Pulmonary Embolism (PE)

Pulmonary thromboembolism refers to obstruction in the pulmonary arteries due to a thrombus/emboli, tumor, air, or fat.

Acute PE refers to an emboli identified on radiographic imaging within 14 days of PE symptoms.

- Central PE: includes saddle and emboli located in the mains or lobar pulmonary arteries
    - A saddle PE is described as an emboli located in the main pulmonary artery that traverses the right and left pulmonary arteries
- Distal PE: emboli located in the segmental and subsegmental branches of the pulmonary arteries.

CLASSIFICATION AND ASSESSMENT

There is no universal classification system for PE severity and variation exists among international guidelines: American Heart Association (AHA), American College of Chest Physicians (ACCP), and European Society of Cardiology (ESC).

One of the major advantages of the ESC classification of PE is the focus on short term PE-related mortality.

- To integrate patients' clinical status and comorbidities, ESC guidelines recommend the best validated simplified Pulmonary Embolism Severity Index (sPESI) score.
    - *Any patient with a positive sPESI score is not low risk*.

sPESI score

Parameter	Points
• Age >80 yr	1 point
• History of cancer	1 point
• History of Chronic cardiopulmonary disease*	1 point
• HR >110 beats/min	1 point
• SBP <100 mm Hg	1 point
• Oxygen saturation <90% on RA	1 point

*Chronic cardiopulmonary disease (history of chronic lung disease, or history of heart failure, or history of both).

The location of the thrombus or clot burden seen on a CTA is in general not part of the risk stratification because not all of the central including saddle PEs are associated with RV dysfunction.

However, they should be considered in the making decision process because:

- The majority of patients with RV dysfunction have central PE
- In contrast, isolated clots at the segmental or more distal level are less commonly associated with RV dysfunction and an alternate cause should be considered when present

Mortality Risk Stratification (see algorithm 1)

	Shock	**sPESI**	**RV dysfunction or troponin elevation**
Low risk	No	0	None
Intermediate			
Low-risk	No	1 or more	Either one or none positive
High-risk-submassive	No	1 or more	Both positive
High Risk-massive	Yes	1 or more	Both positive

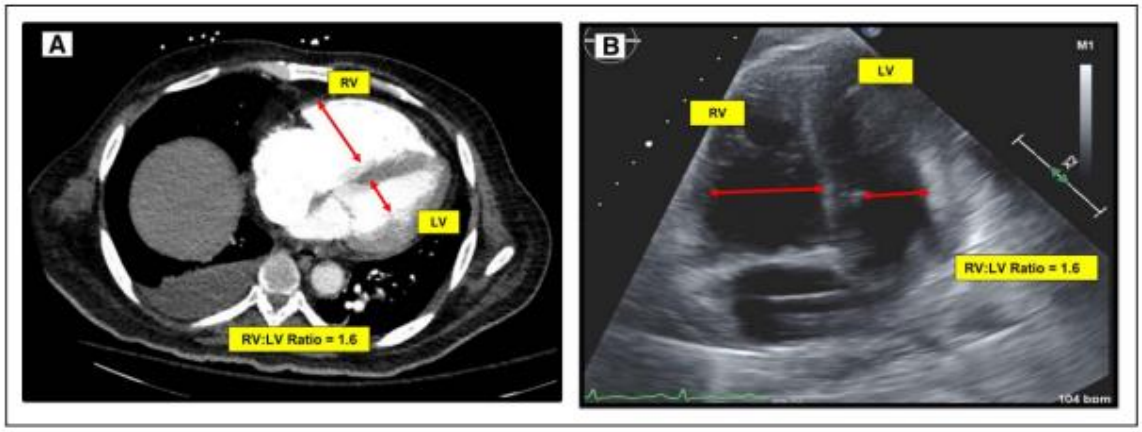
Shock: persistent SBP <90 mmHg x15 min after IVF not explained by other causes such as hypovolemia, sepsis, arrhythmia, or known baseline heart failure.

Systolic shock index (SSI): HR/SBP >1 predicts high mortality.

RV dysfunction - concomitant RV dysfunction on CTA and echocardiogram is a better predictor of an adverse outcome.

- CTA chest: RV:LV ratio >1 or reflux of contrast into the IVC and hepatic veins
- Echocardiogram:
    - RV dilatation.
    - RV free wall hypokinesis with apical sparing (McConnell's sign).
    - Interventricular septal flattening is a sign of severity.
    - Decreased RV function: TAPSE <1.6 cm (1.6-1.8 cm is borderline RV function).
    - Elevated estimated sPAP: TR max velocity >2.8 m/s suggest pulmonary hypertension.

Acute RV dilation associated with pulmonary embolism as seen on CT and TTE



Other than contrast in the liver, chest CTA chest is imprecise for RV assessment. CTA chest findings of RV enlargement should prompt echocardiography.

Biomarkers – Elevation of biomarkers carries an independent risk of short-term mortality and RV dysfunction.

- Myocardial injury-ischemia: elevated troponin
- RV strain - pressure overload: elevated BNP

DIAGNOSTIC STRATEGIES (see algorithm 2)

The first step is to determine the clinical probability of PE based on:

- Provider implicit sense
- Pulmonary Embolism Rule-out Criteria (PERC)
- Wells score

PE is excluded and no further tests are needed if PERC is negative (none of the 8 clinical items) and the provider has the implicit sense that is not PE.

PERC and Clinical Probability Scores

Wells score	Points
PE is the most likely diagnosis	3.0
Signs and symptoms of DVT	3.0
Heat rate >100 beats/min	1.5
In previous 4 wk, immobilization for >3 days or surgery	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Active cancer	1.0

YEARS items

- PE is the most likely diagnosis
- Hemoptysis
- Clinical signs of DVT

Geneva score	Revised points	Simplified points
Age >65 yr	1	1
Previous DVT or PE	3	1
Surgery or fracture within mo	2	1
Active cancer	2	1
Pain in one lower limb	3	1
Hemoptysis	2	1
Heart rate 75–94 beats/min	3	1
Heart rate ≥95 beats/min	5	2
Pain on lower-limb deep-vein palpitation and edema in one leg	4	1

PERC
(If any items are present, PERC test is positive)

- Age ≥50 yr
- Heart rate ≥100 beats/min
- Oxygen saturation <95% while patient is breathing room air
- Swelling in one leg
- Hemoptysis
- Surgery or trauma within past 4 wk
- Previous DVT or PE
- Hormone use

If PERC is positive OR the provider has the implicit sense that could be PE, calculate the Wells score and request D-dimmer

D-dimmer normal value

- Less than 0.5 mcg/ml or age-adjusted if over 50 years (less than age x 10)

Wells score

- Traditional clinical probability
  - Low <2, moderate 2 to 6, and high >6
- Simplified clinical probability
  - PE unlikely ≤4, PE likely >4

If Wells score ≤4, use D-dimer threshold of 1 mcg/ml if >4, use age-adjusted D-dimer threshold

PE can be excluded without imaging studies if there is a low likelihood for PE and D-dimer level of less than 1 mcg/mL or if there is not a low likelihood for PE and a D-dimer is below the age-adjusted threshold

- D-dimmer <1 mcg/mL and Wells score ≤4, **or**
- D-dimmer <age-adjusted D-dimmer cutoff and Wells score >4

Present guidelines recommend no need for D-dimmer in patients with high probability of PE (Wells score >6). However, new data suggests that D-dimmer may also be useful.

- Post hoc analysis of three European studies (PROPER, MODIGLIANI, and TRYSPEED)
  - Among the 12,300 patients included, 651 had high clinical probability of PE (31.3%). Seventy of the 651 patients (10.7%) had negative D-dimer levels (<0.5 mcg/mL age-adjusted) and none of them had a PE after follow-up

Based on above data PE can also be excluded if:

- D-dimer <0.5 mcg/ml and Wells score >6

If PE is suspected based on clinical probability, request chest imaging studies

- CTA chest
- Consider V/Q scan in patient with clear CXR and GFR <30 ml/min/m^3
  - Relatively low sensitivity for PE and lack the ability to identify alternative diagnoses and limited accuracy in patients with abnormal CXR

If PE is confirmed

- *Determine the associated mortality risk*
  - Calculate the sPESI score
    - Patients with sPESI ≥ 1 should undergo cardiac biomarker testing (troponin, pro-BNP) and imaging for RV dysfunction (RV/LV ratio or reflux of contrast into the IVC and hepatic veins on CT and RV size and function on echocardiography)
    - Routine performance of echocardiogram or laboratory testing (or both) in the presence of a low risk (sPESI score < 1) is usually not considered necessary because it is unlikely to direct management
  - Calculate the systolic shock index (SSI), assess respiratory status (oxygenation, tachypnea), and end-organ tissue perfusion

- *Determine the bleeding risk*
  - Presence of severe anemia or thrombocytopenia
  - Calculate VTE-BLEED and/or HAS-BLED scores
    - Although there are currently no well validated scoring systems that can be used to assess bleeding risk across interventional radiologic procedures, the VTE-BLEED and HAS-BLED scores (available in MDCalc) are often used in clinical practice as a general guide
      - VTE -BLEED score ≥2: higher bleeding risk
      - HAS-BLED >3: higher bleeding risk

- *Determine is the PE is central or distal*

TREATMENT OF ACUTE PE (see algorithms 3, 4, and 5)

An integrative approach using the associated mortality and bleeding risks and the localization of the emboli should be used in conjunction to drive the therapeutic decision-making process.

- Ideally, the goal of the initial therapy should be the prevention of shock, rather than "rescue" treatment

Hemodynamic support

- Cautious IVF – usually 250 -500 ml crystalloids in 15 -30 min.
    - Excessive IVF can promote ventricular interdependence and LV failure
- Inopressors with norepinephrine and vasopressin, occasionally cautious use of inodilator with dobutamine-milrinone.
- If refractory hypoxemia or hypotension or RV failure.
    - Pulmonary vasodilators – prostacyclins/Flolan.
    - Mechanical circulatory support devices.
        - VV ECMO for respiratory failure or VA ECMO if there is hemodynamic compromise due to LV dysfunction.
            - Allow the RV to beat in a decompressed state with minimal preload and afterload while augmenting systemic perfusion.
            - Relative to the severity of illness at presentation, survival and RV recovery are excellent.
        - MCS/Impella RP
            - The experience and data are insufficient to draw any meaningful conclusions about its safety and efficacy in the setting of acute PE, however, on individual cases may be useful.
            - An important limitation in the setting of acute PE is that by diverting RV preload into the obstructed pulmonary circulation, the RV may not be able to adequately empty against an increased afterload.

Anticoagulation

Parenteral

- Low molecular-weight heparin (LMWH)
- Unfractionated heparin (UFH)
    - LMWH is preferable to UFH unless GFR <30 ml/min/m^3:
        - Better bioavailability and longer half-life which allows a simplified dose and predictable anticoagulation response
        - Lower risk of HIT

Oral anticoagulation usually with DOACs and warfarin for antiphospholipid syndrome

Rapid reperfusion therapy

Thrombolysis

- Systemic with full or reduced dose
- Catheter directed thrombolysis (CDT)
    - The method of administration (eg, catheter-directed versus systemic) and dosing (full or reduced dose, infusion versus bolus) depend on factors including hemodynamic instability, risk of bleeding, oxygen requirement, and extent/localization of the emboli.

        - CDT is a preferable options compared to systemic thrombolysis because of the lower bleeding risk
        - CDT due to proximity to the thrombus is expected to have better efficacy than systemic thrombolysis
            - When a thrombolytic drug is used systemically, part of the drug flows away from the obstructing clot (ie, Venturi effect) toward the open nontarget vessels
            - CDT can potentially override the Venturi effect because a catheter with multiple side holes can be directly inserted under image guidance into the thrombosed target vessel to provide direct intraclot drug infusion
        - Bolus of systemic thrombolysis, even delivered over two hours, is nearly always faster than a catheter-directed approach

Thrombectomy

- Large bore mechanical thrombectomy (LBMT)
- Surgical

When the indication for rapid reperfusion therapy is established, it is reasonable to expect to start without a delay within a maximum of 60 minutes after its indication (not from PE diagnosis).

The aim of rapid reperfusion therapy is to stabilize the patient hemodynamically (decreased HR, increase in systemic BP, reduction of vasopressor doses) therefore hemodynamic stabilization should be regarded as clinical success. For this purpose:

- Patients require continuous monitoring of systemic BP, HR and EKG
- When using CDT or LBMT
    - It is important to carefully evaluate hemodynamic parameters (pressure in the right heart chambers and pulmonary artery) before and after the procedure to assess the effects of the therapy
    - Ultrasonography of proximal leg veins is indicated to rule out coexisting DVT at the vascular access site
- When using LBMT only a partial reduction in thrombotic burden of pulmonary arteries is required
    - Attempts to remove all clots during the procedure are not necessary and can be harmful, due to increased use of contrast media and potential risk of arterial wall damage

LOW RISK AND INTERMEDIATE-LOW RISK MORTALITY

Without contraindication for anticoagulation*

- Patients with low-risk PE and no other indication for admission can be treated in the outpatient setting with oral anticoagulation usually DOACs
- LMWH is preferable for inpatients
    - Parenteral anticoagulation can be switched to oral usually DOACs in 24-48 hours

With relative contraindications for anticoagulation

- Consult hematology for consideration of IVC filter versus anticoagulation

With absolute contraindications for anticoagulation

- IVC filter and consult Hematology

INTERMEDIATE HIGH-RISK (submassive) - It remains controversial
Current guidelines continue recommending systemic anticoagulation due to lack of randomized trials, different clinical endpoints, and lack of long-term follow-up data on the safety and efficacy of rapid reperfusion therapy but may be considered in the following conditions:

- Severe RV dysfunction and injury
- Extensive clot burden in patients with others high risk mortality factors
- Severe hypoxemia (particularly in those with a contribution from concomitant cardiopulmonary disease
- Acute PE who appears to be decompensating after starting anticoagulant therapy but are not yet hypotensive

Presently there is a trend favoring rapid reperfusion therapy rather than anticoagulation for patients with intermediate-high risk PE based on:

- Recognition that clinical progression to *massive high-risk PE* can occur rapidly
    - Early mortality for patients with intermediate-high risk PE with objective evidence of RV dysfunction ranges from 3–15% and clinical deterioration occurs in 5-18%
- Early rapid reperfusion therapy may prevent long-term complications and improve patient functional outcomes
    - Less RV dysfunction
    - Lower risk of developing chronic thromboembolic pulmonary disease (CTEPD) with or without pulmonary hypertension (CTEPH)
    - Lower risk of persistent dyspnea and reduced quality of life, collectively referred as post PE syndrome (PPS)
- Newer available data suggesting immediate and long-term benefits including clinical symptoms, oxygenation, hemodynamics, pulmonary pressures, and RV function when using rapid reperfusion therapy

The PEERLESS Trial

- RCT comparing LBMT versus CDT in patient with central PE and intermediate high risk mortality showed that both strategies were effective and safe without any meaningful difference between them
- LBMT compared to CDT had fewer episodes of clinical deterioration, shorter hospital stays, and fewer all-cause readmissions
- It did not include anticoagulation arm

Intravenous peripheral reduced-dose thrombolysis

- Pilot study using a peripheral IV infusion of 25 mg of tPA over 6 hours without bolus suggested that extended infusion of low-dose tPA is safe and effective in treating massive PE which makes this option attractive to be used in intermediate-submassive high risk PE

Ongoing trials

- PEERLESS II
    - Will test FlowTriever™ against anticoagulation alone in up to 1200 patients with intermediate-risk PE
- PEITHO-3 (Pulmonary Embolism International Thrombolysis)
    - To assess the efficacy and safety of a reduced dose of thrombolytic therapy in intermediate-high-risk acute PE

    - Patients will receive Alteplase as a 15 min intravenous infusion at a dosage of 0.6 mg/kg with a total dose not exceeding 50 mg or placebo and parenteral anticoagulation.
- STORM (System for the Treatment of Intermediate-high risk acute PE)
    - To evaluate the safety and efficacy of treating acute, intermediate-high risk pulmonary embolism with anticoagulants alone versus anticoagulants plus computer assisted vacuum thrombectomy (CAVT) with the Indigo® Aspiration System.

Our approach for intermediate-high risk (submassive):

Without contraindication for anticoagulation* or thrombolysis**
For patients who meet all the following criteria:

- RV dysfunction by echocardiogram/CTA chest
- RV injury with elevated troponin
- Shock index (HR/SBP) >1 or severe hypoxemia with O2 <90% on RA, or end-organ tissue hypoperfusion, or syncope or postural hypotension attributed to PE
- Duration of symptoms ≤14 days

1. Initiation of full systemic anticoagulation preferable with UFH (LMWH is not contraindicated)
2. Immediate rapid reperfusion therapy (necessary invasive procedures, eg, IV access, should be quickly performed while the infusion or IR team are being prepared and all other invasive procedures delayed until after treatment is completed)
    - Distal PE
        - Reduced-dose systemic thrombolysis
    - Central PE
        - LBMT or CDT at the discretion of IR or reduced-dose systemic thrombolysis
        - LBMT for patients who failed thrombolysis

When the indication for rapid reperfusion therapy is uncertain, for instance:

- Patients with RV dysfunction and elevated troponin with duration of symptoms ≤14 days but do not meet all the clinical criteria stated above

1. Observe the response to anticoagulation during the first 24-48 hours following the diagnosis.
2. We consider initiation of rapid reperfusion therapy after starting anticoagulant therapy for patients who appears to be decompensating but are not yet hypotensive
    - Severe tachycardia >120, tachypnea, borderline BP, poor oxygenation, tissue hypoperfusion such as decreased capillary refill, decreasing urine output, increasing lactate levels

On case-by-case analysis will consider rapid reperfusion therapy for patients with:

- Extensive clot burden associated with others high risk mortality factors
- Severe hypoxemia (particularly in those with a contribution from concomitant cardiopulmonary disease

For patients who do not meet the criteria stated above:

- Full anticoagulation preferable with LMWH

With relative contraindications for anticoagulation* or thrombolysis**

- Distal PE
  - Consider anticoagulation or reduced-dose systemic thrombolysis
  - IVC filter if anticoagulation or thrombolysis not used
- Central PE
  - LBMT and IVC filter

With absolute contraindications for anticoagulation* or thrombolysis**

- Distal PE
  - IVC filter
  - Consider anticoagulation
- Central PE
  - LBMT and IVC filter

HIGH RISK MORTALITY (massive)

Without contraindication for anticoagulation* or thrombolysis**

- Full or reduced-dose systemic thrombolysis

With relative or absolute contraindication for anticoagulation* or thrombolysis**

- Similar to intermediate-high risk mortality

***Contraindication for anticoagulation**

Absolute

- Any of the conditions stated as absolute contraindication for thrombolysis

Relative

- VTE -BLEED score ≥2 and or HAS-BLED 3

****Contraindications for thrombolysis**

Absolute

- Prior intracranial hemorrhage
- Known structural cerebral vascular lesion
- Known malignant intracranial neoplasm
- Ischemic stroke within 3 months (excluding stroke within 3 hours*)
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed-head trauma or facial trauma within 3 months

Relative

- Age >75
- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP >180 mmHg or DBP >110 mmHg)
- History of ischemic stroke >3 months prior
- Traumatic or prolonged (>10 minutes) CPR or major surgery <3 weeks
- Recent (within 2 to 4 weeks) internal bleeding
- Noncompressible vascular punctures
- Recent invasive procedure

- Pregnancy
- Active peptic ulcer
- Pericarditis or pericardial fluid
- Diabetic retinopathy
- Current use of anticoagulant
    - Warfarin with an elevated INR >1.7
    - Antiplatelet therapy including DAPT increases the risk of bleeding but, in isolation, is not contraindications to thrombolytic therapy
    - DOACs need to be assess on a case-by case basis

Following rapid reperfusion therapy, patients should be fully anticoagulated with UFH IV infusion for at least 24 hours to ensure that there is no delayed bleeding that would require immediate cessation of anticoagulation.

- Repeat echocardiogram in 24 hours to assess RV size and function
- After 24-48 hours of stability and clinical response patients can be switched to LMWH (preferable) or DOACs
    - For patients initiated with LMWH, it should be continued and switched to DOACs after 24-48 hours

CDT – LBMT: thrombolytic dosing and procedure

Thrombolytic dosing

When thrombolytics are used clinical improvement is typically noted within the first hour of the infusion.

- Guidelines recommend the use of tPA-Alteplase for continuous infusion
- TNK - Tenecteplase IV push is reserved for emergency cases as a lifesaving maneuver for suspected PE-induced or impending cardiac arrest

Choosing the dose

- Systemic thrombolysis
    - Full dose tPA-Alteplase: IV peripheral infusion of 100 mg over 2 hours
    - Reduced dose tPA-Alteplase:
        - IV peripheral infusion of 50 mg over 2 hours
        - IV peripheral IV infusion of 25 mg of over 6 hours

- CDT
    - The dose of tPA-Alteplase is usually 1 mg bolus followed by infusion at 1 mg/h per lung to complete 25 mg.
        - The duration of the infusions varies from over 4 to 6 hours to reduce the risk of bleeding to 24 hours
    - There are no universally accepted anticoagulation protocols for CDT. Most groups including the Society of Interventional Radiology recommend the use of subtherapeutic low-dose heparin during CDT. The regimen most commonly recommended is:
        - UFH infusion dose to 300 to 500 units/hour while infusing tPA
        - Following the infusion of tPA, the sheath is removed within 5 to 30 minutes, the UFH infusion is held for 30 minutes and restarted at full dose without a

bolus when the PTT is less than twice its upper limit of normal or UFH anti-Xa activity is ≤0.3 to 0.7 IU/mL
- If the patient is already receiving therapeutic LMWH, no anticoagulation is needed during CDT

CDT and LBMT procedure
Choosing how many catheters to place, whether a bolus of thrombolytic agent is administered before the infusion, and whether lysis should be combined with other clot removal procedures is individualized and dependent on the operator, their experience, and the location and volume of emboli. For instance:
- The presence of large central main pulmonary artery thrombus in addition to significant peripheral segmental/subsegmental thrombus might prompt debulking with percutaneous clot extraction devices followed by infusion with CDT lysis
- For those with just central main pulmonary artery embolus or right atrial clot in transit, mechanical clot extraction alone may be enough
- For thrombolytic infusions, one catheter is typically placed per affected lung (ie, two for bilateral PE and one for unilateral PE)

Monitoring and treatment of bleeding after thrombolysis
Signs of major bleeding (eg, hemodynamic compromise, mental status changes, reduction in hemoglobin [eg, 1 to 2 g/dL], need for transfusion, or copious amounts of bleeding) are indications to immediately stop the infusion and investigate, locate, and treat the source
- When considering reversal, the relative severity of the bleeding and the thromboembolic process must be weighed in view of the potential to exacerbate thrombosis. In general, if patients continue to have significant or refractory bleeding despite cessation of the thrombolytic agent:
  - Transfuse 10 units of cryoprecipitate with or without two units of fresh frozen plasma and then reassess
  - In addition, protamine, should be considered to reverse the effect of any heparin that may remain in the patient's plasma

Complications during percutaneous embolectomy include haemodynamic decompensation, respiratory failure, alveolar hemorrhage, pulmonary artery perforation, and hematomas at the vascular access site, all dependent on the technique and system that were utilized

EVALUATION AFTER INITIAL TREATMENT (see algorithm 6)
Hemodynamic, respiratory, and tissue perfusion status should be evaluated 24 to 48 hours after anticoagulation, 2 to 4 hours after the completion of thrombolysis, or immediately after LBMT
- A systolic shock index (HR/SBP) >1 or NEWS2 score of 7 or higher are a key trigger threshold for an emergency response
- A NEWS2 score of 5 or higher is a key trigger threshold for urgent clinical re-evaluation and action
  - NEWS2 score includes 7 physiological parameters:
    - Respiratory rate
    - Hypercapnic respiratory failure
    - Oxygen saturation
    - Temperature

- Systolic blood pressure
- Heart rate
- Level of consciousness

If treatment success, no escalation of therapy is required

- Initial treatment results in the improvement of initially compromised haemodynamic status, i.e., decrease in HR and RR, increase in systemic BP, O2 Sat, and improvement of peripheral perfusion

If treatment failure, consider rescue rapid reperfusion therapy

- Systemic thrombolysis after anticoagulation for distal PE
- LBMT for central PE after anticoagulation or thrombolysis for central PE
    - *It should be considered* if there is lack of improvement or worsening in initially hemodynamically stable PE patients indicated by a progressive increase in heart rate or respiratory rate, a progressive decrease in systemic blood pressure or oxygen saturation, or by worsening signs of organ hypoperfusion (decrease in urinary output, increase in lactate levels) over at least 15 minutes, even without meeting the criteria of an overt shock
    - *It is indicated* if, following the initiation of treatment, the patient develops overt cardiorespiratory instability necessitating CPR, mechanical ventilation, vasopressors, or mechanical circulatory support (ECMO or Impella RP)

SPECIFIC CONSIDERATIONS FOR TREATMENT

Cardiac arrest or impending arrest

Thrombolytic therapy for patients with PE-related cardiac arrest given simultaneously with unfractionated heparin infusion can be considered.

Tenecteplase-TNK single IV dose given over five seconds based on patient weight, as follows:

<60 kg – 30 mg
≥60 to <70 kg – 35 mg
≥70 to <80 kg – 40 mg
≥80 to <90 kg – 45 mg
≥90 kg – 50 mg

Inferior vena cava filter

Should be reserved for patients with:

- Acute PE and absolute contraindications for anticoagulation
- Recurrent PE despite therapeutic levels of anticoagulation

Clot-in-transit

- Free-floating thrombus in the RA or RV
- Thrombus in a PFO.

Treatment options include anticoagulation alone, thrombolysis, catheter-directed or surgical thrombectomy or combinations.

- Most groups prefer an individualized approach depending on hemodynamic status, size of the clot and bleeding risk

- For instance, patients with small thrombi and hemodynamically stable may be simply anticoagulated, alternatively, patient with a large thrombi in the RA or RV at risk for deterioration and the consequence of embolization may require catheter directed thrombectomy together with CDT

Subsegmental PE

Management of single or multiple subsegmental PE without more proximal PE or DVT is uncertain.

- Some guidelines suggest clinical surveillance instead of anticoagulation but a recent prospective cohort study involving such patients who were treated without anticoagulation therapy showed a higher-than expected incidence of recurrent VTE without anticoagulation.
- Clinical Surveillance vs. Anticoagulation for Low-risk Patients with Isolated Subsegmental Pulmonary Embolism (SAFE-SSPE) is an ongoing trial of clinical surveillance as compared with anticoagulation in this patient population

Pregnancy

Diagnosis

- CTA chest and V/Q scan present no measurable increased risk of fetal death or developmental abnormalities.
    - This is according to the International Commission of Radiologic Protection.
- Regarding fetal safety, CTA chest and V/Q scan are interchangeable, but some debate remains.
    - CTA chest may deliver higher doses of radiation to maternal breast tissue, which may be more susceptible to radiation-induced damage during the high mitotic period of pregnancy.
        - Therefore, the American Thoracic Society, the American College of Obstetricians and Gynecologists, and the American Society of Hematology acknowledge that the evidence is weak but recommend lung scintigraphy over CTA chest for pregnant individuals with normal CXR.
        - Conversely, the ESC believes that CTA chest no longer poses the cancer risk to maternal breast tissue that it once did.
- Regarding the V/Q scan, the perfusion-only component performs well and is safer than the combined V/Q. The perfusion-only scan is the recommended diagnostic strategy in pregnant patients.
- Negative D-dimer in pregnant patients with low suspicion exclude PE.
    - Although D-dimer becomes less useful with gestational age because levels increase during the course of a normal pregnancy, most groups agree with this statement using a cutoff value of < <500 ng/mL

Treatment

- The drug of choice in pregnancy for both prophylaxis and therapeutic anticoagulation is subcutaneous LMWH over IV or subcutaneous UFH
- Vitamin K antagonists should not be used antepartum because of teratogenicity, particularly in early pregnancy, but can be used during lactation
- DOAC are not as well studied and should not be used during pregnancy or lactation
- There are some data regarding the use of fondaparinux in pregnancy or during lactation, and it can be used in cases of heparin allergy or heparin-induced thrombocytopenia

Treatment for patients with life-threatening PE

- The principles are the same as for nonpregnant patients depending on the risk of bleeding:
    - Thrombolysis if there is no contraindication
        - While pregnancy is listed as a relative contraindication to thrombolysis, case reports and anecdotal evidence suggest successful use when reserved for life-threatening PE.
    - Thrombectomy for patient with contraindication for thrombolysis

VTE prophylaxis

- Indications:
    - History of a pregnancy related VTE
    - History of a VTE that was associated with another hormonal risk factor (such as estrogen or oral contraceptive related)
    - History of a single idiopathic, unprovoked VTE; and in those with a history of multiple VTEs, regardless of the cause
- Not indicated if previous VTE associated with a nonhormonal, temporary provoking risk factor such as trauma, immobility, surgery, and no additional risk factors
    - Low-dose LMWH throughout the pregnancy and generally for at least 6 weeks after delivery
    - LMWH is preferred over UFH because of convenience and reliability and lower risks of osteoporosis/osteopenia, and thrombocytopenia

POST ACUTE PE MANAGEMENT

Anticoagulation

- The presence and determination of reversibility of risk factors are required to guide duration of anticoagulation treatment

Predisposing factors for venous thromboembolism

Strong risk factors (OR > 10)
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

Moderate risk factors (OR 2–9)
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

Weak risk factors (OR < 2)
Bed rest >3 days
Diabetes mellitus
Arterial hypertension
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy
Varicose veins

Taken from EAC 2019 guidelines: European Heart Journal (2019) 00, 1-61

PE associated with reversible risk factors

- Surgery with general anesthesia lasting >30 minutes
- Confinement to bed in the hospital for ≥3 days due to an acute illness
- Major trauma or fracture

- Three months anticoagulation
- Consider six months anticoagulation if the PE was very large or associated with RV dysfunction or persistent residual symptoms, some experts recommend that treatment extend to 6 months

PE associated with persistent risk factors

- Indefinite anticoagulation
  - Full dose DOAC (i.e., rivaroxaban or apixaban) for 6 months.
  - Low-dose direct oral anticoagulant regimens (i.e., rivaroxaban or apixaban) after initial 6 months.
    - Not applicable for patients with cancer, those with anatomically extensive pulmonary embolism, or those at high risk for recurrent PE.

If a decision to continue anticoagulation indefinitely is made, it should be reassessed at least annually. Anticoagulation may need to be discontinued if the risk of bleeding increases, a major bleeding event occurs, or the patient prefers to stop treatment.

PE without identified risk factors (unprovoked)

- Indefinite anticoagulation.
- Time-limited treatment may be appropriate in some patients depending on bleeding risk and PE recurrent risk.

Adjuncts to anticoagulation

Aspirin and sulodexide therapy have been evaluated to prevent recurrence of VTE after discontinuation of anticoagulation treatment with the evidence favoring sulodexide

- Sulodexide is a mixture of glycosaminoglycans (GAGs) that enhances antithrombin III activity, inhibits thrombin formation, and promotes fibrinolysis.
- Studies have shown that sulodexide can reduce the recurrence of VTE with a low risk of bleeding.

Screening for hypercoagulable states

- Limited cancer screening guided by medical history, physical examination, basic laboratory tests and chest radiographs, and age-specific and sex-specific cancer screening within 1 year after a diagnosis of unprovoked PE.
- Need for thrombophilia testing to guide treatment in patients with reversible risk factors according to the 2023 ASH guideline:
  - Indications
    - Patients with VTE provoked by a nonsurgical major transient risk factor.
    - VTE provoked by pregnancy or postpartum or oral contraceptives.
  - Not indicated for patients with VTE provoked by surgery

Thrombo-embolic pulmonary disease (CTEPD)

Patients should be evaluated at 3 to 6 months after acute PE to assess for dyspnea or functional limitation, which may indicate the development of CTEPD with or without PH.

- CTEPD with or without PH was officially introduced, acknowledging the presence of similar symptoms, perfusion defects, and organized fibrotic obstructions in patients with or without PH at rest.

- Chronic thrombo-embolic pulmonary hypertension (CTEPH) is defined as:
    - mPAP greater than 20 mm Hg
    - Pulmonary capillary wedge pressure less than 15 mm Hg
    - And at least one (segmental) perfusion defect detected on a V/Q, scan, CTA, or pulmonary angiogram after 3 months of effective anticoagulation

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