European Society of Cardiology Guidelines for Management of PE

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Introduction and Epidemiology

PE is one of the most common forms of VTE with an estimated number of over 295,000 cases of PE occurring every year in six European countries (total population of 454.4 million) is globally the third most frequent acute cardiovascular syndrome behind MI and stroke. Every country or continent has one of the primary goals to diagnose and manage VTE. In recent years, the case fatality has decreased, likely due to increased incidence through the diagnosis of subsegmental PE.

Introduction and Epidemiology. contd.

The ESC has been updating its guidelines on a regular basis (2000, 2008, and 2014). Over the past 16 years, the annual incidence rate of diagnosis of acute PE has increased throughout the world (Figure 1). This is evidenced by a reported prevalence of 50% per diagnostic study in North America, with current confirmation rates as low as 5%. New data from the optimal diagnosis, assessment, and treatment of patients with PE, necessitated a revision of the guidelines in 2019. We researched the 2019 ESC guidelines for the diagnosis and management of acute PE, which were developed in collaboration with the European Respiratory Society.

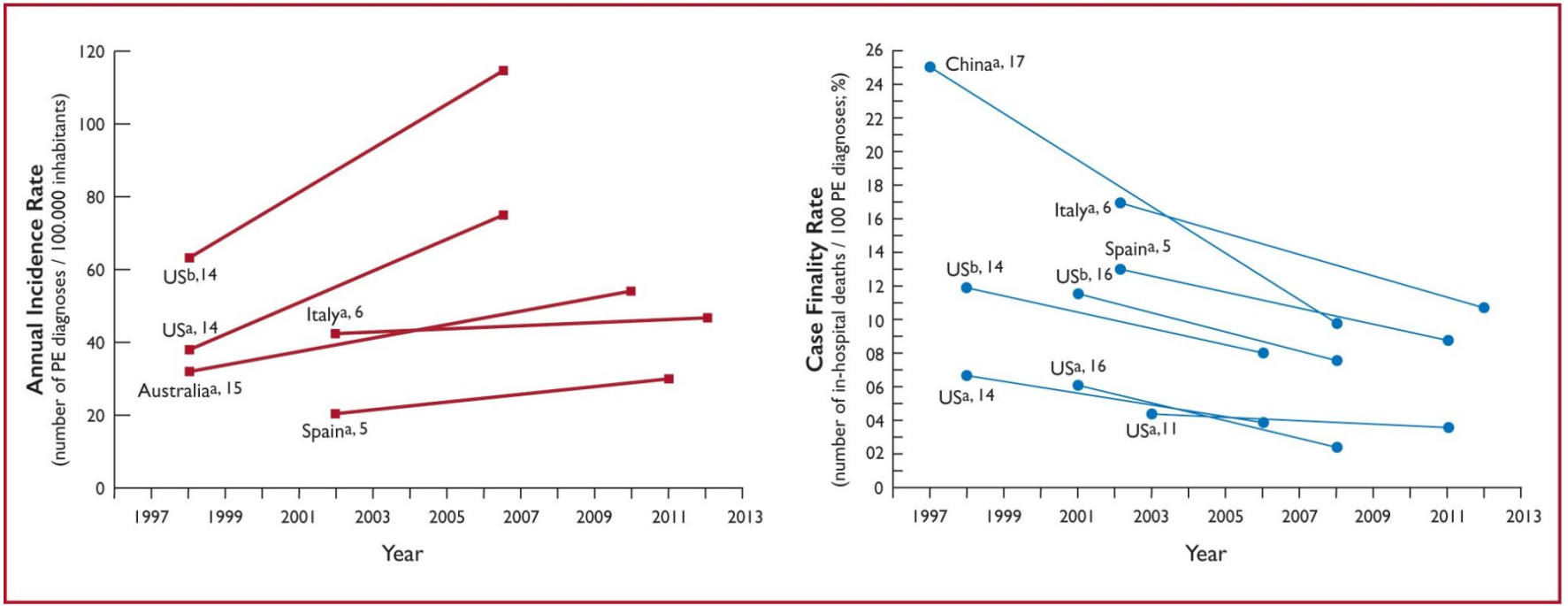

Figure 1: Trends in annual incidence rates (left panel) and case fatality rates (right panel) of pulmonary embolism around the world, based on data retrieved from various references. PE = pulmonary embolism; US = United States. a=PE listed as principal diagnosis. b=Any listed code for PE was considered.

Process of development of guidelines

- The guidelines were developed addressing the needs for cardiologists and allied professionals.
- Collecting high-quality observational data, at appropriate time intervals following the release of ESC Guidelines, will help evaluate the level of implementation of the Guidelines.
- The Members of this Task Force were selected by the ESC.

Process of development of guidelines, contd.

- Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines policy.
- A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio.
- Classes of recommendations (Table 1), and the changes in the guidelines from 2014 to 2019 (Table 2) were reviewed.

Table 1: Classes of recommendations

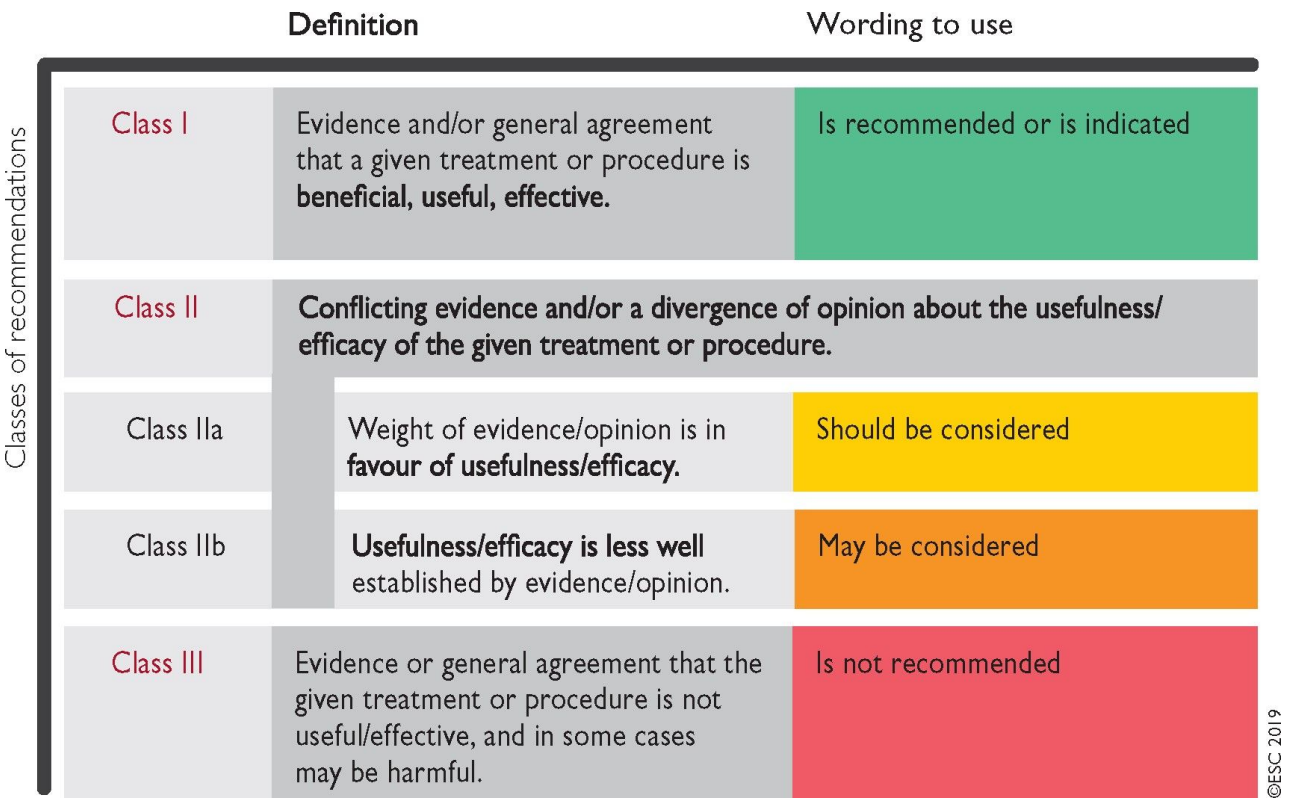

Table 2: Changes in the guidelines between 2014 and 2019

Recommendations	2014	2019
Rescue thrombolytic therapy is recommended for patients who deteriorate haemodynamically.	IIa	I
Surgical embolectomy or catheter-directed treatment should be considered as alternatives to rescue thrombolytic therapy for patients who deteriorate haemodynamically.	IIb	IIa
D-dimer measurement and clinical prediction rules should be considered to rule out PE during pregnancy or the post-partum period.	IIb	IIa
Further evaluation may be considered for asymptomatic PE survivors at increased risk for CTEPH.	III	IIb

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Risk Assessment of PE

- The risk challenge is the risk assessment is obtained by the pretest probability scores, that include the revised Geneva Score and the Wells rule.
- Expected rates of PE confirmation based on pre-test probability are 10% in low, 30% in moderate, and 65% in high pretest probability.
- The Pulmonary Embolism Rule-out Criteria (PERC) score is intended for patients in the emergency department who have such low pretest probability that diagnostic testing should not be initiated.

Risk Assessment of PE cont.

The PERC score includes the following parameters significantly associated with an absence of PE:

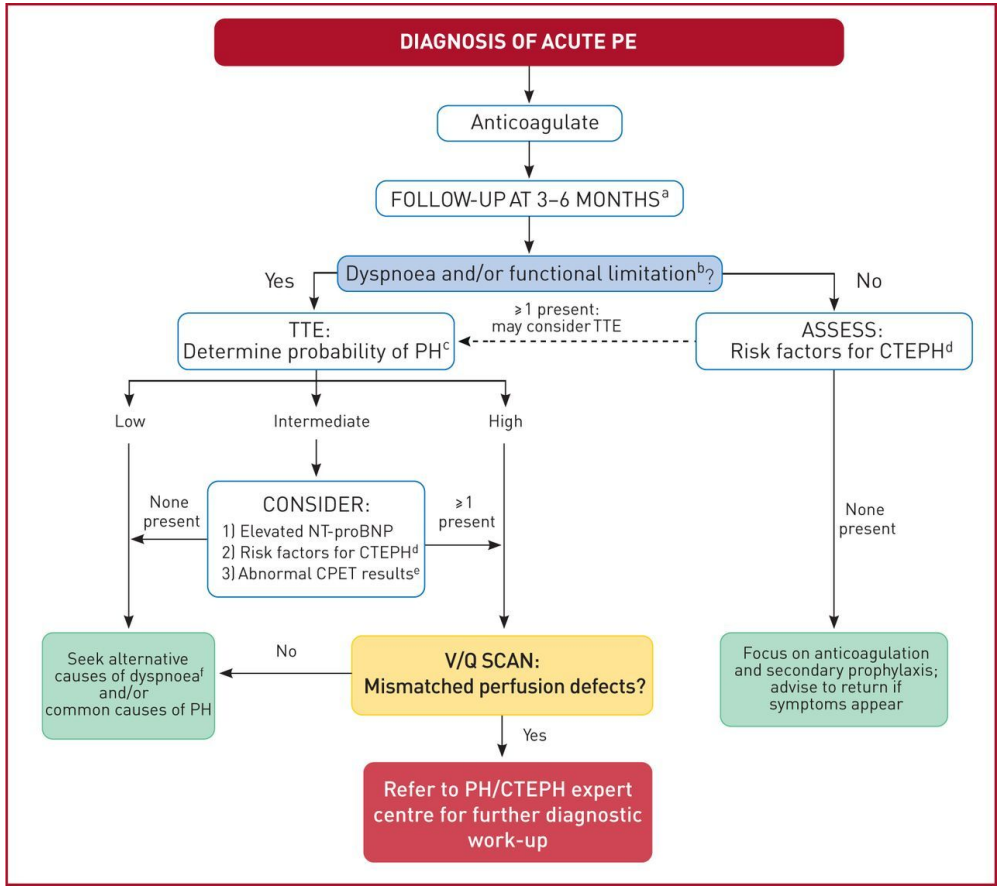
- Age <50 years
- Pulse <100 beats per minute
- Oxygen saturation >94%
- No unilateral leg swelling
- No hemoptysis
- No recent trauma or surgery
- No history of venous thromboembolism
- No oral hormone use.

Antithrombin levels

Patients with decreasing antithrombin (AT) levels are at greater risk of experiencing a thrombotic episode, which underscores the importance of finding the balance between VTE risk and AT levels.

Diagnosis of acute PE

Diagnosis of acute PE involves a careful evaluation of various diagnostic techniques such as d-Dimer, V/Q scan, chronic thromboembolic pulmonary hypertension (CTEPH), anticoagulation, transthoracic echocardiography (TTE), etc (Figure 2).



Diagnosis of acute PE (Figure 2)

D-dimer

- In patients with low to intermediate clinical probability of PE, D-dimer should be the initial test.
- If negative, no treatment is indicated.
- If positive, computed tomographic pulmonary angiography (CTPA) should be performed for definitive diagnosis.
- Age-adjusted D-dimer (age x 10 mcg/L) for patients older than 50 years should be considered to identify low-risk patients.

The Point-of-care D-dimers should be used only in patients with a low pretest probability because there is a reduced sensitivity (88%) compared with the standard laboratory-based assay (95%).

Hemodynamic instability

- Cardiac arrest
- Obstructive shock (systolic BP <90 mmHg or need for vasopressors to achieve BP ≥ 90 mmHg and end organ hypoperfusion
- Persistent hypotension (systolic BP <90 mmHg or systolic BP drop ≥ 40 mmHg lasting longer than 15 minutes and not due to another identifiable cause
- In patients with high clinical probability of PE, CTPA should be performed as the initial test.
- The detrimental effects of acute PE on the RV myocardium and the circulation are summarized in Figure 3.

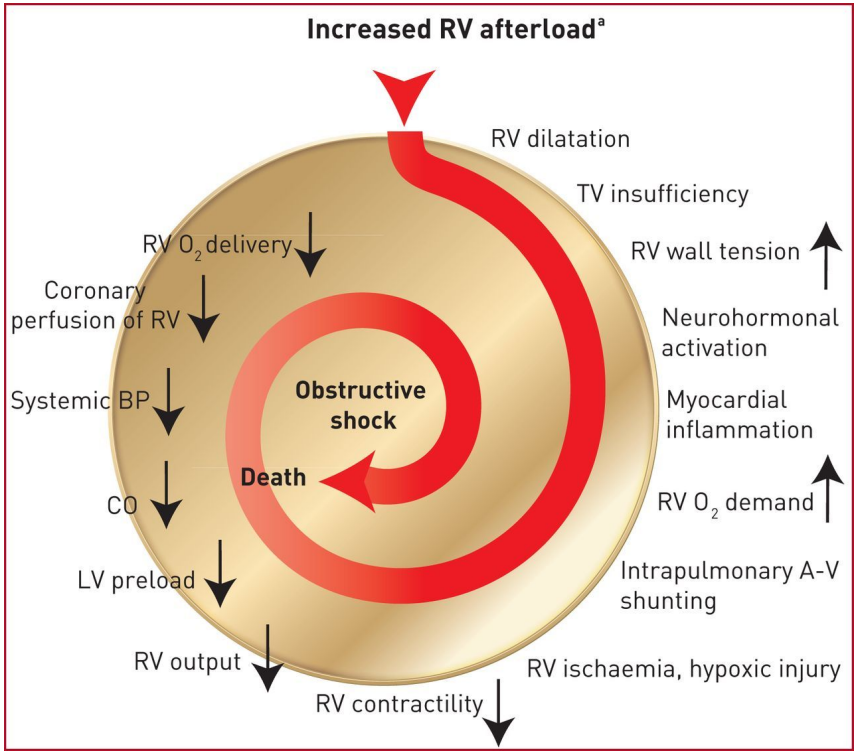


Figure 3: The detrimental effects of acute PE on the RV myocardium and the circulation

Imaging

- The diagnosis of VTE and PE should be accepted if compressive ultrasonography shows a proximal DVT in a patient with clinical suspicion for PE.
- Echocardiography (ECHO) alone cannot be used to rule out PE.
- ECHO is useful in suspected high-risk PE, in which the absence of ECHO signs of RV overload or dysfunction essentially rules out PE as the reason for hemodynamic instability.
- CTPA is the most accessible procedure for the diagnosis of PE, with an excellent specificity (96%)

Issues in imaging

- Effective radiation dose is 3-10 mSv, which should be of concern especially in young women for radiation exposure to the breast tissue.
- Renal dysfunction can be induced or accelerated due to the use of iodinated contrast

Imaging cont.

- Planar ventilation/perfusion (V/Q) scan is inexpensive with few contraindications and relatively low radiation exposure (2 mSv).
- It is often unable to provide an alternative diagnosis and is inconclusive in 50% of cases.
- Lung ventilation (V) and perfusion (Q) (V/Q) single-photon emission computed tomography provides the lowest rate of non-diagnostic tests (<3%), has few contraindications, and provides a binary result with low radiation (2 mSv).
- Pulmonary angiography is the gold standard, but it is an invasive procedure with the highest radiation dose (10-20 mSv).

Prognosis

- Prognostic assessment should include clinical parameters (simplified Pulmonary Embolism Severity Index (PESI) score, RV function, hemodynamics, and elevated biomarkers).
- Echocardiographic findings associated with a poor prognosis are an RV/left ventricular diameter ratio ≥1.0 and tricuspid annular plane systolic excursion <16 mm.
- An RV/left ventricular diameter ratio ≥1.0 on computed tomography is associated with a 2.5-fold increased risk of all-cause mortality and 5-fold increased PE-related mortality.

Prognosis, contd.

- High-sensitivity troponin has a 98% negative predictive value when <14 pg/mL for excluding an adverse in-hospital clinical outcome.
- B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide, and troponin have low specificity and positive predictive value for early mortality for normotensive patients with PE.
- Elevated lactate, high serum creatinine, and hyponatremia are some of the other laboratory markers of adverse prognosis.

Prognosis contd.

- Of the clinical scores integrating PE severity and comorbidity, the PESI weighted score that uses 7 variables including age, cancer, chronic cardiopulmonary disease, heart rate, systolic BP, and oxyhemoglobin saturation levels.
- Elevated lactate, high serum creatinine, and hyponatremia are some of the other laboratory markers of adverse prognosis.
- Of the clinical scores integrating PE severity and comorbidity, the PESI weighted score that uses 7 variables including age, cancer, chronic cardiopulmonary disease, HR, systolic BP, and oxyhemoglobin saturation levels.

Management of acute PE (Figure 4)

- Initial anticoagulation with high or intermediate probability PE while awaiting results of diagnostic testing.
- LMWH and fondaparinux are preferred over UFH because there are lower risks of major bleeding or heparin-induced thrombocytopenia.
- UFH should be reserved for hemodynamically unstable patients or patients awaiting reperfusion therapy.
- DOACs are noninferior to LMWH and vitamin K antagonists (VKA), with significantly lower rates of major bleeding
- Dabigatran parenteral anticoagulation for ≥5 days followed by dabigatran given orally 150 mg BID
- Rivaroxaban 15 mg BID for 3 weeks followed by 20 mg QD

Management of acute PE, contd.

- Apixaban 10 mg BID for 7 days followed by 5 mg BID
- Edoxaban UFH or LMWH for ≥5 days followed by 60 mg daily or 30 mg daily if creatinine clearance = 30-50 mL/min or body weight <60kg
- If VKA is given, UFH, LMWH, or fondaparinux should be continued for ≥5 days until the INR (2.5, range 2.0-3.0).
- Initial starting dose of warfarin may be 10 mg when <60 years in healthy patients, though 5 mg starting dose is suggested for all others.
- DOACs are contraindicated in severe renal impairment, during pregnancy and lactation, or with anti-phospholipid syndrome.

Management of acute PE, contd.

- Systemic thrombolytic therapy should be reserved for high-risk, hemodynamically unstable patients.
- Catheter-directed thrombolysis should be reserved for high-risk patients in whom thrombolysis has failed or is contraindicated.
- Surgical embolectomy, if the patient is not a candidate for thrombolytic therapy.
- Routine use of inferior vena cava filters is not recommended.
- The Hestia exclusion criteria integrate aspects of PE severity, comorbidity, and the feasibility of home treatment by means of a checklist of 12 questions that can be answered at bedside.

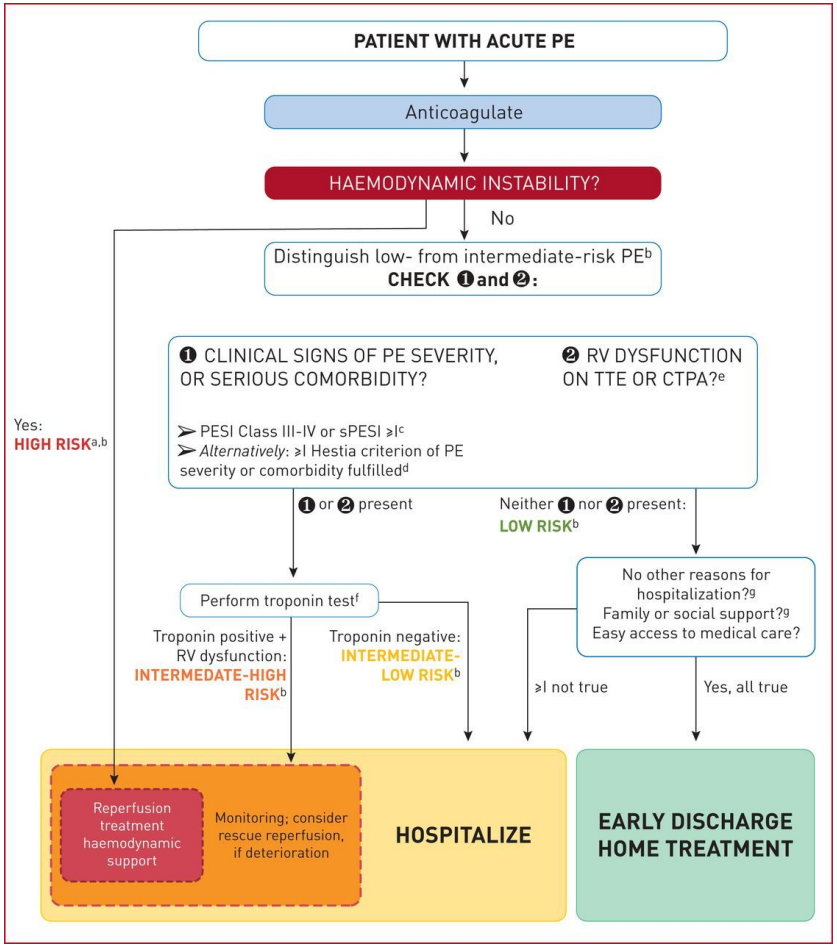


Figure 4: Management of acute PE

Duration of Anticoagulation

- All patients should receive 3 months of therapy.
- Discontinuation is recommended after 3 months if index PE/DVT is low.
- The risk of recurrence is similar when therapy is withdrawn at 3-6 months versus 12-24 months.
- Extended duration of anticoagulation increases bleeding risk but decreases recurrence risk by ≤90%.
- Indefinite anticoagulation for recurrent VTE not related to a major transient or reversible risk factor.
- Indefinite anticoagulation with VKA is recommended for patients with antiphospholipid syndrome.

Groups at Increased Risk of Recurrence (high at >8% per year)

- A strong (major) attributable transient or reversible risk factor, such as major surgery or trauma
- Persistence of a weak transient or reversible risk factor or a non-malignant risk factor for thrombosis
- Index episode that occurred in the absence of any identifiable risk factor
- One or more previous episodes of VTE and those with a major persistent prothrombotic condition
- Active cancer

Cancer Population

- LMWH reduces VTE recurrence by up to 40% compared to VKAs and should be considered over VKA for the first 6 months of treatment.
- All patients should be treated for ≥3-6 months with acute PE, especially with gastrointestinal cancers. Extended therapy for an indefinite period could be considered for patients who have not been "cured" of their cancer.
- Rivaroxaban or edoxaban should be considered for patients with low risk of bleeding and without gastrointestinal cancer.
- If PE is detected in patients without cancer, investigation into an underlying malignancy should be limited to history, exam, basic laboratory studies, and a chest X-ray if a CTPA was not performed.
- Asymptomatic PE should be treated the same way as symptomatic PE.

Pregnancy and PE (Figure 5)

- Risk factors include *in vitro* fertilization, prior VTE, obesity, medical comorbidities, stillbirth, pre-eclampsia, post-partum, hemorrhage, and cesarean section.
- LMWH is the treatment of choice for PE and VTE during pregnancy. The last dose of LMWH should be ≥24 hours prior to epidural anesthesia.
- DOACs are contraindicated in pregnancy.
- If pre-test probability is high, or low/intermediate with positive D-dimer, anticoagulation should be initiated with LMWH.
- A chest X-ray and/or compressive proximal duplex ultrasound should be performed following initial assessment.
- CTPA radiation is well below the fetal risk level and should be considered as the initial imaging test of choice for diagnosis with an abnormal chest X-ray.

Pregnancy and PE, contd.

- V/Q scans expose low levels of radiation and may be considered as an alternative to CTPA in patients with a normal chest X-ray.
- In high-risk patients (recent episode of PE), LMWH should be converted to UFH ≥36 hours prior to delivery, and the infusion should be stopped 4-6 hours prior to delivery.
- Reinitiation of anticoagulation should be decided by a multidisciplinary team and should occur no earlier than 4 hours after removal of an epidural catheter.
- Treatment should continue for ≥6 weeks after delivery, with a minimum total treatment duration of 3 months.
- LMWH and warfarin can be given to breastfeeding mothers; DOACs (Class III) are contraindicated.

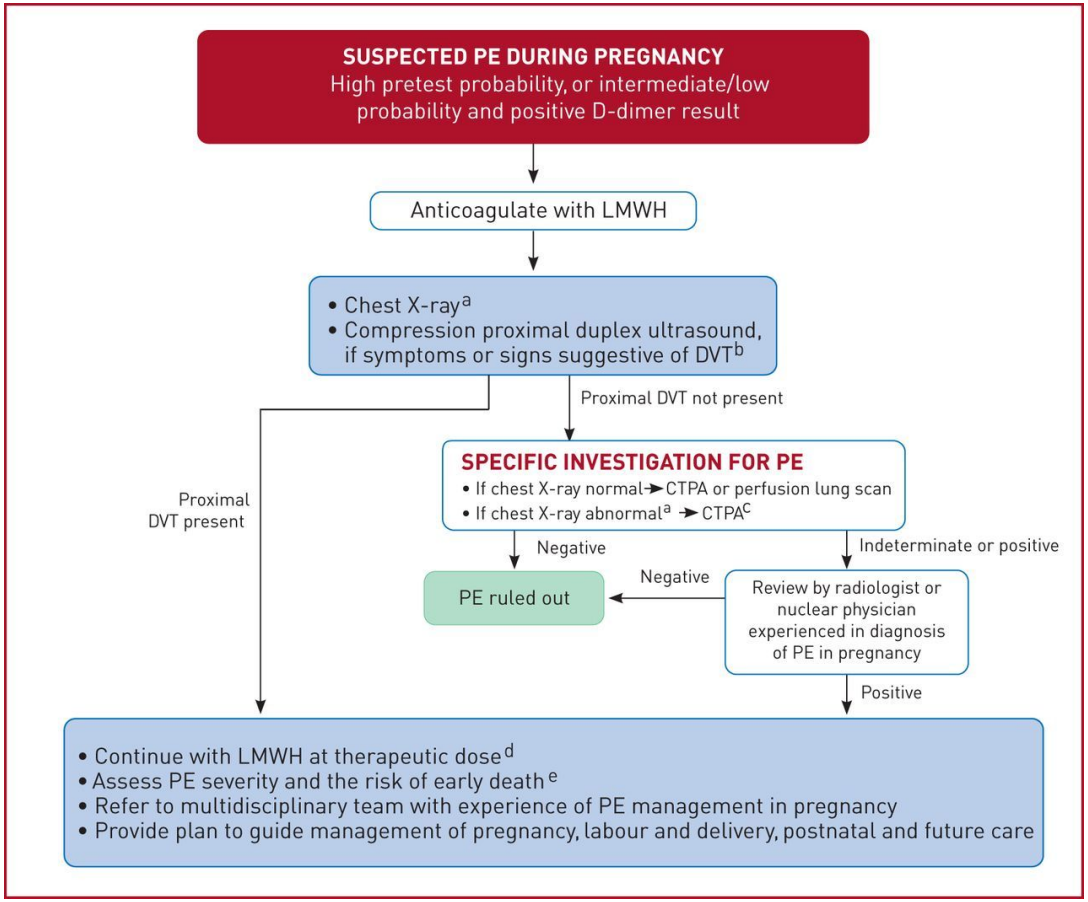


Figure 5: Pregnancy and PE

Follow-Up

- Three-six months after diagnosis of acute PE, with dyspnea assessed by either the Medical Research Council scale or World Health Organization functional scale.
- A transthoracic echocardiogram should be ordered if the patient has persistent dyspnea at 3-6 months.
- A V/Q scan should be considered at 3-6 months should there be concern for pulmonary hypertension (PH) to assess for chronic thromboembolic PH, with referral to a PH or chronic thromboembolic PH specialist if abnormal.

Conclusions

- PE ranks as one of the most prevalent forms of VTE, with an estimated 295,000 cases occurring annually across Europe.
- The incidence of PE has been steadily increasing over the past 16 years.
- The guidelines were prepared by collecting high quality data by a group of experts in the Task Force.
- Diagnosis is completed through D-Dimers, hemodynamic instability, and imaging.
- The prognosis assessment includes clinical parameters, PESI score, RVF, hemodynamics, and biomarkers.

Conclusions, contd.

- Management of PE is accomplished through the use of anticoagulants including LMWH, DOACs, systemic thrombolytic therapy, catheter-directed thrombolysis, and surgical embolectomy.
- It is recommended that patients are on anticoagulants for three months. Cancer patients should consider the use of rivaroxaban or edoxaban.
- Pregnant patients should consider LMWH, and DOACs are contraindicated. There is usually a 3-6 month follow up after the therapy begins.

Acknowledgements

We would like to thank our parents for their constant encouragement as well as Dr. Atul Laddu, the GTF team, and the management of IUA for giving us this opportunity.

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Practice Sessions

- Monday, April 8th at 21h00