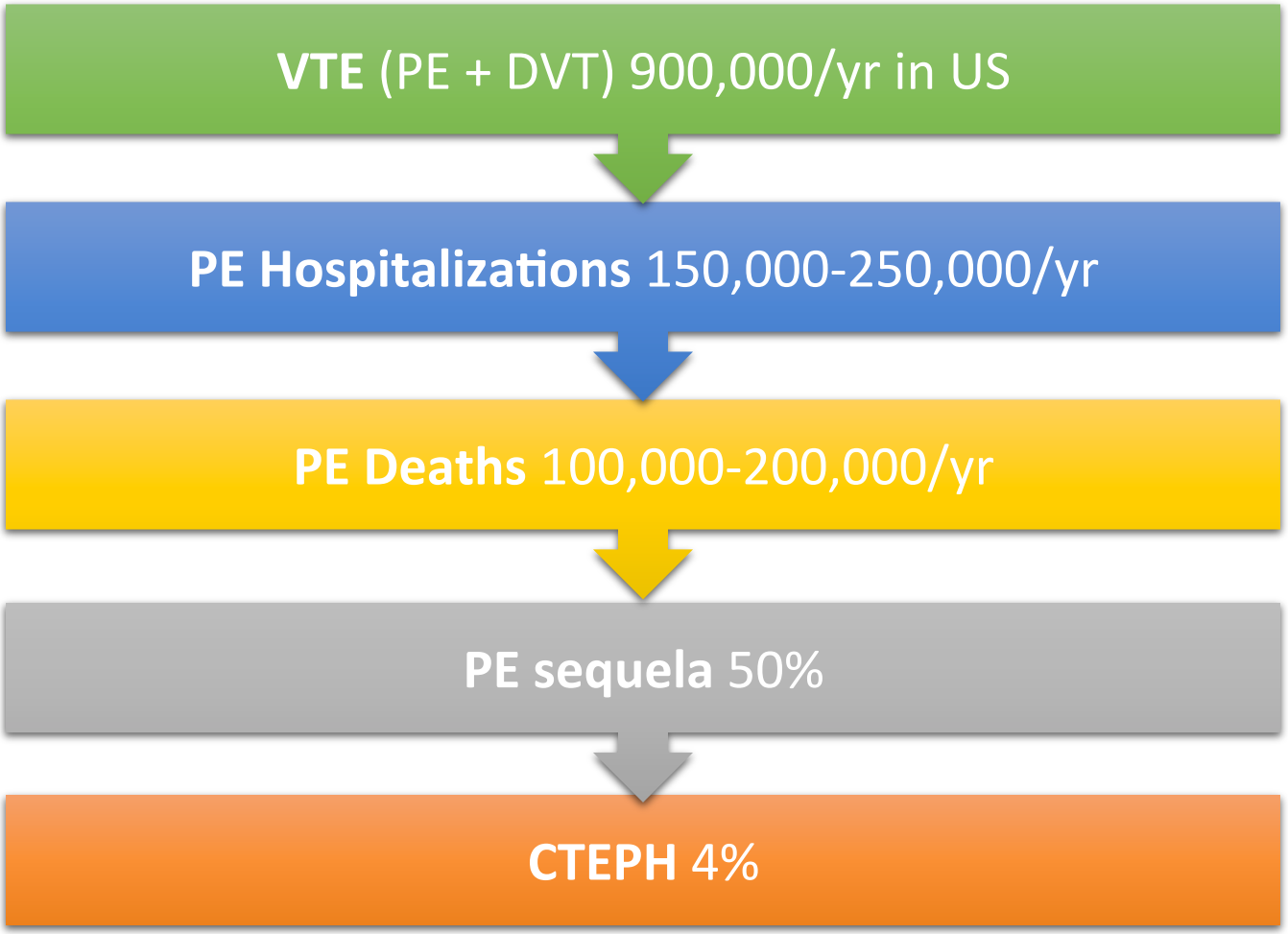
Contemporary Treatment of Pulmonary Thromboembolism

Belinda Rivera-Lebron, MD MS

Assistant Professor of Medicine

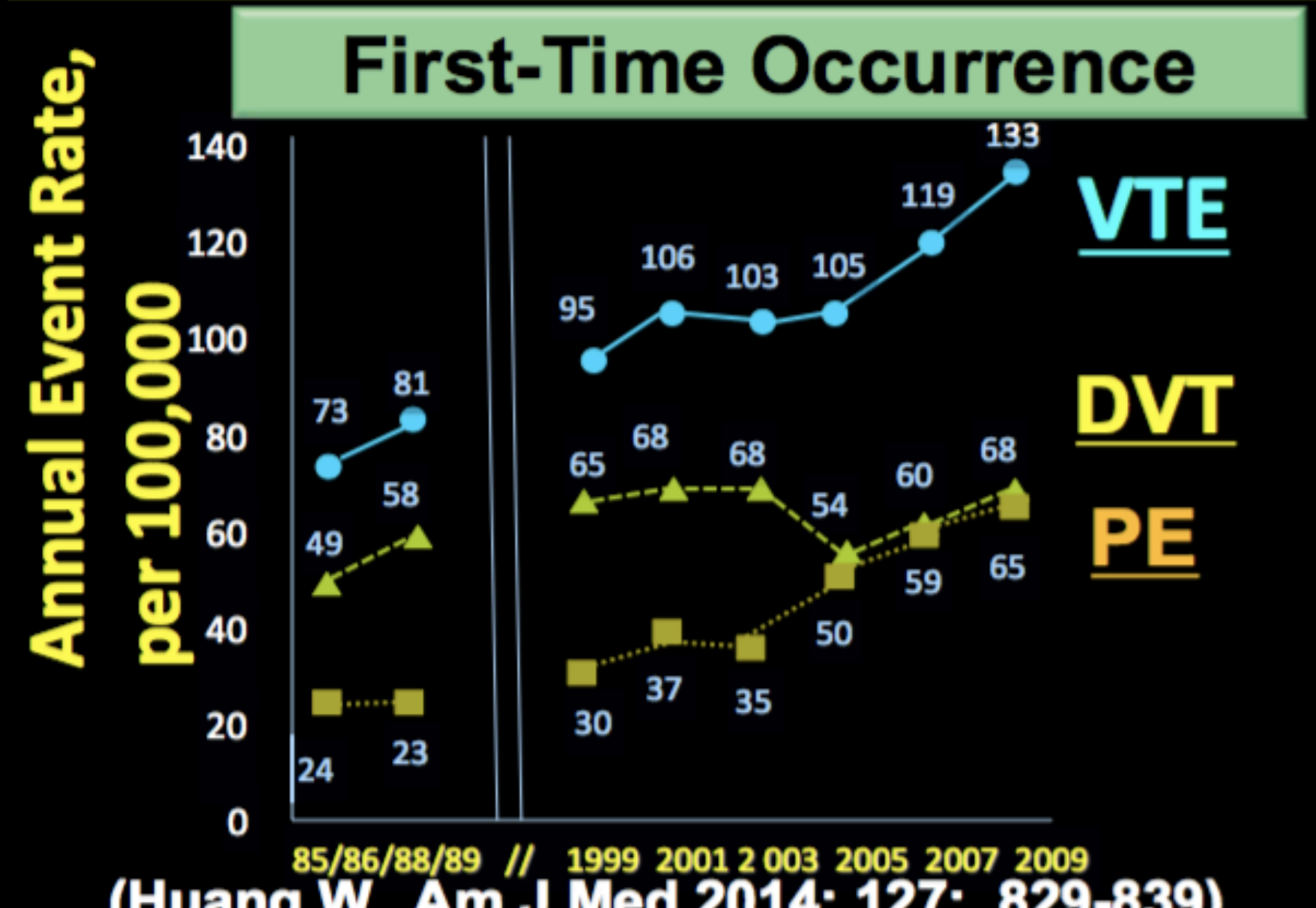
Division of Pulmonary, Allergy & Critical Care

PE is a Serious Problem



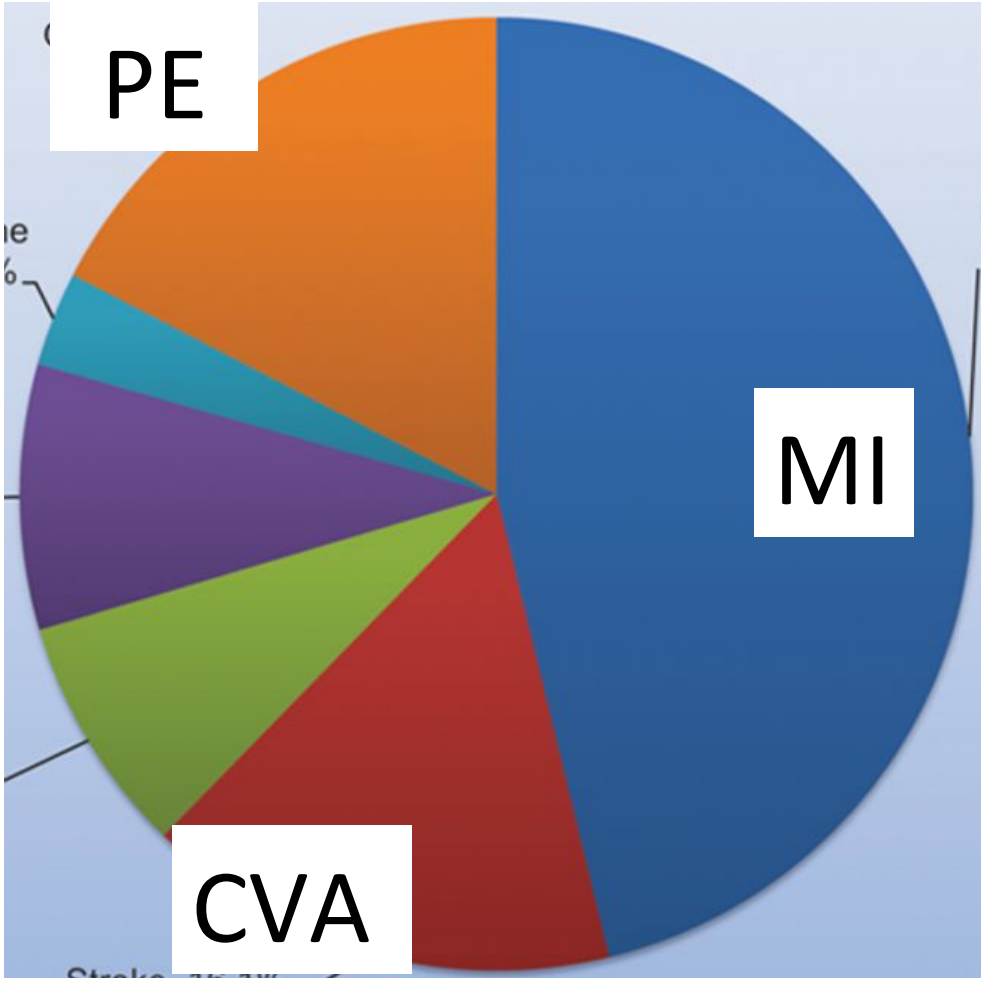
cdc.gov

VTE INCIDENCE: INCREASING



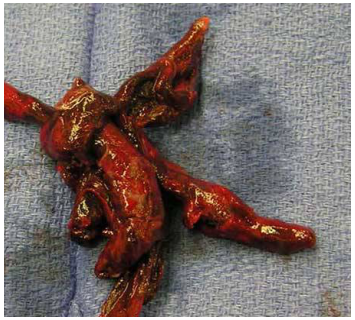
(Huang W. Am J Med 2014; 127: 829-839)

PE is the #3 cause of CV death



AHA Heart disease and stroke statistics. Circulation 2016

PE Natural History



>90% complete resolution

Full recovery

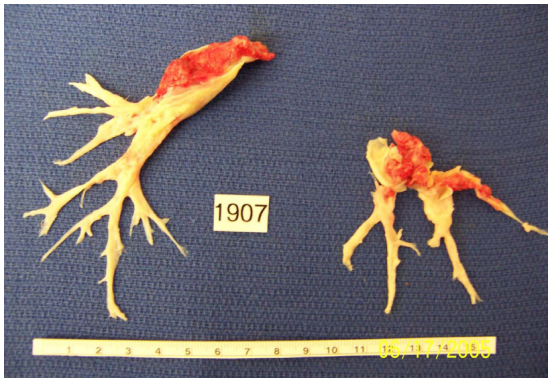
Acute PE

Partial recovery

30% recurrence within 10 yrs

CTEPH

4% CTEPH



Adapted from Fedullo

American Classifications of PE

Low Risk	Submassive (Intermediate Risk)	Massive (High Risk)

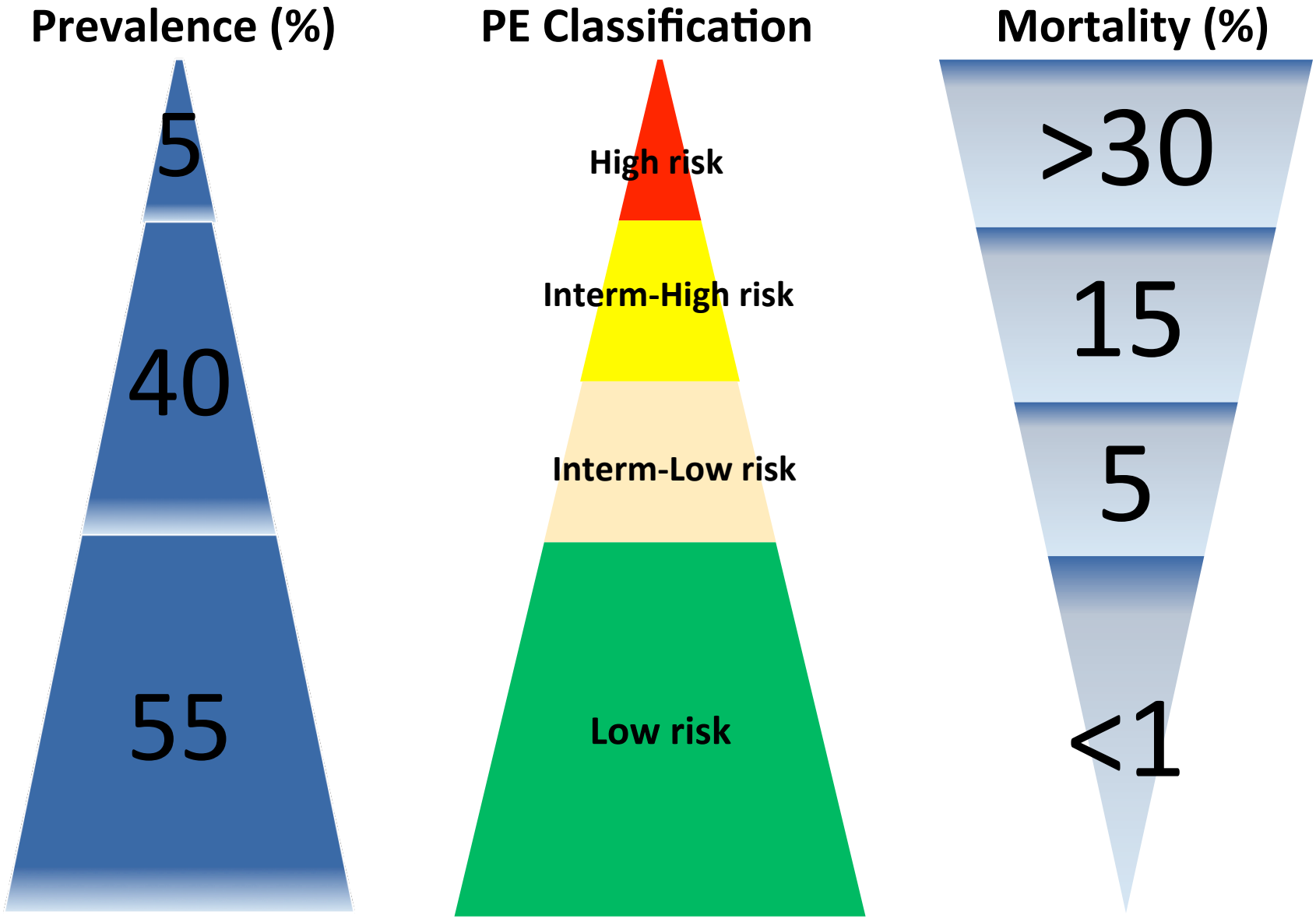
• Normotensive
• No RV dysfunction
• Normal biomarkers
	• Normotensive
	• **RV strain (CT/TTE)**
	  • RV dilation
	  • RV dysfunction
	  • BNP > 90 pg/mL, pro-BNP > 500 pg/mL
	• **Myocardial necrosis**
	  • Trop I > 0.4 ng/mL, Trop T > 0.1 ng/mL
		• **Hypotension** (SBP < 90 for > 15 min)
		• **Shock**(on pressor)
		• **Pulselessness**

Jaff. Circ 2011

European Classifications of PE

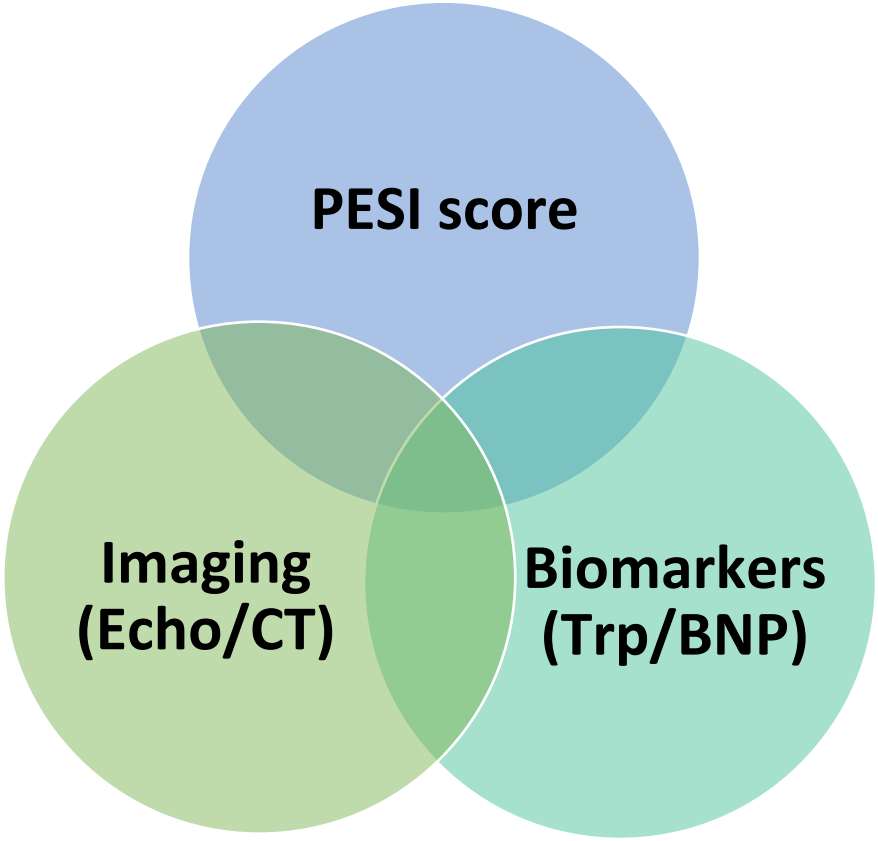
Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V or sPESI ≥I[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	-	+	Both positive	
	Intermediate–low	-	+	Either one (or none) positive[e]	
Low		-	-	Assessment optional; if assessed, both negative[e]	

Konstantinides. European Heart J. 2014



Adapted from Dudziski

Integrated Prognostic Factors



PE Severity Index (PESI)

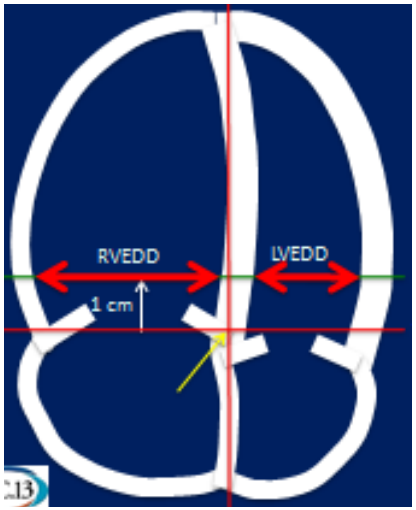
Parameter	Original version[214]	Simplified version[218]
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
	Risk strata[a]	
	Class I:≤65 points very low 30-day mortality risk (0–1.6%) **Class II: 66–85 points** low mortality risk (1.7–3.5%) **Class III: 86–105 points** moderate mortality risk (3.2–7.1%) **Class IV: 106–125 points** high mortality risk (4.0–11.4%) **Class V: >125 points** very high mortality risk (10.0–24.5%)	**0 points**= 30-day mortality risk 1.0% (95% CI 0.0%–2.1%) **≥1 point(s)**= 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

Aujesky. Am J Respir Crit Care Med 2005
Jimenez. Arch Intern Med 2010
Zamorano. European Heart J 2014

Imaging

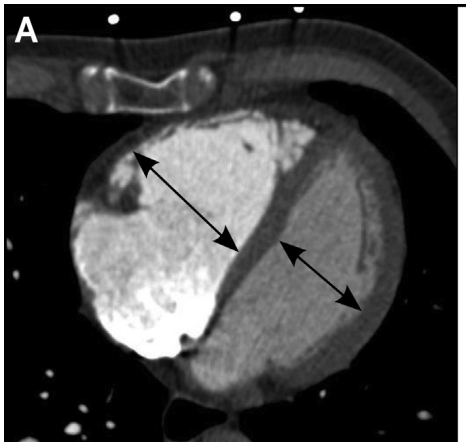
Echo

- RV:LV > 0.9 or RV dysf
  - Sens 74%, Spec 54%
  - 7% in-hospital mortality
  - 41% worse outcomes (pressors, thrombolysis, CPR)



CT scan

- RV_D:LV_D > 0.9
  - Sens 84%, Spec 35%
  - 5-fold risk for PE-related mortality
- Thrombus load and central PE **not** associated with mortality



J Am Coll Cardiol 1997
Int J Cardiovasc Imaging 2015

Biomarkers

Test	Cut-off value	NPV (%)	PPV (%)	OR or HR (95%CI)
Troponin I	Different cut-off values	NR	NR	4.0 (2.2-7.2)
Troponin T	14 pg/mL	98	9	5.0 (1.7-14.4)
BNP	75-100 pg/mL	98	14	6.5 (2.0-21)
NT-pro BNP	600 pg/mL	99	7	6.3 (2.2-7.2)

Konstantinides. European Heart J. 2014

Combined Approach to Risk Stratification

Parameter	30-day complications
sPESI	10%
sPESI + BNP	14%
sPESI + BNP + Troponin	20%
sPESI + BNP + Troponin + DVT	26%

Handoko. Am J Respir Crit Care Med. 2014

Management Alternatives

MCS

Anticoagulant

IVC Filter

Mechanical

Syst

Percutaneous Fragmentation & Aspiration

Surgical Embolectomy

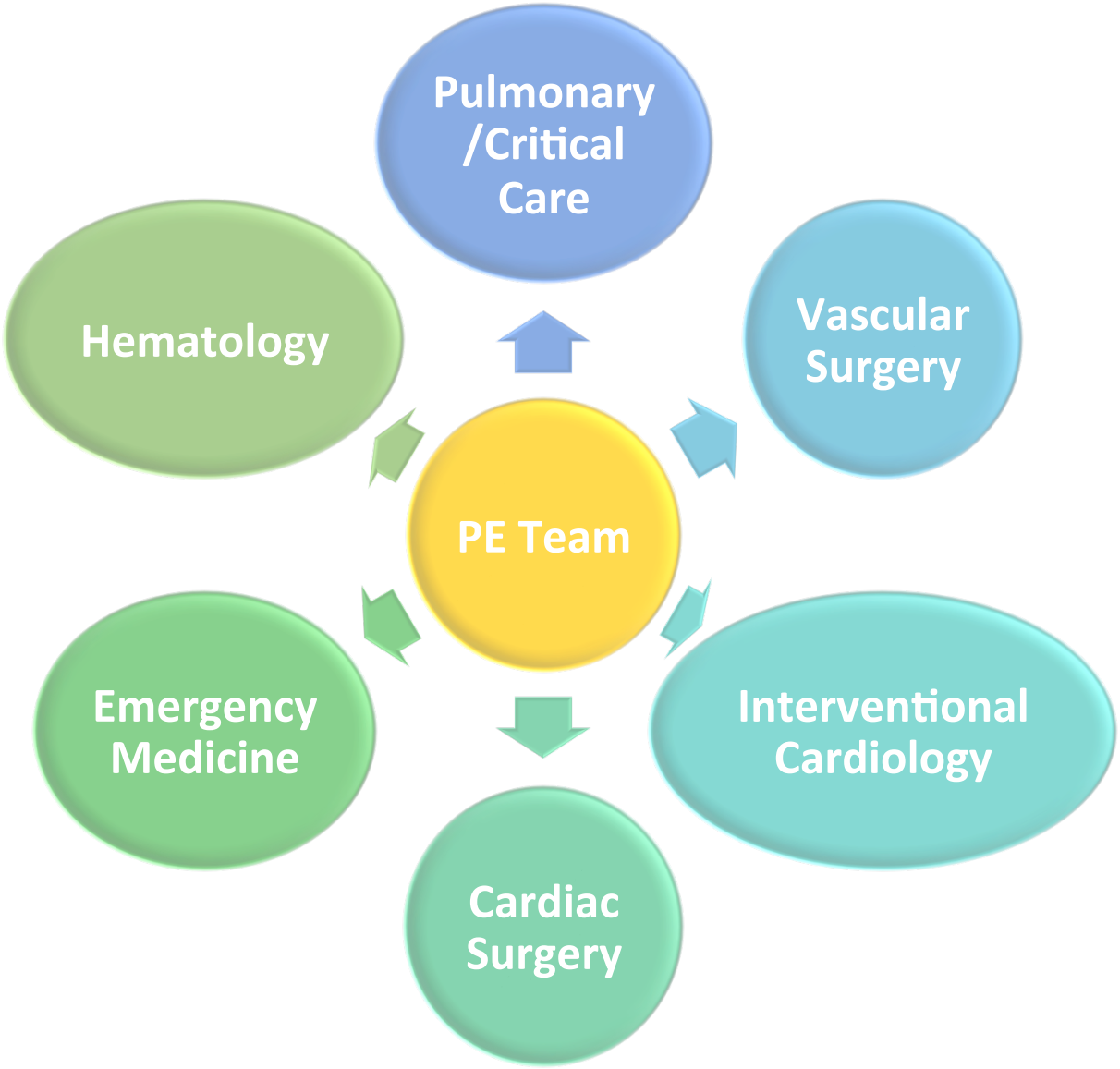
Pharmaco-mechanical

~More likely with ↑ severity

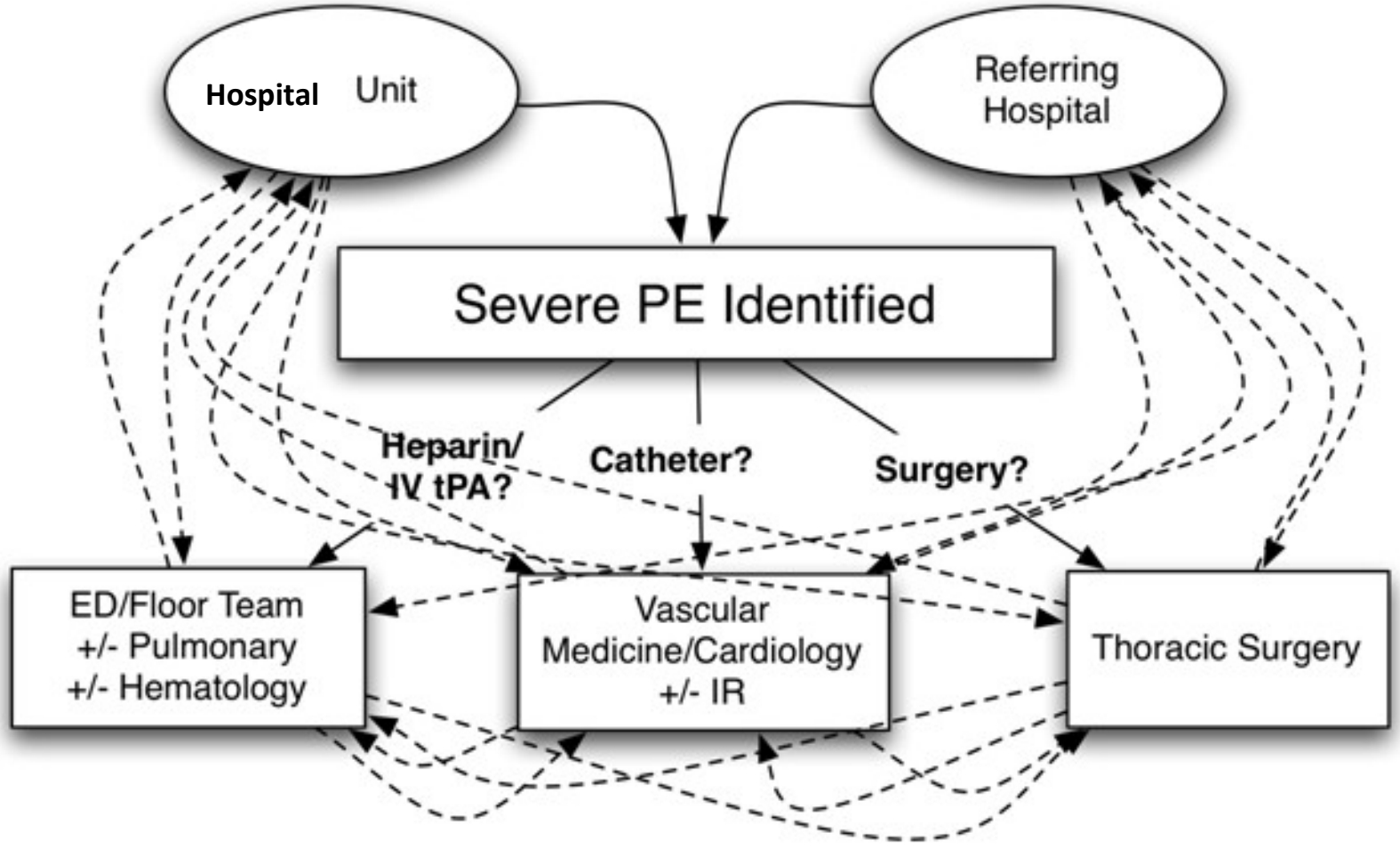
Acute PE Team (PERT)

- A multidisciplinary group with expertise in the diagnosis, medical, surgical and interventional management of PE who collaborate to improve patient care
- Goals
  - Improve patient care
  - Facilitate multidisciplinary consultation with rapid mobilization
  - Outpatient follow up: Post-PE clinic
  - Regular meetings to discuss cases
  - Facilitate research (PE registry, clinical trials)
  - National PERT consortium

Multidisciplinary Collaboration

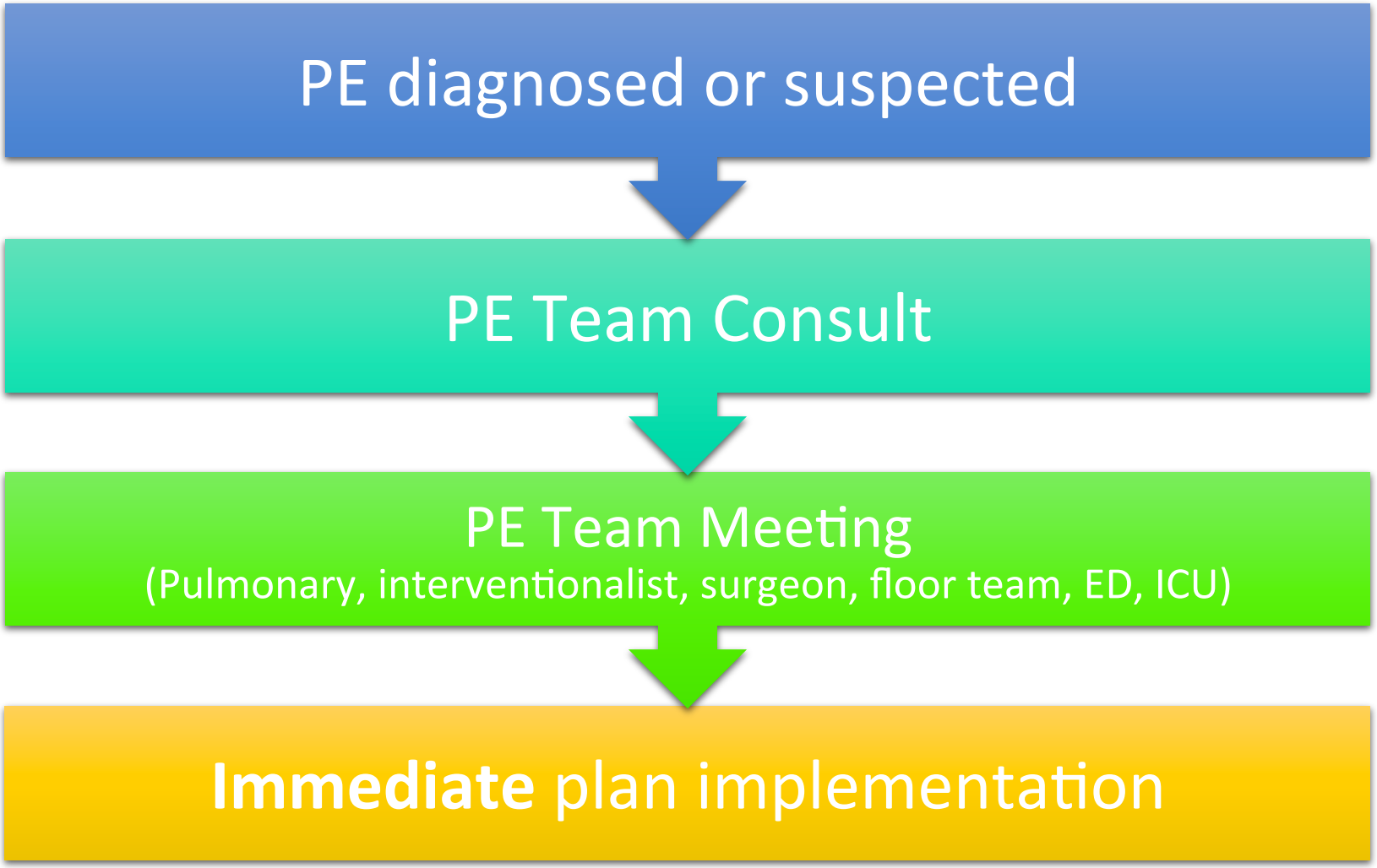


Previous Paradigm



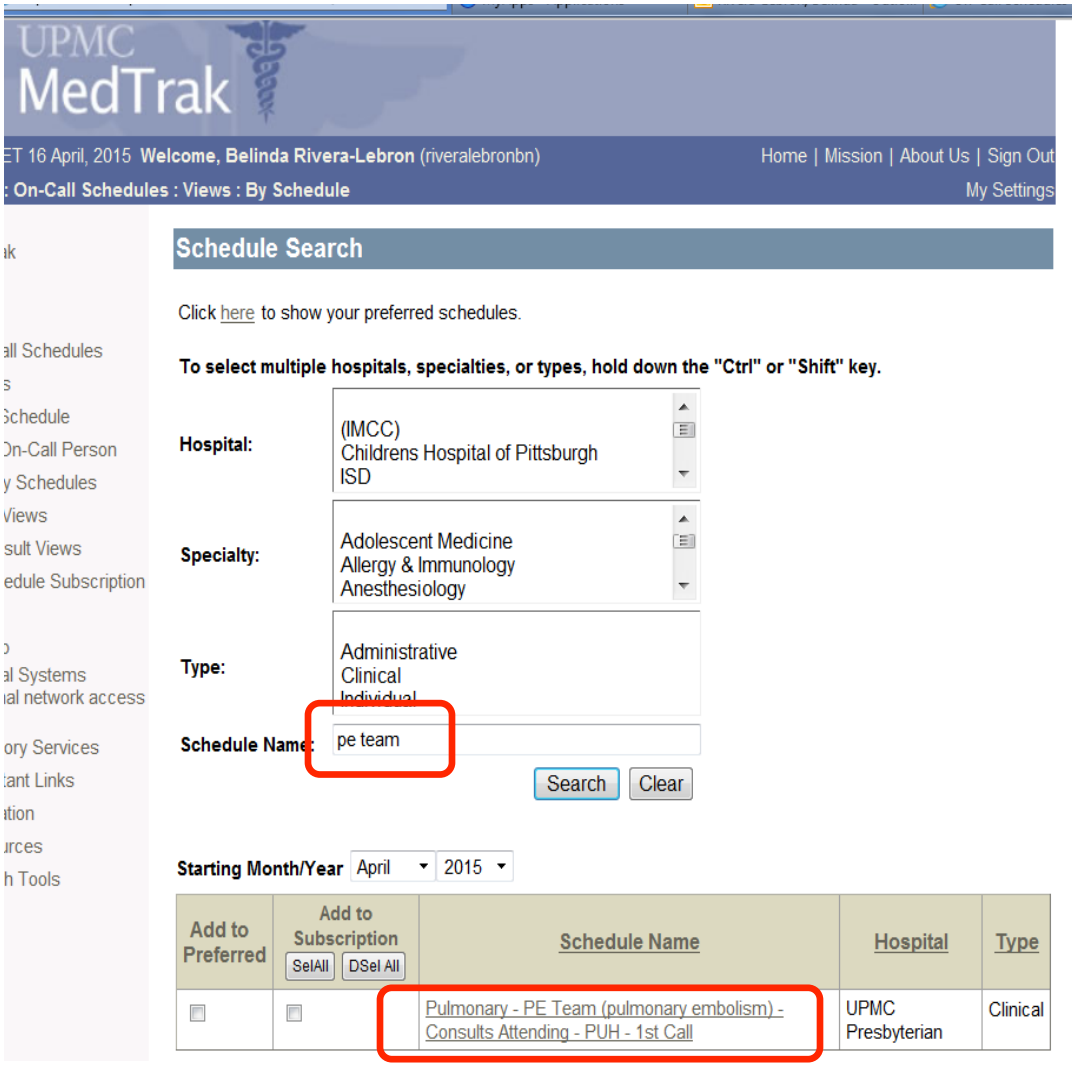
Adapted from Rosenfield, Kabrhel

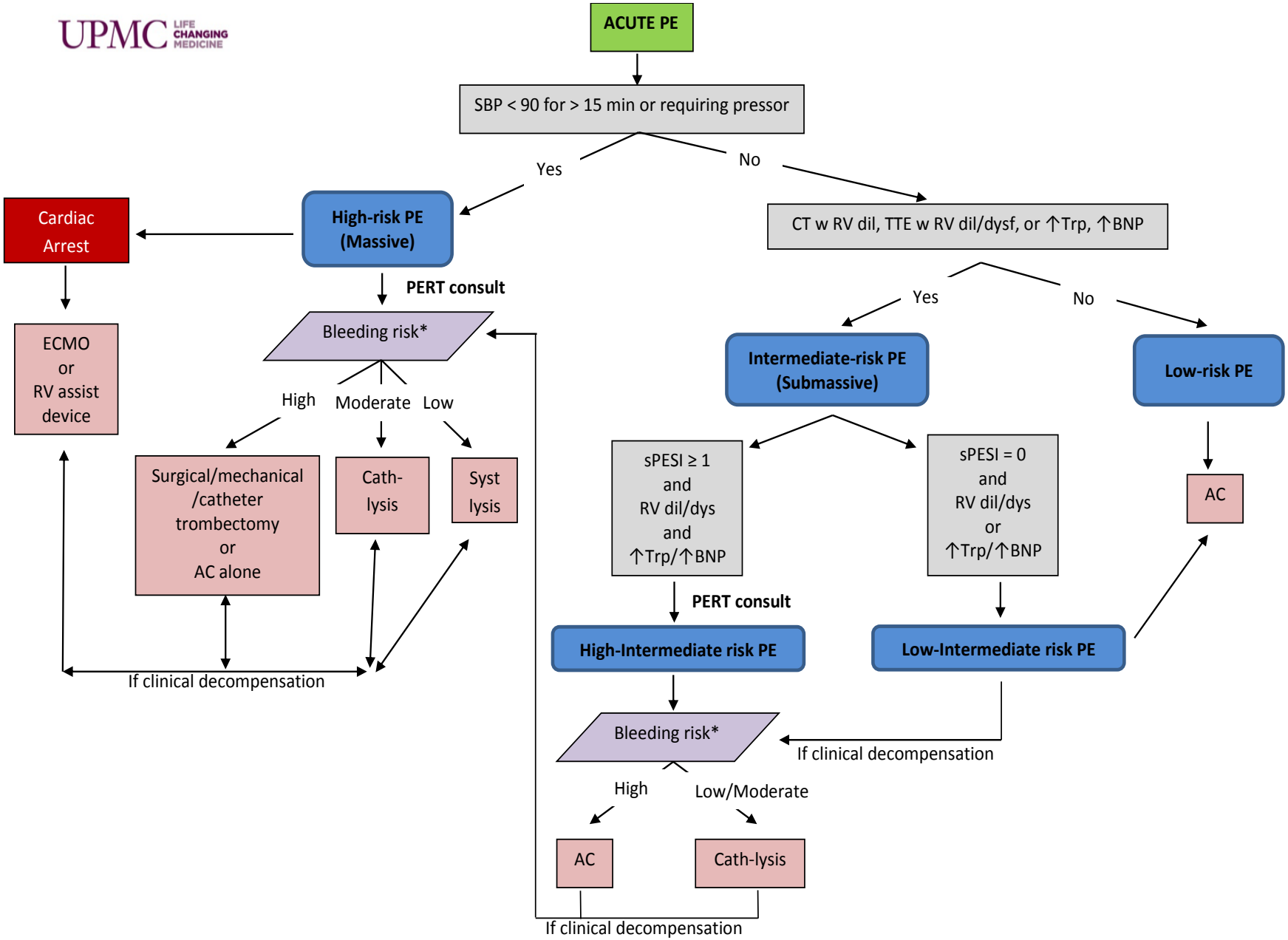
New Model

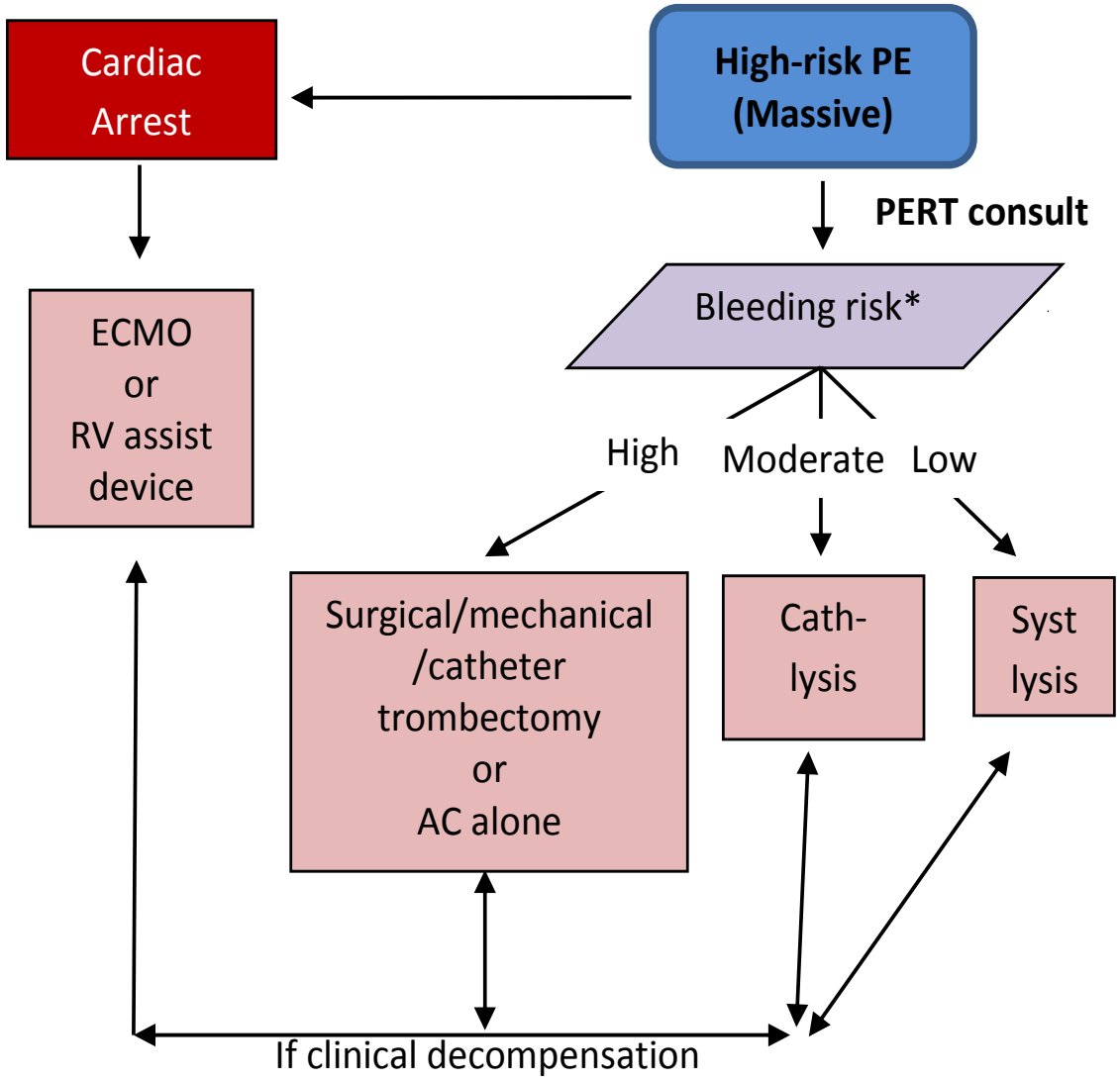

PE diagnosed or suspected
PE Team Consult
PE Team Meeting
(Pulmonary, interventionalist, surgeon, floor team, ED, ICU)
Immediate plan implementation

How to Consult the PE Team?

- **Operator**
- UPMC **MedCall** 412-647-7000 and ask for PE Team consult
- UPMC **MedTrack**: type PE Team




UPMC LIFE CHANGING MEDICINE
ACUTE PE
SBP < 90 for > 15 min or requiring pressor
Yes
No
Cardiac Arrest
High-risk PE (Massive)
CT w RV dil, TTE w RV dil/dysf, or ↑Trp, ↑BNP
PERT consult
Yes
No
ECMO or RV assist device
Bleeding risk*
Intermediate-risk PE (Submassive)
Low-risk PE
High
Moderate
Low
Surgical/mechanical /catheter trombectomy or AC alone
Cath-lysis
Syst lysis
sPESI ≥ 1 and RV dil/dys and ↑Trp/↑BNP
sPESI = 0 and RV dil/dys or ↑Trp/↑BNP
AC
PERT consult
If clinical decompensation
High-Intermediate risk PE
Low-Intermediate risk PE
Bleeding risk*
If clinical decompensation
High
Low/Moderate
AC
Cath-lysis
If clinical decompensation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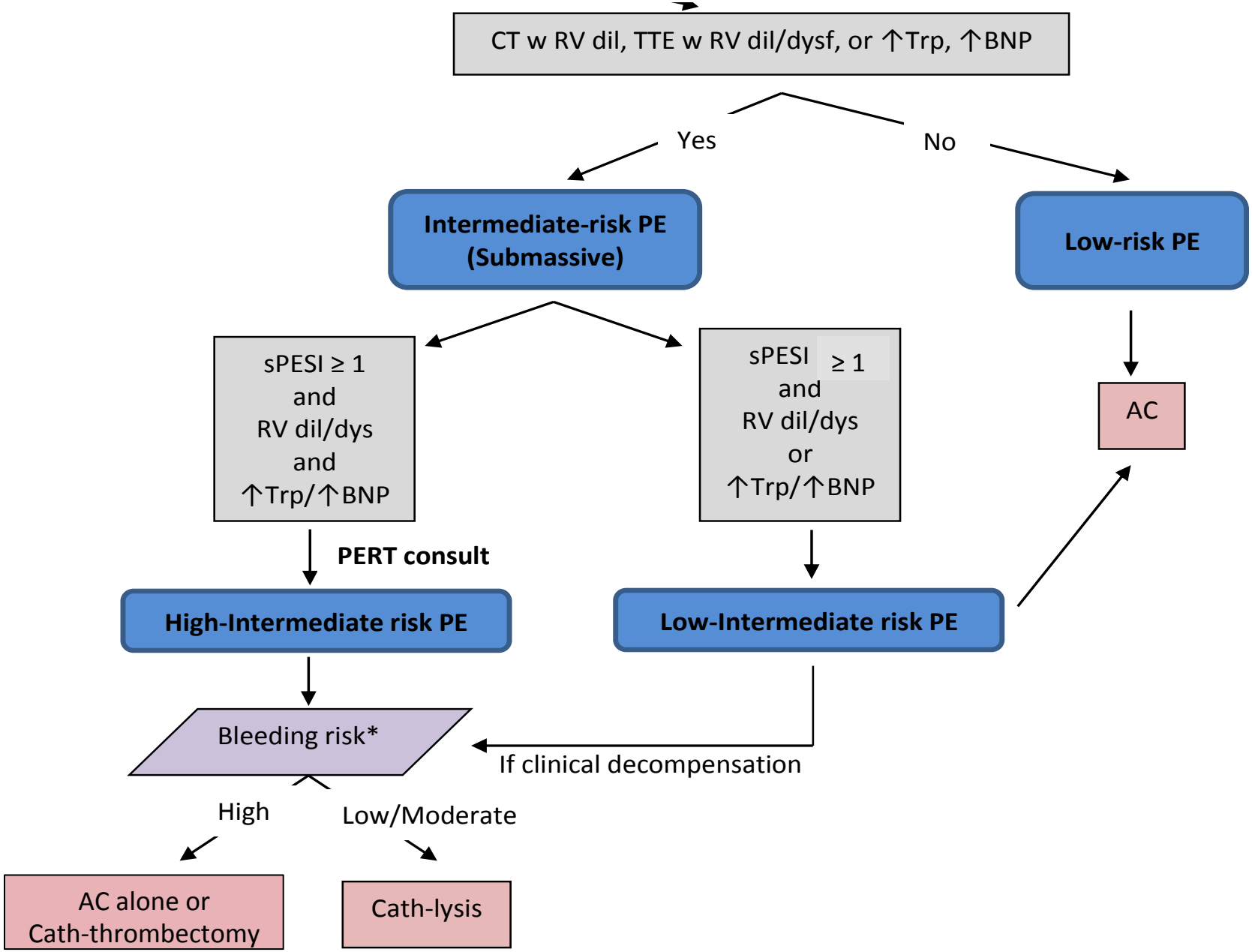
CT w RV dil, TTE w RV dil/dysf, or ↑Trp, ↑BNP
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Intermediate-risk PE (Submassive)
Low-risk PE
sPESI ≥ 1 and RV dil/dys and ↑Trp/↑BNP
sPESI ≥ 1 and RV dil/dys or ↑Trp/↑BNP
AC
PERT consult
High-Intermediate risk PE
Low-Intermediate risk PE
Bleeding risk*
If clinical decompensation
High
Low/Moderate
AC alone or Cath-thrombectomy
Cath-lysis

New ACCP Anticoagulation Guidelines 2016

- **VTE w/o cancer**: 1st line tx NOAC (dabigatran*, rivaroxaban, apixaban and endoxaban*)
  - * Bridging required
  - 39% lower major bleeding, 64% lower fatal bleeding, 63% lower ICH
  - Reversal agent for dabigatran: Idarucizumab (Praxbind ®). Dexanet alpha awaiting FDA approval
- **VTE w cancer**: 1st line tx LMWH

- **Provoked** VTE: treat x 3 mo
- **Unprovoked** VTE: treat indefinitely (until risk of bleeding>clotting)

- No IVC Filter unless unable to tolerate AC

Antithrombotic Therapy for VTE Disease. CHEST. 2016
Blood 2014

New ACCP Anticoagulation Guidelines 2016

Out of Hospital

- Low-risk PE
- Clinically stable with good cardiopulmonary reserve
- No contraindications (recent bleeding, severe renal or liver disease, or low platelets)
- Compliant
- Patient feels well enough to be treated at home
- PESI score <85 or sPESI = 0

Subsegmental PE

- No AC for indicated for:
  - Single PE
  - With low risk for recurrence
  - No DVT in LE dopplers
  - Asymptomatic

Antithrombotic Therapy for VTE Disease. CHEST. 2016

Systemic Thrombolysis in High Risk (Massive) PE

- Meta analysis of 11 RCT comparing lysis vs UFH
  - All PE (748 pts): OR 0.67 (CI 0.4-1.12)
  - Massive PE: 9.4% vs 19%, OR 0.45 (CI 0.22-0.92)

Wan. Circulation 2004

- Cohort study of 72,230 HD unstable patients 1999-2008
  - HD unstable = shock or ventilator
  - Mortality 15% vs 47%, RR 0.2 ($p < 0.001$)

Stein. Am J Med 2012

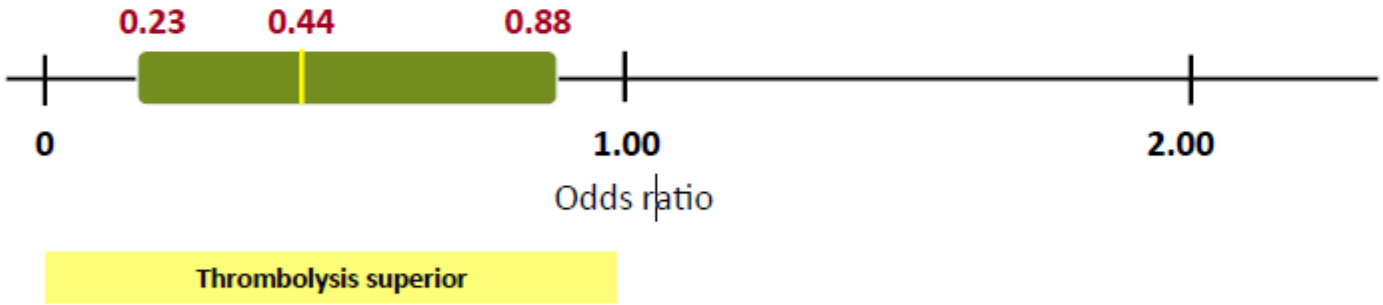
Systemic Thrombolysis in Intermediate Risk (Submassive) PE

- **PEITHO Trial**: RCT lysis/heparin vs placebo/heparin
- 1006 patients w RV dysfunction (CT/TTE) and myocardial injury (Trop I or T)
- Primary endpoint: All cause mortality **or** Hemodynamic collapse within 7 days of randomization (CPR, SPB < 90 mmHg for 15 min or drop ≥ 40 mmHg with end organ hypoperfusion, pressor initiation)

NEJM 2014; 370: 1402-11

PEITHO: Primary efficacy outcome

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality or hemodynamic collapse within 7 days of randomization	13	(2.6)	28	(5.6)	0.015



Meyer. NEJM 2014

Table 3. Efficacy Outcomes.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — 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
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12
Fatal	0	3 (0.6)		
Nonfatal	1 (0.2)	2 (0.4)		
Other in-hospital complications and procedures — no. (%)				
Mechanical ventilation	8 (1.6)	15 (3.0)		
Surgical embolectomy	1 (0.2)	2 (0.4)		
Catheter thrombus fragmentation	1 (0.2)	0 (0.0)		
Vena cava interruption	5 (1.0)	1 (0.2)		
Thrombolytic treatment other than study medication	4 (0.8)	23 (4.6)		
Death from any cause between randomization and day 30 — no. (%)	12 (2.4)	16 (3.2)	0.73 (0.34–1.57)	0.42
Patient still hospitalized at day 30 — no. (%)	59 (11.7)	50 (10.0)		
Rehospitalization between randomization and day 30 — no. (%)	22 (4.4)	15 (3.0)		

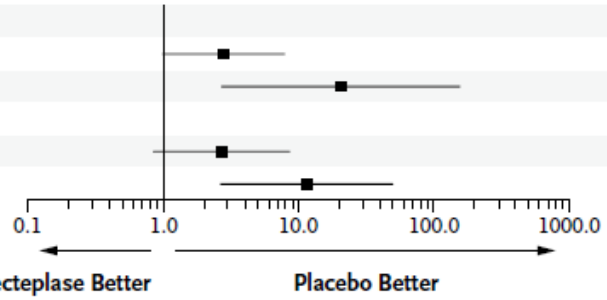
Meyer. NEJM 2014

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 randomization and day 30	55 (10.9)	59 (11.8)	0.91 (0.62–1.34)	0.63

B Major Extracranial Bleeding

Subgroup	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Age				0.09
≤75 yr	14/344 (4.1)	5/335 (1.5)	2.80 (1.00–7.86)	
>75 yr	18/162 (11.1)	1/164 (0.6)	20.38 (2.69–154.53)	
Sex				0.13
Male	11/242 (4.5)	4/231 (1.7)	2.70 (0.85–8.61)	
Female	21/264 (8.0)	2/268 (0.7)	11.49 (2.67–49.53)	



Meyer. NEJM 2014

How about Low-dose Thrombolysis?

- Meta-analysis of 5 studies
- **Low-dose tPA** (50mg) vs. standard dose (100mg)
- No difference in all-cause mortality or recurrent PE
- Less major bleeding with low-dose tPA (OR 0.33, 95% CI 0.12-0.91)

Sharifi M et al. Am J Cardiol 2013
Zhang Z et al. Thromb Res. 2013
Armstrong PW et al. Am Heart J 2015

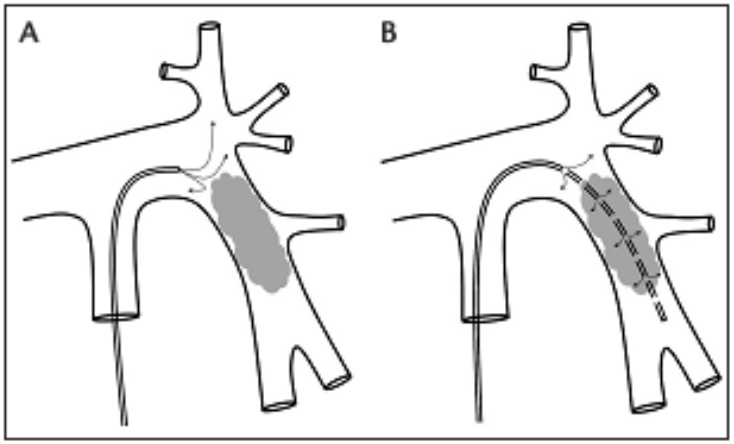
ACCP Antithrombotic Guidelines 2016: Systemic Thrombolysis

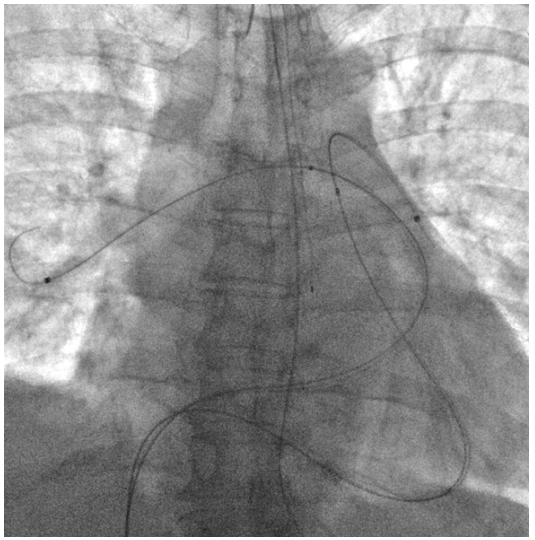
- PE with **hypotension** and low bleeding risk
- PE with **deterioration after starting AC**, but yet to develop hypotension and with low bleeding risk
- PE w/o hypotension, with **severe symptoms or marked cardiopulmonary impairment** - *may benefit from lytics*

Antithrombotic Therapy for VTE Disease. CHEST. 2016

Catheter-directed tPA in Intermediate Risk (Submassive) PE

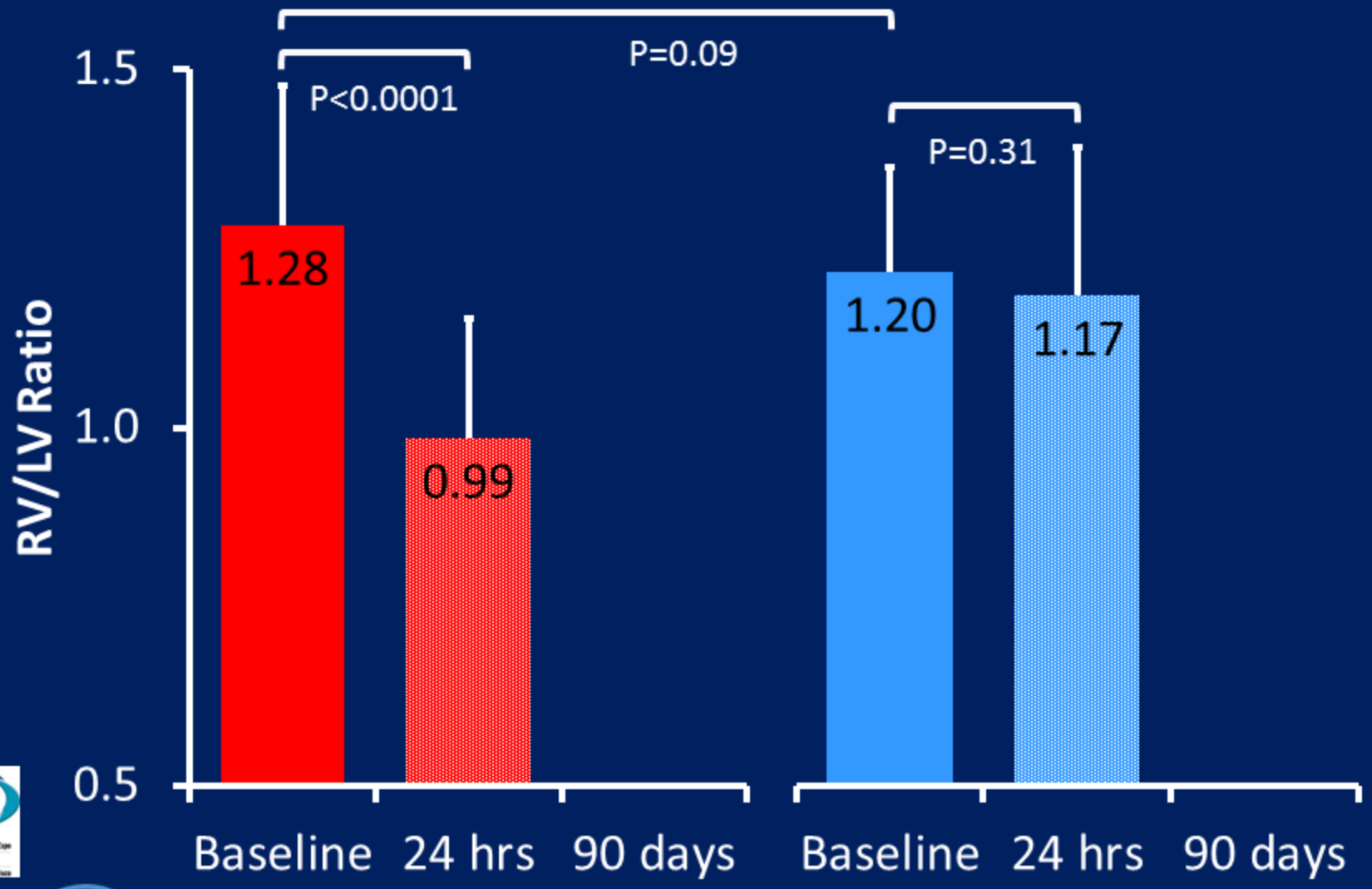
- **ULTIMA (ULT**rasound accelerated thrombolys**I**s of pul**M**on**A**ry embolism with EKOS): Heparin/EKOS vs Heparin
- 59 patients with submassive PE (RV:LV ratio >1)
- Primary outcome: Δ RV/LV at 24 hrs





Kucher. Circulation 2014

RV/LV ratio (echo)

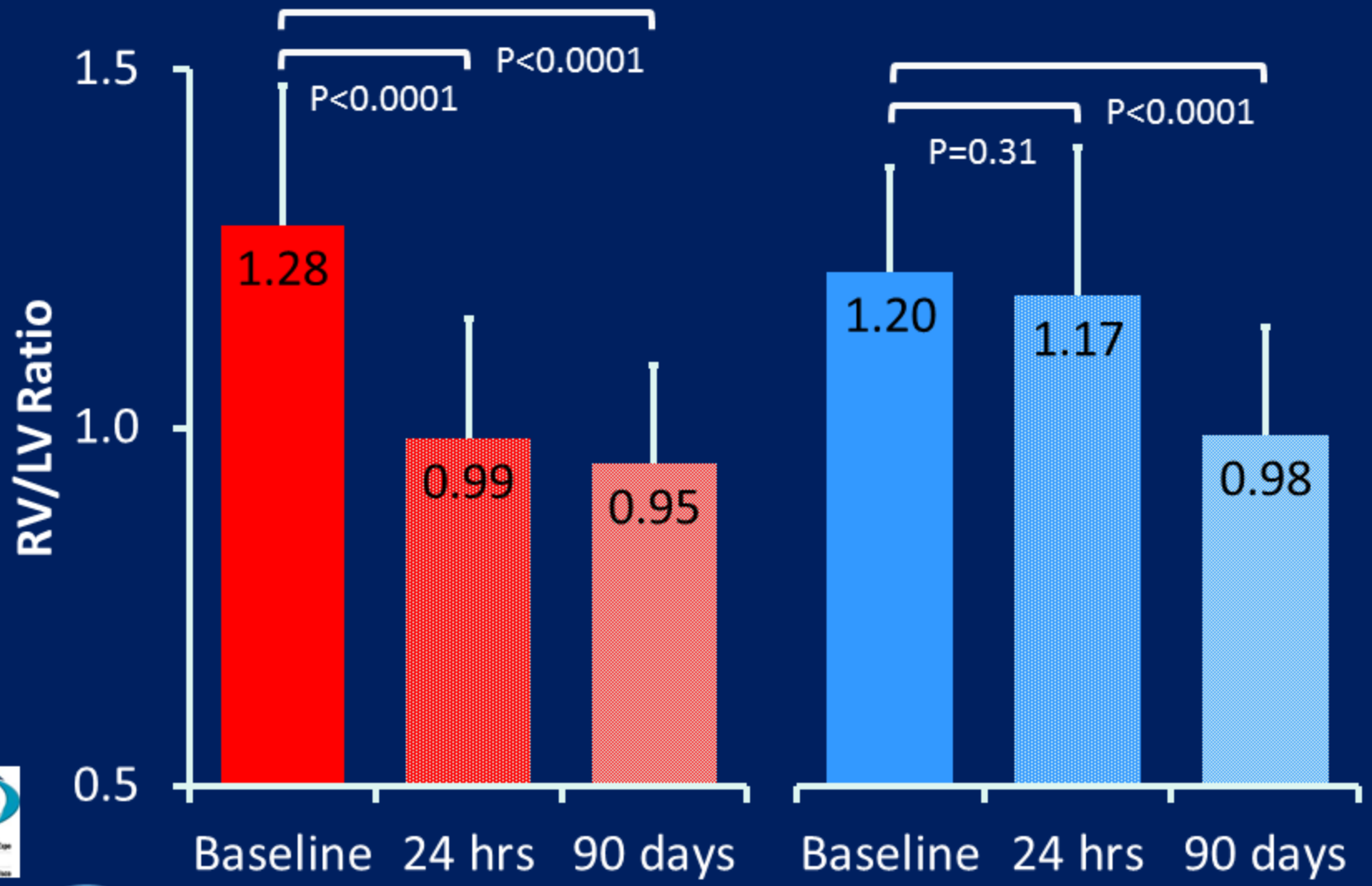


ACC.13

Kucher 2013

ULTIMA

RV/LV ratio (echo)



Kucher 2013

Catheter-directed tPA in Intermediate Risk (Submassive) PE

- **SEATLE II Trial: S**ubmassive and massive pulmonary **E**mbolism treatment with ultrasound **A**ccelera**T**ed **T**hrombolysis th**E**rapy
- Single arm, prospective, multicenter trial
- 150 patients (119 submassive, 31 massive)
- Results at 48 hrs:
  - ↓ 25% CT-measured RV:LV
  - ↓ 30% in PASP by echo
  - ↓ 30% clot burden by PA angiogram
- Bleeding risk: moderate 10%, severe <1%, ICH none

Does catheter-based interventions improve outcomes?

- **PERFECT trial**: prospective, multicenter registry
- 101 patients (Massive 28; Submassive 73)
- Primary outcome: clinical success (stabilization of HD + improvement in PH or RV strain) and survival to discharge
- Results:
  - Clinical success 24/28 Masive; 71/73 Submassive
  - Decrease mPA from 51 to 37 mmHg
  - Improved RV strain in 89%
  - No major complications related to procedure or bleeding
  - No differences among various techniques/devices

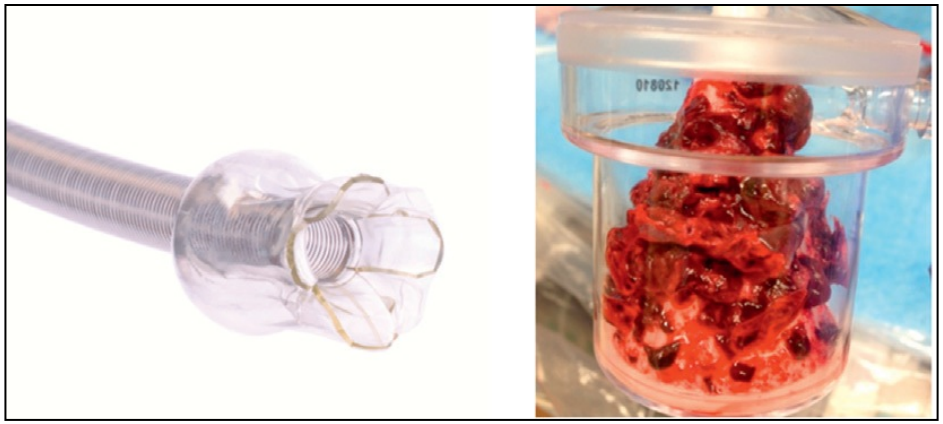
What about survival benefit?

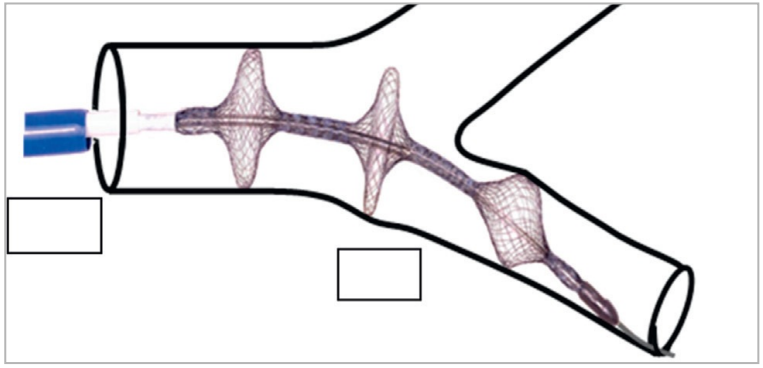
- National Inpatient Sample 2010-2012 identified 110,731 PE → 1,521 (1.4%) patients received thrombolysis
  - 77% systemic and 23% catheter-directed (CDL)
  - ↓ **in-hospital mortality** 22% vs. 13%, OR 0.55 (CI 0.36-0.85, p = 0.007)
  - Similar length of stay 7 days
  - ↑cost of hospitalization $23,799 vs $17,218
- UPMC Registry w submassive and massive PE
  - CDL higher clinical success rate (87% vs. 68%, p = 0.001)
  - Lower rate of major bleeding (7% vs. 22%, p = 0.001)

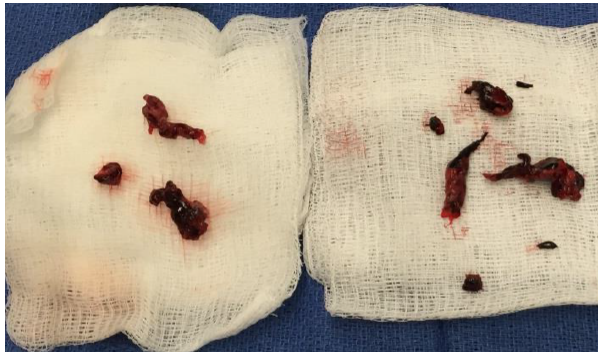
Patel et al. Cath and Card Interv 2015
Avgerinos, Rivera-Lebron et al. Society of Vascular Surgery

Catheter-based Embolectomy

- Thrombus fragmentation/aspiration
- Can be alone or in combination CDL
- Fragmentation may cause distal embolization and worsen obstruction







ACCP Antithrombotic Guidelines 2016: Catheter-based interventions

- Recommend systemic over CDL
- PE with hypotension with high bleeding risk or failed systemic thrombolysis or shock that will lead to death before systemic thrombolysis can take effect – recommend catheter-assited thrombus removal +/- CDL

Antithrombotic Therapy for VTE Disease. CHEST. 2016

Surgical Embolectomy

- Requires median sternotomy with bypass
- Mortality rate 5%
- Preoperative thombolysis increases risk of bleeding but is not absolute contraindication

RV assist devices

- Impella, ECMO
- Reserved for cardiac arrest or refractory shock

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Belinda Rivera-Lebron
riveralebronbn@upmc.edu

Thank you!