Data Collection

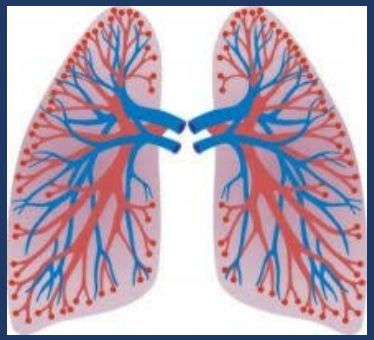
In order to support the growth of the ECHO movement, Project ECHO® collects participation data for each teleECHO™ program. This data allows Project ECHO to measure, analyze, and report on the movement's reach. It is used in reports, on maps and visualizations, for research, for communications and surveys, for data quality assurance activities, and for decision-making related to new initiatives.

Intermountain Healthcare
Healing for life®

Project ECHO®
Intermountain Healthcare
Utah

Intermountain Project ECHO
TeleCritical Care Medicine

Thrombolytics in Intermediate Pulmonary Embolism (PE)



Rachel Belcher, PharmD

PGY2 Critical Care Pharmacist Resident

Intermountain Medical Center/Tele-Critical Care

Intermountain Healthcare
Healing for life®

Project ECHO
Intermountain Healthcare
Utah

Objectives

- *Discuss risk stratification of massive and intermediate PE requiring thrombolytics*
- *Review guideline recommendations and key randomized controlled trials for/against thrombolytic use in intermediate PE*
- *Patient case-based application of literature*

Abbreviations

Alteplase – tPA or r-tPA
American Heart Association – AHA
American College of Chest Physicians – CHEST
Anticoagulation Forum – AC Forum
Blood pressure – BP
Cardiopulmonary resuscitation – CPR
CT pulmonary angiography – CTPA
Direct oral anticoagulant – DOAC
Electrocardiogram – ECG or EKG
Emergency department – ED
European Society of Cardiology – ESC
Gastrointestinal bleed – GIB
Heart rate – HR
Hemoglobin – Hgb
Hypertension – HTN
Intensive care unit – ICU
Intravenous – IV
Left ventricle – LV
Length of stay – LOS
Low molecular weight heparin – LMWH
Mean arterial pressure – MAP
National Institute for Health and Care Excellence – NICE
Past medical history – PMH
Pulmonary arterial systolic pressure- PASP or SPAP
Pulmonary embolism – PE
Pulmonary embolism severity index – PESI
Pulmonary embolism rule out criteria – PERC
Pulmonary hypertension – pHTN
Respiratory rate – RR
Revised Geneva score – RGS
Right ventricle – RV
Right/left ventricle end-diastolic diameter ratio – RVED/LVED
Shortness of breath – SOB
Systolic blood pressure – SBP
Transient ischemic stroke – TIA
Unfractionated heparin – UFH
Upper limit of normal – ULN
Venous thromboembolism – VTE
Ventilation perfusion – V/Q

Background

Background

- *PE is considered the third most common cause of cardiovascular death after heart attack and stroke*
- *Approximately 60,000 to 100,000 deaths reported each year*

Hereditary risk factors	Acquired risk factors
Antithrombin, Protein C, Protein S deficiencies	Reduced mobility
Factor V Leiden	Advanced age
Prothrombin gene mutation	Cancer
Plasminogen deficiency	Acute medical illness/major surgery
Antithrombin, Protein C, Protein S deficiencies	Trauma/Spinal cord injury
	Pregnancy and post-partum period
	Hormone replacement therapy, oral contraception

Turetz M, et al. Semin Intervent Radiol. 2018; 35:92-98.

Presentation

- *PE presenting symptoms can be variable*

Common presenting symptoms	Common presenting signs
Dyspnea	Tachypnea (≥ 20 breaths/min)
Pleuritic pain	Tachycardia (> 100 bpm)
Cough	Rales
Wheezing	Decreased breath sounds
Hemoptysis	Jugular vein distention

Turetz M, et al. Semin Intervent Radiol. 2018; 35:92-98.

Risk-assessment

Pre-test risk assessment can help to rule out a PE before additional imaging is performed

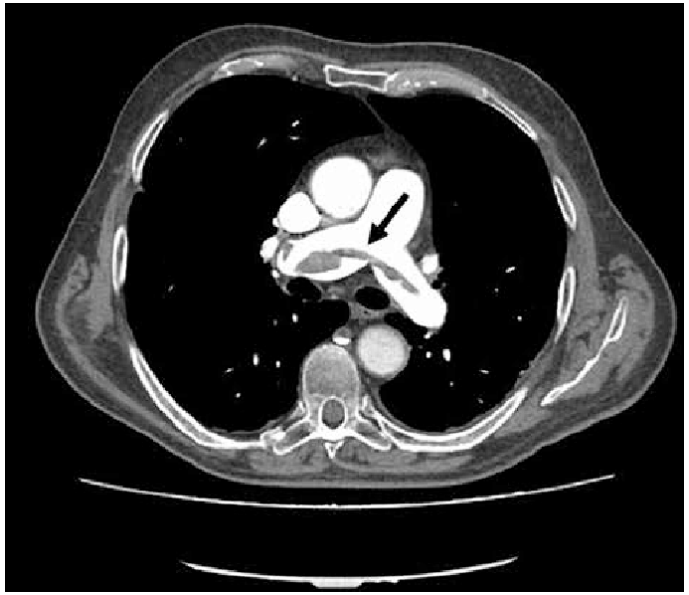
- ***Pulmonary Embolism Rule Out Criteria (PERC)***
- ***Revised Geneva Score (RGS)***
  - *Assesses patients' likelihood of having a PE based on risk factors and signs/symptoms present*
  - *If no criteria met, PE can be ruled OUT (no further imaging needed)*

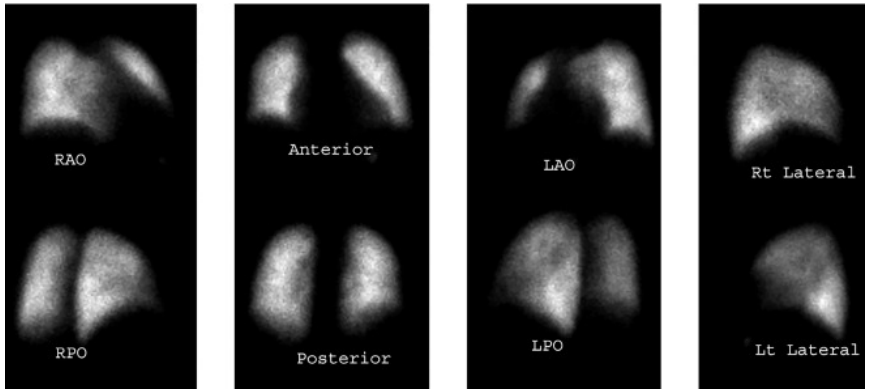
Rivera-Lebron B, et al. Clin Appl Thromb Hemost 2019.
Wells PS, et al. Thromb Haemost 2000.
Donze J, et al. Thromb Haemost 2008.

Diagnosis Confirmation

Imaging and further testing is the next step in risk stratification

- *CT pulmonary angiography (CTPA)*
- *Ventilation/perfusion (V/Q) scan*
- *Electrocardiogram*
- *Echocardiogram*
- *Cardiac biomarker labs*



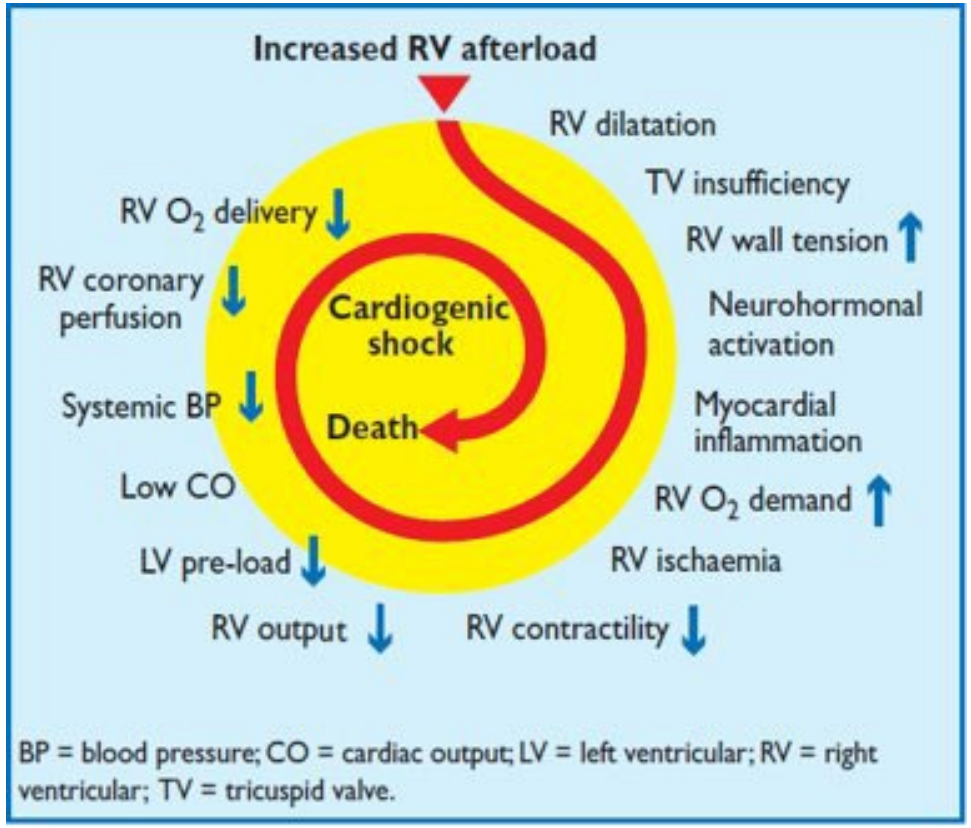


Rivera-Lebron B, et al. Clin Appl Thromb Hemost 2019.
Wells PS, et al. Thromb Haemost 2000.
Donze J, et al. Thromb Haemost 2008.

Pathophysiology

Why are PE's so deadly if not caught and treated?

- *Acute PEs interfere with circulation and gas exchange*
- *Patients with enough clot burden to create right ventricular dysfunction are at risk for further hemodynamic decompensation*



Konstantinides SV, et al. Europ Heart Journal 2014.

PE Classification

- *Traditional definitions and terms for PE included massive, submassive and low-risk*

PE classification	Hypotension (SBP < 90 mmHg)	RV dysfunction or elevated troponin
Massive	+	+
Submassive	-	+
Low-risk	-	-

Tapson V. N Engl J Med 2008; 358:1037-52.
Stevens SM, et al. CHEST 2021.

Pulmonary Embolism Severity Index (PESI)

- *Predicts 30-day mortality and morbidity*

Class	Score	30-day mortality	Risk category
Class 1	< 65	0-1.6%	Very low
Class 2	66-85	1.7-3.5%	Low
Class 3	86-105	3.2-7.1%	Intermediate
Class 4	106-25	4.0-11.4%	High
Class 5	> 125	10.0-24.5%	Very high

Rivera-Lebron B, et al. Clin Appl Thromb Hemost 2019.
Wells PS, et al. Thromb Haemost 2000.
Donze J, et al. Thromb Haemost 2008.

PE Clinical Classification

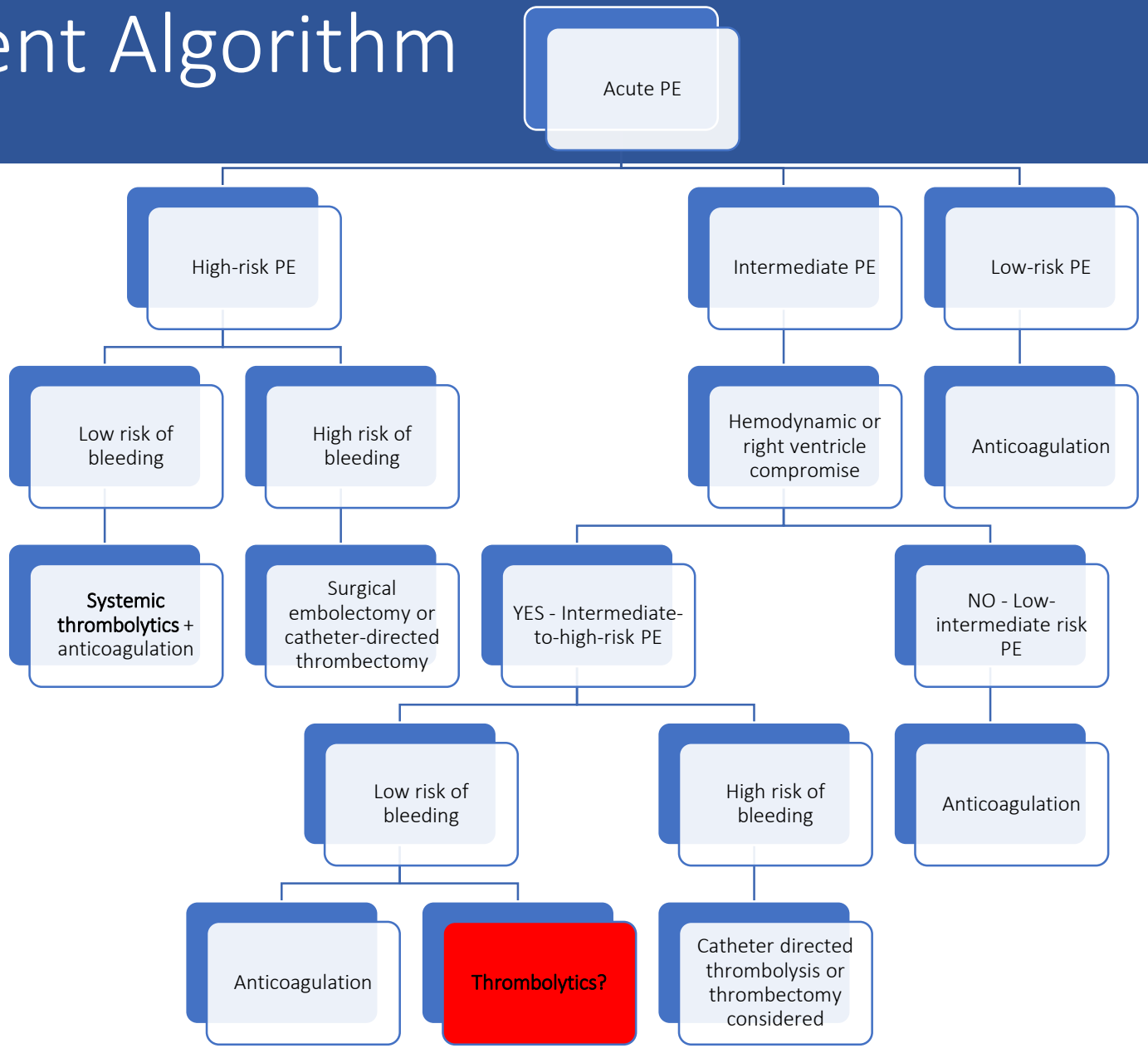
Early mortality risk		Shock or hypotension	PESI class III-V	Signs of RV dysfunction on imaging	Cardiac biomarkers
High		+	+	+	+
Intermediate	High	-	+	Both positive	
	Low	-	+	Either one (or none) positive	
Low		-	-	-	-

Konstantinides SV, et al. Europ Heart Journal 2014.

Intermountain Healthcare
Healing for life®

Project ECHO®
Intermountain Healthcare
Utah

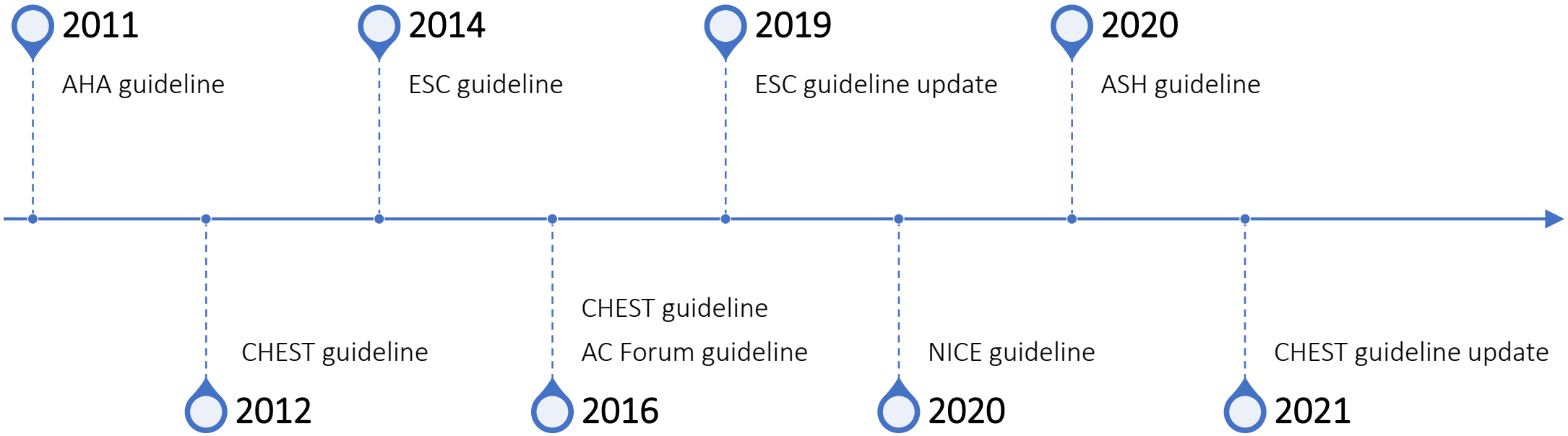
PE Treatment Algorithm



Adapted from IHC Diagnosis and Management of Venous Thromboembolism CPM, June 2021

Clinical Treatment Guidelines

PE Treatment Guidelines



Guideline Summary

Guideline (Year)	"Submassive" or "intermediate-risk" PE Recommendation
AHA (2011)	***Can consider*** in those who have evidence of adverse prognosis
AC Forum (2016)	***Can consider*** on an individual case-by-case basis
ESC (2019)	***No recommendation*** can be made until solid evidence has been published
NICE (2020)	***Recommend against*** administration in patients who are hemodynamically stable regardless of presence of RV dysfunction
ASH (2020)	***Recommend against*** administration in patients who are hemodynamically stable
CHEST (2016;2021)	***Recommend against*** administration in ***most*** patients who are hemodynamically stable ***Recommend*** administration in ***select*** patients who decompensate after anticoagulation initiation

Jaff MR, et al. Circulation. 2011; 123(16):1788-1830; Vedantham S, et al. J Thromb Thromboysis. 2016; 41:68-80; Konstantinides SV, et al. Eur Heart J. 2020; 41(4):543-603; National Institute for Health and Care Excellence. NICE Guideline [NG158]. 2020; American Society of Hematology. ASH guideline. 2020; Kearon C, et al. CHEST. 2016; Stevens SM, et al. CHEST. 2021.

Patient Case 1

TJ is a 70M brought in by EMS after GLF

***HPI**: SOB, severe chest pain, became dizzy and fell*

***PMH**: prior hx small DVT, HTN*

***Home meds**: amlodipine*

***Vitals**: BP 60/39 (MAP 50 mmHg), HR 100 bpm, RR 30 br/min, SpO2 70%*

***Notable imaging, labs, other**: CTPA (+) PE, TTE shows enlarged right ventricle with strain, troponin 0.5 ng/mL, D-dimer 10.0 mcg FEU/mL (ug/mL)*

- *PESI score = 130*

Intermountain Healthcare
Healing for life®

Project ECHO
Intermountain Healthcare
Utah

Patient Case 1

TJ is a 70M brought in by EMS after GLF

***HPI**: SOB, severe chest pain, became dizzy and fell*

***PMH**: prior hx small DVT, HTN*

***Home meds**: amlodipine*

***Vitals**: BP 60/39 (MAP 50 mmHg), HR 100 bpm, RR 30 br/min, SpO2 70%*

***Notable imaging, labs, other**: CTPA (+) PE, TTE shows enlarged right ventricle with strain, troponin 0.5 ng/mL, D-dimer 10.0 mcg FEU/mL (ug/mL)*

- *PESI score = 130*

Based on guideline recommendations, should TJ receive thrombolytics?

1. **YES**
2. **NO**

Intermountain Healthcare
Healing for life®

Project ECHO
Intermountain Healthcare
Utah

Patient Case 2

WJ is a 62F admitted to the medical ICU

***HPI**: SOB and chest pain for 8 hours*

***PMH**: HTN, HLD, hysterectomy 7 days ago*

***Home meds**: rosuvastatin, lisinopril*

***Vitals**: BP 93/59 (MAP 70 mmHg), HR 132 bpm, RR 38 br/min, SpO2 80%*

***Notable imaging, labs, other**: CTPA (+) saddle PE, TTE shows enlarged right ventricle with strain, troponin 0.3 ng/mL, D-dimer 7.0 mcg FEU/mL (ug/mL)*

- *PESI score = 102*

Intermountain Healthcare
Healing for life®

Project ECHO
Intermountain Healthcare
Utah

Patient Case 2

WJ is a 62F admitted to the medical ICU

***HPI**: SOB and chest pain for 8 hours*

***PMH**: HTN, HLD, hysterectomy 7 days ago*

***Home meds**: rosuvastatin, lisinopril*

***Vitals**: BP 93/59 (MAP 70 mmHg), HR 132 bpm, RR 38 br/min, SpO2 80%*

***Notable imaging, labs, other**: CTPA (+) saddle PE, TTE shows enlarged right ventricle with strain, troponin 0.3 ng/mL, D-dimer 7.0 mcg FEU/mL (ug/mL)*

- *PESI score = 102*

Based on guideline recommendations, should WJ receive thrombolytics?

1. **YES**
2. **NO**
3. **Maybe?**

Intermountain Healthcare
Healing for life®

Project ECHO
Intermountain Healthcare
Utah

MAPPET-3, 2002

Heparin + alteplase vs. heparin alone

- *N=256*
  - *Intermediate risk patients*
- *Outcomes*
  - ***Primary**: in-hospital death or clinical deterioration after alteplase infusion*
  - ***Secondary**: recurring PE, major bleeding, ischemic stroke*

Konstantinides SV, et al. N Eng J Med. 2002; 347(13):1143-50

MAPPET-3, 2002

Primary outcomes

- *All cause mortality = **no difference***
- *Composite outcome = statistically significant*
- *Treatment escalation = statistically significant*

Outcome	Heparin + alteplase	Heparin alone	p-value
All-cause mortality	3.4%	2.2%	0.71
Composite end point	11%	24.6%	**0.006**
Treatment escalation	10.2%	24.6%	**0.004**

Konstantinides SV, et al. N Eng J Med. 2002; 347(13):1143-50

MAPPET-3, 2002

Secondary outcomes

- *Recurrent PE = **no difference***
  - *Alteplase group (3.4%) vs placebo group (2.9%), p=0.89*
- *Major bleeding = **no difference***
  - *Alteplase group (0.8%) vs placebo group (3.6%), p=0.29*
    - *Fatal bleed – None in either group*
    - *Hemorrhagic stroke – 0% vs 0.7%, p=1.0*
- *Ischemic stroke = **no difference***
  - *Alteplase group (0%) vs placebo group (0.7%), p=1.0*

Konstantinides SV, et al. N Eng J Med. 2002; 347(13):1143-50

TOPCOAT, 2013

LMWH + tenecteplase vs. LMWH alone

- *N=83*
  - *Intermediate risk patients*
- *Outcomes*
  - ***PE related**: death, circulatory shock or intubation within 5 days of diagnosis*
  - ***Treatment related**: death from hemorrhage, active bleed, surgery*
  - ***Functional**: progression or resolution of RV strain, pulmonary htn, exercise tolerance*

Kline JA, et al. K Thrombos Haemo. 2014; 12:459-68.

TOPCOAT, 2013

PE related outcomes

Table 3 Breakdown of all adverse outcomes in each treatment group

	Within 5 days		At 90-day follow-up						
Treatment	Death	Shock/ intubation	Recurrent VTE* and poor functional capacity† and low perception of wellness‡	Poor functional capacity† and low perception of wellness‡	Recurrent VTE* and low perception of wellness‡	Poor functional capacity† only	Recurrent VTE only	Low perception of wellness‡ only	None§
Placebo ($N = 43$)	1	2	1	5	2	2	1	2	27 (63%)
Tenecteplase ($N = 40$)	1	0	0	1	0	3	1	0	34 (85%)

Kline JA, et al. K Thrombos Haemo. 2014; 12:459-68.

TOPCOAT, 2013

Functional outcomes at 90-day follow up

Table 3 Breakdown of all adverse outcomes in each treatment group

	Within 5 days		At 90-day follow-up						
Treatment	Death	Shock/ intubation	Recurrent VTE* and poor functional capacity† and low perception of wellness‡	Poor functional capacity† and low perception of wellness‡	Recurrent VTE* and low perception of wellness‡	Poor functional capacity† only	Recurrent VTE only	Low perception of wellness‡ only	None§
Placebo ($N = 43$)	1	2	1	5	2	2	1	2	27 (63%)
Tenecteplase ($N = 40$)	1	0	0	1	0	3	1	0	34 (85%)

Kline JA, et al. K Thrombos Haemo. 2014; 12:459-68.

PEITHO, 2014

Heparin + tenecteplase vs. heparin alone

- *N=1005*
  - *Intermediate risk patients*
- *Outcomes*
  - ***Primary**: clinical composite of death or hemodynamic decompensation within 7 days*
  - ***Secondary**: major adverse effects or mortality within 30 days*
  - ***Safety**: ischemic or hemorrhagic stroke within 7 days, extracranial bleeding and serious adverse events*

Meyer G, et al. N Eng J Med. 2014; 370:1402-11.

PEITHO, 2014

Primary and secondary outcomes

- *Mortality at 7 and 30-days = **no difference***
- *Hemodynamic decompensation = higher in placebo group*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	p-value
Composite end point – no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23 - 0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23 - 1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14 - 0.68)	0.002
Death from any cause at day 30	12 (2.4)	16 (3.2)	0.73 (0.34 - 1.57)	0.42

Meyer G, et al. N Eng J Med. 2014; 370:1402-11.

Intermountain Healthcare
Healing for life®

Project ECHO®
Intermountain Healthcare
Utah

PEITHO, 2014

Safety outcomes

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	p-value
Bleeding between randomization and day 7				
Major extracranial	32 (6.3)	6 (1.2)	5.55 (2.3-13.99)	**< 0.001**
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7				
Stroke	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, randomization to day 30	55 (10.9)	59 (11.8)	0.91 (0.62 - 1.34)	0.63

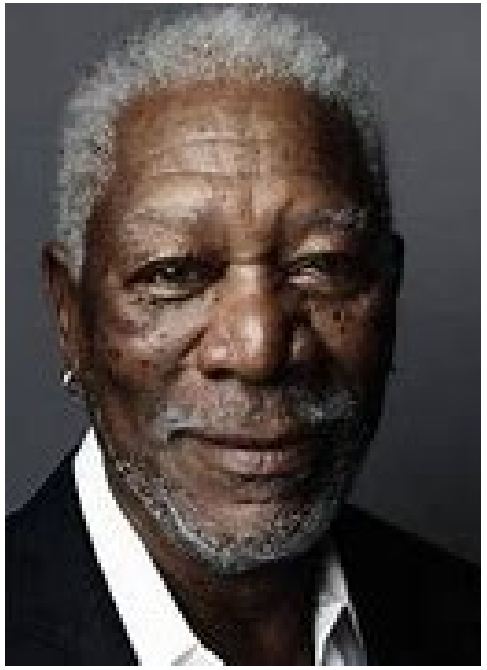
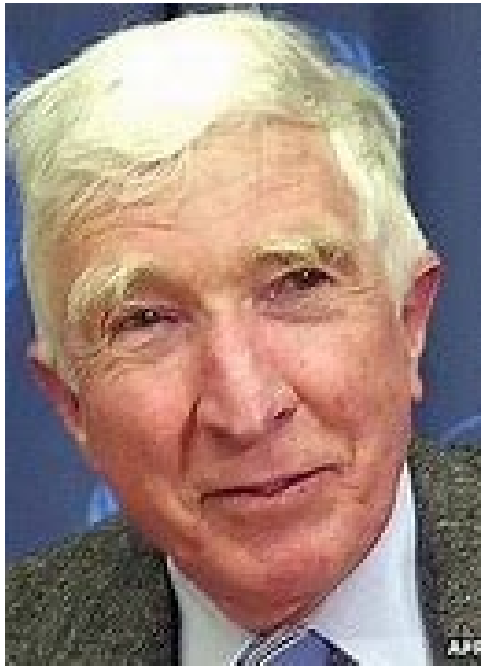
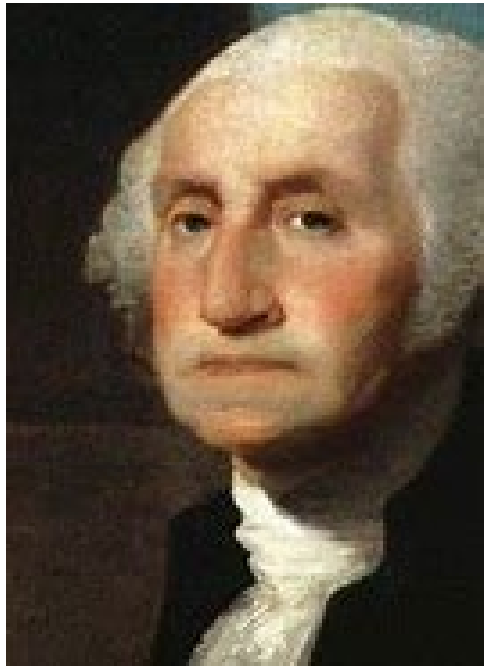
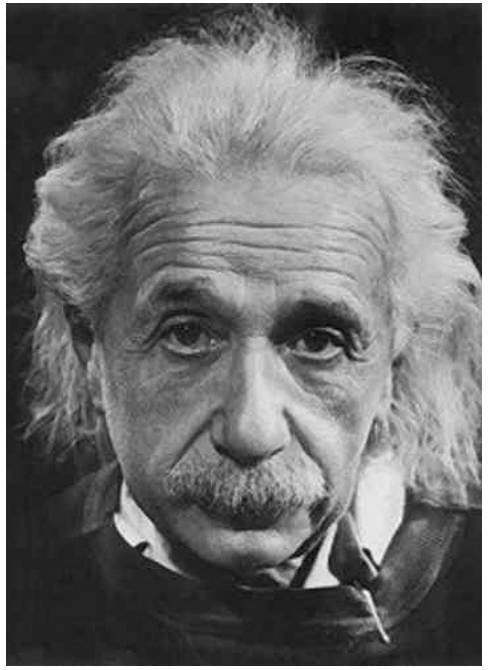
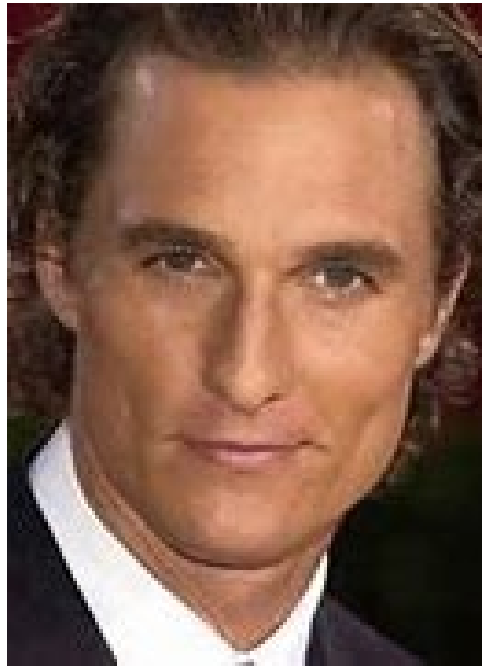
Meyer G, et al. N Eng J Med. 2014; 370:1402-11.

Thrombolytics vs. Placebo Summary

Study	MAPPET-3	TOPCOAT	PEITHO
Patients	N=256	N=83	N=1005
Lytic agent used	Alteplase	Tenecteplase	Tenecteplase
NNT	7.5	4.5	33.3
Mortality benefit?	No	No	No
Increase bleeding?	No	No	Yes
Primary Outcome	Composite outcome (death or clinical deterioration)	Composite outcome (considered death = a low score on a QOL survey)	Composite outcome (death or hemodynamic collapse within 7 days)
Other considerations	Clinical deterioration not objectively defined	Study terminated early Enrolled patients with active cancer, older age and surgical history within 6 weeks	

Dosing and Administration

What do these famous people have in common?

Intermountain Healthcare
Healing for life®

Project ECHO
Intermountain Healthcare
Utah

Patient Case 1 – Part 2

TJ is our 70M brought in by EMS after GLF

- *Having a massive PE with hemodynamic decompensation*
- *ER physician requests alteplase*
- *Package insert dosing options for alteplase in massive PE:*
  - *100 mg over 2 hours*
  - *20 mg bolus, 80 mg over 2 hour*
  - *50 mg bolus over 2 min, can repeat in 15 min if warranted (associated with cardiac arrest)*

Activase (alteplase) [prescribing information] San Francisco, CA: Genentech; February 2018.

Patient Case 2 – Part 2

WJ is a 62F admitted to the medical ICU

- *Intermediate risk PE with evidence of RH strain*
- *On admission she was hemodynamically stable but now has soft pressures, MAP of 65 mmHg*
- *Additional considerations: hysterectomy 7 days prior*

ICU team wants to give her alteplase given she is starting to clinically decompensate, ***what dose should they give?***

Wang et al, 2010

Full dose (100 mg) vs. half dose (50 mg) alteplase

- *N=127*
  - *Hemodynamically massive and anatomically massive (intermediate) PE*
- *Outcomes*
  - ***Efficacy**: PE recurrence, mortality, improvement in RV function, pulmonary artery pressure, lung perfusion*
  - ***Safety**: bleeding*

Wang C, et al. CHEST. 2010; 137(2):254-62.

Wang et al, 2010

Efficacy outcomes

- *Mortality, bleeding = no difference*

Variable	Hemodynamically Massive			Anatomically Massive		
	100 mg (n=19)	50 mg (n=18)	P-value	100 mg (n=34)	50 mg (n=47)	P-value
Death, n(%)	1 (5)	1 (6)	1	2 (6)	0	0.417
Due to PE	1 (5)	0	-	1 (3)	0	-
Due to bleeding	0	1 (6)	-	1 (3)	0	-
Recurrent PE, n(%)	1 (5)	1 (6)	1	1 (3)	0	0.418
Bleeding complications, n(%)	7 (37)	5 (28)	0.728	10 (29)	6 (13)	0.090
Major bleeding	2 (11)	2 (11)	1	3 (9)	0	0.070
Minor bleeding	5 (26)	3 (17)	0.693	7 (21)	6 (13)	0.373

Wang C, et al. CHEST. 2010; 137(2):254-62.

Wang et al, 2010

Safety outcomes

- *What about body weight?*

Subgroup	rt-PA 50mg	rt-PA 100mg
Body weight tertiles (kg)		
<65	4/27(14.8%)	7/17(41.2%)
65 to 74	4/15(26.7%)	6/15(40.0%)
≥75	3/22(13.6%)	4/21(19.0%)
BMI tertiles (kg/m²)		
<24	2/23(8.7%)	6/14(42.9%)
24 to 25.9	5/18(27.8%)	6/19(31.6%)
≥26	3/21(14.3%)	4/17(23.5%)
BMI group (kg/m²)		
<25	4/35(11.4%)	9/23(39.1%)
≥ 25	6/27(22.2%)	7/27(25.9%)

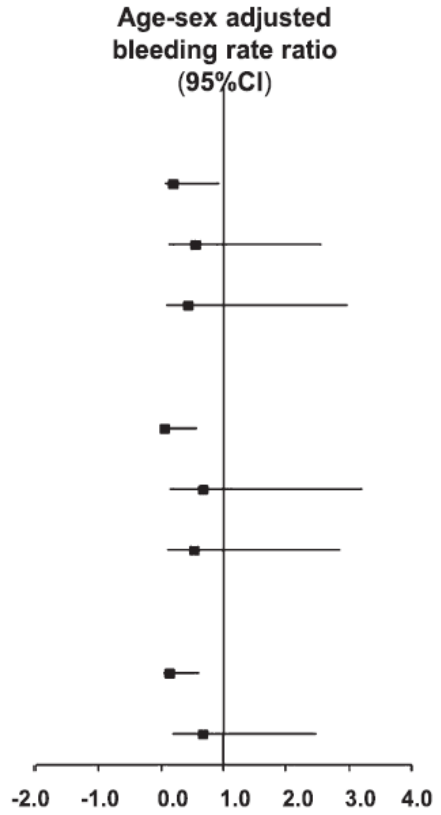


FIGURE 3. Comparisons of total bleeding complications between two treatments for PTE in patients with different body weights and BMI subgroups. See Figures 1 and 2 legends for expansion of other abbreviations.

Wang C, et al. CHEST. 2010; 137(2):254-62.

MOPETT, 2013

50 mg alteplase vs. placebo

- *N=121*
  - *Moderate PE*
    - *≥ 2 signs/symptoms of PE AND*
    - *CTPA with >70% thrombus in left main, right main, or ≥ 2 lobar pulmonary arteries OR V/Q mismatch in ≥ lobes*
- *Outcomes*
  - ***Primary**: composite of pulmonary HTN AND recurrent PE at 28 months*
  - ***Secondary**: mortality, hospital LOS, recurrent PE, composite of recurrent PE, mortality or bleed*

Sharifi M, et al. Am J Cardiol. 2013; 111(2):273-7.

MOPETT, 2013

Primary outcomes

- *Mortality = no difference*
- *Bleeding = no difference*

Outcome	tPA + AC	Placebo + AC	p-value
pHTN and recurrent PE, n (%)	9 (16)	35 (63)	**< 0.001**
Mortality and recurrent PE, n (%)	1 (1.6)	6 (10)	**0.049**
pHTN	9 (16)	32 (57)	**<0.001**
Hospital stay (days)	2.2	4.9	**<0.001**
PASP (mmHg)			
Within 48 hours	34	41	**<0.001**
6 months	31	49	**<0.001**
28 months	28	43	**<0.001**

Sharifi M, et al. Am J Cardiol. 2013; 111(2):273-7.

Zhang et al, 2018

Alteplase 30 mg vs. placebo

- *N=66*
  - *Intermediate risk PE*
- *Outcomes*
  - ***Primary**: changes in LV/RV ratio, PAP, subjective improvement at 24 hours*
  - ***Secondary**: bleeding, mortality, decompensation, recurrent PE at f/u*

Zhang L-Y, et al. Saudi Med J 2018;39:1090–5.

Zhang et al, 2018

Primary outcomes

Variable	tPA + LMWH	Placebo + LMWH	P-value
Difference from baseline at 24 hours (mean ± SD)			
PASP, mmHg	**17.0 ± 10.2**	**4.6 ± 9.8**	**0.001**
RV/LV	**0.31 ± 0.18**	**0.04 ± 0.16**	**0.001**
Symptom severity	**5.6 ± 1.5**	**1.0 ± 0.4**	**0.001**

Zhang L-Y, et al. Saudi Med J 2018;39:1090–5.

Zhang et al, 2018

Secondary outcomes

- *Mortality = no difference*

Variable	tPA + LMWH	Placebo + LMWH	P-value
Death	0 (0)	0 (0)	-
Hemodynamic decompensation	0 (0)	9%	0.24
Recurrent PE	3%	6%	1.0
Major bleeding	0%	0%	-
Minor Bleeding	**24%**	**3%**	**0.0268**

Zhang L-Y, et al. Saudi Med J 2018;39:1090–5.

Yilmaz et al, 2021

Alteplase 50 mg vs. placebo

- *N=76*
  - *Intermediate risk PE*
- *Outcomes*
  - ***Primary**: death from any cause, death or decompensation at 7 and 30 days*
  - ***Secondary**: recurrent PE, pHTN at 6-months*
  - ***Safety**: ischemic or hemorrhagic stroke within 7 days, major extracranial bleeding within 7 days*

Yilmaz ES, et al. J Investig Med 2021;69: 1439-1446.

Yilmaz et al, 2021

Outcomes

- *Total mortality at 7/30 days = no difference*
- *Major/minor bleeding = no difference*

Variable	tPA + LMWH	LMWH	P-value
Death/hemodynamic decompensation at 7 days	1 (3)	8 (21)	**0.028**
Death/hemodynamic decompensation at 30 days	1 (3)	10 (26)	**0.009**

Yilmaz ES, et al. J Investig Med 2021;69: 1439-1446.

Dosing Trials Summary

Trial	Dose	Efficacy	Safety
Wang, 2010	50 mg vs 100 mg tPA	• No difference in mortality, recurrent PE, or pulmonary artery obstruction improvement	• Increased bleeding in patients < 65 kg or BMI < 25
MOPPET, 2013	50 mg tPA vs placebo	• Improvement in PASP, reduced mortality, decreased occurrence of recurrent PE, and shorter LOS	• No difference in bleeding
Zhang, 2018	30 mg tPA vs placebo	• Improvement in PASP and symptom severity • No mortality benefit, difference in PE recurrence, or hemodynamic decompensation	• Increased minor bleeding
Yilmaz, 2021	50 mg tPA vs placebo	• Reduced occurrence of composite outcome (death or hemodynamic decompensation) • No difference in mortality alone, recurrent PE, or pHTN	• No difference in bleeding

Additional Considerations

Patient specific factors

- *Past medical history*
- *Past or recent surgical history*
- *Active home medications*
- *Weight/BMI*
- *Quality of life*

Additional Considerations

Contraindications to thrombolytics

Absolute Contraindications	Relative Contraindications
History of intracranial hemorrhage	Systolic BP > 180 mmHg or diastolic BP > 110 mmHg
Known cerebral arteriovenous malformation	Prolonged CPR (> 10 min)/Traumatic CPR
Aortic dissection	Ischemic stroke > 3 months prior
Significant trauma in the past 3 months	Major surgery in past 3 weeks
Active bleeding (excluding menses)	Recent bleeding (non-intracranial)
Ischemic stroke in past 3 months	Pregnancy or week one post-partum
Neoplasm in central nervous system	Anticoagulated
	Age > 75
	Dementia

Stevens SM, et al. CHEST 2021.
Activase (alteplase) [package insert]. Genetech Inc.

Additional Considerations

Dosing and administration of thrombolytics

- *50 mg vs 30 mg vs something else?*
- *No need for 100 mg*
- *Bolus then infusion*
- *Infusion alone*
- *Is catheter directed an option?*

Patient Case 2 – Part 3

WJ is a 62F admitted to the medical ICU

- *Intermediate risk PE with evidence of RH strain*
- *On admission she was hemodynamically stable but now has soft pressures, MAP of 65 mmHg*
- *Additional considerations: hysterectomy 7 days prior*

ICU team wants to give her alteplase given she is has a soft blood pressure, ***what dose should they give, or should you ask some more questions?***

Bottom Line

Do what's best for your patient and remember the literature!

- *Risk versus benefit*
- *Lytics versus anticoagulation alone*
  - *No mortality benefit*
  - *Potential reduction in hospital stay*
  - *Potential reduction in occurrence of pHTN*
  - *Outcomes included subjective variables, that make results hard to interpret*
- *Dosing strategies*
  - *Reduced dose tPA can be considered*
  - *No primary outcome differences between 100 mg dose and reduced dose, but reduced dose is still superior to placebo*
  - *Potentially an increase in bleeding when comparing 100 mg to reduced dose (especially in smaller patients), but inconsistent results when comparing reduced dose to placebo*

Intermountain Healthcare
Healing for life®

Project ECHO
Intermountain Healthcare
Utah

Discussion

Should you give thrombolytics to a patient with intermediate risk PE?

References

Turetz M, Sideris AT, Friedman, OA, et al. Epidemiology, pathophysiology, and natural history of pulmonary embolism. Semin Intervent Radiol 2018; 35:92-98.

Chatterjee S, Chakraborty A, Weinberg I, 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.

Tapson V. Acute pulmonary embolism. N Engl J Med 2008; 358:1037-52.

Rivera-Lebron B, McDaniel M, Ahrar K, et al. Diagnosis, Treatment and Follow Up of Acute Pulmonary Embolism: Consensus Practice from the PERT Consortium. Clin Appl Thromb Hemost 2019.

Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83:416-20.

Donzé J, Le Gal G, Fine MJ, Roy PM, Sanchez O, Verschuren F, Cornuz J, Meyer G, Perrier A, Righini M, Aujesky D. Prospective validation of the Pulmonary Embolism Severity Index. A clinical prognostic model for pulmonary embolism. Thromb Haemost. 2008 Nov;100(5):943-8

Jaff MR, et al. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension. Circulation. 2011; 123(16):1788-1830.

Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. European Heart Journal 2014.

Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. CHEST guideline and expert panel report. CHEST (2016).

Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE diease: second update of the CHEST guideline and expert panel report, CHEST (2021).

Project ECHO Intermountain Healthcare Utah

Intermountain Healthcare

References

Konstantinides S, et al. Heparin plus alteplease compared with heparin alone in patients with submassive pulmonary embolism. N Eng J Med. 2002; 347(13): 1143-50.

Kline JA, et al. Treatment of submassive pulmonary emboliusm with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thombos Haemo. 2014; 12:459-68.

Meyer G, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014; 370:1402-11.

Budaj-Fidecka A, et al. In-hospital major bleeding predicts mortality in patients with pulmonary embolism: an analysis of ZATPOL Registry data. Int J Cardiol. 2013; 168(4):3543-3549.

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(2):273-7.

Zhang L-Y,Gao B-A, Jin Z, et al. Clinical efficacy of low dose recombinant tissue-type plasminogen activator for the treatment of acute intermediate-risk pulmonary embolism. Saudi Med J 2018;39:1090–5.

Amini S, et al. Efficacy and safety of different dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of Acute Pulmonary Embolism: A systematic review and meta-analysis. Iran J Pharm Res. 2021; 20(2):441-454.

Activase (alteplase) [package insert]. South San Fransisco, CA: Genetech, Inc.; 2015.

Yilmaz ES, Unzun O. Low-dose thrombolysis for submassive pulmonary embolism. J Investig Med 2021;69: 1439-1446.

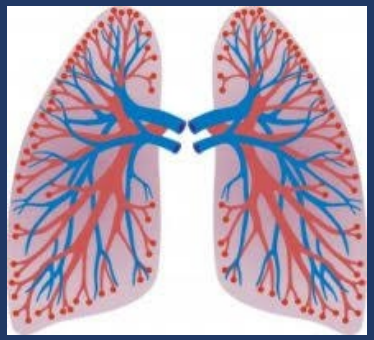
Intermountain Healthcare. Diagnosis and management of VTE: care process model. 2021.

Project ECHO Intermountain Healthcare Utah

Intermountain® Healthcare

Intermountain Project ECHO
TeleCritical Care Medicine

Thrombolytics in Intermediate Pulmonary Embolism (PE)



Rachel Belcher, PharmD

PGY2 Critical Care Pharmacist Resident

Intermountain Medical Center/Tele-Critical Care

Intermountain Healthcare
Healing for life®

Project ECHO
Intermountain Healthcare
Utah