Managing Pulmonary Embolism

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INTRODUCTION

Pulmonary embolism (PE) is commonly encountered in the emergency department, with an estimated annual incidence of 39 to 115 per 100,000 individuals.[1] Classic risk factors include major trauma, lower extremity surgery, prior venous thromboembolism, recent hospitalization, oral contraception, postpartum period, malignancy, and thrombophilias.[2-4] However, numerous other risk factors exist.[5,6]

Historically, mortality after PE was reported as 18% to 30%.[7] However, more recent studies have found that PE-related mortality is estimated at 1% to 3%.[8,9] In the decades following the introduction of computed tomography pulmonary angiography, an increasing incidence of PE has been accompanied by a lower case-fatality rate coupled with an increase in complications of anticoagulation for PE.[10,11] Together, these features suggest overdiagnosis of PE, warranting reconsideration of the evaluation and management of PE to minimize the harms from overevaluation and overtreatment. There is a need to better understand the nuanced evaluation and treatment of PE. This article does not intend to be a comprehensive review of all aspects pertaining to PE but rather seeks to provide the key tenets of management based on the current literature and years of practice.

ASSESSMENT

The signs and symptoms of PE are nonspecific and can include chest pain, dyspnea, cough, syncope, or hemoptysis. Consequently, the diagnostic approach for suspected PE typically involves pretest probability assessment and potentially D-dimer testing and/or imaging (Figure 1).

Elevated D-dimer levels are nonspecific; however, the D-dimer assay plays an important role in risk stratification for suspected PE because a normal D-dimer level in non–high-risk patients can safely exclude PE.[12-14] D-dimer values rise with age, which has led to research on age-adjusted D-dimer levels for assays using fibrin equivalent units. In patients older than 50 years with a low or intermediate risk of PE, an age-adjusted cutoff of age×10 μg/L can be used.[12,15-17] Although research evaluating some assays that report D-dimer units demonstrates good performance of an age-adjusted dimer using age×5 μg/L, it is not clear whether this threshold can be applied to all D-dimer unit assays.[12,18,19]

Computed tomography pulmonary angiography is the imaging modality of choice for PE in high-risk patients or those with clinical suspicion for PE and elevated D-dimer levels because it is highly sensitive and specific for diagnosis.[20] However, radiologist agreement on the presence or absence of a PE varies. Up to 25% of computed tomography pulmonary angiographies interpreted as diagnostic for PE, particularly at the subsegmental and segmental levels, are false positives.[21-24] Ventilation/perfusion (V/Q) scans can be used in patients with a normal chest radiograph but is complicated by a substantial number of nondiagnostic tests and the inability to identify an alternative diagnosis.[25]

Risk Stratification

Risk stratification can occur by clinician gestalt or a risk stratification tool. The most commonly used risk stratification tools for PE in the United States are the Wells' Criteria and the Pulmonary Embolism Rule-Out Criteria (PERC) (Tables 1 and 2).[26-28] The Wells' Criteria may be perceived as complex because several scoring systems exist.[29] The proportion of patients with PE in each risk group depends on the study setting. These scoring systems perform similarly with regard to diagnosis of PE; however, the 3-tier Wells' Criteria may allow more individuals to avoid imaging because only patients with a Wells' score of >6 proceed directly to computed tomography pulmonary angiography, rather than the threshold of 4.5 in the dichotomized Wells' score.[30]

Whether to use a risk stratification tool or clinical gestalt is a topic of debate.[31] A meta-analysis of prospective studies

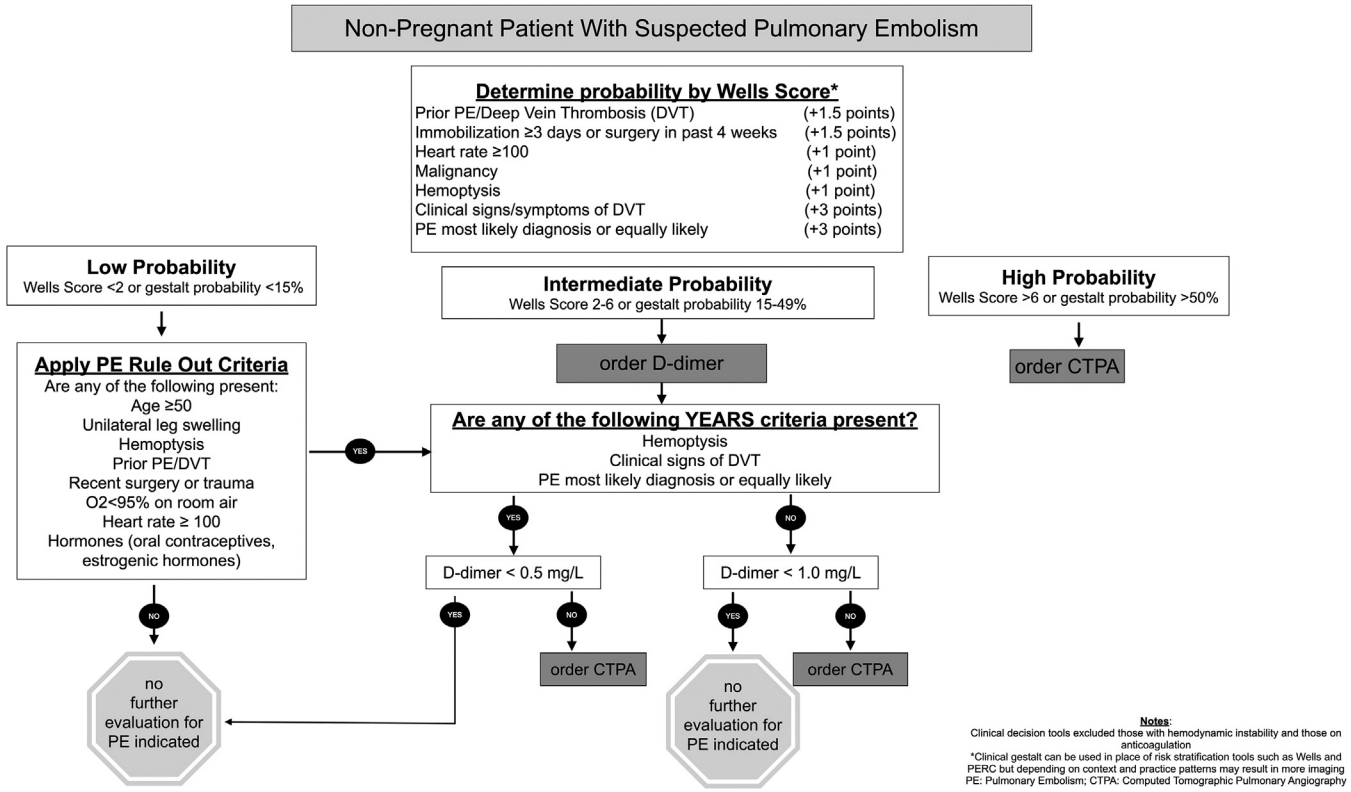

Figure 1. Possible diagnostic algorithm for nonpregnant patients with suspected PE. *CTPA*, computed tomography pulmonary angiography; *DVT*, deep venous thrombosis; *RV*, right ventricular; *SBP*, systolic blood pressure.

found that the sensitivity of clinician gestalt was comparable to that of risk stratification tools; however, the specificity of risk stratification tools was higher (81% versus 52%), suggesting that risk stratification tools may have value in decreasing imaging studies.[15,32-34] A randomized trial of PERC reported 9.7% fewer imaging studies compared with usual care.[32]

Table 1. Wells' Criteria for PE.

Consideration	No	Yes
Clinical signs and symptoms of DVT	0	+3
PE is #1 diagnosis or equally likely	0	+3
Pulse rate of >100 beats/min	0	+1.5
Immobilization at least 3 d or surgery in the previous 4 wk	0	+1.5
Previous, objectively diagnosed PE or DVT	0	+1.5
Hemoptysis	0	+1
Malignancy with treatment within 6 mo or palliative	0	+1

Score	
Three-tier model	Risk (prevalence of PE in the US studies)
0-1	Low risk (1%-3%).[79-81]
2-6	Intermediate risk (8.5%-15%).[79-81]
>6	High risk (37%-43%).[79,81]
Two-tier model	Risk (prevalence of PE in the US studies)
≤4	PE unlikely (1.8%-7.2%).[79]
≥5	PE likely (28%).[79]

Low Probability

Low-risk patients (<15% estimated probability or a Wells' Criteria score of <2) should be evaluated using the PERC criteria. Those who do not meet the PERC criteria can forgo further evaluation for PE.[26,32] Low-risk patients with suspected PE and a PERC criteria score of ≥1 should undergo D-dimer testing. Importantly, PERC should not be used for high-risk patients.[35,36]

Intermediate Probability

Patients with an intermediate probability of PE (15% to 50% estimated probability of PE or a Wells' Criteria score of 2 to 6) require D-dimer testing. A negative D-dimer in this population safely excludes PE.[12-14,20] More recently, the introduction of risk stratification algorithms using a probability-adjusted D-dimer threshold has demonstrated promise in increasing PE evaluation efficiency.[37-39] Among these algorithms, the YEARS algorithm has the most robust evidence (Table 3).[15,38,40,41] YEARS allows a D-dimer threshold of up to 1.0 μg/mL in patients without

Table 2. PERC rule for PE.

Consideration	No	Yes
Age of ≥50 y	0	+1
Pulse rate of ≥100 beats/min	0	+1
Oxygen saturation on room air of <95%	0	+1
Unilateral leg swelling	0	+1
Hemoptysis	0	+1
Recent surgery or trauma (≤4 wk ago, requiring general anesthesia)	0	+1
Prior PE or DVT	0	+1
Hormone use (eg, oral contraceptives, hormone replacement, or estrogenic hormone use in male or female patients)	0	+1

Score: if any criteria are positive, PE is not excluded

hemoptysis, deep venous thrombosis, or PE as the most likely diagnosis.[38] This algorithm, combined with PERC, has been validated in multiple settings and can safely exclude PE and reduce imaging studies in non–high-risk patients.[15,40,41] An observational study found that YEARS would have a sensitivity of 92.6% (95% CI 87.0% to 96.0%) in evaluating all patients for PE, with an overall miss rate within accepted safety margins (0.59%; 95% CI 0.3% to 1.1%).[42] Importantly, YEARS cannot be used for anticoagulated or critically ill patients.

High Probability

Patients with a high probability of PE (eg, a Wells' score of >6) should undergo imaging. The ability of computed tomography pulmonary angiography to exclude PE in patients with a high likelihood of PE is controversial.[43] A meta-analysis of 22 studies found that 0.56% (95% CI 0.39% to 0.72%) of patients with a computed tomography pulmonary angiography scan negative for PE were diagnosed with PE during follow-up; however, this proportion was higher in studies in which ≥40% of patients were diagnosed with PE (1.3%; 95% CI 0.69% to 2.3%).[44]

Table 3. YEARS algorithm for PE.

Consideration	No	Yes
Clinical signs of DVT	0	+1
Hemoptysis	0	+1
PE most likely diagnosis	0	+1

If no criteria present, use a FEU D-dimer threshold of 1,000 ng/mL.
If ≥1 criterion present, use a FEU D-dimer threshold of 500 ng/mL.
If the patient is pregnant and clinical signs of DVT are present, perform compression ultrasonography of the symptomatic leg; if normal, perform D-dimer testing.
FEU, fibrin-equivalent units.

Pregnancy

Recent studies have demonstrated that pregnant patients can safely undergo evaluation for PE using risk stratification tools, D-dimer, and ultrasound for deep venous thrombosis, which may prevent the need for further imaging.[33,45,46] In a prospective evaluation of 498 pregnant patients using the YEARS algorithm and deep venous thrombosis ultrasound (Figure 2), no patients who initially had PE excluded were diagnosed with PE in the following 3 months, and a significant proportion of patients avoided imaging (65% in the first trimester, 46% in the second trimester, and 32% in the third trimester).[33] This algorithm has been retrospectively validated in other pregnant cohorts and found to be safe and associated with reduced need for imaging.[46,47] As a result, professional society guidelines are beginning to recommend YEARS in pregnant patients.[20]

In pregnant patients who warrant imaging for PE, there is debate over the use of computed tomography pulmonary angiography or V/Q imaging. The estimated fetal radiation exposure is minimal and safe for both V/Q scans and computed tomography pulmonary angiography.[48] Although computed tomography pulmonary angiography results in higher radiation exposure to breast tissue in the pregnant patient (3 to 10 mGy), this dose has negligible implications for their lifetime cancer risk.[49] Computed tomography pulmonary angiography may be preferred by some physicians because it may reveal an alternative diagnosis.

MANAGEMENT

Management is influenced by the severity of the PE. Although PEs were formerly described as "massive" or "submassive," these categories have been replaced by high, intermediate, and low risk categories, which predict early mortality (Figure 3).[20] These categories integrate clinical, imaging, and laboratory parameters and can be used to guide treatment decisions. Although laboratory tests and/or echocardiography may be helpful for patients with clinical features suggesting right ventricular strain (eg, electrocardiogram, brain natriuretic peptide, and troponin), these evaluations are not necessary for all patients with PE.

For most patients with PE who are eligible for oral anticoagulation, direct oral anticoagulants (eg, apixaban and rivaroxaban) are recommended over vitamin K antagonists for treatment of PE owing to their efficacy, safety, and convenience. Patients with cancer-associated thrombosis can be treated with low–molecular-weight heparin or, in the absence of high risk of gastrointestinal or

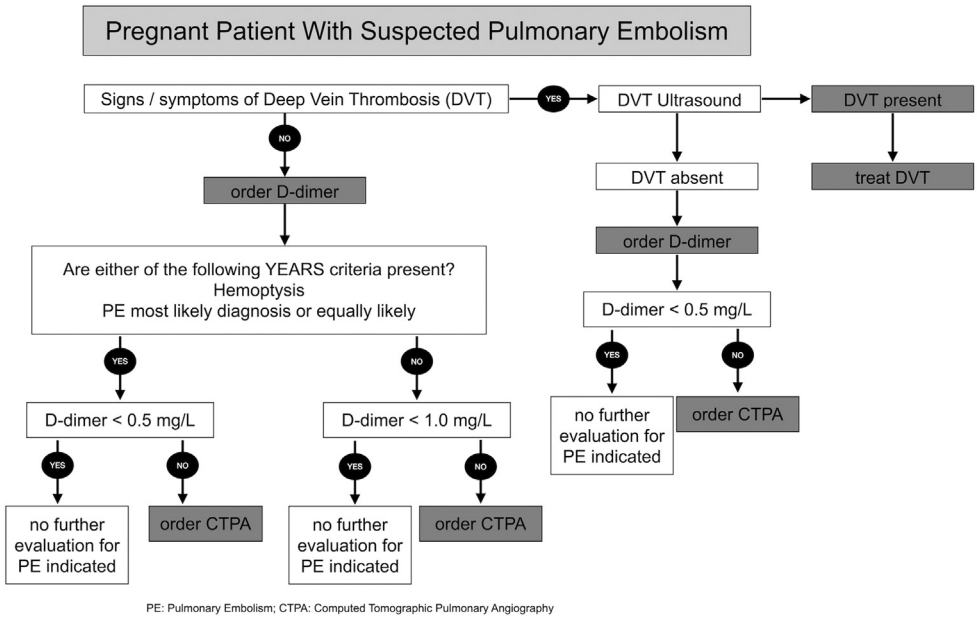

Figure 2. Possible diagnostic algorithm for pregnant patients with suspected PE.

genitourinary bleeding, an oral Xa inhibitor (eg, apixaban and rivaroxaban).[50,51] In patients who warrant parenteral anticoagulation, low–molecular-weight heparin is generally recommended over unfractionated heparin in most patients owing to the unpredictable pharmacokinetics of unfractionated heparin and increased risk of bleeding.[20,52-54] Unfractionated heparin is recommended in patients with serious renal impairment (creatinine clearance of $\leq$30 mL/min).[20]

High-Risk PE ("Massive")

Patients with high-risk PE and those who deteriorate despite anticoagulation warrant treatment with thrombolysis. The American College of Chest Physicians and the European Society of Cardiology recommend that patients with high-risk PE and absence of high bleeding risk receive systemic thrombolysis (Figures 4 and 5).[20,50] Although an increasing amount of observational data have examined surgical embolectomy

		Hemodynamic instability[1]	Right Ventricular (RV) Dysfunction (RV strain on echocardiography more predictive than CTPA)	Elevated cardiac troponin	Higher risk based on clinical parameters/comorbidities (PESI III/IV or sPESI ≥1)
High		Present	Present	Not necessary	Not necessary
Intermediate	Intermediate-high	Absent	Present	Present	May be present (elevated troponin or right ventricular dysfunction may be present in patients with calculated higher risk, but the implications for treatment of these patients is uncertain)
	Intermediate-low	Absent	No more than one category positive (e.g. right ventricular dysfunction present with a negative cardiac troponin)		May be present (elevated troponin or right ventricular dysfunction may be present in patients with calculated higher risk, but the implications for treatment of these patients is uncertain)
Low		Absent	Absent	Optional assessment but negative if assessed	Absent

CTPA: Computed Tomographic Pulmonary Angiography; PESI: Pulmonary Embolism Severity Index; sPESI: Simplified Pulmonary Embolism Severity Index
1. Hemodynamic instability: Cardiac arrest ***OR*** hypotension with systolic blood pressure (SBP) <90 mmHg or vasopressors required to achieve SBP ≥90 mmHg despite adequate filling status and signs of end organ dysfunction ***OR*** persistent SBP <90 mmHg or SBP drop >_40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolemia, or sepsis

Figure 3. PE risk stratification for mortality.

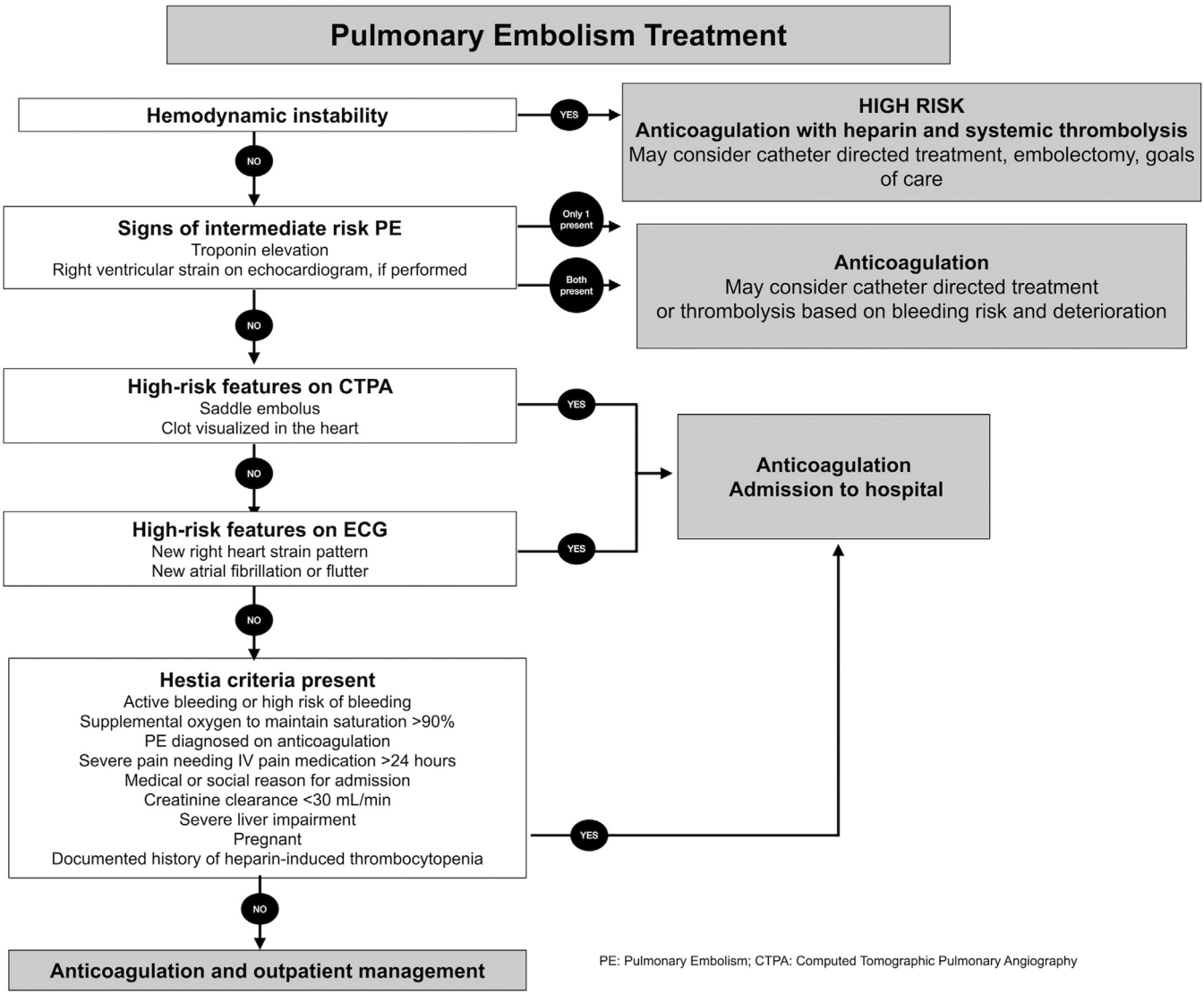

Figure 4. Algorithm for the treatment of acute PE. *IV,* intravenous.

and catheter-directed treatments (including catheter-directed thrombolysis and suction embolectomy), there are minimal comparative randomized trial data.[55-58] These treatments may be associated with less bleeding than that with systemic thrombolysis; however, selection bias complicates direct comparison. Currently, guidelines recommend that embolectomy or catheter-directed treatments be reserved for patients with contraindications to systemic thrombolysis or who deteriorate despite thrombolysis.[20,50]

Intermediate Risk PE ("Submassive")

Patients with intermediate-risk PE ("submassive") are hemodynamically stable but exhibit signs of right ventricular dysfunction. Patients with intermediate to low–risk PE should be started on oral anticoagulation or low-molecular-weight heparin, depending on their clinical factors. Patients with intermediate to high–risk PE should receive anticoagulation with low-molecular-weight heparin or heparin for the first 2 to 3 days, the time frame in which patients are most likely to decompensate.[20,59] Adjunct treatment (eg, thrombolytics or catheter-directed treatment) of patients with intermediate to high–risk or "submassive" PE is more controversial. Overlapping meta-analyses of randomized trials comparing thrombolytic therapy with anticoagulation alone have found an all-cause mortality benefit coupled with a wide range of major bleeding events.[60] As a result, current guidelines recommend thrombolytics only for patients with intermediate-risk PE who deteriorate despite systemic anticoagulation.[20,50] In contrast, catheter-

	Dose	Concurrent Anticoagulation	Notes
Alteplase	**100 mg infusion over 2 hours*** **OR** **In emergent situations such as impending cardiac arrest: a bolus, quick infusion, or 20 mg bolus followed by 2 hour infusion for remaining 80 mg may be used although these are not US FDA approved** **Or** **Reduced-dose thrombolysis (0.5 mg/kg up to 50 mg) alteplase has been studied in**	**Hold unfractionated heparin (UFH) infusion and restart near or at the completion of the alteplase infusion when the partial thromboplastin time or thrombin time returns to less than or equal to twice normal**	*Currently, only the 100 mg infusion is approved by the United States Food and Drug Administration (US FDA) for this use at this dose.
Tenecteplase	**Weight-based intravenous push of 30-50 mg**** (30 mg: ≤60 kg, 35 mg: 61-69 kg, 40 mg: 70 -79 kg, 45 mg: 80-89, 50 mg: ≥90 kg	**Full-dose low-molecular weight heparin (LMWH): enoxaparin 1 mg/kg or weight-based dalteparin prior to bolus and throughout hospital stay** **OR** **Unfractionated heparin bolus and infusion** (no need to hold UFH unless patient received LMWH or fondaparinaux in which case bolus should not administered the infusion should be held for 12 hours after LMWH or 24 hours after fondaprinaux)	**Not official approved for this indication by the US FDA

Figure 5. Possible thrombolytic doses for acute PE. *FDA*, Food and Drug Administration; *LMWH*, low–molecular-weight heparin; *UFH*, unfractionated heparin.

directed treatment has been increasingly performed for patients with intermediate-risk PE and may be associated with improvement in surrogate markers (eg, right ventricle dilation and mean pulmonary artery pressure).[61-64]

Table 4. Hestia criteria for outpatient PE treatment.

Consideration	No	Yes
Hemodynamically unstable—SBP of <100 mmHg and PR of >100, requires ICU care, or clinician judgment	0	+1
Thrombolysis or embolectomy needed—for reasons other than hemodynamic instability	0	+1
Active bleeding or high risk of bleeding—GI bleeding or surgery <2 wk ago, stroke <1 mo ago, bleeding disorder or platelet disorder $<75\times10^9$/L, uncontrolled HTN (SBP of >180 mmHg or DBP of >100 mmHg), or clinician judgment	0	+1
>24 h on supplemental oxygen required to maintain an SaO_2 of >90%	0	+ 1
PE diagnosed while on anticoagulation	0	+1
Severe pain needing IV pain medication required >24 h	0	+1
Medical or social reason for admission >24 h (infection, malignancy, no support system)	0	+1
Creatinine clearance of <30 mL/min by Cockcroft-Gault	0	+1
Severe liver impairment by clinician judgment	0	+1
Pregnant	0	+1
Documented history of heparin-induced thrombocytopenia	0	+1

Score: if ≥1 present, patient is not eligible for outpatient management.
DBP, diastolic blood pressure; *GI*, gastrointestinal; *HTN*, hypertension; *IV*, intravenous; *PR*, pulse rate; SaO_2, oxygen saturation; *SBP*, systolic blood pressure.

Low-risk PE

Patients with low-risk PE may be treated with low-molecular-weight heparin or oral anticoagulation, depending on their clinical factors.

Subsegmental PE

Treatment of subsegmental PEs is controversial because several guidelines recommend close observation in low-risk patients with subsegmental PE in the absence of deep venous thrombosis.[12,65] This is, in part, because the interrater reliability of radiologists in diagnosing subsegmental PE is slight to moderate, and false positive results of subsegmental PEs are common (5% to 25% of computed tomography pulmonary angiographies).[21,23,24,66] However, a prospective study found that among 266 patients with isolated subsegmental PE, 3.1% had venous thromboembolism recurrence by 90 days, half of which had PEs. Recurrence was more common in those with multiple subsegmental PEs and in those aged >65 years.[67] Although these data suggest that anticoagulation may be indicated in patients with subsegmental PE, the patient population and testing pattern in this international cohort included patients with a higher probability of PE than that in US cohorts.[68] We recommend anticoagulation in patients with deep venous thrombosis and subsegmental PE; however, younger patients with subsegmental PE and no evidence of deep venous thrombosis may not require anticoagulation on the basis of patient risk factors.

DISPOSITION

Historically, patients with PE have been admitted to the hospital. However, 2 clinical trials and several observational studies have found outpatient management of select

patients with acute PE to be safe and effective.[69-74] The introduction of direct oral anticoagulants has increased the ease of outpatient treatment. As a result, professional society guidelines recommend that patients with low-risk acute PE be managed as outpatients.[12,20,50,75] Several risk stratification tools are available to identify patients who can be safely managed as outpatients, including the Pulmonary Embolism Severity Index (PESI), Simplified PESI (sPESI), and Hestia criteria.[76-80] The PESI and sPESI were developed to predict 30-day mortality using comorbidities and features of clinical presentation. Patients with a PESI of I or II or a sPESI of 0 are considered low-risk, with a 90-day mortality of 0.8% (95% CI 0.4% to 1.8%).[81]

Both PESI and sPESI identify patients with low risk of mortality but do not encompass all patients who may need hospitalization. Unlike PESI and sPESI, the Hestia criteria were specifically created to identify patients who can be safely treated as outpatients and includes comorbidities and psychosocial factors. As a result, we recommend using the Hestia criteria to identify patients eligible for outpatient management (Table 4).[76] Figure 4 demonstrates one possible treatment pathway recommended by a consensus group on criteria for outpatient treatment with international treatment guidelines.[20,76]

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