

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

Jiří Widimský*

Department of Cardiology, IKEM, Prague, Czech Republic

Corresponding Author: Jiri Widimsky, Institute for Clinical and Experimental Medicine, Videnska Prague, Czech Republic; E-mail: widimsky@seznam.cz

At the ESC (European Society of Cardiology) congress 2014 in Barcelona S. Konstantinides and A. Torbicki presented the 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism including the web addenda. These were simultaneously published in the European Heart Journal at the congress.

Acute Pulmonary Embolism (PE) is associated with significant morbidity and mortality. As many as 15% of all patients suffering PE will die within the first month and, of those who do survive 30%, will develop recurrent PE over the next 10 years. Of those who died, only 7% were correctly diagnosed during their lifetime. Incomplete resolution of PE may lead to the development of chronic thromboembolic pulmonary hypertension with an estimated prevalence of 0.1-4.0% at 2 years.

According to the 2014 ESC guidelines, predisposing factors for Venous Thromboembolism (VTE) are divided into strong risk factors (odds ratio > 10), moderate risk factors (odds ratio 2-9), and weak risk factors (odds ratio <2).

VTE is considered to be provoked in the presence of a temporary or reversible risk factor (such a surgery, trauma, immobilization, pregnancy, oral contraceptive use or hormone replacement therapy) within the last 6 weeks to 3 months before

diagnosis and unprovoked in the absence thereof. PE may also occur in the absence of any known risk factor. The presence of persistent – as opposed to major, temporary – risk factors may affect the decision on the duration of anticoagulation therapy. Major trauma, surgery, lower limb fractures and joint replacements, and spinal cord injury are strong provoking risk factors for VTE.

Cancer is a well-recognized predisposing risk factor for VTE. The risk of VTE varies with different types of cancer; hematological malignancies, lung cancer, gastrointestinal cancer, pancreatic cancer, and brain cancer carry the highest risk. Moreover, cancer is a strong risk factor for all-cause mortality following an episode of VTE. Infection has been found to be a common trigger for hospitalization for VTE.

Diagnosis

Pulmonary embolism may escape prompt diagnosis since clinical signs and symptoms are non-specific.

The authors of the 2014 ESC guidelines stress the non-specificity of the following symptoms: dyspnea, pleuritic chest pain, cough, substernal chest pain, fever, hemoptysis, syncope, and signs of DVT. Among these, only pleuritic chest pain, hemoptysis, and signs of DVT are somewhat more frequent in PE patients.

Assessment of clinical probability

Clinical prediction rules include the Wells and Geneva scores. The 2014 guidelines include also simplified versions of both the Wells and Geneva scores, which are very practical.

D-dimer testing

The 2014 ESC guidelines stress decreasing specificity of D-dimer in suspected PE with age to almost 10% in patients >80 years. In a recent meta-analysis, age-adjusted cut-off values (age x 10 µg/L above 50 years) were presented. This age-adjusted equation allowed increasing the specificity from 34-46% while retaining a sensitivity above 97%. A multicentre, prospective management study evaluated this age-adjusted D-dimer value in a cohort of 3346 patients.

Patients with a normal age-adjusted D-dimer value did not undergo computed tomographic pulmonary angiography and were left untreated and formally followed up for a three-month period. Among the 766 patients who were ≥75 years old, 673 had a non-high clinical probability. On the basis of D-dimer values, use of the age-adjusted cut-off (instead of the standard 500 µg/L cut-off) increased the number of patients in whom PE could be excluded from 43 (6.4%) to 200 (29.7%), without any additional false-negative findings. D-dimer is also more frequently elevated in patients with cancer, in hospitalized patients, and pregnant patients.

Simplified PESI

A simplified version of the PESI-sPESI consists of the following parameters: age 1 point (if age is >80 years), cancer 1 point, chronic heart failure or chronic pulmonary disease 1 point, heart rate ≥ 110 b.p.m. 1 point, systolic blood pressure <100 mm Hg 1 point, and arterial oxyhemoglobin saturation <90% 1 point.

Risk strata

0 points = 30-day mortality risk 1.0% (95% CI 0.0%-2.1%)

≥1 point(s) = 30-day mortality risk 10.9% (95% CI 8.5%-13.2%)

Biomarkers

New information also comes in concerning some of the biomarkers.

New information is dealing with hs-cTnT and H-FABP (Heart-Type Fatty Acid Binding Protein)

hs cTnT	H-FABP
cut-off values 14 pg/mL	6 ng/mL
Sensitivity 87% (71-95)	89% (52-99)
Specificity 42% (38-47)	82% (74-89)
NPV 98% (95-99)	99% (94-99)
PPV 9% (6-12)	28% (13-47)
OR 5.0 (1.7-14.4)	36.6 (4.3-304)
No. of patients 526	126

Abbreviations: NPV = Negative Prognostic Value, PPV = Positive Prognostic Value.

Heart-type fatty acid-binding protein (H-FABP), an early marker of myocardial injury, has also been found to possess a prognostic value in acute PE. In normotensive patients, circulating H-FABP levels ≥6 ng/mL had a positive predictive value of 28% and a negative predictive value of 99% for an adverse 30-day outcome. A simple score, based on the presence of tachycardia, syncope, and a positive bedtest for H-FABP, provided prognostic information similar to that of RV dysfunction on echocardiography.

Echocardiography

Acute PE may lead to RV pressure overload and dysfunction, which can be detected by echocardiography. Given the peculiar geometry of the RV, there is no individual echocardiographic parameter that provides fast and reliable information on RV size or function. This is why echocardiographic criteria for the diagnosis of PE differed between studies. Because of the reported negative predictive value of 40-50%, a negative result cannot exclude PE. On the other hand, signs of RV overload or dysfunction may also be found in the absence of acute PE and be due to concomitant cardiac or respiratory disease.

In suspected high-risk PE, the absence of echocardiographic signs of RV overload or dysfunction virtually excludes PE as a

cause of hemodynamic instability. In the latter case, echocardiography may be of further help in the differential diagnosis of the cause of shock by detecting pericardial tamponade, acute valvular dysfunction, severe global or regional LV dysfunction, aortic dissection, or hypovolemia. Conversely, in a hemodynamically compromised patient with suspected PE, unequivocal signs of RV pressure overload or dysfunction justify emergency reperfusion treatment for PE if immediate CT angiography is not feasible.

Mobile right-heart thrombi are detected by TTE, TEE or by CT angiography. Their prevalence may reach 18% in the intensive care setting. Mobile right-heart thrombi essentially confirm the diagnosis of PE and their presence is associated with RV dysfunction and high early mortality.

Lung scintigraphy

The following classification is preferable: normal scan (excluding PE), high-probability scan (considered diagnostic in most patients), and a non-diagnostic scan.

Being a radiation- and contrast medium-sparing procedure, the V/Q scan may be preferentially applied in outpatients with a low clinical probability and a normal chest X-ray, in young (particularly female) patients, in pregnancy, in patients with a history of contrast medium-induced anaphylaxis and strong allergic history, in severe renal failure, and in patients with myeloma and paraproteinemia.

Recent studies have suggested that data acquisition in tomographic mode in Single-Photon Emission Computed Tomography (SPECT) imaging, with or without low-dose CT, may reduce the frequency of non-diagnostic scans. SPECT imaging may even allow the use of automated detection algorithms for PE. According to the authors of the new guidelines, large-scale prospective studies are needed to validate these new approaches.

2014 ESC guidelines divide acute PE into 4 groups of risk, as follows:

2014 ESC guidelines. New classification of acute PE based on early mortality risk

1. The presence of shock or hypotension – high risk group

Hypotension is defined as a systolic blood pressure <90 mmHg, or a systolic pressure drop by ≥ 40 mmHg for >15 minutes, if not caused by new-onset arrhythmia, hypovolemia or sepsis.

In these patients, signs of RV dysfunction on an imaging test may be valuable. x)

2. Intermediate-high risk group without shock or hypotension

(a) PESI class sPESI >1, (b) signs of RV dysfunction on an imaging test, and (c) cardiac laboratory biomarkers. b and c both positive.

The PEITHO study [1] was performed in these patients.

3. Intermediate-low risk group without shock or hypotension

Classified as sPESI >1, and either one or none of the two further tests positive (b and c).

4. Low risk group: hemodynamically stable assessment of parameters b and c optional. If assessed, both negative.

x) Echocardiographic criteria of RV dysfunction include RV dilation and/or an increased end-diastolic RV-LV diameter (in most studies, the reported threshold was 0.9 or 1.0); RV free wall hypokinesia; increased velocity of tricuspid regurgitation jet; or a combination of the above. On CT angiography (4-chamber view of the heart), RV dysfunction is defined as an increased end-diastolic RV/LV diameter ratio (with a threshold of 0.9 or 1.0).

High-risk PE (massive pulmonary embolism)

Thrombolytic treatment

It is recommended that intravenous anticoagulation with UFH be initiated without delay in patients at high risk of PE.

This year, the largest trial – the PEITHO study - with thrombolytic treatment was published [2]. The PEITHO study included 1005 patients. It evaluated the role of a novel thrombolytic treatment with tenecteplase given as a loading dose with heparin in patients in the intermediate high-risk group and compared it with heparin + placebo treatment. The study was not able to find superiority of thrombolytic treatment + heparin to the heparin-only treatment.

Tenecteplase treatment increased hemorrhagic complications including hemorrhagic stroke (6.3% vs 1.5%, $p < 0.001$). Thus, this study did not provide evidence justifying thrombolytic treatment in this group of patients.

The hemorrhagic complications were less frequent in the age group of ≤ 75 years. A strategy using reduced-dose rtPA appeared to be safe in the setting of “moderate” PE in a study that included 121 patients.

Thus the present recommendation of the 2014 ESC guidelines in patients in the intermediate-high risk group is to start all patients on anticoagulation treatment and give thrombolytic only to patients who are hemodynamically deteriorating.

Close monitoring is, however, recommended in patients with intermediate-high risk PE to permit early detection of hemodynamic decompensation and timely initiation of “rescue” reperfusion therapy.

Table 1: demonstrates the approved thrombolytics for pulmonary embolism by the 2014 ESC guidelines

rtPA	100 mg over 2 hours
rtPA	0.6 mg/kg during 15 minutes (maximum dose 50 mg)
Streptokinase	Accelerated regimen: 1.5 million IU over 2 hours

Table 1: Thrombolytics approved for pulmonary embolism by the 2014 ESC guidelines

Absolute contraindications to thrombolytic treatment

Hemorrhagic stroke or stroke of unknown origin at any time
 Ischemic stroke in the preceding 6 months
 Central nervous damage or neoplasm
 Recent major trauma/surgery/head injury in the preceding 3 weeks
 Gastrointestinal bleeding within the last month
 Known bleeding risk
 Absolute contraindications to thrombolysis might become relative in a patient with immediate life-threatening high-risk PE

Anticoagulation treatment

New oral anticoagulants (NOACs) include:
 Factor IIa inhibitor
 Dabigatran 150 mg b.i.d. or 110 mg b.i.d., to be given after enoxaparin

Factor Xa inhibitors

Rivaroxaban 15 mg b.i.d for 3 weeks, followed by 20 mg o.d. thereafter
 Apixaban 10 mg b.i.d. for 7 days, followed by 5 mg b.i.d. thereafter. These three drugs are approved in Europe and the US.
 The results of the trials using NOACs in the treatment of VTE indicate that these agents are non-inferior (in terms of efficacy) and possibly safer (particularly in terms of significant bleeding) than the standard heparin/VKA regimen in all trials. At present, NOACs can be viewed as an alternative to standard treatment.

Duration of anticoagulation

- In patients with a first episode of PE induced by a transient risk factor duration of anticoagulation treatment should be at least 3 months.
 - After withdrawal of anticoagulant treatment, the risk for recurrence if anticoagulants are stopped after 6 or 12 months can be expected to be similar to that after 3 months

-Indefinite treatment reduces the risk of recurrent VTE by about 90%, but this benefit is partially offset by a 1% or higher annual risk of major bleeding.

Active cancer is a major risk factor for VTE recurrence, with the rate of recurrence being approximately 20% during the first 12 months after the index event. Therefore, patients with cancer are candidates for indefinite anticoagulant treatment after the index event. At least 3-6 months of treatment with LMWH are recommended for patients with VTE and cancer. Treatment with LMWH or VKA is recommended as long as the disease is considered to be active.

VTE is held to be provoked in the presence of a temporary or reversible risk factor (such as surgery, trauma, immobilization, pregnancy, oral contraceptive use or hormone replacement therapy) at the time of diagnosis, and unprovoked in the absence thereof. For patients with provoked PE, treatment with a VKA for 3 months is preferable. Treatment for longer than 3 months is generally not recommended provided that the transient risk factors no longer exist.

The assessment of the risk of recurrence in patients with unprovoked PE is rather difficult. The following risk factors may help identify patients at higher long-term relative risk of recurrence: (a) one or more previous episodes of VTE, (b) antiphospholipid antibody syndrome, (c) hereditary

thrombophilia and, (d) residual thrombosis in the proximal veins.

Carriers of molecular thrombophilia including

- Patients with lupus anticoagulant,
- Those with a confirmed deficit of protein C or S, and patients with homozygous factor V Leiden or homozygous prothrombin G20210A (PTG20210A) may be candidates for indefinite anticoagulant treatment after a first unprovoked VTE episode.

No evidence of the clinical benefit of extended treatment is currently available for carriers of heterozygous factor V Leiden or PTG20210A.

References

1. Meyer G, Vicaut E, Danais R, et al. (2014) for the PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*; 370: 1402-1411
2. Konstantinides S, Torbicki A, Agnelli G, et al. for the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Endorsed by the European Respiratory Society (ERS). 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014.