

# Guidelines on acute pulmonary embolism from the European Society of Cardiology: reflections from the perspective of the emergency physician

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The European Society of Cardiology published "Guidelines on the diagnosis and management of acute pulmonary embolism" at the end of 2008. This document provides an exhaustive review of the epidemiologic, diagnostic, therapeutic, and prognostic evidence related to acute pulmonary embolism. The aim of the present review is to synthesize the points of greatest interest for the emergency physician, with particular emphasis on the use of the various risk factors proposed. The guidelines suggest adopting clinical variables and signs of right ventricular dysfunction or markers of myocardial injury given their prognostic value, rather than applying traditional scales. The emergency echocardiograph to detect signs of right ventricular dysfunction probably has the greatest prognostic value in the emergency setting. This test is indispensable for emergency department physicians who manage patients suspected to be at high risk of pulmonary embolism. [Emergencias 2010;22:61-67]

**Key words:** Acute pulmonary embolism. European Society of Cardiology Emergency physician.

## Introduction

Pulmonary thromboembolism (PTE) is today a diagnostic and therapeutic challenge for emergency physicians. The low sensitivity and specificity of its clinical manifestations, the absence of a simple test for diagnosis and fear of incorrect diagnosis with serious prognostic implications make PTE a frequent challenge for the emergency physician<sup>1</sup>.

In the last decade, there has been a great amount of scientific evidence focused basically on the diagnosis of PTE, proposing the use of algorithms to minimize the number and cost of complementary tests with high performance rating. This cost-effective view of PTE management has led to a deluge of diagnostic schemes, which often confuse instead of helping. In this sense, many societies have made efforts to gather relevant scientific evidence and issue their findings in the form of recommendations. In late 2008, the European Society of Cardiology (ESC) published in its journal a review: "Guidelines on the diagnosis and management of acute pulmonary embolism"<sup>2</sup>, which could lead to changes in PTE management from

the point of view of diagnosis and treatment, given the clear emphasis placed on risk stratification. Although not strictly following the structure proposed in the guide, this review covers the most relevant points.

## Relevance of the application of clinical prediction models and D-dimer measurement

The guide clearly states that the evaluation of clinical probability involves applying so-called pre-test predictive models and, specifically, the Canadian or Wells model. The importance of applying these pre-test predictive models is that patient identification within a certain group or category is associated with an increased prevalence of PTE (65% in the high probability group, 30% in the intermediate probability group and 10% in the low probability group) which has a large influence on the interpretation of complementary investigations. The use of these models, together with D-dimer measurement, may exclude the diagnosis in up to one third of patients

attending the emergency department (ED) with suspected PTE<sup>3</sup>. However, the guide emphasizes the need to know if the technique used for determining D-dimer is of high or moderate sensitivity. When using highly sensitive techniques<sup>3</sup>, it is safe not to initiate anticoagulant therapy or perform other diagnostic investigations to rule out PTE if the patient presents low or moderate clinical probability (or is clinically unlikely to have PTE according to the latest review of the Wells predictive model) and D-dimer is negative. But if the techniques available are of moderate sensitivity<sup>4</sup>, the diagnosis can only be excluded when clinical probability is low (or clinically unlikely). The authors also stress one of the main drawbacks to the application of predictive models; although they have been widely validated, they present significant inter-observer variability on one of the rateable items: the nonexistence of an alternative diagnosis by itself means that the probability of PTE is moderate (or clinically probable). It should be recalled that D-dimer has poor specificity in certain patient populations, such as the elderly over 80 years, where the number of patients who must undergo D-dimer measurement to exclude the diagnosis of PTE or the required number of tests (NNT) is 20<sup>5</sup>. Also worth recalling is the low specificity of D-dimer, which can even be used as an inflammatory marker in paediatric patients<sup>6</sup>. In the ED, the fastest and cheapest test for measuring D-dimer is probably SimpiRED<sup>®</sup>, an agglutination technique that can be performed at the bedside, of moderate sensitivity, which was used by Wells and others for the external validation of their clinical prediction model<sup>7</sup>.

### Validated diagnostic criteria

The guide provides an exhaustive review of the scientific evidence regarding the validity of five complementary tests for the diagnosis of PTE: vein compression ultrasonography, lung scan of ventilation and perfusion, CT scan, pulmonary angiography and echocardiography. It should be pointed out that, for the authors of the guide, the terms PTE confirmed and PTE excluded refer to sufficiently high or low probability to be able to indicate or not the specific treatment; these terms do not indicate absolute certainty about the presence of emboli in the lung.

The detection of proximal deep vein thrombosis (DVT) proximal in patients with suspected PTE mandates initiating anticoagulant therapy without

the need for further tests<sup>8</sup>. However, only 20% of patients with suspected PTE have a positive compression ultrasonography for DVT. In addition, sensitivity increases only slightly when including more distal sites (from 22% to 43%). Obviously, the sensitivity of the test significantly increases when clinical features are suggestive of DVT.

Lung ventilation (V) and perfusion (Q) scintigraphy (known as a V/Q scan) remains a very useful technique, especially in certain areas where there are no more sophisticated techniques. The results of the scan are classified according to the classic study PIOPED<sup>9</sup> into four categories: normal, low probability, intermediate probability (or non-diagnostic) and high probability. A low-probability V/Q scan, combined with low clinical probability, excludes the diagnosis of PTE and anticoagulant treatment is not indicated. Although less validated, a non-diagnostic V/Q scan in patients with low clinical probability also allows exclusion of the diagnosis of PTE. Obviously, patients with a high probability scan require anticoagulant therapy, but there is an exception: those with low clinical probability, in that before starting such therapy other diagnostic tests should be performed. In all other scenarios, other tests are necessary before exclusion or initiating anticoagulation.

Unfortunately, all these other scenarios constitute the majority, and that more than half the cases present non-diagnostic V/Q scan results<sup>10</sup>. CT angiography alone can not rule out the diagnosis of pulmonary embolism, but can in combination with negative venous compression ultrasound of the extremities in patients with low or intermediate probability, since this circumstance is associated with a mere 1% of venous thromboembolic events at 3 months follow up. On this point, it should be noted that the authors do not favor venography of the lower limbs by CT angiography, arguing that it does not increase negative predictive value (PIOPED II study data) and also adds more time and radiation contrast dose. The authors believe that multidetector CT angiography has become the technique of choice for the diagnosis of PTE. Apart from the PIOPED II study, four other studies provide the latest evidence that a positive multidetector CT angiography confirms intermediate clinical probability and, conversely, a negative multidetector CT angiography in clinically intermediate or low probability patients excludes the diagnosis of PTE.

Although considered the gold standard, lung angiography is an invasive procedure, with a peri-

procedural mortality of 0.2%. Now CT angiography offers similar or better information and hemodynamic measurements can be replaced by echocardiographic findings and biomarkers. However, the authors claim that lung angiography should be considered when these non-invasive techniques are inconclusive. Echocardiography will be covered in the next section.

Based on the above information, it can be concluded that the diagnosis of pulmonary embolism can be excluded in following situations: normal lung angiography with any clinical probability; negative D-dimer determined using specific techniques of high sensitivity and low or intermediate clinical probability (or clinically unlikely); in patients with negative D-dimer determined using specific techniques of moderate sensitivity and low clinical probability (or clinically unlikely); in patients with normal V/Q scan; in patients with indeterminate V / Q scan and low clinical probability (or clinically unlikely); in patients with indeterminate V / Q scan and negative compression ultrasound and low or intermediate clinical probability; in patients with CT angiography and normal compression ultrasound with low or intermediate clinical probability and in patients with normal multidetector CT angiography and low or intermediate clinical probability.

Conversely, the diagnosis of pulmonary embolism can be confirmed in the following situations: compatible with PTE in all situations; with a V/Q scan indicating high probability in patients with intermediate or high clinical probability; in patients with compression ultrasonography in all proximal DVT situations; in patients with CT angiography or multidetector CT with segmental defects or more in any situation.

From the perspective of the emergency physician in a high-tech hospital ED, the technique of choice is the angio-CT multidetector. In EDs with lower level technology, a simple CT angiography combined with limb compression ultrasonography, or a V/Q scan, should suffice to indicate anticoagulation in these patients.

However, there are several areas of uncertainty in the diagnosis of PTE, such as the interpretation of a defect in subsegmental multidetector CT angiography, negative findings in patients with high clinical probability, or a V/Q scan of high probability in patients with low clinical probability. In these situations, the decision to initiate anticoagulation should be based on the results of other diagnostic tests or the particular characteristics of each case.

### **Prognostic evaluation and risk stratification, and the importance of echocardiography**

The guideline authors, following the current trend of doing away with the words "massive", "sub-massive" or "not massive" (terms based on morphological data) propose risk stratification with high or not high (which in turn is sub-classified into the intermediate or low), associated with early mortality (hospital or 30 days) rates of 15%, 3-15% and less than 1%, respectively. They advocate stratifying risk according to a series of clinical risk markers suggestive of right ventricular dysfunction (RVD) or myocardial damage. The clinical risk markers are shock or hypotension; the markers of RVD are RV dilatation, hypokinesia or right ventricular (RV) overload determined by echocardiography, the existence of RV dilatation by CT and elevated atrial natriuretic peptides; and the markers of myocardial damage are the presence of positive troponin I or T. Patients with high risk PTE are those presenting clinical markers (Hypotension or shock). Patients not at high risk, by definition without clinical markers, could be intermediate-risk patients who present RVD markers and / or myocardial damage, or low-risk patients without these markers (Table 1).

According to the authors, this risk stratification should also be used in patients with suspected pulmonary embolism, not only in those with suspected PTE, as it helps to select the optimal diagnostic strategy and initial treatment.

It seems unnecessary to dwell on the scientific evidence provided by the guidelines in supporting the use of these prognostic markers. However, it is well to recall that there are other "classical" prognostic markers and scales based primarily on age, comorbidities and some data from standard laboratory tests<sup>12</sup>.

The following lines discuss the role of echocardiography. Given the low sensitivity of this technique (60-70%) for the diagnosis of PTE, it should not be used as the diagnostic strategy for PTE in normotensive or hemodynamically stable patients. However, in relation to risk, up to 25% of patients with PTE present echographic findings that indicate RVD, which is crucial, since mortality rate in these patients is more than double that of patients without echocardiographic RVD data. Moreover, the presence of echographic RVD data in normotensive patients is related with an absolute increase in mortality of 4-5%. Echocardiographic data suggestive of RVD include dilated RV, hypokinesia, increased ratio of left-right ventricular diam-

**Table 1.** Risk stratification, markers and therapeutic implications

Risk of early PTE-related mortality		Risk markers			Treatment
		Clinical	RVD	Myocardial damage	
High		+	+	+	Thrombolysis
Not high	Intermediate	-	+	+	Hospital
		-	+	-	Hospital
		-	-	+	Hospital
	Low	-	-	-	Early discharge

PTE: Pulmonary thromboembolism. RVD: right ventricular dysfunction.

eter and increased flow rate in the renal tricuspid<sup>13</sup>. However, it is necessary to recall that RVD signs may be due to heart disease or respiratory disease in the absence of acute PTE. Echocardiography in the ED is indicated in all patients with unexplained shock. The emergency physician should be able to perform echocardiography, not only for the differential diagnosis with shock, but for improved management of the PTE patient, as indicated by many societies of emergency medical science, including the American College of Emergency Physicians in their Emergency Ultrasound Guidelines reviewed and approved in October 2008<sup>14</sup>.

## Diagnostic Strategies

Based on risk stratification and evidence related to validated diagnostic criteria, the authors propose certain diagnostic algorithms.

In patients at high risk (Figure 1) if multidetector CT angiography is immediately available and the patient is stable, this must be performed. If not, the authors propose the use of an echocardiogram (Class IC). The presence of RVD signs, persistent instability and non-availability of CT justify the indication for treatment, which in this case is thrombolysis.

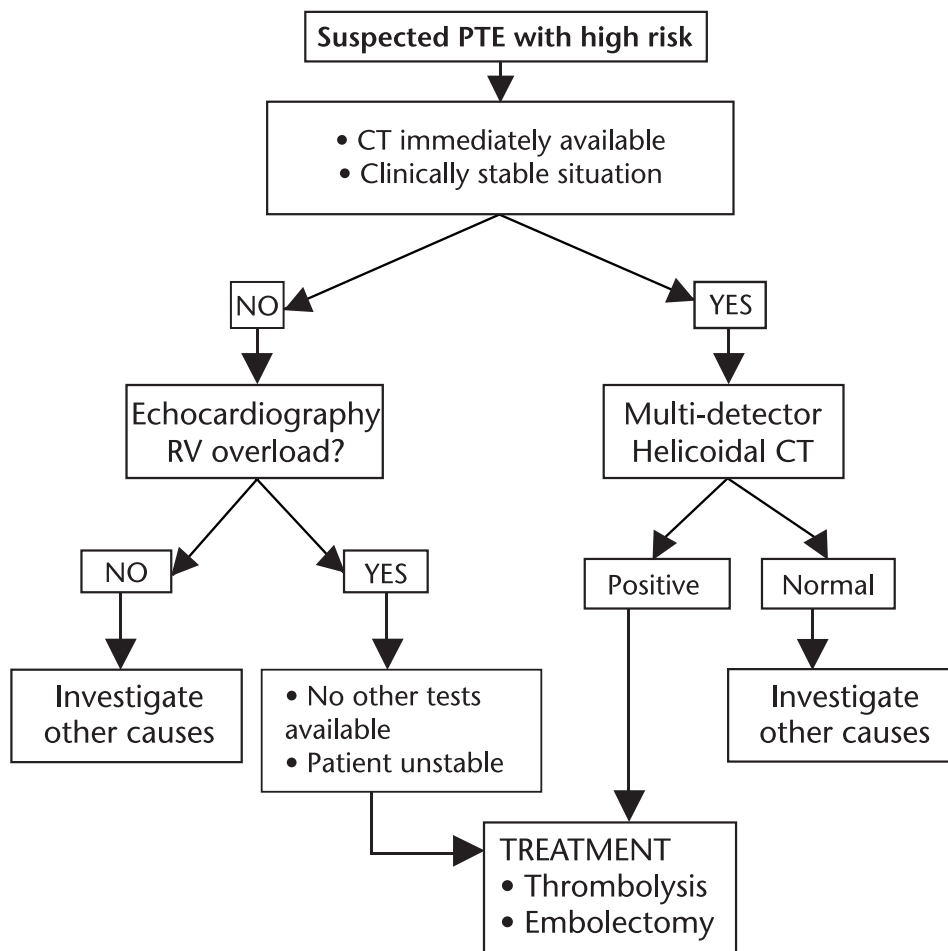
In patients who are not at high risk (Figure 2), clinical probability should be assessed as a first step (class IA). In patients with high probability, multidetector CT angiography is indicated, without the need for D-dimer determination due to its low negative predictive value in this group in this group. In patients with low or intermediate probability, D-dimer values should be used to indicate whether this imaging technique is required.

## Short-term or initial treatment

The guidelines also develop the topic of long-term anticoagulation and secondary prophylaxis, but this is beyond the scope of this article.

From the therapeutic point of view, the guidelines do offer something new. In patients with high risk PTE, the recommendations include unfractionated heparin (Class IA), vasoactive drugs (dobutamine and dopamine) to correct systemic hypotension and increase cardiac output (class IC), no fluid overload (class IIIB) and, of course, systemic thrombolysis (class IA). In this sense, although the evidence as of today is based on only nine trials, rapid administration (within 2 hours or less) appears to be somewhat more effective (speed and reduction of thrombus and improvement of hemodynamic parameters) and safe (incidence of bleeding) than non-accelerated treatment (12-24 hours). The three thrombolytics approved for the treatment of PTE are streptokinase, urokinase and plasminogen activator factor (t-PA). If systemic thrombolysis is contraindicated, the guidelines recommend surgical thrombectomy (class IC) over thrombectomy or fragmentation with a catheter (class IIIBc).

In non-high risk PTE, the guidelines recommend starting anticoagulant therapy in patients with intermediate or high clinical probability before confirming the diagnosis (class IC). The recommended treatment is low molecular weight heparin (LMWH) and fondaparinux, and recall that there are two LMWH approved for the treatment of PTE (enoxaparin and tinzaparin), except for patients with renal creatinine clearance below 30 ml / min or high risk of bleeding where unfractionated heparin is recommended (class IC). But any of the three options (LMWH, fondaparinux or unfractionated heparin) is equally valid. One of the points that differs significantly from the American guides, the eighth edition of the Antithrombotic and Thrombolytic Therapy American College of Chest Physicians Evidence-Based Clinical Practice Guidelines<sup>15</sup> which recommend simultaneous antivitamin K (AVK) and heparin, is that the European guidelines recommend postponing AVK drugs for a few days, maintaining heparin treatment during 5 days and only withdrawing it when a standard index for anticoagulation (ACI) has been achieved during two con-



**Figure 1.** Proposed diagnostic algorithm in pulmonary thromboembolism (PTE). RV: right ventricular. CT: computed tomography.

secutive days. This difference probably lies in the use of warfarin instead of acenocoumarol, the AVK drug most used in Europe. Pharmacokinetic differences and the onset of action (greater for warfarin) could explain the differences between the two guidelines.

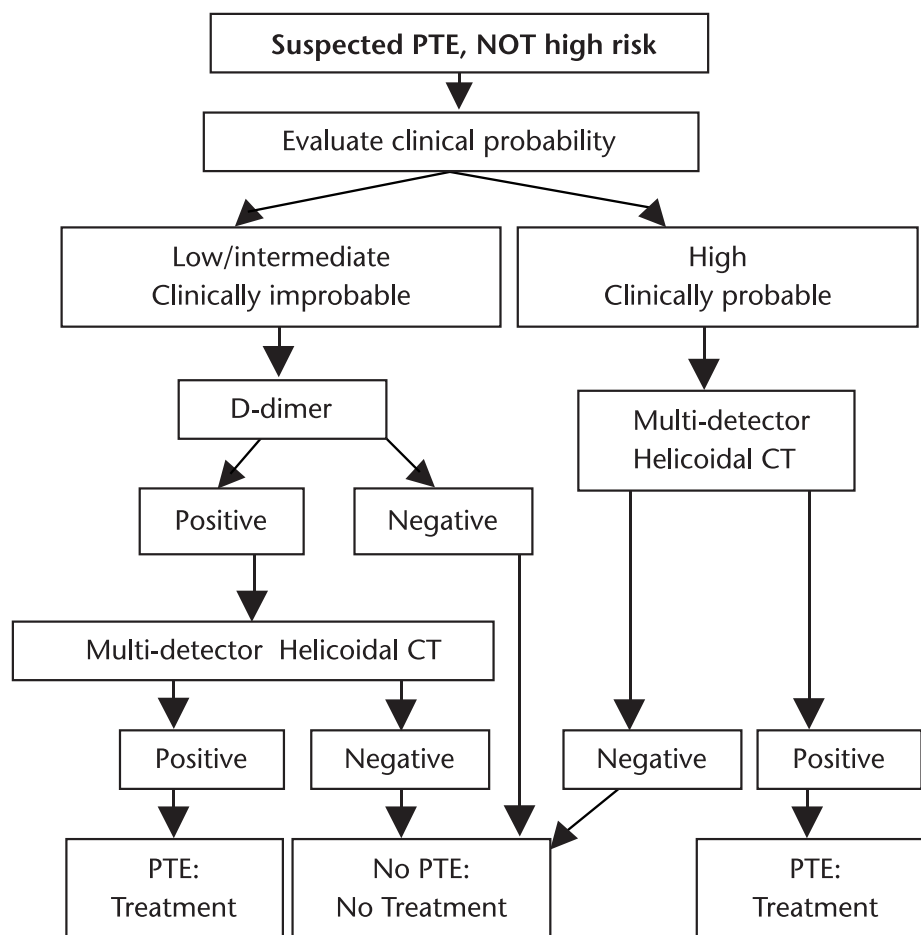
In relation to filters in the vena cava, the guidelines recommend placement only when anticoagulation is completely contraindicated and there is a high risk of recurrence of venous thromboembolic events (Class IIBB).

### Specific problems: pregnancy

To finalize, the guidelines also report on specific problems (pregnancy, cancer, thrombus of the right heart cavities, heparin-induced thrombocytopenia, chronic pulmonary hypertension and non-thrombolytic chronic pulmonary embolism), which aspects are not reviewed in this article.

However, one point will be discussed: the problems posed by pregnant patients.

PTE is a leading cause of maternal mortality related to pregnancy in developed countries, and occurs primarily in the postpartum and post-caesarean period. With this premise, it seems necessary to comment briefly on the recommendations of the guidelines. It is necessary to indicate that, regardless of the risk of foetal radiation, the workup should be directed toward diagnostic accuracy, given the risk to the mother of anticoagulant treatment. It is important to note that although D-dimer may increase during gestation, up to 50% of pregnant women have normal levels, so a negative value during pregnancy has the same value as in other patients. With suspected PTE in pregnant women with positive D-dimer, lower limb compression ultrasonography must be performed. If negative, either a perfusion V/Q scan (without ventilation) or thoracic CT angiography should be performed. In relation to treat-



**Figure 2.** Proposed algorithm for pulmonary thromboembolism (PTE). CT: computed tomography.

ment, LMWH should be administered throughout pregnancy, since AVK drugs are teratogenic and there is little experience with fondaparinux. Monitoring of LMWH anticoagulant effect may be considered by measuring anti-Xa levels.

## Conclusions

The decision on anticoagulation or not for patients with suspected PTE remains a daily dilemma in the emergency department. Its potentially life-threatening prognosis and the risk of bleeding inherent to anticoagulation in a population which is increasingly old and multi-pathological require the most accurate diagnosis possible.

Scientific evidence and its collection in the form of guidelines help in the management of these patients. The guidelines lay down the need for an approach in accord with risk criteria in the same way as for other entities. In this regard,

echocardiography is a crucial technique in patients at high risk, which highlights the need for emergency physician training in this technique, not only from the healthcare and patient management point of view, but also to reduce the dependence on other specialists that echocardiography currently entails.

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## Guías de la Sociedad Europea de Cardiología 2008 para el tromboembolismo pulmonar: una lectura comentada desde la perspectiva del *urgenciólogo*

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A finales de 2008 la Sociedad Europea de Cardiología publicó las *Guidelines on the diagnosis and management of acute pulmonary embolism* donde se revisa exhaustivamente toda la evidencia científica epidemiológica, diagnóstica, terapéutica y pronóstica relacionada con el tromboembolismo pulmonar (TEP). Esta revisión sintetiza los puntos de mayor relevancia para el *urgenciólogo*, con especial hicampié en la utilización de los distintos factores de riesgo propuestos. A diferencia de escalas pronósticas clásicas, en la guía referida se utilizan parámetros clínicos, de disfunción del ventrículo derecho y de daño miocárdico. De ellos, probablemente el más interesante es la utilización de la ecocardiografía urgente para demostrar signos de disfunción del ventrículo derecho, lo que convierte esta exploración en un instrumento indispensable para los *urgenciólogos* en el manejo de pacientes con sospecha de TEP de alto riesgo en urgencias. [*Emergencias* 2010;22:61-67]

**Palabras clave:** Tromboembolismo pulmonar. Sociedad Europea de Cardiología. *Urgenciólogo*.