MORNING
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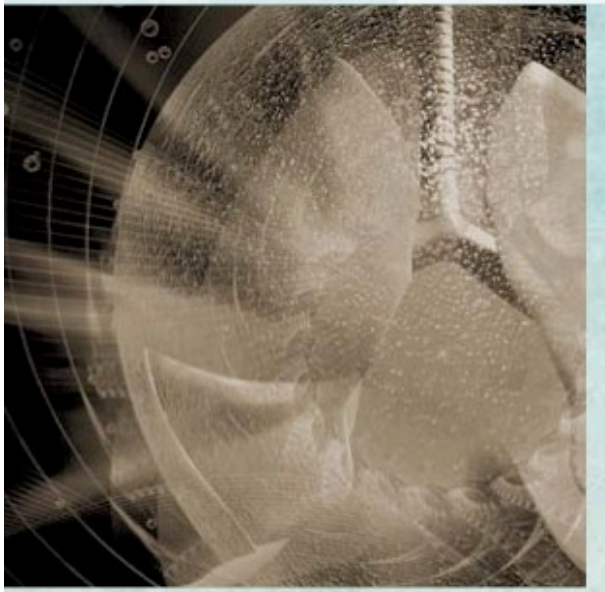
CHEST 2014



Evolving Strategies in Venous Thromboembolism

Thrombolysis in PE

Richard Channick, MD


Thrombolysis in PE
Richard Channick, M.D.
Massachusetts General Hospital

Disclosures

- Nothing to disclose

Objectives

- Identify patients that may benefit from thrombolytic therapy for VTE

PE: Pathophysiology

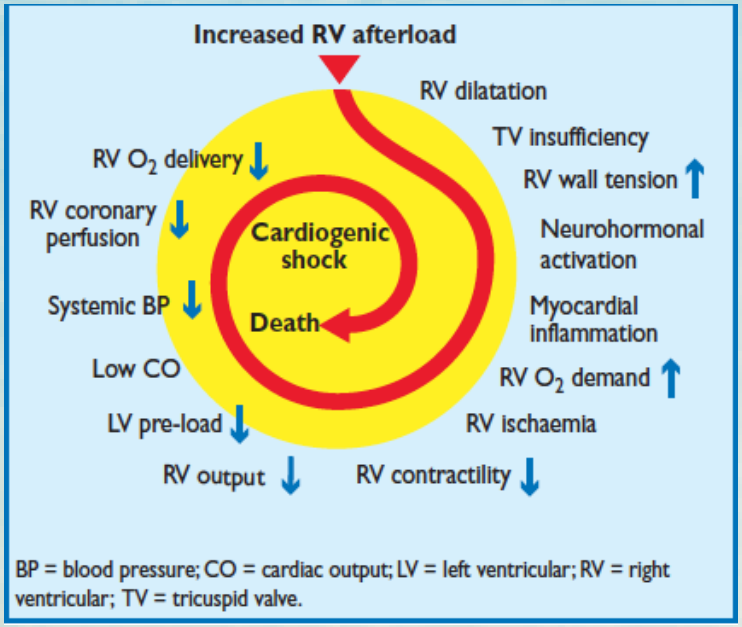
- The consequences of acute PE are primarily *hemodynamic* and become manifest when 30–50% of the pulmonary arterial bed is obstructed
- Secondary and less important mechanisms: *Inflammatory mediator release* with pulmonary vasoconstriction, atelectasis, shunting, surfactant dysfunction

Why Give Thrombolytics? Only 2 possible reasons

- Save lives
- Reduce morbidity (and costs), short or long term, including the sequelae of VTE: CTEPH and post-phlebitic syndrome

PE: Pathophysiology

- When the pulmonary vascular bed is obstructed by ~ 75%, the RV must generate a systolic pressure > 50 mmHg (mean PAP ~ 40 mmHg) to maintain perfusion. A normal RV cannot typically attain this pressure and *fails*



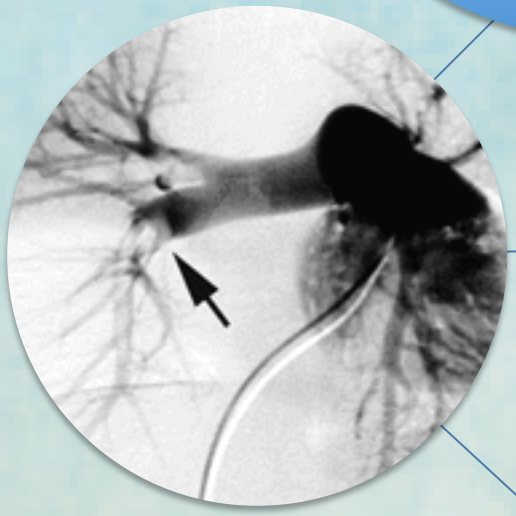
BP = blood pressure; CO = cardiac output; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.

ARS Question

What defines “submassive” PE?

A. Size of the embolus, i.e. main/lobar vs. segmental
B. Comorbidities
C. Blood pressure
D. The effect the PE is having on the right ventricle

PE: Clinical Presentation



Non Massive

Low Risk

NL RV & Biomarkers

Submassive

Intermediate Risk

+/- RV dysfunction

+/-Biomarkers

Massive

High Risk

Massive vs. Submassive PE

Massive PE

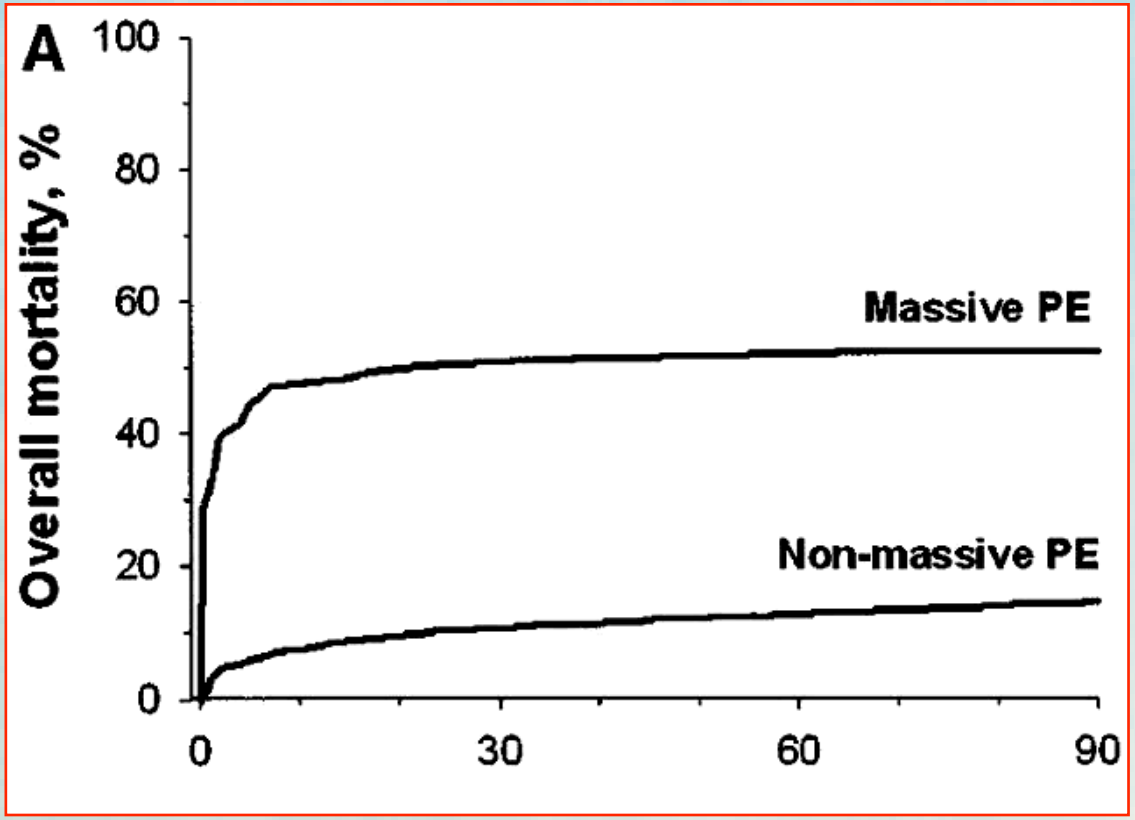
- SBP<90mmHg or decrease ≥ 40 mmHg from baseline for > 15 min
- Inotropic support
- Pulselessness
- Persistent bradycardia (HR < 40 bpm)

Submassive PE

- SBP≥90mmHg
- RV dysfunction
- RV dilatation ECHO or CT (RV/LV diameter > 0.9)
- BNP > 90 pg/mL
- EKG changes
- Myocardial necrosis:
  - Troponin I > 0.4 ng/mL
  - Troponin T > 0.1 ng/mL

Circulation 2011;123:1788

PE Mortality (ICOPER)



52.4%*

15%

***62.5% from recurrent PE**

Kucher et al Massive PE Circulation 2006

PE patients with right ventricle dysfunction (RVD) unresolved prior to discharge suffered **3X** mortality rate than patients whose RVD resolved

ORIGINAL INVESTIGATION

Association of Persistent Right Ventricular Dysfunction at Hospital Discharge After Acute Pulmonary Embolism With Recurrent Thromboembolic Events

Stefano Grifoni, MD; Simone Vanni, MD; Simone Magazzini, MD; Iacopo Olivotto, MD; Alberto Conti, MD;

PE related mortality rate at 3 years:

- 13.3% if RVD unresolved at discharge
- 4.4% if RVD resolved at discharge

bolism (VTE).

Methods: Echocardiography was used to assess RVD on admission and before hospital discharge in 301 consecutive patients with the first episode of acute pulmonary embolism occurring from January 1998 through July 2004. Right ventricular dysfunction was diagnosed in the presence of 1 or more of the following: right ventricular dilation (without hypertrophy), paradoxical septal systolic motion, and Doppler evidence of pulmonary hypertension. Patients were followed up at 2, 6, and 12 months and yearly thereafter. The primary end point was symptomatic, recurrent fatal or nonfatal VTE.

increased risk of recurrent VTE (14 patients, 9.2% patient-years) compared with those without RVD (15 patients, 3.1% patient-years) or RVD regression (3 patients, 1.1% patient-years) ($P=.001$). Six of 8 deaths related to pulmonary embolism occurred in patients with RVD persistence. At multivariate analysis, adjusted by anticoagulant treatment duration, RVD persistence was an independent predictor of recurrent VTE (hazard ratio, 3.79; $P<.001$).

Conclusion: Persistent RVD at hospital discharge after an acute pulmonary embolism is associated with recurrent VTE.

Arch Intern Med. 2006;166:2151-2156

Patients with right heart dysfunction defined as RVD/LVD > 0.9 have a significantly higher chance of adverse events within 30 days

Adverse event rate:

54% if RVD/LVD ratio < 0.9

82% if RVD/LVD ratio ≥ 0.9

OR : 4.02 (p=0.041)

Computed Tomography

Prognostic Role in Acute Pulmonary Embolism

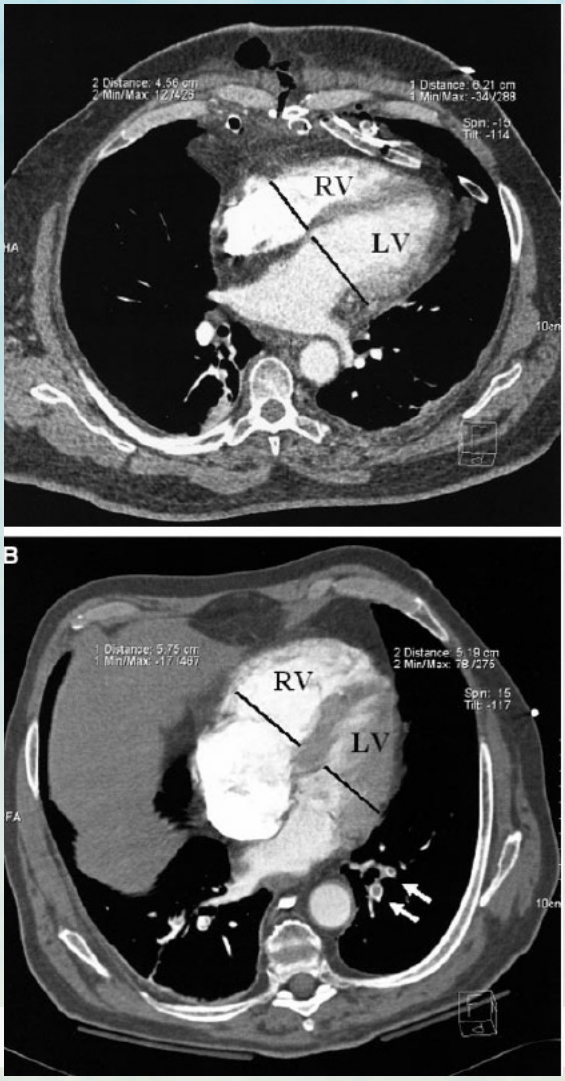
Rene Quiroz, MD, MPH*; Nils Kucher, MD*; U. Joseph Schoepf, MD; Florian Kipfmueller, BS; Scott D. Solomon, MD; Philip Costello, MD; Samuel Z. Goldhaber, MD

Background—We investigated the prognostic role of right ventricular enlargement on multidetector-row chest CT in acute pulmonary embolism (PE).

Methods and Results—We studied 63 patients with CT-confirmed PE who underwent echocardiography within the ensuing 24 hours. Adverse clinical events, defined as 30-day mortality or the need for cardiopulmonary resuscitation, mechanical ventilation, pressors, rescue thrombolysis, or surgical embolectomy, were present in 24 patients. We performed off-line CT measurements of right and left ventricular dimensions (RV_D, LV_D) with axial and 2-dimensional reconstructed 4-chamber (4-CH) views. The proportion of patients with $RV_D/LV_D>0.9$ on the axial view was similar in patients with (70.8%) and those without adverse events (71.8%; $P=0.577$). In contrast, $RV_D/LV_D>0.9$ on the 4-CH view was more common in patients with (80.3%) than without (51.3%; $P=0.015$) adverse events. The area under the curve of RV_D/LV_D from the axial and 4-CH views for predicting adverse events was 0.667 and 0.753, respectively. Sensitivity and specificity of $RV_D/LV_D>0.9$ for predicting adverse events were 37.5% and 92.3% on the axial view and 83.3% and 48.7% on the reconstructed 4-CH view, respectively. $RV_D/LV_D>0.9$ on the 4-CH view was an independent predictor for adverse events (OR, 4.02; 95% CI, 1.06 to 15.19; $P=0.041$) when adjusted for age, obesity, cancer, and recent surgery.

Conclusions—Right ventricular enlargement on the reconstructed CT 4-CH views predicts adverse clinical events in patients with acute PE. Ventricular CT measurements obtained from 4-CH views are superior to those from axial views for identifying high-risk patients. (*Circulation.* 2004;109:2401-2404.)

Key Words: tomography ■ embolism ■ prognosis ■ thrombosis



Guidance in the Literature for Treatment of Massive/Submassive PE: Very Little

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
Learn and Live℠

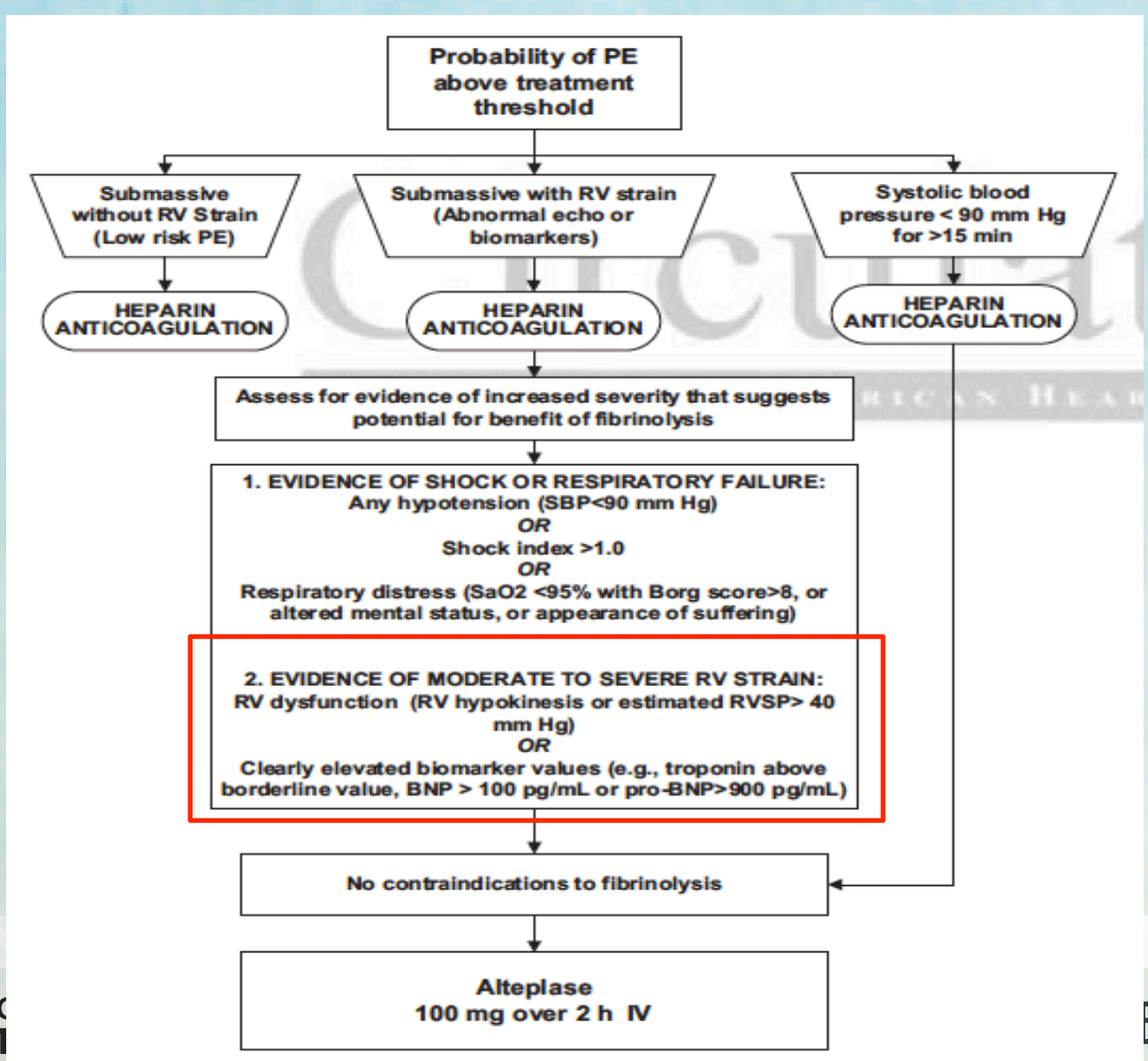
Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association

Michael R. Jaff, M. Sean McMurtry, Stephen L. Archer, Mary Cushman, Neil Goldenberg, Samuel Z. Goldhaber, J. Stephen Jenkins, Jeffrey A. Kline, Andrew D. Michaels, Patricia Thistlethwaite, Suresh Vedantham, R. James White, Brenda K. Zierler and on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Peripheral Vascular Disease, and Council on Arteriosclerosis, Thrombosis and Vascular Biology

Circulation published online Mar 21, 2011;

Circulation 2011;123:1788-830

Acute Massive/Submassive PE Therapy



Thrombolysis for PE: Recent Trials

Full dose systemic lysis:

-PEITHO

-TOPCOAT

Reduced dose lysis:

-MOPPET: half dose systemic lysis

-ULTIMA, SEATTLE II: Ultrasound enhanced lysis

ARS Question

What was the primary conclusion of the PEITHO trial?

A. tPA reduces mortality in submassive PE
B. Tenectaplase reduces the likelihood of death or hemodynamic collapse at day 7
C. Thrombolysis has a more favorable risk/benefit ratio in older patients with submassive PE
D. Tenectaplase is the treatment of choice in patients with large PEs, provided RV function is normal

PEITHO: A 10 Year Trial to Finally Answer the Question

- Purpose:
  - To investigate the benefit and safety of thrombolysis (Tenecteplase) versus placebo for normotensive patients with intermediate risk PE.

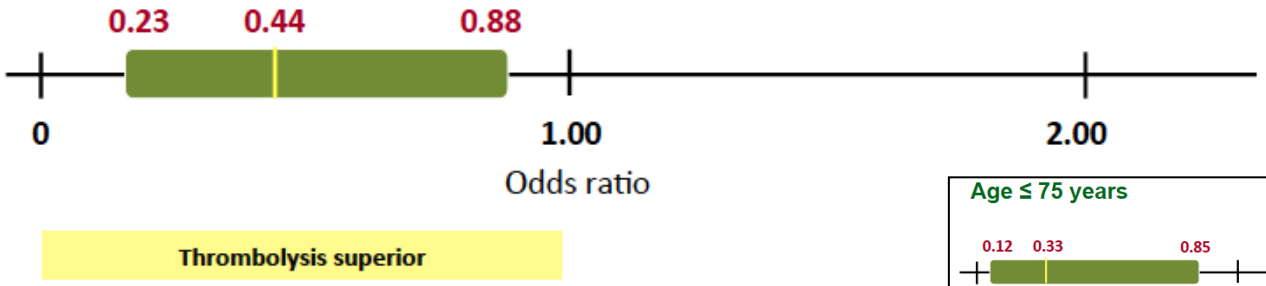
- Randomized Trial
  - double blind
  - placebo controlled
  - 1006 patients

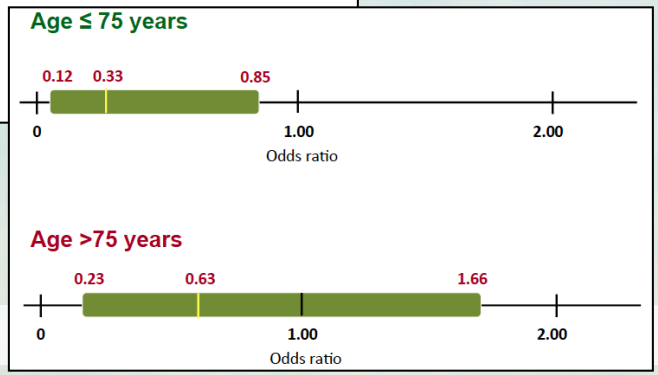
PE-related early MORTALITY RISK		RISK MARKERS: CLINICAL (Shock or hypotension)	RISK MARKERS: RV Dysfunction	RISK MARKERS: Myocardial injury	Potential treatment implications
HIGH > 15%		+	(+)*	(+)*	Thrombolysis or Embolectomy
NON HIGH	Inter mediate 3 - 15%	–	+	+	Thrombolysis?
			+	–	Hospital Admission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

Meyer et al. N Engl J Med 2014; 370:1402-1411

PEITHO

	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



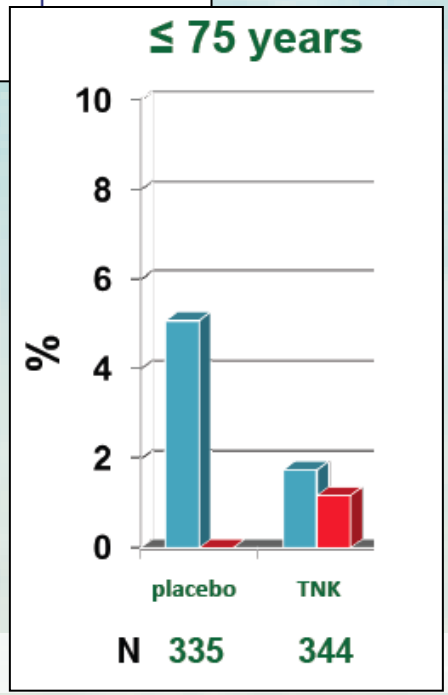


Meyer et al. N Engl J Med 2014; 370:1402–1411

Intravenous Thrombolysis
PEITHO

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
Non-intracranial major bleeding	**32**	**(6.3)**	**6**	**(1.5)**	**<0.001**
Severe	16		2		
Moderate	16		4		

- **Death or hemodynamic collapse (primary EP)**
- **Stroke *without* primary EP *(not* leading to death or hemodynamic collapse)**



TOPCOAT

- Investigator-initiated, Industry-funded
- Double blind RCT
- Novel composite endpoint: favorable composite patient-oriented outcome at 90 days
- 8 U.S. centers
- Ended early due to principal investigator changing jobs (!)

Kline et al J Thromb Haemost. 2014.;12:459-68

Intravenous Thrombolysis
TOPCOAT

5 Days

Adverse outcome	PLACEBO		TENECTEPLASE	
TOTAL	**3**	**7%**	**1**	**3%**
Death	*1*	*2%*	*1*	*3%*
Circ shock + thrombectomy	*1*	*2%*	*0*	*0%*
Intubation + thrombectomy	*1*	*7%*	*0*	*0%*

Kline et al J Thromb Haemost. 2014

Intravenous Thrombolysis
TOPCOAT

90 Days

Adverse outcome	PLACEBO		TENECTEPLASE	
TOTAL UNIQUE PATIENTS	**13**	**30%**	**5**	**12.5%**
Poor functional capacity	2	5%	3	7.5%
Recurrent VTE	1	2%	1	2.5%
Low perception of wellness	2	5%	0	0%
Two of the above	**7**	**16%**	**1**	**2.5%**
All three of the above	1	2%	0	0%

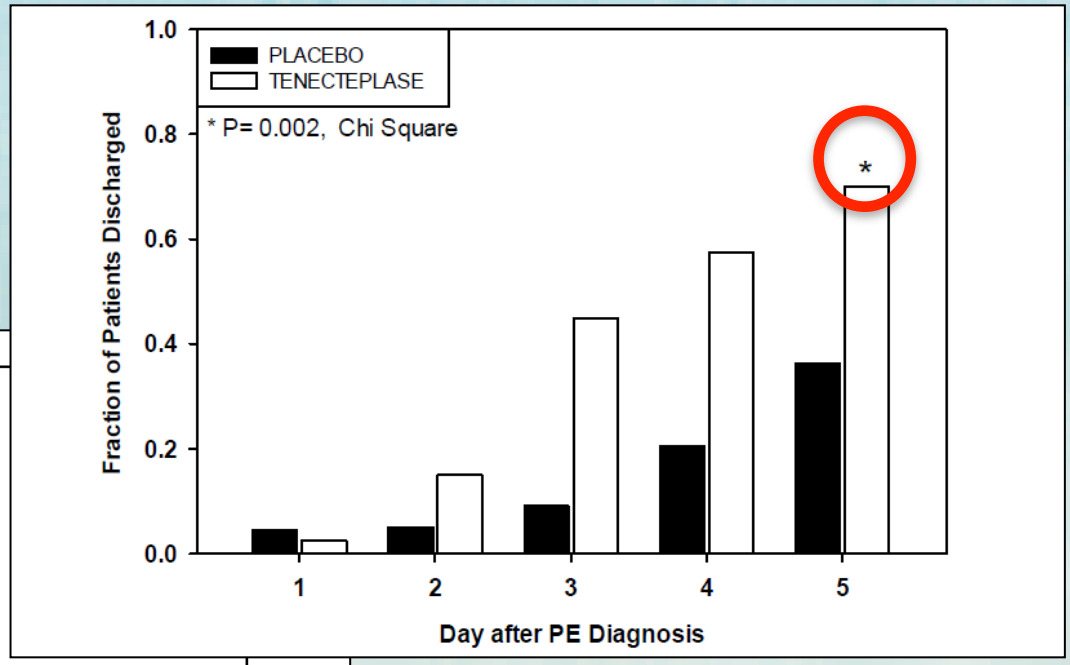
Kline et al J Thromb Haemost. 2014

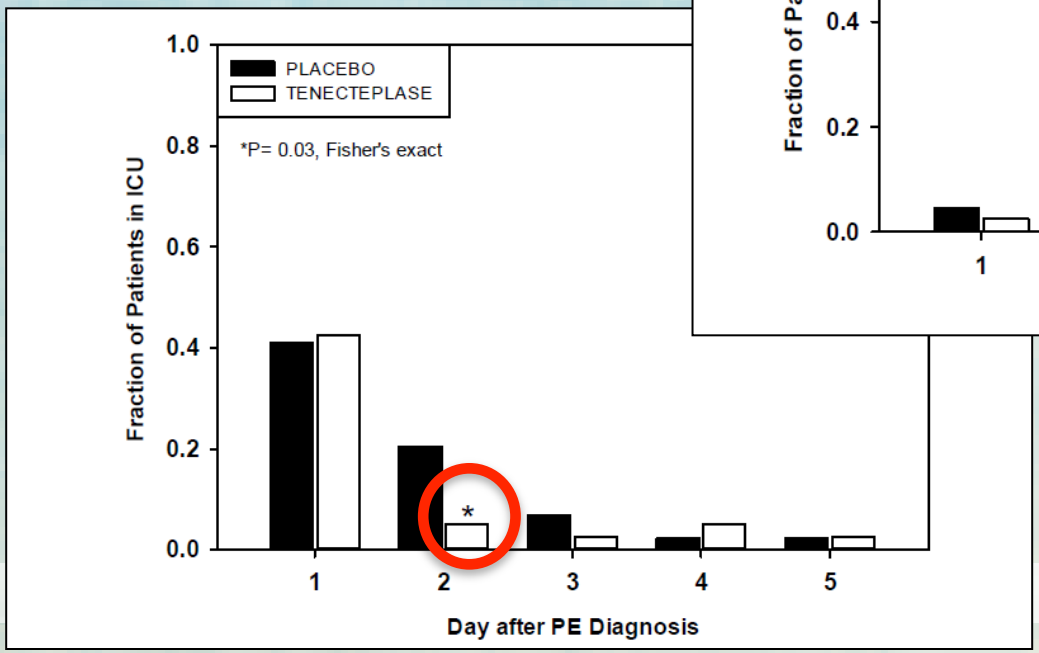
Proportion free of any adverse outcome:

63% (Placebo) vs 85% (Tenecteplase), p=0.017

TOPCOAT

Hospital Resource Utilization





Kline et al J Thromb Haemost. 2014

TOPCOAT
Conclusion

Patients with submassive pulmonary embolism who were treated with tenecteplase were more likely to have a good health related quality of life at three months

Reduced dose systemic thrombolysis: MOPETT Trial

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 Cardiol 2013;11:273-277

MOPETT: Definition of Moderate PE

- Involvement of >70% in either at least 2 lobar arteries or left or right main PA
- At least 2 new signs or symptoms (chest pain, tacypnea, tachycardia, cough, dyspnea, O2 dsat (<95%) or elevated JVP.
- Echo measured but not element of inclusion or exclusion

MOPETT: 121 patients randomized

TG: Enoxaparin 1 mg/kg q 12 with initial dose not to exceed 80 mg. UF 70 U/kg bolus not to exceed 6000, dose adjustment to keep PTT 1.5-2. No higher than 10 U/kg/hour. After tPA, 18 U/kg/Hr.

CG: LMWH 1 mg/kg bid. UFH 80 U/kg then 18 U/kg/hr.

tPA dose: For patients > 50 kg, dose 50 mg given as 10 mg push Over 1 minute followed by 40 mg over 2 hours

MOPETT: Primary Endpoint

Table 2
Primary end points at 28 ± 5 mo of follow-up

Variable	TG (n = 58; 100%)	CG (n = 56; 100%)	p Value
Pulmonary hypertension*	9 (16%)	32 (57%)	<0.001
Pulmonary hypertension plus recurrent pulmonary embolism	9 (16%)	35 (63%)	<0.001

* Pulmonary artery systolic pressure ≥40 mm Hg.

MOPETT

Table 4
Differences in pulmonary artery systolic pressure between the 2 groups

Timing	Pulmonary Artery Systolic Pressure (mm Hg)		p Value
	TG	CG	
On admission	50 ± 6	51 ± 7	0.4
Within 48 h	34 ± 7	41 ± 4	<0.001
6 mo	31 ± 6	49 ± 8	<0.001
28 ± 5 mo	28 ± 7	43 ± 6	<0.001

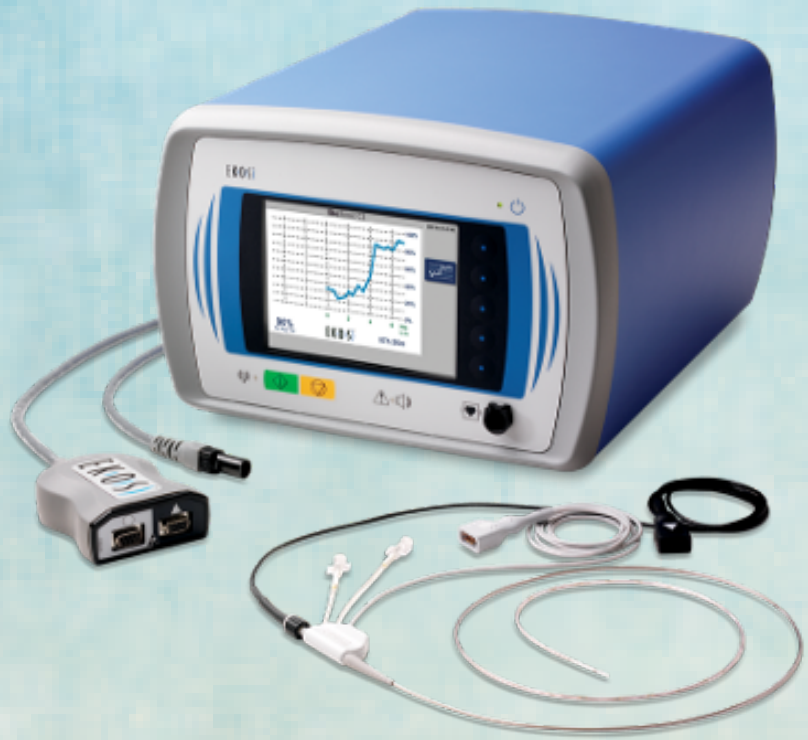
Data are presented as mean ± SD.

RV enlargement in 20% of TG and 23% CG at baseline
RV hypokinesis in 4.4% of TG and 6.6% CG at baseline

Reduced dose thrombolysis via catheter

- Direct infusion of lytic agent into clot
- Higher local concentration by lower doses of lytic agent
- PA pressure monitoring
- Direct clot fragmentation

EKOS Thrombolysis

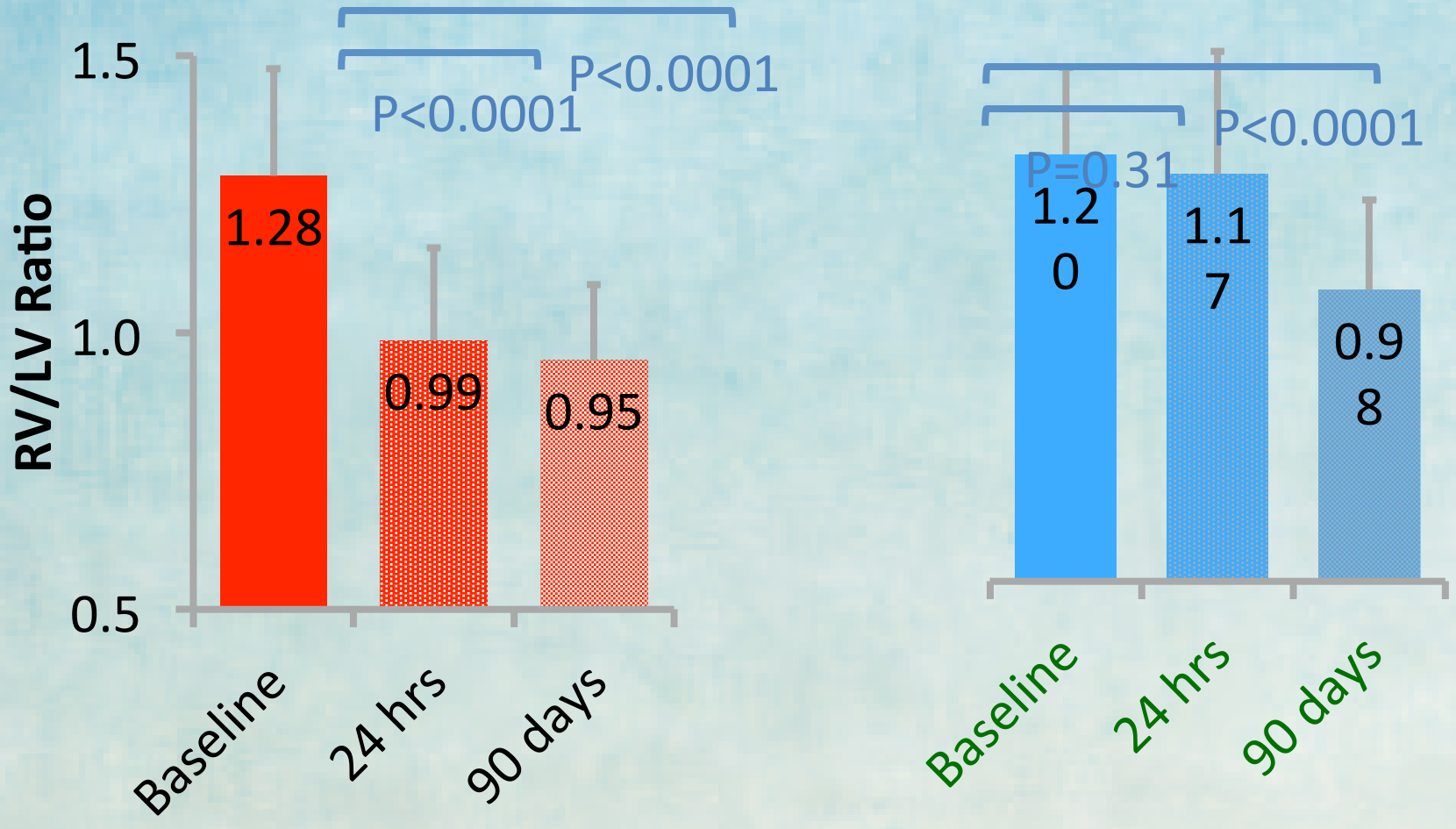


- Ultrasonic pressure waves emitted along the catheter
- Lower drug dose (16-24 mg rt-PA) delivered at 1-2 mg/hour

ULTIMA: Randomized, Controlled Trial: Ultrasound Accelerated Thrombolysis with ≤ 20 mg TPA: Rx of Acute Submassive PE

Kucher N et al. Circulation. 2014;129:479-486

ULTIMA: 59 patients randomized
RV/LV ratio (echo)



SEATTLE II

A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II)

Gregory Piazza, MD, MS
on behalf of the SEATTLE II Investigators

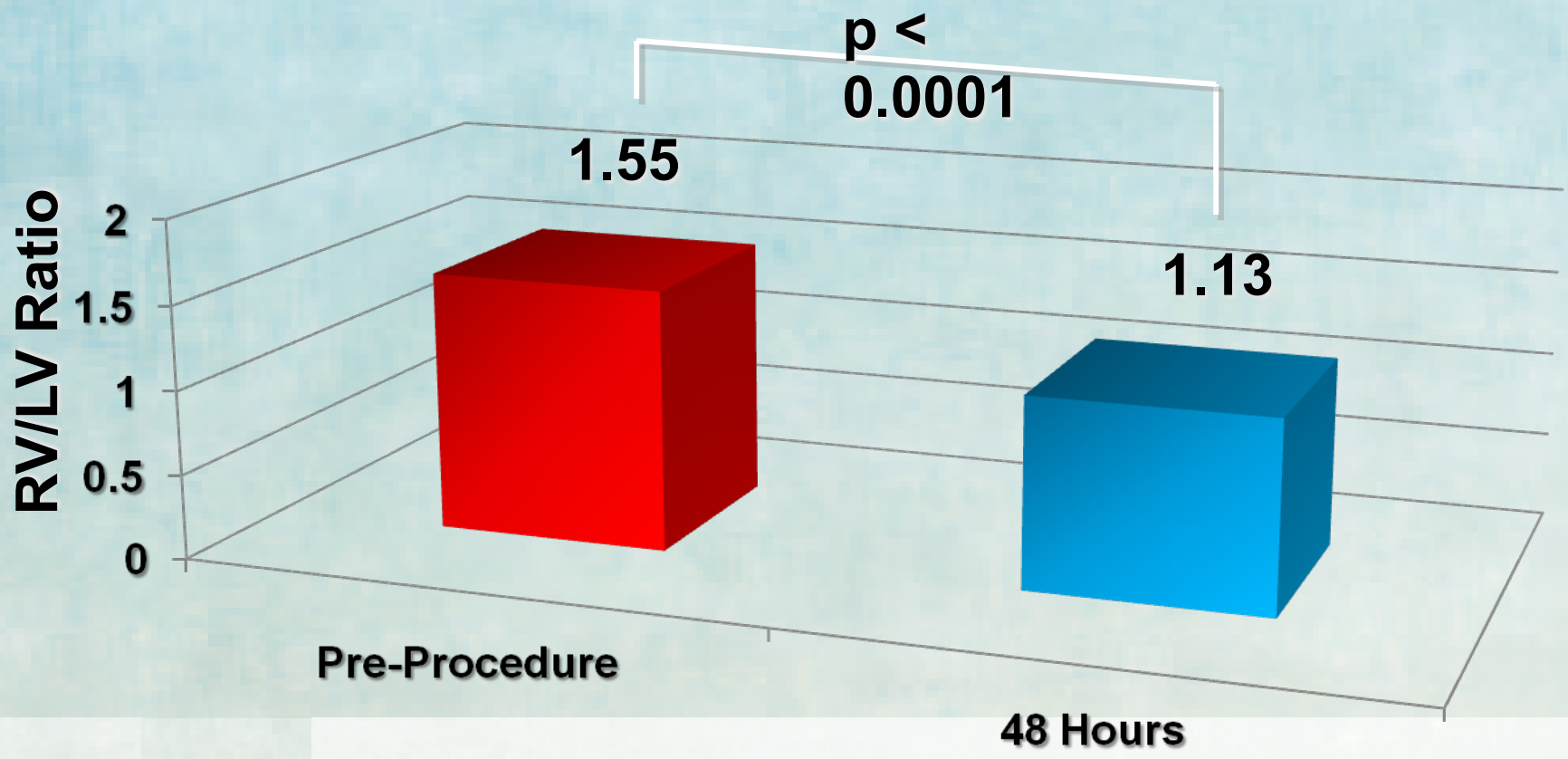
ACC: March 30, 2014

MORNING EDUCATIONAL SYMPOSIA

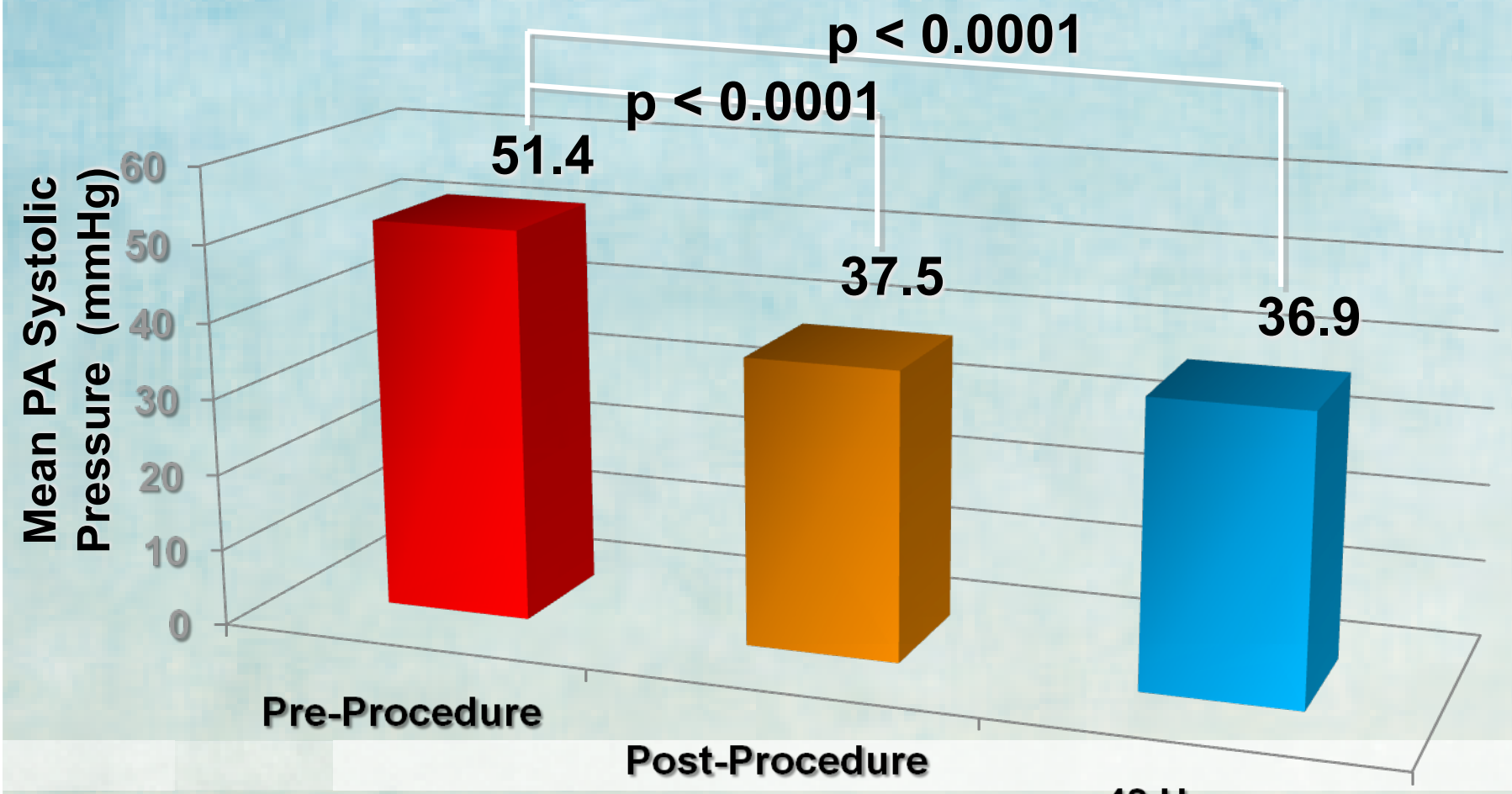
Sponsored by the EKOS Corporation

CHEST 2014

SEATTLE II: 150 patients treated
Outcomes: RV/LV Ratio



SEATTLE II Outcomes: PA Systolic Pressure



Clinical Outcomes

Clinical outcomes*	N = 150
Mean length of stay ± SD, days	8.8 ± 5
In-hospital death, n (%)	3 (2)
30-day mortality**, n (%)	4 (2.7)
Serious adverse events due to device, n (%)	2 (1.3)
Serious adverse events due to t-PA, n (%)	2 (1.3)
IVC filter placed, n (%)	24 (16)
Major bleeding within 30 days**, n (%) GUSTO moderate** GUSTO severe**	17 (11.4) 16 (10.7) 1 (0.7)
Intracranial hemorrhage, n (%)	0 (0)

*All death, serious adverse, and bleeding events were adjudicated by an independent safety monitor.
**N = 149 (1 patient lost to follow-up)