JAMA Clinical Guidelines Synopsis

Management of Acute Pulmonary Embolism

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GUIDELINE TITLE 2019 ESC Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism

DEVELOPER European Society of Cardiology (ESC) in collaboration with European Respiratory Society (ERS)

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PRIOR VERSION 2014

FUNDING SOURCE ESC

TARGET POPULATION Adult patients with acute pulmonary embolism (PE)

MAJOR RECOMMENDATIONS

- In patients without hemodynamic instability, stratification of patients with acute PE into intermediate- and low-risk categories is recommended (class I, level B recommendation).
- Systemic thrombolytic therapy is recommended for high-risk PE patients (class I, level B), and rescue thrombolytic therapy is recommended for patients with hemodynamic deterioration despite anticoagulation treatment (class I, level B).
- When oral anticoagulation is initiated in a patient with PE who is eligible for a direct oral anticoagulant (DOAC; apixaban, dabigatran, edoxaban, or rivaroxaban), a DOAC is recommended over a vitamin K antagonist (VKA) (class I, level A).
- Oral anticoagulant treatment of indefinite duration is recommended for patients with recurrent venous thromboembolism (VTE) not related to a major transient or reversible risk factor (class I, level B) and for those with a first PE and no identifiable risk factor (class IIa, level A).

Summary of the Clinical Problem

Venous thromboembolism is a common and potentially fatal disease. The estimated incidence of first acute VTE is 0.7 to 1.4 per 1000 person-years and VTE is mostly observed in patients older than 55 years.[1] Between 0.1% and 4% of survivors develop chronic thromboembolic pulmonary hypertension within 2 years of the event, with the greatest risk in patients with recurrent VTE, large perfusion defects, and echocardiographic signs of pulmonary hypertension at initial presentation.[2]

Characteristics of the Guideline Source

The Committee for Practice Guidelines of the ESC tasked a panel of 21 European experts (led by chairpersons from the ESC and ERS) to update previous ESC PE guidelines (**Table 1**).[3] Only peer-reviewed literature was considered part of the formal review. Representatives from 44 national cardiac societies participated in the peer-review process. All authors disclosed potential conflicts of interest, and many reported significant financial relationships with industry.

Evidence Base

The guideline's treatment recommendations depend on proper risk classification,[3] outlined in **Table 2**. Systemic thrombolysis is recommended for high-risk PE patients and non–high-risk patients with hemodynamic deterioration despite receiving anticoagulation treatment. These recommendations are based on data from about 2000 patients demonstrating significant reductions in PE-related mortality (3.0% vs 0.6%; odds ratio [OR], 0.29; 95% CI, 0.14-0.60) and recurrent PE (2.9% vs 1.3%; OR, 0.50; 95% CI, 0.27-0.94) at the cost of severe bleeding (9.9% vs 3.6%; OR, 2.91; 95% CI, 1.95-4.36) and intracranial hemorrhage (1.7% vs 0.3%; OR, 3.18; 95% CI, 1.25-8.11).[4] Percutaneous catheter-directed treatment (CDT) or surgical embolectomy are recommended as alternative therapies for this group, though the supporting evidence base is less robust (class IIa, level C).

Systemic thrombolysis is not recommended for intermediate-risk patients as initial therapy, primarily based on unacceptably high rates of major bleeding (11.5% with tenecteplase vs 2.4% with placebo) and hemorrhagic stroke (2.0% vs 0.2%), with no significant difference in death (1.2% vs 1.8%).[5] The trial that yielded this data showed improvement in the primary outcome of death from any cause or hemodynamic decompensation at 7 days (2.6% with tenecteplase vs 5.6% with placebo), with the benefit due largely to the reduction of the latter (1.6% with tenecteplase vs 5.0% with placebo). Although this data does not support routine use of thrombolysis in intermediate-risk patients, the guideline recommends rescue thrombolytic therapy when a patient decompensates while receiving anticoagulation. The recommendation for surgical embolectomy or CDT in this population is upgraded from the 2014 guidelines from class IIb to class IIa, level C.

When patients start oral anticoagulation, DOACs are recommended over a VKA unless contraindicated (ie, patients with severe renal impairment, during pregnancy and lactation, and patients with antiphospholipid antibody syndrome). A meta-analysis of DOAC vs VKA trials including 24 455 patients with acute VTE demonstrated no significant difference in recurrent VTE (2.0% vs 2.2%),

Table 1. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Good
Updating	Good
Implementation issues	Good

Table 2. Risk Stratification[a]

Early mortality risk	Hemodynamic instability[b]	PESI III-V or sPESI ≥1	RV dysfunction on TTE or CTPA[c]	Elevated cardiac troponin levels
High	Present	Present[d]	Present	Present[d]
Intermediate-high	Absent	Present	Present	Present
Intermediate-low	Absent	Present	RV dysfunction or elevated troponin present or both absent	
Low	Absent	Absent	Absent	Absent[e]

Abbreviations: CTPA, computed tomographic pulmonary angiography; PESI, Pulmonary Embolism Severity Index; RV, right ventricular; sPESI, simplified PESI; TTE, transthoracic echocardiography.

[a] Adapted from Konstantinides et al.[3]

[b] Cardiac arrest, obstructive shock (systolic blood pressure [BP] <90 mm Hg or vasopressors required to achieve BP ≥90 mm Hg despite adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic BP <90 mm Hg or systolic BP decrease ≥40 mm Hg for >15 minutes, not caused by new-onset arrhythmia, hypovolemia, or sepsis).

[c] Suggested by features such as enlarged right ventricle, dilated RV with RV/left ventricular ratio >1.0, flattened interventricular septum, dilated inferior vena cava with diminished inspiratory collapsibility, decreased tricuspid annular plane systolic excursion measured by M-mode (<16 mm), and others.

[d] Hemodynamic instability, combined with pulmonary embolism confirmation on CTPA and/or evidence of RV dysfunction on TTE, is sufficient to classify a patient as high risk.

[e] Assessment optional; if assessed, negative.

fatal PE (0.07% vs 0.07%), and overall mortality (2.4% vs 2.4%), with a lower risk of major bleeding with DOACs (1.1% vs 1.7%; relative risk, 0.60; 95% CI, 0.41-0.88).[6] High-risk PE patients were excluded from phase 3 DOAC trials, so optimal timing of oral anticoagulant initiation in this group is not known.

Duration of anticoagulation and risk of recurrence after PE depends on presence of major transient or reversible risk factors at the time of the index event and persistent risk factors such as active cancer or some forms of hereditary thrombophilia.[3] The guideline avoids terms such as *provoked*, *unprovoked*, or *idiopathic* VTE and recommends therapeutic anticoagulation for at least 3 months in all patients with PE (class I, level A). After 3 months, the guideline recommends discontinuation of anticoagulation in patients with a first PE/VTE secondary to a major transient risk factor (class I, level B). Indefinite anticoagulation should be considered in patients with recurrent VTE not related to a major transient risk factor (class I, level B), with no identifiable risk factor (class IIa, level A), or with a persistent risk factor (class IIa, level C).

Benefits and Harms

The ESC guidelines stress the importance of risk stratification prior to choice of therapy for acute PE. Using a combination of imaging studies, biomarkers, and physiologic metrics, clinicians can select high-risk patients in whom reperfusion therapy (systemic treatment, CDT, or surgical embolectomy) may be beneficial. Adoption of this guideline will likely lead to more evidence-based use of thrombolytic therapy for patients most likely to benefit from its use. Conversely, the upgrade in surgical embolectomy or CDT for intermediate-risk PE from class IIb to class IIa may lead to an increase in these procedures, potentially exposing lower-risk patients to increased complications.

Discussion

After a first PE episode, there is a lifelong risk of VTE recurrence, except in patients with a strong reversible risk factor. Moreover, VTE is likely to result from an interaction between patient-related (usually irreversible) and situational (possibly reversible) risk factors. Duration of anticoagulation has traditionally been based primarily on presence or absence of a few situational risk factors, but VTE risk is increased in the setting of a number of other conditions (eg, infection, active autoimmune diseases, and use of blood transfusion or erythropoiesis-stimulating agents).[7] For this reason, the terms *provoked* and *unprovoked* for VTE are no longer supported by the guidelines, which favor terms such as *reversible*, *any persistent*, or *no identifiable* risk factors.

Areas in Need of Future Study or Ongoing Research

Management of isolated subsegmental contrast-filling defects and incidentally found PE on computed tomographic pulmonary angiography remains controversial. Risk stratification of intermediate-risk PE relies on biomarker elevation; however, optimal cutoff values are not well defined. Benefits and risks of CDT and thrombectomy procedures for intermediate- and high-risk patients have not been evaluated in a randomized clinical trial, although such a study is in final planning (PE-TRACT).

Related guideline

American Society of Hematology Clinical Practice Guidelines on Venous Thromboembolism

ARTICLE INFORMATION

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