Pulmonary Embolism Debate
All Sub-Massive Pulmonary Embolism Should Be Treated with Medical Therapy ONLY

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29 April 2022

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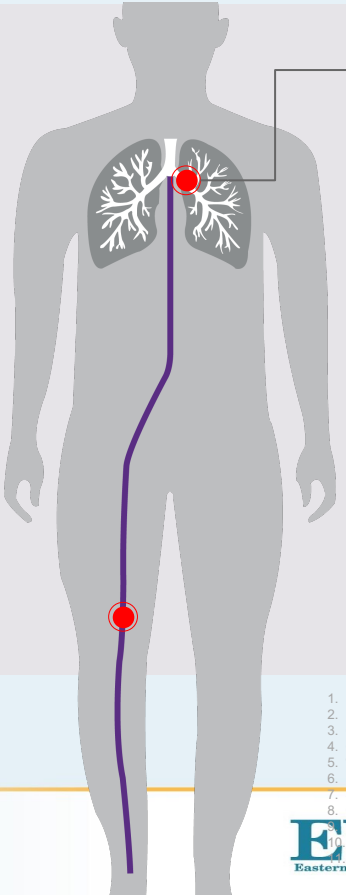
Disclosures

Financial Relationship with:
Inari
Penumbra
Boston Scientific
Local Primary Investigator for 4 trials in Pulmonary Embolism

Understanding the Clinical Question



PULMONARY EMBOLISM (PE)

Most serious complication of DVT, when part of the clot travels to the lungs, causing a blockage. This is potentially life threatening.

3rd	**leading cause of cardiovascular death**[5] (and a leading cause of preventable deaths in hospital)
Up to **15%**	30-day all-cause **mortality**[6,7] (**28%** for high-risk PE[6])
Up to **50%**	**have residual vascular obstruction**[8-10], and long-term complications are common[11]

1. Kahn, Susan R. Hematology Am Soc Hematol Educ Program. 2016 Dec 2; 2016(1): 413–418
2. Kahn, et al. Arch Intern Med. 2004;164:17-26
3. Galanaud, et al. Thromb Haemost 2018; 118(02): 320-328
4. Office of the Surgeon General (US); National Heart, Lung, and Blood Institute (US). Office of the Surgeon General (US); 2008.
5. "Pulmonary Embolism in 2017: Increasing Options for Increasing Incidence", National Center for Biotechnology Information, May 2017.
6. PERT Consortium® Registry Data. Interim results on 5,048 Patients presented at PERT Symposium October 2021
7. Schultz J, et al. Pulm Circ. 2019 Jan 11;9(3):2045894018824563;
8. Chopard, et al. Am J Cardiol. 2017 Jun 1; 119(11): 1883-1889.
9. Mirati, et al. Medicine (Baltimore). 2006 Sep;85(5):253-262
10. Mrozek et al. Acta Chir Orthop Traumatol Cech. 2018;85(1):16-21
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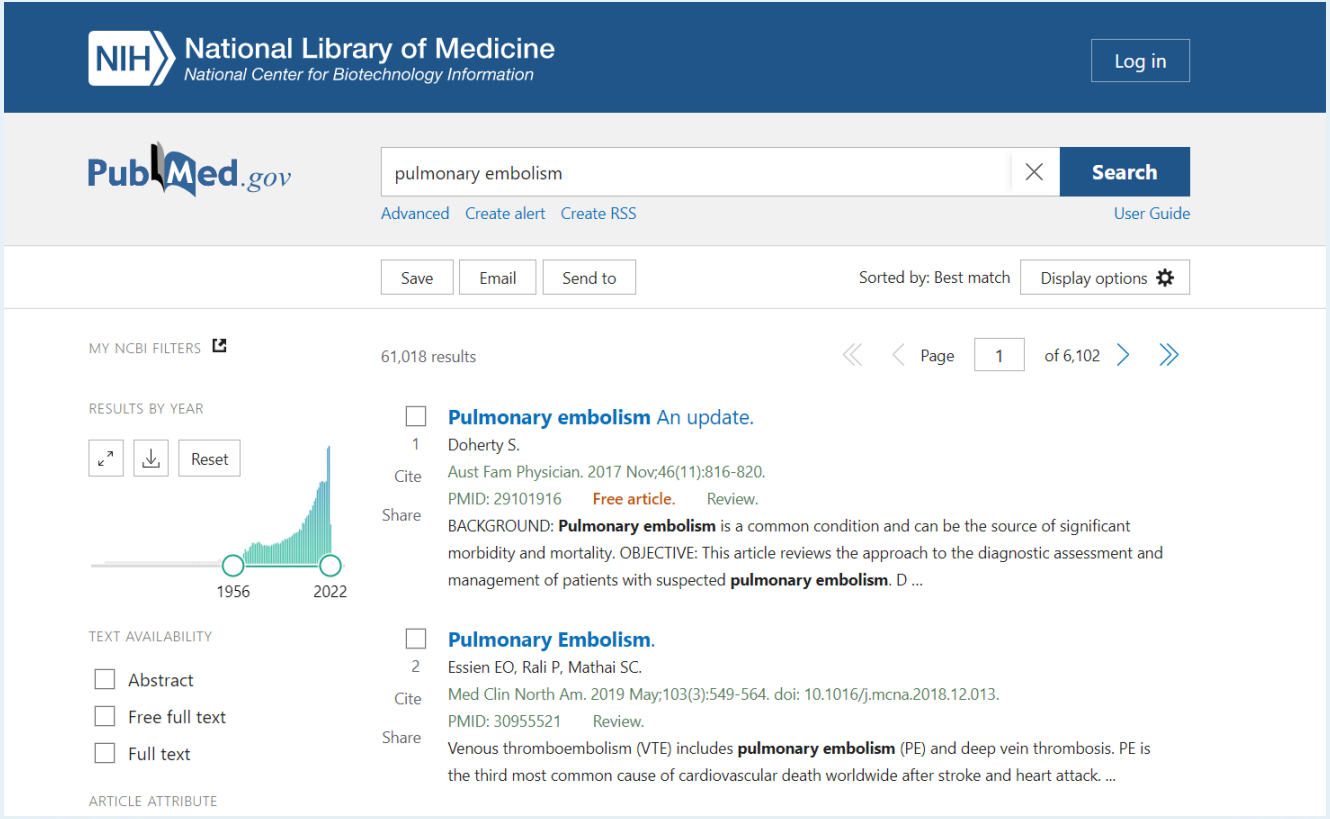
Framing the Argument



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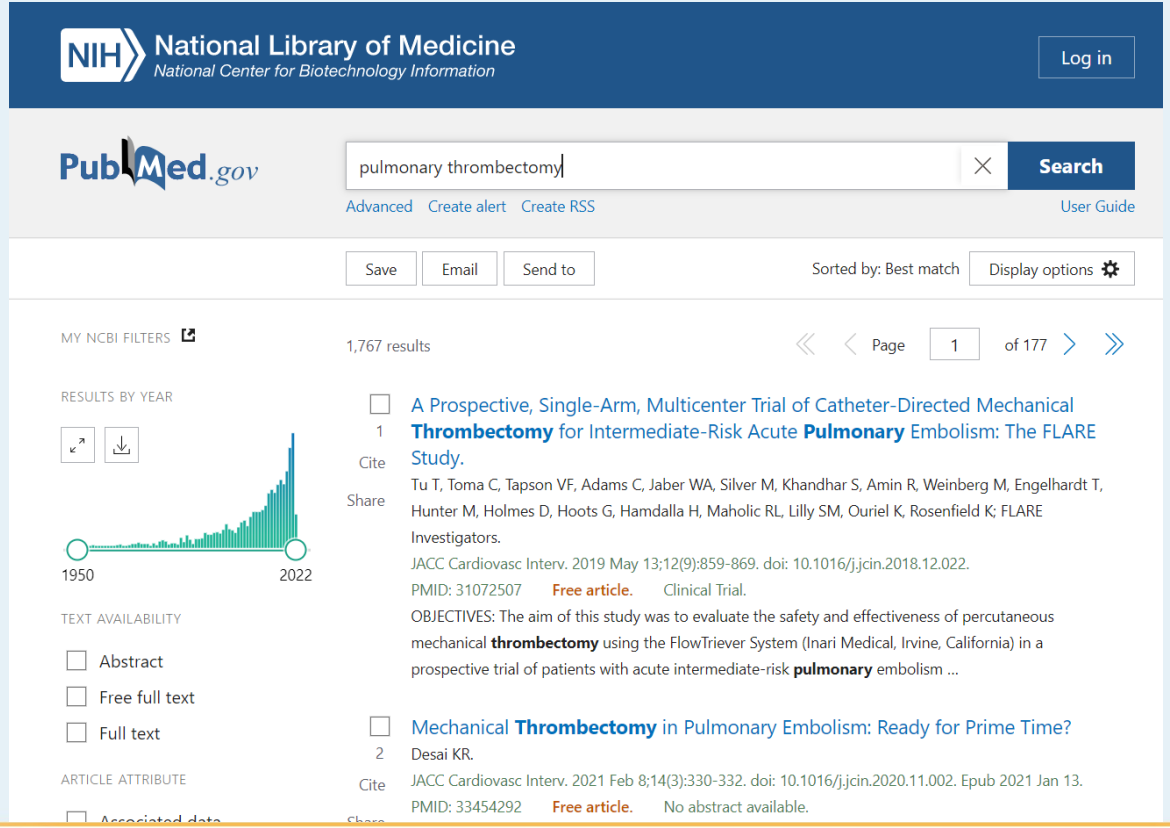
Framing the Argument



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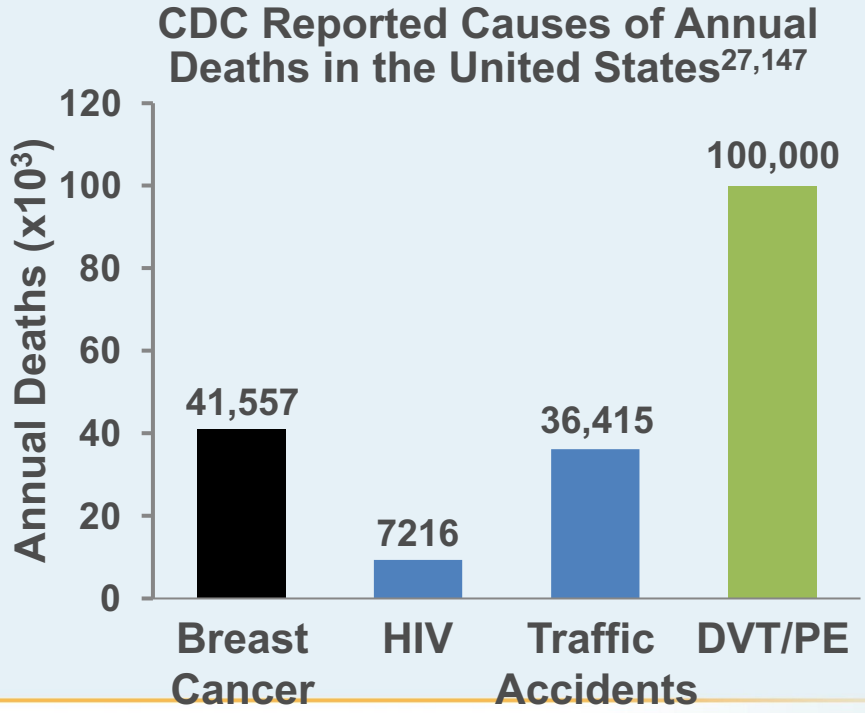
VTE Is a Major Cause of Morbidity and Mortality With a Significant Economic Burden in the United States

VTE kills more people each year than breast cancer, HIV, and traffic accidents…combined[27,147]

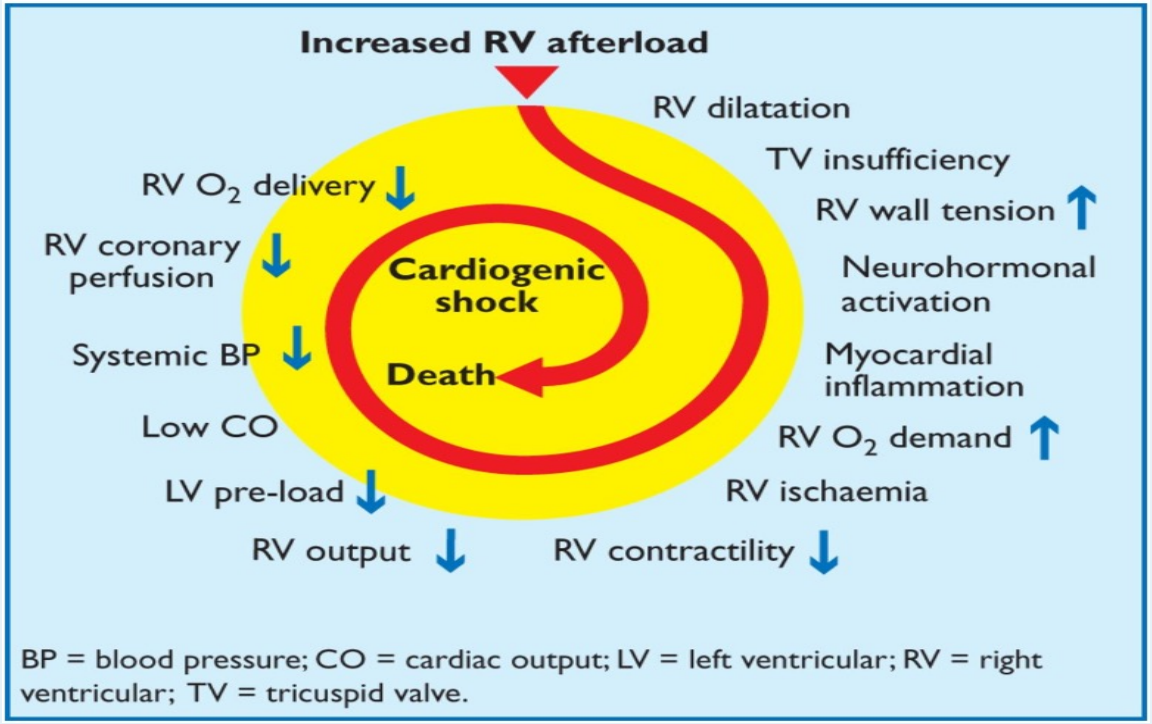
Up to 900,000 people are affected by DVT/PE annually[71]

≈550,000 hospitalizations annually in the United States for DVT and/or PE[28]

Healthcare costs associated with DVT/PE in 2011 were estimated to be up to $10 billion[26]



WHY PE PATIENTS ARE AT RISK: KEY FACTORS CONTRIBUTING TO HEMODYNAMIC COLLAPSE IN ACUTE PE

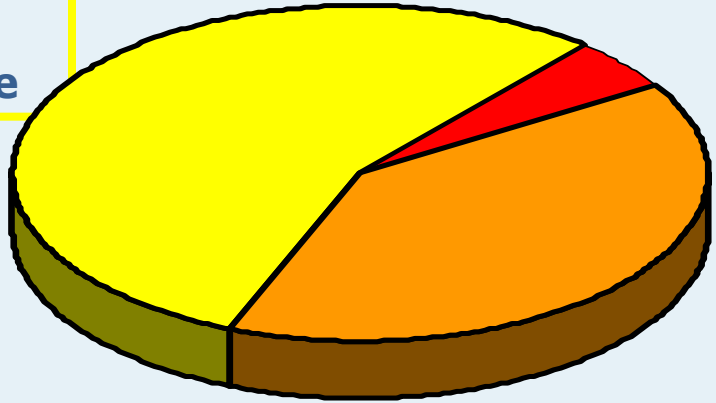


BP = blood pressure; CO = cardiac output; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.

ESC 2014 Guidelines

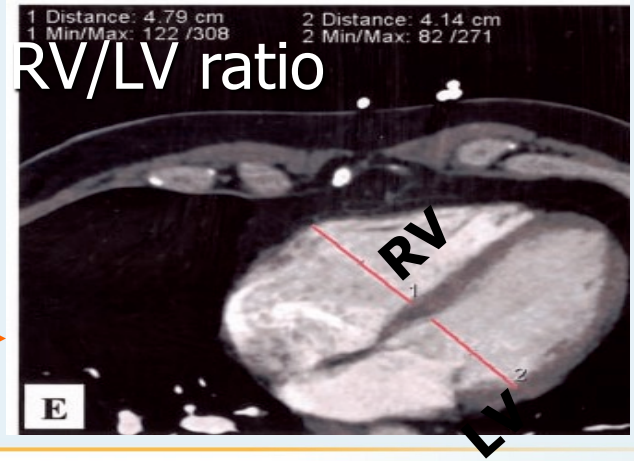
PE Patient Risk Stratification

Minor PE
- 55% PE population
- Good prognosis
- **Low mortality rate**



Massive PE
- 5% PE population
- Sustained hypotension
- Inotropic support
- **58% mortality** @ 3 mo

Submassive PE
- 40% PE population
- Systemic normotension
- **RV dysfunction**
- **22% mortality** @ 3 mo

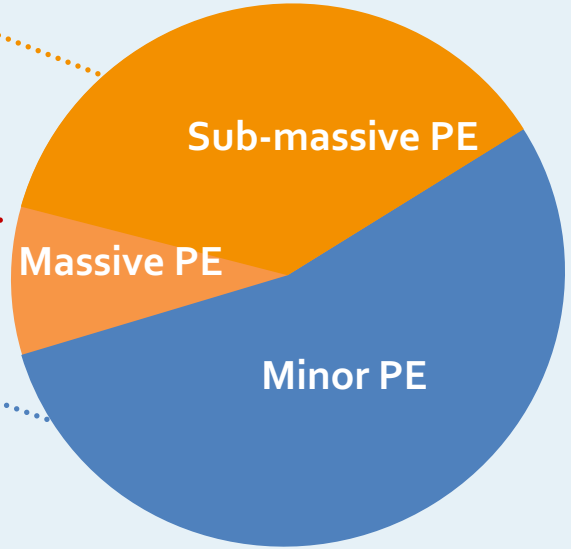


Jaff et al. Circulation 2011;123(16):1788-1830.
Goldhaber et al. Lancet. 1999;353(9162):1386-9.
Quiroz et al. Circulation (2004);109;2401-2404
Frémont, Chest 2008; 133;558-362
Schoef, Circ 2004; 110:3276-3280
Kucher, Arch Intern Med 2005; 165:1777-1781

PE PATIENT POPULATION PROFILE

Massive PE

- [High risk]
- 5% PE population
- 58%[1] mortality @ 3 months



Immediate Management Decision
Anticoagulation
Consider Open Embolectomy vs. Systemic TPA vs. ECMO
In High Risk Cases with Institutional Expertise can consider Catheter Directed Therapy

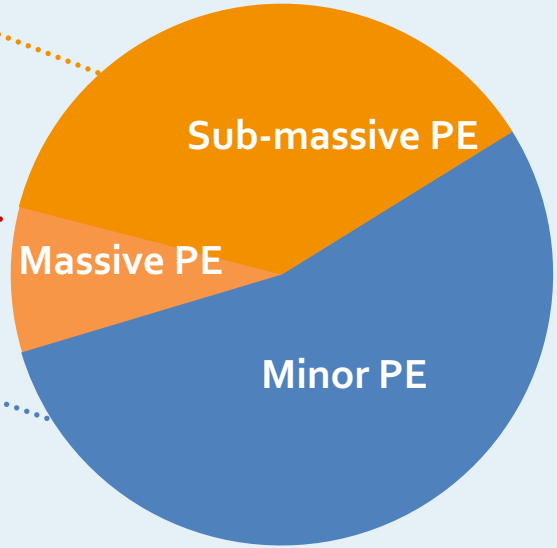
1. Goldhaber SZ et al. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386-1389
2. Meyer G et al. Fibrinolysis for Patients with Intermediate Risk Pulmonary Embolism. New Engl J Med 2014; 370: 1402-11
3. Casazza F et al. Clinical features and short term outcomes of patients with acute pulmonary embolism. The Italian Pulmonary Embolism Registry (IPER). Thrombosis Research 2012; 130:847-852

IV THROMBOLYSIS WITH TPA

- 100 mg tPA infused over **two hours**
- Indicated for management of acute **massive PE** in adults
  - For the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs
  - For the lysis of pulmonary emboli accompanied by unstable hemodynamics, e.g., failure to maintain blood pressure without supportive measures

See instructions for use Activase Alteplase for complete indications.

PE PATIENT POPULATION PROFILE



Minor PE

- [Low risk]
- 55% PE population
- Good prognosis
- Low mortality rate

Anticoagulation

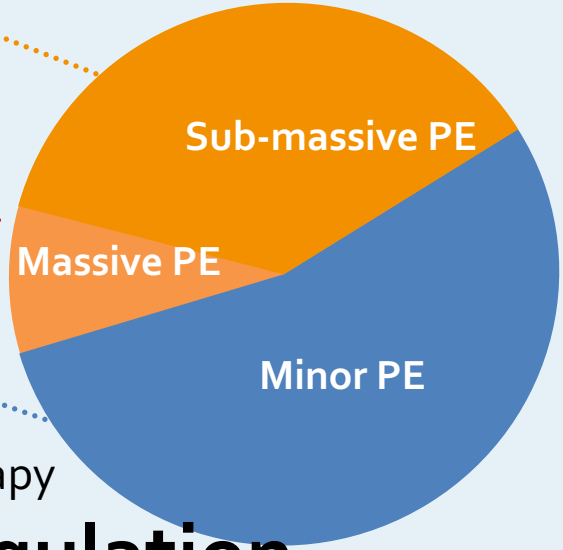
Consider for outpatient therapy

Intervention only if patient decompensates

PE PATIENT POPULATION PROFILE

Sub-massive PE

- [Moderate/Intermediate risk]
- 40% PE population
- 21% mortality @ 3 months



Controversial need for interventional therapy

Start systemic anticoagulation

Risk/Benefit for Intervention

The PESI and Simplified PESI Are Validated Tools to Identify Low-Risk Patients

Variable	Score	
	PESI	sPESI
Age >80 years	Age in years	1
Male sex	10	0
History of cancer	30	1
History of heart failure	10	1*
History of chronic lung disease	10	
Pulse ≥110 bpm	20	1
Systolic BP <100 mm Hg	30	1
Respiratory rate ≥30 breaths/min	20	0
Temperature <36°C	20	0
Altered mental status†	60	0
SaO_2 <90%‡	20	1

*Heart failure or history of chronic lung disease combined into a single category of chronic cardiopulmonary disease. †Disorientation, lethargy, stupor, or coma. ‡With or without the administration of supplemental oxygen.

Classification by Total Score			
PESI		sPESI	
Class I	≤65	Low risk=0	
Class II	66-85		
Class III	86-105	High risk≥1	
Class IV	106-125		
Class V	>125		

BOVA Score

TABLE 2

Bova scoring system for estimating 30-day risk of complications or death in acute pulmonary embolism

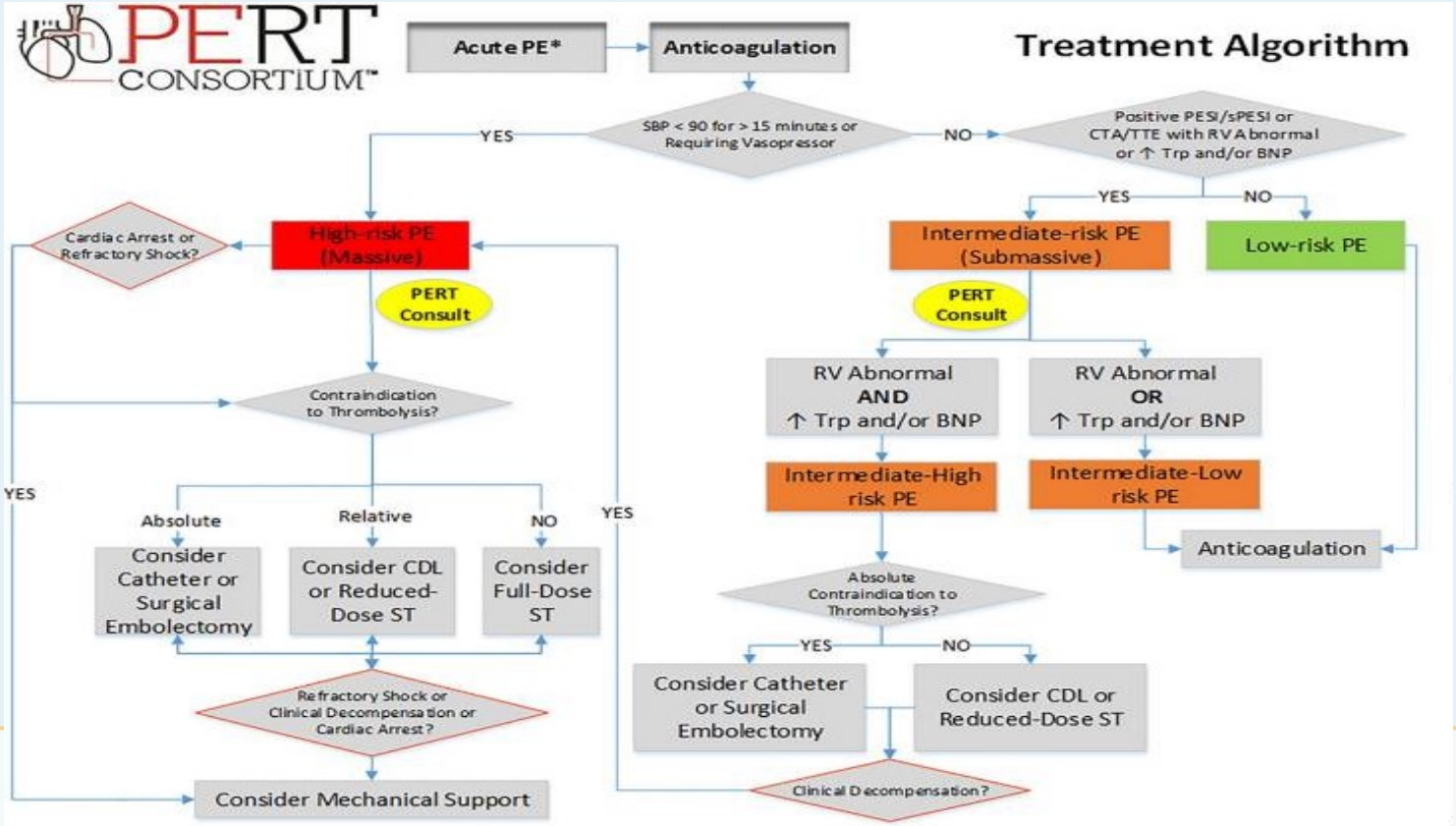
Predictor variable	Points
Systolic blood pressure 90–100 mm Hg	2
Elevated cardiac troponin	2
Right ventricular dysfunction on echocardiography or computed tomography	2
Heart rate ≥ 110/min	1

Points [a]	Stage	30-day risk of complications[a]	30-day risk of death
0–2	I	4.4%	3.1%
3–4	II	18%	6.8%
> 4	III	42%	10%

[a]The Bova score predicts the 30-day risk of complications and death in hemodynamically stable patients. Complications include hemodynamic collapse and recurrent nonfatal pulmonary embolism.

Based on information in reference 4.

Treatment Algorithm

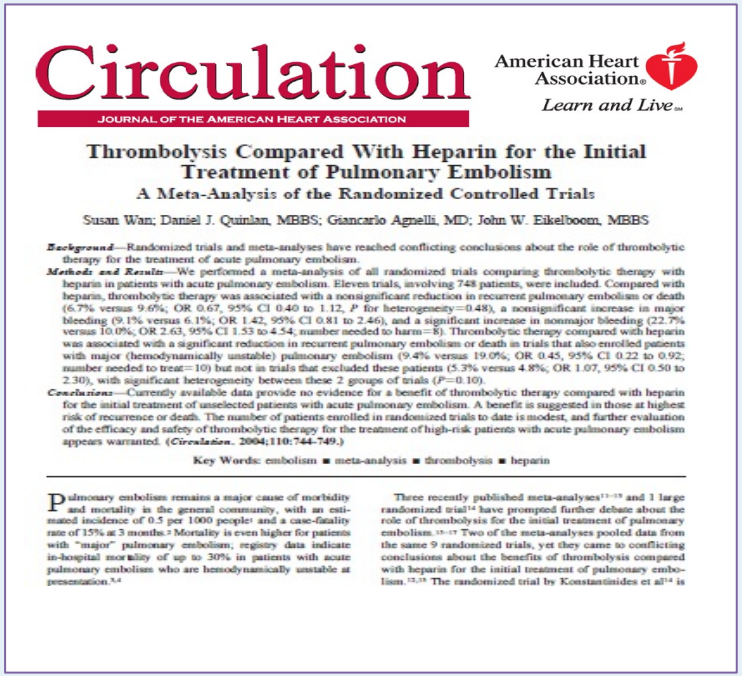


META-ANALYSIS SUGGESTS REDUCED RISK OF RECURRENTPE OR DEATH FROM THROMBOLYSIS COMPARED WITH HEPARIN

- Meta analysis of randomized clinical trials for PE comparing thrombolytic therapy with heparin
- Total of 11 trials, 748 patients included
- Data from trials that included massive PE

	Trials that included patients with major PE		
Outcome	Thrombolysis n/N(%)	Heparin n/N(%)	OR (95% CI)
Recurrent PE or death	12/128 (9.4)	24/126 (19.0)	0.45 (0.22–0.92)
Recurrent PE	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)

PE Indicated Pulmonary embolism



Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

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

Background—Randomized trials and meta-analyses have reached conflicting conclusions about the role of thrombolytic therapy for the treatment of acute pulmonary embolism.

Methods and Results—We performed a meta-analysis of all randomized trials comparing thrombolytic therapy with heparin in patients with acute pulmonary embolism. Eleven trials, involving 748 patients, were included. Compared with heparin, thrombolytic therapy was associated with a nonsignificant reduction in recurrent pulmonary embolism or death (6.7% versus 9.6%; OR 0.67, 95% CI 0.40 to 1.12, *P* for heterogeneity=0.48), a nonsignificant increase in major bleeding (9.1% versus 6.1%; OR 1.42, 95% CI 0.81 to 2.46), and a significant increase in nonmajor bleeding (22.7% versus 10.0%; OR 2.63, 95% CI 1.53 to 4.54; number needed to harm=8). Thrombolytic therapy compared with heparin was associated with a significant reduction in recurrent pulmonary embolism or death in trials that also enrolled patients with major (hemodynamically unstable) pulmonary embolism (9.4% versus 19.0%; OR 0.45, 95% CI 0.22 to 0.92; number needed to treat=10) but not in trials that excluded these patients (5.3% versus 4.8%; OR 1.07, 95% CI 0.50 to 2.30), with significant heterogeneity between these 2 groups of trials (*P*=0.10).

Conclusions—Currently available data provide no evidence for a benefit of thrombolytic therapy compared with heparin for the initial treatment of unselected patients with acute pulmonary embolism. A benefit is suggested in those at highest risk of recurrence or death. The number of patients enrolled in randomized trials to date is modest, and further evaluation of the efficacy and safety of thrombolytic therapy for the treatment of high-risk patients with acute pulmonary embolism appears warranted. (*Circulation*. 2004;110:744-749.)

Key Words: embolism ■ meta-analysis ■ thrombolysis ■ heparin

Pulmonary embolism remains a major cause of morbidity and mortality in the general community, with an estimated incidence of 0.5 per 1000 people[1] and a case-fatality rate of 15% at 3 months.[2] Mortality is even higher for patients with "major" pulmonary embolism; registry data indicate in-hospital mortality of up to 30% in patients with acute pulmonary embolism who are hemodynamically unstable at presentation.[3,4]

Three recently published meta-analyses[13–15] and 1 large randomized trial[16] have prompted further debate about the role of thrombolysis for the initial treatment of pulmonary embolism.[15–17] Two of the meta-analyses pooled data from the same 9 randomized trials, yet they came to conflicting conclusions about the benefits of thrombolysis compared with heparin for the initial treatment of pulmonary embolism.[13,15] The randomized trial by Konstantinides et al[16] is

Wan S et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism. Circulation. 2004 Aug. 10;110(6):744-9.

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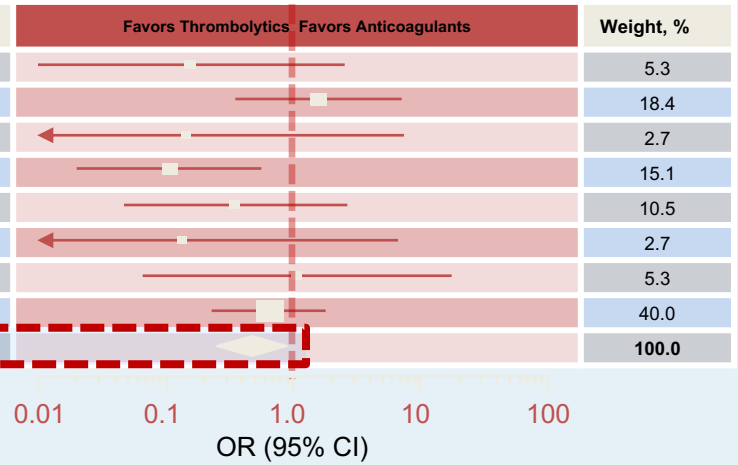
Lysis in submassive PE

Mortality meta-analysis

Source	Thrombolytics # of Events	Thrombolytics # of Patients	Anticoagulants # of Events	Anticoagulants # of Patients	OR (95% CI)	Weight, %
Goldhaber et al,[2] 1993	0	46	2	55	0.16 (0.01-2.57)	5.3
Konstantinides et al,[3] 2002	4	118	3	138	1.58 (0.35-7.09)	18.4
TIPES,[29] 2010	0	28	1	30	0.14 (0.00-7.31)	2.7
Fasullo et al,[11] 2011	0	37	6	35	0.11 (0.02-0.58)	15.1
MOPETT,[10] 2012	1	61	3	60	0.35 (0.05-2.57)	10.5
ULTIMA,[30] 2013	0	30	1	29	0.13 (0.00-6.59)	2.7
TOPCOAT,[9] 2014	1	40	1	43	1.08 (0.07-17.53)	5.3
PEITHO,[8] 2014	6	506	9	499	.66 (0.24-1.82)	40.0
Total	**12**	**866**	**26**	**889**	**.48 (0.25-0.92)**	**100.0**



Heterogeneity: $\chi^2_7 = 7.63$; $P = .37$; $I^2 = 8\%$
Overall effect: $z = 2.22$; $P = .03$

Intermediate-risk PE

All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT=65	.03
Major bleeding (8)[a]	67/866 (7.74)	20/889 (2.25)	NNH=18	<.001

Chatterjee S et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: a Meta-analysis. JAMA 2014; 311(23):2414-2421.

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PE Evidence for Thrombectomy

1 Completed Trials in Mechanical PE

FLARE (IDE) study
106 pts. | 18 Sites | 30-day f/u

FLASH registry
Up to 1,000 pts. | Up to 100 Sites | 6-mo. f/u

Extract PE
119 pts. | 22 sites | 6-month f/u

FLAME study (PE)
200 HR pts. | In hosp. F/u

1 Completed Trials in Catheter Directed Thrombolysis

Seattle II

Sunset PE

Knockout PE.

Optilyse PE

2 Ongoing Trials or Planned Thrombectomy Trials

PEERLESS trial vs. Lytics
550 patients | | Up to 60 Sites | 30-day f/u

Strike PE

FLAME study (PE)
200 HR pts. | In hosp. F/u

Wolf PE

Angiovac PE

JETI PE

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Trials Comparing CDT to Anticoagulation

1

Completed Trials

Ultima

2

Ongoing Trials or Planned Trials

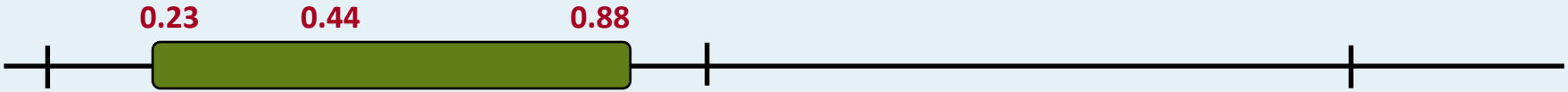
PE Tract

PEITHO Trial Systemic Thrombolysis for SUBMASSIVE PE

1005 Patients
Prospective randomized
Acute PE: normotensive with evidence of Right Heart Strain
Treatment within 2 weeks
Tenectaplase IV Bolus vs. IV Heparin

PEITHO Trial

	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



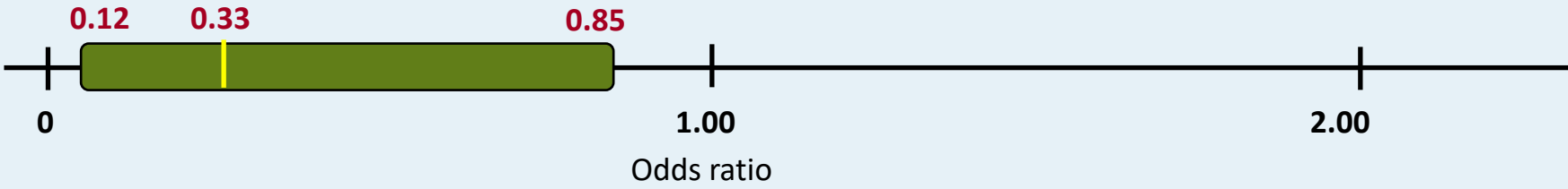
Thrombolysis superior

PEITHO Trial

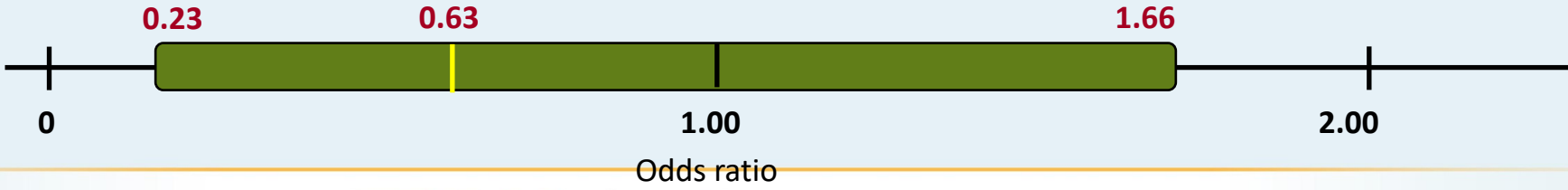
	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
Non-intracranial major bleeding	**32**	**(6.3)**	**6**	**(1.5)**	**<0.001**
Severe	16		2		
Moderate	16		4		
ISTH major bleeding	**58**	**(11.5)**	**12**	**(2.4)**	**<0.001**
Type of bleeding					
Fatal	1		0		
Intracranial/hemorrhagic stroke	10		1		
Extracranial major	4		1		
Hemoglobin drop ≥2g/dL	46		11		
Transfusion of ≥2 units	10		0		
Minor bleeding	**165**	**(32.6)**	**43**	**(8.6)**	**<0.001**

Outcomes by Age

Age ≤ 75 years



Age >75 years



Conclusions

- Systemic Thrombolytics reduce the change of death or hemodynamic collapse
- This benefit comes at the cost of increased major bleeding
- Patient age and comorbidities need to be evaluated before dosing with thrombolytics.

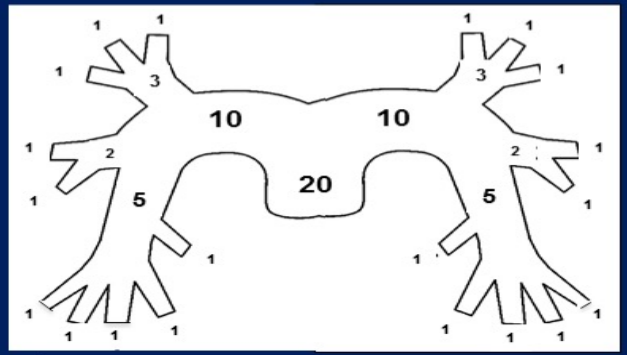
Ultima Trial

Multicenter, randomized controlled trial
Ultrasound assisted catheter directed thrombolysis
Superior to heparin alone for reversing RV enlargement
Acute symptomatic PE confirmed by CT
RV/LV ration >1 on echo (normal is 0.6)

Ultima Trial

PE severity (Biomarker & CT)

	EKOS + Heparin N = 30	Heparin N = 29	p-value
Troponin test positive, n (%)	16/20 (80%)	17/22 (77%)	1.00
Pulmonary occlusion score (CT)[1], mean ± SD	26 ± 7	24 ± 8	0.24
Pulmonary occlusion score (CT)[1], median (min-max)	26 (9-36)	22 (13-38)	



Pulmonary occlusion score[1]

- Multiply score points for non-occlusive embolus by one
- Multiply score points for occlusive embolus by two
- Maximum score is 40.

[1]Qanadli Am J Roentgenology 2001;176:1415-20

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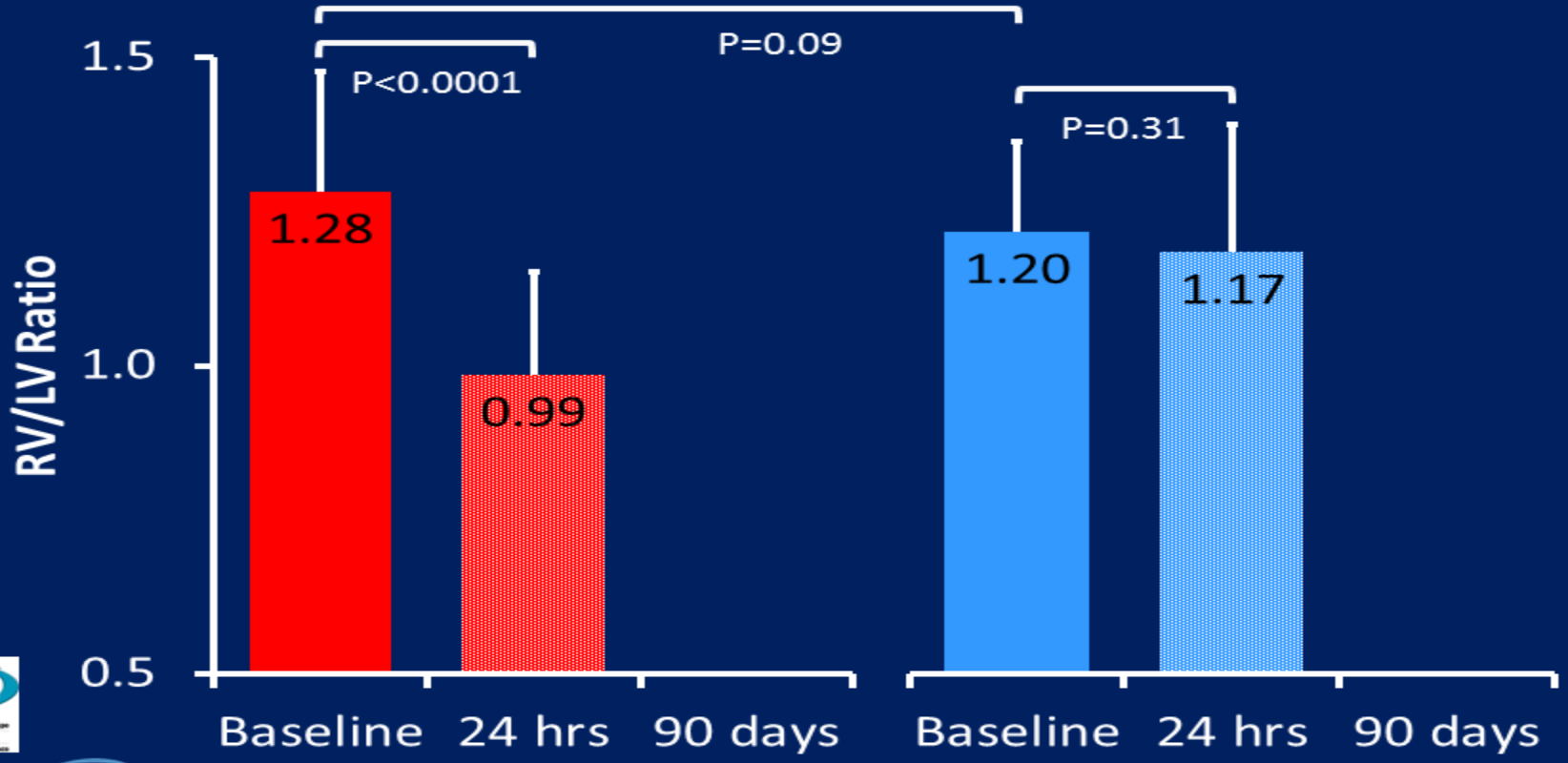
RV/LV ratio (echo)

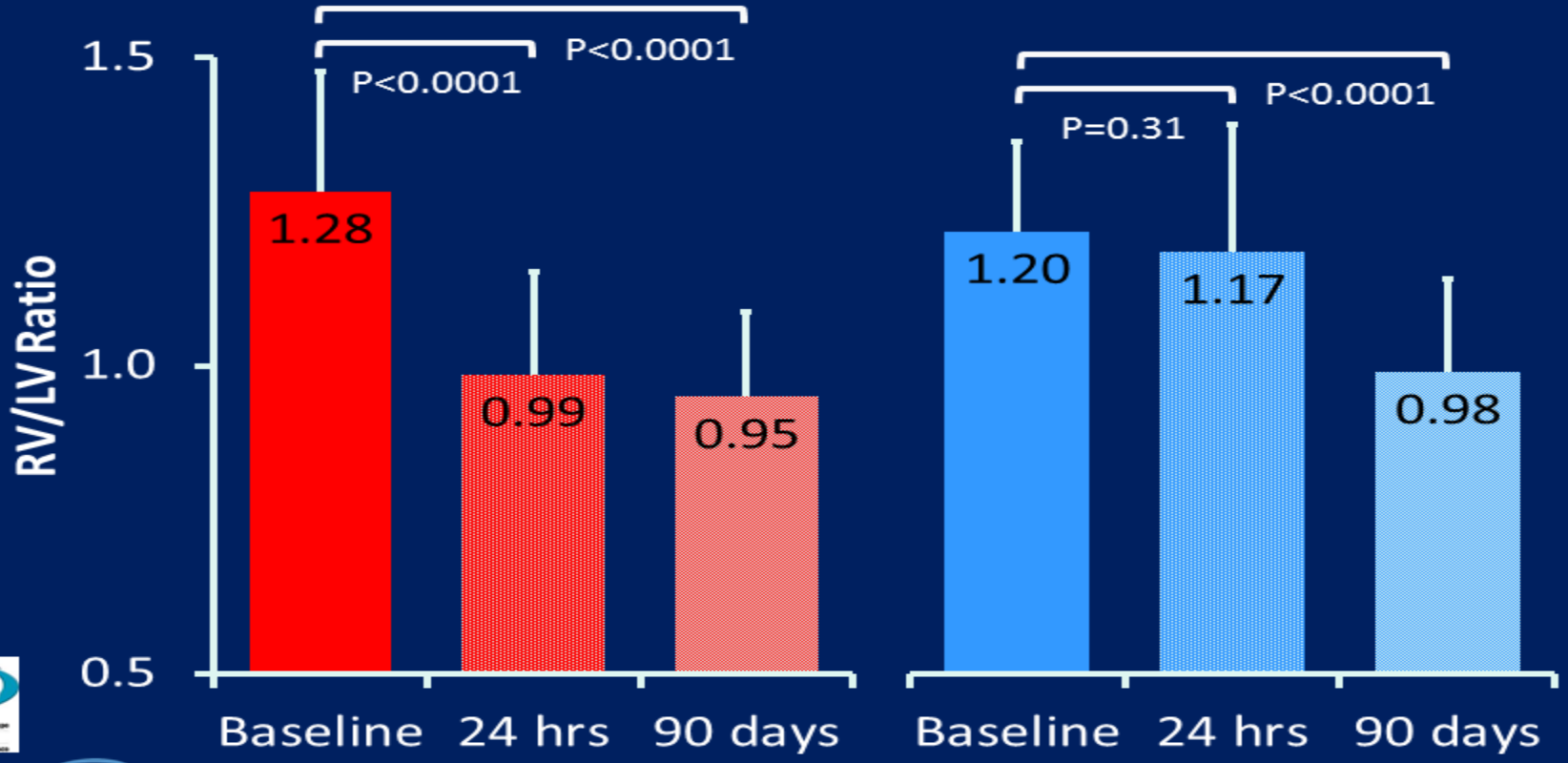


ACC.13

Kucher 2013

ULTIMA

RV/LV ratio (echo)

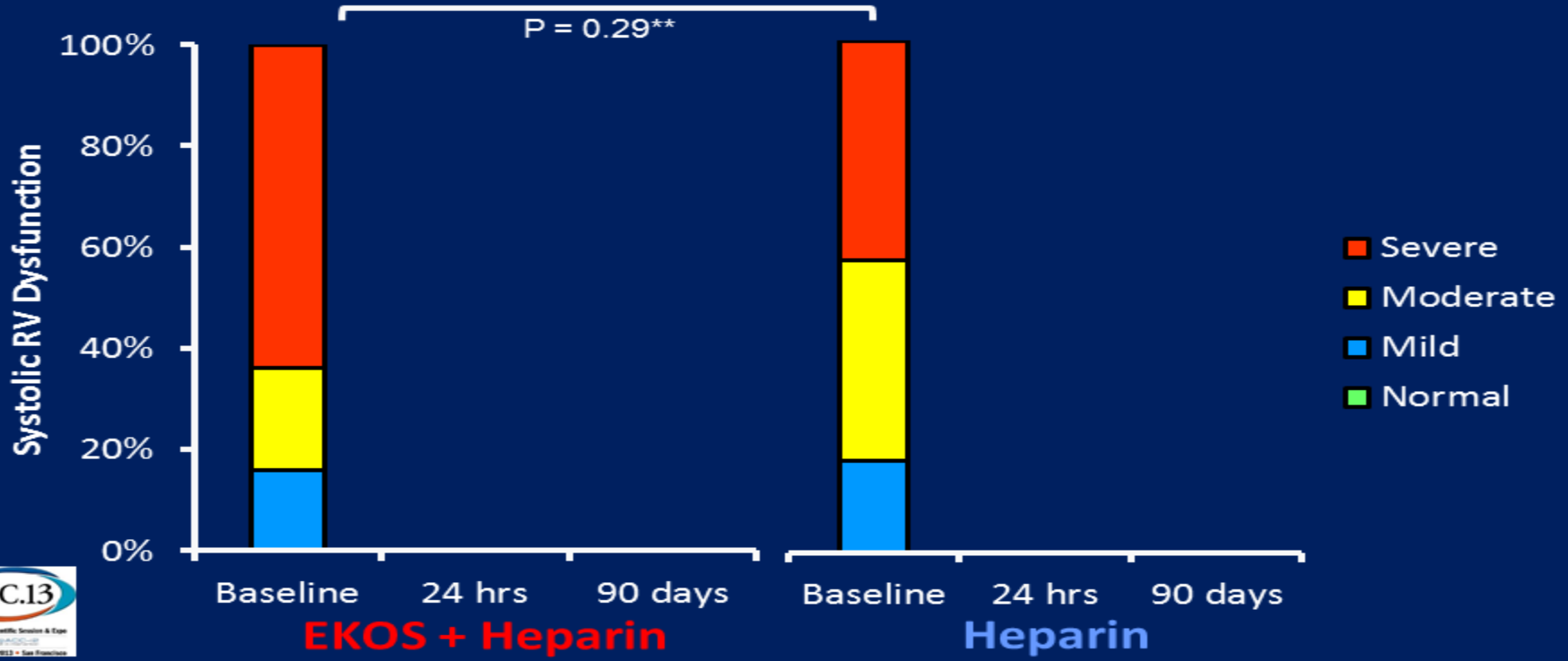


ACC.13

Kucher 2013

ULTIMA

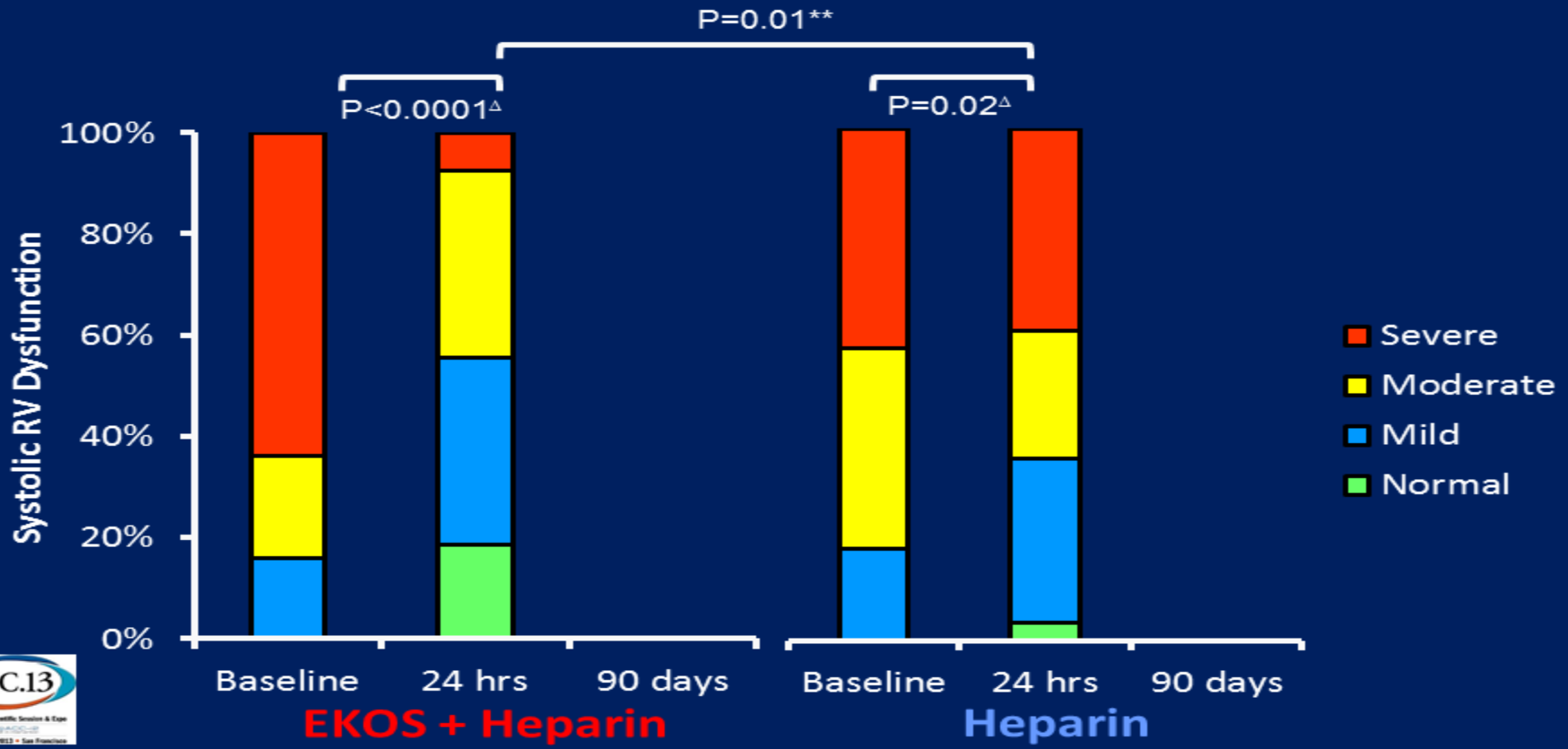
Systolic RV dysfunction



**Two-sided exact Mantel-Haenzel test

Δ Wilcoxon rank sum test

Systolic RV dysfunction



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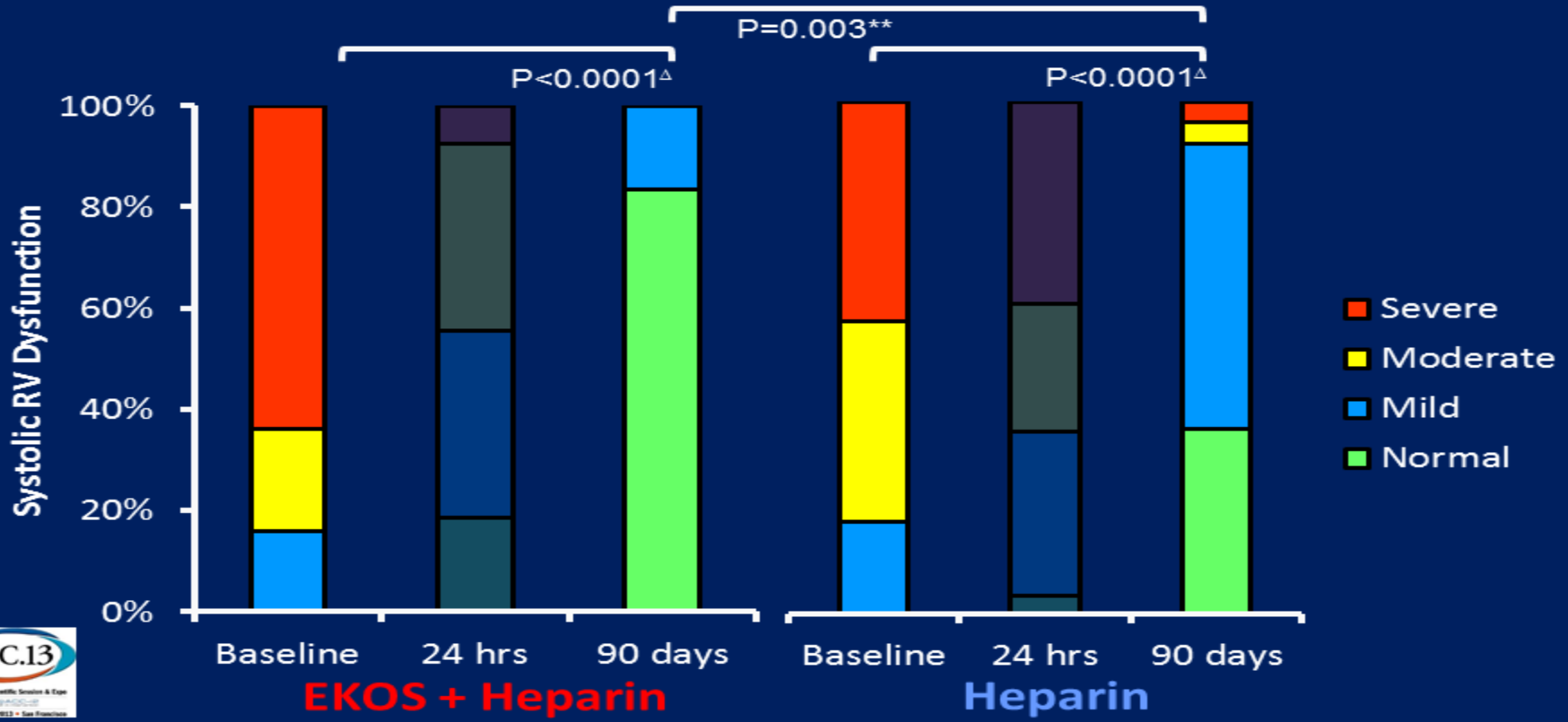
Systolic RV dysfunction



**Two-sided exact Mantel-Haenzel test

Δ Wilcoxon rank sum test

Secondary endpoint analysis

Clinical outcomes at 90 days	EKOS + Heparin N = 30		Heparin N = 29		p-value
Death	0	0%	1*	3%	0.49
Recurrent venous thromboembolism	0	0%	0	0%	1.00
Major bleeding	0	0%	0	0%	1.00
Minor bleeding	3**	10%	1§	3%	0.61

* rehospitalization and death from advanced pancreatic cancer

** two patients with transient mild hemoptysis without medical intervention, one patient with groin hematoma requiring manual compression

§ one patient with transient anal bleeding following endoscopic removal of colon polyp

Kucher 2013

ULTIMA

Conclusions

Catheter directed (ultrasound accelerated) thrombolysis was superior to heparin in reversing right heart dysfunction.
No increase in bleeding complications
At 90 days the right heart function is improved with CDT over Heparin
No change in mortality

What will Dr. Hariri Tell You?

Sentara Actively Performs Pulmonary Thrombectomy safely
We have been doing these procedures for years

He may even show you my involvement in device trials

1

Indigo Aspiration System for Treatment of Pulmonary Embolism: Results of the EXTRACT-PE Trial.

Sista AK, Horowitz JM, Tapson VF, Rosenberg M, Elder MD, Schiro BJ, Dohad S, Amoroso NE, Dexter DJ, Loh CT, Leung DA, Bieneman BK, Perkowski PE, Chuang ML, Benenati JF; EXTRACT-PE Investigators.

JACC Cardiovasc Interv. 2021 Feb 8;14(3):319-329. doi: 10.1016/j.jcin.2020.09.053. Epub 2021 Jan 13.

PMID: 33454291 Free article.

OBJECTIVES: This study sought to prospectively evaluate the safety and efficacy of the **Indigo** aspiration system in submassive acute pulmonary embolism (PE). ...Intraprocedural thrombolytic drugs were avoided in 98.3% of patients. (Evaluating the Safety and Efficacy of the ...

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What will Dr. Hariri Tell You?

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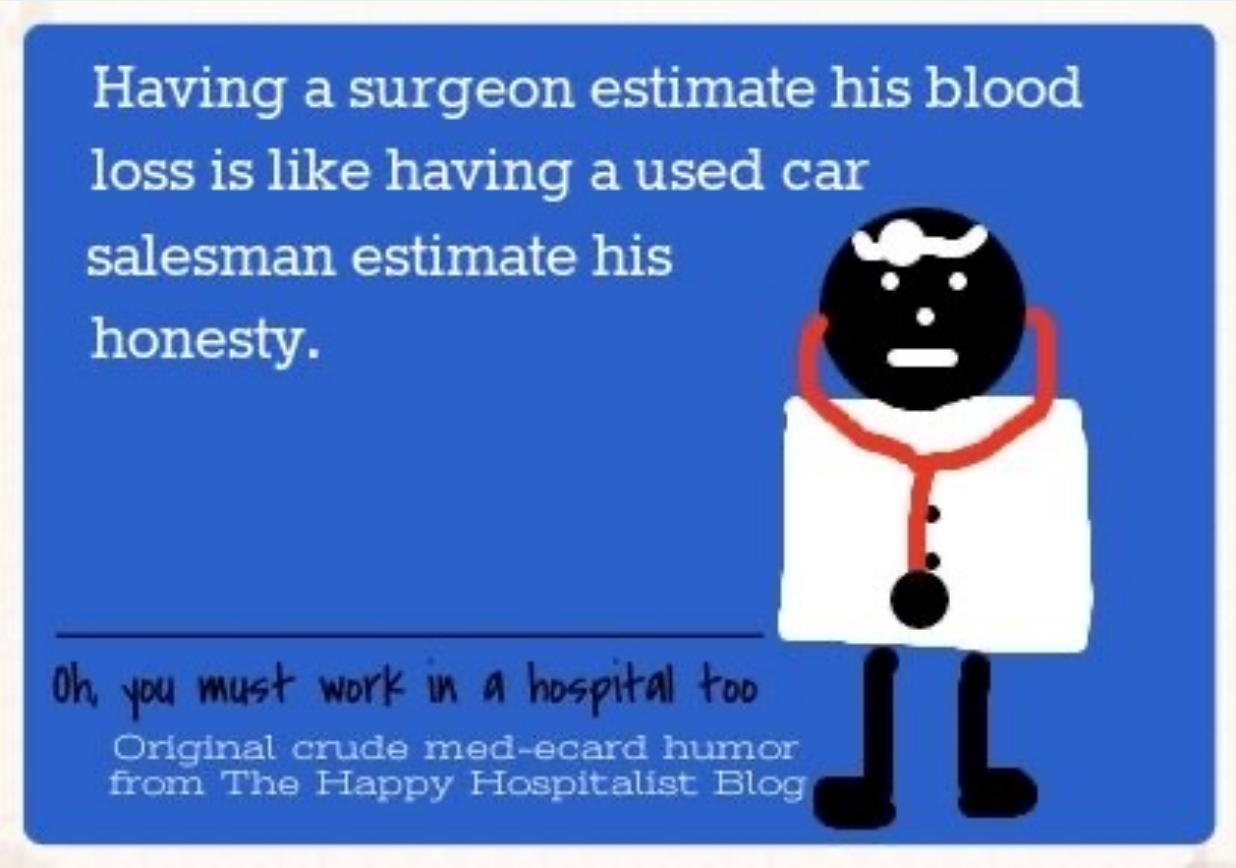


What is the argument for Catheter Directed Therapy?

Removal of clot may make patients better faster
- At the expense of a major operation

Removal of clot may lead to less long term dysfunction
- No evidence at any level

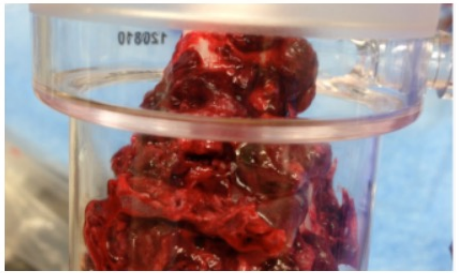
Removal of clot may lead to better clot clearance (less RPVO)
- Limited clinical impact

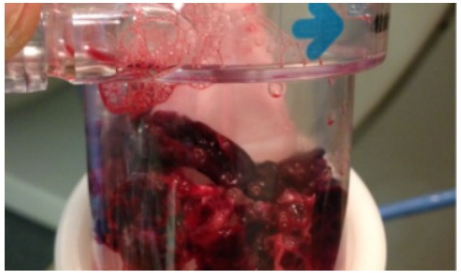
Clot Porn

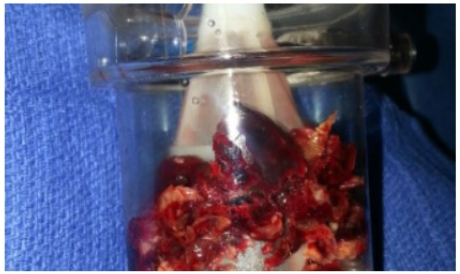
Indigo System

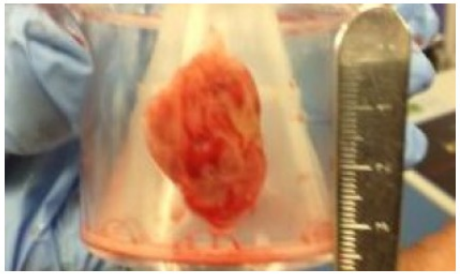
Actual Procedure Results[1]











How common is this procedure?

Outcomes in PE Grossly Unchanged

20 Years Ago: ICOPER 1999[1]

90-day Follow-Up:

Mortality: **17.4%** overall

- **52.4%** for massive
- **14.7%** for sub-massive
- **45.1%** of deaths ascribed to PE

Major Bleeding: **10.5%**

ICH: **0.6%** overall

Today: 2018 MGH PERT data[2]

90-day Follow-Up:

Mortality: **16.3%** overall

- **41.3%** for massive
- **12.3%** for intermediate-risk (sub-massive)
- **37%** of deaths directly attributed to PE

Major Bleeding: **14.2%**

ICH: **4.3%** in massive, **0.8%** in intermediate

2/3 of intermediate-risk deaths were post discharge

1. Kucher et al., Massive pulmonary embolism. Circulation. 2006;113(4):577-582
2. Secemsky et al., Contemporary Management and Outcomes of Patients with Massive and Submassive Pulmonary Embolism. *The American Journal of Medicine* (2018), doi: https://doi.org/10.1016/j.amjmed.2018.07.035

Summary

Current guidelines (Standard of Care)
Anticoagulation first and only
In decompensating patients refer to massive PE guidelines
In decompensating patients in limited centers with expertise can consider CDT
This hardly seems like a strong sell

Medical Management for Sub Massive PE should be primary therapy and this is NOT Controversial

Thank You

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