

REVIEW ARTICLE

The Diagnosis and Treatment of Acute Pulmonary Embolism

Alexander Schellhaaß, Andreas Walther, Stavros Konstantinides, Bernd W. Böttiger

SUMMARY

Background: Pulmonary embolism (PE) is a cardiovascular emergency with high morbidity and mortality.

Methods: Review of relevant literature retrieved by a selective Medline search, including current guidelines.

Results: Hemodynamically unstable patients are considered to have high-risk PE, whereas hemodynamically stable patients are considered to have non-high-risk PE. After classification into one of these two risk groups, patients undergo further diagnostic evaluation for PE according to the appropriate risk-adapted algorithm. Patients who are in cardiogenic shock or have persistent arterial hypotension (high-risk PE) should undergo multidetector computed tomography (MDCT) or echocardiography at once, so that a PE, if present, can be treated immediately by thrombolysis. For hemodynamically stable patients with non-high-risk PE the proper diagnostic strategy is determined by the clinical probability of PE, which can be calculated with the aid of validated scoring systems and is based on both MDCT and D-dimer levels. For further risk stratification in hemodynamically stable patients, tests are performed to detect right ventricular dysfunction or myocardial injury, either of which indicates intermediate-risk PE. In addition to specific therapy, patients with high-risk PE, patients at high risk for hemorrhage and these with severe renal insufficiency should be anticoagulated with unfractionated heparin. All other patients should be treated with low-molecular-weight heparin or fondaparinux. Thereafter, long-term oral anticoagulation with vitamin K antagonists is recommended.

Conclusion: Modern algorithms have considerably simplified the diagnosis and treatment of acute PE. It would be desirable for these algorithms to be rapidly implemented in routine practice, because speedy diagnosis and immediate treatment can lower the morbidity and mortality associated with PE.

Despite many medical advances, acute pulmonary embolism (PE) remains a cardiovascular emergency with high morbidity and mortality. With clinically suspected PE, rapid and targeted treatment is essential because speedy diagnosis and immediate therapy can lower the morbidity and mortality associated with PE (1). However, the non-specific clinical presentation and the variety of suggested diagnostic algorithms, some of which are complex, can impede speedy and certain diagnosis (2). In light of this, the authors carried out a selective Medline literature review for this review article, taking into consideration a recent comprehensive review of the guidelines issued by the European Society for Cardiology (ESC) (3), the official comments from the German Cardiac Society (4) and the German interdisciplinary S2 guidelines (5). The authors would like to inform the reader of clear diagnostic procedures—dependent on the hemodynamic status of the patient—which have been simplified compared to previous review articles. The authors would also like to suggest risk-adapted, evidence-based therapeutic strategies that conform to these guidelines.

Definition, epidemiology and clinical issues

A pulmonary artery embolism is defined as a partial or complete occlusion of a pulmonary arterial branch (6). Approximately 70% of cases are caused by pelvic or leg thromboses (e1, e2, 3). Deep vein thrombosis and PE are different presentations of the same underlying pathophysiological event, venous thromboembolism (VTE) (1). Precise figures for the incidence of PE are not available. The annual incidence of diagnosed VTE is 150 to 200 cases per 100 000 population (7). As well as an unknown number of clinically silent embolisms, the non-specific clinical presentation hampers diagnosis, meaning the actual disease frequency is underestimated. The diagnosis is made within the lifetime only in about 30% of cases with confirmation via post mortem examination (8). Estimates for Germany begin at more than 350 000 cases annually. In the acute phase the mortality rate is 7% to 11%, meaning that up to 40 000 patients probably die as a result of a PE each year in Germany (2–4, e3).

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TABLE 1

Predisposing factors for venous thromboembolisms (3, 9)

Strong predisposing factors (odds ratio >10)	Moderate predisposing factors (odds ratio 2–9)	Strong predisposing factors (odds ratio <2)
Bone fractures (hip, leg)	Arthroscopic knee surgery	Bed rest >3 days
Hip or knee replacement	Central venous lines	Immobility due to sitting (e.g., prolonged car or plane travel)
Major general surgery	Chemotherapy	Increasing age
Major trauma	Chronic heart or respiratory failure	Laparoscopic surgery (e.g., cholecystectomy)
Spinal cord injury	Hormone replacement therapy	Obesity
	Malignancy	Pregnancy (antepartum)
	Oral contraceptive therapy	Chronic venous insufficiency, varicose veins
	Immobility after stroke	
	Pregnancy (peripartum)—Lactation	
	Previous venous thromboembolism	
	Thrombophilia	

The statistical measure odds ratio indicates how high the chance is that a feature (of two alternative features) is present in a group (of two groups).

Risk factors

Many patient-related and situational factors may contribute to the development of a VTE (*Table 1*) (1, 9). As well as those patients that have to undergo major surgical procedures, non-surgical patients are also at risk. Awareness of the risk factors is essential if individualized and risk-adapted prophylaxis is to be implemented (10). In clinical practice, however, PE also occurs in about 20% of cases in patients without recognizable risk factors (11).

Pathophysiology

With acute PE there is a mechanical obstruction of the pulmonary circulation system (1). The hemodynamic consequences are determined by the size of the embolism, any pre-existing cardiopulmonary diseases, and the intensity of pulmonary vasoconstriction. With hemodynamically significant PE, the sudden increase in pulmonary arterial pressure can cause acute right ventricular dysfunction and lead to the interventricular septum deviating to the left with a fall in the left ventricular preload (1). There is a danger of a subsequent reduction in coronary perfusion and cardiac output with cardiogenic shock and myocardial ischemia (2, 6). In most cases death due to acute PE can be traced back to acute right heart failure.

Clinical presentation

Suspicion of acute PE is raised by symptoms such as sudden onset dyspnea and tachypnea, chest pain, hemoptysis or syncope but these symptoms are neither sensitive nor specific due to the variety of possible differential diagnoses (1). Additional examinations such as chest x-rays, ECG or blood gas analysis are also unsuitable to confirm or exclude suspected PE with sufficient certainty but they do help with differential diagnosis (12).

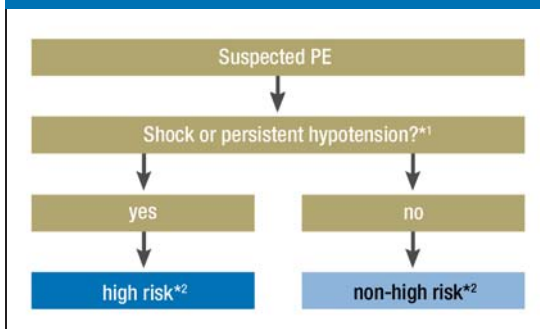
Initial risk stratification and diagnostic strategies

In contrast to earlier recommendations, the current guidelines recommend a practical procedure if acute PE is suspected (3). Initially the hemodynamic stability of the patient (shock, persistent arterial hypotension) should be assessed to enable evaluation of the likely risk of patient death due to PE during the acute phase in the hospital or within 30 days (*Figure 1*). The advantage of this simplified division is that the diagnostic and therapeutic strategies can be adapted to the urgency of the situation and that no invasive hemodynamic parameters are required (2). Previous classification systems (such as the classification of severity according to Grosser) should no longer be used (3). The current ESC guidelines suggest risk-adapted management and therefore recommend two different diagnostic algorithms for patients with suspected high-risk versus non-high-risk PE (3).

Suspected high-risk PE

Suspected high-risk PE (hemodynamically unstable patient) is an acute life-threatening medical emergency

FIGURE 1



*¹, systolic blood pressure <90 mmHg or a drop of >40 mmHg for more than 15 minutes that was not triggered by new onset arrhythmia, hypovolemia or sepsis; *², risk of early PE related mortality (in-hospital or 30-day mortality); (modified from Walther A, Schellhaaß A, Böttiger BW, Konstantinides S: Diagnosis, therapy and secondary prophylaxis of acute pulmonary embolism. *Anaesthesist* 2009; 58: 1048–54. With kind permission of Springer Science and Business Media).

(2). The clinical probability of PE is (almost) always high in this situation (12). The suggested algorithm (Figure 2) recommends using multidetector computed tomography (MDCT) with imaging of the pulmonary arteries to confirm PE (3). Bedside emergency echocardiography should only be carried out if there is significant hemodynamic instability (transport into CT not possible) to immediately determine if there is an indication for—potentially life-saving—thrombolysis. In light of the urgency and the non-invasiveness, transthoracic echocardiography should initially be carried out (6). The following echocardiographic parameters are indicative of pulmonary embolism (e4):

- Abnormal right ventricular wall motion
- Right ventricular dilatation
- Paradoxical septal motion
- Tricuspid valve insufficiency
- Increased pulmonary arterial pressure
- Inferior vena cava congestion
- Dilated pulmonary artery

Thrombi can occasionally be documented in the right heart transthoracically while transesophageal echocardiography allows direct imaging of thrombi in the pulmonary arteries (3). Taking into consideration availability, the individual ability of the examiner, and the extent of the hemodynamic instability, a transesophageal echocardiogram can also be done. In case of a negative MDCT or echocardiogram, other causes of the hemodynamic instability must be sought.

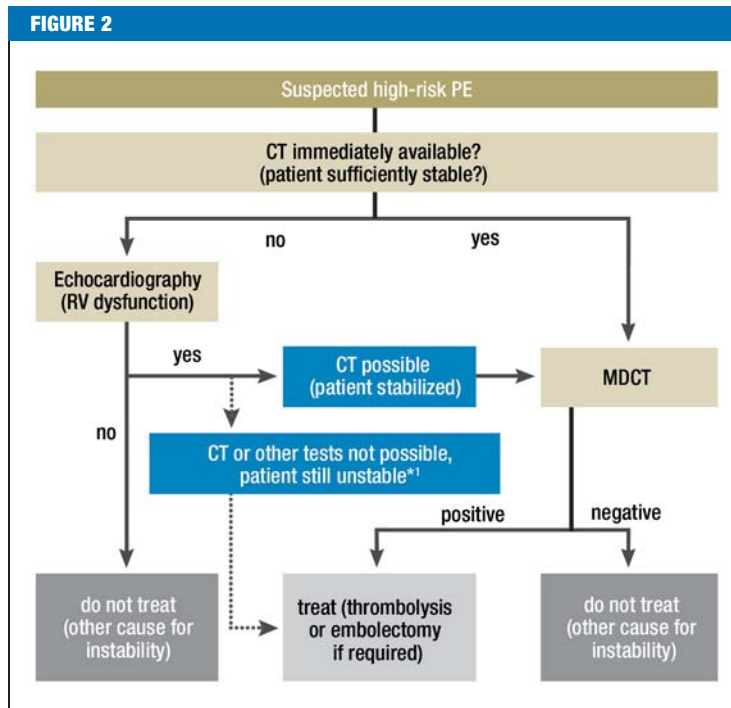
This algorithm is based on the consensus of the ESC Committee for Practice Guidelines (evidence level C).

Suspected non-high-risk PE

To select a suitable diagnostic strategy for hemodynamically stable patients prior to laboratory tests or imaging, the clinical probability of PE is estimated using a simple and validated scoring system (1, 2). The Wells score (Table 2) (13) allows standardized classification of patients on the basis of the clinical probability of PE (low, intermediate, or high). The result should be documented (12).

In order to prevent patients being placed unnecessarily on potentially hazardous long-term anticoagulation, diagnostic certainty has priority with suspected non-high-risk PE. In principle, many diagnostic procedures or combinations of examinations are suitable to reliably confirm or exclude PE (2, 3). Taking current diagnostic and management studies (14–16) and clinical reality into consideration, the ESC Committee for Practice Guidelines has decided to recommend a uniform diagnostic algorithm (Figure 3) on the basis of highly sensitive (enzyme linked immunosorbent assay [ELISA]) D-dimer determination and MDCT (3).

The fibrin fragment D-dimer is produced by degradation of crosslinked fibrin by plasmin (1). The negative predictive value is extremely high, meaning that PE is unlikely with a D-dimer antigen level below a test-specific threshold (12, e5). Modern ELISA test kits have a sensitivity of >95% and a specificity of about 40% (3). Further diagnostics and anticoagulation



MDCT, multidetector computed tomography with imaging of the pulmonary arteries; RV, right ventricular; CT, computed tomography; *1, For high-grade unstable patients a treatment decision can be made using indirect echocardiographic signs of PE alone (LV dilatation, RV hypokinesia, RV pressure overload, paradoxical septal motion, free-floating thrombi); (modified from Walther A, Schellhaaf A, Böttiger BW, Konstantinides S: Diagnosis, therapy and secondary prophylaxis of acute pulmonary embolism. *Anaesthesist* 2009; 58: 1048–54. With kind permission of Springer Science and Business Media).

can be omitted for patients with a low or intermediate clinical probability if a highly sensitive assay yields a negative result (15). A positive result, however, only indicates the necessity of further (imaging) diagnostics. Age, pregnancy and a range of pathological conditions often lead to fibrin formation, which may lead to a non-specific increase in the D-dimer antigen level, and the predictive value of a positive result with regard to the presence of PE is still further reduced (5). Immediately postoperatively the D-dimer antigen level is likewise regularly elevated above the normal value, meaning that exclusion of PE using D-dimer determination is difficult (e5, e6). With a high clinical probability of PE D-dimer determination is not recommended, because a negative test result is only expected for a few patients (2).

MDCT reveals the extent of the PE and also allows possible differential diagnoses. It has replaced ventilation-perfusion scintigraphy and pulmonary angiography as the gold standard. The PIOPED II study documented a sensitivity of 83% and a specificity of 96% (14). The negative predictive value of a negative MDCT is significantly dependent on the clinical probability ascertained with the Wells score (low: 96%, intermediate: 89%, high: 60%). Pelvic or leg CT venography can in principle be included in the same

TABLE 2

Determination of the clinical probability of a pulmonary embolism: Wells score (13)

Clinical variable	Points
Clinical signs or symptoms of deep vein thrombosis	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100 beats/min	1.5
Immobility or surgery in the past four weeks	1.5
Previous deep vein thrombosis or PE	1.5
Hemoptysis	1.0
Cancer (being treated, after treatment within the last 6 months, or palliative therapy)	1.0
Probability of PE	Total
Low	<2.0
Intermediate	2.0–6.0
High	>6.0

examination in order to determine the presence and extent of a pelvic or leg thrombosis. In light of the additional radiation exposure, the ESC recommends compression ultrasonography of the lower extremities as an additional examination to increase the level of diagnostic certainty in case of doubt (Figure 3) (3).

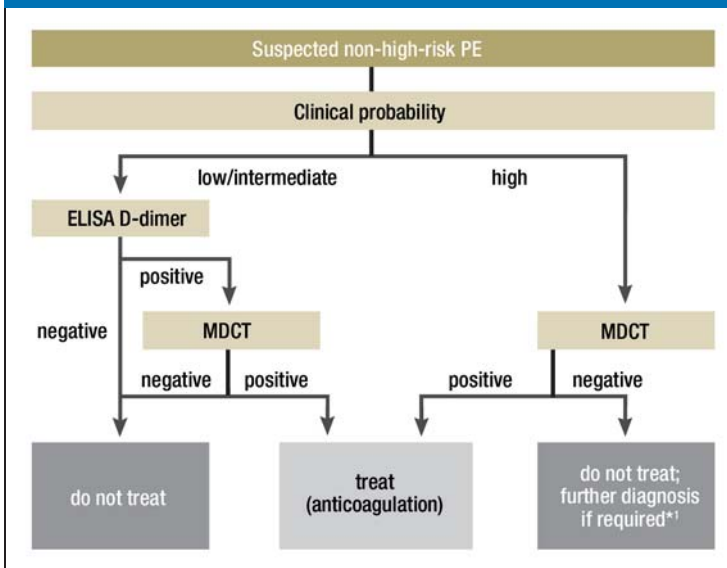
Further risk stratification

For non-high-risk PE (no hemodynamic instability) the ESC recommends additional early risk stratification (evidence level B) (Table 3). Patients with right ventricular (RV) dysfunction and/or myocardial injury have an intermediate PE-related early mortality risk, as the mortality rate in studies was 3% to 15% (3, 17, 18, e7). Patients without RV dysfunction or myocardial injury have the best prognosis in studies (mortality rate <2%) and are therefore classified in the low risk category (4).

Because of its non-invasiveness and rapid availability even in an emergency, transthoracic echocardiography is of value to assess right ventricular function (6). In a current meta-analysis the risk of death due to PE is elevated by a factor of 2.5 with evidence of RV dysfunction (17). On the other hand, normal echocardiographic findings indicate a very good prognosis, as in prospective randomized studies the PE-related early mortality was about 1% for this constellation (e8, 19). That no uniform criteria for verification of RV dysfunction have been established is problematic (2, 17).

Cardiac biomarkers are a sensible addition to echocardiography for further risk stratification of hemodynamically stable patients with acute PE (20, 21). In a recent meta-analysis, elevation of cardiac troponin I or T indicated increased mortality and risk of complications (18). Normal troponin levels on the other hand indicate a very good prognosis in the acute phase of PE (2). B-type (brain) natriuretic peptide (BNP) and N-terminal fragment of BNP (NT-proBNP) are synthesized after myocardial stress and reveal the neuro-humoral activation that takes place with ventricular dysfunction (2). Negative test results have a high predictive value for a good prognosis (22); however, the specificity is low and prospectively validated cutoffs are not yet available (e9). In the early phase of myocardial ischemia there is already detectable elevation of the cytoplasmic protein h-FABP (heart-type fatty acid binding protein). Study results indicate that h-FABP determination would allow better prognostic assessment in future (e9).

FIGURE 3



MDCT, multidetector computed tomography with imaging of the pulmonary arteries; *1, For negative MDCT despite high clinical probability, further diagnostic clarification using compression ultrasonography or ventilation-perfusion scintigraphy to increase diagnostic certainty may be sensible—particularly before a final decision against anticoagulation is made. However, prospective management studies indicate that a negative MDCT finding obviates the need for anticoagulation (15, 16). With low or intermediate clinical probability, the MDCT is only considered positive if more than one subsegmental thrombus or at least one proximal thrombus can be detected. If single detector CT is performed instead of MDCT, due to the low sensitivity compression ultrasonography of the lower extremities should also be performed if there is a negative finding in order to be able to exclude PE with sufficient certainty; (modified from Walther A, Schellhaaß A, Böttiger BW, Konstantinides S: Diagnosis, therapy and secondary prophylaxis of acute pulmonary embolism. *Anaesthesist* 2009; 58: 1048–54. With kind permission of Springer Science and Business Media)

Risk-adapted therapeutic strategies with acute PE

Apart from hemodynamic stabilization and reversal of hypoxemia, the therapeutic goals for acute PE are—depending on the severity—prevention of appositional thrombus growth, restoration of pulmonary blood flow, and prevention of recurrences (8). If there is no contraindication, parenteral anticoagulation is therefore obligatory. The options available include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux (3). Where suspicion of an

acute PE is high (high or intermediate clinical probability), initial anticoagulation—with consideration of the bleeding risk—must be initiated before a definitive diagnosis is available (evidence level C) (2).

Therapeutic strategies with high-risk PE

As well as general circulatory support and therapeutic anticoagulation, hemodynamically unstable patients with confirmed PE require immediate thrombolysis to relieve the right ventricle (evidence level A) (3). The following active substances and dosage regimens are recommended in the literature (5, 12):

- Alteplase (rtPA): 10 mg IV bolus over 1 to 2 minutes followed by 90 mg over 2 hours (with body weight <65 kg maximal 1.5 mg/kg)
- Urokinase: 3 million IU over 2 hours
- Streptokinase: 1.5 million IU over 2 hours.

In Germany, reteplase and tenecteplase are not approved for acute PE.

International guidelines for cardiopulmonary resuscitation recommend the administration of a thrombolytic agent for suspected pulmonary embolism even during resuscitation (23, e10). Resuscitation should then be continued for 60 to 90 minutes if stabilization is not achieved. With an absolute contraindication to thrombolysis (e11) or failure of thrombolytic therapy, surgical or interventional restoration of blood flow can be used depending on logistics and expertise on site (evidence level C) (2).

In addition to a specific therapy, supportive measures are also of central importance in the treatment of PE patients with hemodynamic instability, because acute right heart failure is the primary cause of death. In the case of hypotension, noradrenaline (norepinephrine) is the catecholamine of first choice. For normotensive patients with low cardiac output, dobutamine is used and for hypotensive patients with cardiogenic shock adrenaline (epinephrine) is used (3). Selective reduction of pulmonary arterial pressure using inhalative nitric oxide or prostacyclin aerosol in smaller clinical trials led to an improvement in the ventilation-perfusion ratio with improvement in oxygenation, reduction in pulmonary arterial pressure, and an increase in cardiac output (6).

Therapeutic strategies with non-high-risk PE

Normotensive patients (non-high-risk PE) receive therapeutic anticoagulation using LMWH or fondaparinux in a weight-adjusted dose (evidence level A) (5). UFH is preferable for patients with a very high risk of bleeding or severe renal insufficiency (target aPTT is 1.5 to 2.5 times normal value) (evidence level C) (2). Routine thrombolytic therapy is not recommended (evidence level B).

Patients with normal arterial blood pressure at the time of diagnosis but with evidence of RV dysfunction and/or myocardial injury (Table 3) have an intermediate risk of PE-related early mortality (18). The therapeutic consequences of assignment to this category, apart from the necessity of hospitalization and initial

TABLE 3

Parameters for further risk stratification of non-high-risk pulmonary embolism (3)

Markers of right ventricular dysfunction	RV dilatation, RV hypokinesis, RV pressure overload or paradoxical septal motion on echocardiography
	RV dilatation on CT
	BNP or NT-proBNP elevation
	Elevated pulmonary arterial pressure at right heart catheter
Markers of myocardial injury	Troponin T or I elevation
	H-FABP elevation

RV = right ventricle; BNP = B-type (brain) natriuretic peptide; NT-proBNP = N-terminal proBNP; H-FABP = human fatty acid binding protein

intensive care monitoring, have not yet been definitively clarified. A large European multicenter study (Pulmonary Embolism International Thrombolysis Study; EudraCT No.: 2006–005328–18) is currently investigating the significance of thrombolysis in PE patients with intermediate risk (12).

Hemodynamically stable patients with no evidence of RV dysfunction or myocardial injury (low risk) have a mortality rate of <2% with effective anticoagulation (e7). There is, therefore, no indication for thrombolysis or mechanical restoration of flow (evidence level B) (3, 12). Selected patients may be suitable for early discharge or treatment on an outpatient basis (e7). Precise criteria for outpatient treatment of PE are, however, not currently available (3).

Secondary prophylaxis and prevention of recurrence

The ESC recommendations regarding the duration of oral anticoagulation agree for the most part with the current guidelines of the American College of Chest Physicians (3, e12). For hemodynamically stable patients the administration of vitamin K antagonists (VKAs) should be initiated as early as the first or second day. Heparin or fondaparinux therapy is continued in conjunction for at least five days (evidence level A) and only stopped when the international normalized ratio (INR) is in the therapeutic range (2.0 to 3.0) on two consecutive days (evidence level C) (12). For PE secondary to reversible risk factors, treatment with a VKA for three months is recommended (evidence level A). In light of the lasting increase in the risk of recurrence after the initial occurrence of an ‘idiopathic’ (unprovoked) PE, we recommend continuing treatment with a VKA for at least three months (evidence level A). Provided anticoagulation is stable and the risk of bleeding is low, indefinite continuation of this therapy should be considered (evidence level B). Patients with PE and malignancies should be treated with LMWH for

the first three to six months (evidence level B) and they should subsequently receive lifetime anticoagulation with VKA or LMWH or until the cancer is 'cured' (evidence level C).

Venous filters

Systematic use of venous filters to prevent PE recurrence is not recommended (evidence level B) (3, 24). Venous filters may, however, be indicated in exceptional cases if therapeutic anticoagulation is absolutely contraindicated or a PE has recurred despite adequate anticoagulation (evidence level C) (2, 25). The venous filter should be removed as soon as possible in order to avoid secondary vena cava thromboses and thromboembolisms.

KEY MESSAGES

- If acute pulmonary embolism (PE) is suspected, rapid and targeted treatment is essential, because speedy diagnosis and immediate therapy can lower the morbidity and mortality associated with PE.
- If acute pulmonary embolism is suspected, the diagnosis should be risk adapted. Patients are classified into two groups (high-risk PE versus non-high-risk PE) using simple hemodynamic parameters according to different diagnostic algorithms.
- In patients with cardiogenic shock or persistent arterial hypotension (high-risk PE), the diagnosis must be made immediately using multidetector computed tomography (MDCT) with imaging of the pulmonary arteries or bedside emergency echocardiography (if CT transport is not possible due to patient instability) to immediately determine the indication for—potentially life-saving—thrombolysis, which should also be administered in case of ongoing cardiopulmonary resuscitation.
- For suspected non-high-risk PE the diagnostic strategy is determined by the clinical probability of PE, which can be calculated with the aid of validated scoring systems (such as the Wells score) and should be documented. Depending on this clinical probability further diagnosis is made using D-dimer determination and multidetector computed tomography for imaging of the pulmonary arteries. The presence of right ventricular dysfunction and/or myocardial injury is also determined for further risk stratification.
- In addition to specific therapy, patients with high-risk PE, patients at high risk of bleeding and those with severe renal insufficiency should receive the required anticoagulation treatment with unfractionated heparin. All other patients should be treated with low-molecular-weight heparin or fondaparinux. The patients should subsequently receive long-term oral anticoagulation with vitamin K antagonists.

Conflict of interest statement

Prof. Böttiger is Chairman of the European Resuscitation Council (ERC). The remaining authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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