

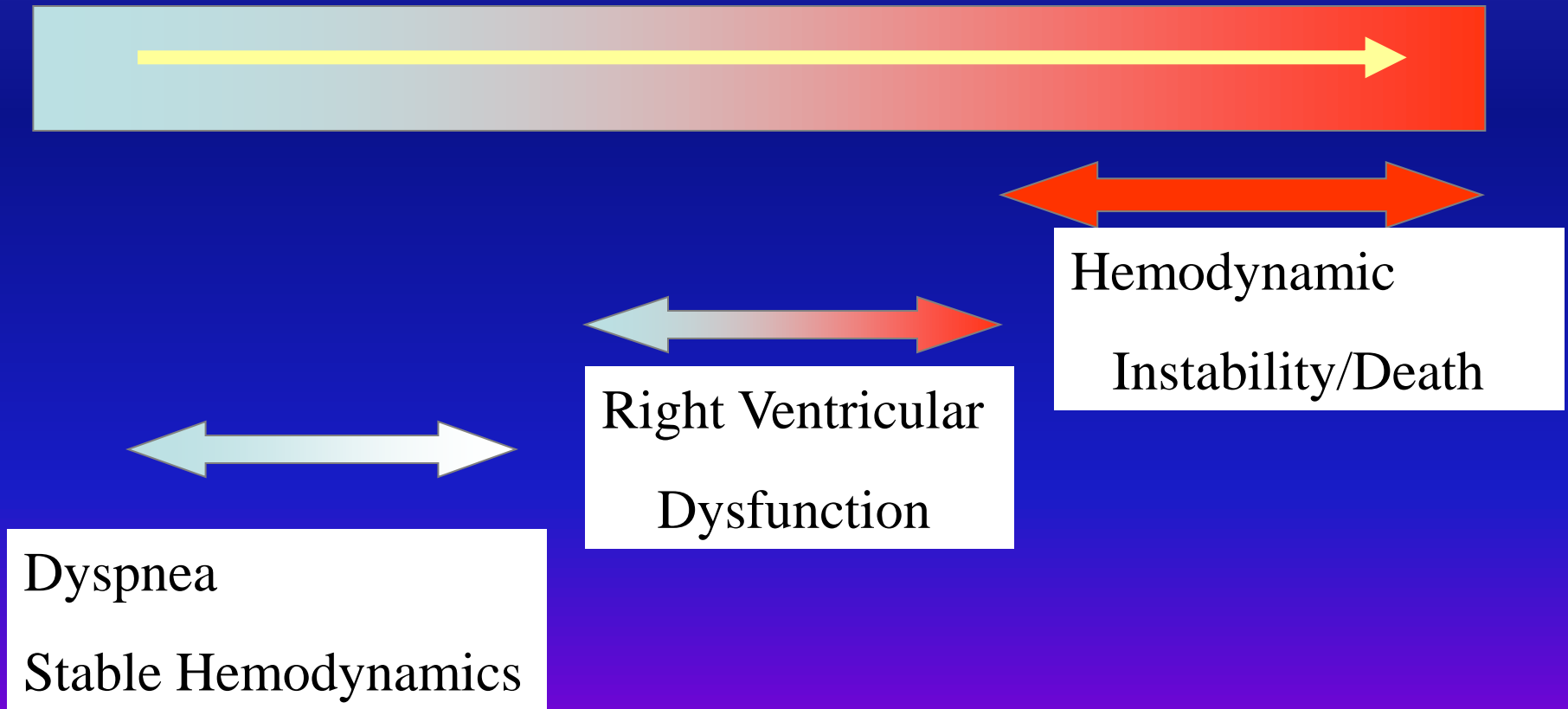


Pulmonary embolism

**H. Hod M.D., FACC, FESC.
I.C.C.U. - Leviev Heart Center
Sheba Medical Center, Tel-Aviv University
ISRAEL**

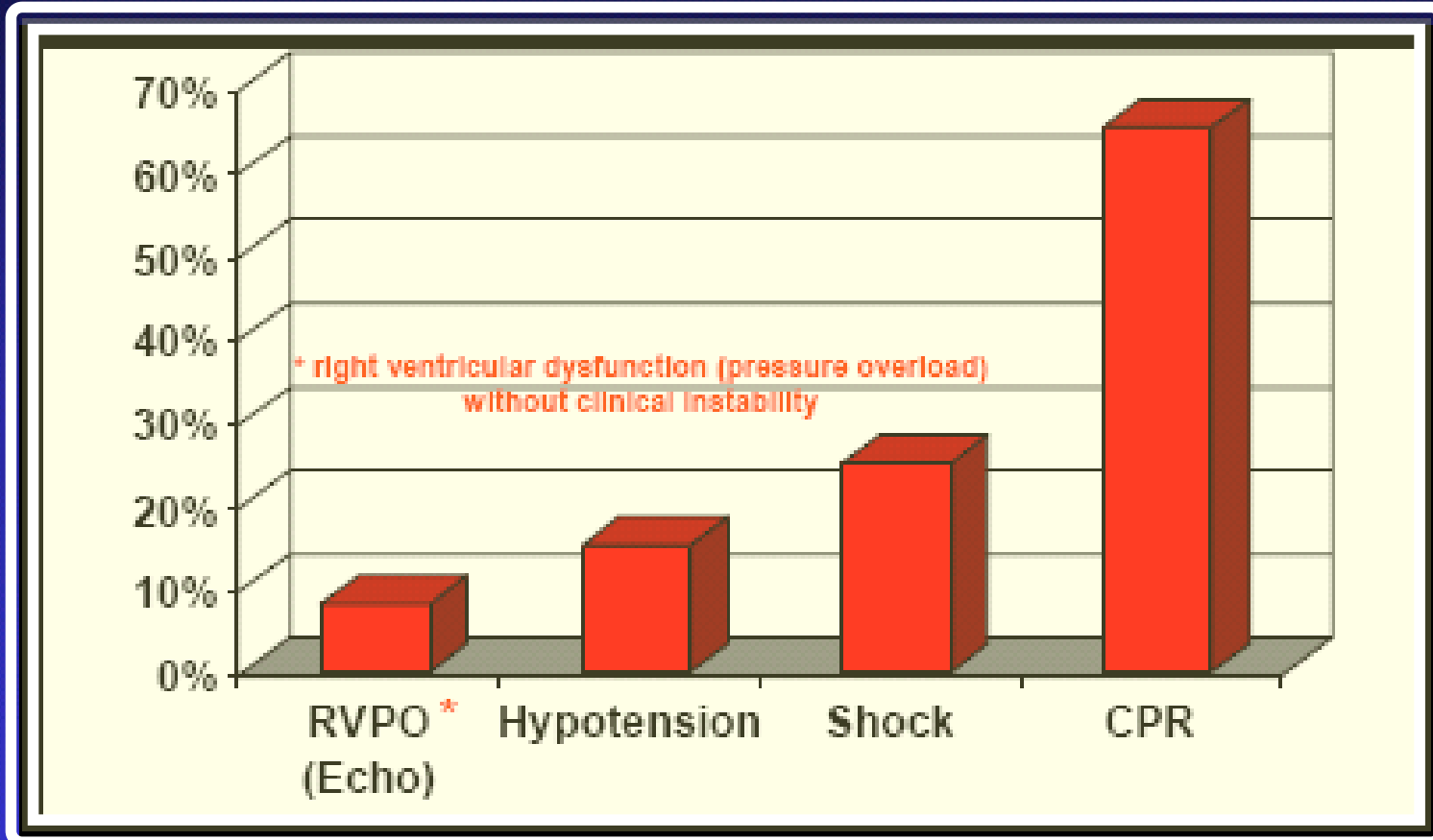


THE SPECTRUM OF PULMONARY EMBOLISM



Mortality Rates in Relation to the Severity of Clinical Instability at Presentation

Data from the MAPPET Registry



W Kasper et al, *J Am Coll Cardiol* 1997;30:1165-1171

AHA Scientific Statement

Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension

A Scientific Statement From the American Heart Association

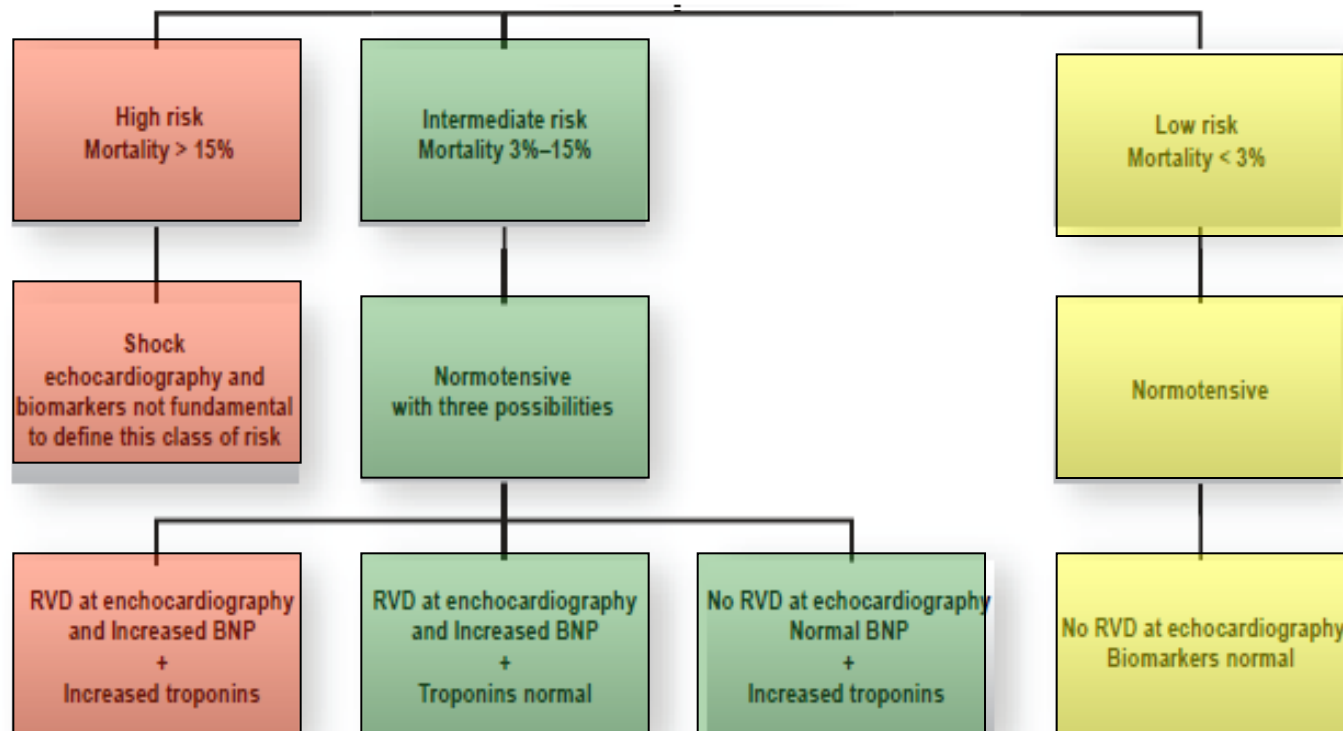
- **Massive PE:** Sustained hypotension, pulselessness, or persistent bradycardia
- **Submassive PE:** RV dysfunction or myocardial necrosis, without hypotension
- **Low Risk PE:** No markers of adverse prognosis

(Circulation 2011; 123: 1788-1830)



Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)



Goals of therapy

- **Normalize pulmonary vascular resistance by immediate relief of right heart failure**
- **Prevention of recurrent thromboembolism**



Anticoagulation

- Immediate full anticoagulation is mandatory for all patients suspected to have pulmonary embolism
 - Diagnostic investigations should not delay empirical anticoagulant therapy
- (ESC/AHA Guidelines)**



Which parental anticoagulant should be selected?

- 1. Unfractionated heparin:** use if patient might require thrombolysis, embolectomy, or IVC filter
- 2. Low molecular weight heparins or fondaparinux:** use for patients only requiring anticoagulation
- 3. Direct thrombin inhibitors:** use for confirmed or suspected HIT



SITES OF ACTION

Coagulation Pathway

Drug Action

Initiation

New-Agents

VIIIa IXa
Va

Xa

II

IIa

Fibrinogen → Fibrin

Rivaroxaban

Apixaban

Edoxaban

Betrixaban

Dabigatran

Fibrin formation

(Hankey GJ and Eikelboom JW. *Circulation* 2011;123:1436-1450)

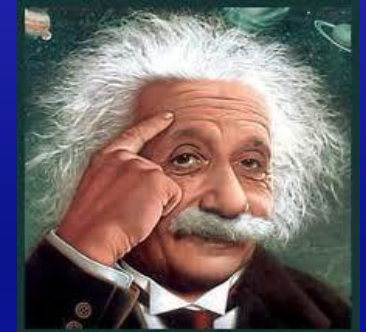


Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

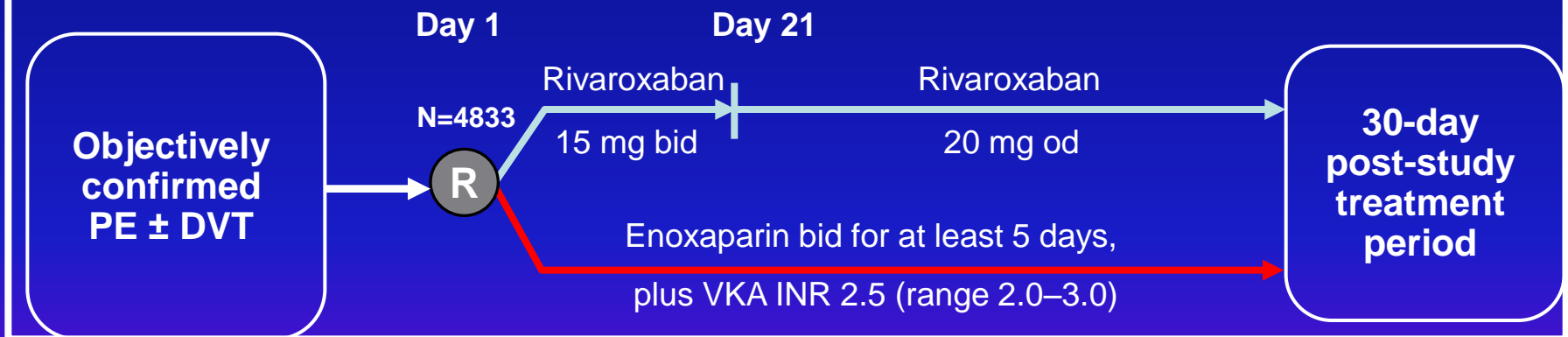
The EINSTEIN-PE Investigators. N Engl J Med 2012;366:1287-97.

Randomized, open-label, event-driven, non-inferiority study (N=4,832)

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



Predefined treatment period of 3, 6, or 12 months



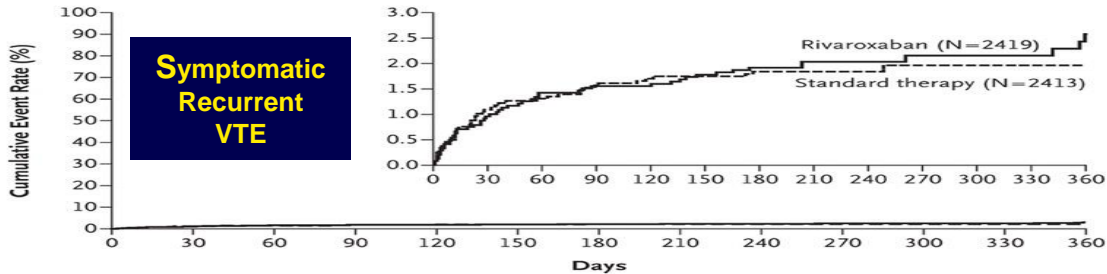
Primary efficacy outcome: first recurrent VTE ♦

Principal safety outcome: first major or nonmajor clinically relevant bleeding ♦



(N=4,832)

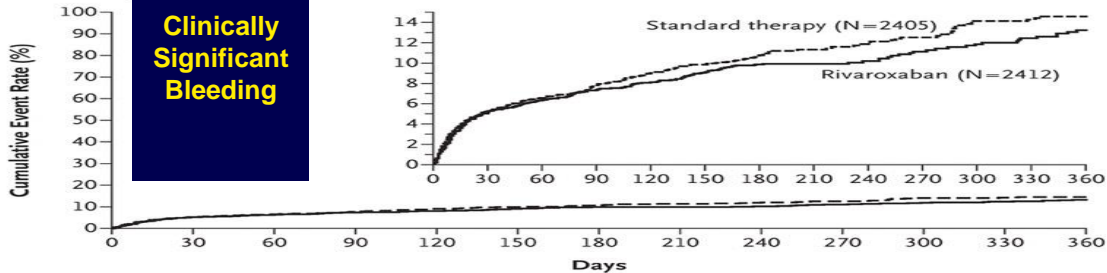
A Primary Efficacy



No. at Risk

Days	Rivaroxaban	Standard therapy
0	2419	2413
30	2350	2316
60	2321	2295
90	2303	2273
120	2180	2155
150	2167	2146
180	2063	2050
210	837	835
240	794	787
270	785	772
300	757	746
330	725	722
360	672	675

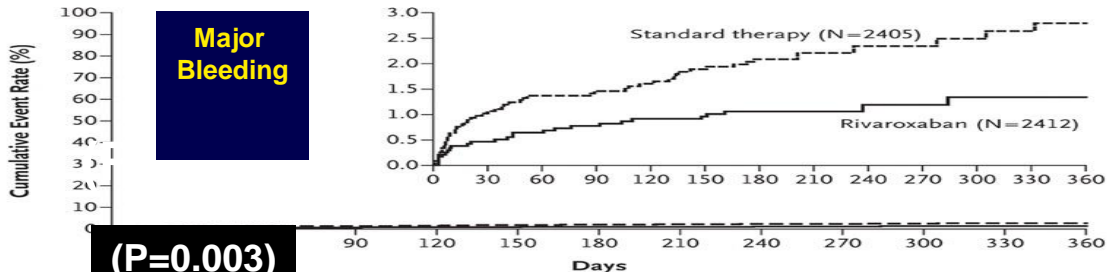
B Clinically Significant Bleeding



No. at Risk

Days	Rivaroxaban	Standard therapy
0	2412	2405
30	2183	2184
60	2133	2115
90	2024	1990
120	1953	1923
150	1913	1887
180	1211	1092
210	696	687
240	671	660
270	632	620
300	600	589
330	588	574
360	313	251

C Major Bleeding



No. at Risk

Days	Rivaroxaban	Standard therapy
0	2412	2405
30	2281	2270
60	2248	2224
90	2156	2116
120	2091	2063
150	2063	2036
180	1317	1176
210	761	746
240	735	719
270	700	680
300	669	658
330	659	642
360	350	278



Minor
PE

Non-massive
Low-risk
No RVD
Normal BNP and
troponins

SC LMWH or
fondaparinux

Low risk patients are treated with anticoagulation alone

Massive PE

- **Thrombolysis** (but contraindicated in 20- 40% pts')
- **Surgical Embolectomy**
- **Catheter Thrombectomy**



WHAT IS THE EVIDENCE FOR THE USE OF THROMBOLYSIS IN MASSIVE PE?



Fibrinolysis in high-risk PE

	Thrombolysis (n = 128)	Heparin (n = 126)	Odds Ratio
Recurrences	3.9%	7.1%	0.61 (0.23-1.62)
Deaths	6.2%	12.7%	0.47 (0.20-1.10)
Death or recurrence	9.4%	19.0%	0.45 (0.22-0.92)
Haemorrhage	21.9%	11.9%	1.98 (1.00-3.92)

Wan et al. Circulation 2004; 110: 744-9

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

Thrombolytic Therapy in Unstable Patients with Acute Pulmonary Embolism: Saves Lives but Underused

Paul D. Stein, MD,^{a,b} Fadi Matta, MD^{a,b}

^aDepartment of Research, St Mary Mercy Hospital, Livonia, Michigan; ^bDepartment of Medicine, Michigan State University College of Osteopathic Medicine, East Lansing.

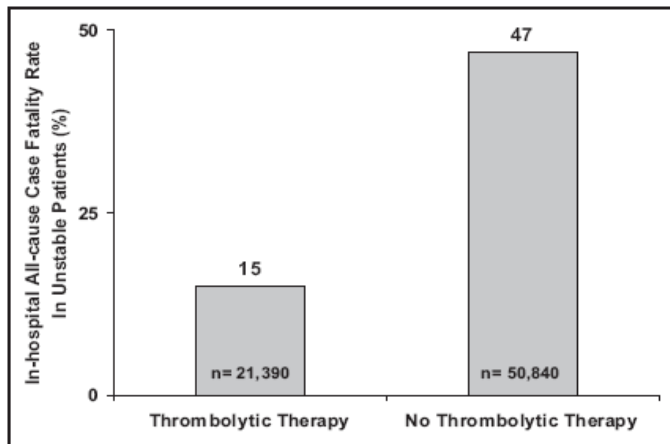


Figure 2 In-hospital all-cause case fatality rate in unstable patients with pulmonary embolism who received thrombolytic therapy and in those who did not. The number (n) in both groups is shown within the bar. Difference of mortality, $P < .0001$.

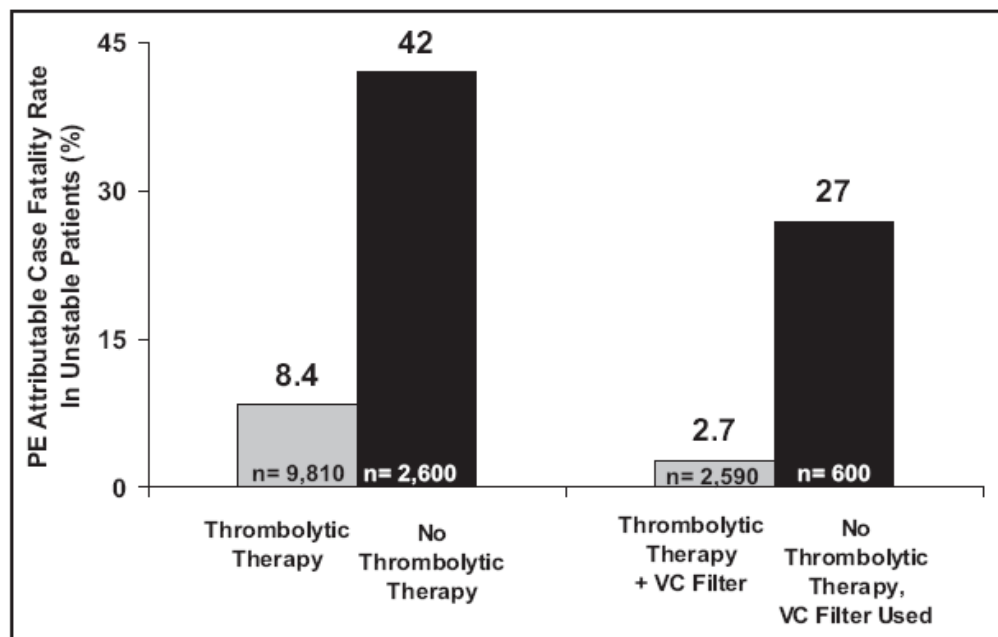


Figure 3 In-hospital death attributable to pulmonary embolism in unstable patients with pulmonary embolism. All unstable patients (left). Unstable patients who received a vena cava filter (right). The number (n) in each group is shown within the bar. Differences of case fatality rate, $P < .0001$. PE = pulmonary embolism; VC = vena cava.

HCUP Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 1998-2008. Agency for Healthcare Research and Quality, Rockville, MD. Available at: www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed November 11, 2011.

Intracerebral Hemorrhage with Thrombolytic Therapy for Acute Pulmonary Embolism

Paul D. Stein, MD,^{a,b} Fadi Matta, MD,^{a,b} David S. Steinberger, MD,^c Daniel C. Keyes, MD^{d,e}

^aDepartment of Research, St Mary Mercy Hospital, Livonia, Mich; ^bDepartment of Internal Medicine, College of Osteopathic Medicine, Michigan State University, East Lansing; ^cDepartment of Internal Medicine, St Mary Mercy Hospital, Livonia, Mich; ^dDepartment of Emergency Medicine, St Mary Mercy Hospital, Livonia, Mich; ^eDepartment of Emergency Medicine, St Joseph Mercy Hospital, Ann Arbor, Mich.

Table 3 Intracerebral Hemorrhage in All Patients Who Received Thrombolytic Therapy

	Intracerebral Hemorrhage	95% CI	P Value	Relative Risk* (95% CI)
All PE	430/49,500 (0.9%)	0.79-0.95		
Stable	280/27,900 (1.0%)	0.86-1.10		
Unstable	150/21,600 (0.7%)	0.58-0.80	.0003	0.7 (0.57-0.84)
Primary PE	250/39,300 (0.6%)	0.56-0.72		
Secondary PE	180/10,300 (1.7%)	1.50-2.00	<.0001	0.4 (0.30-0.44)

PE = pulmonary embolism.

*Stable vs unstable and primary vs secondary.

HCUP Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 1998-2008. Agency for Healthcare Research and Quality, Rockville, MD. Available at: www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed August 10, 2011.

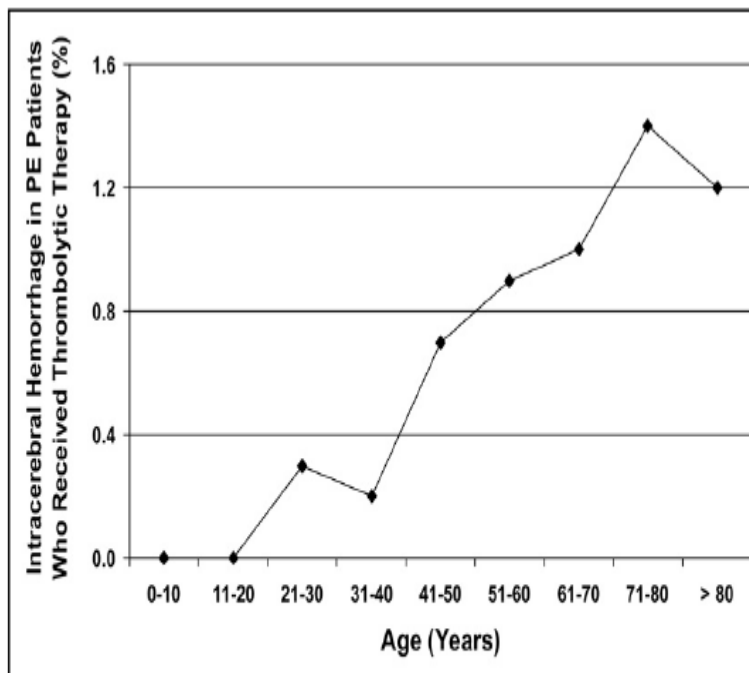
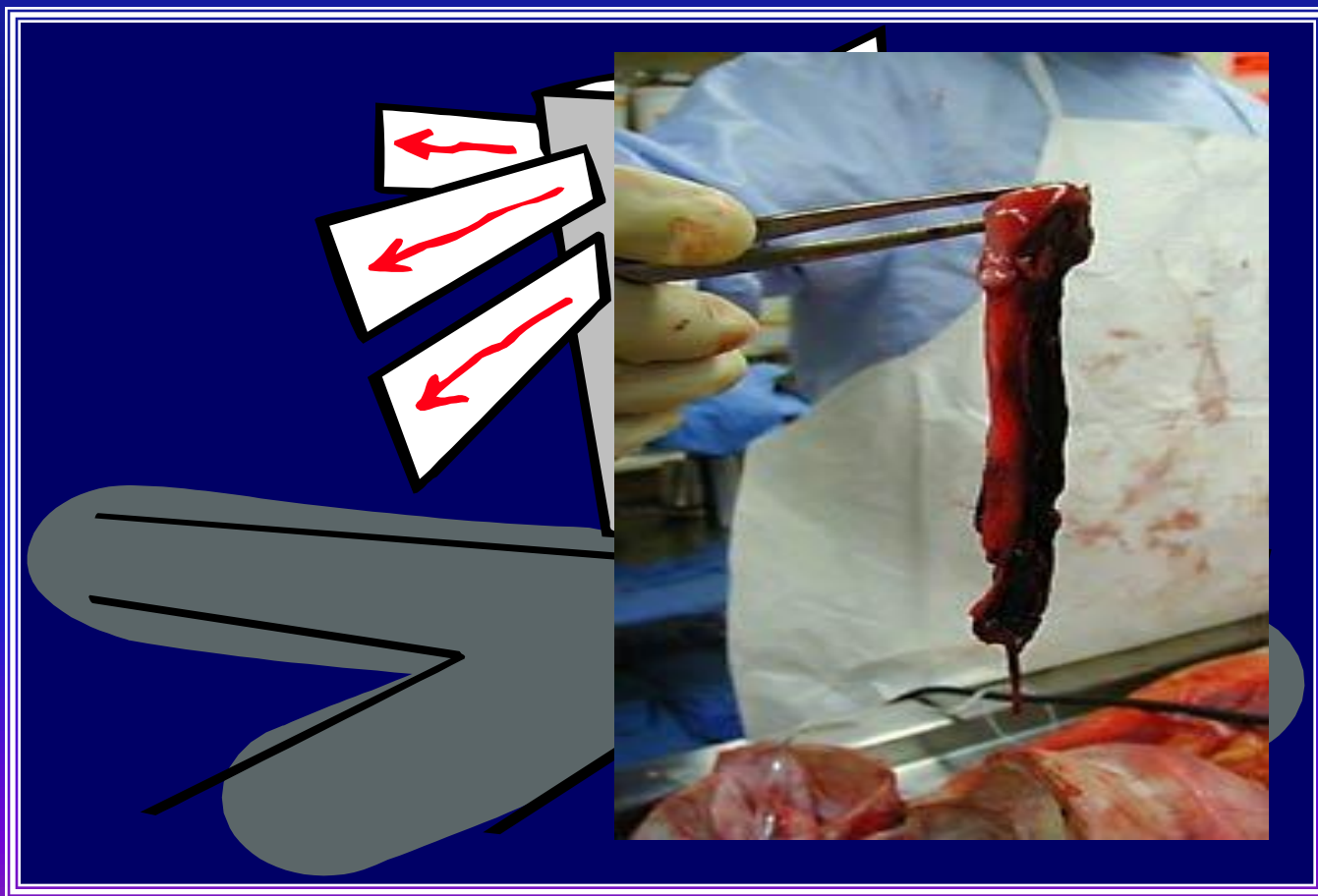


Figure 3 Proportion of patients with pulmonary embolism who received thrombolytic therapy and had an intracerebral hemorrhage in relation to age. For patients aged more than 10 years, $r = -0.9572$, $P = .0002$, slope = 0.1964/decade of age. PE = pulmonary embolism.

WHAT ARE THE ALTERNATIVES TO THROMBOLYSIS ?



Case Fatality Rate with Pulmonary Embolectomy for Acute Pulmonary Embolism

Paul D. Stein, MD, Fadi Matta, MD

Department of Research, St. Mary Mercy Hospital, Livonia, Mich; and Department of Osteopathic Medical Specialities, Michigan State University College of Osteopathic Medicine, East Lansing.

Table 4 Case Fatality Rate with Pulmonary Embolectomy According to Use of Vena Cava Filters

	Case Fatality Rate		Relative Risk	
	Fatal/Embolectomy (%)	95% CI		95% CI
II PE unstable				
Vena cava filter	130/520 (25)	22-29		
No vena cava filter	250/430 (58)*	53-63	0.43 ^a	0.36-0.51
All unstable	380/950 (40)	37-43		
II PE stable				
Vena cava filter	210/1500 (14)	12-16		
No vena cava filter	480/1320 (36)*	34-39	0.39 ^a	0.33-0.44
All stable	690/2820 (24)**	23-26	0.61 ^b	0.55-0.68
Primary PE unstable				
Vena cava filter	80/390 (21)	17-25		
No vena cava filter	155/280 (55)*	50-61	0.37 ^a	0.30-0.46
All primary unstable	235/670 (35)	32-39		
Primary PE stable				
Vena cava filter	105/960 (11)	9-13		
No vena cava filter	165/440 (38)*	33-42	0.29 ^a	0.23-0.36
All primary stable	270/1400 (19)**	17-21	0.55 ^b	0.47-0.64
Primary PE no comorbidity unstable				
Vena cava filter	10/130 (7.7)	4-14		
No vena cava filter	45/90 (50)*	40-60	0.15 ^a	0.08-0.29
All primary no comorbidity Unstable	55/220 (25)	20-31		
Primary PE no comorbidity stable				
Vena cava filter	35/440 (8.0)	6-11		
No vena cava filter	55/175 (31)*	25-39	0.25 ^a	0.17-0.37
All primary no comorbidity stable	90/615 (15)***	12-18	0.59 ^b	0.43-0.79

CI = confidence interval; PE = pulmonary embolism.

* $P < .0001$, filter vs no filter.

** $P < .0001$, stable vs unstable.

*** $P < .001$, stable vs unstable.

^aRelative risk vena cava filter vs no vena cava filter.

^bRelative risk stable vs unstable.

HCUP Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP); 1998-2008. Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.hcup-us.ahrq.gov/nisoverview.jsp. Last accessed December 5, 2011.



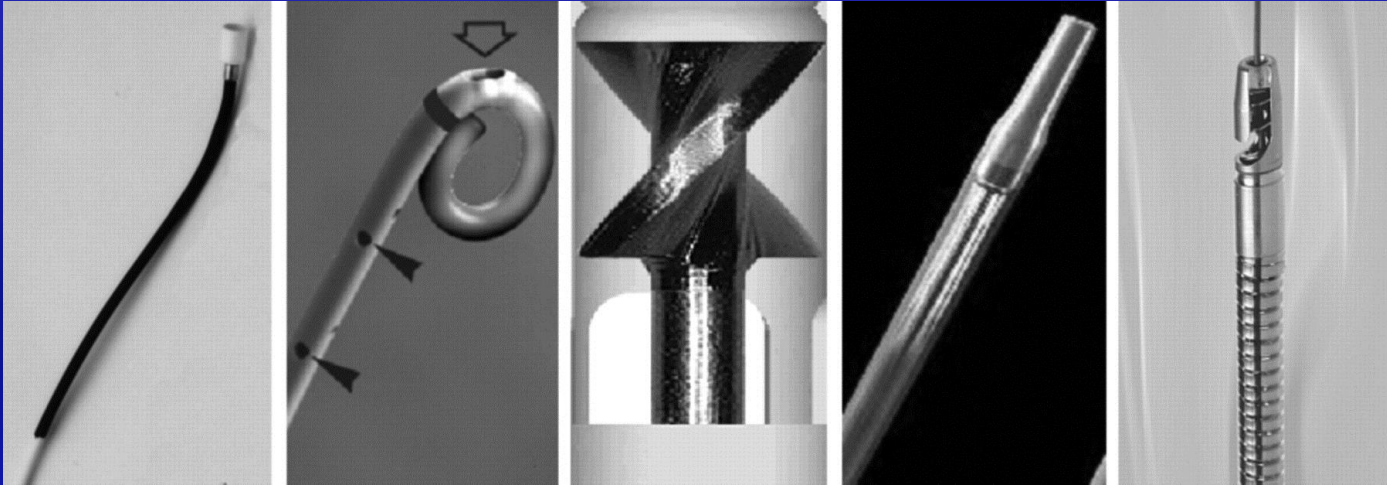
Catheter Thrombectomy

The only alternative to thrombolysis or surgical embolectomy

- 1. Hemodynamic instability**
- 2. Subtotal or total filling defect in left and/or right main PA**
- 3. Failed thrombolysis or contraindication to thrombolysis**



Catheter Thrombectomy



There currently are 4 categories of catheter interventional techniques for removing PE:

- **Aspiration thrombectomy (syringe suction applied to a vacuum suction cup at the tip of the catheter)**
- **Fragmentation (manually breaking clots with pigtail or Amplatz catheters)**
- **Rheolytic thrombectomy (a high-speed jet of saline)**
- **Rotational thrombectomy (ASPIREX)**



- **Limited experience**
- **Best results when pulmonary catheter embolectomy was used adjunct to thrombolytic therapy =**
“Pharmacomechanical Thrombolysis”
- **No RCT (Grade IIb C)**



Pooled data of hemodynamic parameters, clinical success rates, and rates of major bleeding in patients who underwent embolectomy with and without thrombolytic agents

Catheter Type and Technique	No. of Patients	Hemodynamic Parameters						Clinical Success n (%)	Major Bleeding	
		Mean Systemic BP		Mean PAP		† Mean PaO ₂			Catheter Insertion Site	Other Site
		Before	After	Before	After	Before	After			
Aspiration technique										
Greenfield/pulmonary embolectomy catheter										
No lytics ^{5-7,19-22}	89	60	81	33	21	46	81	72 (81)*	4 (15)	2 (2)
Systemic lytics ^{21,23}	9	50	87	31	20	50	75	9 (100)	0 (0)	0 (0)
Local lytics ²⁰	9	—	—	31	24	—	—	9 (100)	0 (0)	0 (0)
Systemic and local ²⁴	1	—	—	20	19	—	—	1 (100)	0 (0)	0 (0)
Fragmentation technique										
Pigtail or other angiographic catheter										
No lytics ^{25,26}	3	28	63	38	29	32	77	2 (67)	0 (0)	0 (0)
Systemic lytics ²⁷	21	70	93	25	21	—	—	15 (71)	0 (0)	0 (0)
Local lytics ^{12,25,28-35}	121	67	81	33	22	53	90	115 (95)	1 (1)	1 (1)
Systemic and local ^{26,43,34}	30	65	69	32	30	37	135	24 (80)	2 (7)	1 (3)
Amplatz catheter										
No lytics ^{36,37}	8	86	108	49	53	—	—	7 (88)	1 (13)	0 (0)
Local lytics ^{36,37}	6	85	93	64	60	—	—	6 (100)	0 (0)	0 (0)
Rheolytic technique										
Rheolytic angiojet catheter										
No lytics ^{4,38,39}	8	—	—	42	30	85	91	6 (75)	0 (0)	0 (0)
Local lytics ^{40,41}	23	—	—	—	—	—	—	20 (87)	0 (0)	0 (0)
Hydrolyzer catheter										
Local lytics ^{42,44}	12	47	97	46	30	73	94	11 (92)	0 (0)	0 (0)
Systemic and local ⁴³	8	—	—	43	36	—	—	8 (100)	0 (0)	0 (0)

* Clinical success with steel cup = 23 of 27 patients (85%); clinical success with plastic cup = 49 of 62 patients (79%).

† Preoperative blood gases were obtained under varying levels of FiO₂.

Abbreviations as in Table 1.



Complications of catheter thrombectomy

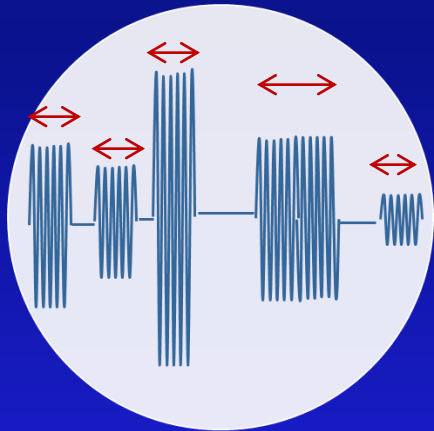
- Pericardial tamponade
- Pulmonary hemorrhage
- Pulmonary artery perforation
- Distal embolization



Ultrasound accelerated thrombolysis

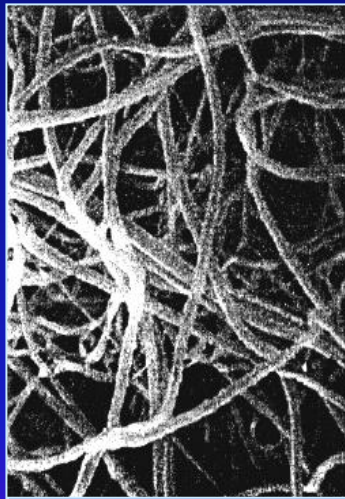
Mechanism of Action

Ultrasound pulses

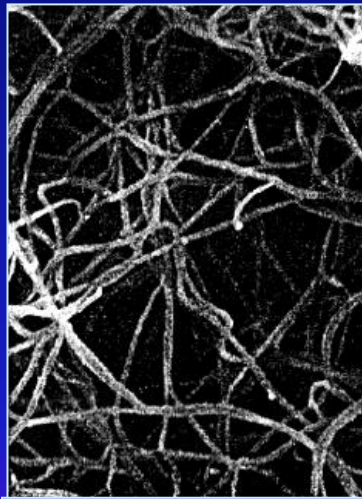


Ultrasound delivered in:
High frequency (2.2 Mhz)
Low power (0.5 W per element)
Pulses of varying waveforms

Fibrin separation

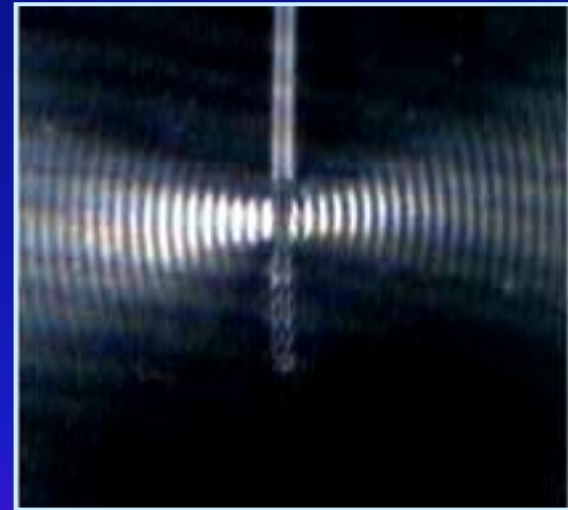


**Fibrin without
Ultrasound**



**Fibrin With
Ultrasound**

Active drug delivery by acoustic streaming



The ULTIMA Trial

A Prospective, Randomized, Controlled Study of
Ultrasound Accelerated Thrombolysis for the
Treatment of Acute Pulmonary Embolism

EKOS EkoSonic® Mach 4e Endovascular System

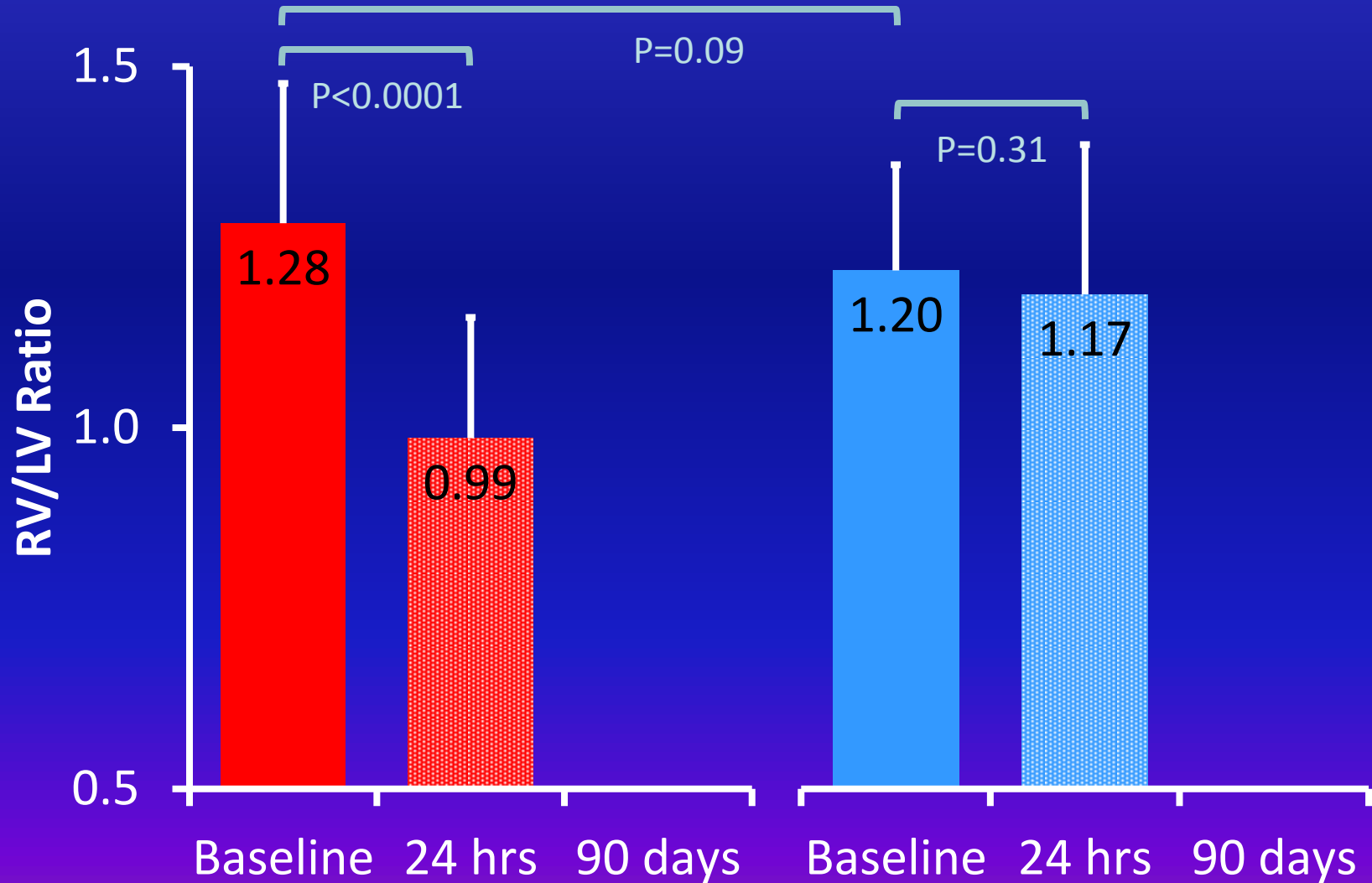


Nils Kucher, M.D.
Clinics for Angiology & Cardiology
University Hospital Bern
Bern, Switzerland

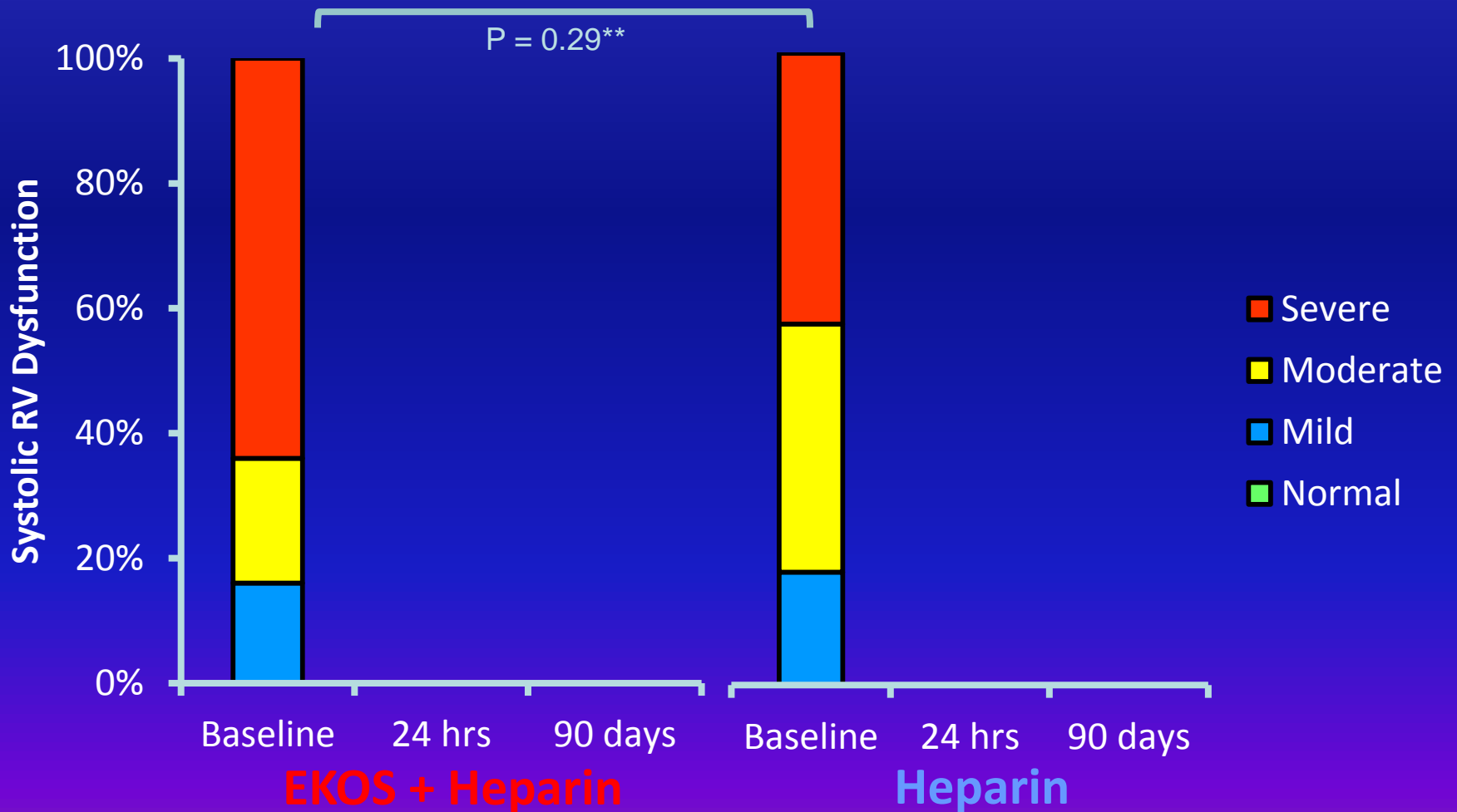
59 Patients



RV/LV ratio (echo)



Systolic RV dysfunction

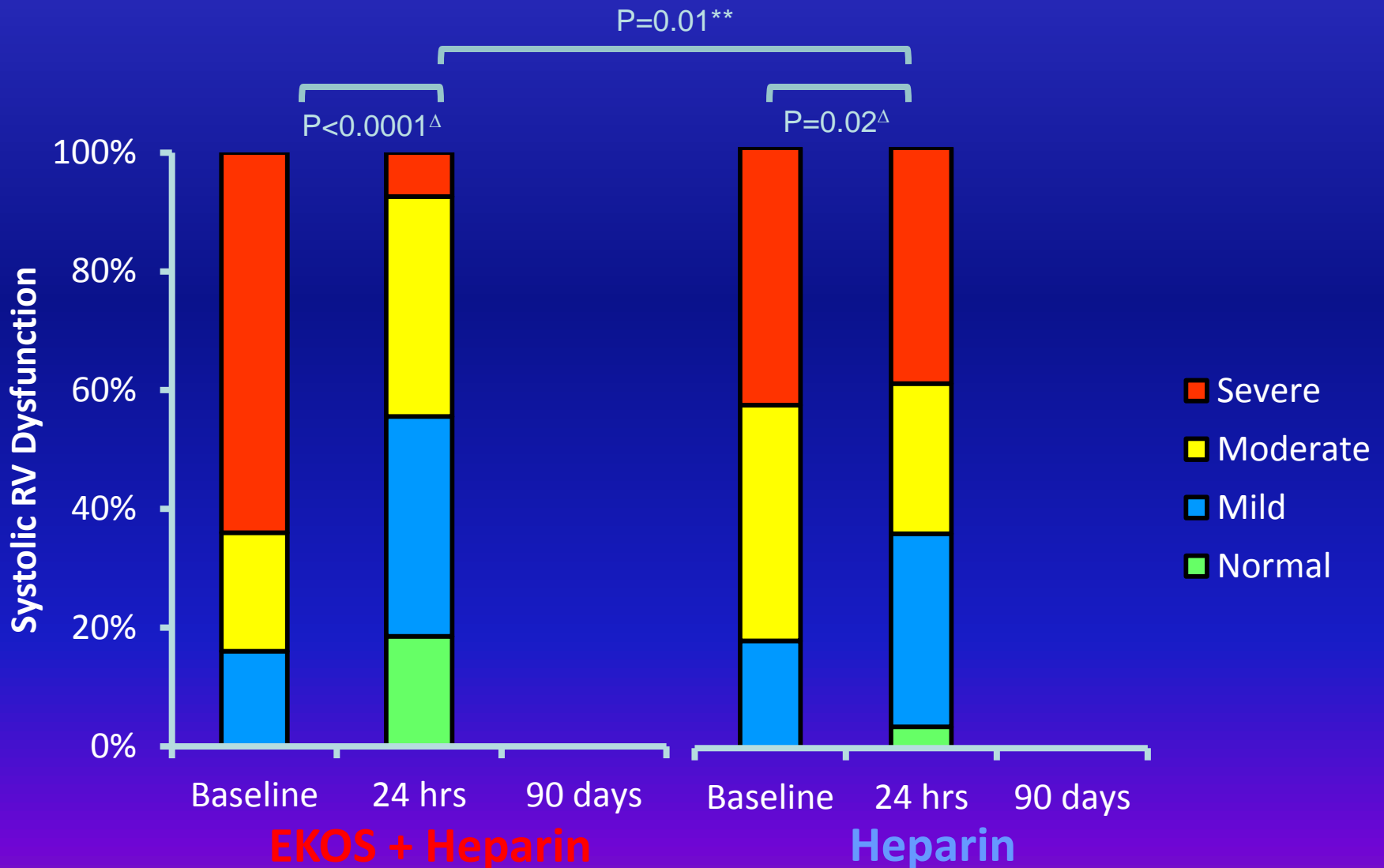


**Two-sided exact Mantel-Haenzel test

Δ Wilcoxon rank sum test



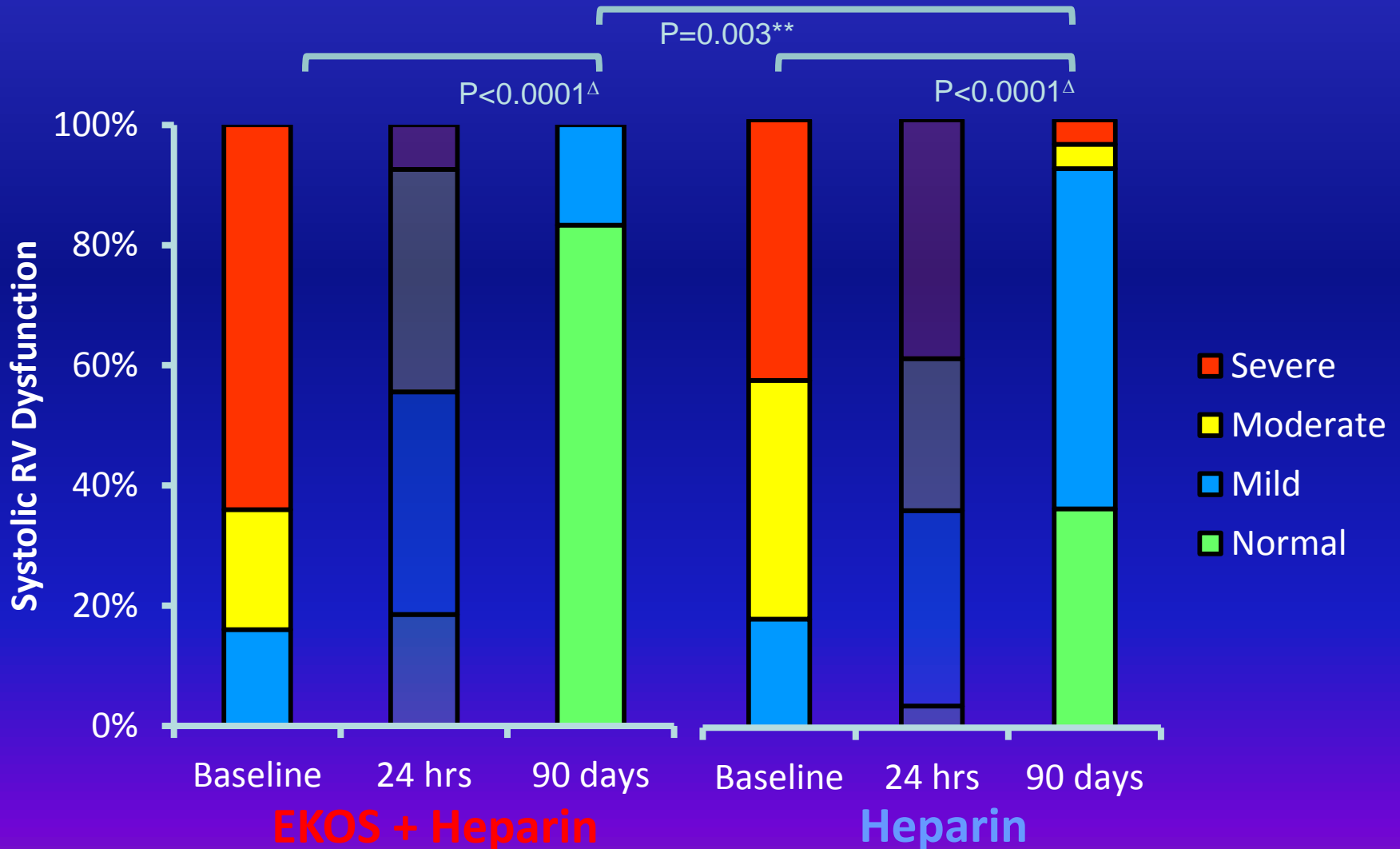
Systolic RV dysfunction



**Two-sided exact Mantel-Haenzel test

Δ Wilcoxon rank sum test

Systolic RV dysfunction

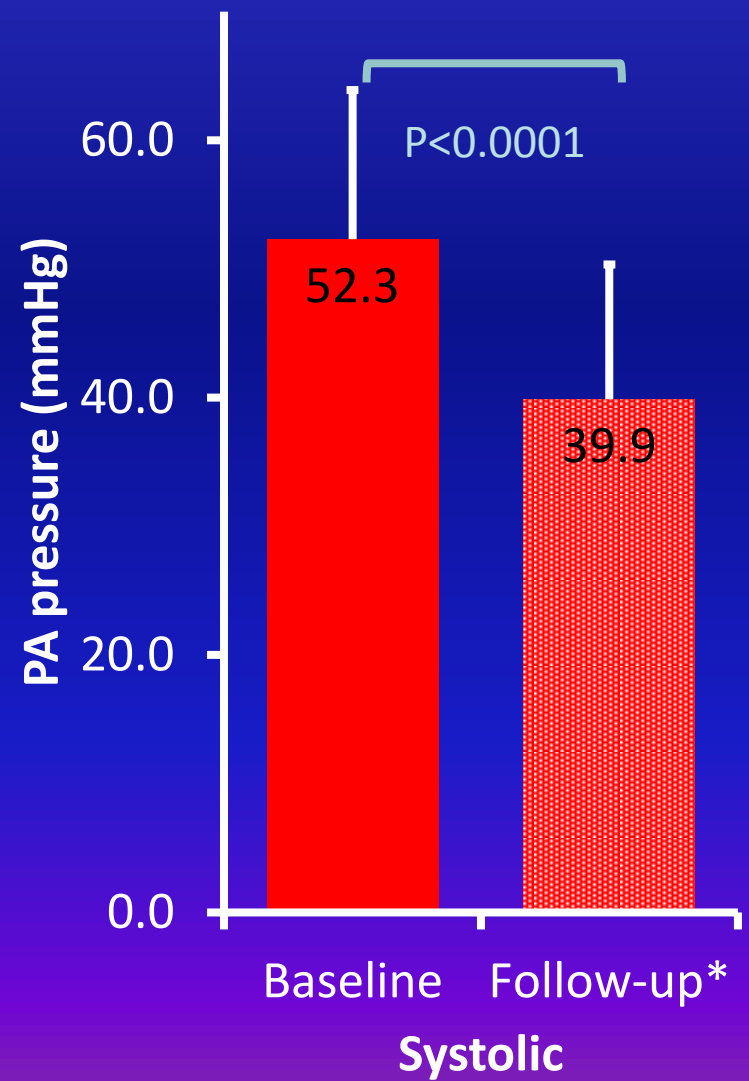


**Two-sided exact Mantel-Haenzel test

^Δ Wilcoxon rank sum test



Invasive PA pressure (EKOS group)



* Measurements obtained at 18 ± 3 hours after initiation of therapy



Sub-massive PE

- 25-40 % of all PE
- 3-15% mortality



Thrombolytic Therapy for Sub-massive PE

- The effect of thrombolytic agents on the outcome of hemodynamically stable patients who have sub-massive PE has been debated for decades:
 - The risk of serious hemorrhage associated with thrombolytic therapy
 - Patients may gradually improve with heparin Tx alone



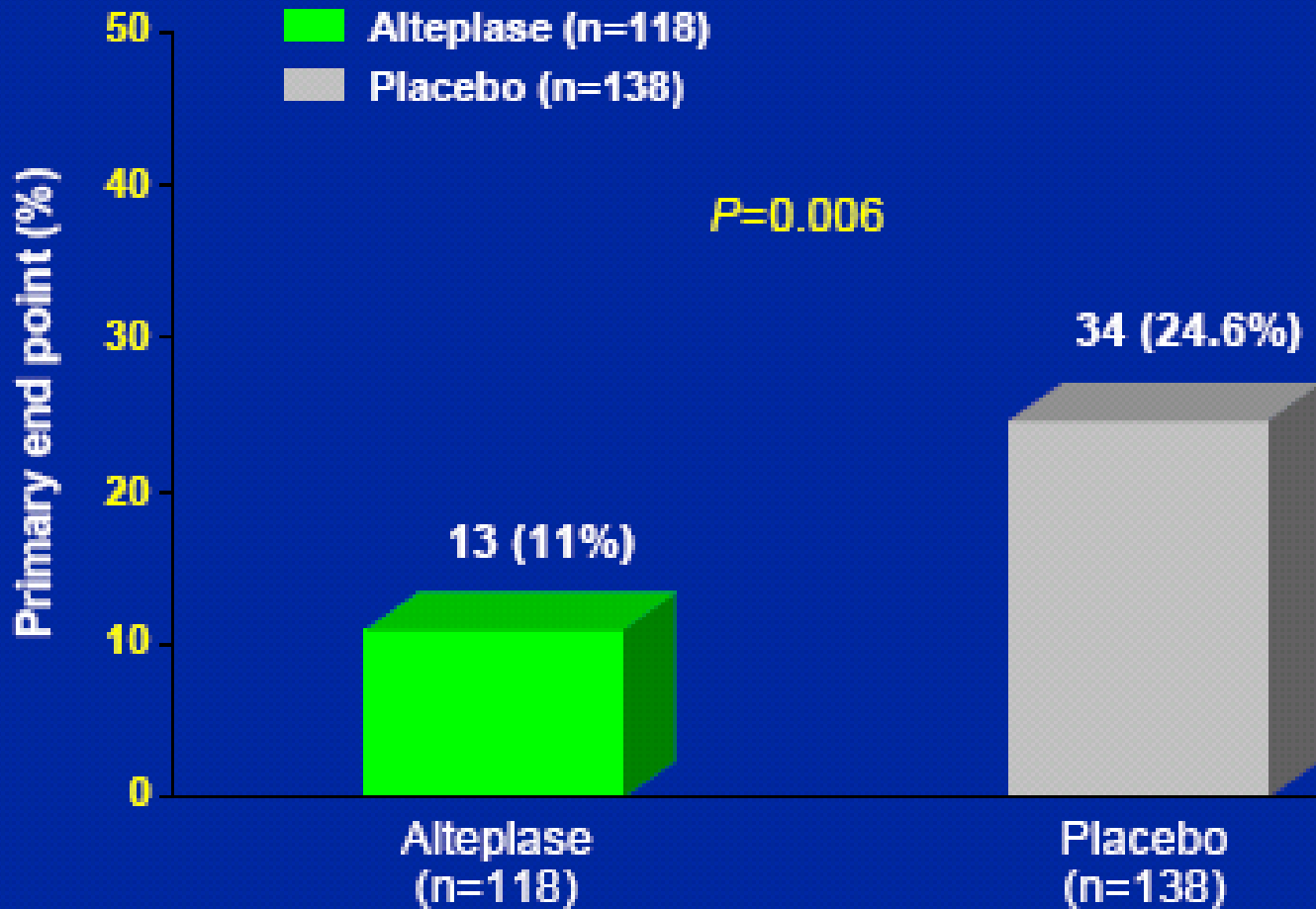
HEPARIN PLUS ALTEPLASE COMPARED WITH HEPARIN ALONE IN PATIENTS WITH SUBMASSIVE PULMONARY EMBOLISM **MAPPET-3**

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* (N Engl J Med 2002;347:1143-50.)

- **Multicenter randomized placebo-controlled trial**
- **118 pts w/ sub-massive PE were randomized to receive heparin plus alteplase vs heparin plus placebo**



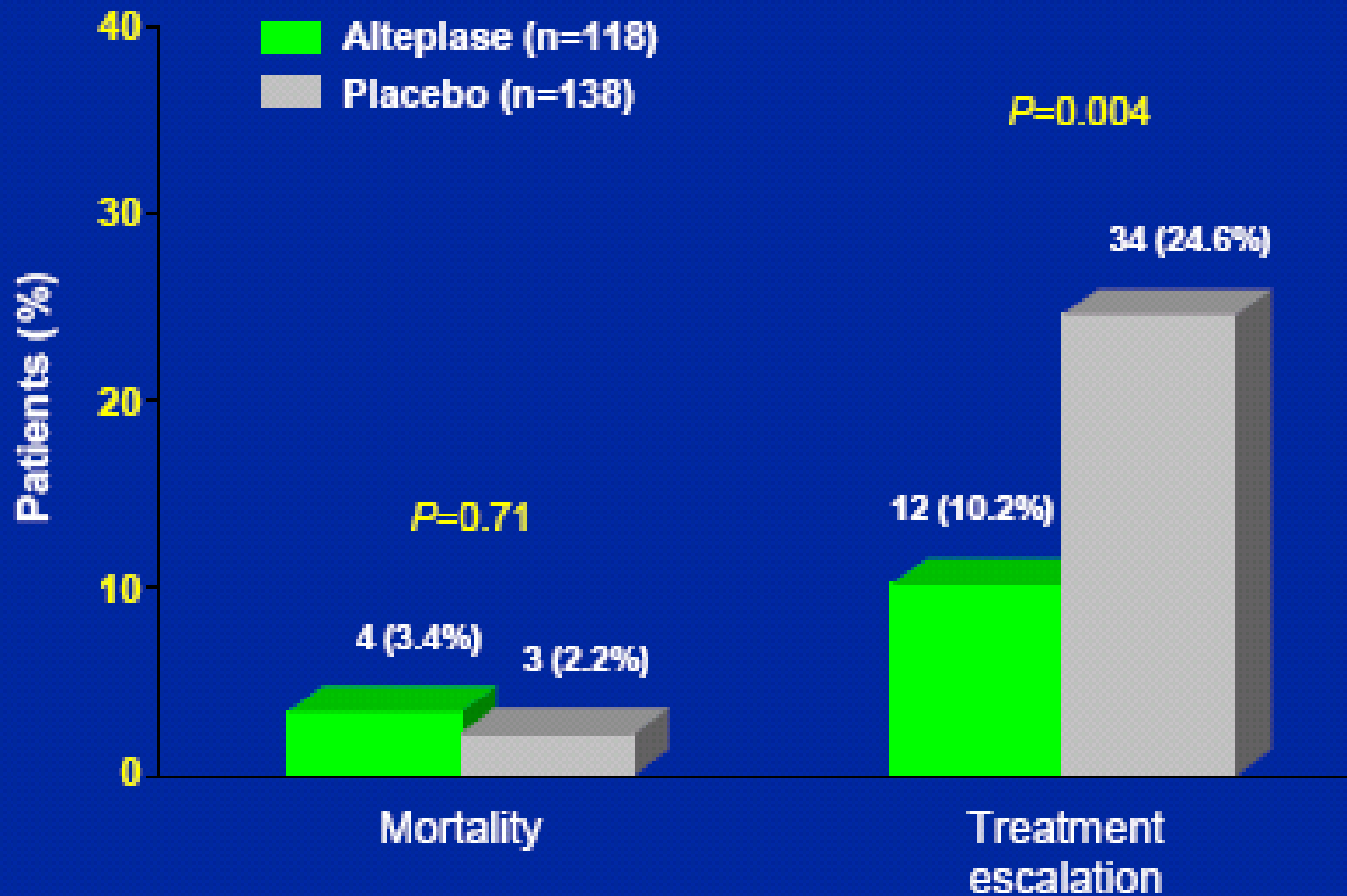
Mortality Or Escalation of Treatment



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



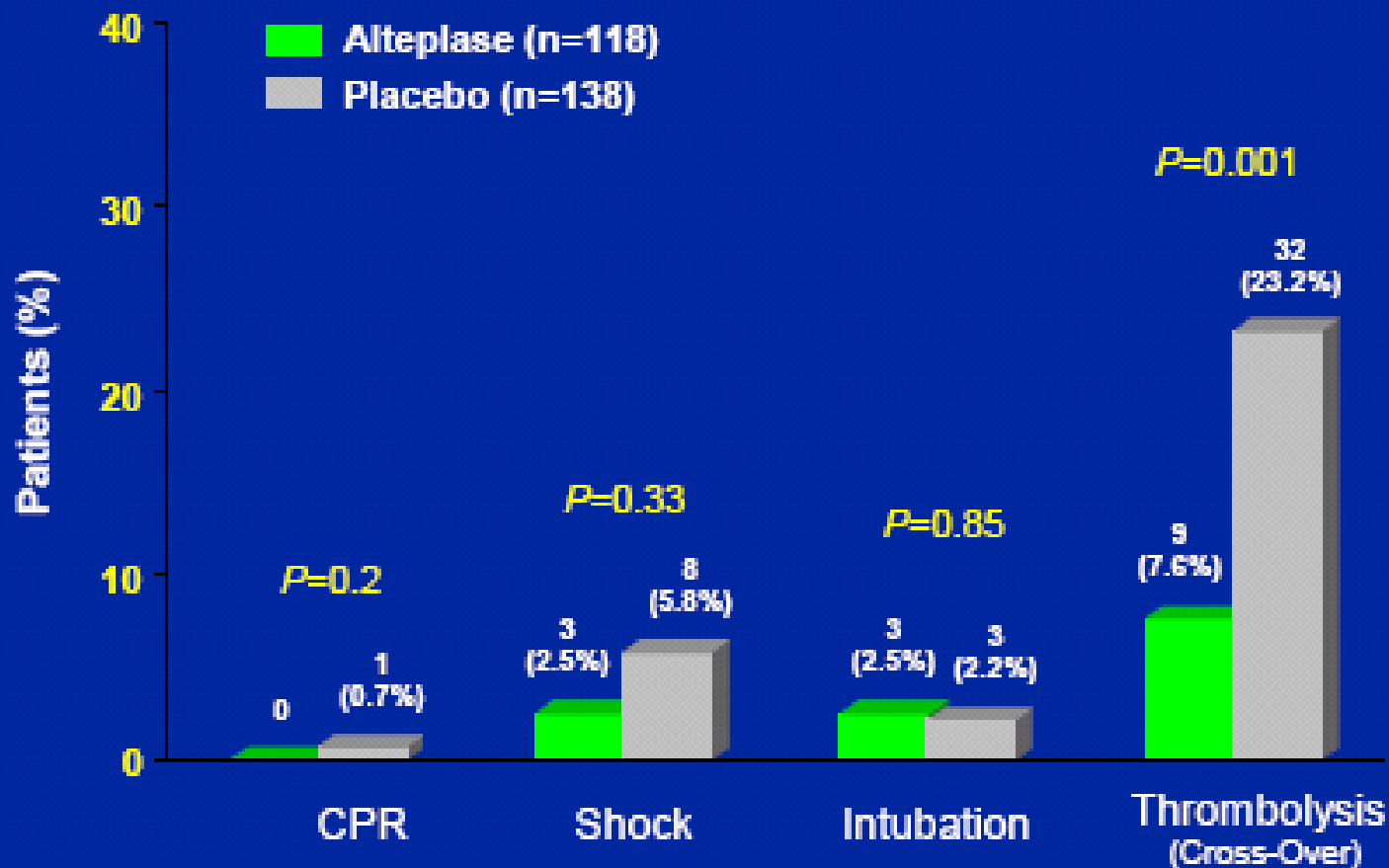
Analysis of the Primary End Point



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



Analysis of Escalation of Treatment



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

Fibrinolysis in intermediate-risk PE



European Heart Journal
doi:10.1093/eurheartj/ehn310

ESC GUIDELINES

Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Routine use of thrombolysis in non-high-risk patients is not recommended, but may be considered in selected patients with intermediate-risk PE and after thorough consideration of conditions increasing the risk of bleeding. Thrombolytic therapy should be not used in patients with low-risk PE.

Grade IIb, level B

Torbicki et al. Eur Heart J 2008; 29: 2276-2315



Fibrinolysis for submassive PE

AHA PE Guidelines 2011

- Submassive PE: severe RV dysfunction, or major myocardial necrosis, or worsening respiratory insufficiency, with low risk of bleeding (class IIb, Level of evidence C)

(Circulation 2011; 123: 1788-1830)



The logo for the PEITHO study, featuring the word "PEITHO" in a stylized, rounded font. The letters "P", "E", "I", "T", and "H" are red, while "O", "E", "I", "T", and "H" are blue. The letters are slightly overlapping and have a soft shadow effect.

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 (or spiral CT) and laboratory evidence of right ventricular dysfunction.

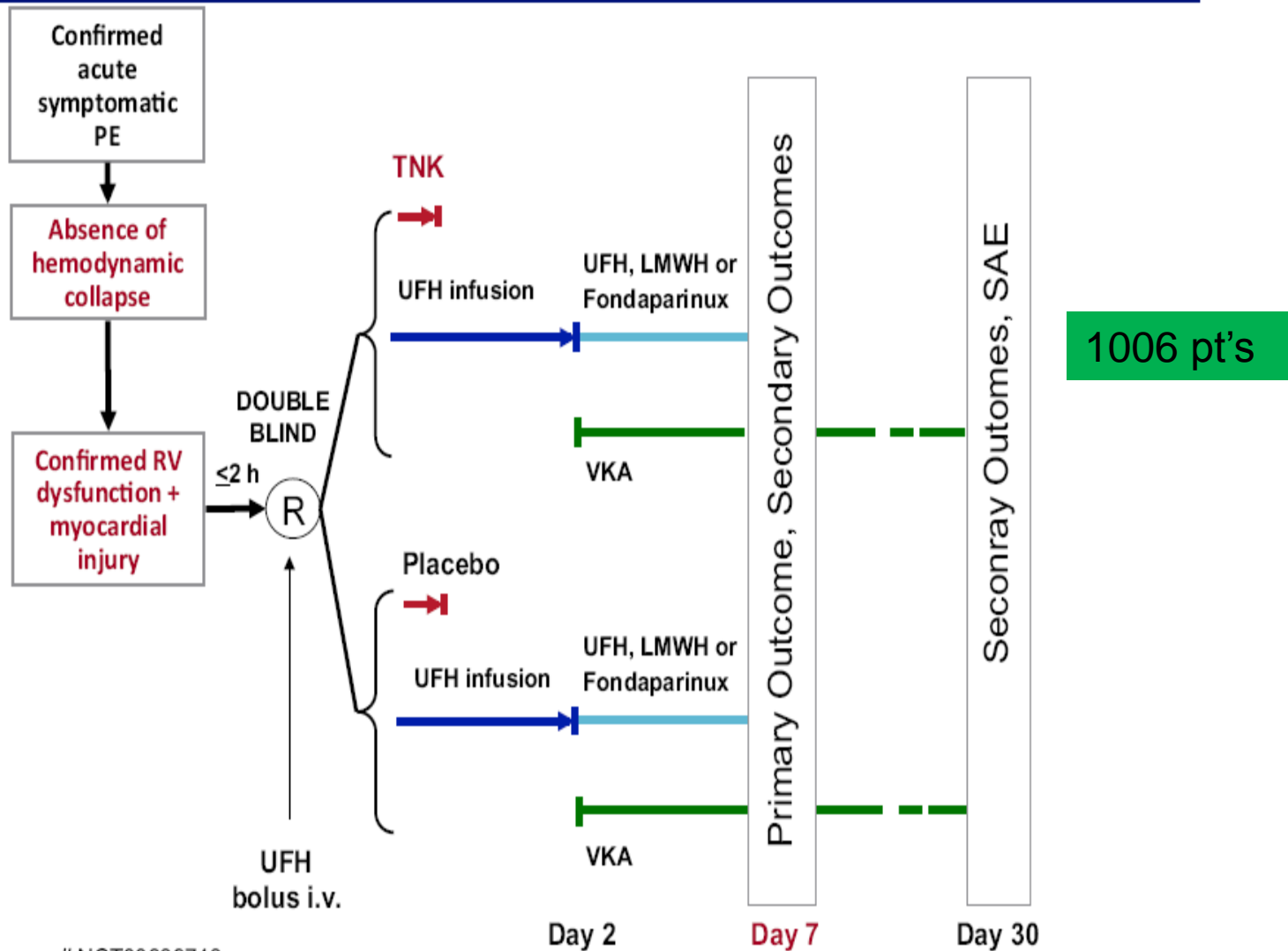


PEITHO: Inclusion criteria

- 1) Age \geq 18 years
- 2) Acute PE confirmed by:
 - a) lung scan, *or*
 - b) spiral CT, *or*
 - c) pulmonary angiogram
- 3) RV dysfunction *plus* myocardial injury:
 - a) echocardiography *or* CT
PLUS
 - b) positive troponin I *or* T test



PEITHO: Overview of study design



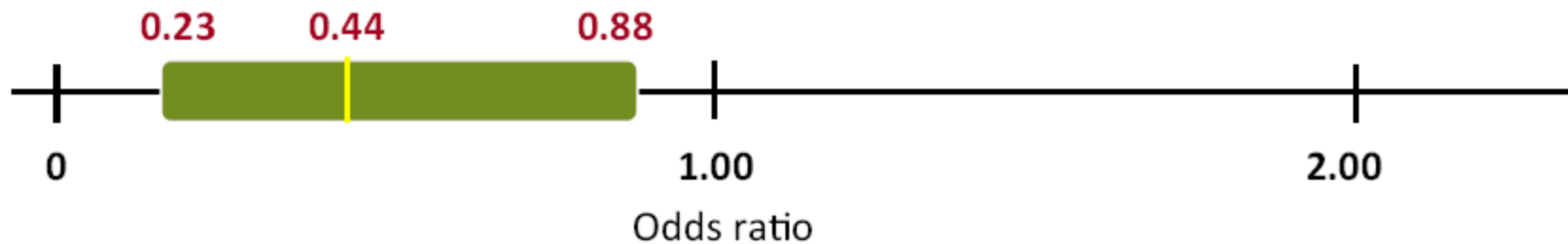
ClinicalTrials.gov # NCT00639743
 EudraCT # 2006-005328-18

S Konstantinides for the PEITHO Steering Committee. Am Heart J 2012;163:33-38.e1



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



Thrombolysis superior

PEITHO: Analysis of primary efficacy outcome

	Tenecteplase (n=506)		Placebo (n=499)		P value
	n	(%)	n	(%)	
All-cause mortality within 7 days	6	(1.2)	9	(1.8)	0.43
Hemodynamic collapse within 7 days	8	(1.6)	25	(5.0)	0.002
Need for CPR	1		5		
Hypotension / blood pressure drop	8		18		
Catecholamines	3		14		
Resulted in death	1		6		

All stroke	2.4%	0.28%	0.03
Major bleeding	6.3%	1.5%	<0.005

PEITHO: Conclusions

- ❖ In patients with intermediate-risk pulmonary embolism, intravenous bolus tenecteplase significantly reduced the primary end point of death or hemodynamic collapse within 7 days of randomization.
- ❖ The results of PEITHO justify the concept of risk stratification of normotensive patients with acute PE.
- ❖ They confirm the notion that early “advanced” (recanalization) treatment prevents clinical deterioration in patients with evidence of right ventricular dysfunction and myocardial injury.
- ❖ In PEITHO, the benefits of thrombolysis came at the cost of a significantly increased risk of major, particularly intracranial, hemorrhage.
- ❖ The patient’s age should be taken into account when weighing the expected benefits versus risks of systemic thrombolysis in clinical practice.



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 Am.J.Card 2013

“Safe Dose” t-PA

- For $\geq 50\text{Kg}$ = 10mg in 1 min followed by 40 mg in 2 hr
- For $< 50\text{ Kg}$ = 0.5mg/Kg total dose : 10 mg in 1 min followed by remainder in 2 hr

Concomitant Anticoagulation

TG

- Enoxaparin (80%) : 1mg/Kg/SQ (not to exceed 80 mg for initial dose)
- Heparin (20%) Bolus = 70 U /Kg, and not to exceed 6000U

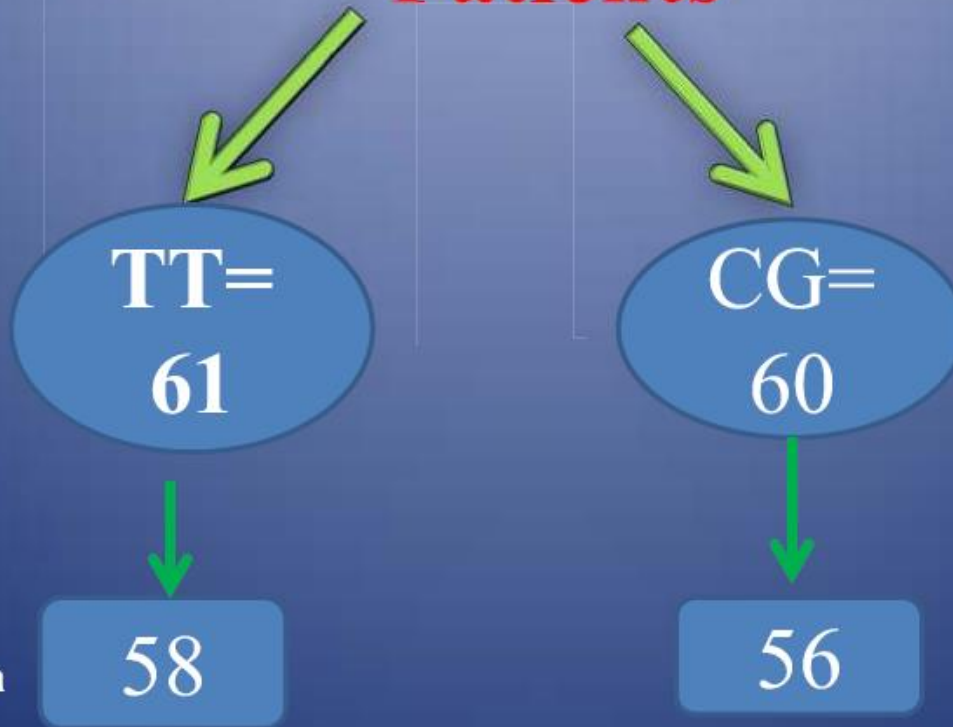
Maintenance 10 U/Kg/ Hr while tPA being infused (not to exceed 1000U/Hr)
1 hr after termination of t-PA increased to 18 U/Kg/Hr

Adjusted to PTT 1.5-2 X baseline



MOPETT Trial

121
Patients



F/U= 28±5 m



Primary Endpoints

	TG N=58	CG N=56	p Value
Pulmonary HTN at 28 m	9 (16)	32 (57)	p<0.001
Pulmonary HTN + recurrent PE at 28 m	9 (16)	35 (63)	p<0.001

Pulmonary HTN= PASP> 40 mmHg



Secondary Endpoints

	TG N= 61	CG N=60	p Value
Recurrent PE	0	3 (5)	0.077
Mortality	1(1.6)	3 (5)	0.301
PE + Mortality	1 (1.6)	6 (10)	0.0489
Hospital Stay	2.2±0.5	4.9±0.8	<0.001
In-hospital Bleeding	0	0	-



Conclusions

- **Low dose thrombolysis is safe and effective in moderate PE**
- **Rapid reduction in PA pressures**
- **Reduction of Pul HTN & recurrent PE at 28 m**
- **No bleeding/ ICH**



Treatment Protocol I

- **All patients admitted to the ICCU were closely monitored for:**

Respiratory status :

(RR and O₂ saturation)

Hemodynamic status:

(BP,HR,urine output)



Treatment Protocol II

- Unfractionated heparin (UFH) with a target PTT of 80-90 seconds
- Daily echocardiographic exams to evaluate RV size , function and PA pressure were preformed
- Escalation therapy (thrombolysis or embolectomy) was considered if the clinical status of the patient deteriorated or did not improve within 24-48hrs

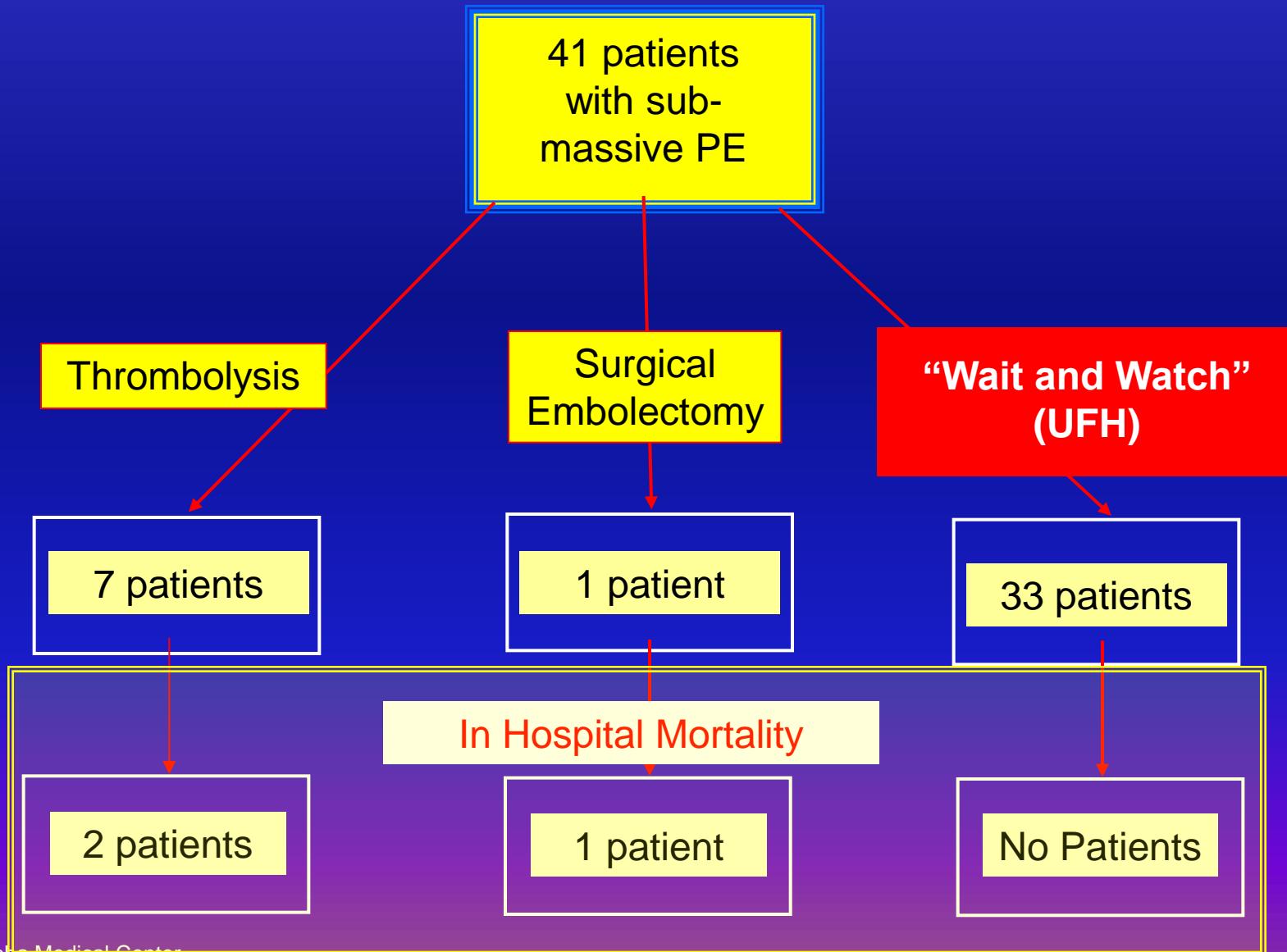


Risk Markers and Clinical Characteristics

Risk Marker (number of patients)		Clinical Characteristics (at admission to ICCU)		
RV Dysfunction	Elevated Troponin	Blood Pressure (MAP)	Pulmonary Hypertension (maximal SPAP)	O2 Saturation in room air
41(100%)	24(59%)	100±13mmHg	54±16mmHg	88%



Outcome-Summary

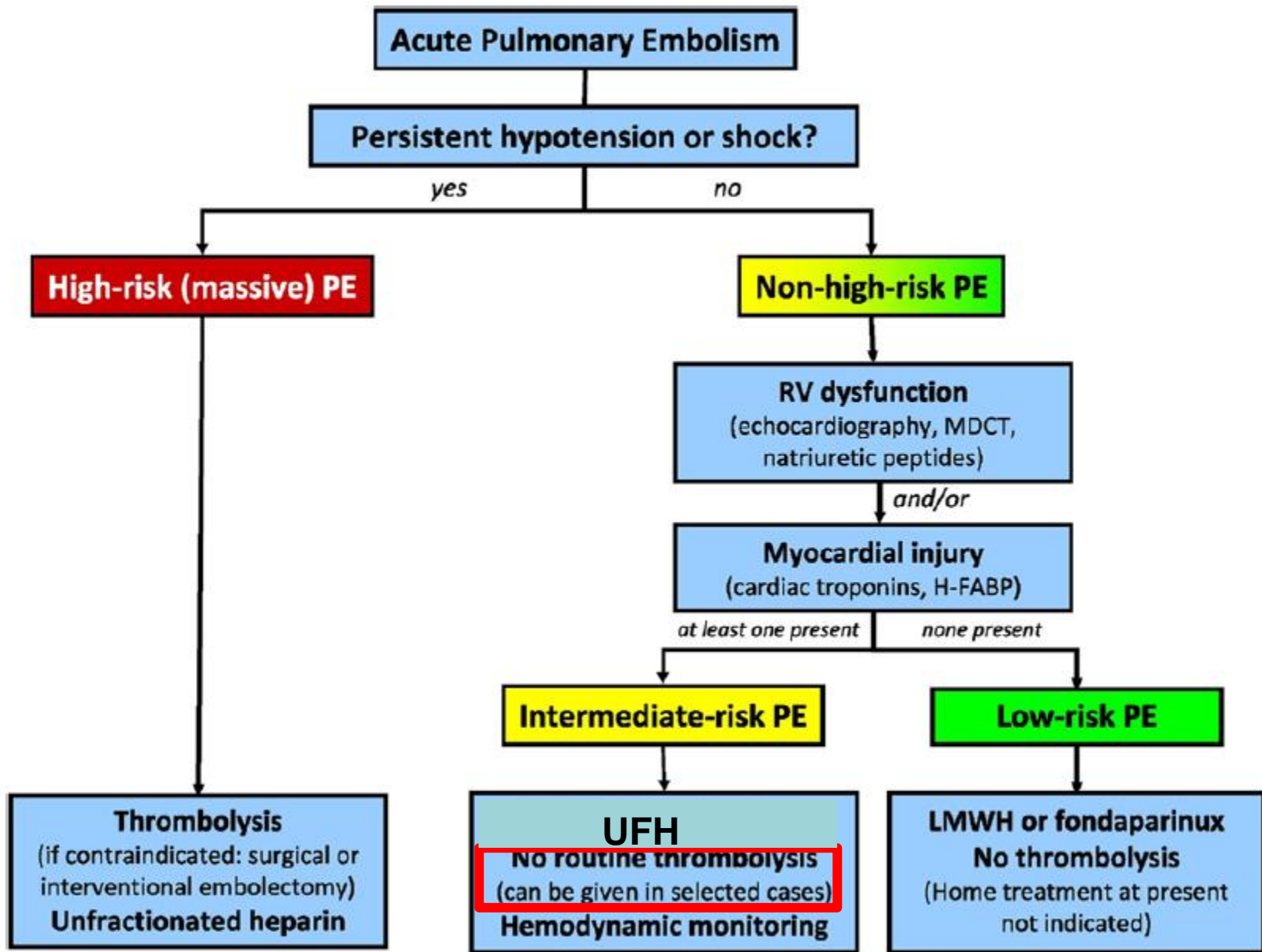


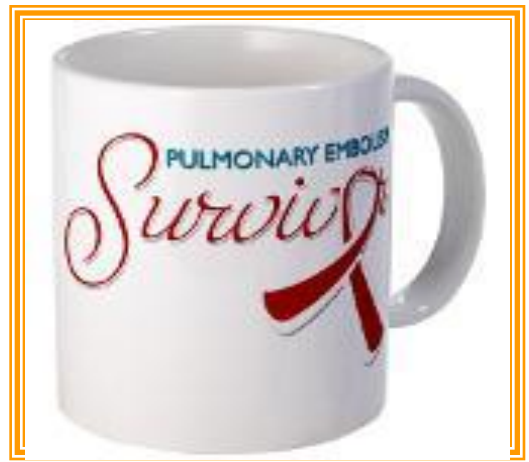
“Wait and watch” (UFH)- Outcome

Improved RV Size and Function	Improvement in Hypoxemia	Pulmonary Hypertension at Admission	Pulmonary Hypertension After Treatment	In Hospital Mortality
25(100%)*	33(100%)	52±15* mmHg	37±12* mmHg	0 (0%)

*Data available for 25 patients







Thank you