



**TARGET AUDIENCE:** All Canadian health care professionals.

**OBJECTIVE:**

To define a diagnostic algorithm and treatment strategy for patients with acute pulmonary embolism.

**ABBREVIATIONS:**

<b>BNP</b>	brain natriuretic peptide
<b>CrCl</b>	creatinine clearance
<b>CT</b>	computed tomography
<b>CTPA</b>	computed tomography pulmonary angiogram
<b>CUS</b>	compression ultrasound
<b>DVT</b>	deep vein thrombosis
<b>ECG</b>	electrocardiogram
<b>HIT</b>	heparin-induced thrombocytopenia
<b>INR</b>	international normalized ratio
<b>LMWH</b>	low-molecular-weight heparin
<b>MRI</b>	magnetic resonance imaging
<b>PE</b>	pulmonary embolism
<b>PERC</b>	Pulmonary Embolism Rule-out Criterion
<b>rtPA</b>	recombinant tissue plasminogen activator
<b>RV</b>	right ventricle
<b>SBP</b>	systolic blood pressure
<b>SC</b>	subcutaneously
<b>UFH</b>	unfractionated heparin
<b>V/Q</b>	ventilation-perfusion
<b>VTE</b>	venous thromboembolism

**BACKGROUND:**

Although Canadian data are lacking, venous thromboembolism (VTE) is a common disease, affecting approximately 1-2 in 1,000 adults per year. Approximately one third of first VTE presentations are due to pulmonary embolism (PE) and the remainder are due to deep venous thrombosis (DVT) (see DVT: Diagnosis and DVT: Treatment guides). The incidence of PE has increased significantly since the advent of computed tomography (CT) angiography due to its widespread availability and diagnostic sensitivity. The majority of PEs originate in the proximal deep venous system of the leg, despite the fact that only 25-50% of patients with PE have

clinically-evident DVT. Active malignancy (see Cancer and Thrombosis guide), surgery (especially orthopedic; see Thromboprophylaxis: Orthopedic Surgery guide), immobilization > 8 hours, and estrogen use/pregnancy (see Thromboprophylaxis: Pregnancy guide) are transient provoking factors. Up to 50% of first-time PE is unprovoked (or idiopathic).

Symptoms of PE include sudden onset dyspnea, syncope, pleurisy. Signs of PE may include tachypnea, tachycardia, hypoxemia, hypotension, features of right ventricular dysfunction (distended jugular veins) and right ventricular strain on electrocardiogram (ECG) (S1Q3T3, right bundle branch block and T-inversion in leads V1-V4). Up to 10% of symptomatic PEs are fatal within the first hour of symptoms. Independent predictors of early mortality include hypotension (systolic blood pressure [SBP]  $\leq$  90 mmHg), clinical right heart failure, right ventricle (RV) dilation on CT/echocardiography, positive troponin and elevated brain natriuretic peptide (BNP). Early diagnosis and treatment of PE reduces morbidity and mortality.

Patients who present with a first PE are more likely to have subsequent VTE (risk varies between 3-10%/year depending on underlying cause; see Duration of Anticoagulant Therapy guide); however, recurrent events are more commonly PE (80%) rather than DVT.

## **DIAGNOSIS:**

Diagnostic algorithms have been suggested in major society guidelines. The constellation of symptoms and signs of PE are suggestive, but do not have the necessary specificity or sensitivity to rule in or out the diagnosis. When the diagnosis is entertained, clinical stability and pre-test probability will dictate the diagnostic approach (see **Figure 1**).

In patients without hypotension (SBP  $\geq$  90 mmHg), pre-test probability should be assessed by experienced clinician 'gestalt' or a validated clinical prediction rule (see **Table 1**). In cases of low to intermediate clinical probability, a negative D-dimer result rules out the diagnosis of PE. However, a positive D-dimer test must be followed up with a definitive test to confirm/refute the diagnosis of PE. Multidetector CT pulmonary angiography (CTPA) is widely available in Canada, and sufficiently sensitive and specific to exclude the diagnosis of PE when negative and to confirm it when positive in the context of a low pre-test probability.

When the pre-test probability is high, there is no value in checking a D-dimer level, as the post-test probability of a negative result is unacceptably high. Therefore, when the pre-test probability is high, one should go directly to CTPA to establish the diagnosis.

In patients with low clinical probability of PE, and in the absence of D-dimer assay testing, the diagnosis can be safely excluded using the PERC (**P**ulmonary **E**mbolism **R**ule-out **C**riteria) rule for pulmonary embolism.

In patients with renal failure or an allergy to contrast dye in whom a CTPA is felt to be contraindicated, it may be reasonable to start with lower extremity compressive ultrasound (CUS) looking for evidence of DVT (see DVT: Diagnosis guide). A positive result will mandate the

same treatment as PE, and no further investigations are indicated. Since up to 30% of patients may not have concurrent DVT with PE, a negative result does not rule out PE. Therefore, a ventilation-perfusion (V/Q) scan should be obtained in this instance.

In patients with hypotension who are too unstable to undergo CTPA, or if CTPA is not immediately available, an urgent echocardiogram should be obtained looking for evidence of clot in the RV or pulmonary arteries, or of right heart overload. If present, and in the absence of an alternative diagnosis, treatment for PE should be initiated. Presently, defined echocardiographic signs of PE are sensitive enough to exclude massive PE (i.e. PE associated with hypotension), if absent. However, RV dysfunction alone is not specific enough to exclude an alternate diagnosis (e.g. RV infarction); therefore, if feasible, confirmatory evidence of VTE should be sought with CTPA or CUS prior to initiation of therapy.

## **TREATMENT:**

Patients who have a high pre-test probability of having PE should be initiated promptly on anticoagulant therapy. Treatment can be withheld in patients with intermediate and low pre-test probabilities of PE, assuming definitive diagnostic testing will be completed within 4 or 24 hours, respectively. All patients with confirmed PE should be risk-stratified to determine whether they require in-hospital treatment or if outpatient management is sufficient. Patients presenting with hypotension (SBP  $\leq$  90 mmHg or a 40 mmHg drop from baseline) that is not responsive to a fluid challenge or due to another cause (e.g. tachycardia) carry a 15% risk of early mortality and should be admitted to an intensive care unit. Patients who are clinically-well and do not have evidence of myocardial injury or RV dysfunction are at low risk for early mortality (< 1%) and are appropriate for early discharge or home treatment.

The initial anticoagulant treatment is with a parenteral agent, typically unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), which serves as a bridge until warfarin therapy takes effect (international normalized ratio [INR]: 2.0-3.0). Warfarin should be initiated at the same time as parenteral therapy and the dose should be adjusted to achieve an INR range of 2.0-3.0 (target INR: 2.5). Parenteral therapy should be continued for at least 5 days and, ideally, until the INR is  $\geq$  2.0 for two consecutive days. Anticoagulation should be continued for at least 3 months (see Duration of Anticoagulant Therapy guide and **Table 2** below).

### **Low-molecular-weight heparin**

LMWH may be used as initial therapy in conjunction with warfarin or may be used as monotherapy for the full duration of treatment. It is the preferred long-term treatment for cancer patients. Most patients have little difficulty with self-administration. LMWH offers advantages over UFH, including better bioavailability when administered subcutaneously, longer duration of anticoagulant effect enabling once daily treatment, lower risk of heparin-induced thrombocytopenia (HIT), predictable anticoagulant effect allowing fixed dosing based on body

weight and renal function, less effect on bone metabolism and no requirement for laboratory monitoring.

## **AGENTS AND DOSING:**

### **Low-molecular-weight Heparin**

Dalteparin (Fragmin®): 200 U/kg subcutaneously (SC) once daily or 100 U/kg SC twice daily (once daily dosing preferred).

Enoxaparin (Lovenox®): 1 mg/kg SC twice daily.

Tinzaparin (Innohep®): 175 U/kg once daily.

For patients with severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min), clinical data on the use of LMWH for the treatment of PE are limited and LMWHs should be avoided. If used, the dose of LMWH should be reduced by approximately 50% and monitoring with anti-factor Xa levels may be required.

### **Unfractionated Heparin**

UFH use in the treatment of PE is limited by a narrow therapeutic range, inter-individual variation in anticoagulant effect and the increased risk of HIT. The use of UFH should be limited to: (1) patients with severe renal insufficiency (CrCl < 30 mL/min), in whom LMWHs should be avoided; (2) patients at increased risk for bleeding, in whom rapid reversal of the anticoagulant effect may be needed; and (3) patients who receive thrombolytic therapy. In addition, UFH is an alternative to LMWH if LMWH is not feasible because of cost considerations or intolerance.

UFH can be used intravenously, administered to achieve an activated partial thromboplastin time (aPTT) of 1.5 to 2.0 times the control aPTT. UFH can also be given subcutaneously with a 333 U/kg initial dose, followed by 250 U/kg twice daily, and without aPTT monitoring.

### **Thrombolysis**

In most patients with PE the risk of major bleeding outweighs the benefit from thrombolysis, except those who present with massive PE, which is defined by persistent hypotension or respiratory failure, where the short-term mortality is > 15%. Therefore, until further data are available, thrombolysis should be reserved for patients with ongoing hypotension (SBP  $\leq$  90 mmHg), respiratory failure. When used, thrombolysis is given as follows: recombinant tissue plasminogen activator (rtPA) 100 mg over 2 hours or 0.6 mg/kg as a bolus. Intravenous UFH should be used after thrombolytic therapy. Patients still require anticoagulation for at least 3 months after receiving thrombolytic therapy. Intravenous UFH should be used after thrombolytic therapy. Patients still require anticoagulation for at least 3 months after receiving thrombolytic therapy. Intravenous UFH should be used after thrombolytic therapy. Patients still require anticoagulation for at least 3 months after receiving thrombolytic therapy.

## **Warfarin**

Initial treatment with warfarin should be combined with an immediate-acting agent such as LMWH for at least 5 days and until INR is at least 2.0. Initial dosing is typically 5 mg once daily, but the therapeutic dose is highly variable. The elderly, infirm and those with low body-weight typically require a lower dose. Initial dosing with 2-3 mg should be considered in such patients. Frequent monitoring is required until a stable, in-range INR is reached, after which monthly testing is usually adequate. Warfarin is associated with many drug and food interactions that affect INR. Alterations in concomitant medications and new concurrent illness should be associated with INR testing. Patients should not be encouraged to reduce intake of foods high in vitamin K, but maintain a consistent, balanced diet.

## **Dabigatran (Pradaxa®), Rivaroxaban (Xarelto®), Apixaban (Eliquis®)**

Large phase 3 studies that have been completed, or are ongoing, demonstrate benefit of these agents for the initial (rivaroxaban, apixaban), acute (all agents) and extended (all agents) treatment of PE. As of mid-2013, rivaroxaban is approved for the treatment of patients with PE (See Rivaroxaban guide). The recommended dosing is 15 mg twice daily for the first 21 days, followed by 20 mg once daily for the duration of treatment.

## **SPECIAL CONSIDERATIONS:**

### **Catheter-directed thrombolysis for massive PE**

In some hospitals where there is requisite expertise, catheter-directed thrombolysis may be considered since it is able to deliver a thrombolytic agent directly into one or more large emboli and can rapidly relieve pulmonary artery occlusion. Such treatment should be undertaken in consultation with a specialist.

### **Chronic thromboembolic pulmonary hypertension**

Chronic thromboembolic pulmonary hypertension is present in up to 3% of patients after an episode of symptomatic or asymptomatic PE. There is no high-quality evidence to assist with treatment decisions in this area. Therefore, management of such patients should be guided in consultation with a specialist in thrombosis. Pulmonary thrombendarterectomy may reduce pulmonary pressures and symptoms of pulmonary hypertension, but mortality for such surgery is about 5% even in the most experienced centres. Subsequent VTE events are considered to be extremely high-risk due to already reduced cardiopulmonary reserve and, therefore, these patients should be strongly considered for indefinite anticoagulant therapy.

### **Patients contraindicated for anticoagulation**

See Vena Cava Filter guide.

## **Pregnancy**

See Thromboprophylaxis: Pregnancy guide.

## **Cancer**

See Cancer and Thrombosis guide.

## **PEDIATRICS:**

Diagnosis should be confirmed with a V/Q scan, CT with contrast or magnetic resonance imaging (MRI). However, the sensitivity and specificity of these diagnostic methods in children has not been determined. Treatment may be initiated with either age-appropriate UFH or LMWH followed by 3 months (etiology determined), 6-12 months (idiopathic) or long-term (recurrent) of either LMWH or vitamin K antagonists. Life-threatening PE should be treated with thrombolysis, either pharmacologic (rtPA) or mechanical, or with thrombectomy. After thrombolytic therapy, conventional anticoagulation should be administered as above. See Pediatrics guide.

## **REFERENCES:**

Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011;123:1788-1830.

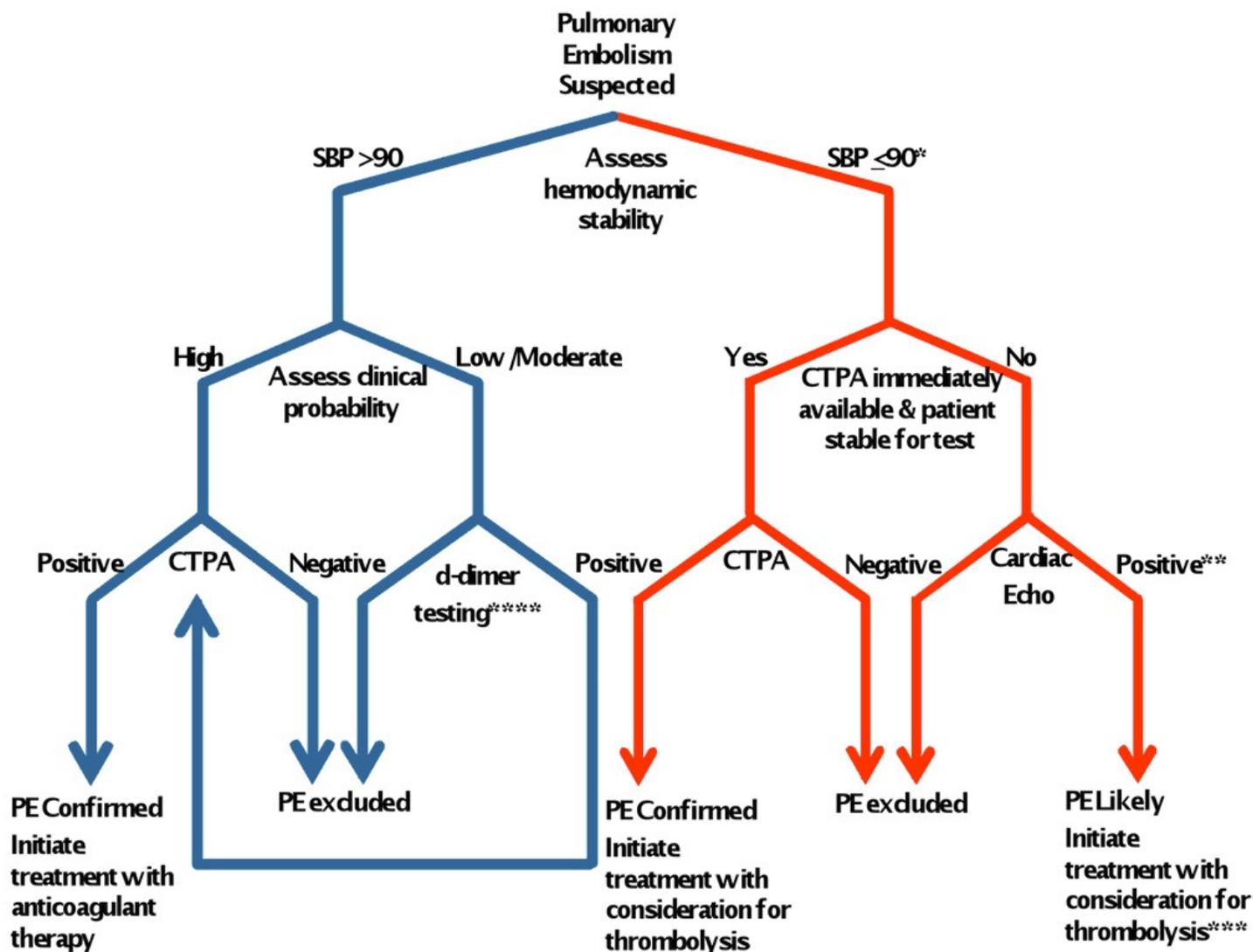
Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9<sup>th</sup> ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):e419S-494S.

Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008;6:772-780.

Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008;29:2276-2315.

Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med* 2001;135:98-107.

Figure 1: Suggested Diagnostic Algorithm for Suspected Pulmonary Embolism



- \* Consideration for thrombolysis without diagnostic test confirmation should be made if the patient is very unstable or moribund
- \*\* Features on echocardiography suggestive of massive PE include RV overload and RV/pulmonary artery thrombus
- \*\*\* If patient condition stabilizes, consideration for CTPA can be given to confirm diagnosis
- \*\*\*\* Excluding a diagnosis of PE with a moderate pre-test probability requires the use of a *highly sensitive* d-dimer assay

**Table 1: Wells Score\* for PE**

Variable	Points
Clinical signs and symptoms of DVT	3
No alternative diagnosis more likely than PE	3
Heart rate > 100 beats/minute	1.5
Immobilization for > 3 days or surgery within 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1
Malignancy	1

\*Total Score: Low Risk: 0 to 1.5; Intermediate Risk: 2 to 5.5; High Risk:  $\geq 6$

**Table 2: Recommendations for Extended Treatment for PE or DVT**

Categories of VTE	Duration of Treatment
Provoked by a transient risk factor*	3 months
First unprovoked <sup>†</sup> VTE	Minimum of 3 months and then reassess
Proximal DVT or PE with no or only minor risk factors for bleeding	Long-term therapy with annual review
Isolated distal DVT	3 months <sup>‡</sup>
Second unprovoked VTE	Minimum of 3 months and then reassess. For patients with no or only minor risk factors for bleeding, long-term therapy with annual review <sup>¶</sup>
Cancer-associated VTE	Minimum of 3 months and then reassess. Continue if active cancer (overt evidence of cancer) or continuing to receive anti-cancer therapy

\* Transient risk factors include: surgery, hospitalization or plaster cast immobilization, all within 3 months; estrogen therapy, pregnancy, prolonged travel (e.g. > 8 hours), lesser leg injuries or immobilizations more recently (e.g. within 6 weeks). The greater the provoking reversible risk factor (e.g. recent major surgery), the lower is the expected risk of recurrence after stopping anticoagulant therapy.

<sup>†</sup> Absence of a transient risk factor or active cancer.

<sup>‡</sup> This decision is sensitive to patient preference.

<sup>¶</sup> Indefinite therapy is suggested if there is moderate risk of bleeding, and 3 months is suggested if there is a high risk of bleeding; both of these decisions are sensitive to patient preference.

*Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.*