INTRODUCTION

Venous thromboembolism (VTE) is a clinical entity which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a common medical condition affecting up to 117 patients per 100,000 populations annually.¹ The diagnosis of VTE is often difficult and is frequently missed. Mortality in untreated PE is approximately 30%, but with adequate anticoagulant treatment, this can be reduced to 2–8%.² The purpose of this monograph is to focus on the diagnosis and treatment of VTE, including PE and DVT in the emergency department (ED).

DIAGNOSIS OF VENOUS THROMBOEMBOLISM

The approach to the diagnosis of deep venous thrombosis and PE is ultimately dependent upon the clinical suspicion of VTE. Specifically, the choice of diagnostic tests depends on the clinical probability of PE, condition of the patient, availability of diagnostic tests, risks of iodinated contrast material, radiation exposure, and cost.³ Recently, diagnostic recommendations based upon the results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II trial and other studies have been published.³-⁵ These recommendations include both evidence-based recommendations and information related to radiation exposure³,⁶,⁷ costs and studies of the positive predictive values of clinical probability assessments³,⁴,⁷-⁹

Clinical Probability Assessment

The first step in approaching a patient with suspected VTE is to assess the probability of VTE as low or high. This assessment should be made prior to any imaging tests and preferably using an objective method.³ While physicians experienced with PE management have shown similar results with either empirical assessment³,¹⁰ or clinical probability assessment scoring indexes,⁸,¹⁰ clinical probability assessment scoring indexes may be better for physicians who are less experienced with the assessment of PE.³

OBJECTIVES:

1. Describe the diagnostic approach to developing a clinical probability of acute venous thromboembolism, including deep venous thrombosis and pulmonary embolism.
2. Expose readers to the latest evidence-based clinical practice guidelines on the treatment of acute venous thromboembolism.
3. Describe the management approach to potential massive pulmonary embolism in the emergency department.
A number of clinical probability assessment tools for PE have been developed, but two of the best studied are relatively simple rules that provide dichotomous risk of either PE “likely or not” (Wells criteria9 (Table 1)) or whether the risk of PE is “safe or not” to depend upon D-dimer testing (Charlotte rule11 (Figure 1)). If the patient is deemed either “unlikely” or “safe”, then the patient is considered to have a low or moderate clinical probability of PE. Conversely, if the patient is deemed “likely” or “unsafe,” then the patient should be considered to have a high clinical probability of PE. In addition, there is a similar clinical probability rule developed by Wells for the evaluation of DVT (Table 2).12

### Table 1. Simplified Wells Criteria for Pulmonary Embolus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of deep vein thrombosis (minimum of leg swelling and pain with palpation of the deep veins)</td>
<td>3.0</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than pulmonary embolism</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt; 100/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization (&gt;3 d) or surgery in the previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous pulmonary embolism or deep vein thrombosis</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy (receiving treatment, treated in the last 6 months or palliative)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<| <= 4 points: Clinical probability of pulmonary embolism unlikely  |
| > 4 points: Clinical probability of pulmonary embolism likely  |

Adapted with permission from Gibson NS, et al. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. Thrombosis and Haemostasis 2008;99:1:229-234.

### Very Low Risk Patients

A recent multicenter ED study suggests that low clinical suspicion be further coupled to the selected risk questions of the pulmonary embolus rule-out criteria (PERC).13 Of 8,138 patients tested for PE, 20% could have been classified as very low risk, defined as a gestalt pretest probability <15% with a negative PERC score (Table 3). In this very low risk subgroup, 1.0% (95% CI 0.6 –1.6%) had VTE within 45 days.

### Table 2. Wells Criteria for Deep Venous Thrombosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (receiving treatment, treated in the past six months, or palliative care)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for three days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

<| <= 1 points: Clinical probability of DVT unlikely  |
| > 1 points: Clinical probability of DVT likely  |

Adapted with permission from Scarvelis D, et al. Diagnosis and treatment of deep-vein thrombosis. CMAJ 2006;175(9):1087-92.
Table 3. Pulmonary Embolism Rule-Out (PERC)

- **FOR PATIENTS WITH LOW SUSPICION (<15% probability)
- MUST ANSWER "NO" TO ALL THESE QUESTIONS:
  1. Is the patient >48 years old?
  2. Is the pulse rate >99 beats/min?
  3. Is pulse oximetry reading <95% on room air?
  4. Is there a history of hemoptysis?
  5. Is the patient taking estrogen?
  6. Does the patient have a prior diagnosis of VTE?
  7. Has the patient had previous surgery or trauma w/n 4 weeks?
  8. Does the patient have unilateral leg swelling?


Approach to Patients with Low or Moderate Clinical Probability of VTE D-dimer Testing

The quantitative rapid ELISA, with a sensitivity of 95%, in general has shown the most clinically useful values among the various D-dimer assays. The posttest probability of PE ranges from 0.7% to 2% with a normal D-dimer rapid ELISA result and objective low probability clinical assessment for VTE. Thus, no further testing is required if the D-dimer is normal in a patient with a low probability clinical assessment. The PIOPED investigators have recommended that no further testing be done if the D-dimer is normal in patients with both low and moderate probability clinical assessment (Figure 2).

CT Imaging of Low and Moderate Probability Patients with Abnormal D-dimer Results

An abnormal D-dimer indicates the need for further testing if PE is suspected. Popular imaging options include contrast-enhanced multidetector computerized tomography (CT) pulmonary angiography and CT venous phase imaging of the proximal leg veins (CT venography).

The recommendations of the PIOPED investigators are that treatment is indicated in all patients with main or lobar pulmonary emboli at CT angiography. Additional imaging options in these patients include venous ultrasound (either single or serial), MRI venography and pulmonary digital subtraction angiography. Treatment with anticoagulants while awaiting the outcome of further diagnostic tests may be appropriate, particularly if the tests cannot be performed immediately.

If the creatinine clearance is reduced, proceeding with CT imaging depends on clinical judgment. Nonionic contrast materials may be less nephrotoxic than ionic contrast material. Propylactic hydration with sodium bicarbonate 3 mL/kg/hr 1 hour before and 1 mL/kg/hr for 6 hours after contrast material exposure reduces the risks of renal dysfunction in patients with renal insufficiency. Alternative pathways to CT scanning in patients with renal insufficiency include D-dimer testing with clinical assessment, venous ultrasound, and VQ scans.
Approach to Patients with a High Clinical Probability of VTE
A D-dimer test is not helpful in high probably patients because a negative D-dimer result does not exclude PE in more than 15% of patients with a high probability clinical assessment.\(^\text{14}\)

If results of CT angiography were positive in a patient with a high probability clinical assessment, PE was present in 96% in the PIOPED II study.\(^\text{3,4}\) If CT angiography results were negative in a patient with a high probability assessment, PE was present in 40% of patients with high clinical probability. If both CT angiography and venography results were negative, PE was present in only 18%.\(^\text{3,4}\)

Alternative Diagnostic Pathways for VTE

**VQ Scans**
Ventilation-perfusion (VQ) lung scans can be considered for further testing of PE. A perfusion lung scan alone can be considered in patients with normal or nearly normal chest radiographs.\(^\text{17}\) More recently, a ventilation-perfusion scan was shown to be diagnostic in 91% of patients suspected of having PE and with a normal chest radiograph.\(^\text{18}\)

A low probability ventilation-perfusion scan result combined with a low probability clinical assessment showed PE in only 4% of patients in the PIOPED study.\(^\text{9}\) A high probability ventilation-perfusion scan result combined with a high probability clinical assessment showed PE in 96% of patients.\(^\text{3,9}\)

Additional considerations for primary VQ scanning could include reduced radiation exposure. While female breast radiation is a concern, the risk of death from undiagnosed PE far exceeds the risk of radiation-induced malignancy.\(^\text{3}\) In a recent survey, most (69%) of PIOPED II investigators still recommend VQ as the primary imaging modality in women of reproductive age with pulmonary CT scans recommended as primary imaging by only 31% of the PIOPED II investigators.\(^\text{3}\)

**Venous Ultrasound**
Venous ultrasound detects deep venous thrombosis in 13%–15% of patients suspected of having PE\(^\text{19}\) and in 29% of patients with proved PE.\(^\text{3}\) Thus, a venous ultrasound examination prior to imaging with CT angiography or CT angiography and venography is optional and may guide treatment if results are positive.\(^\text{3}\)

**Recommendations for Imaging Patients with Allergy to Iodinated Contrast Material**
Beyond D-dimer testing and clinical assessment, patients with mild contrast allergies may be treated with steroids prior to CT imaging. In patients with severe contrast allergy, venous ultrasound and VQ scans are recommended as alternative diagnostic tests.\(^\text{3}\) Other recently described approaches include CT angiography enhanced with 0.3–0.4 mmol gadolinium per kilogram of body weight\(^\text{20}\) and gadolinium-enhanced MR imaging.\(^\text{21}\)
TREATMENT OF VENOUS THROMBOEMBOLISM

Hemostasis and coagulation involves a sequence of interactions of coagulation factor interactions in two pathways called the intrinsic and extrinsic coagulation cascades. The final common pathway involves the transformation of prothrombin to thrombin by factor Xa. Thrombin (factor IIa) then serves to catalyze the activation of fibrinogen to fibrin, in addition to its role in feedback activation of several other clotting factors. Unfractionated heparin (UFH), low molecular weight heparin (LMWH) and the pentasaccharide fondaparinux all exert their anticoagulant effect by binding to and activating antithrombin which then neutralizes selected coagulation factors.\(^2\)

Initial Management

Prior to giving anticoagulation therapy, all patients should have baseline coagulation studies drawn including the activated partial thromboplastin time (aPTT), PT, an international normalized ratio (INR), a complete blood count (CBC), including a platelet count, as well as a baseline renal studies (creatinine).\(^2\)

Heparin – LMWH vs. UFH

Deep Venous Thrombosis

In the most recent American College of Physicians/American Academy of Family Physicians (ACP/AAFP) Clinical Guidelines, low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin (UFH) for the initial inpatient treatment of deep venous thrombosis (DVT).\(^3\) A recent analysis of 17 systematic reviews demonstrated that LMWH results in reduced mortality and less risk for major bleeding during initial therapy.\(^4\) In addition, LMWH was found to result in significant cost savings compared to UFH.\(^2\)

Pulmonary Embolism

Systematic reviews of existing trials indicate that LMWH is at least as effective as UFH for the initial treatment of patients with PE.\(^4\) For acute VTE treatment, limitations of UFH include a less-than-predictable anticoagulant response with the need for frequent monitoring, a relatively narrow therapeutic window and the potential for severe toxicity, especially heparin-induced thrombocytopenia (HIT) in \(\leq 3\%\) of patients.\(^5\)

Importantly, trials of UFH in PE show that many patients are subtherapeutic or supratherapeutic while receiving UFH. In contrast, LMWHs provide a more targeted approach to procoagulant complex inhibition, predictable pharmacokinetic and pharmacodynamic characteristics, and no need for anticoagulant monitoring.\(^5\)

Dosing Considerations

Unfractionated Heparin

When UFH is used for treatment of VTE, a weight-based nomogram is the safest and most effective method to anticoagulate patients.\(^2\) The nomogram includes a heparin bolus of 80 units/kg IV followed by an IV heparin infusion of 18 units/kg/h. In general, the recommended range of an aPTT for therapeutic heparin levels is 1.5 to 2.5 times the control aPTT assessed starting four to six hours after the initial UFH infusion.\(^2\)

Low-Molecular-Weight Heparin

The three LMWH preparations currently approved for use in the United States are enoxaparin, dalteparin, and tinzaparin. They are all administered subcutaneously at intervals of either once or twice daily for both prophylaxis and treatment doses.\(^2\) There was no increase in bleeding in once-daily versus twice-daily dosing of LMWH. Because LMWHs have more predictable pharmacokinetics than UFH, routine coagulation monitoring is not performed.

Because LMWHs are excreted by the kidneys, caution must be used when administering LMWHs for treatment of VTE in patients who have a creatinine clearance of less than 30 mL/min. Enoxaparin can still be used in patients with renal failure, but at a reduced dose of 1mg/kg SC once daily. Another group of patients for whom LMWH dosing is unclear is for obese patients with weights over 150 kg.\(^2\)

In obese patients with body mass index greater than 30, there is evidence that once-daily enoxaparin (1.5 mg/kg) is less effective than twice daily enoxaparin (1 mg/kg).\(^6\)
Pentasaccharides
Fondaparinux is based on the pentasaccharide region of the heparin molecule specific for antithrombin binding. Fondaparinux selectively inhibits factor Xa by binding to antithrombin. Because fondaparinux lacks the longer saccharide chains that bind to thrombin, it has no ability to neutralize thrombin and is entirely specific for factor Xa.22

Fondaparinux is at least as effective as enoxaparin 1 mg/kg twice daily for the initial treatment of acute DVT and as effective as UFH for the initial treatment of acute, nonmassive PE, without increased risk for major bleeding.22,26 The dosing of fondaparinux is weight-dependent: 5.0 mg once daily for <50 kg, 7.5 for 50-100 kg, or 10.0 mg for >100 kg.22,26 Importantly, fondaparinux is contraindicated in patients with severe renal impairment defined as creatinine clearance <30 mL/min.26

Direct Thrombin Inhibitors
The direct thrombin inhibitors lepirudin and argatroban are indicated for acute VTE treatment in the setting of heparin-induced thrombocytopenia (HIT).26 Because these drugs have no structural similarity to heparin, they do not cross-react with heparin-induced antibodies. These therapies significantly reduce the incidence of new thrombosis and death related to thrombosis without increasing major bleeding in patients with HIT. The broader use of these agents in VTE patients is limited by their high drug acquisition costs and the need for frequent monitoring.25

Inpatient vs. Outpatient Treatment of VTE
Deep Venous Thrombosis
A recent systematic review of VTE trials which compared inpatient and outpatient treatment for VTE concluded that the rates of recurrent DVT, major bleeding, and death during follow-up were similar for inpatient and outpatient treatment strategies.24 Across all groups, the percentages of patients having recurrent DVT ranged from 0% to 9%, with minimal differences according to treatment. Pulmonary embolism rarely occurred in any group in any study. The incidence of major bleeding ranged from 0% to 4%, and the percentage of patients dying during follow-up ranged from 0% to 18%, with minimal differences between inpatient and outpatient treatment groups.24 In addition, there appeared to be significant cost savings with outpatient treatment.23,24

Yet all of these studies were conducted among highly selected groups of patients and in clinical systems with the required support services in place. Importantly, most of these studies excluded patients with concomitant PE, previous VTE, thrombophilic conditions, or significant comorbid illnesses, pregnant patients and those deemed unlikely to adhere to outpatient therapy.24

Pulmonary Embolus
There is little evidence regarding the outpatient treatment of PE. The one cohort study that exclusively enrolled patients with PE found no significant difference in event rates.24 All these studies, however, may have been underpowered to detect a difference in event rates between inpatient and outpatient strategies.24 The 2007 ACP/AAFP Clinical Guidelines recommends outpatient treatment of DVT, and possibly PE, with LMWH as safe and cost-effective for carefully selected patients and considered only if the required support services are in place.23

Thus, the consideration of outpatient treatment of DVT patients in the ED must account for the possibility of concomitant PE as well as those exclusion factors listed above. In addition, several of these studies allowed a brief inpatient admission for stabilization of the patients before randomization to the outpatient group.24

VTE Prophylaxis in the ED
Nearly 10% of ED patients admitted to the hospital are at high risk for VTE, yet VTE prophylaxis is rarely administered from the ED.27 Risk scores for VTE have been developed [Table 4] and could be used to identify high-risk VTE patients in the ED.27,28 Thus, the ED could be used to identify and institute thromboprophylaxis to admitted patients at high-risk for VTE.27
Pregnant Patients

Pregnant women have a 5-fold increased risk for VTE compared with nonpregnant women. D-dimer testing with clinical assessment should still be performed in pregnant women even though results may be inherently positive due to pregnancy. If D-dimer results are positive, venous ultrasound is recommended before imaging tests with ionizing radiation are performed. If radiographic imaging is necessary, there is controversy on whether pulmonary VQ scans or CT angiography is preferred. Studies suggest that the radiation dose to the fetus from 16-section CT angiography is the same or less magnitude than that from a pulmonary VQ scan or pulmonary perfusion scan alone. Yet most (69%) PIOPED II investigators recommend pulmonary VQ scans with 31% recommending CT angiography as the radiographic imaging modality of choice in pregnant women.

SUSPECTED MASSIVE PE

Suspected massive PE, which could occur in a patient presenting with shock or hypotension, represents a distinct clinical problem. The clinical suspicion for PE is usually high, and the differential diagnosis includes cardiogenic shock, tamponade and aortic dissection. The most useful initial test in this setting is echocardiography, which will usually show indirect signs of acute pulmonary hypertension and right ventricular overload if acute PE is the cause of the hemodynamic consequences. A positive venous ultrasound result in the appropriate clinical setting could also indicate PE.

The sensitivity of transthoracic echocardiography for right ventricular enlargement or dysfunction in 33 patients with massive PE or unstable patients was 100%. If any two of three assessments (high clinical probability, echocardiography, ultrasound) are positive, the sensitivity for massive PE is 97% with a negative predictive value of 98%.

In a highly unstable patient, fibrinolytic treatment or even surgery for PE may be initiated based on compatible echocardiographic findings alone. If the patient is

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**Table 4. VTE Risk Score for Use in Prophylaxis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major:</strong></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>3</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>Hypercoagulability</td>
<td>3</td>
</tr>
<tr>
<td><strong>Intermediate:</strong></td>
<td></td>
</tr>
<tr>
<td>Major surgery (duration &gt;60 minutes)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Minor:</strong></td>
<td></td>
</tr>
<tr>
<td>Advanced age (&gt;70)</td>
<td>1</td>
</tr>
<tr>
<td>Obesity (BMI &gt;29)</td>
<td>1</td>
</tr>
<tr>
<td>Bed rest (ordered)</td>
<td>1</td>
</tr>
<tr>
<td>HRT or oral contraceptives</td>
<td>1</td>
</tr>
</tbody>
</table>

Score ≥ 4 = increased risk of VTE

BMI = body mass index; HRT = hormone replacement therapy

stabilized by supportive treatment, a definite diagnosis should be sought. The European Society of Cardiology approach to the emergency management of suspected massive PE, including hemodynamic support is highlighted and includes:

- Dobutamine and dopamine may be used in patients with PE, low cardiac index and normal blood pressure.
- Vasopressive drugs may be used in hypotensive patients with PE.
- Monitored oxygen therapy is beneficial in patients with PE and hypoxemia.
- The usefulness of fluid challenge is controversial and should not exceed 500 ml.
- Fibrinolytic therapy is indicated in patients with massive PE, as shown by shock and/or hypotension.
- Most contraindications for fibrinolytic therapy in massive PE are relative.
- Fibrinolytic therapy should be based on objective diagnostic tests, including echocardiography.
- The use of fibrinolytic therapy in patients with sub-massive PE (isolated RV hypokinesia) is controversial.
- Fibrinolytic therapy is not indicated in patients without right ventricular overload.
- Acute pulmonary thrombectomy has a limited role in massive, life-threatening PE.

Fibrinolytic Therapy for Massive PE
The increase in right ventricular (RV) afterload observed in patients with massive PE may induce RV failure, systemic hypotension and shock. In patients with pulmonary hypertension and low cardiac output due to PE, fibrinolytic therapy induces a 30% reduction in mean pulmonary arterial pressure and a 15% increase in cardiac index within two hours of treatment. In addition, fibrinolytic therapy can cause a significant reduction in mean RV end-diastolic area within 3 hours. In contrast, heparin alone did not produce any change in cardiac index, pulmonary artery pressure, or echocardiographic findings at 2 hr or at 72 hr after the beginning of therapy.

There appears to be a survival benefit from fibrinolytic therapy in patients with massive PE, i.e., those with shock and/or hypotension defined as a systolic blood pressure <90 mmHg or a pressure drop of > 40 mmHg for >15 min if not caused by new-onset arrhythmia, hypovolemia or sepsis. Several contraindications exist for fibrinolytic therapy, however, in an unstable patient with a massive PE, most of these are considered only relative contraindications.
REFERENCES


