CLINICAL PRACTICE

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Pulmonary Embolism

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 41-year-old man presents to the emergency department with a 3-week history of breathlessness. He recently completed a course of antibiotic medication for presumed pneumonia. On the day of presentation, he awoke with dull pain on the right side of the back. His medical history is otherwise unremarkable. His heart rate is 88 beats per minute, blood pressure 149/86 mm Hg, respiratory rate 18 breaths per minute, temperature 37°C, and oxygen saturation 95% while he is breathing ambient air. Auscultation of his chest reveals normal breath sounds and normal heart sounds. An examination of the legs is normal. His creatinine and troponin levels are within normal limits, and a radiograph of the chest is normal. The physician's implicit assessment is that the likelihood of pulmonary embolism is greater than 15%. The patient's Wells score is 0 (on a scale of 0 to 12.5, with higher scores indicating a higher probability of pulmonary embolism), and the D-dimer level is 2560 ng per milliliter. How would you evaluate this patient for pulmonary embolism, and how would you manage this case?

THE CLINICAL PROBLEM

Pulmonary embolism occurs when embolic venous thrombi are caught within the branching lung vasculature. These thrombi often develop within the leg or pelvic veins, and approximately half of all deep-vein thrombi embolize to the lungs.[1] The annual incidence of pulmonary embolism worldwide is approximately 1 in 1000 persons.[2,3] Although almost 20% of patients who are treated for pulmonary embolism dies within 90 days,[2] pulmonary embolism is not commonly the cause of death because it frequently coexists with other serious conditions, such as cancer sepsis, or illness leading to hospitalization, or with other events, such as surgeries. The true mortality associated with undiagnosed pulmonary embolism is estimated to be less than 5%,[4] but recovery from pulmonary embolism is associated with complications such as bleeding due to anticoagulant treatment,[5] recurrent venous thromboembolism, chronic thromboembolic pulmonary hypertension,[6] and long-term psychological distress.[7] Approximately half the patients who receive a diagnosis of pulmonary embolism have functional and exercise limitations 1 year later (known as post–pulmonary-embolism syndrome),[8] and the health-related quality of life for patients with a history of pulmonary embolism is diminished as compared with that of matched controls.[9] Therefore, the timely diagnosis and expert management of pulmonary embolism are important.

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KEY CLINICAL POINTS

PULMONARY EMBOLISM

- Pulmonary embolism is a common diagnosis and can be associated with recurrent venous thromboembolism, bleeding due to anticoagulant therapy, chronic thromboembolic pulmonary hypertension, and long-term psychological distress.
- A minority of patients who are evaluated for possible pulmonary embolism benefit from chest imaging (e.g., computed tomography).
- Initial treatment is guided by classification of the pulmonary embolism as high-risk, intermediate-risk, or low-risk. Most patients have low-risk pulmonary embolism, and their care can be managed at home with a direct oral anticoagulant.
- Patients with acute pulmonary embolism should receive anticoagulant therapy for at least 3 months. The decision to continue treatment indefinitely depends on whether the associated reduction in the risk of recurrent venous thromboembolism outweighs the increased risk of bleeding and should take into account patient preferences.
- Patients should be followed longitudinally after an acute pulmonary embolism to assess for dyspnea or functional limitation, which may indicate the development of post–pulmonary-embolism syndrome or chronic thromboembolic pulmonary hypertension.

STRATEGIES AND EVIDENCE

DIAGNOSTIC TESTING FOR PULMONARY EMBOLISM

Perhaps the most challenging aspect of testing for pulmonary embolism is knowing when to test.[10] Common symptoms of pulmonary embolism are fatigue, breathlessness, chest pain, dizziness, cough, diaphoresis, fever, and hemoptysis.[11] A meta-analysis of cohort studies showed that a history of dyspnea, immobilization, recent surgery, active cancer, hemoptysis, previous venous thromboembolism, or syncope was associated with an increased likelihood of pulmonary embolism.[12] Testing for pulmonary embolism should also be considered if a patient appears not to have had a response to treatment for another diagnosed respiratory condition, because initial misdiagnosis is common.

In North America, pulmonary embolism is diagnosed in only 1 patient for every 20 who are tested for the presence of pulmonary embolism when they present to the emergency department.[13] This prevalence has remained stable for two decades and is four times lower than the prevalence reported among patients in Europe.[13] Established guidelines do not stipulate which patients should undergo testing for the presence of pulmonary embolism. Qualitative research suggests that physician norms and local culture are major drivers in the decision to test for pulmonary embolism.[10] Noninvasive tests to rule out the diagnosis that are based on the assessed clinical probability of pulmonary embolism are extremely effective in safely reducing the use of computed tomography (CT),[14] resulting in only 30 to 40% of patients with suspected pulmonary embolism subsequently undergoing diagnostic imaging.[13]

In cases in which physicians have an implicit sense that their patient is very unlikely to have pulmonary embolism (estimated likelihood, <15%), large cohort studies have shown that the Pulmonary Embolism Rule-out Criteria (PERC) rule can safely rule out pulmonary embolism without further diagnostic imaging.[15] In practice, however, implicit estimation typically overestimates the probability of pulmonary embolism, which can limit the use of the PERC rule.[10] Physicians should be familiar with a validated decision rule to guide the use of D-dimer testing. Among patients with a low structured clinical probability score — a Wells score of 4.0 or less (found in 80% of patients tested in North America[16]), a revised Geneva score of 10 or less (on a scale ranging from 0 to 22, with higher scores indicating a greater probability of pulmonary embolism), and a simplified Geneva score of 4 or less (on a scale ranging from 0 to 9, with higher scores indicating greater probability of pulmonary embolism) — pulmonary embolism can be safely ruled out on the basis of D-dimer levels when manufacturer-recommended cutoffs were used (sensitivity, 98 to 99%; specificity, 37 to 40%).[17] Additional details of the scoring systems and their use are provided in Figure 1. Older data from a different D-dimer assay suggested that a D-dimer level of less than 500 ng per milliliter could be used to rule out pulmonary embolism without consideration of clinical risk factors, but

more data are needed to confirm the usefulness of this approach with current assays and relative to currently recommended strategies. The diagnostic accuracy of D-dimer testing in patients with coronavirus disease 2019 (Covid-19) remains unchanged.[18]

Newer approaches have adjusted the D-dimer threshold for ruling out pulmonary embolism and are validated for D-dimer assays for which the manufacturer-recommended cutoff is equivalent to 500 ng per milliliter. These strategies include D-dimer levels that are adjusted for age[19,20] (reported sensitivity for the age-adjusted approach ranges from 97 to 99%, and specificity ranges from 42 to 47%[17]) or that are adjusted to the YEARS algorithm for ruling out pulmonary embolism[21] (sensitivity, 96 to 98%; specificity, 54 to 61%[17]) or the Wells score[16] (sensitivity, 93 to 97%; specificity, 61 to 67%[17]). Randomized trials that compare various D-dimer strategies in patients with pulmonary embolism are lacking.

Diagnostic imaging is reserved for patients in whom pulmonary embolism cannot be ruled out on the basis of a decision rule, given the potential harms of radiation exposure. CT pulmonary angiography is usually the most timely and accessible imaging technique; however, to minimize lung and breast-tissue irradiation in younger patients, ventilation–perfusion single-photon-emission CT (SPECT) is a low-radiation option. The incidence of false positive results from CT screening vary among providers and may be as high as 5%.[22] Within 3 months after having normal results on CT that had been performed because of suspicion of pulmonary embolism, 1.2% of patients receive a diagnosis of venous thrombosis.[23] In contrast, the diagnostic performance of ventilation–perfusion SPECT has not been well established.[24]

Many patients who have been hospitalized for an unrelated condition are also tested for pulmonary embolism; there is less evidence to guide D-dimer use in these patients. Although D-dimer levels may still be highly sensitive for testing patients who are hospitalized, they are less useful in ruling out pulmonary embolism because levels are often elevated during illness and after surgery.

TREATMENT

Initial Management

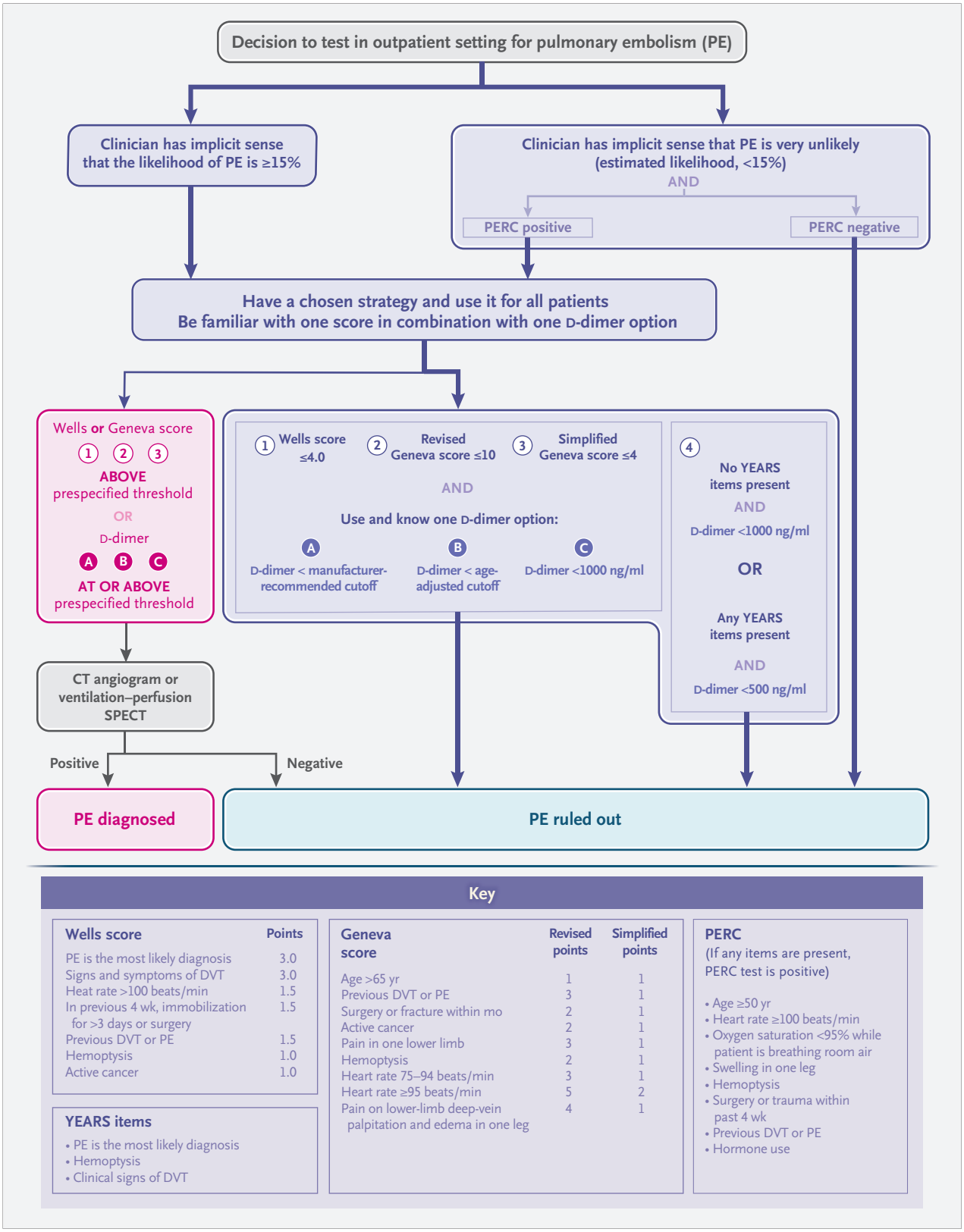
Initial treatment of pulmonary embolism is guided by risk stratification of the pulmonary embolism as high, intermediate, or low risk on the basis of the patient's clinical presentation (Fig. 2).[25] The nomenclature of "massive" and "submassive" in describing pulmonary embolism is confusing, given that clot size does not dictate therapy.

High Risk

Approximately 5% of patients present with high-risk pulmonary embolism, involving shock, end-organ hypoperfusion, hypotension (systolic blood pressure of <90 mm Hg or a decrease in systolic blood pressure of >40 mm Hg that is not caused by sepsis, arrhythmia, or hypovolemia), or cardiac arrest. Observational data support the evaluation of patients with high-risk pulmonary embolism for immediate reperfusion therapy by ruling out contraindications (e.g., brain metastases, bleeding disorders, and recent surgery). Intravenous systemic thrombolysis is the most readily available option for reperfusion, and protocols include a weight-based dose of tenecteplase,[26] alteplase at a dose of 0.6 mg per kilogram of body weight,[27] or alteplase at a dose of 100 mg administered over a period of 1 to 2 hours.[25] There is insufficient evidence to support one of these agents over the other; however, tenecteplase can be administered as a bolus in an emergency, and weight-based dosing may be preferable in elderly patients or patients with low body weight.[26] Alternative reperfusion approaches include surgical thrombectomy and catheter-directed thrombolysis (with or without thrombectomy). Additional supportive measures include the administration of inotropes and the use of extracorporeal life support.

Intermediate Risk

Patients with echocardiographic or CT evidence of right heart strain, elevated cardiac biomarkers (such as troponin or brain natriuretic peptide), or both are considered to have intermediate-risk pulmonary embolism.[25] Systemic thrombolysis is not typically recommended for these patients; in a randomized, controlled trial that assessed the addition of tenecteplase to heparin, treatment with tenecteplase resulted in an absolute reduction in the risk of hemodynamic decompensation of 3 percentage points, at the expense of a 9-percentage-point increase in the risk of major bleeding (and a 2-percentage-point increase in the risk of hemorrhagic stroke).[26] Rather, patients with intermediate-risk pulmonary embolism should receive anticoagulant therapy and be close-



Key

Wells score	Points
PE is the most likely diagnosis	3.0
Signs and symptoms of DVT	3.0
Heat rate >100 beats/min	1.5
In previous 4 wk, immobilization for >3 days or surgery	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Active cancer	1.0

YEARS items

- PE is the most likely diagnosis
- Hemoptysis
- Clinical signs of DVT

Geneva score	Revised points	Simplified points
Age >65 yr	1	1
Previous DVT or PE	3	1
Surgery or fracture within mo	2	1
Active cancer	2	1
Pain in one lower limb	3	1
Hemoptysis	2	1
Heart rate 75–94 beats/min	3	1
Heart rate ≥95 beats/min	5	2
Pain on lower-limb deep-vein palpitation and edema in one leg	4	1

PERC
(If any items are present, PERC test is positive)

- Age ≥50 yr
- Heart rate ≥100 beats/min
- Oxygen saturation <95% while patient is breathing room air
- Swelling in one leg
- Hemoptysis
- Surgery or trauma within past 4 wk
- Previous DVT or PE
- Hormone use

Figure 1 (facing page). Overview of Testing for Pulmonary Embolism in Outpatients or Patients in the Emergency Department.

Physicians may use Pulmonary Embolism Rule-out Criteria (PERC) to rule out pulmonary embolism if their implicit sense suggests there is less than 15% probability that the patient has pulmonary embolism. Otherwise, physicians should use a D-dimer assay to rule out pulmonary embolism in patients who have a low structured clinical probability score (a Wells score of ≤4.0 on a scale of 0 to 12.5, a revised Geneva score of ≤10 on a scale ranging from 0 to 22, or a simplified Geneva score of ≤4 on a scale of 0 to 9; on all three scales, higher scores indicate a greater probability of pulmonary embolism) or should use the YEARS algorithm. Each circled number refers to a different clinical decision rule, and each circled letter to a distinct D-dimer strategy. Imaging can be avoided in patients with clinical probability scores at or below the given cutoff and D-dimer level below the given cutoff. Computed tomography (CT) and ventilation–perfusion single-photon-emission computed tomography (SPECT) are reserved for patients with a clinical probability score above the preset cutoff for the chosen score or a D-dimer at or above the preset cutoff for the chosen D-dimer option. The adjusted D-dimer thresholds have been validated for assays with a manufacturer-recommended cutoff of 500 ng per milliliter. DVT denotes deep-vein thrombosis.

ly monitored to identify the 1 patient in 20 in whom shock may subsequently develop[26] (at which point reperfusion therapy may be administered). There are no guidelines for door-to-needle time for the treatment of pulmonary embolism like those that exist for the treatment of myocardial infarction and stroke.

On the basis of expert opinion, low-molecular-weight heparin is the preferred immediate anticoagulant for patients with intermediate-risk pulmonary embolism. The therapeutic effects of immediate treatment with direct oral anticoagulants rivaroxaban and apixaban as compared with low-molecular-weight heparin have not been studied in patients at intermediate risk for pulmonary embolism, and unfractionated heparin causes excess bleeding.[28] When available, catheter-directed thrombolysis remains an option for patients at intermediate risk who have proximal, central pulmonary embolism; however, there is insufficient evidence to support catheter-directed thrombolysis over low-molecular-weight heparin in these patients.

Low Risk

Patients with pulmonary embolism whose conditions are hemodynamically stable and who have no right ventricular strain and normal cardiac biomarkers are considered to have low-risk pulmonary embolism. Most of these patients can be treated with a direct oral anticoagulant (on the basis of high-quality trial data[29]) and assessed for outpatient treatment. The decision for a patient to be treated at home can be guided by the score on the simplified Pulmonary Embolism Severity Index (PESI)[25,30] or the Hestia score (Fig. 2). In contrast to the Hestia score (a checklist of criteria that preclude treatment at home), the score on the simplified PESI predicts the risk of death rather than nonfatal complications and does not account for important variables such as the availability of support for the patient at home. Results of a randomized, controlled trial showed a low risk of adverse events among patients with no Hestia criteria or with a score of 0 on the simplified PESI who received treatment as outpatients.[31]

Subsequent Management

Direct oral anticoagulants are the first-line treatment for most patients. Randomized trials have shown that direct oral anticoagulants, which do not necessitate monitoring, are as effective at reducing the risk of recurrent venous thromboembolism as vitamin K antagonists and result in a lower risk of major bleeding.[29] Because comparisons of direct oral anticoagulants are lacking, the choice of agent is guided by pharmacologic properties and patient characteristics and preferences (e.g., concomitant interacting medications and patient preference for once-daily or twice-daily medication).[32] In patients with cancer, trials support the safety and efficacy of the direct oral anticoagulants apixaban, edoxaban, and rivaroxaban as alternatives to treatment with low-molecular-weight heparin.[33,34]

Vitamin K antagonists are preferred over direct oral anticoagulants in patients with advanced kidney or liver disease and in patients with antiphospholipid syndrome who are triple-positive (i.e., positive for lupus anticoagulant, anticardiolipin, and anti–β_2-glycoprotein I antibodies), have very high antibody titers, or have a history of arterial thrombosis.[35,36] Low-molecular-weight heparin should be used to treat pregnant women

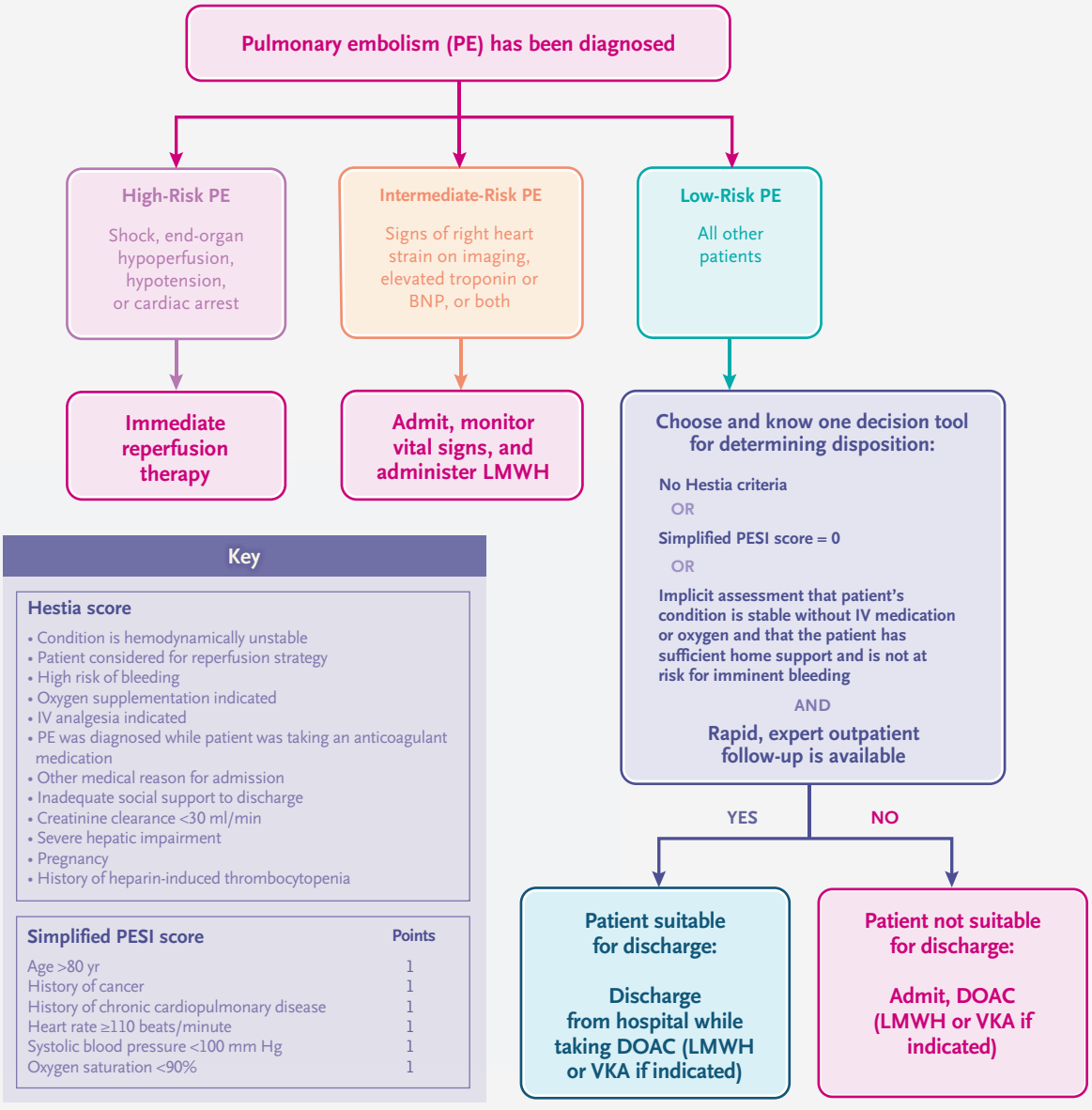


Figure 2. Overview of Pulmonary Embolism Management in the Context of Risk Stratification.

At the time of diagnosis, pulmonary embolism should be stratified as low risk, intermediate risk, or high risk. Patients with high-risk pulmonary embolism should be assessed for immediate reperfusion interventions such as systemic thrombolysis. Patients with intermediate-risk pulmonary embolism should be carefully monitored and assessed for initiation of treatment with low-molecular-weight heparin (LMWH). Most patients have low-risk pulmonary embolism and can be assessed for outpatient anticoagulant therapy according to their Hestia score, score on the simplified Pulmonary Embolism Severity Index (PESI), or the physician's implicit judgment. All patients discharged home would benefit from rapid, reliable outpatient follow-up. BNP denotes brain natriuretic peptide, DOAC direct oral anticoagulant, IV intravenous, and VKA vitamin K antagonist.

Table 1. Anticoagulant Treatment Regimens for Pulmonary Embolism.*

Initial Phase of Anticoagulation	Short-Term Phase of Anticoagulation (3–6 mo)	Indefinite Phase of Anticoagulation (after 3–6 mo)
Apixaban, administered orally, 10 mg twice a day for 7 days	Apixaban, administered orally, 5 mg twice a day	Apixaban, administered orally, 5 mg twice a day or 2.5 mg twice a day†
Rivaroxaban, administered orally, 15 mg twice a day for 21 days	Rivaroxaban, administered orally, 20 mg once a day	Rivaroxaban, administered orally, 20 mg once a day or 10 mg once a day
Low-molecular-weight heparin‡		
Administered subcutaneously for a minimum of 5 days§	Dabigatran, administered orally, 150 mg twice a day	Dabigatran, administered orally, 150 mg twice a day
Administered subcutaneously for a minimum of 5 days§	Edoxaban, administered orally, 60 mg once a day¶	Edoxaban, administered orally, 60 mg once a day¶
Administered subcutaneously for a minimum of 5 days,§ plus vitamin K antagonist, administered orally, with INR ≥2 for 2 days	Vitamin K antagonist, administered orally, with target INR of 2 to 3	Vitamin K antagonist, administered orally, with target INR of 2 to 3

* Direct oral anticoagulants and low-molecular-weight heparin are contraindicated in patients with severe renal impairment. Dosing of these medications in patients with renal impairment differs with the specific agent and among jurisdictions. With regard to use of direct oral anticoagulants in patients with obesity, post hoc analyses of phase 3 trials, observational data, and pharmacokinetic and pharmacodynamic data suggest that direct oral anticoagulants and vitamin K antagonists have similar effectiveness and safety in patients with body weight up to 120 kg or a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of up to 40. For patients who weigh more than 120 kg or have a BMI higher than 40, standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options; fewer supportive data exist for apixaban than for rivaroxaban. Other options include vitamin K antagonists, weight-based low-molecular-weight heparin (administered according to manufacturer recommendations), and fondaparinux.[52] INR denotes international normalized ratio.

† A reduction in dose may be considered after 3 to 6 months of therapy.

‡ Low-molecular-weight heparin may be administered subcutaneously throughout initial, short-term, and indefinite phases of treatment, with dosage according to body weight.

§ Low-molecular-weight heparin should be administered for 5 to 10 days before the initiation of dabigatran or edoxaban and concurrent to initiating vitamin K antagonists.

¶ Edoxaban should be administered at a dose of 30 mg daily if the creatinine clearance is 15 to 50 ml per minute, if the patient's body weight is less than 60 kg, or if potent P-glycoprotein inhibitors are being used.

with pulmonary embolism, since vitamin K antagonists and direct oral anticoagulants cross the placenta and are associated with adverse pregnancy outcomes.[25,37]

Duration of Therapy

Patients with acute pulmonary embolism should receive anticoagulant therapy for at least 3 months to reduce the risks of further embolization, thrombus extension, early recurrence of venous thromboembolism, and death (Table 1).[38] Whether treatment is stopped at 3 months or continued indefinitely depends on whether the reduced risk of recurrent venous thromboembolism with continued anticoagulation therapy outweighs the increased risk of bleeding, and the decision should take patient preferences into account.[39]

Among patients who have pulmonary embolism that was provoked by a major transient (i.e., reversible) risk factor (e.g., surgery with general anesthesia lasting >30 minutes, confinement to bed in the hospital for ≥3 days due to an acute illness, or major trauma or fracture),[40] the long-term risk of venous thromboembolism recurrence is low and anticoagulation therapy can be stopped after 3 months. If the pulmonary embolism was very large or was associated with moderate dysfunction of the right ventricle or if the patient has persistent residual symptoms, some experts recommend that treatment extend to 6 months.[39] In patients with persistent provoking factors such as active cancer or antiphospholipid syndrome or who have had previous episodes of unprovoked venous thromboembo-

Table 2. Summary of Key Guideline Recommendations for the Treatment of Pulmonary Embolism.*

Scenario	American College of Chest Physicians†	American Society of Hematology‡	European Society of Cardiology§
Home vs. hospital treatment for low-risk PE	Recommend outpatient treatment if access to medications, care, and home circumstances adequate	Suggest home treatment	Consider early discharge and home treatment if proper outpatient care and anticoagulation can be provided
Subsegmental PE	In low-risk PE, suggest clinical surveillance and ultrasonography of both legs In high-risk PE (patient is hospitalized, immobile, has cancer, is pregnant, or has unprovoked PE), suggest anticoagulation	In patients with cancer, suggest short-term anticoagulation instead of observation	Not addressed
Choice of anticoagulant	Recommend direct oral anticoagulant instead of vitamin K antagonist In antiphospholipid syndrome, recommend vitamin K antagonist instead of direct oral anticoagulant	Suggest direct oral anticoagulant instead of vitamin K antagonist unless renal impairment, liver disease, or antiphospholipid syndrome is present	Recommend direct oral anticoagulant instead of vitamin K antagonist unless severe renal insufficiency, pregnancy or lactation, or antiphospholipid syndrome is present
Choice of anticoagulant for cancer-associated PE	Recommend direct oral anticoagulant instead of low-molecular-weight heparin for most patients	Suggest direct oral anticoagulant instead of low-molecular-weight heparin for first 3 to 6 mo of treatment	Consider weight-adjusted subcutaneous low-molecular-weight heparin for first 6 mo instead of vitamin K antagonists Consider edoxaban or rivaroxaban as alternative to low-molecular-weight heparin in patients without gastrointestinal cancer
Treatment of incidentally found asymptomatic PE	Suggest same initial and long-term anticoagulation as in patients with similar symptomatic PE	Short-term anticoagulation rather than observation suggested in patients with cancer	In patients with cancer, consider same management as in patients with symptomatic PE
Thrombolysis of PE	If no hypotension, recommend against systemic thrombolysis If patient has hypotension, suggest systemic thrombolysis if bleeding risk is not high If deterioration occurs after starting anticoagulation but there is no hypotension or increased bleeding risk, suggest systemic thrombolysis instead of no thrombolysis When thrombolysis is used, suggest systemic thrombolysis instead of catheter-directed thrombolysis If hypotension and high bleeding risk, failed thrombolysis, or imminent shock is present, suggest catheter-directed thrombus removal	If hemodynamic compromise is present, recommend thrombolysis followed by anticoagulation instead of anticoagulation alone If no hemodynamic compromise is present but evidence exists of right ventricular dysfunction (according to echocardiogram and biomarkers), suggest anticoagulation alone instead of routine use of thrombolysis plus anticoagulation If thrombolysis is used, suggest systemic thrombolysis instead of catheter-directed thrombolysis	In high-risk PE, recommend rapid initiation of unfractionated heparin administered intravenously and systemic thrombolysis In presence of contraindications to or failed systemic thrombolysis, recommend surgical pulmonary embolectomy and consider percutaneous catheter-directed treatment Recommend rescue thrombolysis if hemodynamic deterioration occurs with anticoagulation; as alternative, consider surgical embolectomy or percutaneous catheter-directed treatment In intermediate-risk or low-risk PE, routine use of primary systemic thrombolysis is not recommended.

Use of inferior vena cava filter	Recommend against inferior vena cava filter in patients who can receive anticoagulation	Suggest that inferior vena cava filter not be used in patients who can receive anticoagulation	Recommend against inferior vena cava filters; consider if absolute contraindications to anticoagulation or PE recurrence despite therapeutic anticoagulation are present
Duration of anticoagulant treatment, including cancer-associated PE	Recommend 3 mo anticoagulation for primary treatment In PE provoked by major transient risk factor, recommend stopping anticoagulation at 3 mo In unprovoked PE or PE provoked by persistent risk factor, recommend extended-phase anticoagulation with direct oral anticoagulant; suggest reduced-dose instead of full-dose apixaban or rivaroxaban If patient cannot receive direct oral anticoagulant, suggest extended-phase anticoagulation with vitamin K antagonist If patient has active cancer without high bleeding risk, recommend extended anticoagulation instead of stopping anticoagulation at 3 mo; if high bleeding risk, suggest extended anticoagulation instead of stopping at 3 mo	Suggest 3 to 6 mo of anticoagulation instead of 6 to 12 mo for primary treatment Suggest indefinite anticoagulation if PE is unprovoked, provoked by chronic risk factor, or patient had previous episodes of unprovoked VTE, if bleeding risk not high and patient prefers to stay on anticoagulation For indefinite direct oral anticoagulant treatment, suggest standard-dose or lower dose direct oral anticoagulant If patient has active cancer, suggest long-term anticoagulation with direct oral anticoagulant or low-molecular-weight heparin rather than short-term anticoagulation	For first PE provoked by major transient or reversible risk factor, recommend stopping anticoagulation after 3 mo For recurrent VTE (≥1 previous episode of PE or deep-vein thrombosis) unrelated to major transient or reversible risk factor, recommend indefinite duration oral anticoagulation For antiphospholipid syndrome, recommend treatment of indefinite duration with vitamin K antagonist For first episode of PE without identifiable risk factor, or persistent risk factor other than antiphospholipid syndrome, or minor transient or reversible risk factor, consider treatment of indefinite duration with oral anticoagulation If patient does not have cancer and is receiving extended oral anticoagulation, consider low-dose direct oral anticoagulant (apixaban or rivaroxaban) after 6 mo of therapeutic anticoagulation If patient has cancer, consider extended anticoagulation for indefinite period or until cancer is cured If patient is receiving extended anticoagulation, regularly assess side effects, adherence, hepatic and renal function, and bleeding risk

* These guidelines do not include management of pulmonary embolism (PE) and venous thromboembolism (VTE) risk during pregnancy planning, pregnancy, and post partum; these specialized topics have been addressed in other guidelines.[25,37,54]

† Recommendations are based on a Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach; the strength of the recommendations are categorized as strong (phrased in the American College of Chest Physicians guidelines as "we recommend") or weak (phrased as "we suggest").[30]

‡ Recommendations are based on a GRADE approach; recommendations are labeled as strong (phrased in the American Society of Hematology guidelines as "the guideline panel recommends") or conditional ("the guideline panel suggests").[51,55]

§ The level of evidence and the strength of the recommendations were weighed and graded according to predefined scales. Recommendations are expressed as: class I, in which the evidence or general agreement (or both) is that a given treatment or procedure is beneficial, useful, and effective (phrased in the European Society of Cardiology guidelines as "is recommended"); class II, in which there is conflicting evidence or divergence of opinion (or both) about the usefulness or efficacy of a given treatment or procedure; class IIa, in which the weight of the evidence or opinion is in favor of the usefulness or efficacy of a given treatment or procedure ("should be considered"); class IIb, in which the usefulness or efficacy is less well established by the evidence or opinion ("may be considered"); and class III, in which there is evidence or general agreement that a given treatment or procedure is not useful or effective and in some cases may be harmful ("is not recommended").[25]

lism, the long-term risk of recurrence is high and indefinite anticoagulation therapy is recommended.[25,30,41]

Decision making is more nuanced in patients with a first pulmonary embolism that was unprovoked or weakly provoked (i.e., associated with a minor transient risk factor, such as estrogen therapy, pregnancy, minor surgery, or minor leg injury).[40] Among these patients, the risks of recurrent venous thromboembolism and fatal pulmonary embolism after stopping anticoagulation therapy are 10% and 0.4%, respectively, at 1 year, and 36% and 1.5% at 10 years; the risks are higher among men than among women.[42] Trials have shown that extended anticoagulation therapy, as compared with shorter durations of anticoagulation, is highly effective for the prevention of recurrent venous thromboembolism.[39] However, in a meta-analysis (involving 14 randomized, controlled trials and 13 cohort studies), extended anticoagulation with direct oral anticoagulants was associated with a risk of 1.12 major bleeding events per 100 person-years (case fatality, 9.7%), and extended anticoagulation with vitamin K antagonists was associated with a risk of 1.74 major bleeding events per 100 person-years (case fatality, 8.3%).[43] The risk of bleeding was higher among older patients and among patients who had a creatinine clearance of less than 50 ml per minute, a history of bleeding, had received antiplatelet therapy, or had a hemoglobin level of less than 10 g per deciliter.[43]

Although indefinite treatment with anticoagulation is typically recommended after a first unprovoked or weakly provoked venous thromboembolism event, particularly in patients who are not at high risk for bleeding,[39] time-limited treatment may be appropriate in some patients, including those among whom the estimated risk of recurrent venous thromboembolism is less than 5% within the first year after anticoagulation therapy is stopped.[44] Decision making with regard to the treatment of venous thromboembolism in women may be guided by the HERDOO2 rule, a prospectively validated prediction score that identifies some women with a first unprovoked or weakly provoked venous thromboembolism event who can safely discontinue anticoagulation therapy (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[45] No validated score is currently available for use in men who have had a first unprovoked or weakly provoked pulmonary embolism, and many experts recommend continuing anticoagulation therapy indefinitely in these patients.

In patients who continue to receive anticoagulants indefinitely, data from randomized trials indicate that low-dose direct oral anticoagulant regimens (i.e., rivaroxaban or apixaban) after the initial 6 months of full-dose anticoagulation have effectiveness and safety similar to those of full-dose regimens[46,47] and greater effectiveness than aspirin.[47] However, low-dose regimens have not been assessed in pulmonary embolism in patients with cancer, in those with anatomically extensive pulmonary embolism, or in those at high risk for recurrent pulmonary embolism. Factors that may influence the choice of indefinite anticoagulant regimen are shown in Table S2.

OTHER TESTING

Occult cancer is detected in 5.2% of patients within 1 year after a diagnosis of unprovoked pulmonary embolism.[48] An extensive screening strategy may detect more cancers than limited screening, but data are limited as to whether such screening is associated with better patient outcomes.[48,49] Experts recommend limited cancer screening guided by medical history, physical examination, basic laboratory tests and chest radiographs, and age-specific and sex-specific cancer screening.[49]

Patients should be evaluated 3 to 6 months after acute pulmonary embolism is diagnosed to assess for dyspnea or functional limitation, which may indicate the development of post–pulmonary-embolism syndrome or chronic thromboembolic pulmonary hypertension.[25,50] If a decision to continue anticoagulation indefinitely was made at the time of diagnosis of pulmonary embolism, this decision should be reassessed annually or more often; anticoagulation may need to be discontinued if the risk of bleeding increases, a major bleeding event occurs, or the patient prefers to stop treatment.

GUIDELINES

Current guidelines for pulmonary embolism management include those issued by the American College of Chest Physicians (ACCP),[30] the American Society of Hematology (ASH),[41,51] and the European Society of Cardiology (ESC).[25] A summary

of the key recommendations in these guidelines is provided in Table 2. Our recommendations align with these guidelines, which are largely concordant but differ in the strength of their recommendations for some topics. ACCP and ASH guidelines recommend anticoagulation be stopped at 3 months in the case of a first pulmonary embolism provoked by a weak transient risk factor, a recommendation that diverges from ESC guidelines, which suggest that indefinite anticoagulation be considered in such patients. Our approach to this situation generally aligns with the ACCP and ASH guidelines while taking into account factors that influence the risk of recurrence (e.g., male sex or older age) and patient preference.

AREAS OF UNCERTAINTY

Appropriate management of subsegmental pulmonary embolism (a single isolated subsegmental pulmonary embolus or multiple emboli, without the presence of pulmonary embolism in segmental or more proximal pulmonary vessels and without deep-vein thrombosis in the legs) is uncertain. Although some guidelines suggest clinical surveillance instead of anticoagulation in patients with low-risk subsegmental pulmonary embolism, a recent prospective cohort study involving such patients who were treated without anticoagulation therapy showed a higher-than-expected incidence of recurrent venous thromboembolism during 90-day follow-up.[53] A randomized, placebo-controlled trial of clinical surveillance as compared with anticoagulation in this patient population is ongoing (ClinicalTrials.gov number, NCT04263038).

Whether a particular direct oral anticoagulant is preferable for the treatment of pulmonary embolism is not known. Ongoing randomized trials are assessing apixaban as compared with rivaroxaban for the initial treatment in patients with venous thromboembolism (NCT03266783) and various doses of these drugs for extended treatment of such patients (NCT03285438). A multinational, randomized, controlled trial is under way to assess the efficacy and safety of a therapy involving a reduced dose of thrombolytic medication in patients with intermediate-risk acute pulmonary embolism (NCT04430569). High-quality data are needed to inform the benefits and risks of intravascular thrombolysis and clot-retrieval approaches in the treatment of patients with pulmonary embolism.

CONCLUSIONS AND RECOMMENDATIONS

The patient with breathlessness described in the vignette was estimated to have greater than a 15% likelihood of pulmonary embolism. In the context of the patient's low Wells score for pulmonary embolism, D-dimer testing was warranted to guide the need for imaging; CT is indicated, given the D-dimer level of more than 1000 ng per milliliter. Under the presumption that the patient's CT scan confirms pulmonary embolism and shows normal right-ventricle dimensions, he would be classified as having low-risk pulmonary embolism, given his normal troponin level. Treatment with a direct oral anticoagulant should be started promptly, and the patient should be given information about the pulmonary embolism diagnosis. In the absence of contraindications to treatment on an outpatient basis (no Hestia criteria present), the patient can be discharged directly from the emergency department with prompt clinic follow-up. We would recommend that he undergo cancer screening appropriate for his age and personal risk. After the patient receives 3 to 6 months of therapy with a direct oral anticoagulant administered at a treatment-level dose, in the absence of an increased bleeding risk and considering his preferences, we would recommend switching to a low-dose direct oral anticoagulant on a long-term basis for secondary prevention.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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