PULMONARY EMBOLISM (PE): TREATMENT

OBJECTIVE:

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

BACKGROUND:

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease and affects approximately 1-2 in 1,000 adults per year. 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 of varying clinical significance such as active malignancy, surgery (especially orthopedic), trauma, lower extremity plaster casting, 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 (e.g. 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 (e.g. active bleeding, immediate postoperative 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 if 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 Pulmonary Embolism Severity Index [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. Alternatively, eligible patient for outpatient management can be identified using the HESTIA

criteria (https://www.mdcalc.com/hestia-criteria-outpatient-pulmonary-embolism-treatment). With both methods, approximately 40% of all patients diagnosed in the Emergency Department with PE can be safely discharged with outpatient follow-up and management. However, clinicians should be cautious if the patient deemed at low risk has others higher mortality prognostic markers, such as right ventricular dilation on imaging, elevated troponin or elevated BNP.

Options for initial anticoagulation include direct acting oral anticoagulant (DOAC) monotherapy (for apixaban and rivaroxaban), unfractionated heparin (UFH) or low molecular weight heparin (LMWH) initial therapy followed by DOAC (for dabigatran and edoxaban), LMWH/UFH bridging to therapeutic warfarin, or LMWH monotherapy (**Figure 1**). Recent guideline recommendations express a preference for DOAC therapy over LMWH bridging to warfarin. While both strategies are effective, DOACs are more convenient and appear to have lower bleeding risk. 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 in the short-term due to its short half-life in the context of the bleeding risk associated with thrombolysis. All patients with PE should be treated with anticoagulation for at least 3 months [see **Clinical Guide Venous Thromboembolism: Duration of Treatment** guide].
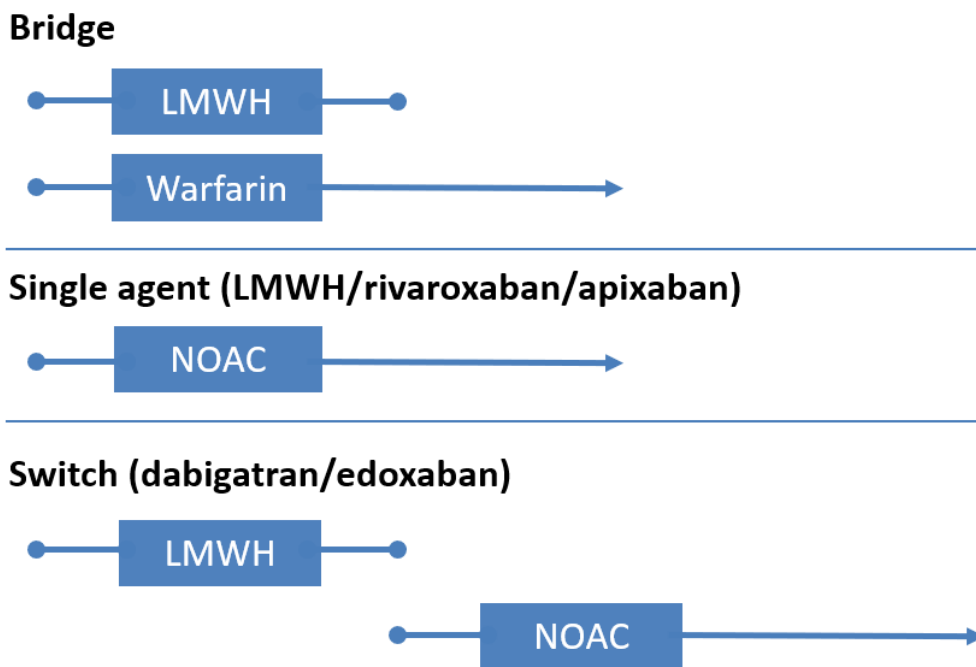

FIGURE 1

ANTICOAGULANT AGENTS AND DOSING:

NOACs/DOACS (Non-vitamin K antagonist Oral AntiCoagulants/Direct Oral AntiCoagulants) - Apixaban (Eliquis®), Dabigatran (Pradaxa®), Edoxaban (Lixiana®) and Rivaroxaban (Xarelto®)
Large phase 3 studies have demonstrated the efficacy and safety of these agents for the acute and extended treatment of PE. Four DOACs have been approved in Canada for the treatment of patients

with PE. On the basis of trial design and dosing requirements, an initial 5- to 10-day course of LMWH is **required** prior to starting dabigatran and edoxaban, but not with apixaban or rivaroxaban.

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

The recommended initial doses of the DOACs from their product monographs are:

Apixaban (Eliquis®): 10 mg twice daily for the first 7 days, followed by 5 mg twice daily. No dose adjustment is necessary in patients with mild or moderate renal impairment (creatinine clearance [CrCl] ≥ 30 mL/min). Apixaban should be used with caution in patients with CrCl 15-29 mL/min as these patients were excluded in clinical trials assessing clinical outcomes. Apixaban is not recommended in those with a CrCl <15 mL/min or undergoing dialysis.

Dabigatran (Pradaxa®): After an initial 5-10 days of therapeutic LMWH, recommended dosing is 150 mg twice daily. Dose reduction has not been studied in the setting of VTE; however, consideration may be given to reducing the dose to 110 mg twice daily in patients 80 years or older, and those at higher risk of bleeding (including age at 75 or older with at least one risk factor for bleeding). Use is contraindicated with CrCl <30 mL/min).

Edoxaban (Lixiana®): After an initial 5-10 days of therapeutic LMWH, recommended dosing is 60 mg once daily (30 mg if less than or equal to 60 kg, creatinine clearance (CrCL) 30-50 mL/min, concurrent use of potent P-gp inhibitors except amiodarone and verapamil). Use is not recommended with CrCl <30 mL/min).

Rivaroxaban (Xarelto®): 15 mg twice daily for the first 21 days, followed by 20 mg once daily for the duration of treatment. No dosing adjustment is recommended in those with CrCl 15-50 mL/min. However, caution is recommended for those with CrCl 15-30 mL/min as these patients were excluded in clinical trials assessing clinical outcomes. Use is not recommended with CrCl <15 mL/min.

For patients continuing on long term anticoagulation with apixaban or rivaroxaban 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 EXT 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 enabling once or twice 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 the 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.

Nadroparin (Fraxiparine®): 171 U/kg SC once daily or 86 U/kg SC twice daily.

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

For patients with severe renal insufficiency (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.

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); (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. A baseline aPTT should generally be obtained prior to UFH administration as a consumptive coagulopathy or nonspecific inhibitor (e.g. lupus anticoagulant) may falsely elevate the baseline aPTT, resulting in underdosing UFH. Such cases should be discussed with a thrombosis specialist. Some centres adjust IV unfractionated heparin based on heparin anti-Xa levels.

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 2 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 and those with low body weight typically require a lower dose, such as 2-3 mg. Conversely, relatively young, healthy, and large patients typically require a higher dose, such as 7.5-10 mg. Frequent monitoring is required until a stable, therapeutic-range INR is reached. Once stable, INR 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 more frequent INR testing. Patients should <u>not</u> 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 high risk (massive) PE. High risk (massive) PE is defined as persistent hypotension despite small fluid challenge (SBP ≤90 mmHg, a 40 mmHg drop from baseline, or vasopressor requirement) or cardiac arrest not caused by an alternative diagnosis. Since the short-term mortality risk is >15%, IV

thrombolysis should be reserved for patients meeting those criteria and who do not have a contraindication.

Thrombolysis is NOT routinely indicated in intermediate risk (also called sub-massive) PE (normotensive with right ventricular dysfunction on imagery or with elevated cardiac biomarkers), as it increases major bleeding and hemorrhagic stroke. For select patients with intermediate risk PE who are not at high risk of bleeding AND who have severe persistent symptoms with signs of right heart failure or cardiopulmonary deterioration, thrombolysis may be considered after discussion with a thrombosis expert.

Thrombolytic regimens are heterogenous in the literature. Some thrombolysis regimens include:
- recombinant tissue plasminogen activator (rt-PA) 100 mg over 2 hours
- rt-PA 0.6 mg/kg (maximum of 50 mg) over 15 minutes
- rt-PA 0.5 mg/kg (maximum of 50 mg) given as a 10 mg bolus, then the remainder over 2 hours if ≥50 kg; if <50 kg total rt-PA dose of 0.5 mg/kg, given as a 10-mg initial bolus followed by the remainder within 2 hours
- rt-PA 50 mg as a bolus over 1 minute in a patient in cardiac arrest
- Tenectaplase (TNK) between 30-50 mg (depending on weight) as a bolus over 5-10 seconds (PEITHO trial regimen)

Intravenous UFH (without a bolus) should be used initially after thrombolytic therapy, followed by a transition to a longer-term agent.

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 routinely in patients with high or intermediate risk PE.

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. Two multicenter, randomized trials compared

either rivaroxaban (EINSTEIN-Jr study) or dabigatran (DIVERSITY study) with standard anticoagulants in children (0 to 17 years of age) who have acute venous thromboembolism. All patients initially received at least 5 days of parenteral anticoagulant (up to 9 days in EINSTEIN-Jr and up to 21 days in DIVERSITY). Both studies found a similarly low recurrence risk of the DOAC as standard anticoagulants without an increased risk of bleeding. However, neither rivaroxaban nor dabigatran are currently licensed for the pediatric population in Canada.

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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