

# Acute Pulmonary Embolism

## A Review

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 Multimedia

**IMPORTANCE** Pulmonary embolism (PE) is characterized by occlusion of blood flow in a pulmonary artery, typically due to a thrombus that travels from a vein in a lower limb. The incidence of PE is approximately 60 to 120 per 100 000 people per year. Approximately 60 000 to 100 000 patients die from PE each year in the US.

**OBSERVATIONS** PE should be considered in patients presenting with acute chest pain, shortness of breath, or syncope. The diagnosis is determined by chest imaging. In patients with a systolic blood pressure of at least 90 mm Hg, the following 3 steps can be used to evaluate a patient with possible PE: assessment of the clinical probability of PE, D-dimer testing if indicated, and chest imaging if indicated. The clinical probability of PE can be assessed using a structured score or using clinical gestalt. In patients with a probability of PE that is less than 15%, the presence of 8 clinical characteristics (age <50 years, heart rate <100/min, an oxygen saturation level of > 94%, no recent surgery or trauma, no prior venous thromboembolism event, no hemoptysis, no unilateral leg swelling, and no estrogen use) identifies patients at very low risk of PE in whom no further testing is needed. In patients with low or intermediate clinical probability, a D-dimer level of less than 500 ng/mL is associated with a posttest probability of PE less than 1.85%. In these patients, PE can be excluded without chest imaging. A further refinement of D-dimer threshold is possible in patients aged 50 years and older, and in patients with a low likelihood of PE. Patients with a high probability of PE (ie, >40% probability) should undergo chest imaging, and D-dimer testing is not necessary. In patients with PE and a systolic blood pressure of 90 mm Hg or higher, compared with heparin combined with a vitamin K antagonist such as warfarin followed by warfarin alone, direct oral anticoagulants such as apixaban, edoxaban, rivaroxaban, or dabigatran, are noninferior for treating PE and have a 0.6% lower rate of bleeding. In patients with PE and systolic blood pressure lower than 90 mm Hg, systemic thrombolysis is recommended and is associated with an 1.6% absolute reduction of mortality (from 3.9% to 2.3%).

**CONCLUSIONS AND RELEVANCE** In the US, PE affects approximately 370 000 patients per year and may cause approximately 60 000 to 100 000 deaths per year. First-line therapy consists of direct oral anticoagulants such as apixaban, edoxaban, rivaroxaban, or dabigatran, with thrombolysis reserved for patients with systolic blood pressure lower than 90 mm Hg.

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**P**ulmonary embolism (PE) is defined as occlusion in the pulmonary arterial tree, preventing blood flow distal to the occlusion. PE is most frequently caused by thrombosis in a systemic blood vessel, usually in a deep vein of the lower limb. In western countries, the incidence of PE in the general population is approximately 60 to 120 cases per 100 000 population per year, with an in-hospital mortality of 14% and a 90-day mortality of 20%.<sup>1-3</sup> It is estimated that approximately 60 to 100 000 patients die of PE each year in the US.<sup>3,4</sup> Because symptoms are nonspecific, PE remains a diagnostic challenge, and fewer than 10% of patients evaluated for PE are ultimately diagnosed with a PE.<sup>5-8</sup> This review summarizes current evidence regarding the diagnosis and treatment of acute pulmonary thromboembolism in adults.

## Methods

We searched PubMed for English-language studies published between January 1, 2010, and March 1, 2022, that examined the epidemiology, diagnosis, and treatment of pulmonary embolism. Articles were screened using the MeSH term *pulmonary embolism* associated with diagnosis, epidemiology, pathophysiology, or therapy. The search was updated on July 1, 2022. Included articles were limited to international guidelines, randomized clinical trials, large prospective clinical studies, and systematic reviews. Articles were selected for inclusion according to the study quality (meta-analyses and randomized clinical trials were prioritized along with large prospective clinical studies) and relevance to general practice.

Of 508 articles identified, 85 were included (1 practice guideline, 21 randomized clinical trials, 31 meta-analyses, 10 systematic reviews, 15 prospective studies, and 7 ancillary analyses of clinical trials). Additional relevant references were identified from selected articles.

## Discussion

### Epidemiology

With increased use of computed tomographic pulmonary angiography, the incidence of PE diagnosis in the US has risen from 62 per 100 000 in 1998 to 112 per 100 000 in 2006 and 120 per 100 000 in 2016.<sup>3,9,10</sup> The increased incidence of PE may be due to increased diagnosis of smaller PEs or PEs that are not life threatening that could be left untreated without adverse outcomes.<sup>11</sup> Older age is associated with a higher annual incidence of PE; the incidence of PE is less than 50 per 100 000 among people younger than 50 years compared with 350 per 100 000 among people older than 75 years.<sup>12</sup>

### Pathophysiology

PEs primarily consist of fibrin and red blood cells. Approximately 70% to 80% of PEs begin as thrombi in the deep veins of the lower extremities or pelvis. Approximately 6% begin in the deep veins of the upper extremities.<sup>13-16</sup> Thrombus formation is facilitated by 3 factors (the Virchow triad): venous stasis, local hypercoagulability, and endothelial injury.<sup>13,14</sup> Other factors such as local infection, extrinsic venous compression, intravenous catheters or devices, or trauma can initiate thrombus formation. Venous thromboembolism (VTE) results from the interaction of environmental and constitutional predisposing risk factors, which can be inherited or acquired. These include nonmodifiable factors such as older age, thrombophilias, or a familial history of VTE, and potentially temporary factors such as immobilization (major trauma or surgery, recent long airplane or car trips), cancer, estrogen-containing oral contraceptives, pregnancy, and postpartum status.<sup>13</sup> Smoking is not associated with higher rates of VTE. Patients with unprovoked PE, defined as PE that occurs without one of the temporary conditions (previously defined) that predisposes to thrombosis, should be evaluated for the presence of blood factors that indicate hypercoagulable state and occult cancer. However, there is no evidence that these investigations improve outcomes.<sup>17-19</sup>

The clinical manifestations of PE range from asymptomatic to hemodynamic collapse and death. Although PE alters pulmonary gas exchange and can cause hypoxemia, hemodynamic compromise is the most significant contributor to worse prognosis. The existence and degree of pulmonary artery occlusion and associated vasoconstriction contribute to increased pulmonary vascular resistance, which increases right ventricular afterload and results in reduced left ventricular preload and decreased cardiac output. The hemodynamic response to PE depends on the size of the occlusion and presence of preexisting chronic right heart failure and left heart failure.<sup>20</sup>

### Clinical Presentation

Because symptoms associated with PE are nonspecific, identifying PE can be challenging. PE should be suspected in patients with chest pain or dyspnea without another obvious cause of the symptoms. Approximately 5% to 10% of patients presenting to the emer-

gency department report chest pain and dyspnea as their primary symptom.<sup>21-23</sup> A retrospective study of 881 patients evaluated in 3 emergency departments in France reported that approximately 30% of patients with chest pain were investigated for PE.<sup>7</sup> PE may also present as unexplained syncope. In 2 multicenter prospective cohort studies that included approximately 20 000 patients with syncope, the overall incidence of PE at 30 days was 0.6% (95% CI, 0.5% to 0.8%) and 2.2% (95% CI, 1% to 4%).<sup>24,25</sup>

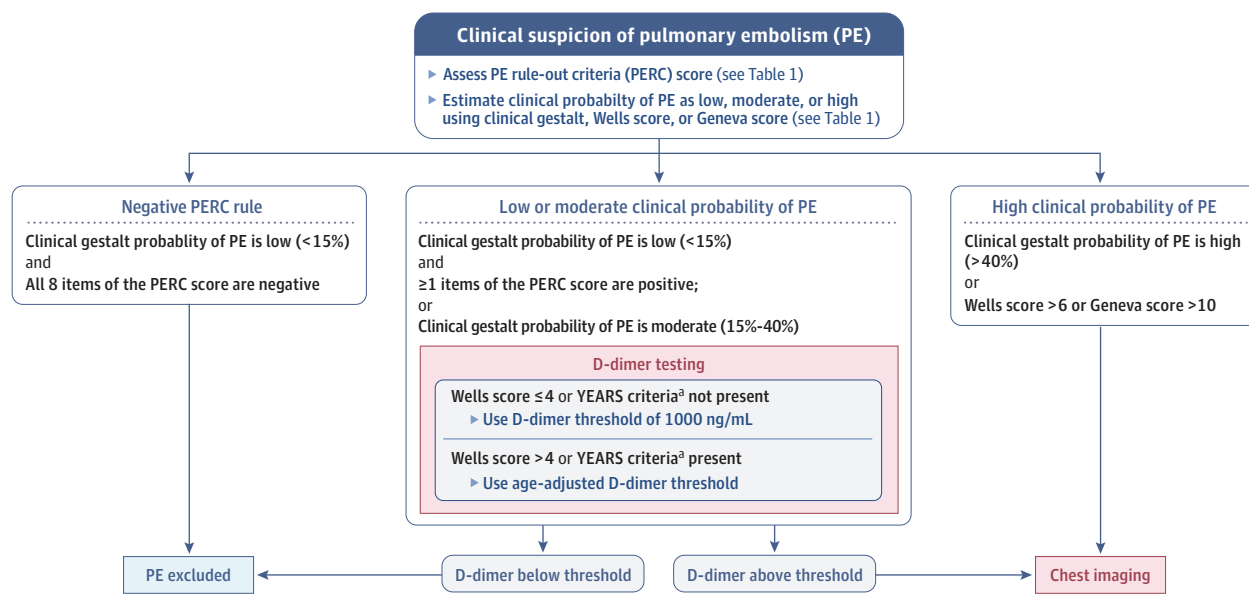
PE may be an incidental finding on chest imaging performed as part of diagnostic evaluations in patients without signs or symptoms typical of PE.<sup>26</sup> Because PE has a high mortality rate, clinicians may initiate diagnostic evaluations for PE even when the likelihood of PE is low. Consequently, PE is diagnosed in less than 10% of people in Europe and less than 5% of people in the US who undergo diagnostic evaluation for PE.<sup>5-7,27</sup> Tachycardia, hemoptysis, and clinical signs of deep venous thrombosis (DVT) are associated with a higher likelihood of PE.<sup>28,29</sup>

### Diagnostic Strategies

D-dimer is a fibrin degradation protein fragment created when fibrin undergoes endogenous fibrinolysis. Blood D-dimer levels are increased in the presence of thrombosis. With a threshold of 500 ng/mL, this D-dimer testing has a 97% to 100% negative predictive value for PE and is often part of diagnostic strategies to rule out PE without the need for unnecessary chest imaging.<sup>30,31</sup> However, depending on a patient's risk of PE, D-dimer can have low specificity (in patients with low probability) and can be insufficiently sensitive (in patients with high probability). Therefore, a bayesian approach is recommended to reduce the use of chest imaging while avoiding an unacceptable high rate of missed PE diagnosis.<sup>32</sup> The scientific and standardization committee of the International Society on Thrombosis and Hemostasis recommends that a diagnostic strategy can be considered safe if it is associated with missing less than 1.85% to 2% of patients with PE.<sup>32-35</sup>

Standard diagnostic strategies for PE consist of 3 steps: evaluating clinical probability, D-dimer testing when indicated, and chest imaging if indicated (Figure 1). The first step of the diagnostic strategy is estimating the clinical probability of PE as low, moderate, or high. The PE prevalence within these 3 categories varies across different clinical prediction rules but is approximately less than 15% among persons with low clinical probability, 15% to 40% among persons with moderate clinical probability, and greater than 40% among persons with high clinical probability.<sup>36,37</sup> Two structured scores have been validated for identifying the clinical probability of PE: the Wells score, and the revised Geneva score (Table 1).<sup>29,38</sup> These scores include consideration of predisposing factors (recent immobilization, malignancy, and history of VTE) and clinical characteristics at presentation (age, heart rate, signs of DVT, hemoptysis). The revised Geneva score includes only objective components, whereas the Wells score also includes 1 subjective item—PE is the most likely diagnosis. In addition to these 2 structured scores, the clinical probability can be estimated by clinical gestalt: an unstructured clinical impression of whether the probability of PE is low (<15%), moderate (15%-40%), or high (>40%). These 3 methods of clinical probability assessment perform equally well.<sup>36</sup> In patients with low or intermediate clinical probability, a D-dimer of less than 500 ng/mL is associated with a posttest probability of PE that is less than 1.85%. In these patients, PE can be excluded without chest imaging.<sup>30</sup>

Figure 1. Diagnostic Strategy for Pulmonary Embolism



<sup>a</sup> PE is unlikely if the Wells score is less than or equal to 4 or if there are no YEARS criteria (ie, no hemoptysis, no clinical sign of deep venous thrombosis, and no opinion from the clinician that PE is the most likely diagnosis).

Although PERC and YEARS criteria have been validated in randomized clinical trials, this overall algorithm has not been validated in randomized clinical trials.

Table 1. Clinical Prediction Rules for the Diagnosis of Pulmonary Embolism

PERC system <sup>a</sup>		Wells system <sup>b</sup>		Revised Geneva system <sup>c</sup>	
Patient characteristic	Score	Patient characteristic	Score	Patient characteristic	Score
Unilateral leg swelling	+1	Clinically suspected DVT	+3	Unilateral lower limb pain	+3
Heart rate >99/min	+1	Heart rate >100/min	+1.5	Pain on lower limb palpation and unilateral edema	+4
Immobilization or surgery in the previous 4 wk	+1	Immobilization or surgery within the previous 4 wk	+1.5	Heart rate 75-94/min	+3
Previous DVT or PE	+1	Previous DVT or PE	+1.5	Heart rate >94/min	+5
Hemoptysis	+1	Hemoptysis	+1	Surgery or lower limb fracture within the previous 4 wk	+2
Age >49 y	+1	Cancer within 6 mo	+1	Previous DVT or PE	+3
Oxygen saturation by pulse oximetry on room air <95%	+1	Alternative diagnosis is less likely than pulmonary embolism	+3	Hemoptysis	+2
Estrogen use	+1			Cancer within 12 mo	+2
				Age >65 y	+1

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; PERC, pulmonary embolism rule-out criteria; DVT, deep venous thrombosis.

<sup>a</sup> The PERC rule is negative if implicit physician's gestalt clinical probability is low and PERC score (range, 0-6) is 0, which is associated with a greater than 98.5% negative predictive value to rule out PE.

<sup>b</sup> Wells score range, 0 to 8. Clinical probability is low (<15%) if score is 4.5 or less; intermediate (15%-40%) if score is 5 or 6; high (>40%) if score is greater than 6.

<sup>c</sup> Geneva score range, 0 to 22. Clinical probability is low (<15%) if score is less than 4; intermediate (15%-40%) if score is 5 to 10; high (>40%) if score is greater than 10.

D-dimer testing is not necessary in 2 situations. First, patients who meet criteria for a negative PE rule out criteria (PERC) rule, defined by having both a low clinical gestalt estimate (<15%) and none of the 8 PERC items: age older than 49 years, heart rate more than 99 beats per minute, oxygen saturation by pulse oximetry (SpO<sub>2</sub>) less than 95%, hemoptysis, previous VTE, trauma or surgery within the previous 4 weeks, unilateral leg swelling, and estrogen use (Table 1).<sup>39</sup> Approximately 30% to 50% of patients with a low clinician-assessed probability of PE have none of the 8 PERC items.<sup>37,40</sup> In the PROPER validation randomized clinical trial (1916 patients presenting with signs and symptoms of PE), the subset of 823 patients who met none of the items of PERC had a prevalence of PE of approximately 0.1% (95%

CI, 0% to 0.8%). Therefore, PE can be safely excluded without further testing in these patients. Applying PERC was associated with a 10% absolute reduction in use of chest imaging in the PROPER trial.<sup>40</sup> Second, in patients with a high clinical probability (defined as >40%), the high prevalence of PE can lower the D-dimer negative predictive value, which could increase the risk of diagnostic failure. Consequently, patients with high clinical probability for PE should undergo chest imaging without prior D-dimer testing.<sup>18,41</sup>

For other patients who do not meet criteria for the PERC and who do not have high clinical probability, D-dimer testing informs the decision to perform chest imaging. Because D-dimer levels are physiologically elevated in older patients, the D-dimer thresholds can

be adapted to the patient's age. The ADJUST-PE clinical trial included 3346 patients with suspected PE and used a D-dimer threshold of 500 ng/mL for patients aged 50 years or younger and a D-dimer value consisting of age multiplied by 10 ng/mL for patients older than 50 years. In this study, the rate of PE in patients older than 50 years whose D-dimer was higher than 500 ng/mL but less than age multiplied by 10 ng/mL was 0.3% (95% CI 0.1%-1.7%).<sup>42</sup> Use of these D-dimer thresholds was associated with a 23% absolute reduction of chest imaging studies.

The optimal threshold for D-dimer to determine the likelihood of PE can be evaluated with either the PEGeD (pulmonary embolism-graduated D-dimer) or YEARS rules. PEGeD uses the Wells Score to define low clinical probability; YEARS defines a low clinical likelihood for PE if none of the following 3 characteristics are present: hemoptysis, clinical sign or symptom of DVT (unilateral leg swelling or pain), and the clinician's sense that PE is the most likely diagnosis.<sup>6,27,43</sup> In these patients with a low likelihood of PE, a D-dimer threshold of 1000 ng/mL can be used instead of the age-adjusted D-dimer threshold. In 2 large prospective cohort studies of 1325 and 3465 patients, the PEGeD- and the YEARS-based strategies were each associated with rates of missed diagnosis of VTE of 0.05% and 0.6% and absolute reductions of chest imaging rates of 18% (95% CI, 16%-19% [from 52% to 34%])<sup>27</sup> and 14% (95% CI, 12%-16% [from 48% to 34%]).<sup>43</sup>

In summary, PE can be excluded without further testing in patients presenting with symptoms of PE who meet none of the 8 clinical items of PERC. In patients with low or intermediate clinical probability, PE can be excluded without imaging studies if there is a low likelihood for PE and D-dimer level of less than 1000 ng/mL or if there is not a low likelihood for PE and a D-dimer below the age-adjusted threshold (Figure 1).

A computed tomographic (CT) pulmonary angiogram is the imaging study of choice for the diagnosis of PE because it has high diagnostic performance and identifies alternative diagnoses such as pneumonia or pleural effusions. In a systematic review and meta-analysis of 16 studies including 6 clinical trials and a total of 4392 patients, evidence of an intraluminal filling defect in the pulmonary arterial tree on chest imaging had a sensitivity of 94% for PE.<sup>44</sup>

The ventilation/perfusion lung scintigraphy (V/Q scan) is a radiologic test for diagnosing PE that has several limitations. V/Q scans are less readily available than CT pulmonary angiograms, have a relatively low sensitivity for PE (56%-98%), and lack the ability to identify alternative diagnoses.<sup>18,44</sup> Pulmonary angiography, the former criterion standard for diagnosing PE, is performed by injecting intravenous contrast directly into the pulmonary arteries via a percutaneous catheter advanced through the heart under fluoroscopic guidance. Pulmonary angiography is rarely used to diagnose PE because it has a diagnostic performance similar to CT pulmonary angiogram, which is a less invasive and less labor-intensive imaging study.

In patients with a suspected PE and hemodynamic instability (defined by a systolic blood pressure <90 mm Hg and end-organ hypoperfusion), bedside echocardiography can detect nonspecific signs of PE such as right ventricular dilatation and a flattened intraventricular septum.<sup>45,46</sup> Rarely, bedside echocardiography can diagnose PE by detecting a thrombus moving between the heart and the pulmonary artery. However, bedside echocardiography has a negative predictive value of 50% and therefore a normal examination cannot exclude PE.<sup>18,47</sup> In unstable or acutely ill patients for whom the clinical probability of PE is high and treatment decisions may be

### Box. Simplified Pulmonary Embolism Severity Index

#### Patient Characteristics<sup>a</sup>

- Age >80 years
- Medical history
  - Cancer
  - Chronic cardiopulmonary disease
- Heart rate >109/min
- Systolic blood pressure <100 mm Hg
- Oxygen saturation by pulse oximetry on room air <90%

<sup>a</sup> Each item on the index, if present, is indicated by a score of 1. Score range, 0 (indicates low risk with a risk of 1.5% recurrent venous thromboembolism and a 1.1% risk of death at 30 days) to 6 (score greater than 0 indicates intermediate or high risk with a 10% risk of death at 30 days).

required, bedside echocardiography can be used before chest imaging is safe to perform.<sup>18</sup>

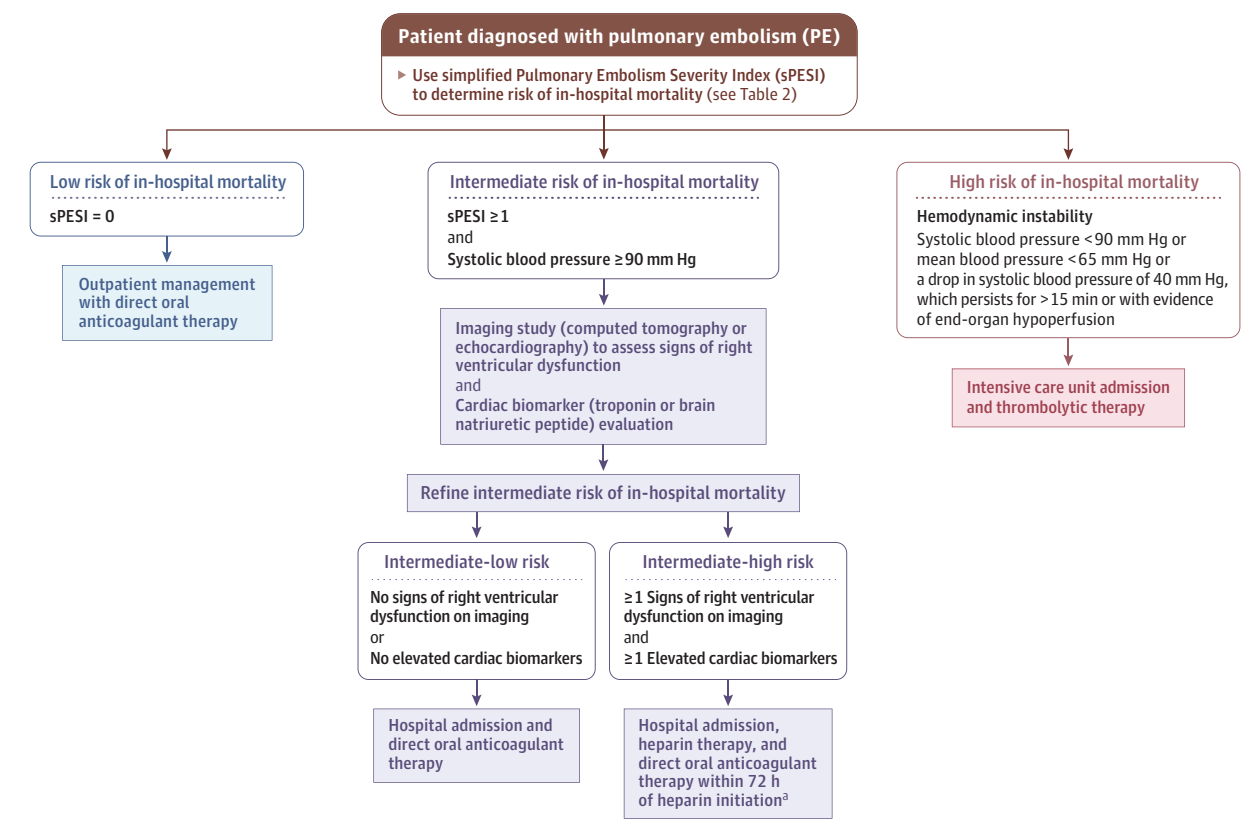
Although pregnancy is a risk factor for thromboembolism, pregnant people who have chest pain or dyspnea do not appear to have a higher risk of PE compared with nonpregnant individuals with chest pain or dyspnea.<sup>48</sup> The D-dimer level increases physiologically during pregnancy, which can result in more frequent use of chest imaging during diagnostic evaluation. In a single-group clinical trial that included 494 pregnant individuals suspected of PE, adopting an elevated D-dimer threshold of 1000 ng/mL in patients with no YEARS criteria allowed the rule out of PE in 39% (95% CI, 35% to 44%) of patients without chest imaging, with a rate of missed VTE of 0.21% (95% CI, 0.04% to 1.2%).<sup>49</sup> In pregnant individuals who have signs or symptoms of PE, lower limb Doppler ultrasonography is recommended prior to chest imaging. Detection of DVT obviates the need to test for thromboembolism, thereby avoiding potentially teratogenic irradiation associated with chest imaging.<sup>18</sup> There are no data to support preferentially using CT pulmonary angiogram or V/Q scan testing for diagnostic evaluation of pregnant individuals who may have PE.

It is unclear whether COVID-19 is a risk factor for PE. A meta-analysis of 102 studies that included 64 503 patients reported a 7.8% (95% CI, 6.2%-9.4%) prevalence of PE in patients admitted to the hospital for COVID-19, with an increased risk in patients admitted to the intensive care unit compared with the general medical unit.<sup>50</sup> However, in an international cohort study of 3358 patients who had CT pulmonary angiograms consistent with possible PE at initial presentation in the emergency department, patients with COVID-19 had similar rates of PE compared with patients without COVID-19 (15% in both groups, difference, 0.3% [95% CI, -3% to 3%]).<sup>51</sup> Therefore, for patients with COVID-19 and suspected PE, no adjustment to a standard PE diagnostic strategy is required.<sup>52</sup>

### Treatment

Patients diagnosed with PE should be stratified according to their risk for in-hospital mortality (low, intermediate, or high risk) when selecting therapy.<sup>18</sup> The simplified Pulmonary Embolism Severity Index (sPESI) (Box) is a 6-item score that classifies patients with PE at low risk for early mortality if all 6 items of the score are negative (ie, sPESI = 0). If at least 1 item is positive, then sPESI = 1 and the patient is not classified with a low risk for PE (Figure 2). In a study of

Figure 2. Treatment of Pulmonary Embolism



sPESI score range, 0 (indicates low risk with a risk of 1.5% recurrent venous thromboembolism and a 1.1% risk of death at 30 days) to 6 (score greater than 0 indicates intermediate or high risk with a 10% risk of death at 30 days).

<sup>a</sup> In patients at intermediate-high risk, monitor over the first hours or days due to the risk of hemodynamic collapse.

This algorithm has not been validated in randomized clinical trials.

995 patients with acute PE who were treated with low molecular-weight heparin (LMWH) followed by a vitamin K agonist (VKA), those with an sPESI score of 0 had a 30-day mortality of 1% (95% CI, 0.0%-2.1%).<sup>53</sup> Additional studies were consistent with these results.<sup>54-56</sup>

In these low-risk patients, compared with the historical conventional treatment strategy of LMWH followed by a VKA, direct oral anticoagulants (DOACs) such as apixaban, rivaroxaban, edoxaban, and dabigatran were noninferior for the outcome of symptomatic VTE recurrence (Table 2), with an absolute difference ranging from -0.4% to 0.3%.<sup>57-60</sup> DOACs were also associated with a lower risk of bleeding.<sup>57-59</sup> A meta-analysis of 27 127 patients with VTE and no hypotension from 6 clinical trials reported that compared with conventional treatment with heparin and VKA warfarin, use of DOACs was not associated with a significant difference in the risk of PE recurrence and was associated with a reduced risk of major bleeding (absolute risk difference, -0.6% [95%CI, -1.0% to -0.3%]).<sup>61</sup>

Patients who have at least 1 positive component in the sPESI score and a systolic blood pressure of at least 90 mm Hg are at intermediate risk, with a reported 30-day in-hospital mortality risk of approximately up to 10%.<sup>53</sup> The safety and efficacy of DOAC therapy have not been specifically studied in this group of patients, but subgroup analyses of previously published trials suggested an im-

proved benefit-risk profile of DOACs compared with LMWH.<sup>57-59</sup> One clinical trial of 2411 patients with PE at intermediate risk reported that patients receiving a delayed DOAC prescription (after 72 hours of LMWH treatment) had a 9% risk of death and shock at 30 days, compared with 4.8% in patients who received a DOAC within 72 hours of LMWH treatment initiation (odds ratio [OR], 0.44 [95% CI, 0.15-1.30]).<sup>62</sup> The safety of introducing DOAC within 72 hours of LMWH was confirmed in the single-group PEITHO-2 trial, in which 402 patients who received 72 hours of heparin followed by dabigatran without overlap had a 2% risk of PE recurrence or death at 6-month follow-up (Table 2).<sup>64</sup>

An individual patient-level meta-analysis of 6 prospective cohort studies that included 2874 normotensive patients with PE reported that right ventricular dysfunction was associated with an increased risk of death, shock, or recurrent PE (OR, 2.28 [95% CI, 1.58-3.29]).<sup>64</sup> A systematic review of 21 studies (11 prospective and 10 retrospective) that included 3111 patients reported that compared to the criterion standard of echocardiography, an increased right ventricular:left ventricular ratio greater than 1.0 had a sensitivity of 83% and a specificity of 75% for right ventricular dysfunction.<sup>65</sup> Patients with 1 or more signs of right ventricular dysfunction on imaging and elevated cardiac biomarker (troponin, brain natriuretic peptide [BNP], or N-terminal pro-BNP) are defined as intermediate-high-risk patients.



Table 2. Oral Anticoagulation Therapies for the Treatment of Pulmonary Embolism

Example medications by therapy category	Mechanism of action	Efficacy	Adverse events
Vitamin K antagonist			
Warfarin	Vitamin K epoxide reductase inhibitor: decreased active vitamin K, decreased activate coagulation factors II, VII, IX, X, and proteins S, C, and Z	In 1426 patients with VTE treated with parenteral anticoagulation followed by warfarin, 1.3% had recurrent VTE, and 0.4% had symptomatic nonfatal PE at 6-36 mo <sup>63</sup>	In 1426 patients with VTE, 10.2% had major or clinically relevant bleeding event, and 1.8% had a major bleeding event at 6 to 36 mo <sup>63</sup>
Acenocoumarol	Vitamin K epoxide reductase inhibitor: decreased active vitamin K, decreased activate coagulation factors II, VII, IX, X, and proteins S, C, and Z	In 2413 patients with PE treated with enoxaparin and warfarin within 48 h, 1.8% had recurrent VTE and 1% had PE at 3, 6, or 9 mo <sup>57</sup> In 886 patients with VTE treated with enoxaparin for 5 d and warfarin, 2.6% had recurrent VTE at 6 mo <sup>58</sup> In 1669 patients with PE, 3.9% had recurrent VTE or VTE-related death at 12 mo <sup>59</sup>	In 2405 patients with PE, 11.4% had clinically relevant nonmajor bleeding, and 2.2% had any major bleeding episode at 3, 6, or 9 mo <sup>57</sup> In 2689 patients with VTE, 8% had clinically relevant nonmajor bleeding, and 1.8% had major bleeding at 6 mo <sup>58</sup> In 4122 patients with VTE, 10.3% had first major bleeding or clinically relevant nonmajor bleeding, and 1.6% had major bleeding at 12 mo <sup>59</sup>
Direct oral anticoagulants <sup>a</sup>			
Dabigatran	Factor IIa (thrombin) inhibitor	In 1430 patients with VTE treated with parenteral anticoagulation followed by dabigatran, 1.8% had recurrent VTE, and 0.7% had symptomatic nonfatal PE at 6-36 mo <sup>63</sup>	In 1430 patients with VTE, 5.6% had a major or clinically relevant bleeding event, and 0.9% had a major bleeding event at 6-36 mo <sup>63</sup>
Rivaroxaban	Factor Xa inhibitor	In 2419 patients with PE with or without DVT, 2.1% had recurrent VTE at 3, 6, or 9 mo <sup>57</sup>	In 2412 patients with PE with or without DVT, 10.3% had clinically relevant nonmajor bleeding, and 1.1% had any major bleeding episode at 3, 6, or 9 mo <sup>57</sup>
Apixaban	Factor Xa inhibitor	In 900 patients with PE treated with apixaban, 2.3% had recurrent VTE at 6 mo <sup>58</sup>	In 2676 patients with VTE, 3.8% had clinically relevant nonmajor bleeding, and 0.6% had major bleeding at 6 mo <sup>58</sup>
Edoxaban	Factor Xa inhibitor	In 1650 patients with PE treated with edoxaban, 2.8% had recurrent VTE or VTE-related death at 12 mo <sup>59</sup>	In 4118 patients with VTE, 8.5% had clinically relevant nonmajor bleeding, and 1.4% had major bleeding at 12 mo <sup>59</sup>

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism (indicates PE or deep venous thrombosis).

<sup>a</sup> Oral anticoagulant therapies for the treatment of PE are indicated for patients with no hemodynamic instability. Hemodynamic instability is defined by

a systolic blood pressure lower than 90 mm Hg, mean blood pressure lower than 65 mm Hg, a drop in systolic blood pressure of 40 mm Hg that persists for more than 15 minutes, or evidence of end-organ hypoperfusion.

Patients with hemodynamic instability, defined by a systolic blood pressure lower than 90 mm Hg that persists more than 15 minutes or that is associated with an end-organ hypoperfusion (such as acute kidney injury) have an approximate 20% risk of 30-day mortality, compared with 5% for non-high-risk PE.<sup>66</sup> In these high-risk patients, thrombolytic therapy with recombinant tissue-type plasminogen activator (rt-PA [eg, tenecteplase, streptokinase, and urokinase]) is recommended.<sup>18,67</sup> In a systematic review of 15 randomized clinical trials that included 2057 patients with PE, compared with heparin alone, thrombolytic therapy with tenecteplase, urokinase, or streptokinase was associated with an absolute 30-day mortality reduction of 1.6% (2.3% vs 3.9% in the heparin-alone group; OR, 0.59 [95% CI, 0.36-0.96]) but a 1.4% increased risk of fatal hemorrhage or intracranial bleeding (1.7% vs 0.3% in the heparin-alone group).<sup>68</sup> However, several of the included studies were at high risk of bias, and the benefit of thrombolytic therapy compared with heparin alone was not statistically significant after clinical trials of patients with hemodynamic instability were excluded.<sup>68,69</sup> Therefore, treatment with thrombolytics is recommended in patients with PE who do not have contraindications to this therapy and are at high risk of death.<sup>18</sup>

Due to the risk of fatal bleeding, thrombolysis should not be prescribed for patients with active bleeding or for those at high risk for bleeding.<sup>18,70</sup> Patients with PE and hemodynamic instability who have a contraindication to thrombolytic therapy may be consid-

ered for percutaneous catheter-directed treatment (mechanical fragmentation or thrombus aspiration) or surgical embolectomy, although there is no evidence from large randomized clinical trials showing that these techniques decrease mortality.<sup>18</sup> In patients with cardiac arrest, venous-arterial extracorporeal membranous oxygenation may be considered.<sup>71</sup>

Clinical trial evidence does not support routine use of thrombolytic agents in intermediate-high-risk patients. The PEITHO trial randomized 1005 patients with intermediate-high-risk PE to receive either 1 dose of tenecteplase plus heparin or heparin alone.<sup>72</sup> At 7 days, tenecteplase was associated with a 3% absolute reduction in the rate of death or hemodynamic decompensation (2.6% vs 5.6% in the heparin-alone group; OR, 0.44 [95% CI, 0.23-0.87]) but a 5% absolute increased rate of major extracranial bleeding (6.3% vs 1.2% in the heparin-alone group; OR, 5.55 [95% CI, 2.3-13.39]). There was no significant difference in rates of death at day 7 and day 30 between the 2 groups.<sup>73</sup>

When anticoagulation is contraindicated or does not prevent PE recurrence, caval interruption with an inferior vena cava filter should be considered.<sup>18,74</sup> However, no clinical trial evidence has demonstrated that placement of an inferior vena cava filter improves prognosis. A systematic review of 11 clinical trials reported that placement of an inferior vena cava filter was associated with an absolute risk reduction of 5% (95% CI, 2%-8%) of recurrent PE, an absolute risk increase of 2% (95% CI, 0%-3%) of DVT, and had no effect on mortality.<sup>75</sup>

### Duration of Treatment

The optimal duration of anticoagulation treatment for patients with PE remains unclear.<sup>67,76</sup> An individual patient-level data analysis of 7 trials consisting of 836 patients with acute PE reported that the rate of 24-month PE recurrence did not differ significantly in patients who received 3 months of anticoagulation with VKA compared with 6 months of the same (5.4% vs 6.7%; difference, 1.3%; hazard ratio [HR], 1.19 [95% CI, 0.86-1.65]).<sup>77</sup> However, for patients with persistent risk factors such as thrombophilia, cancer, or family history of VTE, an extended course of anticoagulation should be considered. The PADIS-PE randomized clinical trial of 371 patients reported that patients with an unprovoked PE who received 24 months of VKA had a 3.3% risk of recurrence of bleeding at 24 months compared with a 13.5% risk of recurrence of bleeding in those who received 6 months of VKA followed by 18 months placebo (absolute difference, 10.2%; HR, 0.22 [95% CI, 0.09-0.55]).<sup>76,78</sup> Studies have also suggested that use of a DOAC is preferable to VKA for anticoagulation of more than 6 months. In the Hokusai-VTE randomized clinical trial, there was no statistically significant difference in the rate of recurrent VTE between patients treated with 12 months of edoxaban vs 12 months of warfarin (<0.1% vs 0.1%). However, major bleeding was less frequent with edoxaban compared with warfarin (0.3% vs 0.7%; HR, 0.45 [95% CI, 0.22-0.92]).<sup>79</sup> In a large retrospective cohort study that included 64 642 patients with acute VTE, anticoagulation with apixaban for more than 90 days was associated with a small but significantly reduced risk of recurrent hospitalization for VTE compared with warfarin for 90 days (0.44% vs 0.70%; HR, 0.69 [95% CI, 0.49-0.99]), and the risk of major bleeding was similar (approximately 45 per 1000 person-years).<sup>80</sup>

### Special Populations

Patients with cancer who are diagnosed with PE may require life-long anticoagulant treatment. For these patients, DOACs are preferred. A randomized clinical trial of 576 patients with cancer and acute VTE reported that DOACs were noninferior to LMWH for recurrent VTE (6% vs 8%) and had similar bleeding rates (4% in both groups).<sup>81</sup>

Patients found to have PE incidentally during chest imaging should receive treatment similar to that for patients with symptomatic acute PE.<sup>26</sup> Although controversial, there are no high-quality data to support treating patients with subsegmental PE differently from those with segmental or lobar PE.<sup>82</sup>

For patients with thrombophilia (such as antiphospholipid antibody syndrome) without a major reversible risk factor, a first episode of PE may be an indication for indefinite anticoagulant treatment.<sup>83</sup> In these patients, VKAs such as warfarin are preferable to DOACs. In a randomized clinical trial of 120 patients with antiphospholipid syndrome and a history of VTE, rates of the composite outcome of major bleeding, VTE, or vascular death were 19% in the rivaroxaban group and 3% in the warfarin group, which led to a decision to stop the trial early.<sup>84</sup>

People with PE who are pregnant should be treated with LMWH because it does not cross the placenta. VKAs and DOACs are both associated with increased risk of fetal anomalies.<sup>85</sup>

Treatment with LMWH is associated with an approximate risk of 1% of heparin-induced thrombocytopenia, which typically develops during the first weeks of treatment and is a contraindication to further treatment with heparin.<sup>86</sup>

### Outpatient Management

In patients with PE and an sPESI score of 0, outpatient management can be considered. Several studies have evaluated the outcomes of patients identified as having low-risk PE by the sPESI rule who were discharged from the emergency department or from the hospital within 48 hours of presentation. A systematic review of 12 clinical trials (including 4 randomized trials) that included 1894 patients with PE treated in the outpatient setting, rates were 0.7% (95% CI, 0.4%-1.2%) for death, 0.8% (95% CI, 0.5%-1.4%) for recurrent PE, and (0.8% (95% CI, 0.5%-1.4%) for major bleeding.<sup>87</sup> Neither the type of anticoagulant treatment (VKA or DOAC) nor the method used to identify eligible patients (PESI or sPESI) affected the results.<sup>87,88</sup> While approximately 50% of patients with PE meet criteria for discharge from the emergency department, only approximately 7.5% to 15% of all patients with PE are discharged from the emergency department.<sup>88,89</sup> In patients at low risk for early PE-associated death, outpatient management should be considered for those considered likely to adhere with treatment and follow-up.

### Prognosis

The sPESI score can be used to estimate the risk of 30-day mortality in patients with acute PE. The 30-day mortality rate is less than 1% in patients with a sPESI score of zero and approximately 5% to 10% in patients with a positive sPESI. Potential long-term sequelae of PE include the post-PE syndrome, consisting of reduced physical activity and reduced health-related quality of life.<sup>90</sup> The most severe form of the post-PE syndrome is chronic thromboembolic pulmonary hypertension (CTEPH), defined as a mean pulmonary arterial pressure of greater than 20 mm Hg with evidence of a perfusion defect on chest imaging.<sup>18,91,92</sup> CTEPH affects 1% to 4% of patients with a history of PE, and if untreated, it is associated with a 25% to 30% mortality rate at 3 years.<sup>3,91</sup> In 314 patients with acute PE, previous PE (OR, 19.0), younger age (OR, 1.79 per decade), a larger perfusion defect (OR, 2.22 per decile decrement in perfusion), and idiopathic PE at presentation (OR, 5.70) were associated with a higher rate of CTEPH.<sup>93</sup> Patients diagnosed with CTEPH should undergo evaluation for pulmonary thromboendarterectomy, a surgical procedure that may be curative and is associated with lower pulmonary artery pressures, improved functional status, and decreased mortality compared with nonoperative treatments for CTEPH.<sup>94,95</sup>

### Limitations

This review has several limitations. First, the quality of included articles was not evaluated. Second, a formal systematic review was not performed. Third, some relevant articles may have been missed. Fourth, some available epidemiologic data are outdated or not precise.

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## Conclusions

In the US, PE affects approximately 300 000 patients per year and may cause approximately 60 000 to 100 000 deaths per year. First-line therapy consists of direct oral anticoagulants such as apixaban, edoxaban, rivaroxaban, or dabigatran with thrombolysis reserved for patients with systolic blood pressure lower than 90 mm Hg.

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**Submissions:** We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at [mmdm608@northwestern.edu](mailto:mmdm608@northwestern.edu).

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