

Editorial

Comments on the 2019 ESC guidelines on acute pulmonary embolism

Comentarios a la guía ESC 2019 sobre embolia pulmonar aguda



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INTRODUCTION

The Spanish Society of Cardiology (SEC) encourages close attention to the clinical practice guidelines (CPGs) of the European Society of Cardiology (ESC). In addition to the translation of each guideline document, the SEC publishes a commentary for each CPG to highlight the most notable points and other important aspects related to its implementation from the Spanish perspective. The CPGs of the ESC use 4 classes of recommendations (I, IIa, IIb, and III) and 3 levels of evidence (A, B, and C, from highest to lowest).¹ Given the eminently multidisciplinary nature of the management of pulmonary embolism (PE) and to provide the broadest view possible, the SEC Guidelines Committee set up a drafting panel that represents the views of physicians working in diverse cardiology subspecialties, as well as experts in pneumology, internal medicine, emergency care, and nursing.

Compared with previous guidelines,² the new CPGs of the ESC/European Respiratory Society (ERS) present some novelties related to the diagnosis, prognostic stratification, initial and long-term treatment, and follow-up of patients with PE.¹ In addition, specific sections have been added for patients with cancer and for pregnant women with suspected or confirmed PE.

GENERAL CONSIDERATIONS

PE is a frequent cause of cardiovascular death, with an increasing incidence and decreasing lethality. This shift is probably related to the improved sensitivity of the available diagnostic tests (which enable the detection of minor embolisms of uncertain clinical significance), the use of safe and effective treatments, and increased adherence to evidence-based recommendations.³ The main determinant of the duration of anticoagulant therapy for patients with PE is the presence or absence of genetic and acquired factors that predispose the development of venous thromboembolic disease (VTE). The main cause of early death after acute PE is right ventricular (RV) failure. This condition develops after a vicious circle triggered by a sudden increase in pulmonary blood pressure due to vascular obstruction, which, in turn, activates various pathophysiological mechanisms that can lead to decreased

systemic cardiac output, with subsequent falls in blood pressure and vital organ perfusion (obstructive shock) and death.

One change is that the 2019 guidelines define the 3 clinical manifestations of patients with high-risk PE: persistent hypotension, obstructive shock, and cardiac arrest (table 4 of the guidelines). Hypotension is defined as systolic blood pressure < 90 mmHg that is not due to reversible factors (sepsis, hypovolemia, and cardiac arrhythmia). Obstructive shock requires the presence of hypotension (or the need for vasopressors to maintain pressure above 90 mmHg) and end-organ hypoperfusion (eg, altered mental status, oliguria/anuria, increased lactate).

DIAGNOSIS OF ACUTE PULMONARY EMBOLISM

Clinical scales and D-dimer testing

The diagnostic approach to patients with suspected symptomatic acute PE depends on their hemodynamic situation. The recommendation for hemodynamically unstable patients is bedside transthoracic echocardiography or pulmonary computed tomography (CT) angiography if it is immediately available and the patient can be transferred to the radiology lab (I C recommendation). The new guidelines recommend a combination of well-validated clinical (pretest) probability scales, with D-dimer being the first diagnostic step for hemodynamically stable patients with suspected PE (I A). One novelty is that the guidelines propose the Pulmonary Embolism Rule-out Criteria (PERC) scale as a tool to rule out PE without the need for additional tests. The combination of PERC with a low clinical probability (according to a well-validated scale) can rule out PE without the need for D-dimer analysis or imaging tests. However, because the prevalence of PE in the studies validating this strategy was significantly lower than that reported in Spain, we do not recommend the systematic use of the PERC scale in this country. The guidelines include 2 new strategies concerning the use of D-dimer for stable patients with suspected PE: use of an age-adjusted D-dimer cutoff (IIa B) or use of a cutoff adjusted to the clinical probability according to the YEARS model² (IIa B). The optimal adjustment method for the D-dimer cutoff is unclear. Adjustment by age is useful only in patients older than 50 years, whereas adjustment by clinical probability is also useful in young people and, thus, in fertile and pregnant women, who should not undergo unnecessary imaging tests. Moreover, the use of different D-dimer cutoff points complicates diagnosis in clinical practice and, therefore, reduces its applicability in Spain. In addition, although the results published with the use of the YEARS

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model are very promising, validation studies from Spain are required before its routine use can be recommended.

It should be remembered that the guidelines recommend that anticoagulant therapy be initiated as soon as possible once PE is suspected in hemodynamically unstable patients and in hemodynamically stable patients with intermediate or high clinical probability or probable PE (I C), a key therapeutic strategy that is not always followed in Spain.

Imaging techniques

For the first time, a table is used to summarize the different imaging techniques suitable for the diagnosis of PE. This table includes the strengths, weaknesses, and limitations of each modality, as well as the radiation dose (table 6 of the guidelines). As a novelty, reference is made to single-photon emission CT (SPECT) as a diagnostic alternative to planar ventilation/perfusion lung scintigraphy (IIb B), whereas pulmonary arteriography is omitted; in previous guidelines, this technique could be considered in individualized patients. CT venography, also known as phlebo CT, is definitively ruled out as a diagnostic method due to the high radiation and low negative predictive value of the technique. As useful information, reference is made for the first time to the radiological signs of pre-existing chronic thromboembolic pulmonary hypertension (CTEPH) that suggest acute PE over underlying CTEPH (table 2 of the supplementary material of the guidelines).

ASSESSMENT OF PULMONARY EMBOLISM SEVERITY AND RISK OF EARLY DEATH

Clinical parameters of severity

As in previous guidelines, early prognostic stratification is recommended for patients with symptomatic PE to determine the treatment and most appropriate treatment location (I B). The first step continues to be the distinction between hemodynamically stable and unstable patients. One of the novelties of these guidelines is that the identification of low-risk patients requires the combination of a negative prognostic clinical scale (eg, Pulmonary Embolism Severity Index [PESI] or simplified PESI) and the absence of RV dilatation/dysfunction (IIa B). There may be difficulties in implementing this recommendation in clinical practice, given that the guidelines do not specify the imaging method that should be used for RV assessment: CT (the diagnostic method available for most patients) or echocardiography. Taking into account clinical experience and logistic considerations (limited echocardiography availability 24 hours a day 7 days a week and overloading of imaging units in cardiology departments), the absence of RV dilatation on CT should be sufficient to identify most low-risk patients. The use of echocardiography to evaluate RV parameters should be reserved for low-risk patients whose treatment can be completely outpatient-based or those with doubts about the results of CT concerning the RV. Although the new guidelines continue to recommend the combination of myocardial damage markers and RV dysfunction to identify patients with intermediate- to high-risk PE, they cite, for the first time, the possibility of using multimarker scales (eg, Bova scale, FAST scale) that combine clinical parameters, biomarkers, and imaging tests to identify this subgroup of patients (IIb C).

Right ventricular size and function

Pulmonary CT angiography, a diagnostic test performed in most patients with PE, also provides prognostic information. The guidelines

explain how RV size should be measured and establishes a cutoff point with prognostic significance, namely, a RV/LV ratio ≥ 1.0 . The text itself, a figure, and a supplementary table all include the cutoff points for various echocardiographic parameters evaluating geometry and RV function with prognostic significance. These cutoffs include a tricuspid annular plane systolic excursion (TAPSE) < 16 mm and the RV/LV diameter ratio, which are easy to quantify and subject to low interobserver variability. The use of simple parameters and validated cutoff points for the echocardiographic definition of RV dilatation and dysfunction can facilitate the performance of echocardiography by qualified noncardiologists, particularly when patients require an urgent diagnosis and prognostic stratification.

TREATMENT IN THE ACUTE PHASE

Hemodynamic and respiratory support

The therapeutic support recommended for high-risk PE is based on the Heart Failure Association document on the management of acute RV failure,³ understanding that the approaches are temporary measures before pharmacological reperfusion (fibrinolysis) or surgical or percutaneous treatment. A major part of the recommendations center on preventing iatrogenic complications, which are relatively frequent in the standard treatment of these patients. Specifically, *a*) to avoid excessive volume loading by only performing volume loading if there are data on baseline hypovolemia and by never using more than 500 mL of serum, and *b*) to avoid hyperoxygenation (using noninvasive supplemental oxygen whenever possible and avoiding the use of very high end-expiratory support pressures if mechanical ventilation is necessary). The guidelines recommend careful consideration of the use of inotropic agents (dobutamine) and vasoconstrictors (noradrenaline) (IIa C) to minimize adverse effects (increased V/Q mismatch or excessive vasoconstriction, respectively). Dobutamine is the drug of choice when signs of low cardiac output are not accompanied by excessively low blood pressure and noradrenaline when the blood pressure is very low (eg, < 70 -80 mmHg). In patients with very severe hemodynamic and respiratory deterioration, for the first time the document proposes the use of temporary mechanical circulatory support in the form of venoarterial extracorporeal membrane oxygenation (ECMO) as a bridge to subsequent surgical or percutaneous embolectomy (IIb C). Notably, ECMO and surgical and percutaneous reperfusion treatments are not available in many Spanish centers. One option in these centers is to consider early transfer of unstable patients to other hospitals equipped with nonpharmacological revascularization treatments and the ability to perform ECMO (if patients are suitable candidates), particularly if fibrinolysis is contraindicated or the response is unfavorable.⁴

Initial treatment: anticoagulation, fibrinolysis, and vena cava filters

The most relevant change from the previous document regarding anticoagulation is that the current guidelines recommend the first-line use of direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) (I A). This change is based on: *a*) the publication of various systematic reviews and meta-analyses that confirm equivalence in terms of efficacy and, above all, a significant reduction in the incidence of major bleeding, intracranial hemorrhage, and fatal bleeding^{5,6}; *b*) the analysis of specific subgroups (eg, patients with PE or kidney disease, as well as elderly, frail, and thin patients) with even more favorable outcomes for DOACs; and *c*) increased clinical experience with these drugs, which confirm the findings of the clinical trials.⁷

There is some debate about this recommendation because the key clinical trials predominantly enrolled patients with deep vein thrombosis, all of the studies had a noninferiority design, and the real-life studies were subject to selection biases. However, it should be remembered that only the EINSTEIN PE trial randomized the anticoagulant therapy to 4832 patients with PE,⁸ a much higher number than that of any other trial published with anticoagulant therapy for PE. In addition, the meta-analyses that evaluated the efficacy and safety of DOACs in patients with VTE included more than 11 000 patients with PE, a much larger study population than those meta-analyses that examined the safety and efficacy of low-molecular-weight heparin (LMWH) for VTE therapy.⁹ In contrast to the clinical trials with DOACs in atrial fibrillation, the use of noninferiority designs is recommended by regulatory bodies,¹⁰ given that VKAs reduce the risk of thrombotic recurrence by 90%.¹¹ Finally, although the limitations of observational studies are well-known, no warning signs suggesting discrepancies with the findings of clinical trials have been found in terms of safety or efficacy and no unexpected complications have been detected. A highly pertinent aspect concerns the application of this recommendation in Spain because the Spanish National Health System does not reimburse these drugs for this indication. Considering all of these aspects, it will be important to monitor their use in well-designed registries and evaluate their safety, effectiveness, and cost-effectiveness in real-life settings in our environment.

Multidisciplinary pulmonary embolism teams

The guidelines propose the creation of multidisciplinary rapid response teams for the management of the acute phase of PE. These teams (also known as Pulmonary Embolism Response Teams [PERTs] or PE codes) comprise various specialists in the treatment of the condition. Their objective is the early evaluation and development of a treatment plan that includes the best treatment and the best treatment location for each patient. Although the number of these teams is continually increasing, the optimal structure and organization are not yet clear and there is a lack of evidence concerning their impact on patient prognosis and on the optimization of health care resources.

INTEGRATED RISK-ADAPTED DIAGNOSIS AND MANAGEMENT

Diagnostic strategies

In the diagnostic algorithm for patients with suspected PE and hemodynamic instability, transthoracic echocardiography is introduced as the bedside diagnostic tool of choice over pulmonary CT angiography for the differential diagnosis of shock. This technique was previously considered only if patient transfer for CT angiography was impossible. Accordingly, echocardiography should be the first-line diagnostic tool for the evaluation of patients with hemodynamic instability and suspected RV failure.

For the diagnosis of hemodynamically stable patients with suspected PE, 2 different strategies are distinguished. One is based on pulmonary CT angiography, whereas the other involves lung V/Q scintigraphy for patients who do not want or cannot undergo CT for any reason (eg, radiation avoidance, contrast agent contraindication). The current CPGs highlight the importance of evaluating RV function through imaging techniques (echocardiography/CT) in hemodynamically stable patients, independently of risk. Given that there is a suboptimal correlation between CT- and echocardiography-obtained RV evaluations and that the intervention protocols of each center will be subject to technical availability,

the performance of echocardiography for RV evaluation at least in patients without hemodynamic instability seems advisable for low-risk patients when considering outpatient management of their disease and for intermediate- to high-risk patients being considered for reperfusion therapy.

Treatment strategies

In the treatment of high-risk PE (hemodynamically unstable), the main novelty is the introduction of ECMO for patients who cannot be stabilized with general measures (chiefly inotropic agents and vasopressors) or who fail to respond to reperfusion therapy. If the patient receives initial ECMO, the reperfusion therapy of choice should be surgical or percutaneous embolectomy over fibrinolysis. The recommended anticoagulant therapy for unstable patients with PE is patient weight-adjusted unfractionated heparin.

For stable patients diagnosed with PE, the guidelines recommend treatment with DOACs (I A), except for patients with severe kidney disease, pregnant and lactating women, and patients with antiphospholipid syndrome (III C). In Spain, the lack of reimbursement for these drugs means that most patients receive parenteral anticoagulation (LMWH or fondaparinux over unfractionated heparin [I A]) overlapped and followed by VKAs.

The guidelines advise consideration of the early discharge of patients with low-risk PE (IIa A) as long as they meet the following criteria: *a*) the patient has been identified using the PESI or simplified PESI scales or the HESTIA criteria; *b*) if the PESI or simplified PESI scales are used to identify patients suitable for early discharge, it should be confirmed that the patient has no other reasons for hospitalization beyond PE, such as inadequate family or social support or complicated access to urgent medical care; and *c*) the patient does not show RV dilatation/dysfunction on CT or echocardiography.

CHRONIC TREATMENT AND PREVENTION OF RECURRENCE

Prediction of the long-term risk of VTE recurrence, key to determining treatment duration, is mainly based on the presence or absence of risk factors (and the type of risk factor) at diagnosis. The supplementary material of the guidelines show different models for predicting risk recurrence (stressing that their usefulness in clinical practice is not confirmed), the variables associated with bleeding risk, and the need to always estimate this risk in each clinical evaluation to: *a*) identify the modifiable aspects that reduce risk; and *b*) review the duration of oral anticoagulant therapy. There are 4 relevant changes regarding the duration and type of anticoagulant therapy: *a*) the recommendation to use DOACs as first-line therapy (I A), an aspect discussed above; *b*) the recommendation of VKAs for patients with antiphospholipid syndrome, due to the lower efficacy of DOACs (I B); *c*) the recommendation to consider prolongation of anticoagulant therapy beyond the first 3 months for patients with PE secondary to a transient and resolved minor risk factor (IIa C); and *d*) the recommendation (IIb B) to use sulodexide to prevent VTE recurrence based on a small trial showing a 50% reduction in the risk of recurrence vs placebo.¹² However, sulodexide does not have this therapeutic indication in Spain.

Management of pulmonary embolism in patients with cancer

Although the recommended treatment for patients with PE and active cancer is LMWH for at least 6 months (IIa A), edoxaban (IIa B) and rivaroxaban (IIa C) can now also be considered for patients

without gastrointestinal tumors. After the first 6 months of treatment, the anticoagulation regimen should be extended if the cancer remains active (IIa B). For patients with unprovoked PE, extensive screening of occult cancer is not generally indicated. These patients require careful medical history taking and physical examination, chest X-ray, basic laboratory tests, and age- and sex-appropriate screening. Patients with PE diagnosed via imaging tests requested for a reason other than suspected PE (incidental PE) should receive the same anticoagulant therapy as symptomatic patients with suspected acute PE if any of the following are involved: a) segmental or more proximal branches; b) multiple subsegmental vessels; or c) a single subsegmental vessel with associated deep vein thrombosis (IIa B).

Diagnosis and treatment of pulmonary embolism in pregnancy

As a novelty, the guidelines recommend the use of clinical probability and D-dimer scales (IIa B) for the diagnosis of pregnant women with suspected PE, which should always be confirmed with imaging tests (I B). In pregnant women with clinical signs of deep vein thrombosis in a limb, confirmatory compression ultrasonography should be performed to avoid unnecessary radiation (IIa B). If an imaging test is required to confirm the PE, the guidelines propose the use of lung scintigraphy or chest CT if the chest X-ray is normal and chest CT if it is abnormal (IIa C). These modern imaging techniques are associated with low exposure of the fetus and the mother to the effects of radiation. With lung scintigraphy, the doses are below the level associated with fetal complications. Chest CT used to increase the risk of breast cancer in mothers, but the risk is minimal with current techniques.

For treatment, fixed-dose LMWH is recommended, based on the patient's prepregnancy body weight, as long as there is no hemodynamic deterioration (I B). In the case of high-risk PE, fibrinolysis or surgical embolectomy can be considered (IIa C). The minimum duration of treatment should be 3 months and it should always extend to at least 6 months after delivery. LMWHs and VKAs can be administered during lactation, unlike DOACs (III C). Spinal puncture or epidural is not recommended until at least 24 hours have passed since the last therapeutic dose of LMWH (III B) and LMWH should not be administered until 4 hours after epidural catheter removal (III C). Although the indications for vena cava filters are similar to those for nonpregnant women, the risks can be higher and there is limited experience.

IDENTIFICATION AND TREATMENT OF LONG-TERM SEQUELAE OF PULMONARY EMBOLISM

Although only a small number of patients develop CTEPH, the guidelines recommend close follow-up after a PE episode to provide adequate care to these patients and to facilitate the early and correct diagnosis and treatment of this disease.

Persisting symptoms and functional limitation after pulmonary embolism

Up to 47% of patients who survive a PE have reduced aerobic capacity (peak oxygen consumption < 80% of the predicted value on cardiopulmonary exercise testing) associated with poor quality of life, dyspnea, and major functional limitations. The independent predictors of these functional limitations are: female sex, a high body mass index, lung disease, elevated pulmonary pressures on echocardiography 10 days after the PE, and higher pulmonary artery diameter on the diagnostic CT for PE. Muscle deconditioning

is the main cause of the post-PE functional limitation, particularly in patients with an elevated body mass index and cardiopulmonary comorbidity, without evidence confirming that RV dysfunction or pulmonary hypertension in the acute phase is correlated with a subsequent functional limitation. Because there is no evidence that early reperfusion in acute PE avoids the functional limitation or onset of CTEPH, this therapy is not recommended to reduce long-term sequelae.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

The incidence of CTEPH after an acute PE episode is difficult to calculate, varying between 0.1% and 9.1% in the first 2 years after a symptomatic PE episode.¹³ This variability is due to the diverse follow-up regimens and referral strategies after PE, the paucity of initial symptoms, and the difficulty of distinguishing acute PE from pre-existing CTEPH.^{14,15} The risk factors for CTEPH are summarized in table 13 of the guidelines, divided into findings related to the acute phase of PE (eg, large or recurrent PE, acute RV dysfunction) and previous predisposing conditions or findings up to 3 to 6 months after the PE (eg, cancer, antiphospholipid syndrome). Due to its high sensitivity, V/Q scintigraphy is recommended as the technique of choice in the diagnostic approach to CTEPH.

Pulmonary endarterectomy is maintained as the first-line therapy for patients with "surgical operability" (technique) and "medical operability" (comorbidities), given the higher survival of operated patients; predictors of poor prognosis in surgical candidates are a mean pulmonary arterial pressure ≥ 38 mmHg and pulmonary resistance > 5 UW. The decision should be made by a multidisciplinary team with expertise in CTEPH that includes cardiac surgeons, interventional cardiologists or radiologists, clinical pulmonologists or cardiologists, and anesthesiologists, with follow-up in an expert CTEPH center for the first 6 to 12 postoperative months. Balloon pulmonary angioplasty (4–10 procedures) is indicated for patients who are not candidates for pulmonary endarterectomy due to a lack of surgical operability, but the guidelines fail to mention its use in technically operable patients ruled out due to comorbidities, who can also benefit from the approach.¹⁶ The prior recommendation is maintained for the use of appropriate drugs to treat pulmonary arterial hypertension in the medical therapy of CTEPH, although specific clinical evidence is available only for riociguat, and it is indicated for nonoperable CTEPH or persistent CTEPH after endarterectomy. Finally, the guidelines recognize chronic thromboembolic disease (residual defects in the pulmonary arterial tree) without pulmonary arterial hypertension at rest as being amenable to surgical thromboendarterectomy in patients with functional deterioration on exercise testing.

Strategies for patient follow-up after pulmonary embolism

For the first time, the guidelines recommend the systematic evaluation of all patients 3 to 6 months after acute PE to determine the response to anticoagulant therapy (thrombotic recurrence), adverse effects, the duration and intensity of the treatment, and the persistence or onset of dyspnea/functional limitation (I C) or cancer identification. Echocardiography should be performed to identify signs of pulmonary hypertension in patients with dyspnea/functional limitation. V/Q scintigraphy should be considered in those with echocardiographic indications of pulmonary hypertension or elevated NT-proBNP or risk factors for CTEPH. If the scintigraphy is positive, the patient should be referred to an expert CTEPH center. If it is negative, cardiopulmonary exercise

testing should be performed because it allows the evaluation of coexisting respiratory and cardiac disease and identification of candidates for pulmonary rehabilitation, exercise programs, or weight loss. As a novelty, clinical follow-up will be scheduled and asymptomatic patients with CTEPH risk factors will be instructed to undergo assessment if symptoms develop 3 to 6 months after the PE (IIb C) (Figure 8 of the guidelines). This model requires interdisciplinary collaboration between the hospital and outpatient care centers to improve the early diagnosis of long-term sequelae after PE.

In summary, the new ESC/ERC guidelines on the diagnosis and treatment of PE have incorporated changes in: *a)* diagnosis, with use of age- or risk-adjusted D-dimer cutoffs, use of D-dimer levels in the diagnostic algorithm for pregnant women with suspected PE, and a recommendation for echocardiography as first-line diagnostic test for hemodynamically unstable patients with suspected PE; *b)* prognosis, with a recommendation for the assessment of RV size and function in patients with low-risk PE; *c)* treatment, with a preference for DOACs if there is no contraindication to their use, as well as consideration of indefinite anticoagulation for more PE patient subgroups; *d)* long-term follow-up, with special attention to the identification of delayed complications; and *e)* specific recommendations for patients with cancer and pregnant women.

CONFLICTS OF INTEREST

The conflicts of interest of all authors can be consulted in the supplemental file of the electronic version of the article, available at <https://doi.org/10.1016/j.recesp.2019.12.011>

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