

Guidelines for the Diagnosis, Treatment, and Follow up of Pulmonary Embolism

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Introduction

Pulmonary embolism (PE) is the most serious manifestation of venous thromboembolic disease. Until the 1980s there had been no substantial changes in either the diagnosis or treatment and follow up of PE. It has only been a little over 10 years since we first witnessed the development of various tools that have improved diagnostic yield and new treatment options that have opened the way to different models for managing this disease. The aim of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) in publishing these guidelines is to provide up-to-date recommendations for the diagnosis, treatment, and follow-up of PE based on the scientific evidence currently available.

Concept and Epidemiology

PE is a complication of deep vein thrombosis (DVT). It occurs when a blood clot originating in a vein, generally in the deep venous system of the lower limbs, travels to the pulmonary arterial tree. PE and DVT are both clinical expressions of the same entity, venous thromboembolic disease (VTED). When venography of the lower limbs has been carried out systematically in patients with symptomatic PE, the presence of DVT has been demonstrated in around 80% of patients; DVT was asymptomatic in over 50% of cases.¹ It has been suggested that when no thrombi are found, it is possible that the emboli could have originated in other venous areas or else that all the thrombotic material may have embolized. Furthermore, 50% of patients with symptomatic DVT develop PE, which in many cases is silent.²

In the epidemiology of VTED reviewed by White,³ the following estimations are of interest: the annual

incidence of VTED is around 1 case per 1000 population, rising with age to reach 1 case per 100 population at 85 years; the rate of recurrence at 6 months is approximately 7% of cases (higher in cancer patients). Mortality at 30 days is 12% and is generally associated with cancer, advanced age, or cardiovascular comorbidity.

Pathogenesis and Risk Factors

The pathogenesis of DVT, the condition that causes PE, is based on the Virchow triad: circulatory stasis, vascular wall injury, and hypercoagulability. These 3 conditions come together in acquired or inherited situations which we call risk factors, present in approximately 75% of cases.⁴ More occult neoplasms⁵ and cases of thrombophilia⁶ have been found in patients with apparently idiopathic PE than in the general population.

Risk factors are the conditions related to either the patient or the clinical situation that are associated with an increase in the incidence of VTED. A number of risk factors are often found concurrently. Quantifying the risk associated with each factor is complicated because the studies that have been carried out are heterogeneous and many of them were retrospective.^{7,8} The factors most closely associated with DVT are immobilization and surgery. There is no consensus on whether advanced age is an independent risk factor since it is also associated with predisposing surgery and medical diseases as well as with a more sedentary lifestyle, a factor that is very difficult to quantify. Other factors, such as obesity and long distance travel, are generally classified as additional, that is to say, they increase the incidence of VTED in the presence of other risk factors.⁹ It is impossible to assess the degree of risk associated with a number of other clinical situations traditionally associated with VTED because of their low prevalence.

In recent years, hereditary thrombophilia has once again come to the fore because of the genetic defects that are being discovered. The classic antithrombin, protein C, and protein S deficiencies and their combinations clearly

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TABLE 1
Independent and Additional Risk Factors for Venous Thromboembolic Disease

Surgery	Prosthesis/hip or knee fracture Major abdominal surgery (>cancer surgery risk) >30 minutes in patients >40 years
Trauma	Pelvic, femoral, or tibial fractures Spinal cord, brain
Immobilization	Immobilization of lower limbs in plaster cast
Thrombophilia	Hospitalization, medical diseases Antithrombin, protein C, or protein S deficiency Homozygotic factor V Leiden mutation Combined deficiencies, others*
Lower limb paralysis	Acute period
Prior history of venous thromboembolic disease	Greater risk in idiopathic cases
Cancer	Greater risk with chemotherapy
Anesthesia	Greater risk with general anesthesia than with spinal-epidural anesthesia
Central venous catheters	Greater risk with femoral catheter
Antiphospholipid syndrome	
Advanced age	
Pregnancy, puerperium	
Obesity	
Long distance travel	
Superficial venous thrombosis, varicose veins	
Oral contraceptives, hormone replacement therapy, tamoxifen	
Miscellaneous factors: polycythemia vera, thrombocytosis, paroxysmal nocturnal hemoglobinuria, nephrotic syndrome, intestinal inflammatory disease, Behçet syndrome, erythematous lupus, antipsychotic medication	

*Heterozygotic factor V Leiden, factor II G20210A prothrombin mutation, hyperhomocysteinemia, increase in plasma levels of factor VIII, factor XI, and of the thrombin-activatable fibrinolysis inhibitor, dysfibrinogenemias.

TABLE 2
Clinical Signs and Symptoms in Patients With Suspected Pulmonary Embolism

Symptoms	Clinical Signs
Dyspnea*	Tachypnea >20/minute*
Pleuritic chest pain*	Tachycardia >100/minute*
Pain and/or edema in lower limbs	Crackles
Hemoptysis	4th/2nd dark
Palpitations	Signs of deep vein thrombosis
Anginal chest pain	Temperature >38°C
Syncope/presyncope	Right gallop rhythm†

*Very common. †Common in pulmonary embolisms with severe cardiac repercussions.

increase the risk of VTED,⁶ although the prevalence of these conditions is low in Spain.¹⁰ Homozygotic factor V Leiden mutation is also an independent risk factor.⁶ However, the question of whether factor II G20210A prothrombin mutations, which are highly prevalent in Spain,¹¹ heterozygotic factor V Leiden mutations, and occasionally an association of both are independent risk factors is more controversial; they do not always behave as such.⁶ The role of hyperhomocysteinemia, a condition that can be inherited or acquired, is not clear.⁶ Newly described inherited or acquired factors, such as elevated plasma concentrations of thrombin-activatable fibrinolysis inhibitor and factors VIII, IX, and XI have been associated with VTED, but this association has not been confirmed.⁶ These risk factors have been stratified primarily in order to guide primary prophylaxis rather than diagnosis.¹² In either case, the long list of risk factors, both independent and additional, should be taken into account (Table 1).

Diagnosis

Clinical Suspicion

Clinical suspicion is established on the basis of the initial signs and symptoms, which are considered in light of the presence or absence of risk factors. Studies of autopsy data indicate that PE was not suspected before death in most cases of death caused by this entity, an indication that the condition is underdiagnosed.¹³ First line diagnostic tests, such as arterial blood gas analysis, chest radiograph, and electrocardiogram, help to establish a differential diagnosis and the degree of suspicion.

Signs and Symptoms

According to data from a prospective study, the signs and symptoms are sensitive but not very specific.¹⁴ They vary depending on severity (Table 2). The presence of more than 1 clinical sign or symptom increases sensitivity.

First Line Diagnostic Tests

– *Chest radiograph.* In prospective studies, 80% of patients with PE and no cardiopulmonary disease have an abnormal chest radiograph, but this is also nonspecific.^{14,15}
– *Electrocardiogram.* Electrocardiography is useful for ruling out other processes (acute myocardial infarction, pericarditis) and for detecting and evaluating signs of right ventricular (RV) overload. In a level I study, signs of RV overload were observed in 50% of the patients with PE and in over 10% of the patients

TABLE 3
Chest Radiograph and Electrocardiogram in Pulmonary Embolism

Chest Radiograph	Electrocardiogram
Normal	Normal
Subsegmental atelectasis	Sinus tachycardia
Small pleural effusion	Signs of right ventricular overload
Right pleural based opacity	Precordial T-wave inversion
Elevated hemidiaphragm	Transient right bundle branch block
Cardiovascular abnormalities	S1Q3T3

without PE.¹⁶ Such signs were, therefore, deemed to be nonspecific. The signs most commonly found in chest radiographs and electrocardiograms are described in Table 3.

– *Arterial blood gases.* Arterial hypoxemia and respiratory alkalosis are common in patients with acute PE. However, the absence of hypoxemia does not exclude PE. In the PIOPED¹⁴ and PISA-PED¹⁶ studies, over 80% of patients presented basal PaO₂ values lower than 80 mm Hg and hypocapnia. Values in the same range were also observed in a similar percentage of patients without PE.

Risk Stratification

Although it has not been demonstrated that grading clinical probability using prediction rules is a more accurate method than the empirical assessment of experienced physicians,¹⁷ there is consensus on the validity of such models in multidisciplinary care settings, such as emergency departments, and for doctors in training. Pretest probability assessment has been developed by various groups.¹⁸⁻²¹ The characteristics, accuracy, validation, and reproducibility of the different models was reviewed in a recent meta-analysis.²² The most prospectively valid grading systems were the simple clinical models devised by Wells et al¹⁸ and the Geneva Group¹⁹ (Table 4).

The simplified clinical model developed by Wells et al¹⁸ comprises 7 weighted variables and is reproducible. It has been validated in both inpatients and outpatients. It classifies clinical probability as low, moderate, or high, or else as improbable or probable. Wells’ model has been criticized because it contains a subjective variable, the physician’s opinion as to whether PE is the most likely diagnosis, which carries a high score. The result of the application of this model in routine practice may be that only a small proportion of patients will be assessed as low probability. It is, however, the easiest rule to apply and the most widely used. The Geneva rule,¹⁹ on the other hand, has 7 objective variables and is reproducible. It has been validated in emergency departments. Although the Geneva rule is useful in routine practice, one disadvantage is that considerable weight is assigned to arterial blood gas results which, in emergency departments in Spain, are often affected by artifacts arising from a variety of circumstances. No differences were observed when these 2 prediction rules were compared.²³

TABLE 4
Scales of Clinical Probability in Pulmonary Embolism (PE)*

Predictive Rules	Points
Wells Scale¹⁸	
PE most likely diagnosis	3
Signs of DVT	3
Previous DVT or PE	1.5
Heart rate >100 beats/minute	1.5
Immobilization or surgery during the previous 4 weeks	1.5
Cancer treated in the prior 6 month or palliative treatment	1
Hemoptysis	1
Clinical probability	
Low	0-1
Moderate	2-6
High	≥7
Improbable	≤4
Probable	>4
Geneva rule¹⁹	
Recent surgery	3
Previous PE or DVT	2
PaO ₂ , mm Hg	
<48.7	4
48.7-59.9	3
60-71.2	2
71.3-82.4	1
PaCO ₂ , mm Hg	
<36	2
36-38.9	1
Age, years	
≥80	2
60-79	1
Pulse rate >100 beats/minute	1
Atelectasis	1
Elevation of hemidiaphragm	1
Clinical probability	
Low	0-4
Moderate	5-8
High	≥9

*DVT indicates deep vein thrombosis.

There are other models, such as the one developed by Kline et al,²⁰ which does not grade clinical probability but identifies whether or not patients are high risk for PE; this model is pending prospective validation. The model developed by Minati et al²¹ contains 15 variables weighted according to a complex system of calculation; this model grades clinical probability as low, intermediate, moderately high, and high. It is also pending prospective validation.

In short, in emergency departments and care settings where the physicians have no specialist training, clinical suspicion of PE should be assessed using validated prediction rules (grade B recommendation).

D-Dimer (DD)

DDs are a product of fibrin degradation. Numerous studies have confirmed that DDs are highly sensitive markers for VTED but lack specificity because elevated DD levels are also associated with various other conditions.²⁴

Most of the assays used to detect DDs are based on monoclonal antibodies. There are 2 types of DD assays as follows: quantitative procedures based on enzyme-linked immunosorbent assay (ELISA) techniques (VIDAS)²⁵ or turbidimetrics (Liatest, Tinaquant, Plus, MDA, IL-test)²⁶; and more subjective qualitative assays that use red cell agglutination (SimpliRED),²⁷ latex agglutination, immunochromatography, or immunofiltration, with the recent incorporation of quantitative variants (microlatex and others).²⁴ The classic latex agglutination assay is the least sensitive of all these tests, and is, therefore, no longer used.²⁴ The ELISA techniques and the turbidimetric assays are the most sensitive. The use of the red cell agglutination assay (SimpliRED) is controversial because it is less sensitive.²⁷

The presence of elevated DD levels is of clinical value because it is a highly sensitive marker. These tests are particularly useful in outpatients and emergency departments. When DD results are evaluated in conjunction with clinical probability in these contexts, the resulting low probability classification has a very high negative predictive value for PE.^{28,29} No evidence has emerged to support the use of these tests in hospitalized patients or those with relevant comorbidities because the DD result in such patients would be unlikely to be negative, and clinical probability would only occasionally be low.³⁰ It should also be remembered that sensitivity may be lower in patients with small thrombi and those receiving anticoagulant therapy.

In summary:

- Clinical probability should be established before DD testing (grade B recommendation).
- A negative DD result does not rule out PE in patients with high clinical probability so that this test is not useful in such cases (grade B recommendation).

TABLE 5
Scintigraphic Patterns of High Probability for Pulmonary Embolism³⁸

<p><i>According to the PIOPED study</i></p> <p>2 or more large segmental perfusion defects (>75% of a segment) without corresponding abnormalities in ventilation or chest radiograph, or defects substantially larger than 75%</p> <p>2 or more mismatched moderate segmental perfusion defects (between 25% and 75% of a segment), and 1 large mismatched segmental defect</p> <p>At least 4 moderate defects without abnormalities in ventilation or chest radiograph</p> <p><i>According to Biello</i></p> <p>1 large perfusion defect (>90% of a segment) without corresponding abnormalities in ventilation or chest radiograph</p> <p>1 perfusion defect substantially larger than the radiographic abnormality</p> <p>Multiple moderate (between 25% and 90% of a segment) or large defects without corresponding abnormalities in ventilation or chest radiograph</p> <p><i>According to Wells</i></p> <p>At least 1 segmental (or larger) perfusion defect with normal ventilation</p> <p>At least 2 subsegmental perfusion defects (<25% of a segment) with normal ventilation</p>
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Helical Computed Tomography (CT) Angiography

Contrast-enhanced CT angiography was developed for the diagnosis of PE during the early 1990s. This technique has gradually replaced lung scintigraphy to become the first line modality even though research undertaken during the early years showed that the sensitivity of CT angiography was suboptimal owing to its scant capacity to discriminate in small vessels.³¹ This limitation has been partially overcome by technological advances (multidetector-row CT) which facilitate better visualization of the vascular structures, reduce scanning time, decrease collimation, and provide more extensive coverage of the thorax.³²

Results will soon be available of a level I prospective investigation (PIOPED II) undertaken to definitively establish the sensitivity and specificity of this technique. In prospective studies of small case series, the sensitivity and specificity for segmental or more central arteries have been around 90%,³² decreasing in subsegmental arteries; this finding would only be of importance in cases of PE affecting subsegmental vessels only in which no more central occlusions were involved. The real frequency of this situation is unknown, but the figures published in the literature vary from 6% to 22%.^{33,34} However, recurrence rates of under 2% during follow up have been observed in patients with a negative CT angiogram who have not received anticoagulant therapy.³² These rates, which are similar to those observed after a normal perfusion scan or negative arteriography results, would appear to diminish the clinical importance of exclusively subsegmental PE.

In 3 prospective studies comparing CT angiography with lung scintigraphy it was found that CT angiography had a substantially higher level of interobserver agreement and greater specificity. An additional advantage of this technique was that in many cases it provided an alternative diagnosis.³⁵ Moreover, CT angiography is currently available in most hospitals and is more accessible outside normal working hours.

Lung Scintigraphy

Until recently lung scintigraphy was the technique most often used, and it had been validated by 2 level I prospective studies.^{36,37} This technique detects the absence of distal perfusion that may be caused by PE, although the lack of perfusion may also be caused by other conditions, such as reflex vasoconstriction or destruction of airway walls in areas of emphysema. This fact explains the lung scan's inherent lack of specificity and is the reason why its interpretation was generally guided by applying patterns of abnormality more or less specific to PE (Table 5).³⁸ A "high-probability" pattern was designed in the PIOPED study. While this pattern was shown to be highly specific, it was only observed in under 50% of the cases of PE; in almost 3 out of 4 suspected cases, the lung scan did not establish a diagnosis.³⁶ The patterns

of probability for lung scans were used in conjunction with clinical probability to ensure predictive values, and the only valid diagnostic combination was a high-probability scan found in conjunction with high clinical probability.

Today, scintigraphy is generally only used in hospitals where the equipment for obtaining a CT angiogram is unavailable and as an alternative option in patients with renal failure or with a history of adverse reactions to contrast agents.

In summary:

- A normal lung scan rules out PE (grade A recommendation).
- A high-probability scan found in conjunction with high clinical probability confirms PE (grade A recommendation).
- PE cannot be diagnosed or ruled out by the remaining "nondiagnostic" scan patterns or a high-probability scan combined with lower clinical probability (grade A recommendation).
- Today, CT angiography is a valid alternative to lung scintigraphy (grade B recommendation).

Venous Ultrasound of the Lower Limbs

Venous compression ultrasound of the lower limbs, duplex ultrasound (which incorporates Doppler assessment of blood flow), and color Doppler ultrasound (which also produces color images) are the techniques most commonly used to detect DVT. It has not been demonstrated that any other technique is superior to the venous compression ultrasound.³⁹ The main diagnostic criteria for thrombosis is the failure of the vein to compress. The vessels most often studied are the proximal veins of the lower extremities; investigation of the smaller, distal veins, which are characterized by low flow and more anatomical variations, greatly prolongs the exploration and lowers the yield, particularly if the DVT is asymptomatic.³⁹

In level I studies carried out using venography, it has been observed that around 60% of patients with confirmed PE have proximal DVT, some 20% distal DVT, and that the condition is asymptomatic in more than 50% overall.¹ This has led to the inclusion of venous ultrasound in the battery of tests used to diagnose patients with suspected PE, although a priori the high percentage of asymptomatic DVT cases reduces the sensitivity of the technique, which is very high in patients who present with symptomatic DVT.³⁹ In fact, in a study carried out in patients with suspected PE, the sensitivity of ultrasound for DVT was less than 30%.⁴⁰ In recent years, venous ultrasound has been included in different rounds of the diagnostic algorithms with a view to reducing the number of patients with no conclusive diagnosis and avoiding invasive testing.

To summarize, in patients with suspected PE, no other tests are strictly necessary after a venous ultrasound confirming DVT (grade B recommendation).

Other Noninvasive Tests

CT Venography

CT venography uses the contrast material introduced for pulmonary CT angiography to analyze the venous system of the lower limbs, the iliac vein, and the inferior vena cava a few minutes later. Sensitivity and specificity in small case series are over 95% in the femoropopliteal region.⁴¹ However, the predictable increase in gonadal radiation associated with this procedure still needs to be assessed, especially in young people. More studies are needed to evaluate all aspects of this technique and define the role it might play in the diagnostic process of PE.

Echocardiography

Echocardiography is not sensitive for the diagnosis of PE. It is used as a severity marker to detect RV dysfunction and it can identify intracardiac thrombi and thrombi located in the main pulmonary artery.⁴² In hemodynamically unstable patients with unconfirmed suspected PE, or in patients with other severity markers, echocardiography can provide useful data to guide urgent therapeutic decisions.

Nuclear Magnetic Resonance Imaging

Like CT angiography, magnetic resonance imaging provides a direct image of the PE. The shorter time required to obtain an image and the use of contrast materials such as gadolinium make it possible to obtain a pulmonary angiogram. In studies of a small number of case series, the sensitivity and specificity for PE were high.⁴³ This technique is used as an alternative to CT angiography in patients with renal failure or a history of adverse reactions to contrast agents. In patients with PE, magnetic resonance imaging can prove useful for detecting DVT in venous areas that are hard to study with other noninvasive techniques, such as the pelvis or the inferior vena cava.

Gold Standard Tests

Pulmonary Angiography

Conventional pulmonary angiography provides a firm diagnosis of PE and remains the gold standard. However, even with selective angiography, interobserver agreement on the interpretation of thrombi in subsegmental arteries is poor, raising some doubt about this technique's position as a reference standard.⁴⁴ Angiography with digital subtraction facilitates a quicker and more comfortable procedure and, when selective, can improve the visualization of small pulmonary emboli. Complications are rare, and improved materials plus the generalized use of nonionic contrast materials have minimized risks.

Conventional Venography

Contrast venography is the gold standard for diagnosing DVT in the upper and lower limbs.³⁹ When PE is suspected, venography is indicated as the last resource if no conclusive diagnosis has been reached using other imaging techniques to detect the PE and any causative DVT. It is also performed before implantation of an inferior vena cava filter.

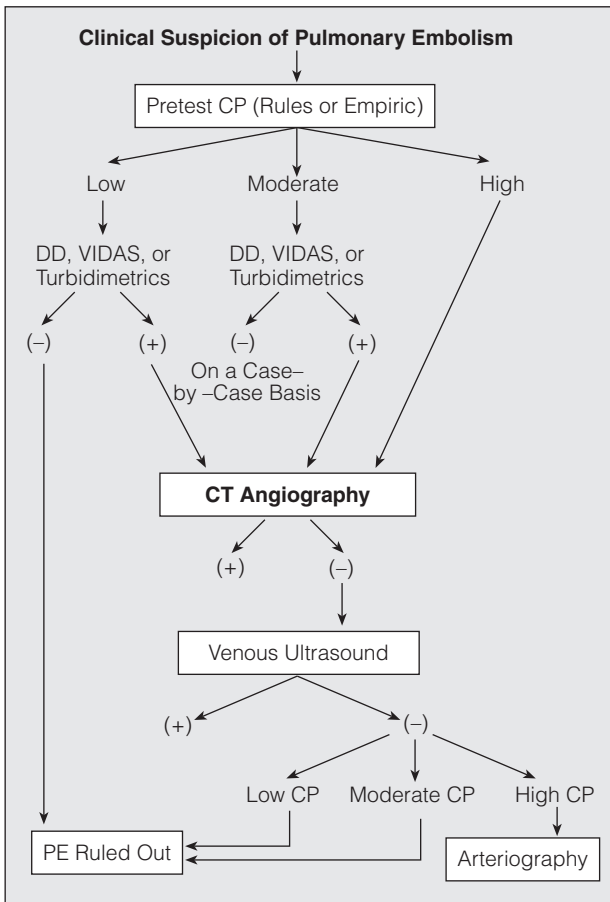


Figure 1. Diagnostic algorithm for pulmonary embolism with helical computed tomography (CT) angiography as the first imaging technique. DD indicates D-dimer assay; CP, clinical probability.

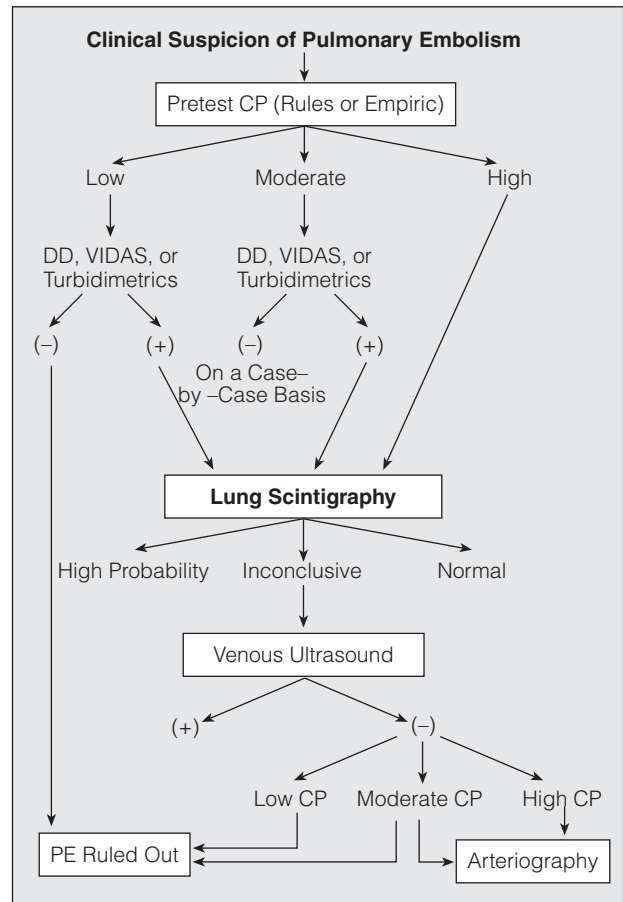


Figure 2. Diagnostic algorithm for pulmonary embolism with scintigraphy as the first imaging technique. DD indicates D-dimer assay; CP, clinical probability.

Diagnostic Algorithm for Hemodynamically Stable Pulmonary Embolism

The high incidence of PE in the general population, the seriousness of this condition, and the difficulties associated with its diagnosis make the design of a strategy for excluding or confirming a diagnosis of PE essential. There is, however, no ideal algorithm applicable in all hospitals. The yield and local availability of diagnostic tests determine the algorithm in each case (Figures 1 and 2). Most diagnostic strategies can be extrapolated to routine practice for hemodynamically stable PE.⁴⁵ All of these strategies comprise various diagnostic rounds:

1. *First round.* The prevalence of PE among patients who come to emergency departments with indicative signs and symptoms is low (around 30%).⁴⁵ Consequently, the basic aim of the first round of tests is to rule out a diagnosis of PE and obviate unnecessary diagnostic testing. The usefulness of using 2 low-cost tools, DD assay and clinical probability, to achieve this objective has been studied by various authors. In current practice, this round is generally omitted in patients with high clinical probability in whom DD testing would not obviate the need for other diagnostic tests.

– *Combination of clinical probability and DD testing.* Low clinical probability, as measured using the simplified scale drawn up by Wells et al,¹⁸ in association with a normal DD level obtained using highly sensitive techniques (VIDAS and turbidimetrics) and even using a less sensitive technique (SimpliRED), has been shown in 1 study to rule out PE (risk of later VTED close to 0).⁴⁵ When clinical probability is intermediate, there is no consensus that PE can be ruled out definitively by DD assay. In 1 study, in which a turbidimetric method (Tinaquant) was used to measure DD levels, the risk of subsequent VTED in patients with moderate clinical probability was 0.29. These results require confirmation. For the present, it would appear to be advisable to make decisions on a case-by-case basis taking into account the sensitivity of the DD testing method used and the cardiorespiratory reserve of the patient.

– *DD testing not combined with clinical probability.* Some studies with a high evidence rating carried out by the same group provide evidence to support this approach. In these studies, DD testing was performed using rapid ELISA (VIDAS).^{46,47} There is no consensus on the widespread application of this approach.

– *CT angiography or lung scintigraphy as the initial test.* Although some studies show that patients with a

negative CT angiogram who do not receive anticoagulant therapy are at low risk for thrombotic events during follow up, CT angiography is not a cost-effective first line diagnostic test.⁴⁸ With respect to scintigraphy, level I evidence indicates that the risk of VTED after a normal lung scan is approximately 1%.⁴⁹ The problem is that lung scan results are only normal in a small minority of cases (fewer than 20%).³⁶

2. *Second round.* The basic objective of the second round of tests is to confirm the diagnosis of PE using noninvasive diagnostic tests. In recent years, CT angiography and venous ultrasound have become the generally accepted tests of choice. The order that should be followed in performing each of these tests, including DD testing and clinical probability, is currently under study and remains controversial. Most of the strategies have been validated in outpatients, and there is less evidence in the literature regarding hospitalized patients.

– *DD testing using ELISA (VIDAS) followed by venous ultrasound, CT angiography, and clinical probability* (measured on the basis of the Geneva rule and clinical assessment) has proved to be the most cost-effective strategy because it confirms or rules out a diagnosis of PE in 99% of patients.⁴⁸ This strategy was developed by a Swiss group, Perrier et al.⁴⁷

– *CT angiography in conjunction with venous ultrasound followed by empiric clinical probability* is a strategy useful in outpatients that has been validated in a French multicenter study.⁵⁰ The results were, however, poor in hospitalized patients. Since DD testing was not included, it is interesting to speculate whether such testing would have improved the cost effectiveness of this strategy.

– *Lung scintigraphy followed by venous ultrasound.* The best results have been obtained with serial venous ultrasound, which is difficult to carry out in routine practice.⁴⁵ In some of the studies undertaken, patients with limited cardiorespiratory reserve were excluded.

3. *Third round:* gold standard tests (conventional arteriography and venography). In hemodynamically stable PE, arteriography is indicated as a last resource in patients with high clinical probability and inconclusive diagnostic test results, especially in patients at risk for hemorrhage, in order to avoid empiric anticoagulant therapy. In strategies for the diagnosis of PE, venography is used only occasionally to avoid arteriography.

In summary:

– In emergency departments, the combination of low clinical probability and negative DD results (obtained using highly sensitive techniques) rules out PE (grade B recommendation).

– The combination of clinical probability, DD testing, CT angiography, and venous ultrasound diagnoses or rules out PE in most cases (grade B recommendation).

Diagnostic Algorithm for Unstable PE

No validated algorithm is available for unstable PE. Diagnosis is conditioned by and inseparable from the need to take urgent therapeutic measures. In such cases, any

decision about what steps are to be taken is determined by the means available. In general, the diagnostic tests most commonly used are echocardiography (the patient's condition permitting) and CT angiography. Another effective option in certain hospitals is arteriography, a technique that not only facilitates diagnosis and treatment with localized fibrinolysis, but which also facilitates other treatments, such as mechanical fragmentation and percutaneous thromboembolectomy.

Treatment During the Acute Phase

Clinical presentation in PE can vary greatly, ranging from asymptomatic cases to patients suffering from hypotension and cardiogenic shock. In most presentations, PE causes symptoms but pressures are maintained and spectacular improvement comes within 1 or 2 days. However, there is no consensus on how to manage a subgroup of PE patients whose blood pressure remains normal but who have right ventricular dysfunction. The prognosis for each group is different, and the therapeutic strategy is not always the same. Expedient assessment of severity and bleeding risk is essential so that therapeutic decisions can be taken immediately.

Assessment of Severity

Clinical Markers

Hypotension is a sign of shock and is an indication for thrombolytic therapy or other available percutaneous procedures in cases where thrombolytic therapy is absolutely contraindicated. Although other symptoms, such as severe dyspnea, cyanosis, and syncope are considered to suggest a more unfavorable prognosis, in isolation they are not considered indications for thrombolytic therapy. Abnormalities in the electrocardiogram (S1 Q3 T3 pattern, T wave inversion in leads V1 to V4, and right bundle branch block) and radiological signs of pulmonary hypertension are also considered to be an indication of greater severity.⁵¹ A relationship between an arterial oxygen saturation of less than 95% and mortality from acute PE has been observed in a study which showed that mortality was significantly lower in patients whose arterial oxygen saturation was 95% or higher.⁵² The shock index (heart rate divided by systolic blood pressure ≥ 1) was used to assess whether or not echocardiography was necessary to identify possible RV dysfunction⁵³; that index needs to be validated.

Clinical risk scoring. The Geneva Group has validated a clinical scoring system that predicts a better or worse prognosis by way of a risk score (score ≥ 3).⁵⁴ This score is based on 6 variables: systolic blood pressure under 100 mm Hg, cancer, PaO₂ less than 60 mm Hg, previous DVT, heart failure, and presence of DVT; the score is calculated by adding 2 points for the first 2 factors and 1 point for each of the remaining 4 factors.

Markers of Cardiac Repercussion

– *Echocardiography.* In addition to helping guide the differential diagnosis of PE by ruling out cardiac

tamponade, aortic dissection, and acute myocardial infarction, transthoracic echocardiography is also an important tool in evaluating the prognosis of submassive PE because the signs of RV dysfunction (moderate or severe hypokinesis), pulmonary hypertension, the presence of right-sided mobile thrombi, and the persistence of patent foramen ovale have all been identified as markers of severity.⁵¹

– *Troponin and brain natriuretic peptide.* Acute cor pulmonale can occur in PE. This causes RV dilatation, an increase in the demand for oxygen in the RV, and a reduction in the perfusion of the right coronary artery. Even in the absence of atherosclerotic lesions, the result may be RV microinfarctions triggering the release of troponin, a good marker of RV dysfunction. In some cases of PE, troponin release may be delayed 6 to 12 hours. Although the validity of using cardiac troponin monitoring to rule out RV dysfunction in normotensive patients is controversial, the results of preliminary studies appear promising.⁵⁵

Brain natriuretic peptide is secreted in response to stretching of the myocardial fibers of the RV or an increase in pressure in such fibers. The cut-off point used to identify normal levels (<50 pg/mL) was lower than that used to detect heart failure. It seems that troponin monitoring could be used to rule out RV dysfunction.⁵⁶

In short, echocardiography is a useful tool for assessing the severity of PE (grade B recommendation).

Assessment of Hemorrhage Risk

Anticoagulant therapy must always be considered except when there are absolute contraindications, such as active internal bleeding or recent spontaneous intracranial hemorrhage. In such cases, the only option open is the insertion of a vena cava filter or, exceptionally, mechanical fragmentation with thromboembolectomy; this decision will depend on the clinical situation of the patient. However, even when there is no absolute contraindication to such treatment, it can be useful to measure the risk of hemorrhage when taking these decisions for the purpose of a) deciding between thrombolytic therapy and heparin and b) designing the intensity and duration of anticoagulant therapy.

Risk markers for hemorrhage. The bleeding index developed by Wells et al,⁵⁷ which has been prospectively validated in outpatients for standard therapy with low-molecular-weight heparin (LMWH) followed by coumarin therapy (Table 6), discriminates between patients at low-risk (no hemorrhage complication) and those at moderate-risk (rate of major hemorrhage 4.3 per 100 person-years). The index has not been validated for patients at high risk for hemorrhage. It is simple to use and can be applied in routine clinical practice.

Four situations associated with an increase in major bleeding have been identified in hospitalized patients starting unfractionated heparin treatment: comorbidity, age over 60, intensity of anticoagulation treatment, and liver dysfunction exacerbated by such treatment.⁵⁸

The variables associated with major bleeding complications in patients receiving thrombolytic

TABLE 6
Bleeding Risk Index Developed by Wells et al⁵⁷

	Points
Age >65 years	1
History of digestive hemorrhage	1
History of stroke	1
1 or more of the following signs:	1
Hematocrit <30%	
Creatinine >1.5 mg/dL	
Diabetes mellitus	
Recent acute myocardial infarction	

Low Risk: 0 points; intermediate risk: 1 or 2 points; high risk: ≥3 points.

therapy have been identified as increasing age, higher body mass index, and femoral vein catheterization.⁵⁹

In emergency departments, assessment of bleeding risk can help guide therapeutic decisions (grade B recommendation).

Initiation and Duration of Acute Treatment

According to studies of patients with DVT, initial anticoagulant treatment at adequate therapeutic doses influences both short-term and long-term efficacy.⁶⁰ In clinical practice, we extrapolate this finding to patients with PE when making decisions about initial treatment, taking into account the greater risk of recurrence inherent in PE.⁶¹ Except in patients at high risk for bleeding, it is advisable to start treatment very early at the intensity corresponding to the therapeutic doses validated for each different type of heparin available. The minimum duration for any type of heparin treatment during the acute phase should be 5 days. When this is followed by coumarin therapy, an overlap of around 4 days is necessary between the 2 treatments, such that coumarin therapy can be started on the first or second day. Treatment should not be withdrawn nor the dose of heparin reduced until an internationalized normal ratio (INR) of 2.0 to 3.0 has been achieved, if possible on 2 consecutive occasions.

Pharmacotherapy During the Acute Phase

LMWHs

LMWHs are created by fractionation of unfractionated heparin using chemical or enzymatic methods to obtain more homogenous mixtures of 1000 to 10 000 daltons. They have a high antifactor Xa activity, with a ratio of antifactor Xa to antifactor IIa that is higher than that of

TABLE 7
Therapeutic Dosages for Pulmonary Embolism of Low-Molecular-Weight Heparins Available in Spain

Drug	Dosage
Enoxaparin	1 mg/kg/12 h or 1.5 mg/kg/24 h
Dalteparin	100 U/kg/12 h or 200 U/kg/24 h
Fraxiparin	85.5 U/kg/12 h or 171 U/kg/24 h
Tinzaparin	175 U/kg/24 h
Bemiparin	115 U/kg/24 h

TABLE 8
Dosages of Systemic Thrombolytic Agents Approved by the United States Food and Drug Administration for Pulmonary Embolism*

Drug	Dosage
rt-PA	100 mg in 2 h
Urokinase	4400 U/Kg in 10 minutes, followed by a perfusion of 4400 U/Kg/h for 12 hours
Streptokinase	250 000 U in 30 minutes, followed by a perfusion of 100 000 U/h for 24 hours

*rt-PA indicates recombinant tissue plasminogen activator.

unfractionated heparin (1:1). The bioavailability of these drugs when administered subcutaneously is over 90%, and they have a long half life. This ensures a lasting and predictable anticoagulant response, so that the drug can be administered in weight-adjusted doses and analytical monitoring of Xa antifactor activity is unnecessary except in morbidly obese individuals and patients suffering from renal failure. Monitoring is also advisable in the case of recurrence of hemorrhagic complications, and the need for monitoring in patients of advanced age is still a matter of debate. These agents reach effective plasma concentrations within approximately 1 hour of administration and maximum levels within 4 hours. They give rise to fewer adverse events than unfractionated heparin (fewer cases of heparin-induced thrombocytopenia and thrombosis) and their osteopenic effect is lower.⁶²

In hemodynamically unstable PE, there is level I evidence that LMWHs are just as effective and safe as unfractionated heparin.⁶³ LMWHs are currently the first line therapy because of their greater convenience compared to unfractionated heparin. The therapeutic doses of the LMWHs available in Spain are described in Table 7.

Unfractionated Heparin

Traditionally and for decades unfractionated heparin was the first line treatment for PE. It is a heterogeneous mixture of polysaccharide chains of different lengths and molecular weights (from 3000 to 30 000 daltons) obtained mainly from pig intestinal mucosa. Unfractionated heparin produces an anticoagulant effect by binding to antithrombin and intensifying its action through the inactivation of a series of activated coagulation factors, principally IIa (thrombin). Treatment must be monitored using activated partial thromboplastin times. The therapeutic range is achieved by prolonging the activated partial thromboplastin time from 1.5 to 2.5 times the control value. Treatment usually takes the form of continuous intravenous infusion of sodium heparin. Other possible routes are intermittent intravenous bolus or subcutaneous calcium-heparin every 12 hours, although with the latter route it is difficult to reach an activated partial thromboplastin time in the initial hours of treatment owing to low bioavailability.⁶² Unfractionated heparin is gradually being replaced by LMWH therapy. In certain cases, mainly in critical care settings where drugs with a short half life are advisable, unfractionated heparin administered via continuous intravenous infusion could continue to be the best option.

Thrombolytic Therapy

Thrombolytic agents intensify natural fibrinolysis by activating plasminogen to increase plasmin production and thereby achieve rapid lysis of recently formed thrombi. There is level I evidence that thrombolytic agents are more effective than unfractionated heparin during the first 24 hours in terms of the improvement of both hemodynamic parameters and pulmonary arterial flow. The evidence suggests that this difference tapers gradually and disappears by the fifth day.⁶⁴ For this reason, there is only consensus about their use in cases of hemodynamically unstable PE.

In recent years, in view of the results of the latest studies, there has been some debate about the possibility of broadening the application of this treatment to include patients with RV dysfunction.⁶⁴ It is not clear whether RV dysfunction is a predictor of recurrence and mortality. The results of the studies that have been undertaken are contradictory. Moreover, some authors report that the prevalence of RV dysfunction in normotensive patients with PE is high (around 30%), and a very substantial change in therapeutic approach would be necessary if that is the case.⁶⁴ It has been suggested that it is necessary to identify more precisely which patients in this subgroup could benefit from thrombolytic therapy.

Table 8 lists the thrombolytic agents approved by the United States Food and Drug Administration for PE that are available in Spain and gives the appropriate dosing information.

Pentasaccharides

A new drug, fondaparinux, will very soon be available for the treatment of PE. A synthetic pentasaccharide made up of units of 5 saccharides, fondaparinux is a selective inhibitor of coagulation factor Xa with a very low molecular weight (1728 daltons). It has a long half life (14 hours), a bioavailability of nearly 100% when administered subcutaneously, and is excreted in urine. Peak plasma concentration is reached within 1 to 3 hours of administration. In a phase III level I study, fondaparinux administered via continuous intravenous infusion was shown to be as effective and safe as unfractionated heparin in the acute treatment of PE.⁶⁵ Consequently, this drug represents a new treatment option.

Ximelagatran

Ximelagatran is an oral direct thrombin inhibitor which, after bioconversion to its active form (melagatran), reaches peak plasma concentrations within 1.3 to 2 hours of administration. It has a half life of about 3 hours, and elimination is primarily renal (80%). The effect of this agent is predictable, making analytical monitoring unnecessary. In phase III studies, the efficacy of ximelagatran administered at fixed doses of 36 mg twice daily for 6 months was as good as standard LMWH therapy with enoxaparin for a minimum of 5 days following by warfarin for 6 months. A transient elevation (over 3 times the normal value) in liver enzymes was observed in nearly 10% of patients.⁶⁶

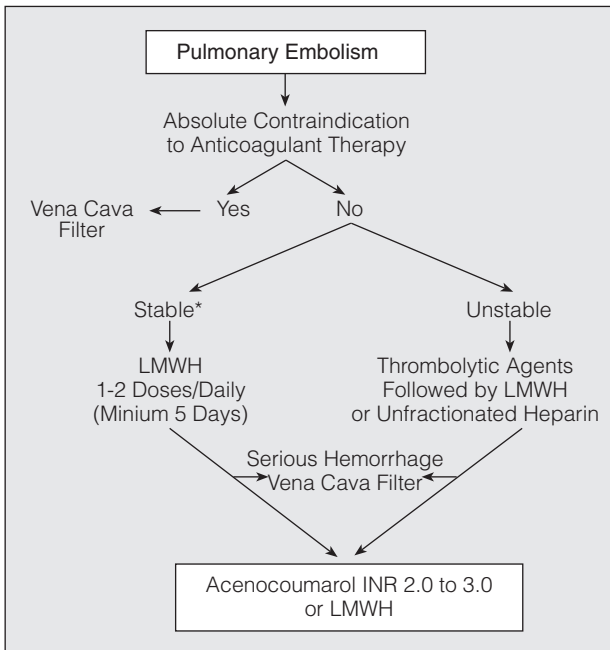


Figure 3. Therapeutic algorithm for pulmonary embolism. LMWH indicates low-molecular-weight heparin, and INR, international normal ratio. *In normotensive patients with elevated troponin levels, clinical markers of severity, or an echocardiogram showing right ventricular dysfunction, the prescription of thrombolytic therapy or LMWH should be decided on a case-by-case basis.

Vena Cava Filters

The indications for vena cava filters have not changed in recent years: absolute contraindication to anticoagulant therapy and an uncontrolled major bleeding event during acute anticoagulant therapy. The efficacy of these filters in preventing PE is offset by the fact that in the medium and long term they constitute a risk factor for recurrence of DVT.⁶⁷ Once the acute situation which motivated the insertion of the filter has passed, indefinite prescription of anticoagulant therapy appears to be more effective in preventing recurrence of DVT and minimizing postthrombotic syndrome. Given that many of the contraindications to anticoagulant therapy and many of the bleeding complications that lead to the insertion of a filter disappear in the short term, the use of retrievable filters is recommended.⁶⁸ Retrievable filters can be removed within 15 days of placement or left in place permanently if this is clinically indicated. There is currently no evidence available concerning the efficacy of these devices.

Other Therapeutic Procedures

Percutaneous Thromboembolectomy, Mechanical Fragmentation, and Local Thrombolysis

Some groups have developed very effective alternative mechanical and local thrombolytic techniques.⁶⁹ In the absence of any evidence supporting the superiority of these techniques over classic treatment with systemic thrombolytic therapy or heparin, they are

currently indicated primarily in individual patients with hemodynamic instability and/or at high risk for hemorrhage.

Surgical Thromboembolectomy

Surgical thromboembolectomy is an option used in very rare cases of patients with hemodynamic instability and massive PE and occasionally in patients with thrombi lodged in the right cardiac chambers or even in the left atrium through the oval foramen.

Therapeutic Algorithm

The therapeutic algorithm for PE must be tailored to the characteristics and experience of each hospital (Figure 3). Certain markers of severity—the echocardiogram and cardiac troponin—have not been validated sufficiently to warrant their incorporation into routine practice. At this time, they appear to be useful in patients with clinical indications of severity.

In summary:

- Thrombolytic therapy is indicated in hemodynamically unstable PE (grade A recommendation).
- The indication for thrombolysis in normotensive patients with right ventricular dysfunction is not well established (grade B recommendation).
- In hemodynamically stable PE, LMWHs are as effective and safe as unfractionated heparins (grade A recommendation).
- In the near future, fondaparinux and ximelagatran will represent new options for acute treatment of PE (grade B recommendation).

Follow-Up Treatment and Monitoring

The follow-up period begins after the first 5 to 10 days of treatment. The chief objective of follow up is to prevent recurrence by continuing anticoagulant therapy, which during this period is called secondary prophylaxis. The duration of secondary prophylaxis must be established by balancing the risk of recurrence against the bleeding risk associated with the treatment. Other objectives that should be taken into account are the need to monitor postthrombotic syndrome of the lower limbs secondary to the DVT diagnosed as a result of the PE, and the possibility of pulmonary hypertension associated with chronic PE, although this is quite rare.

There is no evidence available to indicate what clinical variables should be monitored during the follow-up period, nor what battery of tests should be performed. The most prudent course is to strive to meet the aforementioned objectives by using the tests and monitoring methods most likely to detect markers of recurrence and treatment-induced complications in each individual case (Figure 4).

Markers of Recurrence

During the early months of secondary prophylaxis the risk of recurrence, which is estimated to be around

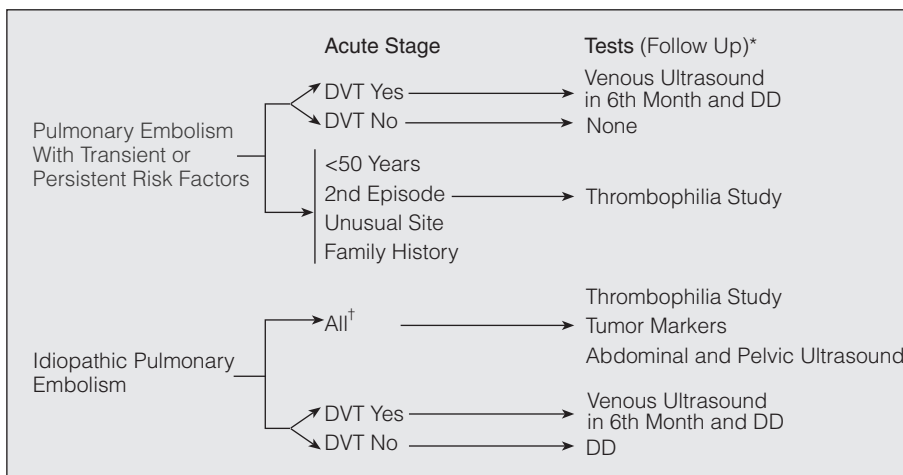


Figure 4. Testing strategy during follow-up of patients with pulmonary embolism. DVT indicates deep vein thrombosis; DD, D-dimer assay. *Echocardiography in the presence of dyspnea unexplained by any other cause at 6 months; †on a case-by-case basis in elderly patients.

5%, is generally associated with cancer, cardiovascular or respiratory comorbidity, or other medical diseases.⁷⁰ A number of variables have been evaluated as risk factors for recurrence after the withdrawal of anticoagulant therapy. With respect to the clinical presentation of PE, there is evidence that patients with symptomatic PE are not only at greater risk for recurrence than those with DVT without symptoms of PE, but also that recurrence once again takes the form of PE.⁶¹ With respect to the pathogenesis of the initial episode, idiopathic PE is an independent risk factor for recurrence⁷¹; it not only recurs significantly more often than PE related to transient risk factors, but also more frequently than PE caused by persistent risk factors. Other clinical factors associated with recurrence in the long term include increasing age, body mass index, and neurological diseases involving lower limb paresis.⁷²

There are also other markers of high risk of recurrence, such as thrombophilia and cancer, which may not have been diagnosed during the acute stage, in addition to residual thrombosis. In recent years, elevated DD levels have also been described as predictors of recurrence.

Congenital or Acquired Thrombophilia

In some studies involving unselected patients, thrombophilia does not appear to predict a risk of recurrence during the first 2 years following cessation of anticoagulant therapy after a first episode of VTED.⁷¹ However, the low prevalence of many of these abnormalities has meant that too few patients have been included in these randomized trials to allow for any firm conclusions, so that these predictions of risk of recurrence are only estimations. The exceptions to this are heterozygotic factor V Leiden mutations and factor II G20210A mutations, which are both considered predictive of low or moderate risk. It appears that the other abnormalities may be associated with a high risk of recurrence, especially homozygotic factor V Leiden mutations, antithrombin deficiency, and both in combination.

The answer to the question of when and in which patients a thrombophilia work up should be undertaken is as follows:

- The advantage of undertaking a thrombophilia work up during the acute stage is that a follow-up strategy can be planned from the outset, but most of the measurements may change during this stage and be affected by coumarin therapy. Usually, the work up is performed after cessation of oral anticoagulant therapy or else before taking any decision regarding the duration of treatment. In the latter case, coumarin therapy can be replaced for approximately 3 weeks by LMWH, which does not interfere with the results of the thrombophilia work up.

- In patients with emboli in unusual sites or a family history of thrombosis, thrombophilia tests should be carried out after an initial episode irrespective of age. There is also consensus that the work up should be carried out in younger patients (the limit is arbitrarily set at around 50 to 60 years) after the first episode, whether or not it was idiopathic. At more advanced ages the question is somewhat controversial, although there is greater consensus with respect to patients with recurring idiopathic PE.

Cancer

In patients with neoplastic disease, the likelihood of recurrence is 3 to 4 times greater and the risk of hemorrhage 3 times greater than in patients without cancer. The risk of recurrence and bleeding is related to the extent of the cancer spread.⁷³ Current practice is to continue long-term anticoagulant therapy, and no period of time free of neoplastic disease has been established after which it is advisable to withdraw treatment.

Idiopathic VTED can be the first manifestation of an occult malignancy. However, intensive screening does not improve survival.⁷³ There is a degree of consensus in favor of initiating a tumor search using basic tests (chest radiograph, abdominal and pelvic ultrasound, standard work up) and desisting if no signs are found.

Residual DVT

In recent years, it has been demonstrated that residual lower limb DVT is an independent risk factor for recurrence.⁷⁴ In this study, residual DVT was defined as a vein diameter of greater than 2 to 3 mm found using ultrasound during maximum compression of the common femoral and popliteal veins. This indicates that monitoring of residual DVT diagnosed as a result of PE can provide useful data for deciding on the duration of secondary prophylaxis.

DDs

Studies have recently assessed the usefulness of DD testing to predict recurrence within 1 to 3 months after cessation of anticoagulant therapy. Recurrence is 2 to 3 times more likely in patients with elevated DD levels. Conversely, DD results within the normal range have a high negative predictive value.^{75,76}

Duration of Secondary Prophylaxis

Decisions concerning the regimen to be used for secondary prophylactic anticoagulant therapy are taken during the acute stage taking into consideration the risk factors that may have triggered the PE and whether these factors were transient or persistent. During follow up, bleeding risk and the presence or absence of new markers for recurrence in each case may give rise to adjustments to the planned duration of secondary prophylaxis (Table 9).

Although the possibility of shortening the duration of anticoagulant therapy has been studied,⁷⁷ level I evidence still indicates that it should be maintained for 6 months after a first episode of PE since this regimen has been shown to be more effective than shorter periods without any significant increase in bleeding risk.

Furthermore, while some authors report that the risk of recurrence tends to stabilize after 9 months irrespective of the duration of secondary prophylaxis,⁷⁸ it has recently been demonstrated that oral anticoagulant therapy for PE only minimizes recurrence while treatment is continued, and that the risk of recurrence after cessation of treatment is high, especially in idiopathic PE.⁷⁹

Level I evidence supports prolonging secondary prophylaxis in idiopathic PE beyond 6 months, although the length of the additional period has not been established.⁸⁰ The tendency today is for long-term or indefinite secondary prophylaxis, although other markers of recurrence and bleeding risk are taken into consideration. This type of PE has recently focused the attention of researchers on how to maintain efficacy while minimizing the bleeding risk associated with very prolonged anticoagulant therapy. As a result of a recent level I study we now know that after the first 6 months, and for at least 2 years on the average, continuing coumarin therapy to maintain a target INR of between 1.5 and 2.0 reduces the risk of recurrence by over 60%

TABLE 9
Duration of Secondary Prophylaxis in Pulmonary Embolism*

6 months	Transient risk factors First idiopathic episode not severe, without markers indicative of recurrence during follow up (thrombophilia, occult cancer, residual venous thrombosis, elevated D-dimer levels)
Long term [†]	Persistent risk factors First idiopathic episode severe or with markers indicative of recurrence during follow up Second episode

*Risk of bleeding conditions duration on a case-by-case basis.
[†]The duration of long-term prophylaxis has not been established. In many cases, after individual assessment, treatment continues indefinitely.

without significantly increasing bleeding complications.⁸¹ However, the matter is still not resolved. After the aforementioned study was completed, another level I study of idiopathic PE demonstrated that an INR of 2.0 to 3.0 was as safe as and more effective than an INR of 1.5 to 1.9 after nearly 2.5 years of treatment.⁸²

In recurrent PE, the evidence on efficacy favors prolonging anticoagulant therapy in the very long term despite the greater risk of bleeding complications this entails.⁸³

In summary:

- The duration of secondary prophylaxis in PE is generally 6 months (grade B recommendation).
- In idiopathic PE, secondary prophylaxis should be prolonged beyond the initial 6-month period, although total duration of treatment has not been established (grade B recommendation).
- In many patients, the duration of anticoagulant therapy is determined by the presence of thrombophilia, residual venous thrombosis, elevated DD levels, or cancer (grade B recommendation).

Anticoagulant Agents Used in Secondary Prophylaxis

Coumarin Agents

Acenocoumarol and warfarin are the 2 coumarin derivatives available in Spain. These agents interfere competitively in the metabolism of vitamin K, preventing the proteins dependent on this vitamin (factors II, VII, IX, and X, and proteins C, S, and Z) from participating in the natural coagulation process. Acenocoumarol has a shorter half life and a faster metabolic clearance than warfarin. Treatment must be guided by way of INR monitoring. Efficacy in the treatment of VTED has been demonstrated at an INR of between 2.0 and 3.0.

The main adverse events are bleeding, sometimes a result of excessive anticoagulation and more often secondary to an underlying disease which is revealed by the bleeding. The clinical impact of bleeding complications in VTED is considerable: the rate of cerebral hemorrhage has been estimated at 1.15 per 100

person-years.⁸⁴ Other less common complications are skin allergies, excessive hair loss, and skin necrosis during the first few days in patients with protein C deficiency.

Acenocoumarol is currently the drug most commonly used for secondary prophylaxis in Spain. The great problem associated with the use of this agent is the difficulty of maintaining the patient's INR within the therapeutic range owing to variable absorption of the drug and the interference of food, concurrent medication, and comorbid diseases.

LMWHs

LMWHs are an alternative to coumarin agents during more or less prolonged periods of secondary prophylaxis. One indication for LMWH therapy supported by 2 level I studies is in cancer patients.^{85,86} In the first of these studies it was demonstrated that enoxaparin at doses of 1.5 mg/kg/day (75% of the accepted dose during the acute stage) is just as effective as and safer than warfarin. The second study showed that dalteparin at a dosage of 200 U/kg/day during the first month (the accepted dosage for the acute stage) and 150 U/kg/day for the 5 following months is just as safe as and more effective than warfarin or acenocoumarol treatment.

Compared to coumarin agents, LMWHs provide stability in anticoagulation and do not, in general, require monitoring. However, the dose for secondary prophylaxis in patients without cancer has not been established. The doses used in the early studies were the same as those indicated for primary prophylaxis in high risk patients; the doses used in later studies were nearer to those accepted for the acute stage.⁸⁷

One of the unresolved concerns regarding LMWH is the possible osteopenic effect of long-term treatment. At primary prophylactic doses during a 2-year period in a level 2 study, it has been shown that LMWHs cause a modest but progressive loss of bone mass that is more noticeable than that caused by acenocoumarol.⁸⁸

Ximelagatran

There is level I evidence that, after an initial 6 months of anticoagulant therapy with coumarin agents, extended ximelagatran treatment at a dosage of 24 mg twice daily is effective in preventing recurrence without significant bleeding risk, making treatment at this dose an alternative for extended secondary anticoagulant therapy.⁸⁹ The only adverse event observed was a temporary elevation of liver enzymes in 6.4% of patients.

In conclusion:

- The bleeding risk associated with the use of coumarin agents is not negligible (grade B recommendation).

- During secondary prophylaxis in cancer patients, LMWHs at doses similar to those used during the acute stage are more effective than coumarin agents (grade B recommendation).

- In the near future, ximelagatran could represent an alternative for prolonged secondary prophylaxis (grade B recommendation).

Summary of Recommendations

- When using DD testing, clinical probability should be previously established (grade B recommendation).

- In emergency departments, the combination of low clinical probability and a negative DD result obtained using highly sensitive techniques rules out PE (grade B recommendation).

- CT angiography can be used as a substitute for lung scintigraphy (grade B recommendation).

- The combination of clinical probability, DD, CT angiography, and diagnostic venous ultrasound diagnoses or rules out PE in the immense majority of cases (grade B recommendation).

- Electrocardiography is useful in assessing the severity of PE (grade B recommendation).

- Thrombolytic therapy is indicated in patients with hemodynamically unstable PE (grade A recommendation).

- The indication for thrombolysis in normotensive patients with RV dysfunction is not well established (grade B recommendation).

- In hemodynamically stable PE, LMWHs are as effective and safe as unfractionated heparin (grade A recommendation).

- The duration of secondary prophylactic treatment in PE is generally 6 months (grade B recommendation).

- In idiopathic PE, secondary prophylaxis should be extended beyond the initial 6 months, even though the total duration of treatment has not been established (grade B recommendation).

- Thrombophilia, residual venous thrombosis, DD levels, and cancer are all factors that determine the duration of anticoagulant therapy in many patients (grade B recommendation).

- During secondary prophylaxis in cancer patients, LMWH in doses similar to those used during the acute stage are more effective than coumarin agents (grade B recommendation).

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