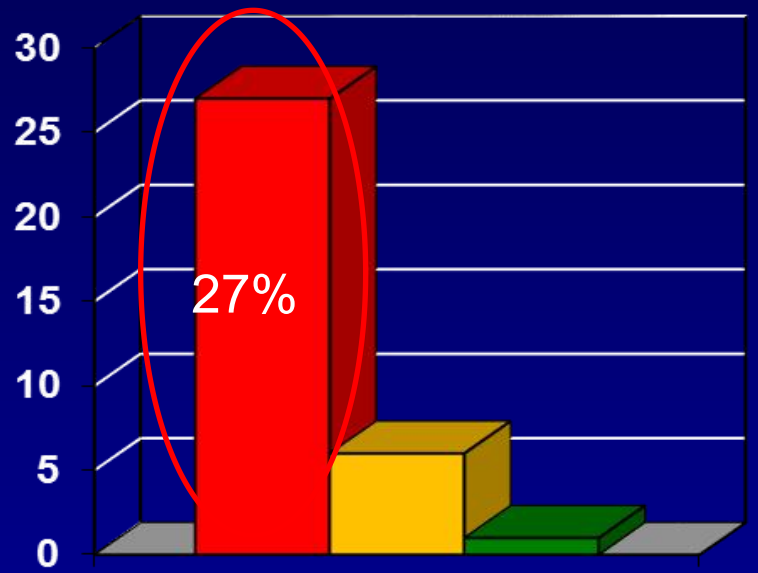
HIGH >15%		+	(+)[a]	(+)[a]	Thrombolysis or embolectomy
NON HIGH	Intermediate 3–15%	–	+	+	Hospital admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment



PE related death



Vanni S, Nazerian P, Pepe G, Baioni M, Risso M, Grifoni G, Viviani G, Grifoni S. J Thromb Haemost. 2011

Diagnostic accuracy of focused cardiac and venous ultrasound examinations in patients with shock and suspected pulmonary embolism

Peiman Nazerian, Giovanni Volpicelli, Chiara Gigli, Alessandro Lamorte, Stefano Grifoni & Simone Vanni

Internal and Emergency Medicine
Official Journal of the Italian Society of Internal Medicine

Shock patients: Diagnosis

105 patients with shock and suspected PE (PE=43: 40.9%)

Table 2 Diagnostic characteristics of focused cardiac and venous ultrasound as single and combined tests

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95
Cardiac US	91% (80–97)	87% (80–91)	83% (74–88)	93% (86–98)	7.03 (4.(
Venous US	56% (46–61)	95% (88–99)	89% (72–97)	76% (70–78)	11.54 (3.7
Positive cardiac or venous US	95% (85–99)	79% (72–82)	76% (68–79)	96% (88–99)	4.56 (3.(
Positive cardiac and venous US	51% (43–51)	100% (94–100)	100% (83–100)	75% (70–75)	Inf (7.2

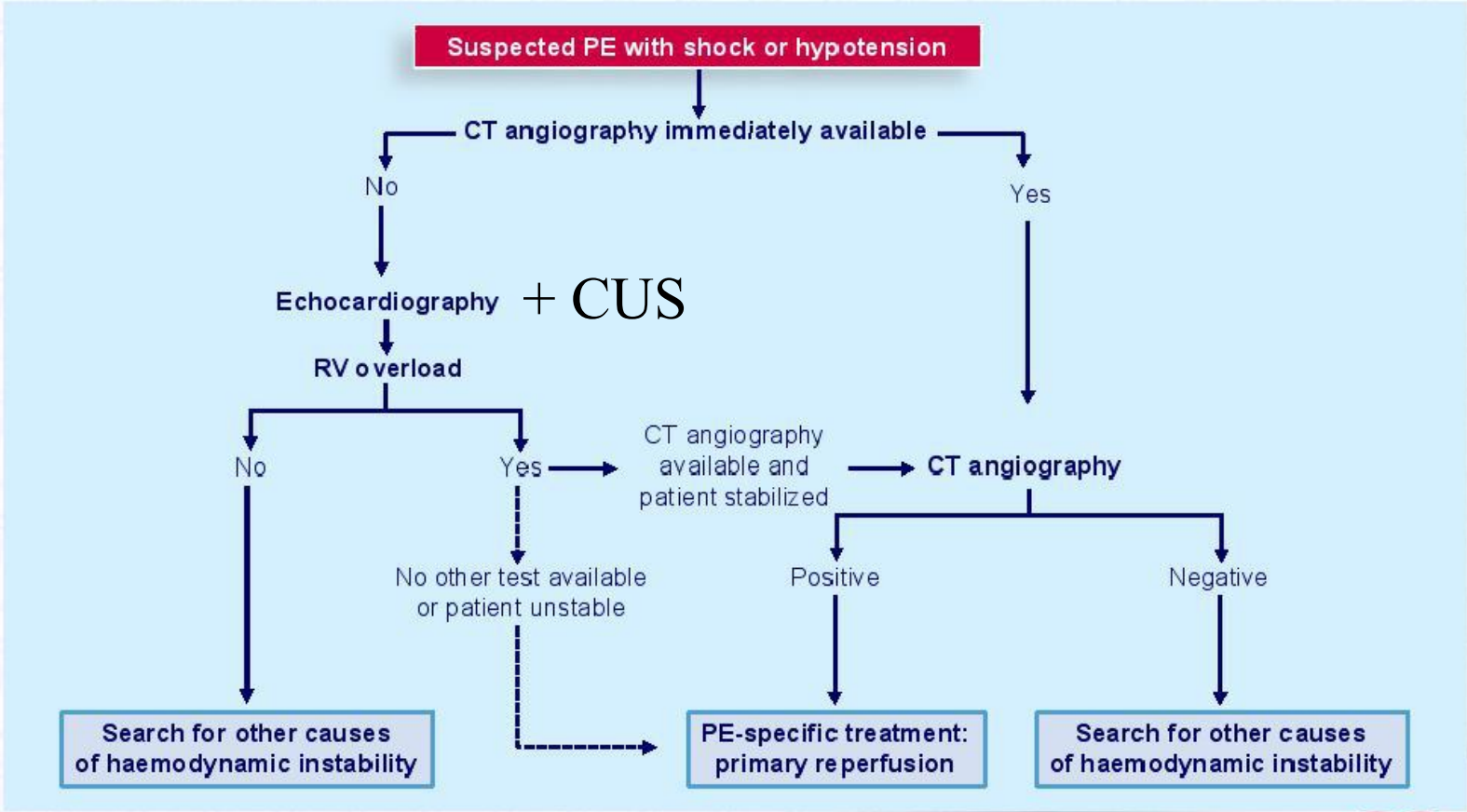
or means that at least one test was positive; *and* means that both tests were positive

US ultrasonography, *PPV* positive predictive value, *NPV* negative predictive value; *+LR* positive likelihood ratio, *95% CI* 95% confidence interval

Nazerian et al, Intern Emerg Med 2017

Shock patients: Diagnosis

Diagnostic algorithm: high-risk PE



European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

EUROPEAN SOCIETY OF CARDIOLOGY®

Shock patients: Treatment

Recommendations for acute phase treatment

Recommendations	Class[a]	Level[b]	Ref[c]
PE with shock or hypotension (high-risk)			
It is recommended that intravenous anticoagulation with UFH be initiated without delay in patients with high-risk PE.	I	C	
Thrombolytic therapy is recommended.	I	B	168
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.[d]	I	C	313
Percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed.[d]	IIa	C	

168. Wan S, Agnelli G et al. Circulation 2004

Thrombolysis

AHA 2011

ESC 2014

Fibrinolytic	FDA Indication for PE?	Direct Plasminogen Activator?	Fibrinolytic Dose
Streptokinase			
Urokinase			
Alteplase			
Reteplase			
Tenecteplase			

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	4,400 IU/kg as a loading dose over 10 min, followed by 4,400 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)

Emorragie maggiori

TABLE 2: Rate of major hemorrhage among PE patients randomized to treatment with heparin +/- alteplase[5]

	Dose	Major hemorrhage, Heparin + Placebo	Major hemorrhage, Heparin + Lytics
PIOPED 1990	40-80 mg alteplase	0/4	1/9
Levine 1990	0.6 mg/kg alteplase	3/25	3/33
Dalla-Volta 1992	100 mg alteplase	2/16	3/20
Konstantinides 2002	100 mg alteplase	5/138	1/118
Fassulo 2011	100 mg alteplase	1/35	2/37
Sharifi 2012	50 mg alteplase	0/60	0/61
All Alteplase v. Placebo		**11/278 (4.0%)**	**10/278 (3.6%)**

Emorragie intracraniche

TABLE 4: Rate of intracranial hemorrhage (ICH) among patients with PE treated with to heparin +/- thrombolysis

	Dose	ICH rate, Heparin + Placebo	ICH rate, Heparin + Lytics
PIOPED 1990	40-80 mg alteplase	0/4	0/9
Levine 1990	0.6 mg/kg alteplase	0/25	0/33
Dalla-Volta 1992	100 mg alteplase	0/16	1/20
Konstantinides 2002	100 mg alteplase	0/138	0/118
Fassulo 2011	100 mg alteplase	0/35	0/37
Sharifi 2012	50 mg alteplase	0/60	0/61
All Alteplase v. Placebo		**0/278**	**1/278 (0.4%)**
Levine 1990	0.6 mg/kg alteplase	0/25	0/33
Sors 1994	0.6 mg/kg alteplase	No placebo arm	0/36
Wang 2010	50 mg alteplase	No placebo arm	0/65
Sharifi 2012	50 mg alteplase	0/60	0/61
Sharifi 2014	50mg alteplase	No placebo arm	0/98
All Alteplase Reduced Dose			**0/293 (0%)**
Becattini 2010	30-50 mg tenecteplase	0/30	1/28
Meyer 2014	30-50 mg tenecteplase	1/499	10/506
Kline 2014	30-50 mg tenecteplase	0/43	1/40
All Tenecteplase v. Placebo		**1/572**	**12/574 (2.1%)**

Epidemiology of «agressive» treatment in PE

In ICOPER, two thirds of the patients with massive PE did not receive thrombolysis

Circulation 2006;113:557-582

TABLE 1. Patient Characteristics (n=2392)

	Massive PE (n=108)	Non–Massive PE (n=2284)	*P*
Therapy			
Thrombolysis	33 (36)	266 (12)	<0.001
Heparin*	102 (94)	2,208 (97)	0.21
Vitamin K antagonist	57 (53)	1,779 (78)	<0.001
IVC filter	11 (12)	227 (10)	0.59
Catheter thrombectomy	1 (1)†	14 (<1)	0.50
Surgical embolectomy	3 (3)‡	11 (<1)	0.02
No reperfusion therapy	73 (68)	1999 (88)	<0.001

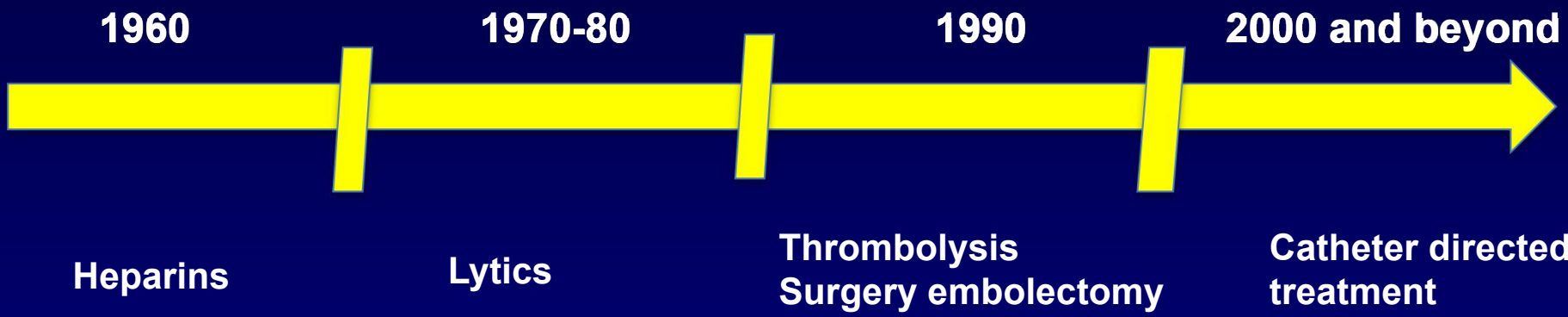
Kucker Circulation 2006; 113:577-582

EP life-threatening
Terapia specifica oltre la terapia anticoagulante.

Registro italiano IPER (1716 pts, 47 ospedali, durante 4 anni)

- Fibrinolisi sistemica:
  - Totale fibrinolisi: 185 pz (10.8% sul totale)
  - Fibrinolisi in pz instabili (201pz): 82 (41%)

Percutaneous catheter-directed treatment of pulmonary embolism



High risk patients

Observation?

reperfusion strategies

Percutaneous catheter-directed treatment of pulmonary embolism

"Pharmacomechanical" Therapy

Mechanical Fragmentation

Hydrodynamic

Ultrasound-Accelerated Fibrinolysis

Suction Embolectomy

Cat		
Technique		
Thrombus frag		, Latham,
Rheolytic thro		ndovascular,
Suction embol		WA, USA)
Rotational thr		ulse™ ctomy
Combined tec		olus AngioJet rombolysis Germany)

Torbicki A et al. EHJ 2014 (ESC guidelines)

Meta-analysis on PE catheter interventions (35 studies)

	Clinical success*	Clinical success in studies with >80% patients receiving thrombolysis	Clinical success in studies with <80% patients receiving thrombolysis	Major complications	Minor complications
N = 594	86%	91%	83%	2%	8%

*defined as stabilization of hemodynamic parameters, resolution of hypoxia, and survival to discharge

Kuo WT, et al. *J Vasc Interv Radiol.* 2009;20:1431-1440

PE-related Cardiac Arrest: mortality 66-95%

Etiology	prevalence
Cardiac	**68.8%**
AMI	43.0%
Arrythmia	19.6%
Pulmonary Edema	6.2%
Non Cardiac cause	**31.2%**
Bleedings	4.6%
Pulmonary embolism	**4.6%**
Other respiratory	5.4%
Intracranial	4.7%
Sepsis	2.0%
Toxic	4.7%
Cause metaboliche	2.2%

- SPES study
- 357 pt with suspected PE
- PE diagnosed in 110
- Cardiac Arrest 2%

Kurkciyan I. Circulation 1998;98:766
593 pts (out-of-H, in-H)

P Nazerian et al Chest 2014

Cardiac Arrest: ALS guidelines

- In patients with cardiac arrest and without known PE, routine fibrinolytic treatment given during CPR shows no benefit and is not recommended

(Class III, LoE A. ALS 2010)

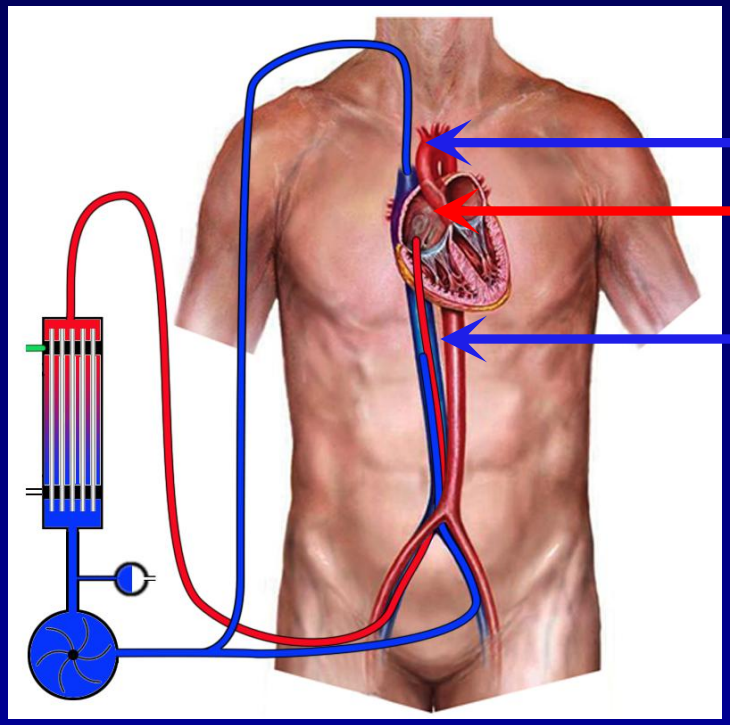
- Fibrinolytics may improve survival to discharge and long-term neurological function in patients with presumed PE-induced cardiac arrest

(Class IIA, LOE B. ALS 2010)

- Survival has been described with percutaneous mechanical thrombectomy or surgical embolectomy with or without prior treatment with fibrinolysis (ALS 2010)

- ECMO could be used as a bridge therapy (case reports)?

ECMO
Extra Corporeal Membrane Oxygenation
ECLS
Extra Corporeal Life Support



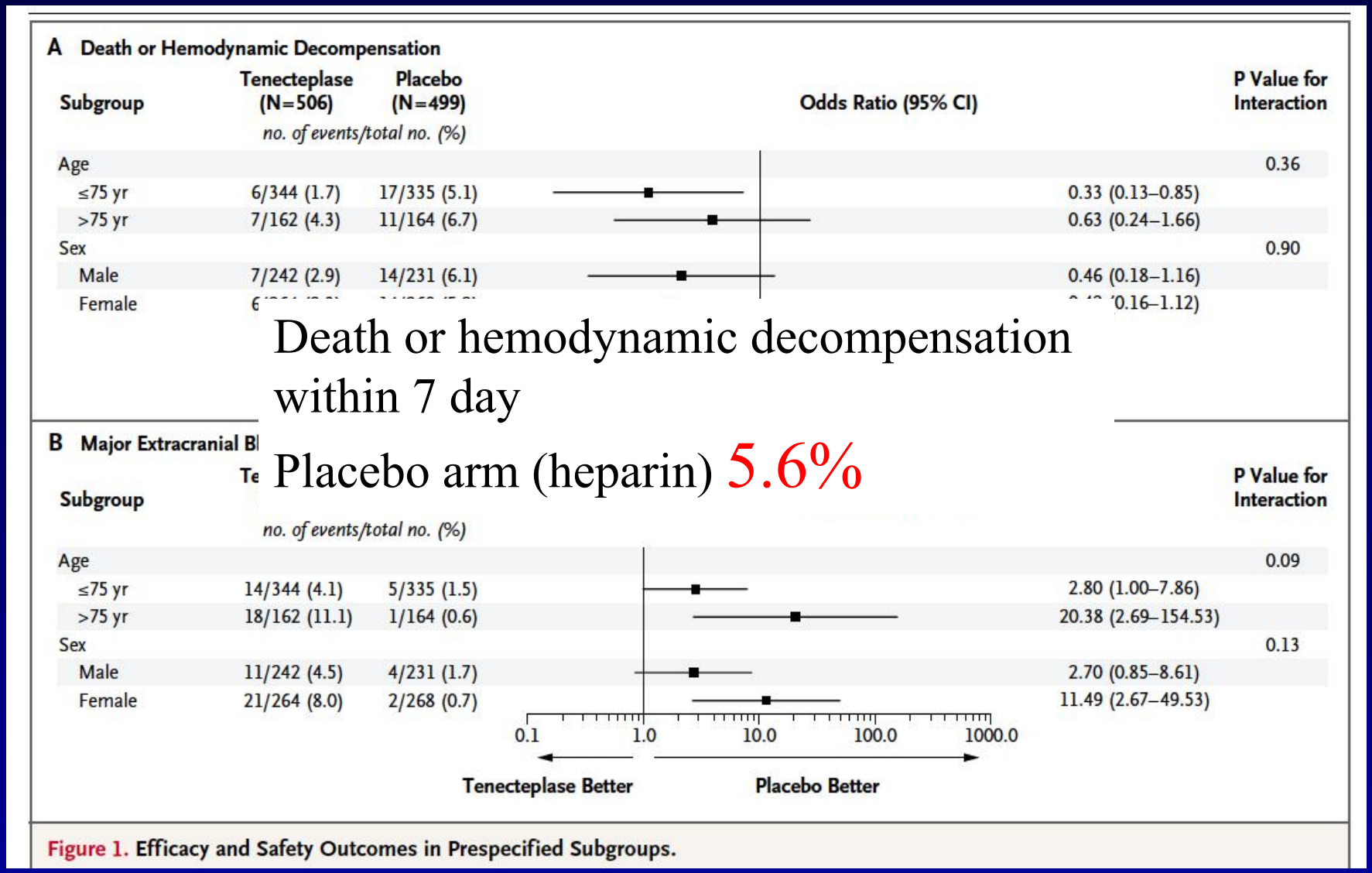
High risk patients who are they?

- Cardiac-arrest, peri-arrest
- Shock
- Severe Hypotension: sBP < 90 mmHg lasting more than 15 min
  - Not due to a cause other than PE (sepsis, hypovolemia, arrythmia).
- What Else?
- Intermediate-high risk?

Classification of patients with PE according to early mortality risk (ESC guidelines 2014)

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]	

Peitho study



Death or hemodynamic decompensation within 7 day

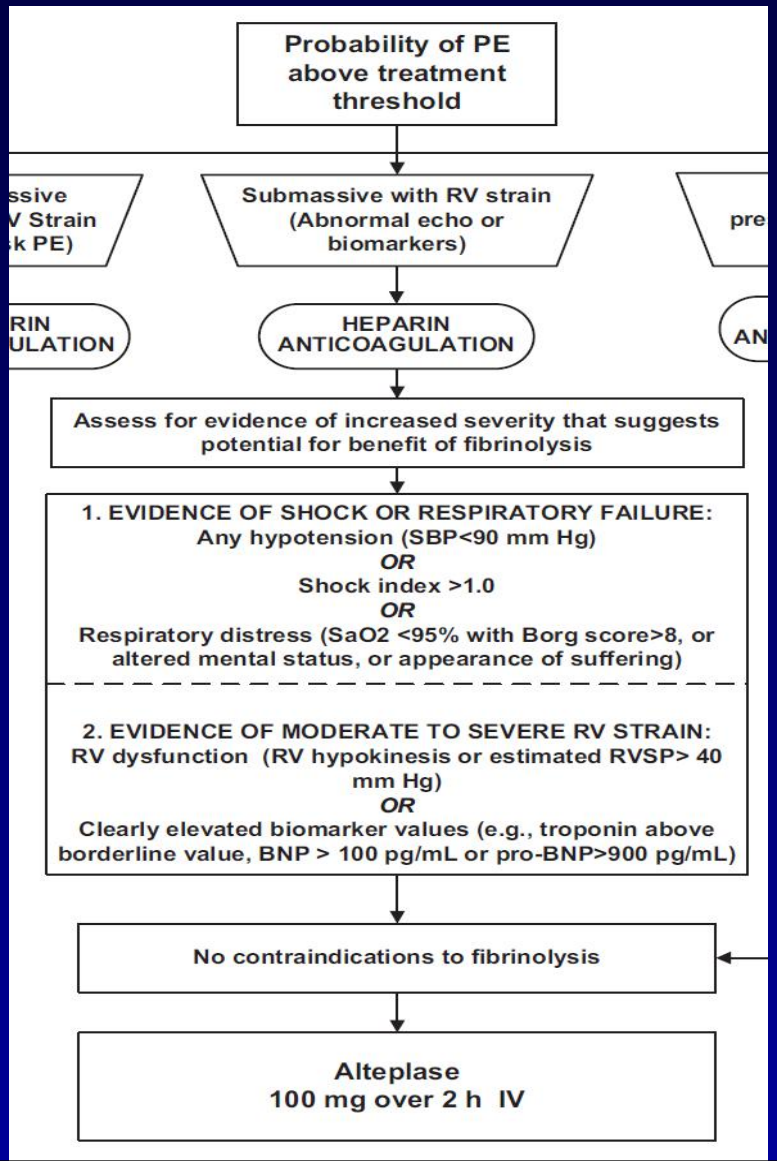
Placebo arm (heparin) 5.6%

Figure 1. Efficacy and Safety Outcomes in Prespecified Subgroups.

New Engl J med 2014

Intermediate-high risk: Who are?

AHA 2011



ESC 2014

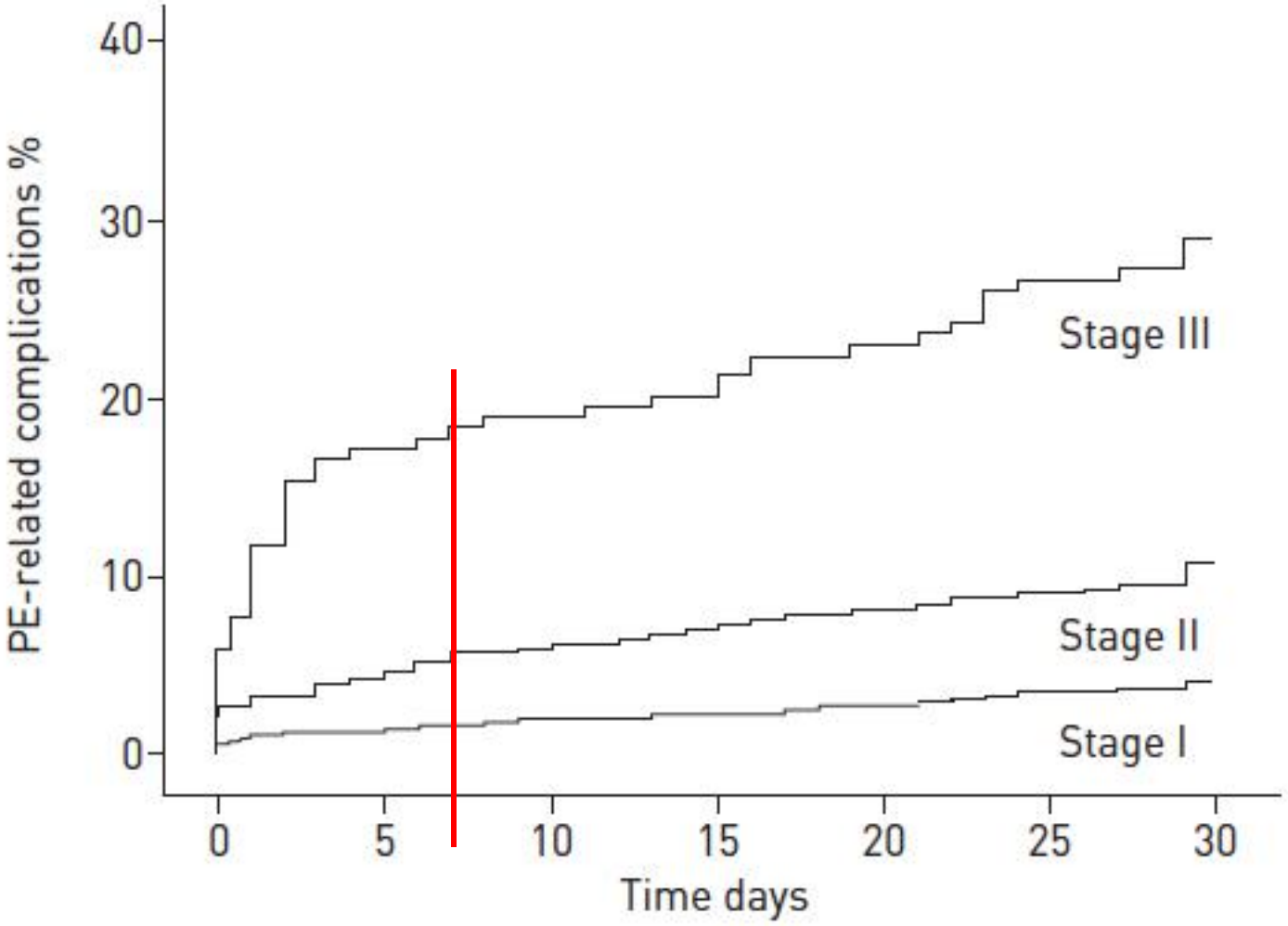
Recommendations for acute phase treatment

Recommendations	Class[a]	Level[b]	Ref[c]
PE without shock or hypotension (intermediate-or low-risk)[d]			
Reperfusion treatment			
Routine use of primary systemic thrombolysis is not recommended in patients not suffering from shock or hypotension.	III	B	253
Close monitoring is recommended in patients with intermediate-high risk PE to permit early detection of haemodynamic decompensation and timely initiation of 'rescue' reperfusion therapy.	I	B	253
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa	B	252, 253
Surgical pulmonary embolectomy may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.[g]	IIb	C	
Percutaneous catheter-directed treatment may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.[g]	IIb	B	336

Perspectives of Thrombolysis in PE

- To upgrade risk stratification tools
- To reduce haemorrhagies
- Use of catheters based reperfusion

Identification of intermediate-risk



Eur Resp J 2014

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]

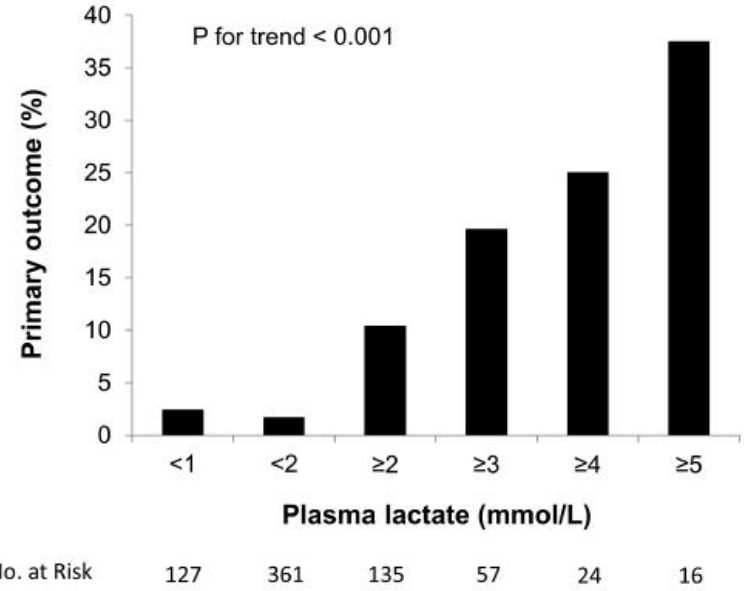


Figure 2 Frequency of the primary outcome according to baseline lactate levels.

N=496

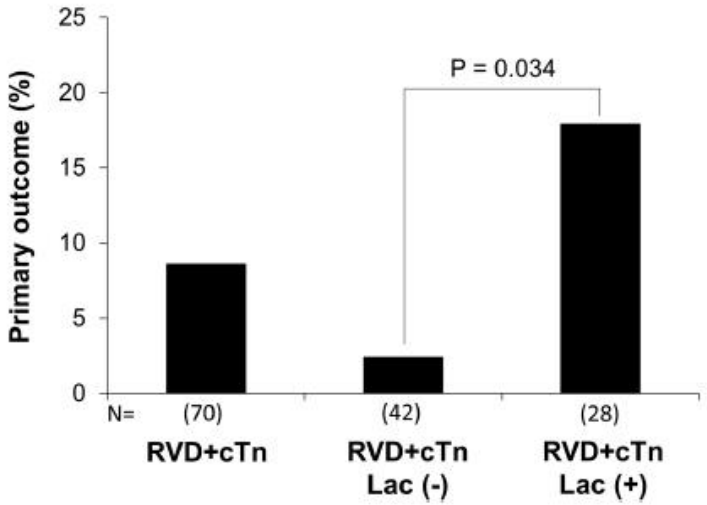
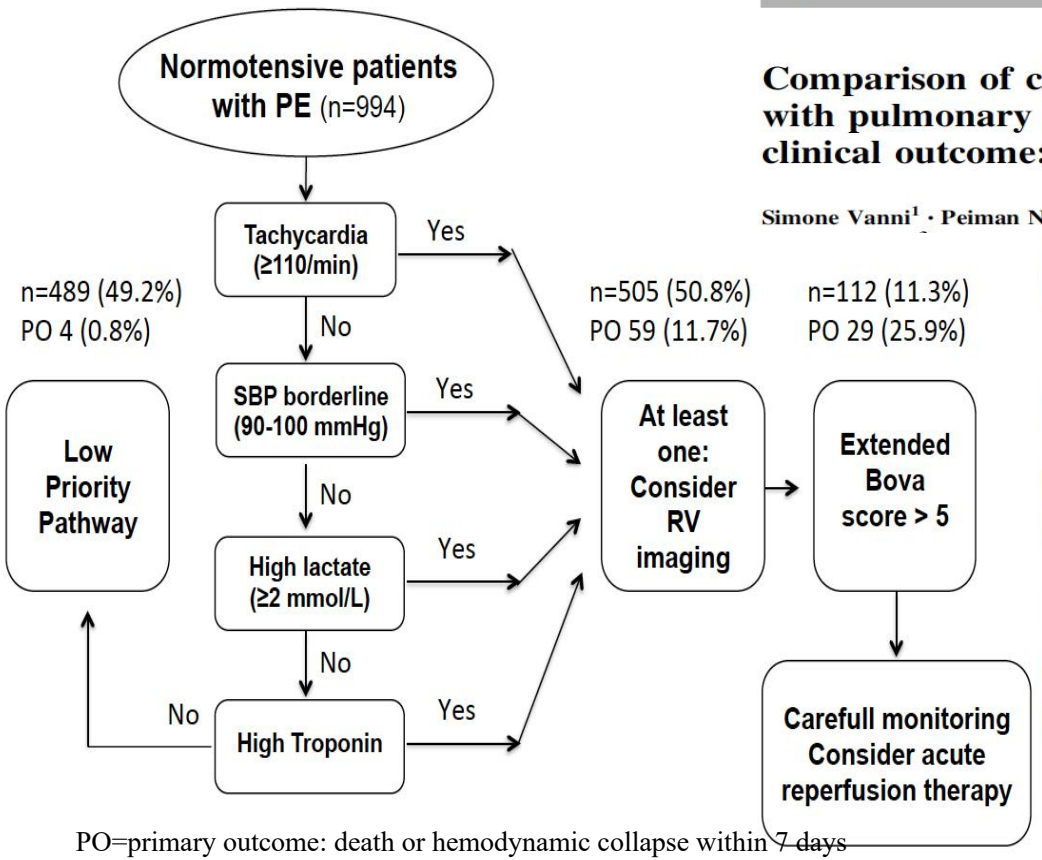


Figure 3 Escalation of PE-related complication rates depending on lactate levels in combination with echocardiography and troponin. cTn, elevated cardiac troponin; Lac (+), lactate ≥2 mmol/L; Lac (–), lactate <2 mmol/L; RVD, right ventricular dysfunction.

Proposta di algoritmo decisionale nei normotesi



PO=primary outcome: death or hemodynamic collapse within 7 days

Intern Emerg Med
DOI 10.1007/s11739-016-1487-6

EM - ORIGINAL

Comparison of clinical scores for identification of patients with pulmonary embolism at intermediate–high risk of adverse clinical outcome: the prognostic role of plasma lactate

Simone Vanni[1] · Peiman Nazerian[1] · Carlo Bova[2] · Ernesta Bondi[1] ·

Conclusions

In conclusion, 2014 ESC model, Bova and TELOS scores recognize without significant differences a small number of intermediate–high risk patients with acute PE. The addition of plasma lactate to the Bova score significantly improves the sensitivity for identifying patients who might develop PE-related hemodynamic collapse or death in the first 7 days.

Vanni et al, intern Emerg Med 2016

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

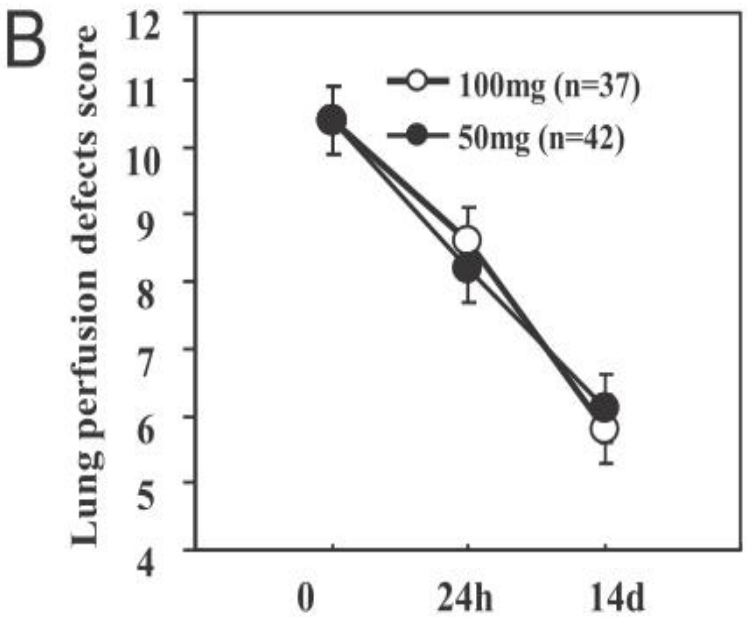


Table 3—*Comparison of Adverse Events During the First 14 d After Treatment, Comparing Two Treatments for PTE*

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

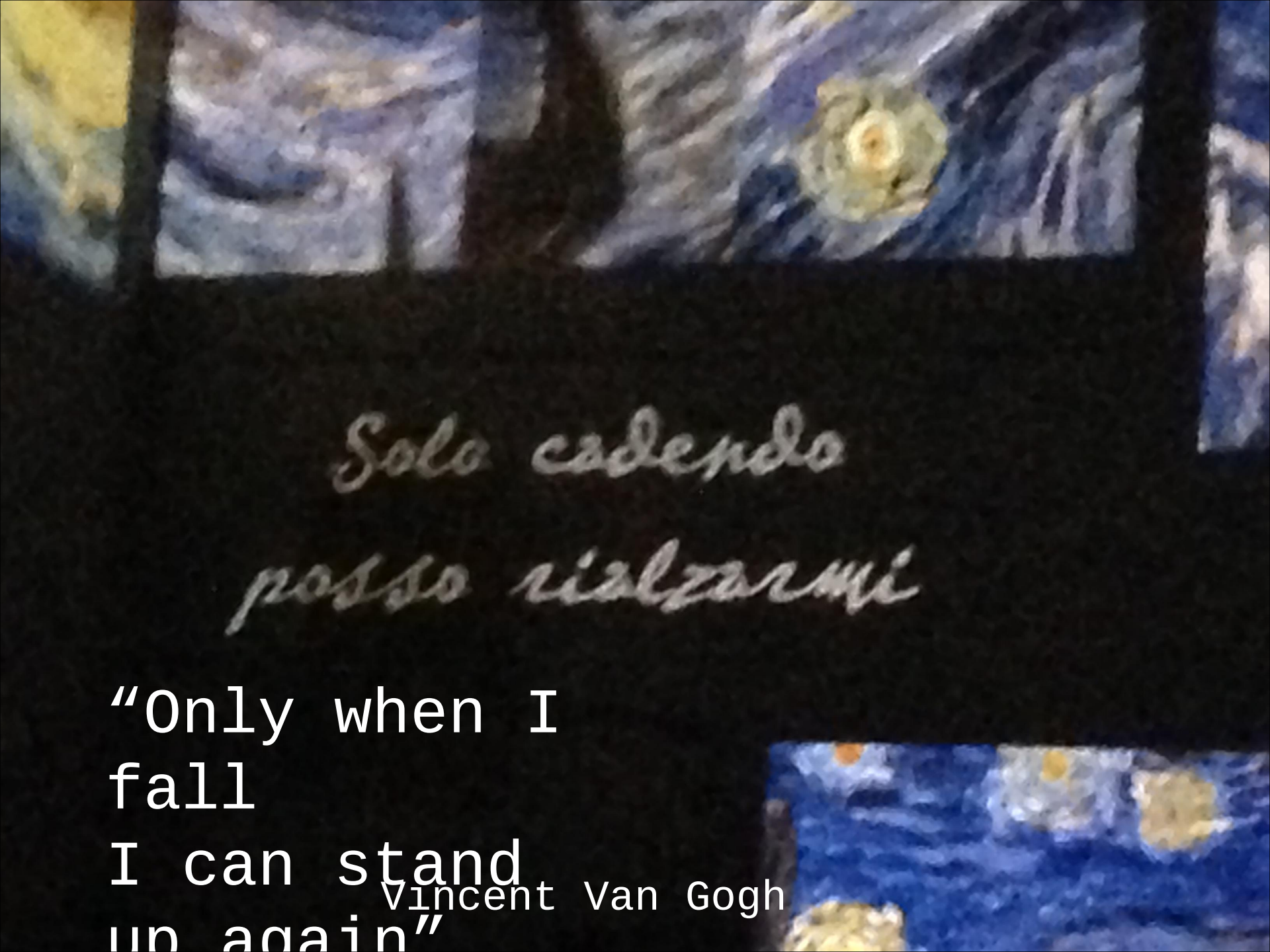
Perspectives: high risk PE

1) Use both echocardiography and CUS to diagnose.

2) Systemic lysis is the only evidence based reperfusion therapy (IB ,rTPA 100 mg in 2 h or 0.6 mg/Kg 15 min)

3) Advanced reperfusion strategies (Catheters, ECMO, Embolectomy) may be alternative but are available only in specialized centres

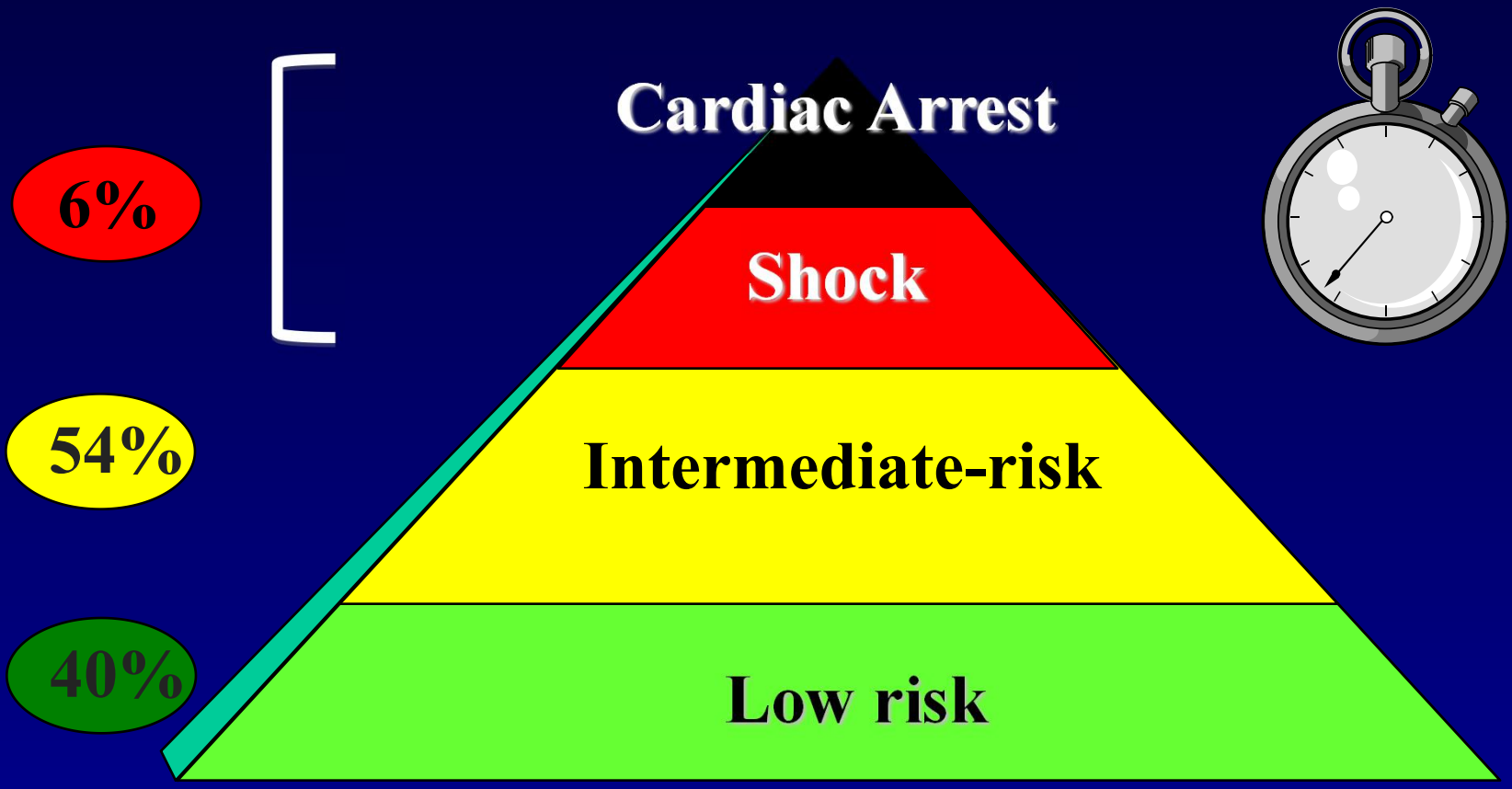
4) Low dose lytics for intermediate-high risk?



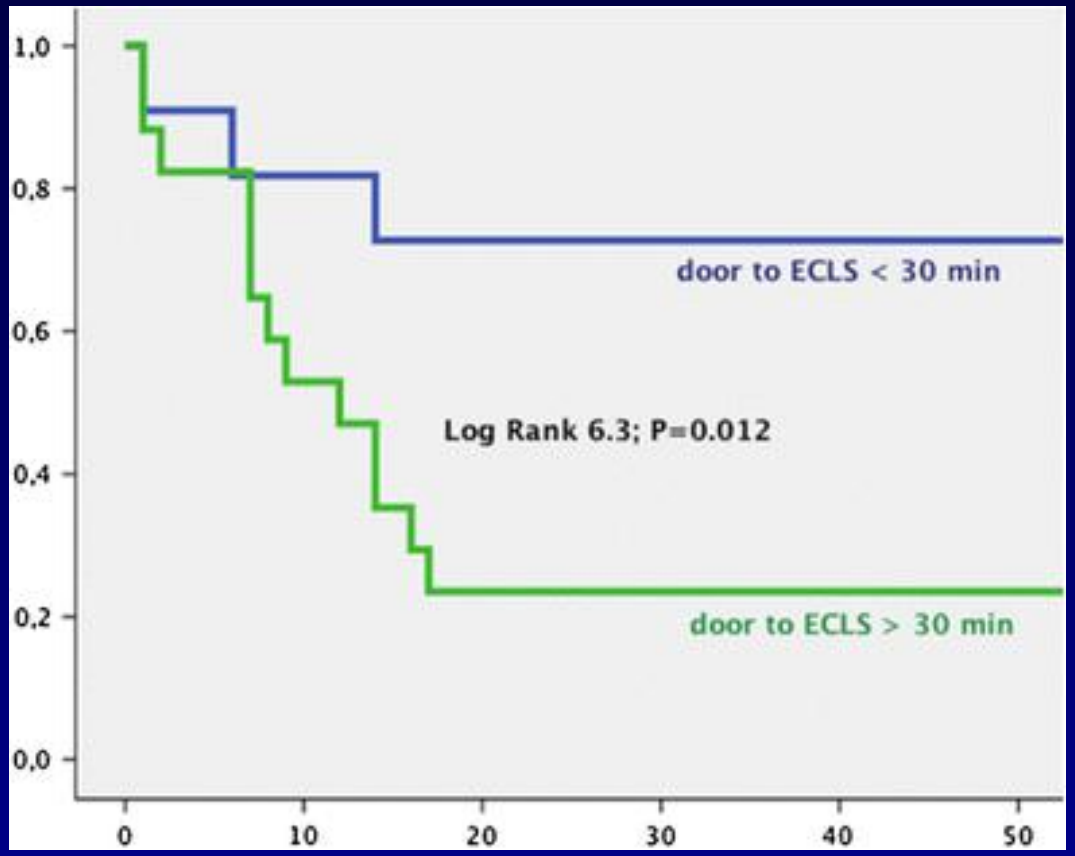
“Only when I fall
I can stand up again”

Vincent Van Gogh

High risk patients who are they?



ECMO/ECLS basic principles

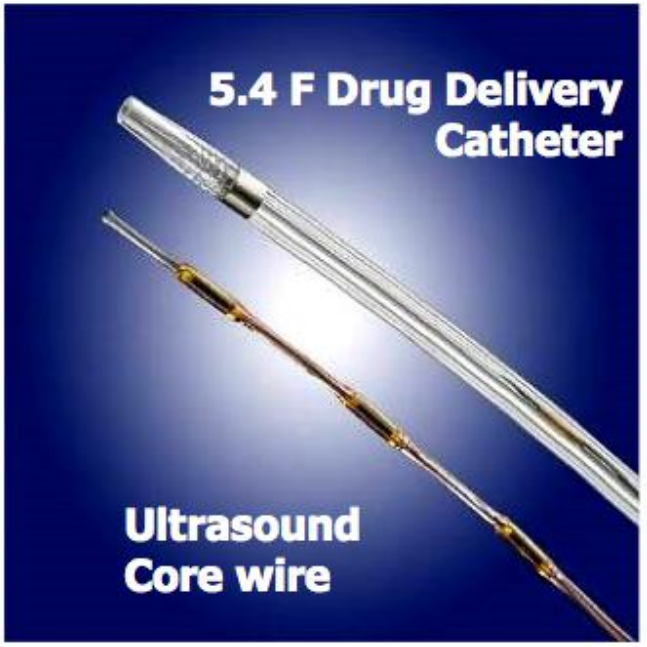


The 30-day mortality rate in patients with witnessed OHCA undergoing ECLS treatment can be significantly improved if ECLS support is established within the first 30 min after admission …rdECMO

Leick et al (2013) Door-to-implantation time of extracorporeal life support systems predicts mortality in patients with out-of-hospital cardiac arrest. Clin Resarch Cardiol 102:661.

Ultrasound assisted thrombolysis

EKOS EkoSonic® Mach 4e Endovascular System



- Infusion side-hole catheter with a multielement ultrasound core
- 12 cm nominal treatment zone length typically used for PE therapy

ULTrasound Accelerated ThrombolysIs of PulMonARy Embolism

Inclusion criteria

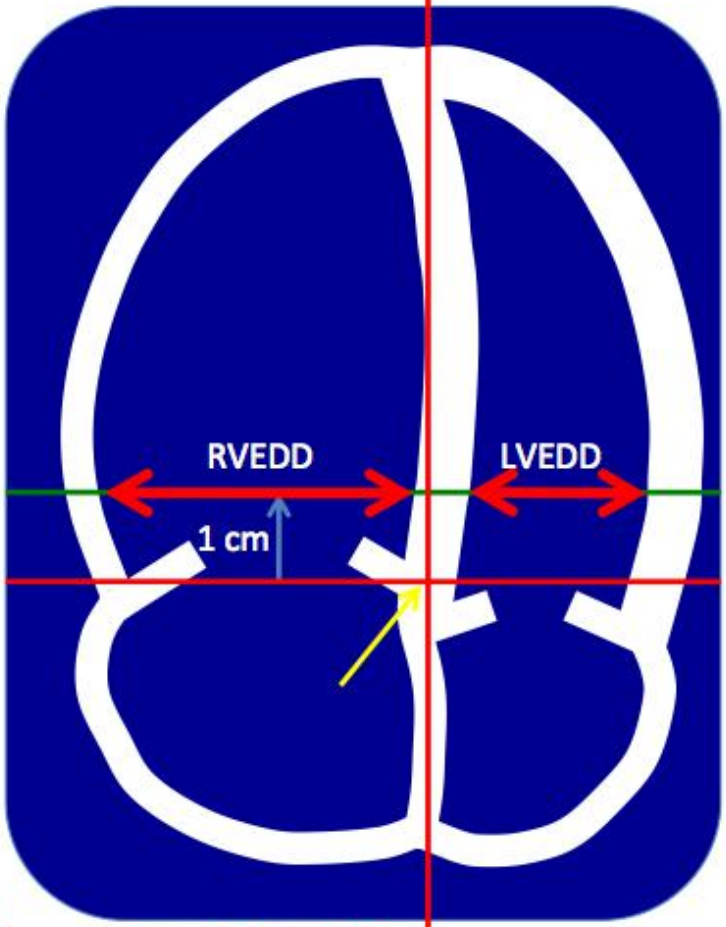
- Acute symptomatic PE confirmed by contrast-enhanced chest CT with embolus located in at least one main or proximal lower lobe pulmonary artery

- RV/LV ratio > 1 on echocardiography

ULTIMA

ULTrasound Accelerated Thrombolys**I**s of Pul**M**on**A**ry Embolism

Measurement of subannular RV/LV ratio (apical 4-CH view)



1.Obtain an end-diastolic image defined as last available image prior to the onset tricuspid valve closure

2. Obtain center line through interventricular septum

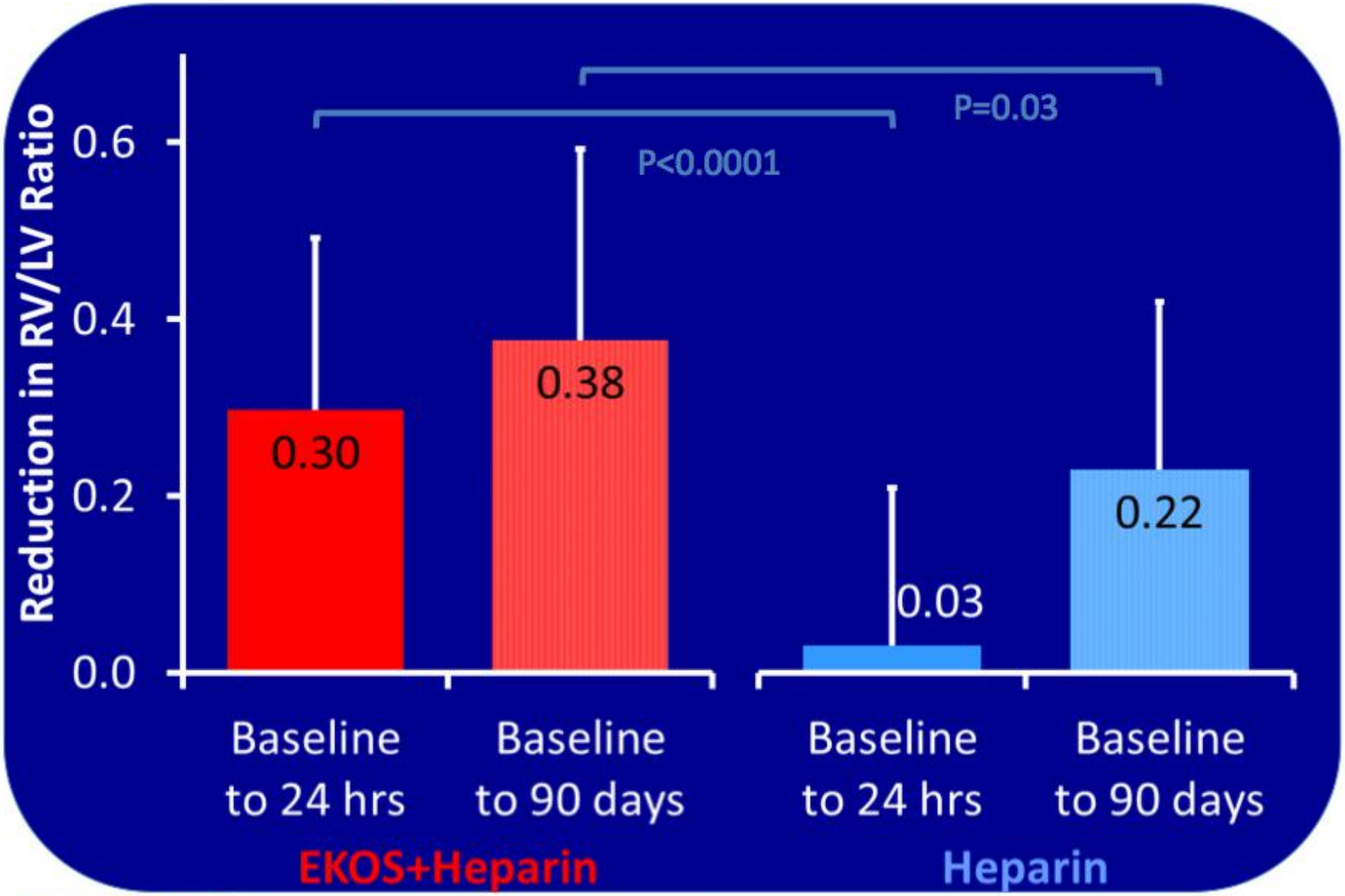
3. Obtain tricuspid annular line at septal insertion point of tricuspid valve, perpendicular to interventricular septum line

4. Obtain subannular line 1 cm above and parallel to annular line

5. Obtain RV and LV dimensions on the subannular line using endocardial borders

6. Calculate the RV/LV ratio: RVEDD divided by LVEDD

Primary endpoint: Reduction in RV/LV ratio



[Original Research **Pulmonary Vascular Disease**]

CHEST

A Multidisciplinary Pulmonary Embolism Response Team

Initial 30-Month Experience With a Novel Approach to Delivery of Care to Patients With Submassive and Massive Pulmonary Embolism

Christopher Kabrhel, MD, MPH; Rachel Rosovsky, MD, MPH; Richard Channick, MD; Michael R. Jaff, DO; Ido Weinberg, MD; Thoralf Sundt, MD; David M. Dudzinski, MD, JD; Josanna Rodriguez-Lopez, MD; Blair A. Parry, CCRC, BA; Savanah Harshbarger, BS; Yuchiao Chang, PhD; and Kenneth Rosenfield, MD

BACKGROUND: Integrating newly developed tests and treatments for severe pulmonary embolism (PE) into clinical care requires coordinated multispecialty collaboration. To meet this need, we developed a new paradigm: a multidisciplinary Pulmonary Embolism Response Team (PERT). In this report, we provide the first longitudinal analysis of patients treated by a PERT.

METHODS: Our PERT includes specialists in cardiovascular medicine and surgery, emergency medicine, hematology, pulmonary/critical care, and radiology, and is organized as a rapid response team. We prospectively captured clinical, therapeutic, and outcome data at PERT