PULMONARY EMBOLISM (PE): TREATMENT

Thrombosis Canada
Thrombose Canada

OBJECTIVE:

To provide an evidence-based approach to treatment of patients with acute pulmonary embolism (PE).

BACKGROUND:

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 PE, while the remainder is deep vein thrombosis (DVT). The incidence of PE has increased significantly since the advent of computed tomography pulmonary angiography (CTPA) due to this test's widespread availability and diagnostic sensitivity. The majority of pulmonary emboli are believed to originate in the proximal deep veins of the leg, despite the fact that only 25-50% of patients with PE have clinically-evident DVT. Up to 50% of first-time pulmonary emboli are unprovoked, while the remainder are associated with risk factors such as active malignancy, surgery (especially orthopedic), immobilization >8 hours, and estrogen use/pregnancy.

Symptoms of PE may include sudden onset dyspnea, palpitations, pleuritic chest pain and syncope. Signs of PE may include tachypnea, tachycardia, hypoxemia, hypotension, and features of right ventricular dysfunction (eg. distended jugular veins). The ECG may show right ventricular strain ($S_1Q_3T_3$, right bundle branch block and T-inversion in leads V1-V4).

Up to 10% of symptomatic PE cases are fatal within the first hour of symptoms. Independent predictors of early mortality include hypotension (systolic blood pressure $\leq$90 mmHg), clinical right heart failure, right ventricular dilatation on CT or echocardiography, positive troponin, and elevated brain natriuretic peptide (BNP). Early diagnosis and treatment of PE reduces morbidity and mortality.

TREATMENT OF PE:

Unless bleeding risk is high (eg. active bleeding, immediate postop state), rapid-acting anticoagulant therapy should be initiated in patients with a high pre-test probability of PE while awaiting diagnostic imaging. 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 [see the PESI and Simplified PESI risk models in the Thrombosis Canada Clinical Tools]. Patients classified as very low and low risk by the PESI models have a low overall risk of severe morbidity and mortality and can be considered for outpatient management or early discharge. However, other factors, such as need for supplemental oxygen or parenteral pain control, high bleeding risk, severe renal dysfunction, or absence of appropriate social supports may also necessitate initiation of treatment in an inpatient setting. Even with these caveats, close to 50% of patients with PE can be managed completely or mostly as outpatients.

Options for initial anticoagulation include direct acting oral anticoagulant (DOAC) monotherapy or initial LMWH followed by a DOAC, unfractionated heparin (UFH) or low molecular weight heparin (LMWH) bridging to therapeutic warfarin, or LMWH monotherapy. The extent of PE or clot burden should not influence choice of anticoagulant, unless thrombolysis is being considered; in that case, intravenous (IV) UFH is preferred. All patients with PE should be treated with anticoagulation for at least 3 months [see Venous Thromboembolism: Duration of Treatment guide]. DOACs are generally preferred given that they are as effective as traditional therapy with LMWH bridging to warfarin and are more convenient and associated with reduced bleeding risks.

For patients who cannot be therapeutically anticoagulated due to active bleeding or high bleeding risks, consultation should be initiated with a hematologist or thrombosis specialist and interventional radiologist regarding placement of an inferior vena cava (IVC) filter [see Vena Cava Filter guide].

ANTICOAGULANT AGENTS AND DOSING:

NOACs/DOACS (Non-vitamin K antagonist Oral AntiCoagulants/Direct Oral AntiCoagulants) - Rivaroxaban (Xarelto®), Apixaban (Eliquis®), Edoxaban (Lixiana®), Dabigatran (Pradaxa®):
Large phase 3 studies have demonstrated the efficacy and safety of these agents for the initial (rivaroxaban, apixaban), acute (all agents) and extended (all agents) treatment of PE. Four DOACs have been approved in Canada for the treatment of patients with PE. An initial 1-week course of LMWH is required prior to starting dabigatran and edoxaban but not with rivaroxaban and apixaban.

DOACs should not be used in pregnant or breastfeeding women or in those with significant renal dysfunction [see Treatment Guides for Rivaroxaban (Xarelto®), Apixaban (Eliquis®), Edoxaban (Lixiana®), Dabigatran (Pradaxa®)]. Individual product monographs should be consulted for important drug interactions prior to prescribing.

The recommended doses of the DOACs are:

Rivaroxaban (Xarelto®): 15 mg twice daily for the first 21 days, followed by 20 mg once daily for the duration of treatment,

Apixaban (Eliquis®): 10 mg twice daily for the first 7 days, followed by 5 mg twice daily.

Dabigatran (Pradaxa®): 150 mg twice daily*

Edoxaban (Lixiana®): 60 mg once daily* (30 mg if < 60 kg)

*In keeping with trial design and recommendations, 5-7 days of therapeutic LMWH should be administered prior to the initiation or dabigatran or edoxaban when these agents are used for the treatment of VTE.

For patients continuing on long term rivaroxaban or apixaban beyond 6 months, dose reduction of rivaroxaban to 10 mg once daily or apixaban to 2.5 mg twice daily can be considered based on the results of the EINSTEIN CHOICE and AMPLIFY Extend studies in which these lower doses were as effective and safe as standard dosing.

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 in those with active cancer. Most patients have little difficulty with LMWH self-administration. LMWH offers advantages over UFH; including better bioavailability when administered subcutaneously, longer duration of anticoagulant effect often 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 routine laboratory monitoring. There is no maximum dose of LMWH and dosing should be based on patient's actual weight. Doses can be rounded off to the nearest prefilled syringe size.

Dalteparin (Fragmin®): 200 U/kg subcutaneously (SC) once daily or 100 U/kg SC twice daily (once daily dosing is generally preferred, but twice daily dosing should be considered in patients >100 kg).

Enoxaparin (Lovenox®): 1 mg/kg SC twice daily or 1.5 mg/kg SC once daily.

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

Nadroparin (Fraxiparine®): 171 U/kg SC once daily or 86 U/kg SC twice 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 generally be avoided. For tinzaparin, available evidence demonstrates no accumulation in patients with CrCl levels down to 20 mL/min. There are limited data available in patients with an estimated CrCl < 20 mL/min. If LMWH is used in patients with severe renal dysfunction, testing anti-factor Xa levels to monitor for accumulation should be considered. Some experts suggest that a dose reduction should be considered if the trough anti-Xa level is >0.4 IU/mL; however, good data showing a correlation between these levels and poor clinical outcomes is lacking.

Unfractionated heparin

UFH use in the treatment of PE is limited by a narrow therapeutic range, inter-individual variation in anticoagulant effect, need for continuous intravenous infusion with laboratory monitoring, and 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 and DOACs should generally be avoided; (2) patients at very high risk for bleeding, in whom rapid reversal of the anticoagulant effect may be needed; and (3) patients who receive thrombolytic therapy. Intravenous UFH is generally started with a bolus of 80 U/kg followed by a continuous infusion starting at 18-20 U/kg/hr. The target therapeutic activated partial thromboplastin time (aPTT) range is defined by the local hospital laboratory.

Warfarin

Initiation of warfarin should be combined with an immediate-acting agent such as LMWH for at least 5 days and until the international normalized ratio (INR) is at least 2.0 for at least two days. As warfarin takes several days to take effect, warfarin monotherapy is <u>not</u> an acceptable treatment option. 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. Conversely, relatively young, healthy and large patients typically require a higher dose; initial dosing with 7.5-10 mg should be considered. Frequent monitoring is required until a stable, therapeutic-range INR is reached, after which testing every 2-6 weeks is usually adequate.

Warfarin is associated with many drug and food interactions that affect the INR. Alterations in concomitant medications and new concurrent illness should prompt INR testing. Patients should not be encouraged to reduce intake of foods high in vitamin K, but to maintain a consistent, balanced diet. Low intake of vitamin K can be associated with more unstable INR levels.

THROMBOLYSIS:

Harm with thrombolysis outweighs the benefit in most patients with PE except in those who present with massive PE. Massive PE is defined as anatomically extensive PE plus persistent hypotension or overt right heart failure, where the short-term mortality is >15%. Therefore, IV thrombolysis should be reserved for patients with persistent hypotension (SBP ≤90 mmHg or a 40 mmHg drop from baseline) refractory to a small fluid challenge or clinical right heart failure and who do not have a contraindication. Thrombolysis is NOT indicated in submassive (intermediate-risk) PE (normotensive with right ventricular dysfunction), as it increases major bleeding and stroke (~12%) without survival benefit. Thrombolysis is given as follows: recombinant tissue plasminogen activator (rt-PA) 100 mg over 2 hours or 0.6 mg/kg as a bolus; or weight-adjusted tenectaplase (TNK) as a bolus. Intravenous UFH should be used initially after thrombolytic therapy, followed by anticoagulation with warfarin or a DOAC.

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 with a lower risk of bleeding. Such treatment should be undertaken in consultation with a specialist. There is no published data to guide which patients would benefit most from this emerging therapy; therefore, it should generally not be used in patients with submassive PE.

Chronic thromboembolic pulmonary hypertension (CTEPH)

CTEPH develops in up to 3% of patients after an episode of PE, usually within the first year. Clinicians should consider CTEPH in patients with PE who have ongoing dyspnea or who develop signs of right sided heart failure despite 2-3 months of anticoagulant therapy. If CTEPH is suspected, an echocardiogram should be done to look for right ventricular dysfunction and a perfusion lung scan is recommended to document pulmonary arterial flow. Patients with CTEPH should be given long-term anticoagulation to prevent recurrent PE. For patients with confirmed CTEPH, referral to a specialized centre is advised to assess for pulmonary thrombendarterectomy or additional medical therapy. Pulmonary thromboendarterectomy often reduces pulmonary pressures and symptoms of pulmonary hypertension, although mortality for such surgery is about 5% even in the most experienced centres.

Patients with contraindication for anticoagulation

[See Vena Cava Filter guide.]

Pregnancy

[See Pregnancy: Venous Thromboembolism Treatment guide]

Cancer

[See Cancer and Thrombosis guide.]

Pediatrics

The diagnosis of PE in children should always be confirmed with a V/Q scan, CT with contrast or magnetic resonance imaging (MRI). Treatment may be initiated with either age-appropriate UFH or LMWH followed by 3 months (for a provoked VTE) or longer-term anticoagulation for recurrent or unprovoked events using either LMWH or warfarin. See Pediatric Thrombosis guide.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- Apixaban (Eliquis®)
- Cancer and Thrombosis
- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis (DVT): Treatment
- Edoxaban (Lixiana®)
- Pregnancy: Venous Thromboembolism Treatment
- Rivaroxaban (Xarelto®)
- Unfractionated Heparin, Low-molecular-weight Heparin, and Fondaparinux
- Vena Cava Filter
- Venous Thromboembolism: Duration of Treatment
- Warfarin

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