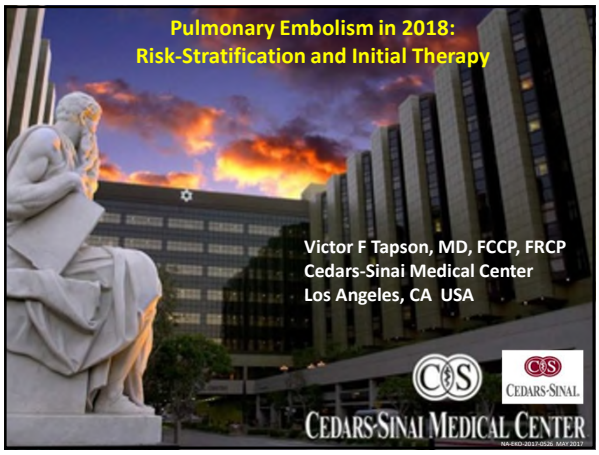


Relevant Financial Disclosures: Previous 12 months

Affiliation/Financial Interest	Name of Affiliated Organization
Grant/Research Support	Bayer, Janssen, BiO2, Portola
Consultant	AngioDynamics, Bayer, Daiichi, Janssen, Inari
Lecture Honoraria	Janssen, BTG/EKOS Corporation*
Royalties	None

*Lecture honoraria are paid to Cedars-Sinai

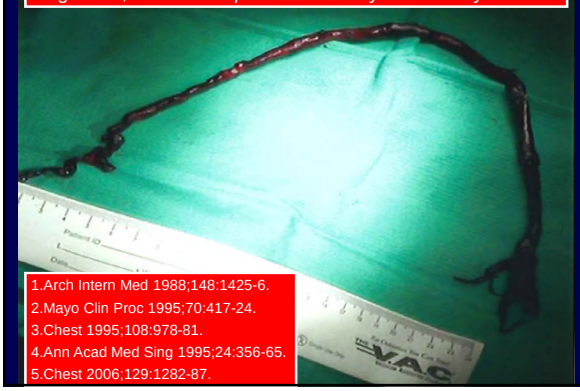
CEDARS-SINAI

LEARNING OBJECTIVES:

- Understand the components needed for risk-stratification for acute PE
- Understand initial treatment options for acute PE

TESLA SAVES MAN WITH PULMONARY EMBOLISM

"Patients who die from acute PE are most commonly not diagnosed, or even *suspected* until they are already dead."



1.Arch Intern Med 1988;148:1425-6.
2.Mayo Clin Proc 1995;70:417-24.
3.Chest 1995;108:978-81.
4.Ann Acad Med Sing 1995;24:356-65.
5.Chest 2006;129:1282-87.

Which of the following is the most common definition for *"massive" or "high-risk"* PE?

A. PE causing systolic BP <90 mmHg for ≥ 15 min
B. PE associated with O2 requirement of > 50%
C. PE causing severe RV dysfunction by echo or CT
D. PE requiring intubation
E. A clot involving both main pulmonary arteries
F. Either A, C, or E

Pulmonary Embolism: Definitions

Patient risk stratification (PE AHA 2011 guidelines)

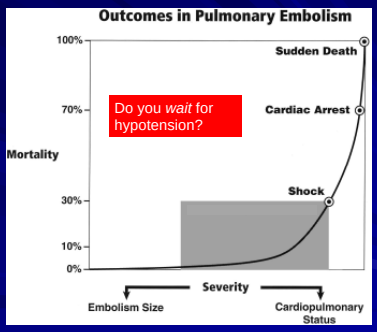
Massive PE	Submassive PE	Minor/Nonmassive PE
High Risk	**Intermediate Risk**	**Low Risk**
•Sustained hypotension - SBP <90 mmHg ≥15 min •Vasoactive support •Pulselessness •Persistent profound bradycardia (HR <40 bpm with signs or symptoms of shock)	• Systolic BP ≥90 • **RV dysfunction** Myocardial necrosis -Elevation of troponin -Elevation of troponin	• Systolic BP ≥90 mmHg • No RV dysfunction • No myocardial necrosis

HETEROGENEOUS!!

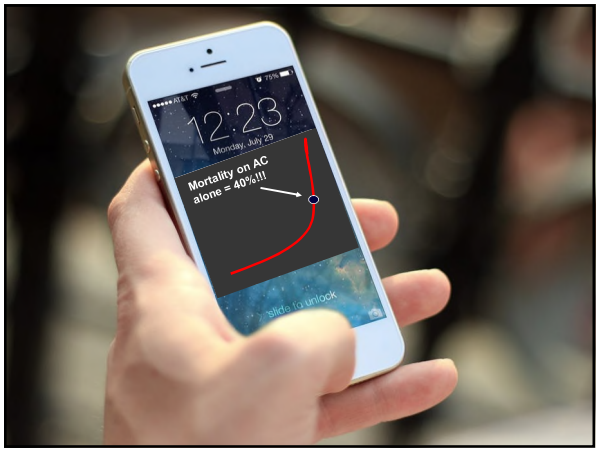
Heart rate?
PE burden?
Leg clot?
Hypoxemia?

Jaff et al. Management of massive and submassive PE, iliofemoral DVT, and C[illegible] statement from the AHA. Circulation 2011;123(16):1788-1830.

The Relationship of Severity and Mortality in Patients with Massive PE



Wood, K. E. Chest 2002;121:877-905



ICOPER:

RV hypokinesis on baseline echo associated with ~40% higher 3 month mortality rate.

Goldhaber S, Visani L, DeRosa M. The Lancet; Apr 24,1999; 353,9162

Prospective registry: 2,454 consecutive PE patients - 52 hospitals in 7 countries

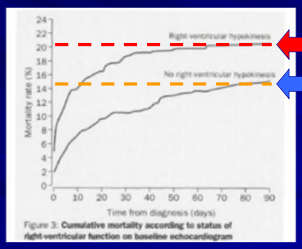


Figure 3: **Cumulative mortality according to status of right-ventricular function on baseline echocardiogram**

Mortality rate:

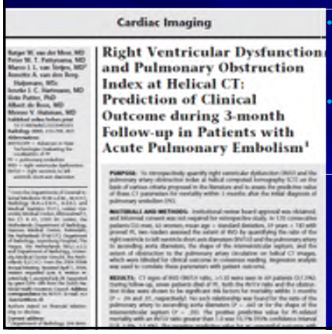
21% with RV hypokinesis

15% with no RV hypokinesis

Mortality risk increases 11-fold for PE patients with an obstructive index > 40% who are treated solely with anticoagulant therapy

(HR, 11.2; 95% CI: 1.3, 93.6).

Van der Meer R, Pattynama P, Van Strijen M, Van den Berg-Huijsmans A, Hartmann I, Putter H, De Roos A, Huisman M, Radiology 2005; 235: 798-803


Cardiac Imaging

Right Ventricular Dysfunction and Pulmonary Obstruction Index at Helical CT: Prediction of Clinical Outcome during 3-month Follow-up in Patients with Acute Pulmonary Embolism[1]

- Retrospective analysis of 120 patients with hemodynamically stable PE based on chest CT
- PE-related mortality at 3 mos:
  - **17%** if RV/LV > 1.5
  - **8%** if RV/LV 1.0 - 1.5
  - **0%** if RV/LV < 1.0

Thus, PE-related mortality risk increases with stepwise increase in RV/LV Ratio

Guidelines do not address DEGREE of RV dysfunction, or extent of obstruction…

BNP and Troponin

BNP

- A meta-analysis found 51% of 1132 unselected acute PE patients had elevated BNP or NT-proBNP on admission.
- Patients had 10% risk of early death (95% CI 8.0–13) and 23% (95% CI 20.0–26) risk of adverse outcome.

Troponin

- A meta-analysis (1985 patients) showed elevated troponin I or -T in 50% of patients with acute PE.
- ↑troponin assoc with high mortality in:
  - Unselected patients (OR 9.44; 95% CI 4.1–21.5) and in
  - Hemodynamically stable patients (OR 5.9; 95% CI 2.7–13).

DOES THIS MEAN THAT *ANY* PT WITH ELEVATED BNP OR TROP NEEDS MORE THAN ANTICOAGULATION?

Klok FA, et al. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with PE. A systematic review and meta-analysis. Am J Respir Crit Care Med 2008;178:425–430.

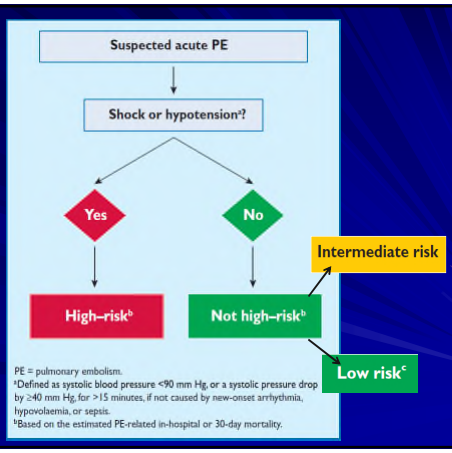
Becattini C, et al. Prognostic value of troponins in acute PE: a meta-analysis. Circulation 2007;116:427–433.

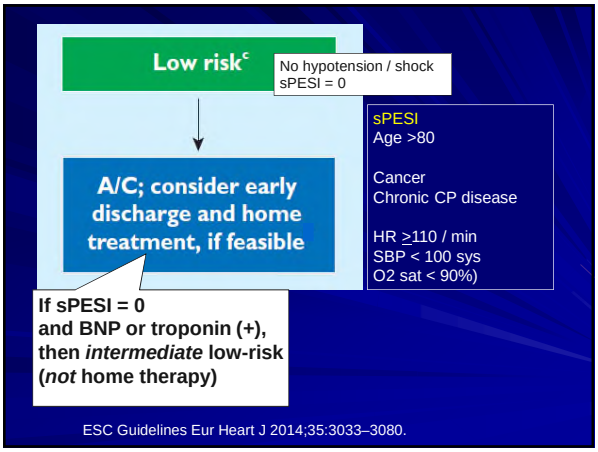
European Heart Journal

2014 ESC 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)Endorsed by the European Respiratory Society (ERS)

Authors/Task Force Members, Stavros Konstantinides , Adam Torbicki , Giancarlo Agnelli , Nicolas Danchin , David Fitzmaurice , Nazzareno Galiè , J. Simon R. Gibbs , Menno Huisman , Marc Humbert , Nils Kucher , Irene Lang , Mareike Lankeit , John Lekakis , Christoph Maack , Eckhard Mayer , Nicolas Meneveau , Arnaud Perrier , Piotr Pruszczyk , Lars H. Rasmussen , Thomas H. Schindler , Pavel Svitil , Anton Vonk Noordegraaf , Jose Luis Zamorano , Maurizio Zompatori

DOI: http://dx.doi.org/10.1093/eurheartj/ehu283 First published online: 30 August 2014





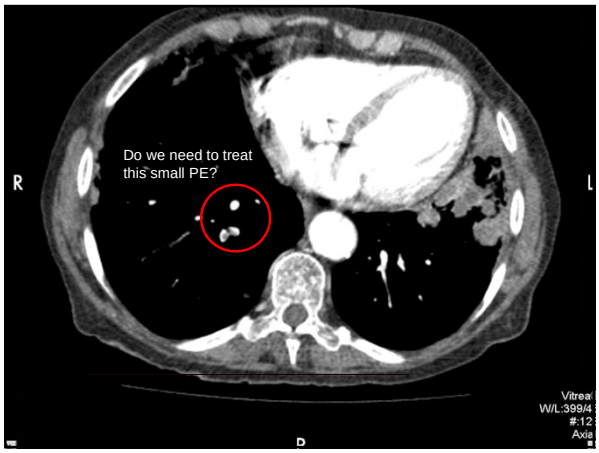
ESC Guidelines Eur Heart J 2014;35:3033–3080.

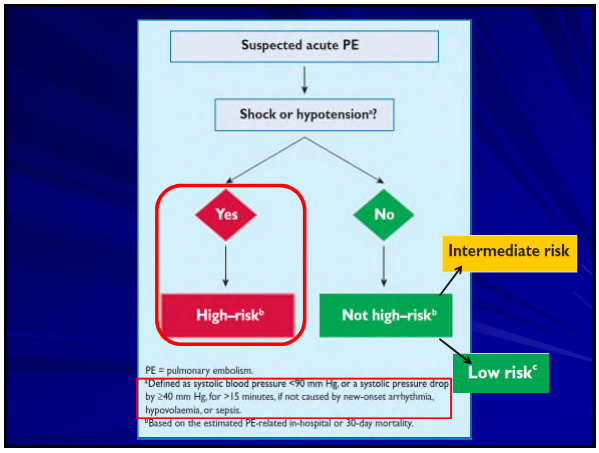
- What is the mortality in the low-risk group?

1.1% risk of 30-day mortality in “low" risk group (sPESI = 0 points), with 1.5% having recurrent VTE or non-fatal bleeding.

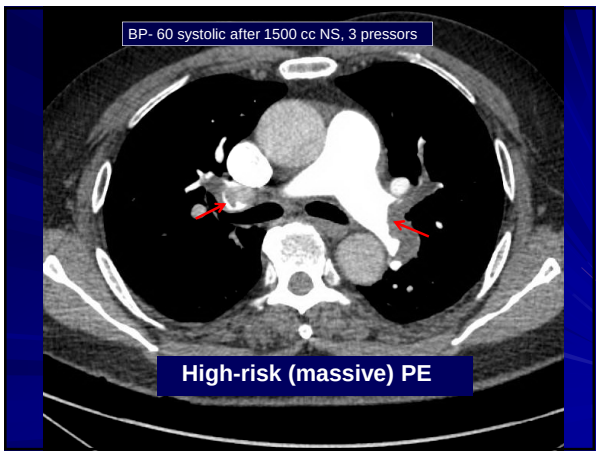
Treatment = anticoagulation

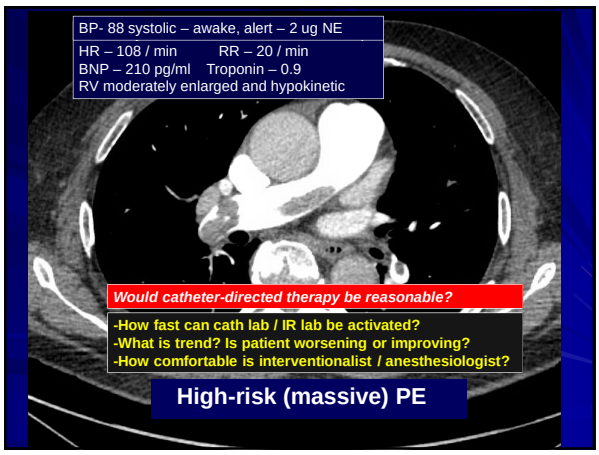
Jiménez D, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010 Aug 9;170(15):1383-9.





- Can we further subdivide the high-risk patients?





- Who are the intermediate-risk patients?
- Can we further subdivide them?

Who *are* the intermediate-risk PE patients? (ESC 2014)

- No hypotension or shock
- sPESI > 0

sPESI – 1 point each
- Age > 80
- Cardiopulm disease
- Cancer
- HR ≥ 110 /min
- SBP < 100 mm Hg
- O2 sat < 90%

Intermediate high-risk =
RV dysfunction (echo / CT) and ↑ BNP or troponin

Intermediate low-risk =
Either echo *or* biomarker abnormal (or neither)
(Or, sPESI = 0 and abnormal RV *or* (+) biomarker)

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

European Heart Journal Advance Access published August 29, 2014

ESC GUIDELINES

European Heart Journal

ESC 2014

RV + troponin (Both positive)

Intermediate–high risk

A/C; monitoring; consider rescue reperfusion[d]

Consider systemic thrombolysis for intermediate-high-risk PE if hemodynamic decompensation appears.

Consider surgical embolectomy or percutaneous CDT for intermediate-high-risk PE when hemodynamic decompensation appears imminent and the anticipated bleeding risk under *systemic* thrombolysis is high.

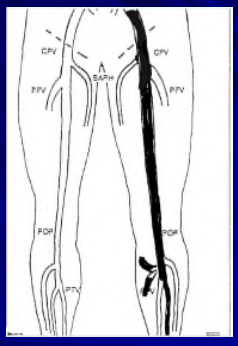
- What is the mortality in the (normotensive) intermediate-risk group?

Patients with sPESI > 0 had mortality up to 11%.
(10 x higher than low-risk group)

What about residual DVT?
Does that impact decisions?

Aujesky D, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172(8):1041–1046.

Jiménez D, et al. Simplification of the PESI for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010 Aug 9;170(15):1383-9.



If a patient has PE and very extensive residual DVT…
… do they need an IVCF?

Risk Stratification in Acute PE Based on Presence or Absence of Lower Extremity DVT: Systematic Review and Meta-analysis

- 272 / 4,379 (6.2%) PE patients with residual DVT died*
- 133 / 3,489 (3.8%) PE patients without residual DVT died*

*Within 30 days after PE diagnosis

(7 cohorts; OR 1.9; 95% CI, 1.5 to 2.4; I^2 = 0%).

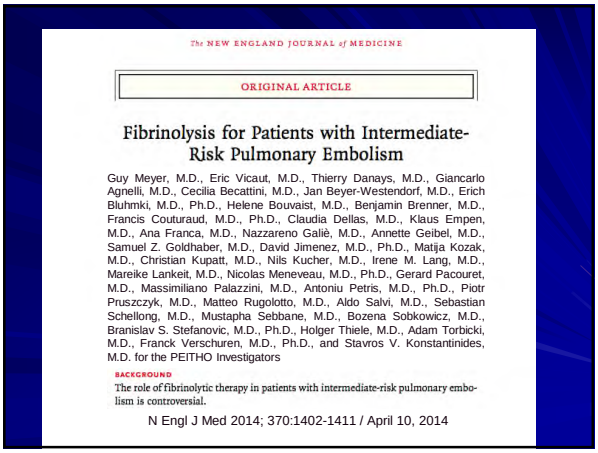
Becattini C, et al. Chest July 23, 2015

RISK STRATIFICATION:

- Symptoms
- General appearance
- RR, **heart rate**, BP, O2 sat
- RV – EKG / CTA / echo / BNP / troponin
- sPESI
- Extent of clot by CTA / VQ scan / D-dimer
- Residual clot in legs
- CP reserve
- Trends
- Lactate
- Bleed risk?
- ***How fast can you implement any given therapy?***

CLINICAL TRIALS!

PE RESPONSE TEAM?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus Empen, M.D., Ana Franca, M.D., Nazzareno Galiè, M.D., Annette Geibel, M.D., Samuel Z. Goldhaber, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian Kupatt, M.D., Nils Kucher, M.D., Irene M. Lang, M.D., Mareike Lankeit, M.D., Nicolas Meneveau, M.D., Ph.D., Gerard Pacouret, M.D., Massimiliano Palazzini, M.D., Antoniu Petris, M.D., Ph.D., Piotr Pruszczyk, M.D., Matteo Rugolotto, M.D., Aldo Salvi, M.D., Sebastian Schellong, M.D., Mustapha Sebbane, M.D., Bozena Sobkowicz, M.D., Branislav S. Stefanovic, M.D., Ph.D., Holger Thiele, M.D., Adam Torbicki, M.D., Franck Verschuren, M.D., Ph.D., and Stavros V. Konstantinides, M.D. for the PEITHO Investigators

BACKGROUND

The role of fibrinolytic therapy in patients with intermediate-risk pulmonary embolism is controversial.

N Engl J Med 2014; 370:1402-1411 / April 10, 2014

PEITHO: Does Thrombolytic Therapy Reduce Mortality in Acute Submassive PE?

- Prospective, randomized, double-blind
- Patients had RV dysfunction based on echo or CT plus a positive troponin I or T test.
- Enrolled 1,006 patients with confirmed acute submassive PE in 13 countries
- Anticoagulated
- Weight-based IV tenecteplase vs placebo
- Enrolled between 2007 and 2012

So, intermediate high-risk patients.

Meyer G, et al. NEJM April 10, 2014

The NEW ENGLAND JOURNAL of MEDICINE

PEITHO: Results

Endpoint:	Tenecteplase (n = 506)	Heparin (n = 499)	P-value
1˚ (combined) endpoint*†	13 (2.6%)	28 (5.6%)	0.02
Death (7d)	6 (1.2%)	9 (1.8%)	0.42
Hemodynamic collapse	8 (1.6%)	25 (5.0%)	0.0002
Major bleeding	32 (6.3%)	6 (1.5%)	< 0.001
Stroke	12	1	0.003
Hemorrhagic	10 (2.0%)	1 (0.2%)	
Ischemic	2	0	
Rescue thrombolysis	4 (0.8%)	23 (4.6%)	

*death / hemodynamic collapse
† 56% reduction

Safety Outcomes in the Intention-to-Treat Population.

Table 4. Safety Outcomes in the Intention-to-Treat Population.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
	no. (%)			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7	12 (2.4)	1 (0.2)	12.10 (1.57–93.39)	0.003
Ischemic stroke	2 (0.4)	0		
Hemorrhagic stroke‡	10 (2.0)	1 (0.2)		
Serious adverse events between	55 (10.9)	59 (11.8)	0.91 (0.62–1.34)	0.63

Of ICH patients, 8/10 were > 70 y-o. Youngest was 65. 4/10 survived.

* Odds ratios and P values are provided for efficacy and safety outcomes that were prespecified in the trial protocol.
† Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis.
‡ Hemorrhagic stroke included hemorrhagic conversion of ischemic stroke.

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

The NEW ENGLAND JOURNAL of MEDICINE

JAMA. 2014;311(23):2414-2421

Research

Original Investigation

Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage
A Meta-analysis

Saurav Chatterjee, MD; Arnaza Chakraborty, MD; Ido Weinberg, MD; Mitul Kadakia, MD; Robert L. Wilensky, MD; Partha Sardar, MD; Dharam J. Kumbhani, MD, SM, MRCP; Debabrata Mukherjee, MD, MS; Michael R. Jaff, DO; Jay Giri, MD, MPH

IMPORTANCE Thrombolytic therapy may be beneficial in the treatment of some patients with pulmonary embolism. To date, no analysis has had adequate statistical power to determine whether thrombolytic therapy is associated with improved survival, compared with conventional anticoagulation.

Editorial page 2385
Supplemental content at jama.com

Table 2. Absolute Risk Metrics of Outcomes of Major Interest

Outcome of Interest (No. of Studies Reporting)	No. of Events/No. of Patients, Absolute Event Rate (%)		No. Needed to Treat or Harm	P Value
	Thrombolytic Group	Anticoagulant Group		
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

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted trial-level data including number of patients, patient characteristics, duration of follow-up, and outcomes.

If We Thrombolyse – What is Dose? Submassive / Intermediate-risk PE

(**FDA:** 100 mg tPA IV over 2 hours)

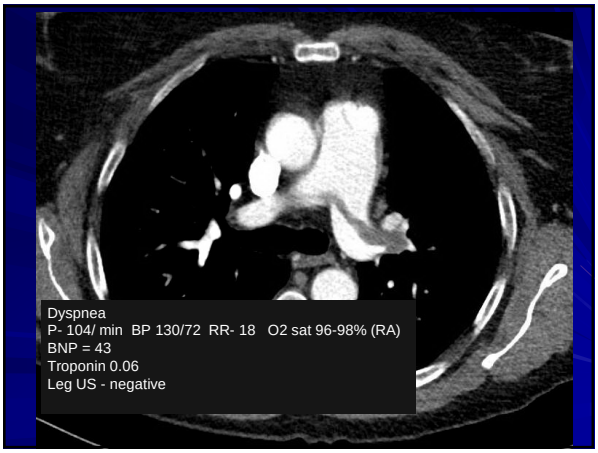
- Wang, et al. A/C → tPA 50 mg vs. 100 mg
- Sharifi, et al. A/C → tPA 50 mg vs. A/C alone

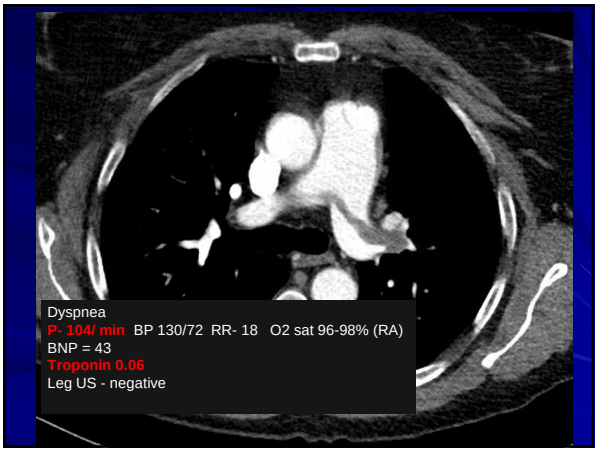
Consider in:
Smaller patients
Older patients
Patients with strong relative contraindications

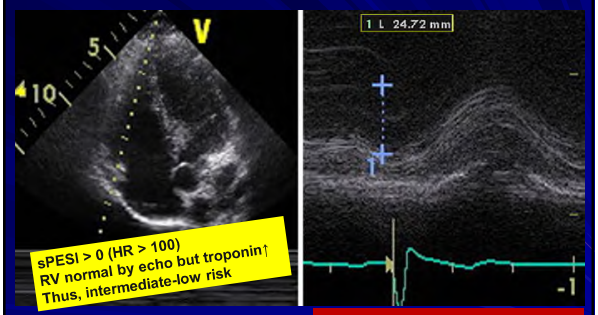
Grade of recommendation: X

Wang C et al. Efficacy and Safety of Low Dose Recombinant Tissue-Type Plasminogen Activator for the Treatment of Acute Pulmonary Thromboembolism. CHEST 2010; 137(2): 254-262.

Sharifi M et al. Moderate Pulmonary Embolism Treated with Thrombolysis (from the MOPETT Trial). Am J Cardiol 2013; 111: 273-277.







RV - NORMAL

What should you do?
PERT team?

TAPSE 24.4 mm - NORMAL

TREATMENT?

- Saddle embolus – but intermediate-low risk
- Enoxaparin 1 mg/kg SC q12h
- Changed to rivaroxaban 15 mg q12h after 24 h

What should initial anticoagulation be?

1. If parenteral, strongly consider LMWH – more bioavailable and therapeutic level in 3-4 hours.

2. If possible procedure, consider standard IV UFH

3. Can you use LMWH if you are considering a procedure?

4. Can you use LMWH if you are considering thrombolysis?

5. When can you go straight to a DOAC?

LMWH Use with Thrombolysis: Is it Effective and Safe? Ten Years' Clinical Experience.

METHODS:

- Retrospective cohort of acut
- Patients received either SC

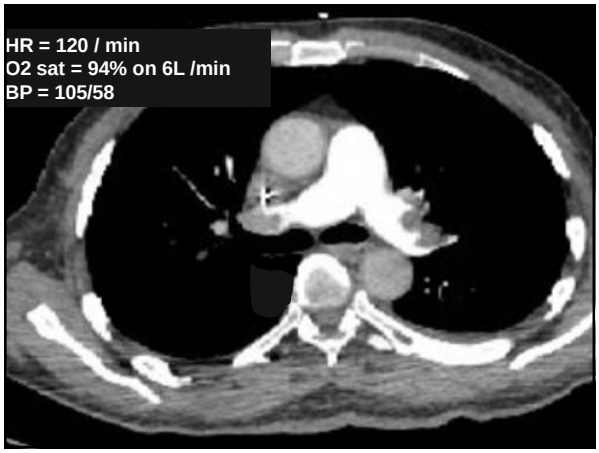
CONCLUSION:
SC LMWH use with thrombolytics seems to be feasible and safe. Prospective, RCTs are still required in order to confirm these results.

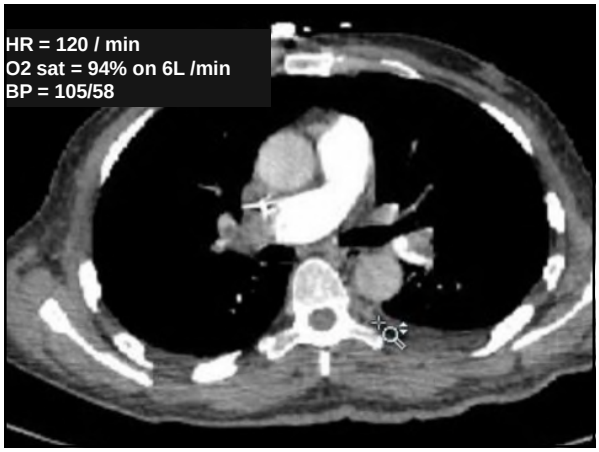
RESULTS:

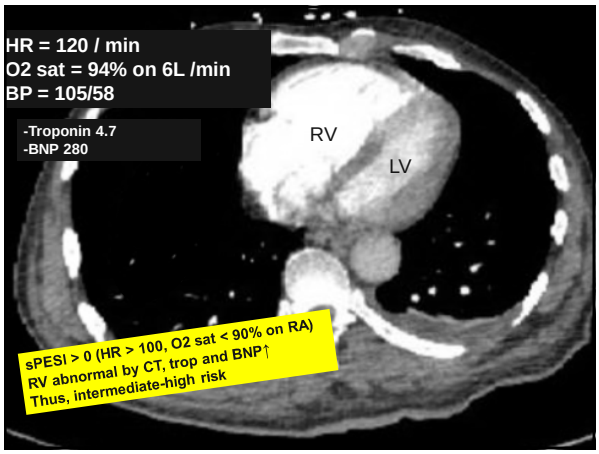
- 392 patients: 107 (27.2%) = massive and 285 (72.8%) = nonmassive.
- Mortality = 16.8% (18/107) in massive and 3.5% (10/285) for nonmassive ($p < 0.001$).

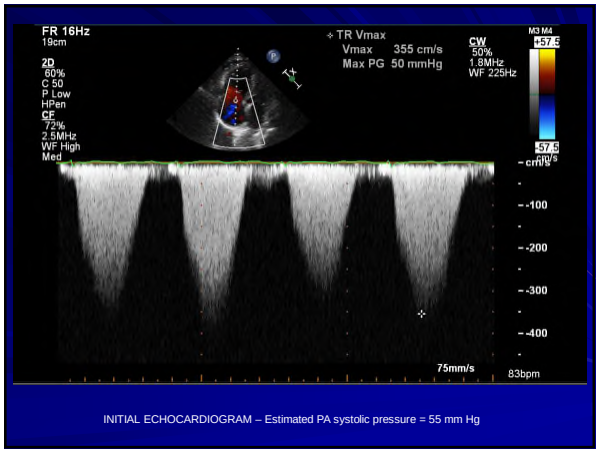
	Major hemorrhage	Minor hemorrhage
LMWH + thrombolytics	3.7% (n=4)	12.1% (n=13)
LMWH + no thrombolytics	0.7% (n=2)	3.8% (n=11)

Ucar EY, et al. Respiration 2013;86:318-23.






HR = 120 / min
O2 sat = 94% on 6L /min
BP = 105/58
-Troponin 4.7
-BNP 280
RV
LV
sPESI > 0 (HR > 100, O2 sat < 90% on RA)
RV abnormal by CT, trop and BNP↑
Thus, intermediate-high risk


FR 16Hz
19cm
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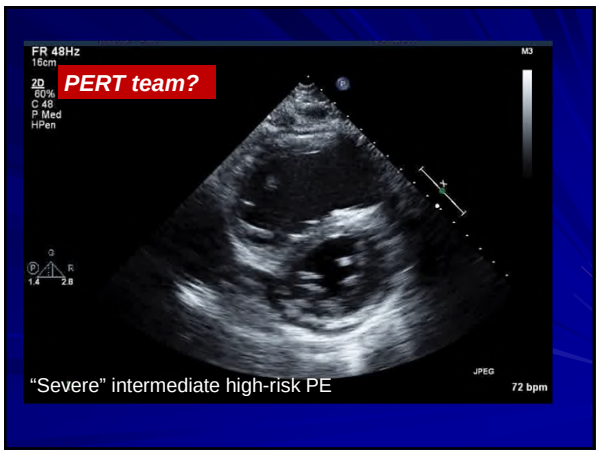
60%
C 50
P Low
HPen
CF
72%
2.5MHz
WF High
Med
TR Vmax
Vmax 355 cm/s
Max PG 50 mmHg
CW
50%
1.8MHz
WF 225Hz
M3 M4
+57.5
-57.5
cm/s
-100
-200
-300
-400
75mm/s
83bpm
INITIAL ECHOCARDIOGRAM – Estimated PA systolic pressure = 55 mm Hg


FR 48Hz
16cm
PERT team?
2D
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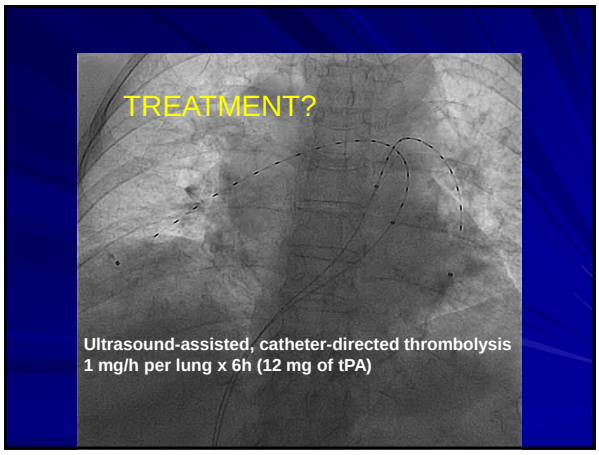
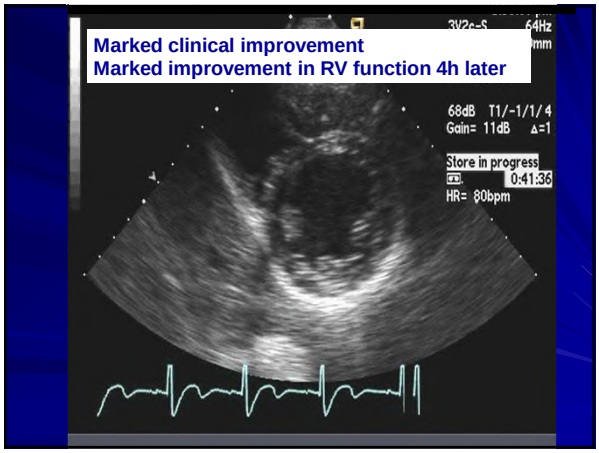
C 48
P Med
HPen
M3
JPEG
72 bpm
"Severe" intermediate high-risk PE





Intermediate-risk PE: Another option?

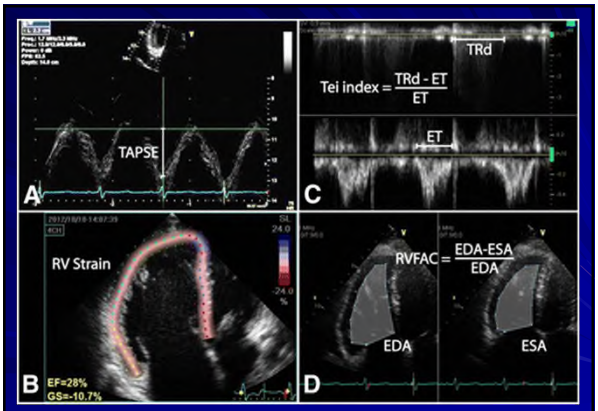
Focus on:

- **Extent of clot**
- **Severity of RV dysfunction by echo**
- **Physiologic parameters**
  - **Heart rate**
  - **Oxygenation**
  - **Trends**

Intermediate-risk PE: Another option?

Focus on:

- **Extent of clot**
- **Severity of RV dysfunction by echo**
- **Physiologic parameters**
  - **Heart rate**
  - **Oxygenation**
  - **Trends**



Dahhan T, Siddiqui I, Tapson, VF, et al. Cardiovascular Ultrasound 2016; 14:44

Intermediate-risk PE: Another option?

Focus on:

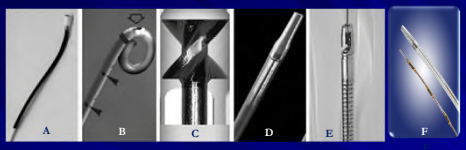
- **Extent of clot**
- **Severity of RV dysfunction by echo**
- **Physiologic parameters**
  - **Heart rate (<110 min / 111-120 / > 120)**
  - **Oxygenation**
  - **Trends**

Intermediate-risk PE: Another option?

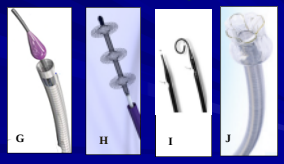
Focus on:

- **Extent of clot**
- **Severity of RV dysfunction by echo**
- **Physiologic parameters**
  - **Heart rate (<110 min / 111-120 / > 120)**
  - **Oxygenation (0-2L / 3-6L / > 6L)**
  - **Trends**

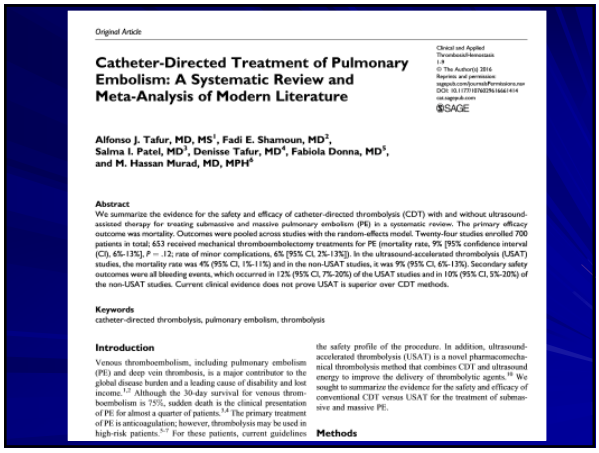
Catheter embolectomy: Catheter devices



A. Greenfield embolectomy catheter
B. 5F pigtail rotational catheter
C. Amplatz Thrombectomy Device
D. AngioJet (rheolytic) Xpeedior catheter
E. Aspirex 11-Flex catheter
F. EKOS® US-assisted thrombolytic catheter
G. Penumbra catheter
H. Inari FlowTriever
I. Pronto 14 F XL-extraction catheter
J. AngioVac cannula



We have lots of devices…..



Original Article

Clinical and Applied Thrombosis/Hemostasis
1–9
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DOI: 10.1177/1076029616641414
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Catheter-Directed Treatment of Pulmonary Embolism: A Systematic Review and Meta-Analysis of Modern Literature

Alfonso J. Tafur, MD, MS[1], Fadi E. Shamoun, MD[2], Salma I. Patel, MD[3], Denisse Tafur, MD[4], Fabiola Donna, MD[5], and M. Hassan Murad, MD, MPH[6]

Abstract

We summarize the evidence for the safety and efficacy of catheter-directed thrombolysis (CDT) with and without ultrasound-assisted therapy for treating submassive and massive pulmonary embolism (PE) in a systematic review. The primary efficacy outcome was mortality. Outcomes were pooled across studies with the random-effects model. Twenty-four studies enrolled 700 patients in total; 653 received mechanical thromboembolectomy treatments for PE (mortality rate, 9% [95% confidence interval (CI), 6%-13%], $P = .12$; rate of minor complications, 6% [95% CI, 2%-13%]). In the ultrasound-accelerated thrombolysis (USAT) studies, the mortality rate was 4% (95% CI, 1%-11%) and in the non-USAT studies, it was 9% (95% CI, 6%-13%). Secondary safety outcomes were all bleeding events, which occurred in 12% (95% CI, 7%-20%) of the USAT studies and in 10% (95% CI, 5%-20%) of the non-USAT studies. Current clinical evidence does not prove USAT is superior over CDT methods.

Keywords

catheter-directed thrombolysis, pulmonary embolism, thrombolysis

Introduction

Venous thromboembolism, including pulmonary embolism (PE) and deep vein thrombosis, is a major contributor to the global disease burden and a leading cause of disability and lost income.[1,2] Although the 30-day survival for venous thromboembolism is 75%, sudden death is the clinical presentation of PE for almost a quarter of patients.[3,4] The primary treatment of PE is anticoagulation; however, thrombolysis may be used in high-risk patients.[5–7] For these patients, current guidelines the safety profile of the procedure. In addition, ultrasound-accelerated thrombolysis (USAT) is a novel pharmacomechanical thrombolysis method that combines CDT and ultrasound energy to improve the delivery of thrombolytic agents.[10] We sought to summarize the evidence for the safety and efficacy of conventional CDT versus USAT for the treatment of submassive and massive PE.

Methods

Tafur et al 3

If our risk-stratification is to *matter*, we need to *prove* that outcomes change with more aggressive therapy!

Table 1. Demographics of Patients in 24 Studies of Catheter-Directed Thrombolysis.

Author, Year of Publication	Country	Patients, No.	Female, %	Patient Age, Mean (SD), y
Randomized controlled trial				
Kucher et al, 2014[2]	Germany and Switzerland	59	53	63 (14)
Registries				
Kuo et al, 2015[12]	United States and Spain	101	47.5	60
Ruzsa et al, 2014[18]	Hungary	26	NR	52.5 (14.9)
Cohort studies				
Arzamendi et al, 2010[19]	Canada	10	70	43.7 (18.8)
Gao et al, 2011[20]	China	46	58	52.3 (13.4)
Retrospective studies				
Chamsuddin et al, 2008[21]	United States	10	50	54.2
Chechi et al, 2009[22]	Italy	60	51	66.7 (13.8)
Lin et al, 2009[17]	United States	25	52	NR
Lin et al, 2009 EKOS[17]	United States	11	55	59 (17)
Zhou et al, 2009[23]	China	28	28.5	63.7 (11.1)
Mohan et al, 2010[24]	India	7	14	46.8 (12.2)
Ferrigno et al, 2011[25]	United States	16	56	54.4 (15.8)
Hubbard et al, 2011[26]	United States	12	18.8	60.2
Cucull et al, 2012[27]	Switzerland	63	41	60 (15)
Engelhardt et al, 2012[16]	United States	42	NR	58 (16)
Liu et al, 2012[28]	China	20	40	NR
Munakata et al, 2012[29]	Japan	10	80	58.1
Nasiri et al, 2012[30]	United States	15	47	59 (16)
Kennedy et al, 2013[31]	United States	60	42	61 (16)
Akin et al, 2014[32]	United States	17	52.9	60.1
Al-Hakim et al, 2014[33]	United States	18	50	54.8
Fernandez et al, 2014[34]	Argentina	14	35.7	64.5 (14.3)
Ivanauskiene et al, 2014[35]	Lithuania	20	35	58.4 (15.3)
Quintana et al, 2014[36]	United States	10	40	NR

Abbreviation: NR, not reported.
[a]EkoSonic, Endovascular System; EKOS Corp.

NEED MORE DATA!!!!

ULTIMA study compared EKOS® to heparin in intermediate risk PE therapy

The first RCT for an advanced catheter-based modality


Circulation

Interventional Cardiology

Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism

Primary Objective:
Determine whether fixed low-dose catheter-directed US-accelerated thrombolysis is superior to heparin alone in reversal of RV dilation in submassive / intermediate risk PE

All received IV heparin for at least 24 h.

Treated patients also received US-accelerated low-dose, intra-clot delivery of rt-PA at ≤ 2 mg/hr for 5 h, and ≤ 1 mg/h for 10 h, for a total infusion time of 15 h and no more than 20 mg in total dose.

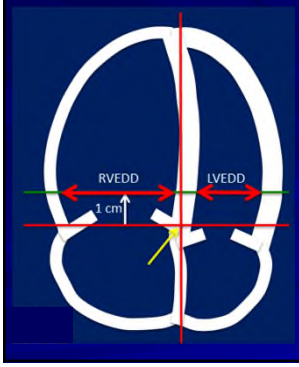
Kucher et al. Circulation. 2014;129:479-486

ULTIMA: ULTrasound Accelerated ThrombolysIs of PulMonAry Embolism

- Phase II, multicenter, open-label, randomized, controlled trial
- RV/LV ratio ≥ 1.0 required for inclusion.
- Primary outcome: Reduction in RV/LV ratio from baseline to 24 hours and 90 days
- Secondary outcome: Mortality, recurrent PE, major and minor bleeding at 90 days

Kucher N, et al. Circulation 2014;129:479

The ULTIMA Trial



Enrollment Criteria

Symptoms < 14 days

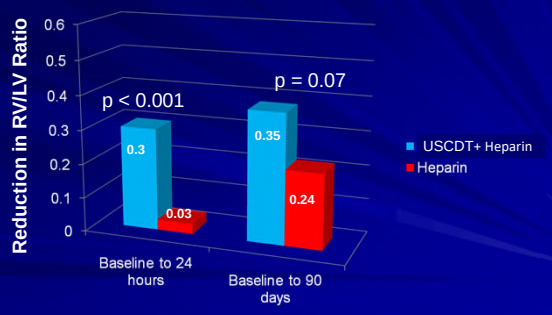
No hemodynamic collapse

No active bleeding

Acute symptomatic PE with PE in at least one main or proximal lower lobe PA

RV/LV ratio > 1 on echo

ULTIMA: Primary Outcomes

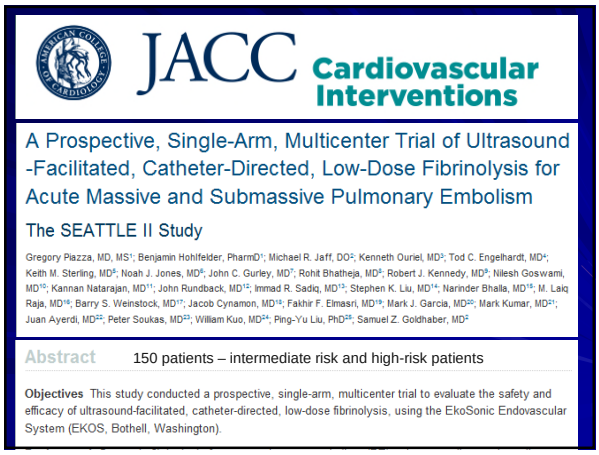


Kucher N, et al. Circulation 2014;129:479

ULTIMA: Safety Outcomes

Clinical outcomes at 3 months	EKOS® +Heparin N=30		Heparin N=29		p-value
Death	0	0%	1	3%	1.00
Recurrent VTE	0	0%	0	0%	1.00
Major bleeding	0	0%	0	0%	1.00
Minor bleeding	3	10%	1	3%	0.61

Kucher N, et al. Circulation 2014;129:479



JACC Cardiovascular Interventions

A Prospective, Single-Arm, Multicenter Trial of Ultrasound -Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism

The SEATTLE II Study

Gregory Piazza, MD, MS[1]; Benjamin Hohlfelder, PharmD[1]; Michael R. Jaff, DO[2]; Kenneth Ouriel, MD[3]; Tod C. Engelhardt, MD[4]; Keith M. Sterling, MD[5]; Noah J. Jones, MD[6]; John C. Gurley, MD[7]; Rohit Bhatheja, MD[8]; Robert J. Kennedy, MD[9]; Nilesh Goswami, MD[10]; Kannan Natarajan, MD[11]; John Rundback, MD[12]; Immad R. Sadiq, MD[13]; Stephen K. Liu, MD[14]; Narinder Bhalla, MD[15]; M. Laiq Raja, MD[16]; Barry S. Weinstock, MD[17]; Jacob Cynamon, MD[18]; Fakhir F. Elmasri, MD[19]; Mark J. Garcia, MD[20]; Mark Kumar, MD[21]; Juan Ayerdi, MD[22]; Peter Soukas, MD[23]; William Kuo, MD[24]; Ping-Yu Liu, PhD[25]; Samuel Z. Goldhaber, MD[2]

Abstract 150 patients – intermediate risk and high-risk patients

Objectives This study conducted a prospective, single-arm, multicenter trial to evaluate the safety and efficacy of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis, using the EkoSonic Endovascular System (EKOS, Bothell, Washington).

OPTALYSE PE:
Lower doses, shorter duration of therapy

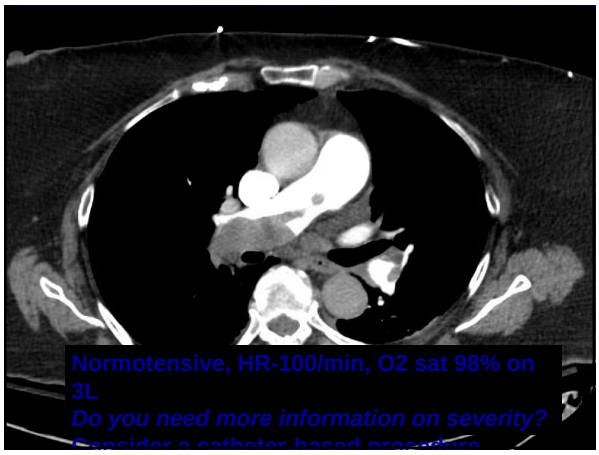
	Abstract (Preliminary) Results		
Treatment Group	N	RV/LV Change at 48h (%); p-value*	MMS % Change; p-value**
2h (8 mg) 2 mg / h / catheter	19	-0.46 (27%); 0.006	-5%; 0.013
4h (8 mg) 1 mg / h / catheter	22	-0.34 (22%); 0.013	-7%; 0.0003
6h (12 mg) 1 mg / h / catheter	22	-0.47 (28%); 0.0004	-15%; 0.00001
6h (24 mg) 2 mg / h / catheter	18	-0.48 (26%); 0.018	-26%; 0.0007

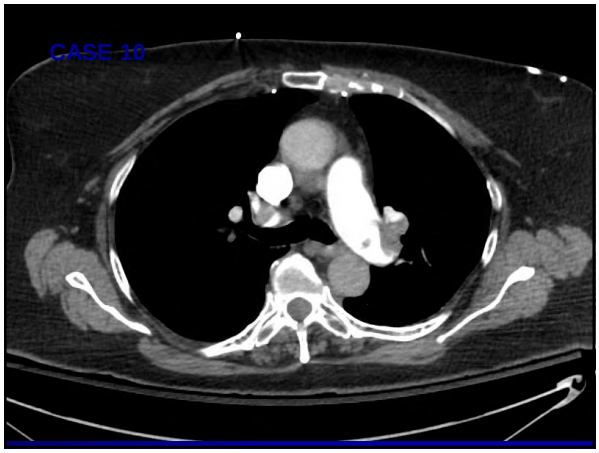
*1-sided compared to 0.2 decrease
** 1-sided compared to 0

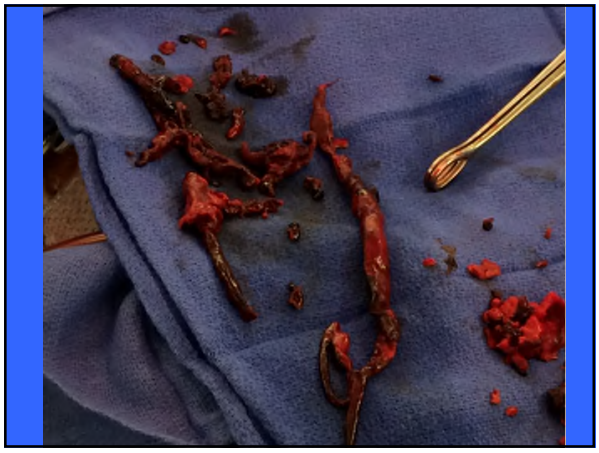
ATS 2017 / Submitted for publication

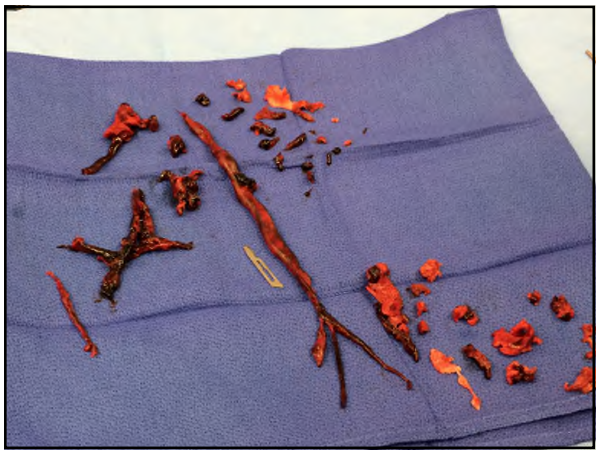
CASE

- 30 year-old with acute PE
- Hypotensive and severely hypoxemic
- Syncope – hit head brain CT negative
- RA/RV clot-in-transit
- PA pressure in OR 80 systolic
- *AngioVac planned*
- Coded in OR
- CPR – resuscitated
- Embolectomy performed

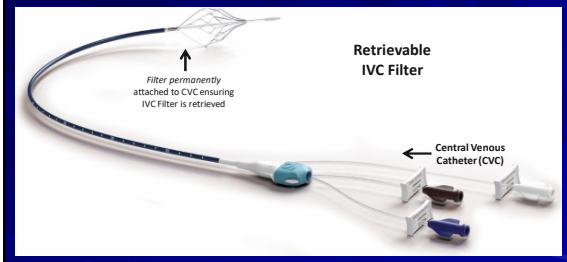

Normotensive, HR-100/min, O2 sat 98% on 3L
Do you need more information on severity?


CASE 10



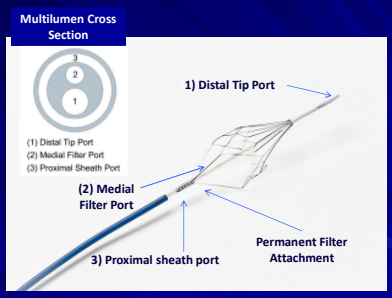


IVCF / central venous catheter



- **IVC filter** *permanently* attached to triple lumen **central venous catheter**
- **First prophylactic indication for use** for IVC Filters—*intended for critically ill ICU patients at a temporarily high risk of PE*
- **Bedside placement**

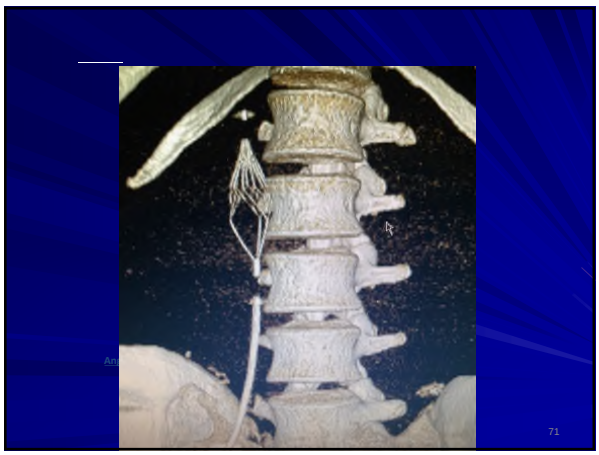
Catheter

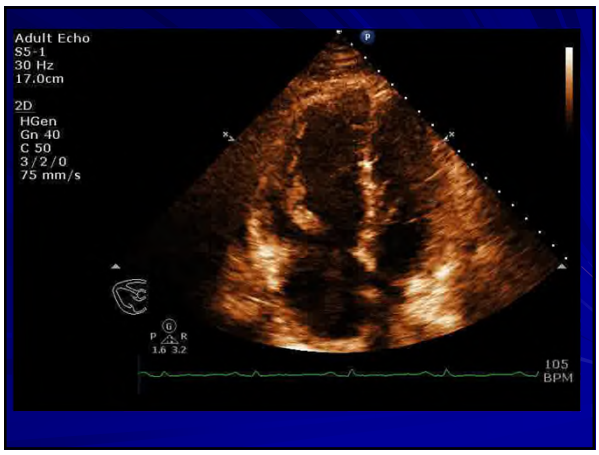


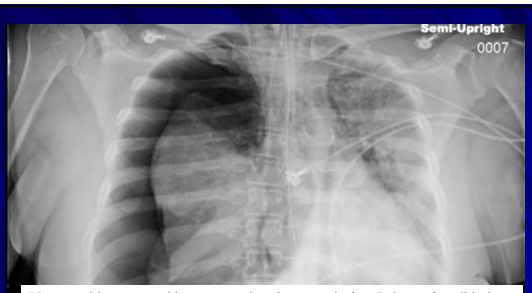
CLINICAL STUDY

Evaluation of a Device Combining an Inferior Vena Cava Filter and a Central Venous Catheter for Preventing Pulmonary Embolism Among Critically Ill Trauma Patients

Victor F. Tapson, MD, Joshua P. Hazelton, DO, John Myers, MD, Claudia Robertson, MD, Ramyar Gilani, MD, Julie A. Dunn, MD, Marko Bukur, MD, Martin A. Croce, MD, Ann Peick, MD, Sonlee West, MD, Lawrence Lottenberg, MD, Jay Doucet, MD, Preston R. Miller, MD, Bruce Crookes, MD, Rajesh R. Gandhi, MD, Chasen A. Croft, MD, Anthony Manasia, MD, Brian A. Hoey, MD, Howard Lieberman, MD, Oscar D. Guillamondegui, MD, MPH, Victor Novack, MD, Gregory Piazza, MD, and Samuel Z. Goldhaber, MD







59 year-old woman with pneumonia – improved after 2 days of antibiotics
Now on 2L nasal cannula

- Sudden onset pleuritic R CP and severe dyspnea
  - Small amount of hemoptysis
  - HR 120/min
  - BP 96/52
- O2 sat 80% on FIO2 100%

IV tPA?

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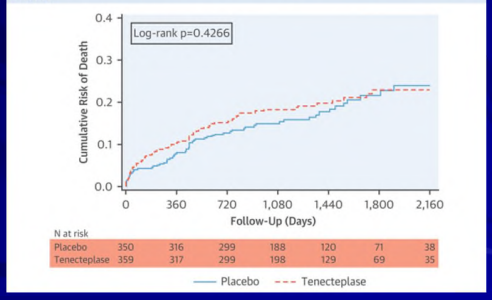
VOL. 69, NO. 12, 2017

Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism

Stavros V. Konstantinides, MD, PhD,[a,b] Eric Vicaut, MD, PhD,[c] Thierry Danays, MD,[d] Cecilia Becattini, MD,[e] Laurent Bertoletti, MD, PhD,[f] Jan Beyer-Westendorf, MD,[g] Helene Bouvaist, MD,[h] Francis Couturaud, MD, PhD,[i] Claudia Dellas, MD,[j] Daniel Duerschmied, MD,[k] Klaus Empen, MD,[l] Emile Ferrari, MD,[m] Nazzareno Galiè, MD,[n] David Jiménez, MD, PhD,[o] Maciej Kostrubiec, MD,[p] Matija Kozak, MD,[q] Christian Kupatt, MD,[r] Irene M. Lang, MD,[s] Mareike Lankeit, MD,[b,t] Nicolas Meneveau, MD, PhD,[u] Massimiliano Palazzini, MD,[v] Piotr Pruszczyk, MD,[p] Matteo Rugolotto, MD,[w] Aldo Salvi, MD,[x] Olivier Sanchez, MD,[m,n,y] Sebastian Schellong, MD,[z] Bozena Sobkowicz, MD, PhD,[aa] Guy Meyer, MD[m,n,bb]

JACC 2017; 69:1536-1544

Thrombolysis for Pulmonary Embolism: Kaplan-Meier Survival Curves of Patients Randomized to Tenecteplase Compared With Placebo



PEITHO 2 – LONG-TERM OUTCOMES

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 30, 2017 VOL. 376 NO. 13

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

ABSTRACT

BACKGROUND

Although many patients with venous thromboembolism require extended treatment, it is uncertain whether it is better to use full- or lower-intensity anticoagulation therapy or aspirin.

METHODS

In this randomized, double-blind, phase 3 study, we assigned 3396 patients with venous thromboembolism to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. All the study patients had completed 6 to 12 months of anticoagulation therapy and were in equipoise regarding the need for continued anticoagulation. Study drugs were administered for up to 12 months. The primary efficacy outcome was symptomatic recurrent fatal or nonfatal venous thromboembolism, and the principal safety outcome was major bleeding.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Weitz at the Thrombosis and Atherosclerosis Research Institute, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at weitzj@taari.ca.

*A list of the Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN CHOICE) investigators and collaborators is provided in the Supplementary Appendix, available at NEJM.org.

Rivaroxaban vs. ASA for the Reduction in the Risk of Recurrent DVT/PE: THE EINSTEIN CHOICE TRIAL

Patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment and were in equipoise regarding the need for extended anticoagulation

RANDOMIZE

Up to 12-month Treatment Duration

- Rivaroxaban 20 mg once daily
- Rivaroxaban 10 mg once daily
- Aspirin 100 mg once daily

Primary efficacy outcome: Symptomatic recurrent VTE*
Principal safety outcome: Major bleeding (ISTH)

Because the benefit-risk assessment favored the 10-mg dose versus aspirin compared to the 20-mg dose versus aspirin, the 10-mg dose is approved for the reduction in the risk of recurrent DVT/PE

Risk Profile	Rivaroxaban 10 mg (N = 1127)	Aspirin 100 mg (N=1131)
Provoked index event	57.4% (n=647)	58.6% (n=663)
Unprovoked index event	42.6% (n=480)	41.4% (n=468)

*Defined as a composite of symptomatic, recurrent fatal or nonfatal VTE and unexplained death where PE could not be ruled out.

Weitz JI, et al. *N Eng J Med.* 2017;376(13):1211-1222.

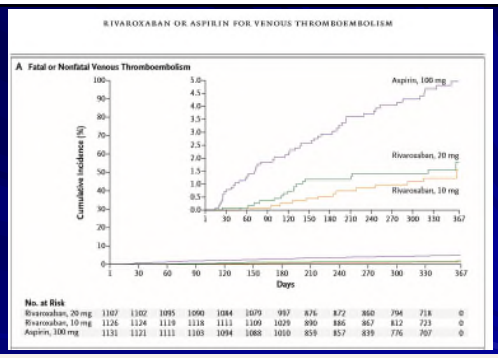
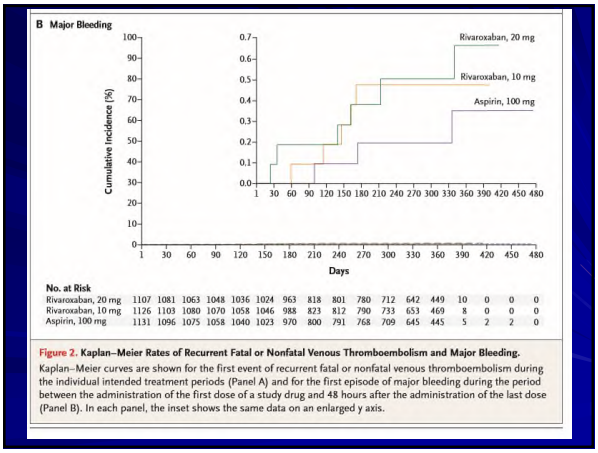


Figure 2. Kaplan–Meier Rates of Recurrent Fatal or Nonfatal Venous Thromboembolism and Major Bleeding.
Kaplan–Meier curves are shown for the first event of recurrent fatal or nonfatal venous thromboembolism during the individual intended treatment periods (Panel A) and for the first episode of major bleeding during the period between the administration of the first dose of a study drug and 48 hours after the administration of the last dose (Panel B). In each panel, the inset shows the same data on an enlarged y axis.



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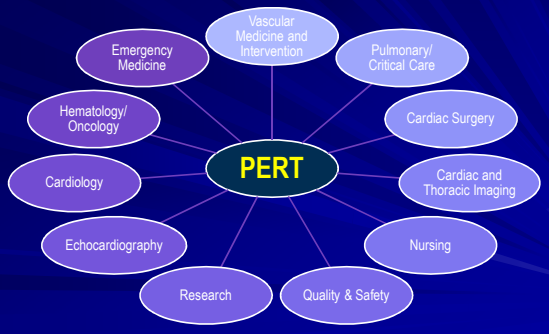
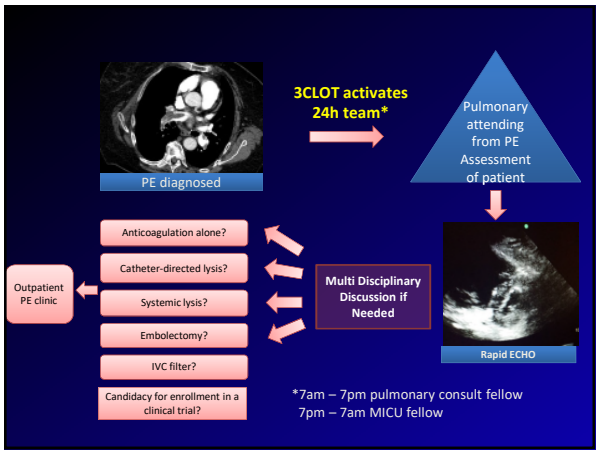
PERT: Pulmonary Embolism Response Team

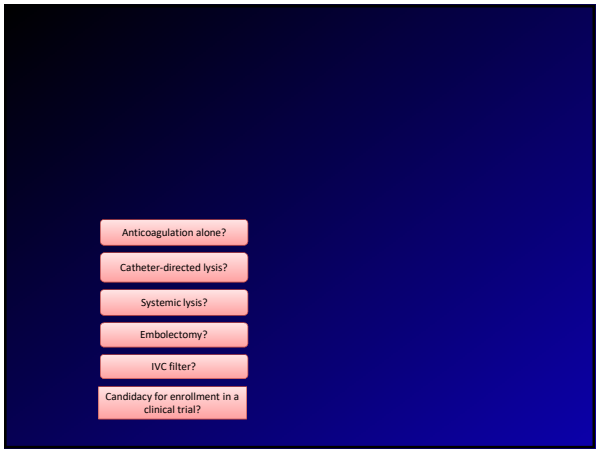
- Mission: *Improve patient outcomes with a collaborative, multidisciplinary team-based urgent consult to treat massive and submassive PE*
- Functionality
  - Modeled on rapid-response concept
  - Multidisciplinary team of experts: convened via electronic meeting
  - Evaluate and offer full range of available treatments

Chest 2013;144:1738.

Multidisciplinary Collaboration




PE diagnosed
3CLOT activates 24h team*
Pulmonary attending from PE Assessment of patient
Rapid ECHO
Multi Disciplinary Discussion if Needed
Anticoagulation alone?
Catheter-directed lysis?
Systemic lysis?
Embolectomy?
IVC filter?
Candidacy for enrollment in a clinical trial?
Outpatient PE clinic
*7am – 7pm pulmonary consult fellow
7pm – 7am MICU fellow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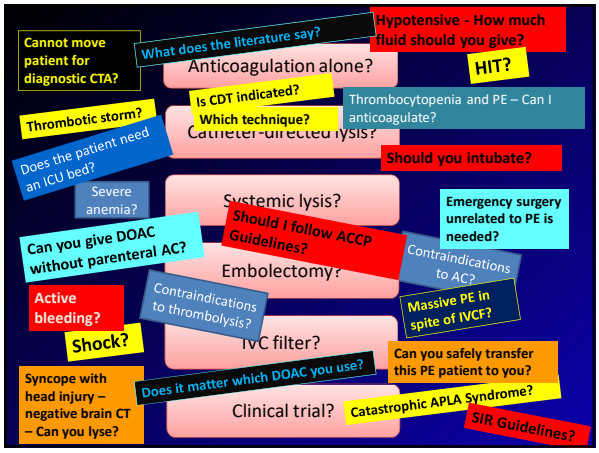

Cannot move patient for diagnostic CTA?
What does the literature say?
Hypotensive - How much fluid should you give?
Anticoagulation alone?
HIT?
Is CDT indicated?
Which technique?
Thrombocytopenia and PE – Can I anticoagulate?
Thrombotic storm?
Does the patient need an ICU bed?
Should you intubate?
Severe anemia?
Systemic lysis?
Emergency surgery unrelated to PE is needed?
Can you give DOAC without parenteral AC?
Should I follow ACCP Guidelines?
Contraindications to AC?
Embolectomy?
Active bleeding?
Contraindications to thrombolysis?
Massive PE in spite of IVCF?
Shock?
IVC filter?
Can you safely transfer this PE patient to you?
Syncope with head injury – negative brain CT – Can you lyse?
Does it matter which DOAC you use?
Clinical trial?
Catastrophic APLA Syndrome?
SIR Guidelines?

Utilizing the PERT adds value to the care

- Leverage "pockets" of experience:
- Critical Care
- Cardiology
- Cardiac surgery
- Interventional cardiology
- Pulmonary hypertension

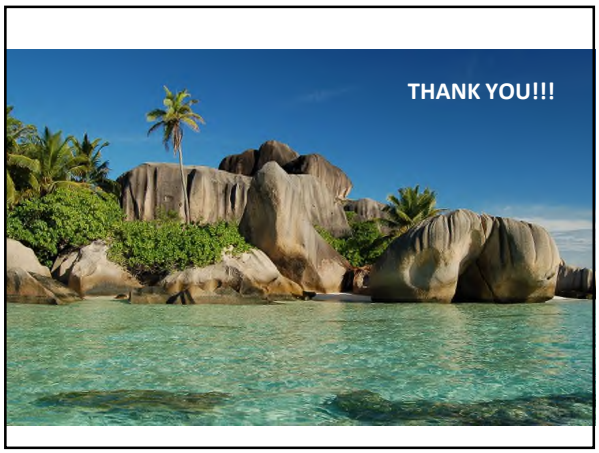
- Decrease bias
- Eliminate serial consults → SPEED
- Shared decision making → Can't leave without an answer
- Insures long term follow-up

CEDARS PERT team next steps

- Short term goal :
  - Increase internal awareness through grand rounds lectures and internal conferences
  - Build our internal volume through good reputation
- Continue to enroll in clinical trials
- We are starting a monthly VTE conference open to multiple disciplines

CONCLUSIONS

- Recognize the varied presentations of acute PE
- Risk stratify patients taking into consideration:
  - History – syncope? Lightheadedness / dizziness
  - Appearance / vital signs – *HR* / *BP* / oxygenation
  - Clot burden (including legs!)
  - RV size / function
  - Troponin / BNP / D-dimer
  - Cardiopulmonary reserve
  - Trends
  - Calculated data (sPESI / Shock index)
- Let's continue to work on improving risk stratification
- We need more outcome data to support therapy beyond anticoagulation.


THANK YOU!!!