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Pulmonary Embolism

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No disclosures

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Pulmonary Embolism

Annual incidence

- United States: 69 per 100,000/year[1]
  - Over 600,000 cases annually[2]
  - 1-2 PE episodes per 1000 people, up to 10 per 1000 in the elderly population[3-6]

Venous thromboembolism[3]

- PE commonly originates from lower limb deep vein thrombosis (DVT)
- 79% of patients presenting with PE have evidence of DVT
- PE occurs in up to 50% of patients with proximal DVT

1. Silverstein et al. Arch intern Med 1998;158:585-93.
2. Wood et al. Chest 2002;121:877-905.
3. Tapson. N Engl J Med 2008;358(10):1037-1052.
4. Geering et al. CMAJ 2012; 184(3):305-310
5. Chunilal et al. JAMA 2003;290:2849–58
6. Siccama et al. Ageing Res Rev 2011;10:304–13

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Pulmonary Embolism

- **PE causes or contributes to 15% of all hospital deaths[1,2]**
- **More people die each year from PE than highway fatalities, breast cancer and AIDS combined[3]**

Cause of Death	# of deaths/yr
PE[4,5]	Up to 200,000
Highway fatalities[6]	42,116
Breast Cancer[7]	40,200
AIDS[8]	14,499

1. *Kasper et al. J Am Coll Cardiol. 1997;30:1165-1171*
2. *According to http://www.sirweb.org/patients/epp-vein/thombosis/*
3. *Goldhaber. Deep-vein thrombosis: Advancing awareness to protect patient lives. American Public Health Association White Paper. 2003.*
4. *Anderson et al. Arch Intern Med. 1991;151:933-938.*
5. *Silverstein et al. Arch Internal Med. 1998;158:585-593.*
6. *National Highway and Traffic Safety Association. Fatality Analysis Reporting System (FARS) Web-Based Encyclopedia. Accessed January 31, 2002.*
7. *American Cancer Society. Breast cancer facts and figures, 2001-2002. Accessed January 31, 2002.*
8. *Centers for Disease Control Report. HIV/AIDS Surveillance Report 2001. Volume 13, Number 2.*

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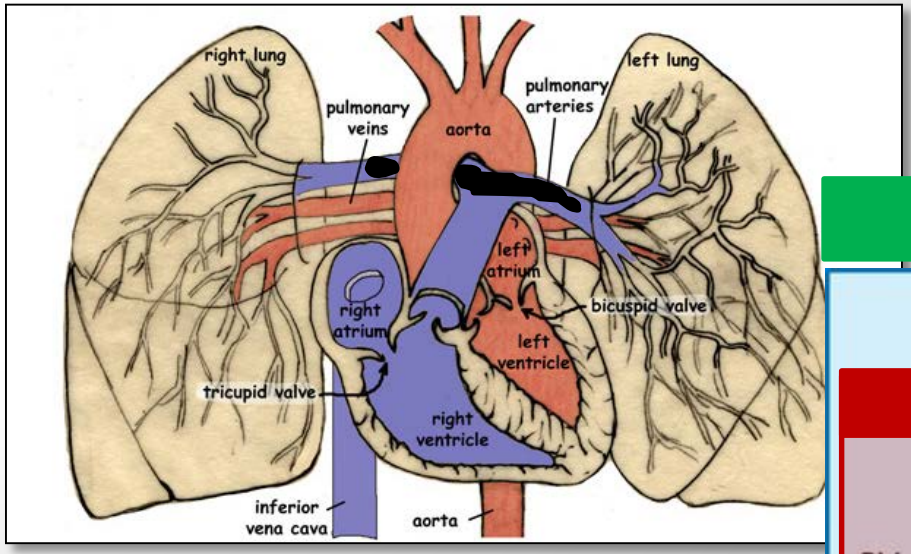
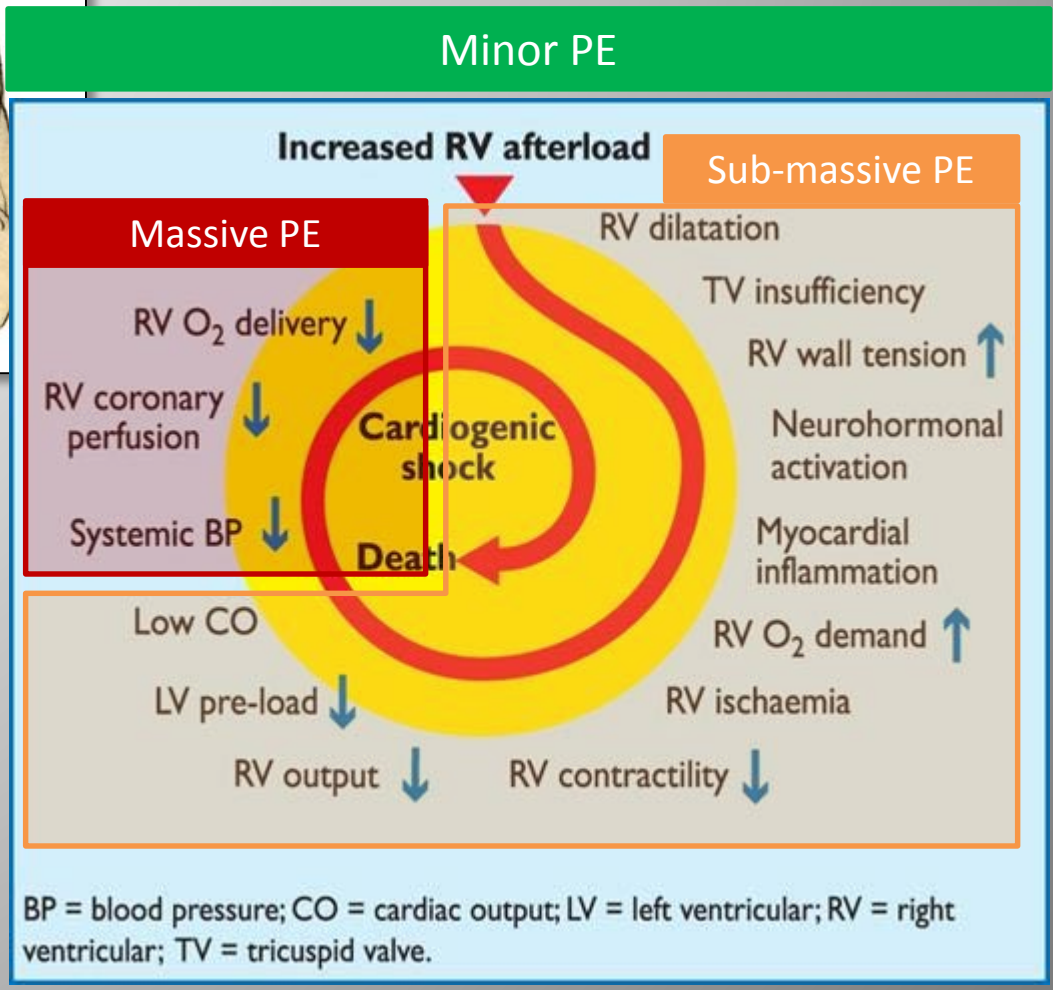
Pulmonary Embolism



Massive PE 5% PE population **58% mortality** @ 3 months	SBP <90mmHg or drop >40mmHg for ≥15 min
Submassive PE 40% PE population **21% mortality** @ 3 months	Normotensive with signs of RV dysfunction
Minor PE 55% PE population **Low mortality rate**	Normotensive without signs of RV dysfunction



Pulmonary Embolism

In patients with acute PE associated with hypotension, systolic BP <90 mm Hg (Massive), who do not have a high bleeding risk

Current ACCP guidelines recommend

1. Anticoagulation alone
2. Systemic thrombolytic therapy followed by anticoagulation
3. Thrombolytic therapy alone without subsequent anticoagulation

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Massive Pulmonary Embolism

In patients with acute PE associated with hypotension (eg, systolic BP <90 mm Hg) who do not have a high bleeding risk,

we suggest systemically administered thrombolytic therapy over no such therapy *(Grade 2B)*

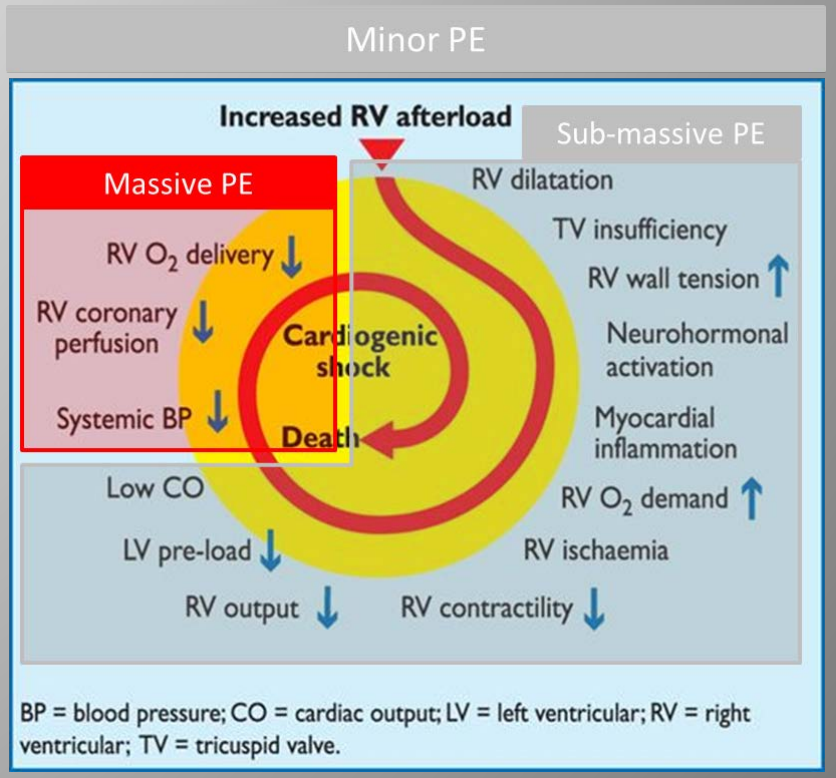
In patients with acute PE associated with hypotension and who have

(i) a high bleeding risk,

(ii) failed systemic thrombolysis, or

(iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours)

if appropriate expertise/resources are available, ***we suggest catheter-assisted thrombus removal over no such intervention*** *(Grade 2C)*



Kearon C, Akl EA, Ornelas J, Blaivas A, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline. Chest 2016

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Rationale for Lysis

STANDARD OF CARE: usually UFH or LMWH, followed by oral warfarin (more recently DOACs if appropriate)

- However, AC therapy relies on endogenous t-PA to dissolve occluding clot[1]
  - **a process that typically occurs over several weeks or months**
  - **endogenous fibrinolysis may often be incomplete at the end**

Thrombolytics provide rapid reduction in clot burden not achievable by anticoagulation alone

- Reverse RV afterload / failure to prevent hemodynamic collapse
- Improve pulmonary reperfusion/capillary blood flow / gas exchange
- Restore systemic arterial perfusion pressure
- Decrease the risk of developing chronic pulmonary hypertension

Current recommendations for massive PE are
100 mg t-PA infused over 2 hours

1. . Arcasoy et al. Clin Chest Med 24 (2003) 73– 91
2. Piazza and Goldhaber. Finbrinolysis for acute pulmonary embolism. Vascular Medicine 2010 15(5):419-428 .

Pulmonary Embolism

In most patients with acute PE not associated with hypotension and who remain stable on anticoagulation therapy
Current ACCP guidelines recommend

1. Anticoagulation alone
2. Systemic thrombolytic therapy followed by anticoagulation
3. Thrombolytic therapy alone without subsequent anticoagulation

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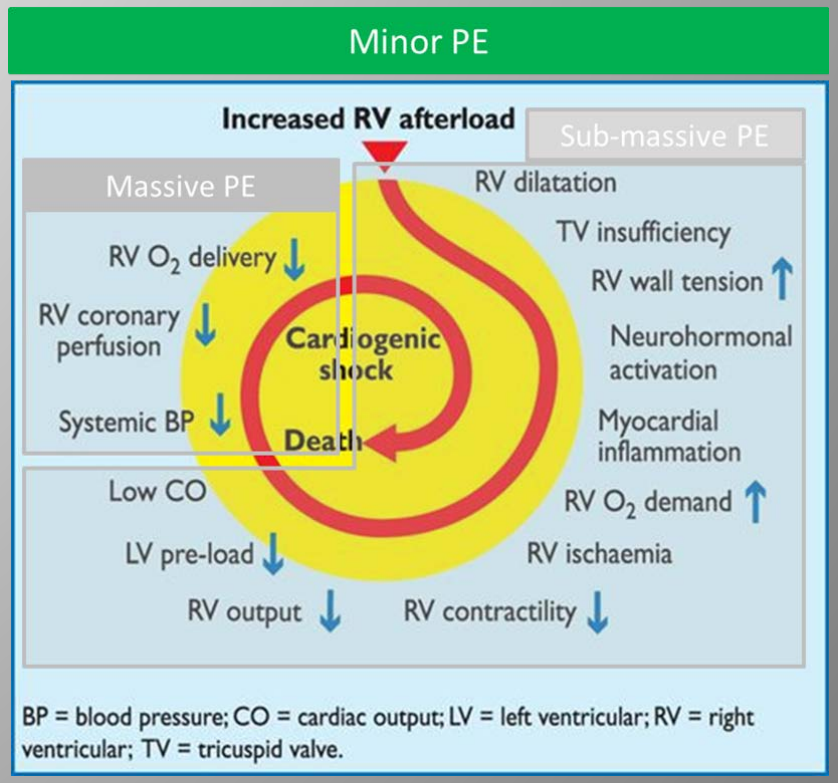
Minor and Sub Massive Pulmonary Embolism

In most patients with acute PE not associated with hypotension ***we recommend against systemically administered thrombolytic therapy*** *(Grade 1B)*



1. Kearon C, Akl EA, Ornelas J, Blaivas A, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline. Chest 2016
2. *European Heart Journal*, Volume 35, Issue 43, 14 November 2014, Pages 3033–3073

Pulmonary Embolism

In selected patients with acute PE who deteriorate* after starting anticoagulant therapy but have yet to develop hypotension, who have a low bleeding risk
Current ACCP guidelines recommend

1. Anticoagulation alone
2. Systemic thrombolytic therapy followed by anticoagulation
3. Thrombolytic therapy alone without subsequent anticoagulation

*Cardiopulmonary deterioration (eg, symptoms, vital signs, tissue perfusion, gas exchange, cardiac biomarkers)

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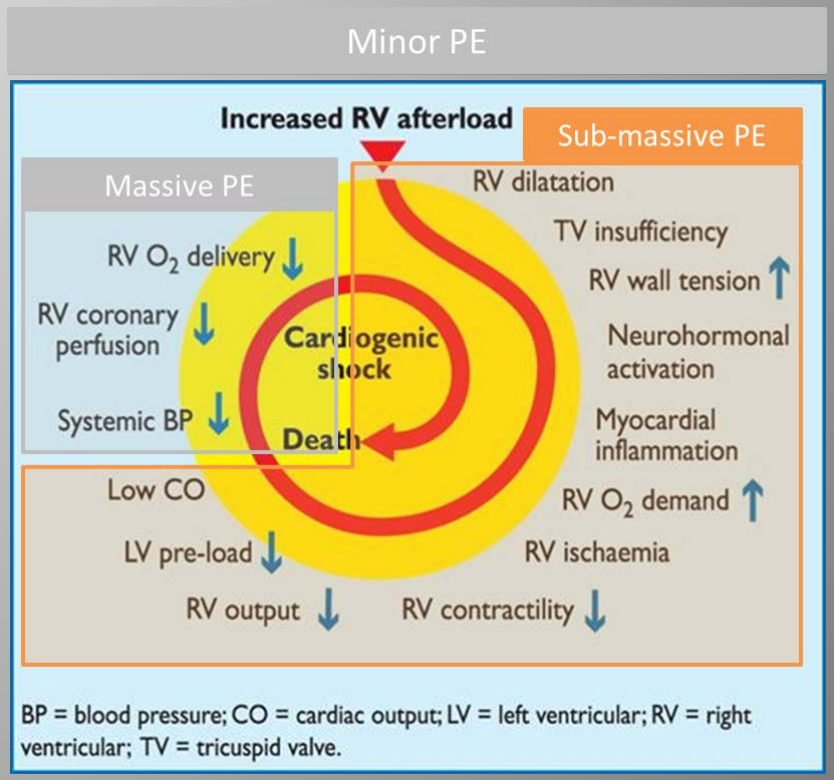
Minor and Sub Massive Pulmonary Embolism

In selected patients with acute PE who deteriorate* after starting anticoagulant therapy but have yet to develop hypotension, who have a low bleeding risk

we suggest systemically administered thrombolytic therapy over no such therapy *(Grade 2C)*

*Cardiopulmonary deterioration (eg, symptoms, vital signs, tissue perfusion, gas exchange, cardiac biomarkers)



1. Kearon C, Akl EA, Ornelas J, Blaivas A, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline. Chest 2016
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Thrombolytics in Sub Massive PE

Trial	n	intervention	1^0 outcomes (Intervention vs control)	Complications (Intervention vs control)	Notes
Mappett 3 2002 Multicenter, DB, randomized placebo controlled	256	Alteplase 100mg with heparin vs. Heparin alone	In hospital death or clinical deterioration 11.0% v. 24.6%, p=0.006, NNT 7 (driven by the later)	Major bleeding 0.8% vs. 3.6% p=0.29 1 fatal bleed in control group No intracranial bleeding	
Moppett 2013 Single-center , randomized, unblinded	121	tPA 0.5mg/kg (max 50mg) vs. Anticoagulation alone	Pulmonary hypertension 16% vs. 57% P<0.001; NNT 2 Pulmonary hypertension or recurrent PE 16% vs. 63% P<0.001; NNT 2	Major or minor bleeding 0 in each group	open-label, single-center design, low rate of patients meeting the traditional definition of submassive PE, and questionable data collection practices
Peitho 2014 Multicenter, DB, randomized placebo controlled	1005	Tenecteplace vs. placebo	All cause mortality or hemodynamic compromise at 7 days 2.6% vs. 5.6%, P=0.02; NNT 33 (driven by the later)	Bleeding at 7 days Intracranial 2.4% vs. 0.2%, P=0.003; NNH 45 Major 6.3% vs 1.6%, P<0.001;NNH 20 Minor 32.6% vs. 8.6%, P=0.004; NNH 45 Majority in age >75	- Not powered for mortality - ?significance of hemodynamic decompensation

Full dose systemic thrombolysis is effective BUT has a high bleeding complication rate
Low dose systemic thrombolysis possibly has less bleeding with equal efficacy but weak data

N Engl J Med 2002; 347:1143-1150
Am J. Cario l 2013 Jan 15;111(2):273-7
N Engl J Med 2014; 370:1402-1411

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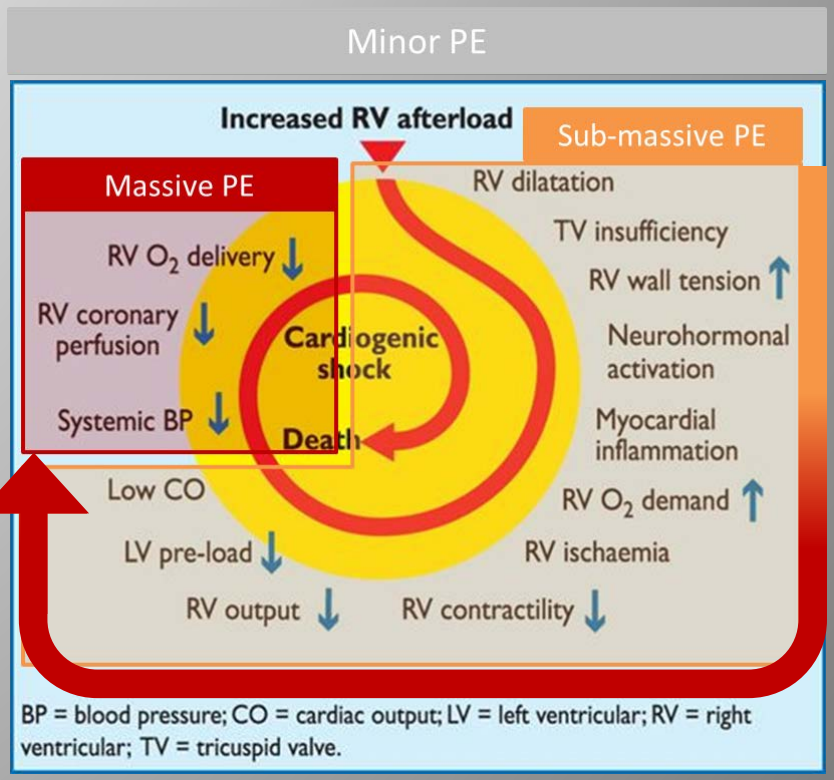
Minor and Sub Massive Pulmonary Embolism

In selected patients with acute PE who deteriorate* after starting anticoagulant therapy but have yet to develop hypotension, who have a low bleeding risk

we suggest systemically administered thrombolytic therapy over no such therapy *(Grade 2C)*

*Cardiopulmonary deterioration (eg, symptoms, vital signs, tissue perfusion, gas exchange, cardiac biomarkers)

How to identify patients at high risk of deterioration?



1. Kearon C, Akl EA, Ornelas J, Blaivas A, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline. Chest 2016
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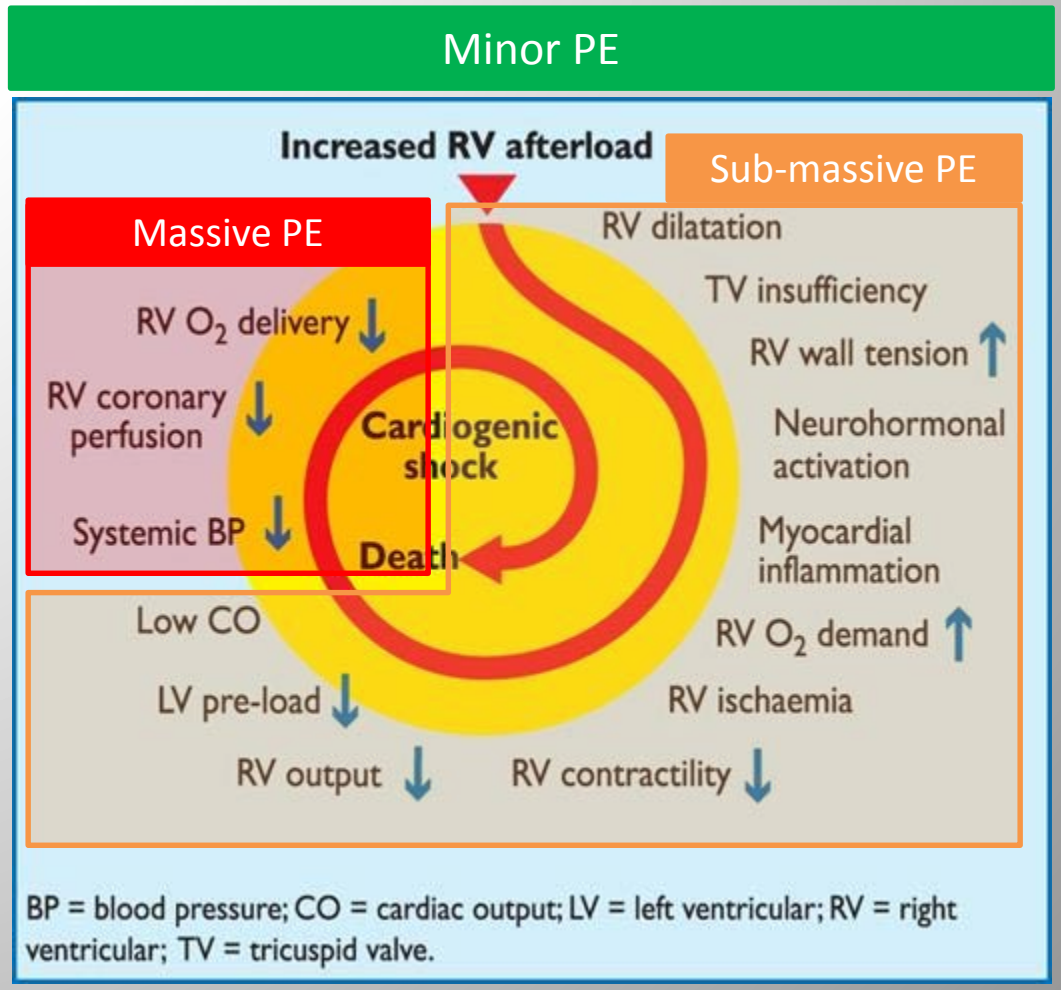
Risk Stratification

Clinical predictors of poor outcome?



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Clinical Picture?

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%)

1. Am J Respir Crit Care Med. 2005 Oct 15;172(8):1041-6

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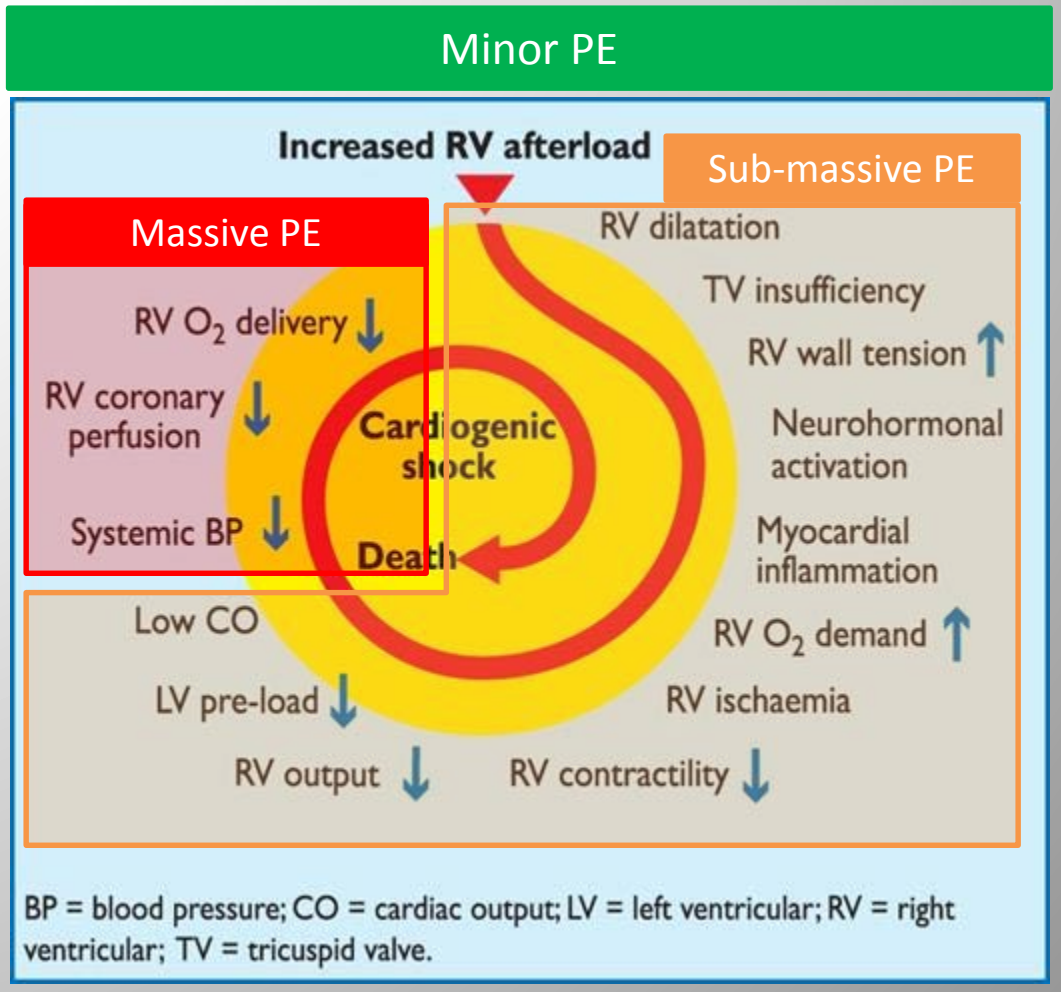
Risk Stratification

Clinical predictors of poor outcome?

PESI III-IV or sPESI ≥1



Biomarkers that predict poor outcomes?

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Risk Stratification

BNP or NTproBNP

- Presumably reflects RV dysfunction/stretch
  - Metanalysis of 1132 unselected patient with acute PE
    - 51% had elevation on admission
    - Subgroup analysis showed they had a 10% risk of early death and 23% risk of adverse outcome
  - Metanalysis of 688 showed
    - negative levels correlated with favorable short term outcomes
- In hemodynamically stable patients a normal/low levels has a strong negative predictive value

1. *European Heart Journal*, Volume 35, Issue 43, 14 November 2014, Pages 3033–3073

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Risk Stratification

Troponin

- Marker for possible RV infarction independent of patency of coronary arteries patency (based on autopsy data)
  - Metanalysis of 1985 acute PE patients
    - Troponin elevated in 50%
    - Associated with higher mortality in unselected and hemodynamically unstable patients
- Similarly a negative value in a hemodynamically stable patient has a strong negative predictive value

1. *European Heart Journal*, Volume 35, Issue 43, 14 November 2014, Pages 3033–3073

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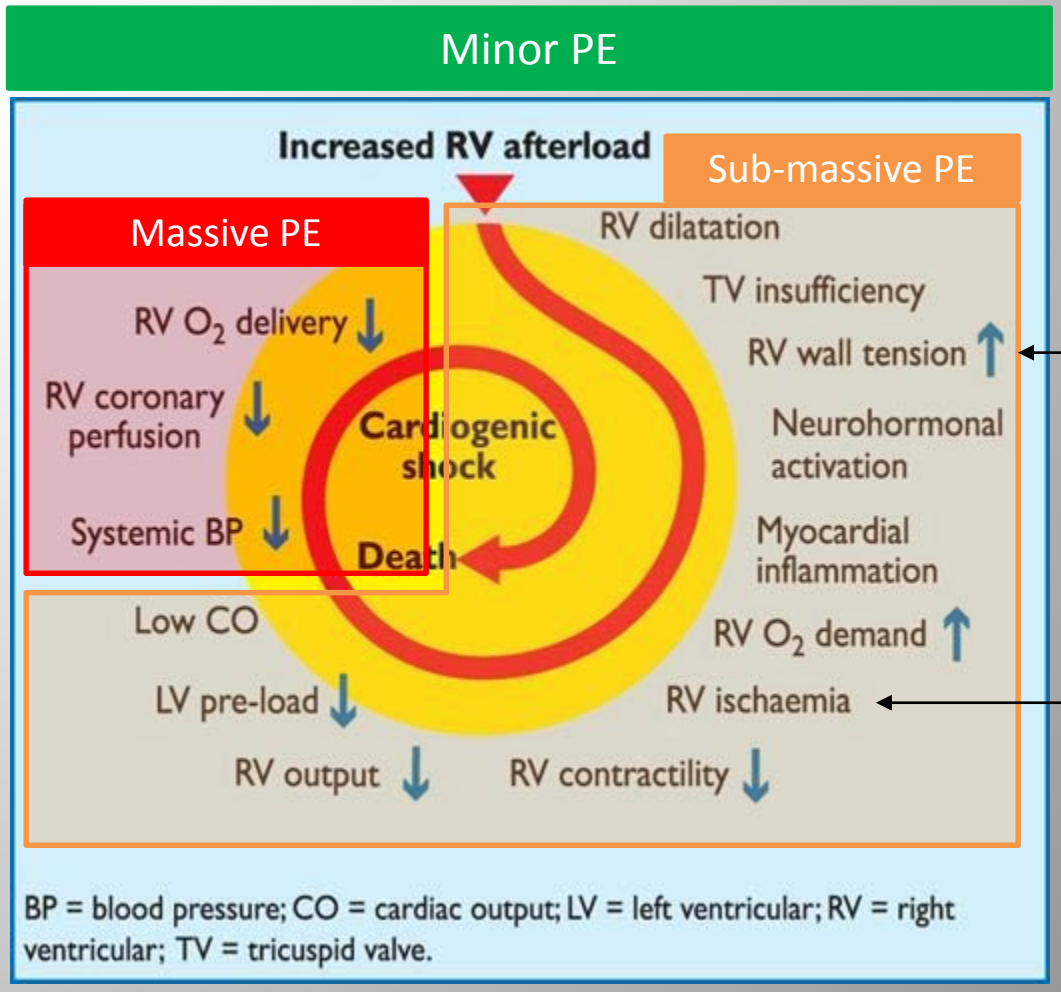
Risk Stratification

Predictors of poor outcomes based on clinical presentation?

PESI III-IV or sPESI ≥1



BNP

Troponin

Biomarkers that predict poor outcomes?

Imaging to suggest RV Dysfunction?

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Risk Stratification

Imaging the right ventricle for dysfunction

- Echocardiograph showing acute RV dysfunction found in about 25% of acute PE patients
  - RV dilation, increased RV-LV diameter ratio, hypokinesis of RV free wall, reduced TAPSE
- Identified as predictor of poor outcome

1. *European Heart Journal*, Volume 35, Issue 43, 14 November 2014, Pages 3033–3073

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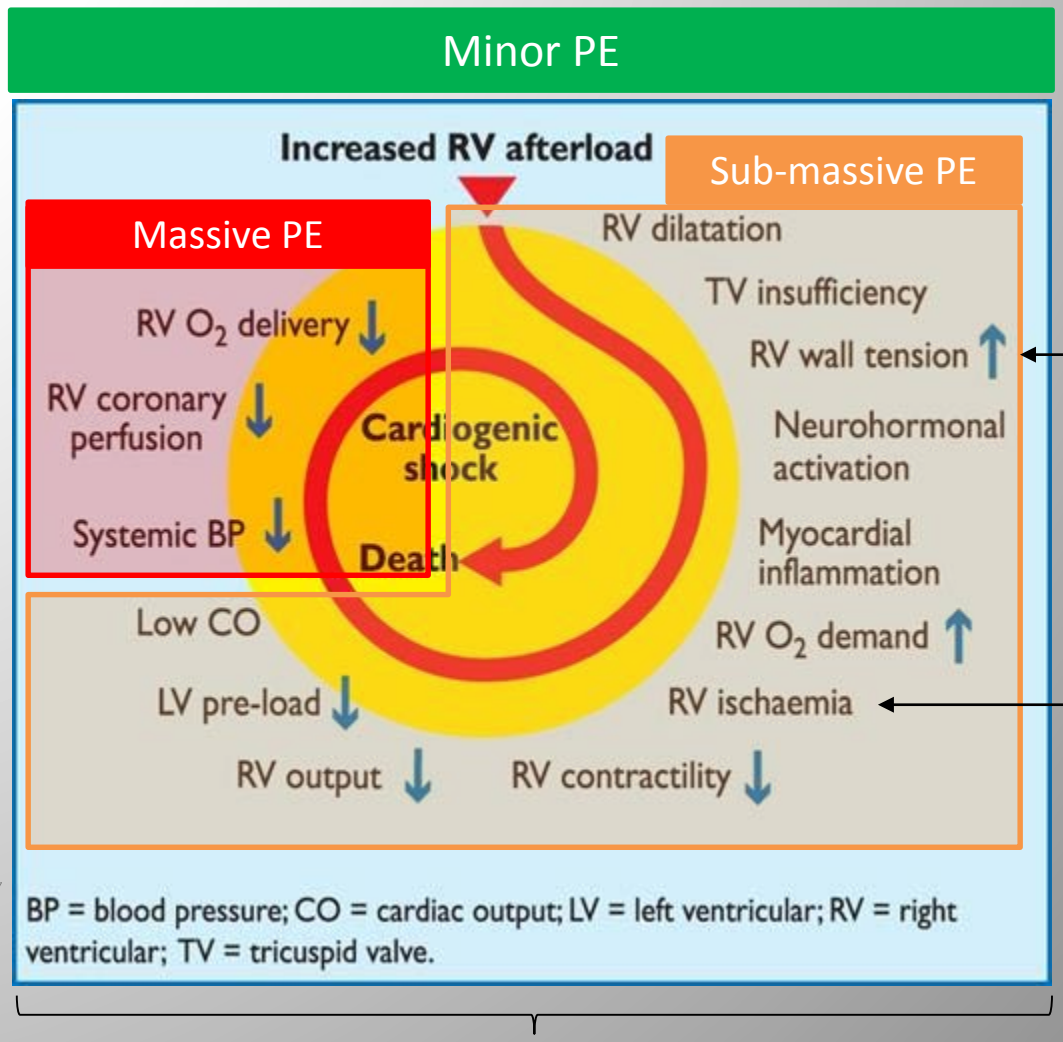
Risk Stratification

Predictors of poor outcomes based on clinical presentation?

PESI III-IV or sPESI ≥1



BNP

Biomarkers that predict poor outcomes?

Troponin

Imaging to suggest RV Dysfunction?

CT or echocardiogram demonstrating RV dysfunction

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"In patients with acute PE who appear haemodynamically stable at diagnosis, no individual clinical, imaging, or laboratory finding has been shown to predict risk of an adverse in-hospital outcome that could be considered high enough to justify primary reperfusion"

European Society of Cardiology

Composite scores?

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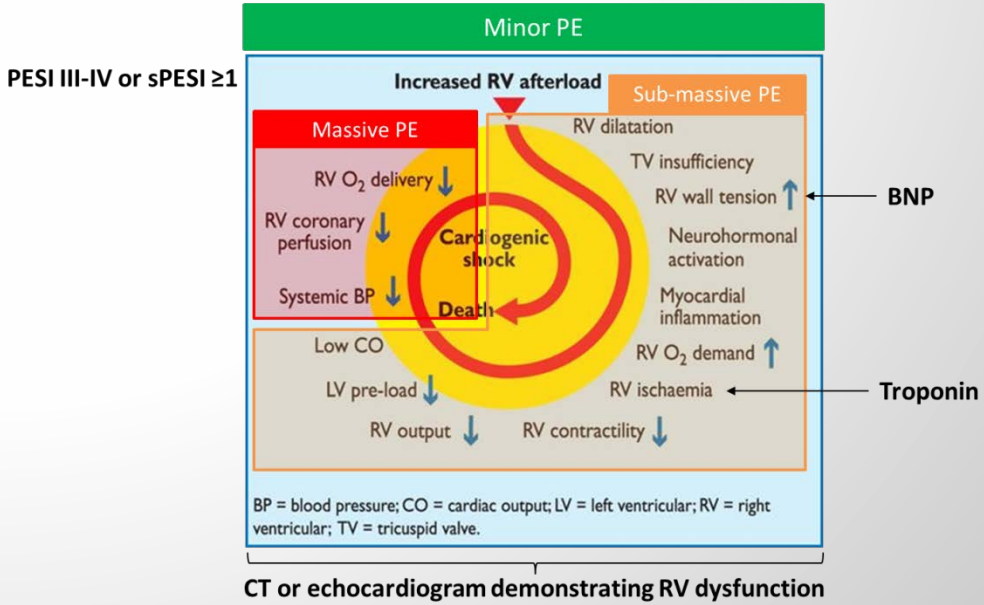
Massive Pulmonary Embolism



Early Mortality Risk		Risk Parameters and Scores			
		Shock or Hypotension	PESI Class III-V or sPESI ≥1	Signs of RV Dysfunction on an Imaging Test	Cardiac Laboratory Biomarkers*
High		+	(+)	+	(+)
Intermediate	Intermediate-high	−	+	Both positive	
	Intermediate-low	−	+	Either 1 (or none) positive	
Low		−	−	Assessment optional: If assessed, both negative	

Konstantinides, S.V. et al. J Am Coll Cardiol. 2016; 67(8):976-90.

1. *European Heart Journal*, Volume 35, Issue 43, 14 November 2014, Pages 3033–3073