

Editorial

Comments on the 2014 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism



Comentarios a la guía de práctica clínica de la ESC 2014 sobre el diagnóstico y tratamiento de la embolia pulmonar aguda

SEC Working Group for the ESC 2014 Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism, Expert Reviewers for the ESC 2014 Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism and the SEC Clinical Practice Guidelines Committee ^{◇,*}

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INTRODUCTION

The guidelines of the European Society of Cardiology (ESC) are endorsed by the Spanish Society of Cardiology (SEC) and translated into Spanish for publication in *Revista Española de Cardiología*. In line with the policy initiated in 2011, each new set of guidelines is accompanied by an article that provides comments according to the objectives and methodology recommended in the article by the SEC Clinical Practice Guidelines Committee.¹

This article discusses the most important and innovative aspects of the new ESC 2014 guidelines on acute pulmonary thromboembolism (PE).² To this end, the Clinical Practice Guidelines Committee formed a working group composed of members nominated by the sections on Clinical Cardiology, Cardiac Imaging, Ischemic Heart Disease, Cardiac Catheterization and Intervention, and the Society of Thoracic-Cardiovascular Surgery.

The previous ESC guidelines on PE were published 6 years ago, and since then important studies have been published that have led to 3 fundamental changes in the current guidelines: *a*) the importance of carrying out early risk stratification to guide the initial treatment of these patients, with more precise definition of intermediate-risk patients; *b*) the use of thrombolysis as the first therapeutic step for these patients at intermediate risk is no longer systematically recommended, and *c*) the recommendations on the use of the new oral anticoagulants (NOACs) in the acute and chronic phases of PE.

Like all clinical practice guidelines, the document consists of a set of recommendations designed to help select the most suitable option for addressing a specific clinical situation. However, out of a total of 71 recommendations, only 10 (14%) are supported by multiple randomized clinical trials or meta-analyses (level of evidence A), 34 (48%) are derived from a single randomized clinical trial or nonrandomized studies with a significant number of patients (level of evidence B), and 27 (38%) are derived from expert consensus

(level of evidence C), confirming the need to implement clinical research in this disease.

The most relevant and innovative aspects of the guidelines are summarized in Table 1, controversial aspects that have yet to be resolved are listed in Table 2.

DIAGNOSIS

Important and Novel Aspects

One of the most important aspects of the new guidelines is the adaptation of diagnostic and therapeutic protocols to the patient's hemodynamic status. For hemodynamically unstable patients with suspected PE, it is recommended to perform multislice CT angiography (CTA, where immediately available) or bedside transthoracic echocardiography (if the patient is too unstable to be moved to radiology or if the room is occupied; recommendation I C). For hemodynamically stable patients, the new guidelines offer various diagnostic strategies to confirm or exclude PE that allow each hospital to adapt to the recommendations depending upon the availability of diagnostic tests.

Standardized assessment based on clinical judgment and the rules for predicting clinical probability are among the most important developments in these guidelines, and allow identification of patients with intermediate or high clinical probability, who should receive anticoagulant therapy pending the performance of diagnostic tests, and selection of patients without high clinical probability, in whom a negative D-dimer excludes the diagnosis of PE. The guidelines include simplified scales, which assign the same score to each variable.

Another of the most innovative aspects of these guidelines is the inclusion of studies evaluating the diagnostic efficacy of D-dimer with an age-adjusted cutoff (age × 10 in individuals older than 50 years).³ This strategy reduces the demand for imaging and is as safe as that which uses a fixed D-dimer cutoff point (> 500 ng/dL).

It has been proposed to combine multislice CTA with a venography study of the abdomen, pelvis and lower extremities (CT venography). This strategy increases sensitivity for the diagnosis of venous thromboembolism (VTE) from 83% to 90%, without changes in specificity. However, the new guidelines do not recommend its systematic use for several reasons: the added radiation dose; the low incidence of thrombus in the inferior vena cava or pelvic veins; and the fact that compression ultrasonography is at least as sensitive as CT

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[◇] A full list of the names of all authors are shown in the Appendix.

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Table 1
Important and Novel Aspects

<i>Diagnosis</i>
<ul style="list-style-type: none"> • Hemodynamically unstable patients: perform multislice computed tomography or transthoracic echocardiography, if the situation is too serious to move the patient, for the diagnosis of PE (I C) • Hemodynamically stable patients: initially estimate the clinical probability of PE during the diagnostic assessment (I A) • In patients with high clinical probability, determination of D-dimer is indicated as the next diagnostic step to avoid unnecessary imaging tests (I A) • In patients with low clinical probability, normal D-dimer excludes the diagnosis of PE (I A) • The cutoff for age-adjusted D-dimer ($\text{age} \times 10$ in individuals over 50 y) is incorporated. • Cardiac MRI is not recommended for the diagnosis of suspected PE (III A)
<i>Prognostic Evaluation</i>
<ul style="list-style-type: none"> • Right ventricular dysfunction is the main cause of complications in PE • It is recommended to use the PESI or sPESI scales for prognostic clinical stratification of patients with nonhigh risk PE (IIa B) in order to better differentiate low-risk patients, who can be discharged early, from those with intermediate risk • Natriuretic peptide and troponin are incorporated as prognostic markers to better differentiate patients with right ventricular dysfunction and categorize them into subgroups of high-intermediate or low-intermediate risk
<i>Treatment in the acute phase</i>
<ul style="list-style-type: none"> • Primary reperfusion is still recommended for patients in shock or who are hypotensive, giving preference to thrombolysis (I C) • For low-risk patients, early discharge and outpatient anticoagulant therapy can be considered (IIb A) • For intermediate-risk patients, the routine use of thrombolysis is not recommended (III B), but should only be considered for patients with ventricular dysfunction demonstrated by imaging and also elevated biomarkers (intermediate-high risk) with hemodynamic decompensation during initial monitoring (I B) • The use of NOACs carries the same degree of recommendation as vitamin K antagonists (I B). Recommended doses of NOACs are: rivaroxaban, 15 mg/12 h for 3 weeks, followed by 20 mg/24 h; apixaban 10 mg/12 h for 1 week, followed by 5 mg/12 h, and dabigatran, 150 mg/12 h or 110 mg/12 h for patients aged 80 years or older or those taking verapamil)
<i>Duration of anticoagulation</i>
<ul style="list-style-type: none"> • The sustained use of NOACs (IIa B) is assigned the same recommendation as vitamin K antagonists (IB). Recommended doses of NOACs are: rivaroxaban 20 mg/24 h; apixaban 2.5 mg/12 h, and dabigatran 150 mg/12 h or 110 mg/12 h for patients aged 80 years or older or those taking verapamil • The use of ASA is considered for patients who refuse or cannot take oral anticoagulants to prolong secondary prophylaxis in venous thromboembolism (IIb B) • Minimum duration of oral anticoagulation of 3 months for all patients diagnosed with PE. It is not necessary to extend this if the risk factor is transient or is not present (I B). Anticoagulant treatment can be prolonged in patients with a first episode of PE without a precipitating cause, and with low risk of bleeding (IIa B). Finally, if there have been 2 or more episodes of PE without a precipitating cause, anticoagulation should be continued indefinitely (I B).
<i>Chronic Thromboembolic Pulmonary Hypertension</i>
<ul style="list-style-type: none"> • It is estimated that the cumulative incidence of CTEPH is between 0.1% and 9.1% of patients with symptomatic PE in the first 2 years • CTEPH should be excluded in patients with previous PE and persistent dyspnea (IIa C), but not in asymptomatic patients with a prior PE during their clinical course (III C) • For patients with CTEPH, oral anticoagulation for life (I C) and pulmonary surgical endarterectomy (IC) are recommended • Riociguat is indicated for inoperable symptomatic patients with CTEPH, and for those who have undergone surgery with persistent or recurrent CTEPH (I B). Other pulmonary vasodilators can be considered (IIb B)
<i>Special populations</i>
<ul style="list-style-type: none"> • During pregnancy, the usual D-dimer cutoff is used (IIb C). If D-dimer is positive, compression ultrasonography of the lower limbs is recommended as the first imaging test, and if thoracic imaging is necessary, perfusion scintigraphy is preferred to multislice computed tomography (IIb C) • During pregnancy, the preferred anticoagulant is low molecular weight heparin (I B). The use of antivitamin K can be considered for 3 months after delivery • In cancer patients, the usual D-dimer cutoff is also maintained (IIa B) • A prognostic scoring system is supplied specifically for cancer patients

ASA, acetylsalicylic acid; CTEPH, chronic thromboembolic pulmonary hypertension; NOACs, new oral anticoagulants; PE, pulmonary embolism; PESI, pulmonary embolism severity index; sPESI, simplified pulmonary embolism severity index.

venography and is safe for patients. Similarly, these guidelines advise against the use of MRI for the diagnosis of patients with suspected PE (recommendation III A).

Controversial Aspects Requiring Clarification

Although the authors emphasize that the negative predictive value of a negative ATC was only 60% in patients with high clinical probability in the PIOPED II study,⁴ the guidelines do not make definitive recommendations on the need for additional testing in these patients, which leaves open the possibility of developing a protocol in each center. Performing compression ultrasonography of

the lower limbs seems reasonable in patients with discordance between the clinical probability and the results of ATC or scintigraphy.

Implications for Clinical Practice

One of the most important problems of D-dimer in clinical practice is its indiscriminate use in patients with chest symptoms. This test should not be requested without first having established a presumptive diagnosis based on clinical judgment and clinical scales set out in the guidelines. In this regard, adherence to the guidelines in relation to diagnosis will improve with the use of electronic systems that incorporate the proposed scales and algorithms.

Table 2
Controversial Aspects Requiring Clarification

<i>Diagnosis</i>
<ul style="list-style-type: none"> • No recommendations are established for patients with high clinical probability and negative multislice computed tomography. Compression ultrasonography of the lower limbs may be useful in this context • No clear recommendations are established for the management of incidental PE (not suspected and diagnosed incidentally, most often in patients with cancer)
<i>Prognostic Evaluation</i>
<ul style="list-style-type: none"> • There are no clear recommendations on which natriuretic peptide and troponin cutoffs should be used in the prognostic and therapeutic evaluation of patients with PE • Guidelines for combining of imaging and biomarkers tests are not established for identifying which intermediate-risk patients will have the poorest clinical course and should therefore receive thrombolytic therapy
<i>Treatment in the acute phase</i>
<ul style="list-style-type: none"> • The guidelines do not provide recommendations on whether anticoagulant treatment is necessary in subsegmental PE • There is no statement on which NOACs may be more beneficial or have greater evidence • The absolute contraindications for thrombolytic therapy in patients with PE are not well defined • There are no established failure criteria for reperfusion treatment with thrombolytics
<i>Duration of anticoagulation</i>
<ul style="list-style-type: none"> • The recommendations on the extension of anticoagulant therapy in patients with PE, even with NOACs, are based on patients with venous thromboembolic disease, less than half of which had symptomatic PE • The use of reduced intensity regimens (INR 1.5-2.0) is not properly justified for patients treated with antivitamin K drugs with respect to the previous recommendations (INR 2.0-3.0) • The use of aspirin in the chronic treatment of these patients once the anticoagulation therapy has ended is not well established in these guidelines
<i>Chronic Thromboembolic Pulmonary Hypertension</i>
<ul style="list-style-type: none"> • The clinical course of patients with persistent or residual CTEPH after surgery does not appear to reflect the pessimism of these guidelines, as these patients have a more favorable prognosis than those with CTEPH who have not undergone surgery
<i>Special populations</i>
<ul style="list-style-type: none"> • During pregnancy, the recommendations on the use of fondaparinux during delivery or of NOACs postpartum are not established due to lack of evidence • No treatment recommendations are provided for tumor patients at high risk of bleeding, a common event in daily practice

CTEPH, chronic thromboembolic pulmonary hypertension; NOACs, new oral anticoagulants; PE, pulmonary embolism.

PROGNOSTIC EVALUATION

Important and Novel Aspects

There are many new features in the section on prognostic evaluation. Dysfunction of the right ventricle (RV) is the main determinant of adverse complications in PE. Thus, the presence of signs and symptoms of RV dysfunction such as persistent arterial hypotension and cardiogenic shock has clear prognostic implications, indicating a high risk of death in the short term, and therapeutic implications, since it indicates reperfusion therapy (recommendation I B).^{5,6}

The prognostic evaluation of patients without high-risk criteria is more complex. The most important development is the recommendation to use the PESI scale (pulmonary embolism severity index) or its simplified version (sPESI) for prognostic stratification (recommendation IIa B), which differentiates between patients with low and intermediate risk.⁷⁻⁹ Low-risk patients have an excellent prognosis and can be given early discharge.¹⁰ Intermediate-risk patients can even be differentiated into intermediate-high or intermediate-low risk based on the presence or absence of signs of RV dysfunction in imaging tests and elevated cardiac biomarkers (recommendation IIa B).¹¹ This distinction is based on the high mortality of patients with intermediate-high risk. This group of patients requires close hemodynamic monitoring to detect signs of destabilization early, which would indicate thrombolytic therapy.

The guidelines incorporate the use of various biomarkers: natriuretic peptides and cardiac troponins, as markers of ventricular overload and injury, respectively. These biomarkers, in combination with imaging tests, are useful for classifying patients at intermediate

risk into subgroups of intermediate-high risk (if both imaging and laboratory tests are positive) or intermediate-low (both tests are negative or only one is positive); this subclassification would have notable therapeutic implications, as discussed below.

Controversial Aspects Requiring Clarification

As in the definition of infarction, there is no cutoff point, for biomarkers of RV dysfunction/injury. In addition, the guidelines do not provide specific indications for the use of imaging and biomarkers to identify intermediate-risk patients at risk for complications. In this respect, the guidelines propose recommendation IIa B in the section on prognostic evaluation, with another recommendation I B in the section on treatment, both based on a single study, the PEITHO study.¹¹

Implications for Clinical Practice

The section on prognostic evaluation includes significant improvements in algorithms for the management of patients with PE, which are very likely to be reflected in widespread daily clinical use. The greatest limitation is the availability of the imaging tests required for the classification of non-high-risk patients in Spain, particularly in first and second level hospitals.

Although the presence of right cavities of normal size and function are associated with the exclusion of PE in an unstable patient and with better prognosis in stable patients, the guidelines do not define normal RV in terms of size and function. There are no measures or cutoffs for the right cavities that can serve as a guide, such that the determination of normality or abnormality of the right heart is left to subjective evaluation, which depends on experience.

TREATMENT IN THE ACUTE PHASE

Important and Novel Aspects

With regard to anticoagulant therapy, the guidelines maintain the indication of parenteral anticoagulation with unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux, initiated immediately in patients with intermediate or high clinical probability, pending diagnostic confirmation (recommendation I C). For most patients with PE or intermediate or low risk without severe renal impairment (creatinine clearance < 30 mL/min), it is preferable to use LMWH or fondaparinux, due to the lower risk of serious bleeding and heparin-induced thrombocytopenia (recommendation I A). UFH is reserved for high-risk patients with an indication of reperfusion therapy (recommendation I C), given the high risk of bleeding involved in thrombolysis and the possibility of stopping the infusion and reversing the effect of the UFH, and for patients with severe renal impairment. Parenteral anticoagulation should be continued for at least 5 days or until an international normalized ratio (INR) of between 2 and 3 for 2 consecutive days is reached with oral anticoagulants using vitamin K antagonists (VKA), which should be started as soon as possible after the diagnosis of PE (recommendation I B). A novelty of these guidelines is the recommendation not to use pharmacogenetic testing to guide AVK dosing and to improve the percentage of time within the therapeutic range, given the negative results of recent randomized trials. However, the document emphasizes the importance of assessing clinical parameters (age, sex, weight, amiodarone, etc.) to improve the quality of oral anticoagulation.

The most significant novelty of these guidelines regarding anticoagulation is their support for NOACs as an alternative treatment to AVK, with the same class range and level of evidence for each (recommendation I B). The new guidelines briefly describe the design and main results of pivotal studies that compared the new direct inhibitors of thrombin and activated Factor X with conventional LMWH and VKA treatment (RE-COVER¹² and RE-COVER II¹³ with dabigatran, EINSTEIN-DVT¹⁴ and EINSTEIN-PE¹⁵ with rivaroxaban, and AMPLIFY¹⁶ with apixaban, and Hokusai-VTE¹⁷ with edoxaban, currently pending approval in Europe). Some usage recommendations based on the design of these studies are established, such as starting oral anticoagulant treatment with rivaroxaban and apixaban directly, although initial treatment with parenteral anticoagulation is recommended for about 5 to 10 days before starting with dabigatran or edoxaban. Based on evidence from these randomized clinical trials, the guidelines mention that NOACs are no less effective than AVK (recurrence of venous thromboembolic events) and possibly safer, as they reduce bleeding.

Thrombolytic therapy is still recommended for high-risk patients (shock or hypotension), but with a lower degree of recommendation (I B), given the limited evidence for a reduction in mortality with thrombolysis in these unstable patients. Adding to the controversy on the benefit of thrombolysis for patients with intermediate-high risk PE, the recently published PEITHO¹¹ study compared thrombolytic therapy with anticoagulation using heparin in 1006 patients with intermediate-risk PE and RV dysfunction determined by echocardiography or CTA, and myocardial damage determined by troponin elevation. The primary endpoint of the study (mortality and hemodynamic instability after 7 days) was reduced by thrombolysis (2.6 vs 5.6%; $P = .015$), but mainly by a reduction in the development of hemodynamic instability (1.6 vs 5.0%; $P = .002$), with no difference in mortality (1.2 vs 1.8%; $P = .43$). Thrombolysis was associated with an increased risk of extracranial hemorrhage (6.3 vs 1.2%; $P < .001$) and hemorrhagic stroke (2.0 vs 0.2%). This study shows that mortality is low in patients with intermediate-low risk PE who have been treated with anticoagulants (< 2%); however, hemodynamic

decompensation can occur in an appreciable percentage of patients (~ 5%) with intermediate-high risk who therefore require close monitoring and surveillance to establish thrombolytic therapy without delay (IIa B).

The guidelines continue to consider percutaneous catheter-directed treatment to be an alternative to surgical embolectomy in high-risk patients (shock or hypotension) in whom thrombolysis is contraindicated or has failed (recommendation IIa C). A novelty is the possibility of percutaneous treatment for patients with intermediate-high risk PE and clinical signs of hemodynamic decompensation when they are considered at high risk of bleeding due to thrombolysis (IIb C). The guidelines also consider the therapeutic option of surgical reperfusion by embolectomy for patients with intermediate-high risk, who are considered to have high risk of bleeding due to thrombolytics, provided this is performed at a center with expertise and resources (recommendation IIb C).

Another novelty refers to the possibility of early discharge and outpatient treatment for patients with low-risk PE and the possibility of compliance with anticoagulation therapy (recommendation IIa B). Early outpatient treatment for low-risk patients is safe and there are no significant differences in terms of clinical complications compared with hospital treatment.

The new algorithm for treatment in the acute phase according to the new risk stratification is shown clearly and concisely in these guidelines. Briefly, for patients with hemodynamic instability (shock or hypotension) reperfusion is recommended: preferably thrombolysis (I B), surgical embolectomy if thrombolysis is contraindicated (I C) or percutaneous embolectomy as an alternative to surgery (IIa C). For patients without hemodynamic instability, risk should be stratified according to the PESI or sPESI clinical scales; low-risk patients can complete treatment at home with early discharge; intermediate-risk patients should be hospitalized and initially treated early with oral parenteral anticoagulants, without thrombolysis being indicated systematically, except for patients with RV dysfunction observed by imaging, and also alteration of biomarkers of ventricular damage (intermediate-high risk), for which thrombolysis can be considered (if there are contraindications, surgical or percutaneous embolectomy is recommended) as a salvage therapy in patients with clinical or hemodynamic destabilization.

Controversial Aspects Requiring Clarification

The guidelines recognize that it has not yet been clarified whether isolated subsegmental PE requires anticoagulation therapy. This is an important gap in knowledge that remains to be resolved, although there is an ongoing clinical trial (NCT01455818) that will clarify this issue.

The clinical guidelines do not state a preference for any particular NOAC, since there are no data that comparing these drugs, although only 1 study has been carried out with rivaroxaban,²¹ which only included patients with PE; other studies included patients with deep venous thrombosis (DVT) or PE. No studies included high-risk patients, so the use of these drugs is not recommended in these patients. In future, it would be interesting to explore the role of NOACs in low-risk patients who are discharged early and given outpatient treatment. There is also a lack of practical recommendations on the use of different NOACs in distinct clinical settings, and for the management of complications. The guidelines merely refer the reader to recent recommendations made by the European Heart Rhythm Association.¹⁸

The use of fibrinolytic therapy in patients with intermediate-high risk PE remains controversial. The guidelines introduce a recommendation to establish reperfusion therapy in patients with clinical signs of hemodynamic decompensation, based on the PEITHO study. The definition of "hemodynamic instability or decompensation" in this study is the need for cardiopulmonary resuscitation, systolic

blood pressure < 90 mmHg for at least 15 minutes or a drop of at least 40 mmHg for 15 minutes with signs of hypoperfusion or the need for inotropes to maintain systolic BP > 90 mmHg. A patient with these characteristics is already at high risk, indicating reperfusion therapy. It would be interesting to have a series of validated clinical variables that could predict the possible hemodynamic instability in patients with intermediate-high risk PE who has already received anticoagulation therapy. The thrombolytic regimen recommended in these guidelines is quite unclear. It mentions 2 general patterns for all thrombolytics, accelerated (2 hours) or nonaccelerated (12-24 hours) but generally recommends brief regimens.

Finally, it would be ideal to define a timeframe for early discharge of patients at low risk.

Implications for Clinical Practice

In the context of treatment in the acute phase, anticoagulant and thrombolytic therapy are widely available and can be used in all types of hospitals, whether first, second or third level. In tertiary referral hospitals it is important to create a heart team involving surgeons with experience in surgical embolectomy, as well as specialists with experience in percutaneous treatment, to protocolize and discuss when to perform each procedure in patients with a contraindication for thrombolysis or after failed thrombolysis. Unstable patients treated in hospitals without this experience should be referred immediately to referral centers.

DURATION OF ANTICOAGULATION

Important and Novel Aspects

Undoubtedly, the principal novelty of these guidelines is the incorporation of NOACs in the therapeutic arsenal for initial and long-term treatment of VTE, both DVT and PE.¹⁹ Also new is the possibility of using aspirin to extend secondary prophylaxis of VTE in patients who refuse treatment with any type of oral anticoagulant or who have a contraindication to these drugs. Furthermore, the specific recommendation to maintain a standard INR target of 2.0-3.0 vs reduced-intensity regimens (INR, 1.5-2.0) disappears for patients with PE treated with VKA, regardless of treatment duration.

In the section on treatment duration, the guidelines cover the main aspects of the proposed recommendations that should be taken into account clearly and concisely: a minimum of 3 months of anticoagulant therapy for all patients with PE; anticoagulant therapy should not be prolonged in cases of PE secondary to a transient risk factor that is no longer present; extending secondary prophylaxis for can be considered in patients with a first episode of idiopathic PE and low risk of bleeding; in patients with 2 or more episodes of idiopathic PE, there is a clear indication for indefinite anticoagulation therapy, unless contraindicated. Finally, it should be emphasized that, when opting for prolonged anticoagulation treatment, regardless of the drug used, it is essential to periodically reassess the risk-benefit ratio of this strategy.

Controversial Aspects Requiring Clarification

The main dilemma is how to stratify the risk of thrombotic recurrence and of hemorrhage in patients with idiopathic PE, in order to select patients who would most benefit from extending anticoagulant therapy. Although there are sufficiently validated scales to aid decision-making among clinicians, there are some variables that must be taken into account to estimate the balance of thrombotic risk (forms of thrombophilia, D-dimer value at the end of anticoagulant therapy, RV dysfunction at the time of discharge) and hemorrhagic risk (essentially, the variables forming the basis of the

HAS-BLED scale, derived and validated in patients with atrial fibrillation).

The reasons for eliminating the recommendation on the intensity of anticoagulation therapy with VKA in extending secondary prophylaxis for patients with PE are not clear. The use of reduced-intensity regimens (therapeutic INR range of 1.5-2.0) was less effective and had a similar bleeding risk to conventional treatment (INR 2.0-3.0).^{20,21}

Another controversial point is the recommendation, although weak (IIb B), to use aspirin to prolong secondary prophylaxis. Currently, the main context for the use of aspirin in this indication would perhaps be among patients with PE for whom, having completed the usual anticoagulant treatment (3 months), the possibility of antiplatelet therapy for another reason is considered (eg, high cardiovascular risk) and it is not deemed appropriate to associate anticoagulation and antiplatelet therapy due to the significant increase in bleeding risk involved.

Although it is a semantic nuance, most experts have positioned themselves against further use of the term "new oral anticoagulants" and have proposed the term "direct oral anticoagulants" (DOAC) or "nonvitamin K oral anticoagulants" (NOACs, which would preserve the same acronym).²²

Implications for Clinical Practice

The positive results from clinical trials of NOACs will encourage increased use of these drugs. Cost-effectiveness studies conducted in other Western countries indicate that the balance would lean even more in favor of the use of NOACs.²³ This will require the reorganization of existing structures (in many autonomous regions INR monitoring is performed in primary care centers). It is essential to create and promote antithrombotic treatment units with a strong multidisciplinary approach to ensure proper use of these drugs (including essential patient education) and patient follow-up. It is important to note that NOACs, as indicated in PE, are not publicly funded and the patient must pay the full amount, a relevant issue in many modern economies.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Important and Novel Aspects

While the guidelines refer to the management of PE, a section is devoted to chronic disease. The novelty is that this point is more extensive and detailed. The previous guidelines established that chronic thromboembolic pulmonary hypertension (CTEPH) was a relatively rare and unquantified complication of PE. However, it is now possible to estimate a more definite prevalence of at least 5 cases per million inhabitants per year. The current guidelines provide an update on the diagnosis and management of this disease by introducing accurate new algorithms. All recommendations for this disease are new. In the field of diagnosis, evaluation of CTEPH is recommended among patients with a previous embolism and persistent dyspnea (recommendation IIa C). However, screening is not recommended in asymptomatic patients after an acute embolism (recommendation III C). For the management of patients with CTEPH, the primary treatment option is established as surgical endarterectomy (I C) and oral guanylate cyclase stimulator (riociguat) is reserved as an alternative for the symptomatic improvement of inoperable patients or those with persistent or recurrent CTEPH after surgery (I B), although it is emphasized that decisions on the management and treatment of these patients should be taken by a multidisciplinary team of experts (I C). Regardless of the option chosen, the indication for anticoagulation therapy is maintained for life in these patients (I C).

Controversial Aspects Requiring Clarification

The diagnostic algorithm is clear when there is clinical suspicion. However, there is no clear recommendation for action after an episode of pulmonary embolism. Almost by definition, screening is considered to be an objective complementary test, but could also be a systematic clinical evaluation.

The assertion that patients with persistent or residual CTEPH after surgery have a poor prognosis cannot be considered controversial, even if it is somewhat disheartening. This topic is under constant reevaluation, and the reality is that the prognosis, in terms of survival, is much more favorable than that of patients considered inoperable.

Implications for Clinical Practice

The overall increase in knowledge about this disease, its diagnosis and management has resulted in more and more patients being diagnosed and undergoing surgery. However, the situation in Spain is far from ideal. In practice, many patients are not diagnosed and, therefore, do not undergo surgery. There is a need for greater awareness among the various specialists involved and a specifically dedicated organization that facilitates referral to experts groups, according to the criteria provided in these guidelines.

SPECIAL POPULATIONS

Important and Novel Aspects

The guidelines places a focus on pregnancy and on tumor patients. In the section on diagnosis of pregnant patients with suspected PE, the need and importance of a formal evaluation in response to this suspicion is highlighted, since this is the most important cause of maternal death related to pregnancy in developed countries. As for diagnostic testing, 2 main recommendations are made: first, D-dimer should be used with its normal cutoff value, as its negative predictive value is maintained in this population; second, escalation of diagnostic tests is recommended, preferring non-emitters of ionizing radiation, such as lower limb ultrasound with venous compression, which if positive would permit initiation of anticoagulant therapy, thus avoiding further testing. If other radiological tests are required, perfusion scintigraphy is prioritized (without ventilation if the chest radiograph is normal) over CTA because of the lower dose of radiation and its comparable diagnostic effectiveness. The guidelines emphasize that all the imaging techniques mentioned have a lower estimated value of fetal and maternal radiation dose than that considered dangerous.

Regarding treatment, the use of LMWH in the acute phase is definitively established, with indication I B. The document advises against the use of fondaparinux, due to the lack of information, as well as AVK or NOACs. After delivery, it is advisable to maintain anticoagulation therapy for 3 months, including AVK at this point, which does not interfere with breastfeeding. No mention is made of NOAC therapy postpartum.

Regarding cancer patients, the ESC 2014 guidelines provide an excellent classification of the topic, aiding comprehension. The section on diagnosis presents a better definition of the risks of thrombosis associated with both the disease itself and with therapy. Moreover, it places value on the use of D-dimer, and does not raise the usual diagnostic cutoff point.

In terms of prognosis, a scoring system is supplied to predict risk of recurrence, including the following items: breast carcinoma (-1), metastatic stage I or II (-1), female sex, lung cancer, previous thromboembolism (1 point each). Patients with a score ≤ 0 have low risk ($\leq 4.5\%$), and those with a score ≥ 1 have high risk ($\geq 19\%$) of recurrence.²⁴

With regard to treatment, the use of LMWH is recommended for 3-6 months following the event (recommendation IIa B). It is recommended that treatment be extended beyond 6 months (recommendation IIa C) indefinitely or until the patient is cured. A recommendation is established to treat incidentally diagnosed PE in tumor patients in the same way as those diagnosed by symptoms.

Finally, another important aspect is that the guidelines delimit diagnosis effort in patients with no known cause, and recommends not performing studies if they are not justified by history, physical examination, laboratory testing, and chest radiography.

Controversial Aspects Requiring Clarification

In these guidelines there is a notable absence of recommendations for the management of patients with high risk of bleeding or with active bleeding, especially tumor patients. This section should also include the problem of heparin-induced thrombocytopenia, a serious complication with the use of heparin (defined as a decrease in platelet count to $< 100\,000/\mu\text{l}$ or $< 50\%$ of baseline), which was dealt with in the previous edition.

Implications for Clinical Practice

The current guidelines will facilitate clinical practice in these special patient groups, since they facilitates planning of the diagnosis and treatment in pregnant and cancer patients. In relation to diagnosis, it clearly specifies the sequence to be followed (use of D-dimer and imaging alternatives conveniently ordered), which is especially important in pregnancy, since the radiation factor is critical in this context. In terms of treatment, the recommendations are sufficiently explicit to avoid delays and save additional consumption of time and resources.

CONFLICT OF INTERESTS

None declared.

APPENDIX

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