Acute Pulmonary Embolism: Contemporary Approach to Diagnosis, Risk-Stratification, and Management

Tahir Tak, MD, PhD¹ Swetha Karturi, MD² Umesh Sharma, MD² Lee Eckstein, MD³
Joseph T. Poterucha, DO⁴ Yader Sandoval, MD¹

¹Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota

²Department of Hospital Medicine, Mayo Clinic Health System, La Crosse, Wisconsin

³Department of Imaging Services, Mayo Clinic Health System, La Crosse, Wisconsin

⁴Division of Critical Care Medicine, Mayo Clinic Health System, La Crosse, Wisconsin

Address for correspondence Tahir Tak, MD, PhD, FACC, FESC, FICA, Department of Cardiovascular Medicine, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905 (e-mail: tak.tahir@mayo.edu).

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Abstract

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Pulmonary embolism (PE) affects over 300,000 individuals each year in the United States and is associated with substantial morbidity and mortality. Improvements in the diagnostic performance and availability of computed tomographic pulmonary angiography and D-dimer testing have facilitated the evaluation of patients with suspected PE. High clinical suspicion is required in those with risk factors and/or those that manifest signs or symptoms of venous thromboembolic disease, with validated clinical risk scores such as the Wells and modified Wells score or the PE rule-out criteria helpful in estimating the likelihood for PE. For those with confirmed PE, patients should be categorized and triaged according to the presence or absence of shock or hypotension. Normotensive patients can be further risk-stratified using validated prognostic risk scores, as well as by using imaging and cardiac biomarkers, with those having either signs of right ventricular dysfunction on imaging studies and/or abnormal cardiac biomarkers categorized as being at intermediate-risk and requiring close monitoring and hospital admission. Early discharge and/or home therapy are possible in those that do not manifest any high-risk features. The initial treatment for most patients that are stable consists of anticoagulation, with advanced therapies such as thrombolysis, catheter-based therapies, or surgical embolectomy deferred for those at high risk. Given the heterogeneous presentations of PE and various management strategies available, the development of multidisciplinary PE response teams has emerged to help facilitate decision-making in these patients.

Venous thromboembolic (VTE) disease is frequently encountered in clinical practice as either deep vein thrombosis (DVT) and/or pulmonary embolism (PE), affects as many as 900,000 individuals in the United States each year, and is associated with substantial morbidity and mortality.¹ PE, defined as an obstruction of the pulmonary vasculature, is a subset of VTE that represents the third most common cause

of vascular disease in the United States after acute myocardial infarction and stroke.²

Numerous advancements have occurred in recent years in the diagnostic evaluation of patients with suspected PE, as well as in the risk-stratification and management of patients with confirmed PE. The use of validated pre-test probability clinical risk scores, D-dimer testing, and computed

tomographic pulmonary angiography has facilitated the diagnostic evaluation of patients with suspected PE. Similarly, novel risk-stratification algorithms integrating prognostic risk scores, echocardiography, and/or cardiac biomarkers have facilitated the triage and management of patients with confirmed normotensive PE. The management of PE has also evolved significantly with the availability and use of direct oral anticoagulants (DOACs) and catheter-based therapies, with or without fibrinolysis, that have emerged as potential options to treat higher-risk, unstable patients.³ Given the wide variation in clinical presentations ranging from low-, mid-, to high-risk, and distinct management options available, several centers have instituted multidisciplinary pulmonary embolism response teams (PERT) to facilitate the evaluation and decision-making for these patients.² The purpose of this review is to provide an overview of the contemporary approach to diagnosis, risk-stratification, management, and prognosis of these patients, as well as delineate future directions moving forward.

Epidemiology

PE affects over 300,000 individuals each year in the United States.⁴ The incidence of PE increases with age.⁴ Men typically have a higher overall incidence of VTE compared with women (1.2:1). Women have a higher incidence after age 75.⁵

At the age of 45 years, there is a lifetime risk of venous thromboembolism of 8.1% with some patient subsets having even higher life time risk, such as African Americans—11.5%, those that are obese—10.9%, those identified to be heterozygous for factor V Leiden—17.1%, or those who have sickle cell disease—18.2%.⁶

The number of PE related admissions has increased from 23 to 65 per 100,000 from 1993 to 2012 with the cost per PE hospitalization steadily increasing from \$5,198 to \$6,928 in 2000 to \$8,764 in 2010.⁷

Following Virchow's triad for thrombosis, patients should be evaluated for factors that increase the risk for VTE based on the presence or absence of issues affecting endothelial injury, stasis of blood flow, and hypercoagulability.⁸ Endothelial injury can result from surgery, trauma, venous catheters, and superficial vein thrombosis. Stasis can be caused by prolonged immobilization during travel, surgery, obesity, and polycythemia vera, with most emboli developing in the lower extremity veins. Hypercoagulability can be either genetic (e.g., factor V Leiden mutation, prothrombin gene mutation, antithrombin III deficiency, protein C, S deficiency, and increased homocysteine levels) or an acquired disorder (e.g., antiphospholipid syndrome, infection, inflammatory conditions, cancer, nephrotic syndrome, smoking, estrogen (e.g., hormonal contraceptives, hormone replacement therapy, or pregnancy).^{3,5-11} Patients with severe obesity (body mass index [BMI] >35) have a six times higher risk of developing VTE compared with patients with normal BMI (<25).⁸

The clinical presentations of PE are heterogeneous and range from asymptomatic in incidentally discovered small subsegmental embolus to massive saddle embolism to car-

diogenic shock and/or sudden death in the context of massive saddle embolism. Typical symptoms and/or signs include pleuritic chest pain, dyspnea, fever, cough, hemoptysis, and syncope. Physical examination may reveal tachycardia, tachypnea, fever, and hypoxia, as well as reduced breath sounds or rales, jugular venous distention, and right ventricular (RV) heave.

Pathophysiology

PE usually results from a DVT traveling proximally toward the lungs, lodging in the pulmonary circulation, and resulting in vascular occlusion. PE leads to ventilation-perfusion (VQ) mismatch and resulting hypoxia. Hypoxia-mediated pulmonary vasoconstriction leads to the elevation of pulmonary vascular resistance and pulmonary artery (PA) pressure. Elevated PA pressure results in the reduction in RV stroke volume and RV dilatation. Elevated RV end-diastolic pressures cause neurohumoral stimulation, increased oxygen demand, and resultant subendocardial hypoperfusion, myocardial ischemia, and subsequent infarction. RV dilatation can lead to RV failure.⁹ Progression of RV failure can lead to impairment in left ventricular filling and may result in myocardial ischemia due to inadequate coronary artery filling with potential for hypotension, syncope, or sudden death.

Hypoxia, elevated alveolar-arterial (A-a) gradient, and hypocapnea are frequently observed arterial blood gas findings in PE. VQ mismatch, right to left shunt, impaired diffusion, and reduced mixed venous oxygen saturation contribute to hypoxia. Massive PE can markedly increase physiological dead space and impair CO₂ exchange.⁹⁻¹⁴

Importantly, not all patients are hypoxemic (32% of PE cases demonstrate PaO₂ > 80 mm Hg), and that the majority of patients (81%) hyperventilate despite the increased dead space with nearly one-third of patients have normal A-a gradient.^{12,13}

Diagnostic Evaluation

Careful clinical history, including detailed assessment of potential risk factors, and physical examination are essential in guiding the appropriate diagnostic evaluations. Those with *high-clinical suspicion*; for example, patients presenting pleuritic chest discomfort and dyspnea who have a history of malignancy and recent immobility that manifest hypoxia, tachycardia, and hypotension and are unstable require a distinct evaluation than those with *low-clinical suspicion* in whom typical symptoms and/or risk factors are not present.

Basic evaluations often performed in these patients include 12-lead electrocardiography (ECG) and/or chest X-ray (CXR).

Abnormal ECG findings are seen in ~15 to 25% of patients.¹⁵ The ECG often, but not always, reveals sinus tachycardia. Patients can also present with supraventricular arrhythmias and there may also be evidence of right axis deviation, S1Q3T3 (—Fig. 1) pattern indicating RV strain (—Fig. 1), incomplete or complete right bundle branch block, and/or inverted T waves.^{9,14,16} CXR features of acute PE

Fig. 1 Electrocardiogram (ECG) of patient with pulmonary embolism. The most common ECG finding in the setting of a pulmonary embolism is sinus tachycardia. However, the “S1Q3T3” pattern of acute cor pulmonale is classic and is sometimes referred to as the McGinn-White Sign.

include enlarged PA (Fleischner sign), regional oligemia (Westermark sign), and Hampton hump (wedge-shaped distal infarct) (►Fig. 2A and 2B). The Westermark sign, like Hampton hump, has low sensitivity (11%) but high specificity (92%).¹⁷

Bedside-focused ultrasound performed by trained personnel is increasingly being utilized in acute care setting and can provide an immediate assessment of RV size and function, especially in patients with high-clinical suspicion who demonstrate an enlarged and poorly contracting RV who could be rapidly identified and managed accordingly.^{18,19}

Risk Scores

To assist with routine clinical assessment and the clinical Gestalt (i.e., unstructured estimate of the likelihood for PE), prediction rules have been developed that are able to more precisely quantify the pre-test probability of PE and help guide the diagnostic process and triaging of patients with suspected PE. Several pre-test probability scores have been studied, including the Wells and modified Wells score,^{20,21} the revised Geneva score,²² and the pulmonary embolism rule out criteria (PERC)²³ (►Tables 1–3).

Wells score and modified Wells score are simple clinical tools to help rule out PE, especially in combination with D-dimer levels and reduce unnecessary testing.^{20,21} Forty clinical variables were initially considered, of which seven were ultimately to derive the rule which had two scoring systems (►Table 1). The first scoring system had three grades, namely, low, moderate, and high, which were later simplified to two grades, namely, PE likely and PE unlikely.^{20,21} With this model, PE was diagnosed in 7.8% of patients with scores < 4 and only in 2.2% when combined with a negative D-dimer. The score has the limitation that one of the variables (no alternative diagnosis) is based on the clinician's judgement.

Fig. 2 (A) A chest X-ray showing the Westermark sign (<http://pixelrz.com/lists/suggestions/hamptons-hump/>). (B) Chest X-ray showing the “Hampton hump.” PE, pulmonary embolism.

Geneva score is a clinical prediction rule used to determine the pre-test probability of PE based on a patient's risk factors and clinical findings. It has been shown to be as accurate as the Wells score and is less reliant on the experience of the doctor applying the rule. It identifies characteristics associated with PE which are easily assessed and can be combined into a score.¹⁹

It is subdivided into low, intermediate, and high probability results. The prevalence of PE in 10% is low probability, in 38% is intermediate probability, and in 81% is high probability.²² This score has variables that are completely standardized and are not dependent on the clinician's judgment. The prevalence of PE is 10% in low probability, 38% in

Table 1 Wells criteria and modified Wells criteria: clinical assessment for pulmonary embolism

Clinical symptoms of DVT (leg swelling, pain with palpation)	3.0
Other diagnosis less likely than pulmonary embolism	3.0
Heart rate >100	1.5
Immobilization (≥3 days) or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Probability	Score
Traditional clinical probability assessment (Wells criteria)	
High	>6.0
Moderate	2.0–6.0
Low	<2.0
Simplified clinical probability assessment (modified Wells criteria)	
PE likely	>4.0
PE unlikely	≤4.0

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism. Source: Data from van Belle A, Buller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 2006;295:172.

intermediate probability, and 81% in high probability. This score has variables that are standardized and not dependent on the clinician's judgement. The Geneva score needs arterial blood gas values while breathing room air which is not always available. As such, the modified/revised Geneva score was developed based on readily available clinical variables, independent of clinicians' judgement, associated with

Table 2 Revised Geneva Score

Variable	Score
Age 65 years or over	1
Previous DVT or PE	3
Surgery or fracture within 1 month	2
Active malignant condition	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate 75–94 beats per minute	3
Heart rate 95 or more beats per minute	5
Pain on deep palpation of lower limb and unilateral edema	4
0–3 Points indicates low probability	
4–10 Points indicates intermediate probability	
11 Points or more indicates high probability	

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 3 The pulmonary embolism rule out criteria (PERC rule)^a

Age <50 years
Heart rate <100 bpm
Oxyhemoglobin saturation ≥95%
No hemoptysis
No estrogen use
No prior DVT or PE
No unilateral leg swelling
No surgery/trauma requiring hospitalization within the prior 4 weeks

Abbreviations: bpm, beats per minute; DVT, deep venous thrombosis; PE, pulmonary embolus; PERC, PE rule-out criteria.

^aThis rule is only valid in patients with a low clinical probability of PE (Gestalt estimate <15%). In patients with a low probability of PE who fulfill all eight criteria, the likelihood of PE is low and no further testing is required. All other patients should be considered for further testing with sensitive D-dimer or imaging.

Source: Kline JA, Courtney DM, Kabrheh C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008;6:772.

PE.^{21–26} The pooled sensitivity and specificity of Gestalt and clinical decision rules are shown in ►Table 4.²⁷ Some studies have shown that Wells and Geneva scores are not as accurate in ruling out PE in pregnant and critically ill patients.^{21–23}

The PERC is used in patients with low probability of PE (►Table 3).

Validated clinical decision tools like the Wells and modified Wells criteria are helpful in determining the pre-test probability of PE. Modified Wells score of <4 makes PE less likely, especially when combined with a negative D-dimer.^{14,15,21,28}

D-Dimer

For normotensive patients in whom PE is deemed to be unlikely (*low or intermediate clinical probability*) using clinical judgment or guideline-recommended prediction rules, laboratory testing using D-dimer, a sensitive marker of thrombosis, is the next diagnostic step. D-dimer is a soluble fibrin degradation product for which numerous assays exist (e.g., whole-blood agglutination assays, enzyme-linked immunosorbent or immunofluorescent assays, and latex agglutination assays) for its measurement in whole blood or plasma.³ Due to the high diagnostic sensitivity and negative predictive value, it is primarily used to help exclude PE when the levels are normal. D-dimer, however, has poor diagnostic specificity, and when elevated, it can be due to other various conditions such as sepsis, trauma, cancer, surgery, other thrombosis, or disseminated intravascular coagulation, among others.

Imaging

In patients in whom PE is likely (*high clinical probability*), for example, those with high-risk features such as hypotension or shock, or those found to have abnormal D-dimer concentrations, *computed tomography angiography* (CTA) is

Table 4 Pooled sensitivity and specificity of Gestalt and clinical decision rules

Gestalt or rule	Studies, <i>n</i>	Prevalence, %	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Estimated sensitivity at a prevalence of 15% (95% CI) ^a	Estimated specificity at a prevalence of 15% (95% CI) ^a
Gestalt	15	16.7	0.85 (0.78–0.90)	0.51 (0.39–0.63)	0.83 (0.81–0.84)	0.52 (0.43–0.62)
Wells cutoff value <2	19	14.7	0.84 (0.78–0.89)	0.58 (0.52–0.65)	0.85 (0.80–0.89)	0.58 (0.52–0.63)
Cutoff value ≤4	11	16.3	0.60 (0.49–0.69)	0.80 (0.75–0.84)	0.58 (0.47–0.68)	0.81 (0.76–0.85)
Geneva	5	29.0	0.84 (0.81–0.87)	0.50 (0.29–0.72)	0.76 (0.71–0.79)	0.61 (0.41–0.78)
Revised Geneva	4	23.7	0.91 (0.73–0.98)	0.37 (0.22–0.55)	0.82 (0.78–0.86)	0.45 (0.32–0.59)

Abbreviation: CI, confidence interval.

^aUsing a theoretical population with a 15% prevalence of pulmonary embolism.

Source: Lucassen W, Geersing GJ, Erkens PM, et al. Clinical decision rules for excluding pulmonary embolism: a meta-analysis. *Ann Intern Med* 2011;155(7):448–460.

the next immediate diagnostic step. Using dose reduction technologies can provide high-quality diagnostic imaging with a significant reduction in patient radiation dose. The first-choice imaging examination in patients with suspected PE is pulmonary CTA.²⁹ The rationale for using this test is based on the high sensitivity and specificity in detecting PE while also helping assess for other clinical conditions in the differential diagnosis. Refinements in CT technology have improved acquisition times to < 2 seconds, providing relatively motion-free images in patients who are suffering from dyspnea. Fast scanning times also allow use of smaller amounts of iodinated contrast dye, thereby reducing the risk of nephrotoxicity. In general, CTA provides good image quality with minimal patient discomfort. The major risks associated with CTA are those of contrast-induced nephropathy and risk of malignancy from radiation exposure.^{30–32}

The VQ scan is an alternative imaging modality to rule out PE. It is usually used in situations where CT scan is contraindicated, like pregnancy, acute renal failure, and/or contrast allergy since it does not expose subject to contrast or radiation.^{3,9,11,14–16,28} The original multicenter Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study classified VQ scans as high-probability, intermediate-probability, low-probability, and indeterminate. The PIOPED study assessed the value of VQ scan in acute PE and concluded that high probability results usually indicated PE; however, only a small proportion of patients with actual PE had high probability results and that low probability results accurately rule out PE with limited value in those with intermediate results. Based on PIOPED study, the VQ scans with high probability had a sensitivity of 41% and specificity of 97%.³³ If all three probabilities (high, intermediate, and low) were combined into one result, then VQ scan has high sensitivity but low specificity (sensitivity, 98%; specificity, 10%).³³ The modified PIOPED II criteria classify studies as high probability, very low probability, normal, and nondiagnostic. Using PIOPED II criteria, the sensitivity and specificity of VQ scanning were 85% and 93%, respectively.^{33–35}

A previous history of PE reduces the validity of a high probability result as it could be falsely positive.^{36,37}

Risk-Stratification for Confirmed PE

Numerous advancements have been made in the risk-stratification of patients with confirmed PE to assist with the triaging and management of these patients. For those with confirmed PE, patients should be categorized and triaged according to the presence or absence of shock or hypotension.

High-risk patients: Patients identified as “high-risk” are those who are hypotensive or in shock. Shock at presentation is associated with a 30 to ~50% risk of death.¹⁶ These patients require immediate CTA to confirm the diagnosis and undergo reperfusion.

Low or intermediate risk: Patients who are normotensive patients can be risk-stratified using validated prognostic risk scores, as well as by using imaging and cardiac biomarkers, with those having signs of RV dysfunction on imaging studies and/or abnormal cardiac biomarkers categorized as being at intermediate-risk and requiring close monitoring and hospital admission. Conversely, those identified to be at low-risk may qualify for early discharge and/or home therapy.

Prognostic Tools to Assess Risk

The simplified Pulmonary Embolism Severity Index (sPESI) (► **Table 5**) is a practical and simplified approach that attributes a score of 1 for age >80 years, cancer, heart failure, pulse >110 beats/minute, systolic blood pressure < 100 mm Hg, and arterial oxygen saturation <90%. Typically, a score of zero is an indicator of low risk, and with a brain natriuretic peptide (BNP) level <100 pg/mL, has been validated and predicts excellent outcomes with a very high negative predictive value (99–100%).

Cardiac troponins (cTn) (I and T) and BNP are cardiac biomarkers that when elevated are associated with less favorable outcomes (death and complications) and are, therefore, used to help risk-stratify patients with PE. Normal cardiac biomarkers in an otherwise normotensive patient with PE are an indicator of good prognosis as compared with those with increased biomarkers.^{9,16} For normotensive patients, contemporary risk-stratification models endorse the use of cardiac biomarkers to help

Table 5 Pulmonary Embolism Severity Index (PESI) scores: full and simplified

PESI—Full		
Clinical feature		Points
Age		x (e.g., 65)
Male gender		10
History of cancer		30
Heart failure		10
Chronic lung disease		10
Pulse $\geq 110/\text{min}$		20
Systolic blood pressure < 100 mm Hg		30
Respiratory rate $\geq 30/\text{min}$		20
Temperature $< 36^{\circ}\text{C}$		20
Altered mental status		60
Arterial oxygen saturation $< 90\%$		20
Class I	Low risk	< 66
Class II		66–85
Class III	High risk	86–105
Class IV		106–125
Class V		> 125
Simplified PESI (sPESI)		
Clinical feature		Points
Age > 80 years		1
History of cancer		1
Chronic cardiopulmonary disease		1
Pulse $\geq 110/\text{min}$		1
Systolic blood pressure < 100 mm Hg		1
Arterial oxygen saturation $< 90\%$		1
Low risk		0
High risk		≥ 1

The full PESI score is rarely calculated in clinical practice since it is generally considered cumbersome. In contrast, sPESI is brief, contains a limited number of easily accessible parameters, and is therefore, much more practical.

Adapted from:

1. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005;172:1041.
2. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010;170:1383.

categorize patients as low-risk or intermediate-high and intermediate-low risk based on the presence of normal or increased biomarker concentrations.³ Similar to D-dimer, the measurement of cTn using contemporary and high-sensitivity cTn assays offers improved diagnostic sensitivity and negative predictive value that can help exclude myocardial injury. The mechanisms leading to increased cTn,

however, are numerous. PE is a condition where cTn increases can occur through various mechanisms, including myocardial oxygen/supply mismatch, occurring from RV strain, coronary hypoperfusion, and/or systemic hypoxemia. For those with fatal massive PE, pathologic studies demonstrate that patients may suffer from RV infarction in the absence of coronary artery disease.

Echocardiography can be used to facilitate diagnosis based on the presence or absence of RV overload especially when CTA is not available. Its primary use is to assist with risk-stratification in those with confirmed PE based on the presence or absence of RV dysfunction. PE may result in right heart strain, especially in the case of a “saddle embolus”; RV strain/dilatation, hypokinesis (McConnell sign—RV free wall hypokinesia/akinesia with preserved or hyperkinetic apical segment wall motion), and elevated right atrial pressure.^{9,14,18} It can also cause right heart failure and cardiogenic shock due to obstruction. Echocardiography can help determine the severity of RV strain and the need for thrombolysis. Echocardiography is not usually used as a first-line tool since a negative result does not rule out PE and evidence of right heart strain can also be seen in several conditions other than PE, such as chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea. Echocardiographic findings of right heart strain are generally associated with worse outcomes.²⁷ Imaging predictors of poor outcome include RV dysfunction with twice the risk of mortality in all-comers and RV thrombus with an increased 2-week risk of mortality.^{38–40}

Treatment

Treatment of PE depends upon the presentation of the patient. The *initial treatment* should begin with oxygenation and stabilization of the patient. Hereafter, a decision should be made whether to initiate anticoagulation with warfarin/DOACs or to use a thrombolytic agent.

- A. *Patients without shock*, or without malignancy, with a sPESI score of = 0 are considered “low risk” and may be treated with anticoagulation agents as outpatients.
- B. Patient *with cardiogenic shock* due to “saddle embolism” with significant RV strain, then hemodynamic and respiratory support are of paramount importance and should be instituted immediately. In cardiogenic shock, echocardiography is helpful.⁴¹ If significant RV strain/hypokinesis with presence of pulmonary hypertension by Doppler echocardiography is identified, it may be sufficient evidence to consider thrombolysis and reperfusion in such “unstable” patients. Volume expansion has not been shown to be significantly effective, since it may cause overstretch of the RV which can further depress its contractility. *Norepinephrine* has been shown to be the best inotrope in this setting since it improves RV contractility in addition to improving RV coronary perfusion by increasing systemic blood pressure.⁴²

Anticoagulation

Anticoagulation is the mainstay of therapy for PE. *Parenteral anticoagulation* is essential as first-line therapy with

Table 6 Pharmacological properties of the DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Half-life (hour)	12–17	5–9	12	6–10
Time to peak effect (hour)	1–3	2–4	1–3	1–2
Dosing in nonvalvular AF	150 mg BID	20 mg OD	5 mg BID	60 mg OD
Dosing in VTE treatment	150 mg BID after 5–10 days of parenteral anticoagulation	15 mg BID for 21 days followed by 20 mg OD	10 mg BID for 7 days followed by 5 mg BID	60 mg OD after 5 days of parenteral anticoagulation
Renal clearance as unchanged drug (%)	80	33	27	50
Drug interactions pathways	P-gp	3A4/P-gp	3A4/P-gp	3A4/P-gp

Abbreviations: AF, atrial fibrillation; BID, two times a day; DOACs, direct oral anticoagulants; OD, once daily; TID, three times a day; VTE, venous thromboembolic.

eventual transition to oral anticoagulation with **Warfarin** or novel oral anticoagulation agents (DOACs).^{42–45} Parenteral agents include either unfractionated heparin or low molecular weight heparin (Lovenox). *Oral anticoagulation with warfarin* should be started at the same time and there should be an overlap of heparin or Lovenox with warfarin for at least 5 days until international normalized ratio is therapeutic between a value of 2 and 3. Anticoagulation therapy is usually continued for 3 to 6 months or “lifelong” if there have been previous DVTs or PEs. The DOACs have their characteristic pharmacologic properties. They carry many advantages over warfarin and are considered by some clinicians as first-line anticoagulation agents. Their pharmacokinetic properties are important to keep in mind when initiating them in patients with multiple comorbidities and medications.

There are *four major DOACs available* in the market: dabigatran, rivaroxaban, apixaban, and edoxaban.^{42–45} Their pharmacological properties are listed in ►**Table 6**.

Thrombolytic Therapy

Thrombolysis is often reserved for patients presenting with hypotension and/or severe hypoxemia. This form of treatment may also be used in patients who demonstrate severe RV dysfunction by echocardiography with concomitant tachycardia (►**Table 7**). Treatment with thrombolytics

will lyse the clot(s) and restore circulation and reduce RV pressures immediately (►**Fig. 3**). The beneficial effects of thrombolytics are apparent in the first week post therapy.⁴² The most common thrombolytic used is tissue plasminogen activator (tPA). Current European Society of Cardiology guidelines recommend infusing 100 mg over 2 hours. First-generation thrombolytics (streptokinase and urokinase) are rarely used due to the long duration of treatment and higher incidence of allergic reactions. Low-dose heparin infusion is typically concomitantly administered after tPA infusion. Peripheral infusion of thrombolytic is considered first, and if this fails, then catheter-directed thrombolysis should be considered. Thrombolytic therapy is not recommended when there is no hemodynamic instability.⁴⁶

There is a high risk of bleeding associated with this therapy. The *Absolute and Relative Contraindications* to thrombolytic therapy are listed in ►**Table 8**.

Catheter Based and Surgical Therapies

Catheter-Based Therapy

Catheter-assisted thrombus removal is recommended when appropriate resources are available for patients with acute PE associated with hypotension who are of high bleeding risk, have failed systemic thrombolysis, or when cardiogenic

Table 7 Potential indications for thrombolytic therapy in venous thromboembolism

High-risk (massive) PE; i.e., presence of hypotension related to PE ^a
Presence of severe hypoxemia (particularly in those with a contribution from concomitant cardiopulmonary disease)
Patients with acute PE who appear to be decompensating but are not yet hypotensive
Patients with severe right ventricular dysfunction and tachycardia due to PE
Clot-in-transit (i.e., right atrium or ventricle)
Extensive deep vein thrombosis

Abbreviation: PE, pulmonary embolism.

^aThis indication is widely accepted; the other potential indications require careful review of the risks of thrombolytic therapy and potential benefits.

Fig. 3 Pre- and post-computed tomography angiography (CTA) images following thrombolysis showing significant improvement in pulmonary blood flow following intervention.

shock is likely to cause death prior to systemic lytic therapy taking effect.^{46–48} The goal of these therapies is to relieve obstructive shock, restore pulmonary blood flow and return blood to the left heart to improve cardiac output, and achieve hemodynamic stability.⁴⁸ Various modalities include catheter-directed thrombolysis (CDT), ultrasound-assisted CDT, rheolytic, rotational, or aspiration thrombectomy.² CDT is the simplest, most studied and utilized catheter-based therapy. Local delivery of low dose slow tPA infusion via catheter proximal to the obstructed PA creates a channel for targeted drug delivery and maximizes drug to clot surface area. Theoretical benefit of this therapy involves increased thrombolytic efficacy with less bleeding risk, including intracranial hemorrhage.² While no controlled investigations comparing CDT with systemic tPA have been performed, studies have

shown that CDT with tPA (10 mg per lung over 15 hours) improves clinical outcomes in addition to reducing RV/LV ratio from baseline to 24 hours when compared with heparin alone.⁴² Ultrasound-assisted CDT utilizes a dual lumen catheter to direct tPA and low energy ultrasound energy lysis. Two prospective studies have shown promising results indicating that this therapy may be superior to systemic tPA, with the added benefit of less tPA use and reduced intracranial bleeding events.

It remains unclear on whether ultrasound lysis is superior to CDT alone. Mechanical thrombectomy may be suitable as salvage therapy in patients with contraindications to thrombolysis or when systemic tPA has failed.⁴⁸ However, mechanical thrombectomy has fallen out of favor due to device bulkiness and rigidity making these devices challenging to

Table 8 Contraindications to fibrinolytic therapy for deep venous thrombosis or acute pulmonary embolism

Absolute contraindications
Prior intracranial hemorrhage
Known structural cerebral vascular lesion
Known malignant intracranial neoplasm
Ischemic stroke within 3 months (excluding stroke within 3 hours ^a)
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head trauma or facial trauma within 3 months
Relative contraindications
History of chronic, severe, poorly controlled hypertension
Severe uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)
History of ischemic stroke > 3 months prior
Traumatic or prolonged (>10 minutes) CPR or major surgery < 3 weeks
Recent (within 2–4 weeks) internal bleeding
Noncompressible vascular punctures
Recent invasive procedure
For streptokinase/anistreplase—Prior exposure (> 5 days ago) or prior allergic reaction to these agents
Pregnancy
Active peptic ulcer
Pericarditis or pericardial fluid
Current use of anticoagulant (e.g., warfarin sodium) that has produced an elevated INR >1.7 or PT >15 seconds
Age >75 years
Diabetic retinopathy

Abbreviations: CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; INR, international normalized ratio; PT, prothrombin time; SBP, systolic blood pressure.

^aThe American College of Cardiology suggests that select patients with stroke may benefit from thrombolytic therapy within 4.5 hours of the onset of symptoms.

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use in the pulmonary vasculature. Rheolytic (fragmentation) thrombectomy has had variable success, limited by poor outcomes from side effect of bradycardia, hemodynamic instability and collapse in some cases thought to result from vasoactive bradykinin and adenosine release. One meta-analysis reported higher mortality with this therapy leading to a Food and Drug Administration black box warning on one such device—the Angiojet Rheolytic Thrombectomy System (Possis, Minneapolis, MN).⁴⁸ Outcome data on aspiration thrombectomy for PE is limited, as the role of this therapy has traditionally been targeted to ilio caval thrombus, tricuspid valve vegetations, and thrombus-in-transit.² Catheter-directed therapy may have the added benefit of potentially reducing chronic thrombotic pulmonary hypertension.⁴⁸

Venous Filters

Venous filters are placed in patients with PE and lower-extremity DVT when there is an absolute contraindication to anticoagulation, when a patient has a very heavy “clot burden” which is concerning for recurrence of PE, or for

recurrent PE despite anticoagulation.⁴⁹ There are two kinds of filters: *nonpermanent filters* and *permanent filters*. Non-permanent filters are classified as temporary and retrievable. Retrievable inferior vena cava (IVC) filters are appropriate in patients with PE or DVT. Retrievable filters can be left in place for 3 to 6 months (depending on the device-specific time window for retrieval).

The complications of leaving a filter long-term include breaking and migration of filter limbs, infection, perforation of caval wall, and thrombosis of the filter device.⁵⁰ Usually filters are removed as soon as it is safe to use anticoagulation.⁴⁹ However, a randomized clinical trial of 399 patients with severe PE comparing anticoagulation alone versus anticoagulation plus retrievable IVC filter demonstrated no difference in PE recurrence rate at 6 months, DVT, major bleeding, death with filter thrombosis occurring in 3 patients.⁵¹ Prophylactic placement of IVC filters in patients at risk of DVT is common, though it provides no benefit related to recurrent PE, DVT, reduction in major bleeding, or mortality.⁵¹

Surgical embolectomy. This therapy has been traditionally thought to be last resort for *unstable* PE primary due to poor outcome data from the 1960s, reporting mortality as high as 50%.⁴⁸ Teams of cardiac surgeons have, therefore, reintroduced the concept of surgical embolectomy for high-risk PE and for selected patients with intermediate- to high-risk PE, particularly if thrombolysis has failed or is contraindicated. Embolectomy may be particularly useful in patients with significant proximal clot burden, thrombus-in-transit, and in impending paradoxical embolism.² Surgical embolectomy has also been successfully performed in patients with right heart thrombi straddling the interatrial septum through a patent foramen ovale.⁵⁰ In the modern era, hospital mortality of patients after embolectomy has improved, ranging from 4.6 to 11.7%.² This is thought to be due to advances in cardiac surgical techniques. Long-term outcome after surgical embolectomy in the modern day is favorable with one study demonstrating a 10-year survival of 93%.⁴⁸ In fact, some centers utilize surgical embolectomy as front-line management of high-risk PE, but it is reasonable to reserve this intervention for massive PE with cardiogenic shock.⁴⁸ The decision to do surgical embolectomy versus catheter-based intervention requires teamwork among various disciplines involving surgeons and interventionists.

Mechanical Circulatory Support

Recent data suggests that for PE complicated by refractory cardiogenic shock, extracorporeal membrane oxygenation (ECMO) may be a useful form of bridging support. ECMO can provide a bridge to recovery after failed systemic thrombolysis, can unload the RV, and aid in stabilizing the patient until bleeding risks are abated so catheter or surgical embolectomy therapies can be implemented.⁴⁸ One single center series reported surgical or percutaneous embolectomy while on ECMO with improved survival to hospital discharge compared with ECMO alone. Percutaneous RV-assist devices, traditionally thought to be contraindicated, are being explored as a tool for RV support, but outcome data has yet to be described.²

Prognosis

Thirty-day mortality associated with PE was 10.6% and 1-year mortality was 23% based on administrative data from the Quebec study.⁵²

In general, as the size of PE increases, so does the degree of hemodynamic compromise and resultant mortality. Advanced age, poor functional status, chronic advanced medical disease, hypotension, right heart failure, and increased cardiac biomarkers such as cTn and/or BNP are associated with poor survival.⁸

Short-term outcome study of PE from the 2013 to 2014 National Readmission Data showed a 21.36% readmission rate. Heart failure, COPD, anemia, and malignancy were associated with a higher readmission and 90-day mortality rate.⁵³

Early complications (2 weeks–6 months) can occur as recurrent PE. It is co-related with underlying co-morbidities like malignancy or failure to achieve therapeutic levels of oral anticoagulation. Late complications (> 6 months) appear to

develop after anticoagulation is discontinued and mostly secondary to the same clinical event as the index episode. These recurrent events can lead to the development of chronic thromboembolic pulmonary hypertension (CTEPH) with resultant chronic hypoxia and dyspnea.

There remains a risk of recurrent thromboembolism in patients who have had prior PE. About 30% of patients experience a recurrent episode of VTE in subsequent decade, with a rate of 4 to 13 per 100,000 person years for PE ± DVT with maximal risk in first 6 to 12 months.⁵⁴

The recurrence rate may be increased in patients who are inadequately anticoagulated or in those patients who have predisposing comorbidities or are otherwise noncompliant with medications. Anticoagulation significantly reduces the mortality associated with PE, which is otherwise thought to be in the order of ~30%. There are prognostic models which can predict death or recurrence. These models, called the PESI and the sPESI, can predict all-cause mortality in patients who have suffered a PE.¹⁶

Late complications, especially in the first 2 years after TE, can lead to the development of CTEPH with resultant chronic dyspnea, hypoxia, and even death.¹⁰

Patients who have had IVC filters placed should have these removed once the contraindication to anticoagulation has resolved with initiation of anticoagulation. Patients with a history of PE should be followed in the clinic for complications after treatment (bleeding, etc.) when anticoagulation is initiated. Therapeutic levels of anticoagulation should be maintained with routine checks. Appropriate recommendations for lifestyle modifications and adherence to medical therapy should be provided to patients during outpatient clinic visits.¹⁵

Conclusion

PE is a relatively common disorder causing significant morbidity and mortality. By combining patient presentation, clinical suspicion, and various scoring systems, diagnosis may be streamlined and focused treatment can be instituted. Increasingly more physicians possess training and have access to portable ultrasound devices, which may help in the early recognition and treatment of VTE and PE. The increased accuracy of CTA and application of guideline-directed therapies have improved our recognition of PE in patients. Several newer oral anticoagulation drugs are now available and gaining favor among physicians either because they are safer or because they are easier to administer without periodic monitoring of anticoagulation status. Future research will continue to focus on improved and timely diagnosis of PE which will likely lead to improved clinical outcomes.

Future Directions

1. Establishment of pulmonary embolism response team. This model was established in 2015 and is a collaborative international network which is gaining momentum. It represents a new model for approaching PE patients by dedicated teams.⁵⁵

2. The safety of treating PE in the outpatient setting in selected low risk patients' needs to be further evaluated. The American College of Chest Physicians' guidelines currently give a Grade 2B recommendation for OP management for low-risk PE Patients.⁵⁶
3. Clinical trials are needed to approach management of PE in pregnant patients. There is paucity of data at the present time. Evaluation of DOACs in pregnant patients will be difficult and likely based on data obtained from case reports.⁵⁷
4. Treatment duration of anticoagulation in patients with first time PE needs to be further evaluated.¹⁴
5. Additional research is warranted to evaluate the safety and efficacy of DOACs after catheter-based thrombectomy, as it may reduce the risk and subsequent development of post-thrombotic complications.¹⁴
6. Advances in technology may likely lead to complex and efficient catheters and pharmaco- mechanical devices, especially for massive and submassive PE, and lead to development and evolvement of mostly endovascular treated approach.⁵⁸
7. Drug-coated balloons, bioresorbable vascular scaffolds, and IVC filters are currently being studied and may contribute to better outcomes and decreased morbidity and mortality while adding more value to quality of life for patients with PE.^{9,14,58,59}

Conflict of Interest

Yader Sandoval is presently on Abbott Diagnostics's advisory board without personal compensation. In the past YS was on Roche Diagnostics's advisory board (nonsalaried).

All other authors have nothing to disclose.

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