PULMONARY EMBOLISM

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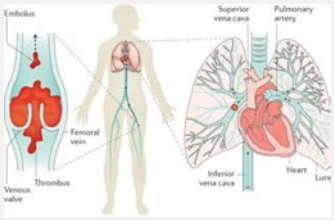
DISCLOSURES AND OBJECTIVES

- Chhaya Patel, MD has no financial relationships with commercial interests to disclose
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed

- Explain how to discern between low, intermediate, and high risk pulmonary embolisms.
- Describe treatment options for treatment of pulmonary embolism.
- Discuss the long term/outpatient consequences of a diagnosis of pulmonary embolism.

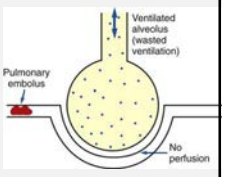
PATHOPHYSIOLOGY

- PE occurs when deep venous thrombi detach and embolize to the pulmonary circulation. Pulmonary vascular occlusion occurs and impairs gas exchange and circulation.
- In the lungs, the lower lobes are more frequently affected than the upper, with bilateral lung involvement being common
- Larger emboli wedge in the main pulmonary artery, while smaller emboli occlude the peripheral arteries

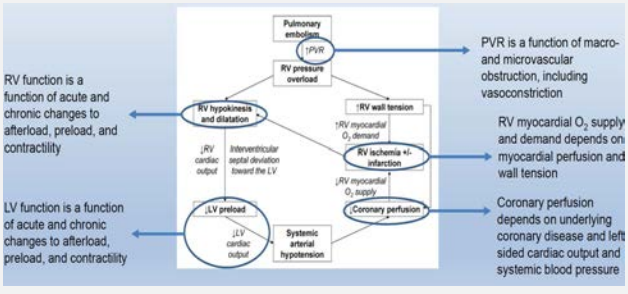


PATHOPHYSIOLOGY

- Obstruction of the pulmonary arteries creates dead space ventilation as alveolar ventilation exceeds pulmonary capillary blood flow.
- This contributes to ventilation-perfusion mismatch, with vascular occlusion of the arteries increasing pulmonary vascular resistance
- As the pulmonary artery systolic pressure increases, right ventricular after load increases, leading to right ventricular failure.
- As the right ventricular failure progresses, impairment in left ventricular filling may develop. Rapid progression to myocardial ischemia may occur secondary to inadequate coronary artery filling, with potential for hypotension, syncope, electromechanical dissociation, or sudden death



PATHOPHYSIOLOGY



SYMPTOMS/CLINICAL PRESENTATION FOR PE

- Dyspnea, chest pain, and cough are the most frequent symptoms of PE, while fever, tachycardia, abnormal pulmonary signs, and peripheral vascular collapse are the most common physical findings.
- Cyanosis, hemoptysis, syncope, and the various manifestations of acute cor pulmonale are less commonly observed.

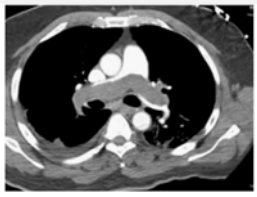
SYMPTOMS/CLINICAL PRESENTATION FOR PE

1. SD (sudden cardiac arrest; SCA)
2. Similar to acute respiratory distress syndrome (ARDS)
3. Typical respiratory failure (hypoxia and hypocapnia)
4. Asthmatic crisis-like syndrome
5. Fever syndrome with or without "pneumonia" (with or without pleural effusion)
6. Acute right heart failure/shock/hypotension (often with epigastric pain)
7. Left heart failure (with pulmonary congestion)
8. Chest pain similar to pleuritic syndrome with or without hemoptysis (with or without effusion)
9. Similar to acute coronary syndrome (ACS) (with or without chest pain)

1. PE with paradoxic embolism (with corresponding clinical picture due to embolization site and resulting in: AMI, stroke, flank pain [due to acute splenic infarction or acute renal infarction], acute abdomen, and upper or lower extremity embolism. In all these paradoxical embolism conditions, the main symptom may be systemic or not)
2. Syncope
3. Complete atrioventricular (AV) block with idioventricular rhythm
4. Persistent or paroxysmal atrial fibrillation (AF), atrial flutter, atrial tachycardia, paroxysmal supraventricular tachycardia (PSVT)
5. DVT and silent PE
6. Platypnea-orthodeoxia
7. Abdominal pain without abdomen acute
8. Delirium

PULMONARY EMBOLISM

- Because of the variable nature of the presentation of PE, the evaluation largely depends on the likelihood of PE and the stability of the patient.
- There are groups of "risk factors" to assist in diagnosis as well as scoring systems to discern the likelihood of a PE diagnosis



RISK FACTORS - STRONG

- Fracture of lower limb
- Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
- Hip or knee replacement
- Major trauma
- Myocardial infarction (within previous 3 months)
- Previous VTE
- Spinal cord injury

RISK FACTORS - MODERATE

- Arthroscopic knee surgery
- Autoimmune diseases
- Blood transfusion
- Central venous lines
- Intravenous catheters and leads
- Chemotherapy
- Congestive heart failure or respiratory failure
- Erythropoiesis-stimulating agents
- Hormone replacement therapy (depends on formulation)
- In vitro fertilization
- Oral contraceptive therapy
- Post-partum period
- Infection (specifically pneumonia, urinary tract infection, and HIV)
- Inflammatory bowel disease
- Cancer (highest risk in metastatic disease)
- Paralytic stroke
- Superficial vein thrombosis
- Thrombophilia

DIAGNOSTIC TESTING

- D-dimer - the negative predictive value of testing is high; normal D-dimer level renders acute PE or DVT unlikely
- CTPA – the Prospective Investigation On Pulmonary Embolism Diagnosis (PIOPED) II study observed a sensitivity of 83% and a specificity of 96%
- V/Q scan purpose is to increase specificity: in acute PE, ventilation is expected to be normal in hypoperfused segments (mismatched).
  - Being a lower-radiation and contrast medium-sparing procedure, the V/Q scan may preferentially be applied in **outpatients with a low clinical probability and a normal chest X-ray, in young (particularly female) patients, in pregnant women, in patients with history of contrast medium-induced anaphylaxis, and patients with severe renal failure**

TABLE 6 Imaging tests for diagnosis of pulmonary embolism

	Strengths	Weaknesses/limitations	Radiation issues[a]

CTPA	• Readily available around the clock in most centres
	• Excellent accuracy
	• Strong validation in prospective management outcome studies
	• Low rate of inconclusive results (3–5%)
	• May provide alternative diagnosis if PE excluded
	• Short acquisition time
		• Radiation exposure
		• Exposure to iodine contrast:
		  • limited use in iodine allergy and hyperthyroidism
		  • risks in pregnant and breastfeeding women
		  • contraindicated in severe renal failure
		• Tendency to overuse because of easy accessibility
		• Clinical relevance of CTPA diagnosis of subsegmental PE unknown
			• Radiation effective dose 3–10 mSv[b]
			• Significant radiation exposure to young female breast tissue

Planar V/Q scan	• Almost no contraindications • Relatively inexpensive • Strong validation in prospective management outcome studies	• Not readily available in all centres • Interobserver variability in interpretation • Results reported as likelihood ratios • Inconclusive in 50% of cases • Cannot provide alternative diagnosis if PE excluded	• Lower radiation than CTPA, effective dose ~2 mSv[b]
V/Q SPECT	• Almost no contraindications • Lowest rate of non-diagnostic tests (<3%) • High accuracy according to available data • Binary interpretation ("PE" versus "no PE")	• Variability of techniques • Variability of diagnostic criteria • Cannot provide alternative diagnosis if PE excluded • No validation in prospective management outcome studies	• Lower radiation than CTPA, effective dose ~2 mSv[b]
Pulmonary angiography	• Historical gold standard	• Invasive procedure • Not readily available in all centres	• Highest radiation, effective dose 10–20 mSv[b]

ANTICOAGULATION

- Despite increasing reperfusion therapies available for intermediate- and high-risk PE, therapeutic anticoagulation remains the primary therapy for acute PE.
- Patients achieving therapeutic anticoagulation within 24 hours of admission have reduced 30-day mortality.
- However, results from a large academic PERT center demonstrated that fewer than half of the patients treated with unfractionated heparin (UFH) achieved therapeutic levels within the first 24 hours.
- Thus, **low-molecular-weight heparin (LMWH)** is favored by many as the initial anticoagulant of choice, based on achieving predictable therapeutic levels within 3 to 4 hours of administration.
- LMWH may be used even if advanced therapies are being considered; however, UFH may be preferred in those with overt hemodynamic instability and imminent need of reperfusion therapy
- Direct acting oral anticoagulants (DOACs) are considered first-line treatment in patients with low-risk PE

ANTICOAGULATION

	Initial Phase	Long-Term	Extended	Not recommended
Rivaroxaban	15 mg BID	20 mg QD	20 mg QD	CrCl<30 Hepatic impairment Combined P-gp and CYP3A4 inhibitors or inducers
Dabigatran	150 mg BID*	150 mg BID	150 mg BID	CrCl <30 P-gp inhibitors or inducers and CrCl <50
Apixaban	10 MG BID for 7 days	5 mg BID	2.5 mg BID	CrCl <15 Severe hepatic impairment CYP3A4 and P-gp
Edoxaban	60 mg QD*	60 mg QD	60 mg QD	CrCl <15 Hepatic impairment Concomitant rifampin

Factor	Preferred anticoagulant
Cancer	LMWH
Parenteral therapy to be avoided	Rivaroxaban; apixaban
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA
Liver disease and coagulopathy	LMWH
Renal disease and creatinine clearance <30 mL/min	VKA
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban
Dyspepsia or history of GI bleeding	VKA, apixaban
Poor compliance	VKA
Thrombolytic therapy use	UFH infusion
Reversal agent needed	VKA, UFH, dabigatran
Pregnancy or pregnancy risk	LMWH
Cost, coverage, licensing	Varies among regions and with individual circumstances

ANTICOAGULATION - INPATIENT

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ANTICOAGULATION – OUTPATIENT

Direct Factor Xa Inhibitors			Direct Thrombin (Factor IIa) Inhibitor
apixaban (Eliquis®)	edoxaban (Savaysa®)	rivaroxaban (Xarelto®)	dabigatran (Pradaxa®)

- In patients with DVT of the leg or PE (w/o active cancer):
  - DOAC's are preferred over warfarin (Grade 2B) –no one over the other
  - Warfarin preferred over LMWH (Grade 2C)
- In patients diagnosed with a subsegmental PE and confirmed to have no proximal DVT and have a low risk for a recurrent clotting event, **surveillance is recommended over anticoagulation** (Grade 2C)
  - But if patient has a high risk for recurrent VTE, anticoagulation is recommended over surveillance (Grade 2C)
- **Lovenox – active cancer and pregnancy**

Lovenox
- Recommended agent in cancer and pregnancy

CHEST 2016 VTE GUIDELINES

- For VTE without an associated cancer diagnosis, all direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban) are recommended over vitamin K antagonist (VKA) therapy (all Grade 2B) and VKA therapy is recommended over low molecular weight heparin (LMWH; Grade 2C).
- For VTE associated with cancer, LMWH is recommended over VKA (Grade 2B) or any direct oral anticoagulants (all Grade 2C).
- Anticoagulants should stop after 3 months of therapy in patients with an acute, proximal deep venous thrombosis (DVT) provoked by surgery rather than shorter or longer treatment courses (Grade 1B).
- Anticoagulants should also be stopped after 3 months in patients with a proximal DVT or pulmonary embolism (PE) provoked by a nonsurgical transient risk factor over shorter or longer courses (Grade 1B for high bleeding risk patients, Grade 2B for low or moderate bleeding risk patients).
- Anticoagulation should be given for 3 months in patients with a first unprovoked VTE and a high risk of bleeding (Grade 1B), but should be extended without a scheduled stop date in patients with a low or moderate risk of bleeding (Grade 2B).

CHEST 2016 VTE GUIDELINES

- For patients with acute VTE who are treated with anticoagulation, the guideline recommends against the use of an inferior vena cava filter (Grade 1B).
- For patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy, the guideline suggests the use of aspirin over no aspirin to prevent recurrent VTE if there are no contraindications to aspirin therapy (Grade 2B).
- For patients with acute DVT, the guideline recommends against the use of compression stockings routinely to prevent the post-thrombotic syndrome (Grade 2B).
- For patient with subsegmental PE and no DVT, the guideline suggests clinical surveillance over anticoagulation when the risk of VTE recurrence is low (Grade 2C). The guideline recommends the use of anticoagulation over surveillance when the risk of VTE recurrence is high (Grade 2C).
- For patients with an acute PE and hypotension (massive PE), the guideline recommends the use of thrombolytic therapy (Grade 2B), preferring systemic therapy over catheter-directed thrombolytic therapy (Grade 2C).
- For patients with recurrent VTE while treated with a non-LMWH anticoagulant, the guideline recommends changing to LMWH therapy (Grade 2C). If patients suffer a recurrent VTE while on LMWH treatment, the guideline recommends increasing the LMWH dose (Grade 2C).

DURATION OF THERAPY

Proximal DVT of the leg or PE provoked by surgery	3 months
DVT of the leg or PE provoked by a nonsurgical transient risk factor	3 months
Isolated distal DVT of the leg provoked by surgery or nonsurgical transient risk factor	3 months
Unprovoked PE or DVT of the leg	At least 3 months ★ Indefinite
Pt's first DVT that is an unprovoked proximal DVT of the leg or PE	Extended therapy (no scheduled stop date)
In patients with a second unprovoked VTE with a low bleeding risk	Extended therapy (no scheduled stop date)
In patients with a second unprovoked VTE with a moderate bleeding risk	At least 3 months
In patients with a second unprovoked VTE with a high bleeding risk	3 months
Patients with DVT of the leg and active cancer w/ or w/o high risk of bleeding	Extended therapy (no scheduled stop date)

IVC FILTER

Absolute Indications (proven VTE)

- Recurrent VTE despite adequate anticoagulation
- Contraindication to anticoagulation
- Complication of anticoagulation
- Inability to achieve/maintain adequate anticoagulation

- Indications for removable filter are the same as for permanent filters
- Patients with removable filters must be followed closely
- Can consider removal when risk acceptably low or when patient can receive adequate primary therapy
- Resume anticoagulation as soon as feasible

VTE PREVENTION

For patients undergoing major orthopedic surgery, extend thromboprophylaxis in the outpatient period for up to 35 days (rather than 10–14 days).

- High risk of VTE -> Orthopedic surgery, Major Trauma, Spinal cord injury
  - (LMWH, fondaparinux, rivaroxaban, VKA) + mechanical
- Moderate risk of VTE -> general med/surg patients on bedrest, antepartum with high risk women
  - LMWH
- Low risk of VTE -> ambulatory patients (includes high risk patients while traveling ex: cancer)
  - Early ambulation only
- NEJM 2019:
  - Among critically ill patients who were receiving pharmacologic thromboprophylaxis, adjunctive intermittent pneumatic compression did not result in a significantly lower incidence of proximal lower-limb deep-vein thrombosis than pharmacologic thromboprophylaxis alone
- Only mechanical ppx if high bleeding risk

TREATMENT OF HYPOXIA

- Administration of supplemental oxygen is indicated in patients with PE and SaO2 <90%.
- Severe hypoxemia/respiratory failure that is refractory to conventional oxygen supplementation could be explained by right-to-left shunt through a patent foramen ovale or atrial septal defect
- Further oxygenation techniques should also be considered, including high-flow oxygen (i.e. a high-flow nasal cannula) and mechanical ventilation (non-invasive or invasive) in cases of extreme instability (i.e. cardiac arrest), taking into consideration that correction of hypoxemia will not be possible without simultaneous pulmonary reperfusion.

PE CLASSIFICATION

Hemodynamic stability must be considered initially

**PE is classified into three main categories:

- High risk PE
- Intermediate/Submassive
- Low-risk - Low-risk patients are normotensive with normal RV function and biomarkers, and they have excellent prognosis once anticoagulation is established

HIGH RISK PE

- High-risk or massive - persistent hypotension (systolic BP [SBP] < 90 mm Hg or a decrease in SBP of >40 mm Hg from baseline, for ≥15 minutes), persistent profound bradycardia (heart rate <40), obstructive shock, evidence of end-organ hypoperfusion, such as altered mental status, cold/clammy skin, oliguria/anuria, increased serum lactate, or cardiac arrest
  - Hypotension not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or LV dysfunction
  - These patients account for 5% to 10% of cases but have a high mortality (30%-50%), requiring rapid decision-making

HIGH RISK PE

TABLE 4 Definition of haemodynamic instability, which delineates acute high-risk pulmonary embolism (one of the following clinical manifestations at presentation)

(1) Cardiac arrest	(2) Obstructive shock [68–70]	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP <90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status *And* End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	Systolic BP <90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis

INTERMEDIATE RISK/SUBMASSIVE

- Intermediate-risk or submassive - Acute PE **without** systemic hypotension (SBP ≥90 mm Hg) but with **either RV dysfunction or myocardial necrosis**
  - Account for 30% to 50% of cases.
- Presence of RV dilation and dysfunction or lab abnormalities such as elevated troponin or BNP/N-Terminal pro-BNP are associated with adverse prognosis and increased mortality.
  - On their own, increased circulating levels of cardiac **troponins** have relatively low specificity and positive predictive value for early mortality in normotensive patients with acute PE.
  - A meta-analysis found that 51% of 1132 unselected patients with acute PE had **elevated BNP/NT-proBNP** concentrations on admission; these patients had a 10% risk of early death (95% CI 8.0–13%) and a 23% (95% CI 20–26%) risk of an adverse clinical outcome

INTERMEDIATE RISK/SUBMASSIVE

- Although multiple CTA and echocardiographic parameters have been associated with worse prognosis in acute PE, there is not one uniform definition of RV dysfunction, and often it is defined by a combination of findings.

**This group is further subclassified into:

- Intermediate-high risk - **both** RV dysfunction on imaging and biomarker elevation
- Intermediate-low risk - RV dysfunction **or** biomarker elevation

MORBIDITY OF SUBMASSIVE PE

- Submassive PE accounts for most deaths from PE
- It leads to **long term morbidity**, especially **chronic** pulmonary hypertension and worse **functional outcome**
- Secondary adverse outcomes such as persistent RV dysfunction, chronic thromboembolic pulmonary hypertension, and impaired quality of life
- In MAPPET-3, most cases of clinical deterioration occurred within the first five days

TREATMENT OF SUBMASSIVE PE

- Systemic anticoagulation is recommended over systemic or catheter-directed thrombolysis (CDL) by the American College of Chest Physicians, American Heart Association, and ESC consensus statements for most patients with intermediate-risk PE.
- Intermediate-risk PE patients **deemed at increased risk of impending clinical deterioration** (based on vital signs, severity of RV dysfunction, tissue perfusion, or gas exchange) who have not yet developed hypotension may be considered for additional interventions, such as systemic thrombolysis, CDL, or catheter embolectomy.

THROMBOLYTIC THERAPY

- Systemic thrombolysis is given to achieve rapid clot resolution and restoration of pulmonary perfusion thereby improving ventilation/perfusion matching, and importantly relieving RV afterload, reducing pulmonary vascular resistance, and thereby improving hemodynamics
- Systemic thrombolysis however, is associated with an increase in hemorrhagic complications including intracranial hemorrhage (ICH)
- Main population for consideration: cardiac arrest with known or suspected PE, right-heart thrombus (RHT) or thrombus-in-transit, high-risk PE, and selected intermediate-high-risk PE cases with low risk of bleeding
- In **high-risk PE**, ST is recommended when there are no contraindications as it has been shown to reduce total and PE-related mortality and PE recurrence when compared to UFH alone.

TPA

Table 1 Key Characteristics of Thrombolytic Agents[23–26]

	Streptokinase	Urokinase	Alteplase	Reteplase	Tenecteplase
Generation	First	First	Second	Third	Third
Clot-specific?	No	No	Yes	Yes	Yes
Half-life (minutes)	12	7–20	4–10	11–19	15–24
FDA-approved for PE?	Yes	Yes	Yes	No	No

PE = pulmonary embolism; FDA = Food and Drug Administration.

Table 2 Contraindications to Systemic Thrombolysis[9,27]

Absolute*	Relative*
• Structural intracranial disease • Previous intracranial hemorrhage • Ischemic stroke within three months • Active bleeding • Recent brain or spinal surgery • Recent head trauma with fracture or brain injury • Bleeding diathesis	• Systolic blood pressure > 180 mm Hg • Diastolic blood pressure > 100 mm Hg • Recent bleeding • Recent surgery or invasive procedure • Ischemic stroke > three months previously • Anticoagulation • Traumatic cardiopulmonary resuscitation • Pericarditis or pericardial fluid • Diabetic retinopathy • Pregnancy • Age > 75 years • Low body weight (e.g., < 60 kg) • Female • African-American

SYSTEMIC THROMBOLYSIS ADMINISTRATION: SELECTION, DOSE AND ROUTE

- Alteplase (patients 65 kg or more) 10 mg IV bolus, followed by 90 mg IV infusion over 2 hours (the MOPPET trial used half-dose, i.e. total of 50 mg)
- For patients weighing less than 65 kg, the total dose should be adjusted so that it does not exceed 1.5 mg/kg
  - This total includes the 10 mg intravenous (IV) bolus dose and the following IV infusion (given over 2 hours)
- Once the initial hemostatic defect has partly resolved, with the APTT less than twice normal, use: unfractionated heparin 1000 units/hour IV infusion, adjusted with frequent APTT measurement to ensure therapeutic anticoagulation
- Use the peripheral IV route – no benefit to 'targeted' thrombolysis via CVC or PAC
- In patients with relative contraindications to ST, a reduced-dose of 50 mg over 2 hours has been suggested as an alternative to full-dose ST, with similar improvements in obstruction, perfusion, PA pressure, and RV size with fewer bleeding complications, although data supporting this approach is limited.

**There is no standardized approach on anticoagulation management during thrombolysis, but a reasonable approach is to hold UFH during the thrombolytic infusion and resume without a bolus once the PTT is less than twice control

THROMBOLYTIC THERAPY IN HIGH RISK PE

- Thrombolytic therapy leads to faster improvements in pulmonary obstruction, PAP, and PVR in patients with PE, compared with UFH alone; these improvements are accompanied by a reduction in RV dilation on echocardiography
- The greatest benefit is observed when treatment is initiated within 48 h of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for 6–14 days
- Unsuccessful thrombolysis, as judged by persistent clinical instability and unchanged RV dysfunction on echocardiography after 36 h, has been reported in 8% of high-risk PE patients

THROMBOLYTIC THERAPY IN HIGH RISK PE

- Thrombolytic therapy is an established treatment option for patients with high-risk pulmonary embolism
- In the setting of massive PE, the benefits of systemic thrombolysis generally outweigh the risks. Although contraindications exist for the administration of thrombolytic agents, their use should be avoided only in the presence of active, uncontrollable bleeding.
- Thrombolytics provide the greatest benefit if they are administered within 48 hours of symptom onset.
- PE patients with transient, less-severe signs of hypotension or shock, but who later experience sudden clinical deterioration, may still be considered for systemic thrombolytics

THROMBOLYTIC THERAPY IN SUBMASSIVE PE

- The use of thrombolytic therapy in patients with intermediate risk pulmonary embolism is **controversial** due to less clear delineation between benefits and risks
- The majority of evidence supporting use of thrombolytic therapy for intermediate risk pulmonary embolism focuses on minimizing treatment escalation, and expediting return to normal functional status with reduced risk of pulmonary hypertension, rather than demonstrating reduced mortality

PROS AND CONS OF SYSTEMIC THROMBOLYSIS FOR SUBMASSIVE PE

- Patients appear to feel better quicker
- Clots resolve faster (30% to 35% reduction in total perfusion defect at 24h, with minimal improvement if just anticoagulated) early reduction in PAP and RV strain
- Decreased recurrence of PE
- Decreased death or hemodynamic stability (composite endpoint) at 7 days (PEITHO trial)
- Improved functional outcome (unproven, TOPCOAT trial)
- Less long term pulmonary hypertension (MOPETT trial)
- Risk of intracerebral hemorrhage (2% in >75y group in PEITHO)
- Risk of other hemorrhage (major bleeding, i.e. transfusion needed, ~6% in PEITHO)
- Similar improvement at 7 days overall ((≈65% to 70% reduction in total defect regardless of whether thrombolysed or anticoagulated)
- Increased cost
- No mortality benefit proven (improved composite of mortality and haemodynamic stability in PEITHO, as yet unpublished)
- Catheter-directed thrombolysis, if available, may be safer and equally effective
- RV dysfunction can markedly improve over 24 to 48h with systemic anticoagulation (e.g. heparin) in some patients

Year	Design	Comparators	Primary Endpoint	Key Results
MAPPET-3[26]				
2002	Prospective, randomized, double-blind, placebo-controlled	Heparin + alteplase (n = 118) vs. heparin + placebo (n = 138)	In-hospital death or clinical deterioration requiring escalation of treatment at end of hospital stay or on day 30 after randomization, whichever occurred first	• Rate of primary endpoint significantly lower with heparin + alteplase than with heparin + placebo (11% vs. 25%, respectively; $P = 0.006$) • Rate of recurrent PE low in both groups • Bleeding incidence similar in both groups
TIPES[38]				
2010	Randomized, double-blind, placebo-controlled	Weight-adjusted, single-bolus tenecteplase (n = 23) or placebo (n = 28), both with heparin	Reduction of RVD at 24 hours	• Reduction of right-to-left ventricle EDD ratio at 24 hours was 0.31 for tenecteplase vs. 0.10 for placebo ($P = 0.04$) • Recurrent PE in one tenecteplase patient and in three placebo patients • Two major nonfatal bleeds with tenecteplase vs. one with placebo
MOPETT[27]				
2012	Prospective, randomized	Low-dose alteplase (10-mg bolus followed by 40 mg over two hours) + heparin vs. placebo + heparin	PHTN at 28 months	• Rate of primary endpoint significantly lower with alteplase + heparin vs. placebo + heparin (16% vs. 57%, respectively; $P < 0.001$) • No bleeding in either group

TOPCOAT[39]				
2014	Randomized, double-blind, placebo-controlled	Weight-adjusted, single-bolus tenecteplase (n = 40) or placebo (n = 43), both with heparin	Composite outcome: 1) death, circulatory shock, intubation, or major bleeding within five days, or 2) recurrent PE, poor functional capacity, or SF36 PCS score of less than 30 at 90-day follow-up	• Adverse outcome rate significantly lower with tenecteplase + heparin vs. placebo + heparin (15% vs. 37%, respectively; $P = 0.017$)
PEITHO[21]				
2014	Randomized, double-blind, placebo-controlled	Tenecteplase + heparin (n = 506) vs. placebo + heparin (n = 499)	Death or hemodynamic decompensation (collapse) within seven days after randomization	• Six patients in the tenecteplase group died vs. nine patients in the placebo group (1.2% vs. 1.8%, respectively; $P = 0.42$) • Extracranial bleeding occurred in 32 patients in the tenecteplase group vs. six patients in the placebo group (6.3% vs. 1.2%; $P < 0.001$) • Stroke occurred in 12 patients in the tenecteplase group vs. one patient in the placebo group (2.4% vs. 0.2%, $P = 0.003$)

CATHETER DIRECTED THERAPY

- When do we do this??
- Absolute **contraindications** to **catheter-directed** pharmacologic **thrombolysis** include active internal bleeding, cerebral infraction, neurological and eye procedures or head trauma within 3 months, and known intracranial tumor, aneurysm, or vascular malformation

PERT CONSORTIUM RECOMMENDATIONS: CATHETER DIRECTED THERAPY

Consider **catheter-directed thrombolysis (CDL) in:

- Intermediate-high risk PE with risk for clinical deterioration based on vital signs, severity of RV dysfunction, tissue perfusion, and/or gas exchange, and without absolute contraindication to thrombolysis.
- High-risk PE with relative contraindications to ST.

Consider **catheter embolectomy in:

- Intermediate high-risk PE with risk for clinical deterioration based on vital signs, severity of RV dysfunction, tissue perfusion, and/or gas exchange, with absolute or relative contraindications to thrombolysis.
- High-risk PE with absolute contraindications to ST.
- After failed ST or CDL.
- Thrombus-in-transit in the right atrium or right ventricle (AngioVac system).

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