ACUTE THROMBOEMBOLIC DISEASE CONSENSUS STATEMENT

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Abbreviations

AAA	Abdominal aortic aneurysm
ABI	Ankle-brachial index
ACEI	Angiotensin converting enzyme inhibitors
ARA II	Angiotensin II receptor antagonists
CS	Carotid stenosis
CTA	Computed tomography angiography
CT	Computed tomography
DA	Digital angiography
HTN	Hypertension
IS	Ischemic stroke
LL	Lower limbs
LLAD	Lower limb arterial disease
LLCI	Lower limb critical ischemia
LLPVD	Lower limb peripheral vascular disease
NMR	Nuclear magnetic resonance
MRA	Magnetic resonance angiography
PTAS	Percutaneous transluminal angioplasty and stenting
PVD	Peripheral vascular disease
SSS	Subclavian steal syndrome
TIA	Transient ischemic attack
VRF	Vascular risk factors

1. INTRODUCTION

Pulmonary embolism (PE) is a cardiovascular emergency with an annual incidence of 70 cases per 100,000 inhabitants. The annual prevalence of the disease increases in elderly persons and it is further enhanced by the presence of multiple comorbidities.

The prognosis may vary broadly depending on the form of presentation. At one end of a wide range of possibilities is high risk PE, with elevated mortality risk and in the other end, low risk PE with little hemodynamic effect and low mortality.

In most cases the clinical presentation is undefined and frequently associated to other diseases with overlapping signs and symptoms generating diagnostic delays.

A timely diagnosis is essential to establish a therapeutic treatment in order to alter the course of the unfavorable prognosis, especially in the more severe disease presentations.

Most pulmonary embolism events are related with proximal lower extremity deep vein thrombosis (DVT). This entity is associated with conditions that determine both congenital and acquired hypercoagulability. However, a significant percentage of patients present with idiopathic thromboembolic disease (TD). Prophylaxis as early diagnosis and adequate TD treatment are essential to obtain the best results.

The purpose of the present document is to provide a practical guideline on the diagnosis, risk stratification and treatment of acute TD.

2. EPIDEMIOLOGY. NATURAL HISTORY OF THE DISEASE. RISK FACTORS

Epidemiology

Thromboembolic disease encompasses DVT and PE. It is the third cause of cardiovascular death after acute myocardial infarction (AMI) and stroke and is considered among the main causes of in-hospital mortality.
Its diagnosis is difficult, as there is no specific clinical presentation.

Mortality for high risk PE is over 15% and can increase to more than 60% in cases of cardiopulmonary arrest or shock. Intermediate risk PE mortality ranges between 3% and 15% and low risk PE mortality is below 1%.

Natural history of acute venous thromboembolic disease

Untreated PE is associated with almost 30% mortality. Episodes with hemodynamic impairment and recurrent embolism represent the most common cause of death.

Older age is correlated with increased mortality, with eight-fold higher rates in patients >80 years than in those <50 years.

Deep vein thrombosis and PE are usually recurrent, so it is important to identify patients at higher risk of presenting them. Thrombophilia or an occult cancer should be investigated in the absence of a cause that justifies them.

Risk factors

Known primary and secondary risk factors are related to the classical Virchow triad: venous stasis, hypercoagulability of the blood and vascular wall lesions. Venous thromboembolism is currently considered to be derived from the interaction between patient and contextual risk factors (Table 1). The most important risk factor is age. Prevalence is higher in men same as TD recurrence.

Without prophylactic measures, the frequency of DVT in patients undergoing a simple hernia surgery may

be up to 5%, in large abdominal surgeries between 15% and 30%, in hip surgery from 50-70% and in severe bone marrow lesions from 50% to 100%.

It is necessary to take into account that 25% of postoperative embolisms may occur after hospital discharge, especially in major orthopedic or cancer surgery.

Hereditary thrombophilias that include antithrombin III, protein C, protein S deficiency and factor V Leiden mutation are independent risk factors for TD.

Table 1. Predisposing factors for venous thromboembolic disease associated with the patient and the clinical context.

Predisposing factor	Associated with the patient	Associated with the context
Strong predisposing factors (odds ratio>10)		
Fracture (hip or leg)		+
Hip and knee prostheses		+
Major general surgery		+
Major trauma		+
Bone marrow lesion		+
Moderate predisposing factors (odds ratio 2-9)		
Knee arthroscopy		+
Central venous access		+
Chemotherapy		+
Chronic heart or respiratory failure	+	
Hormone substitution therapy	+	
Malignancy	+	
Use of oral contraceptives	+	
Stroke with palsy	+	
Pregnancy or postpartum	+	+
Prior venous thromboembolism	+	
Thrombophilia	+	
Mild predisposing factors (odds ratio <2)		
Bedrest >3 days		+
Immobility for long journey (car, plane)		+
Old age	+	
Laparoscopic surgery		+
Obesity	+	
Pregnancy/antepartum	+	
Varicous bed	+	

Clinical presentation of pulmonary embolism

Pulmonary embolism signs and symptoms are nonspecific and clinical suspicion is essential for early diagnosis. The most frequent signs and symptoms are dyspnea, tachypnea, palpitations, chest pain, anxiety, fever, syncope or pre-syncope and hemoptysis. (1)

Hypotension and shock are not frequent but have greater importance because they correlate with large central thrombi in the pulmonary arteries. Their persistence is predictor of high early mortality.

Syncope is infrequent but defines higher risk PE with possible hemodynamic instability.

There is frequent chest pain which may be caused by pleural irritation with or without pulmonary infarction, with frequent inspiratory side stitch produced by distal thrombi. When thrombi are central, chest pain is more severe and with anginal characteristics due to right ventricular (RV) ischemia. In these cases a differential diagnosis must be made with other severe causes of chest pain, as acute coronary syndrome or aortic dissection.

Dyspnea can be the only sudden symptom. It can be transient, and in the absence of signs and symptoms of left heart failure or parenchymal lung disease should increase PE suspicion.

Hypoxemia in blood gases is considered a frequent finding, but 40% of patients have normal oxygen saturation and 20% have a normal A-a gradient. Hypocapnia, elicited by tachypnea, could then be the only sign suggestive of PE. A pattern that should raise PE suspicion is hypoxemia with hypocapnia.

In the absence of any other alternative diagnosis, presence of dyspnea, hypoxemia and normal thorax X-ray suggests PE.

Evaluation of clinical probability

Despite the limited sensitivity and specificity of the different signs and symptoms, their combination seems to establish the clinical probability of PE. The Wells and Geneva scores are the most widely used scores for this purpose. They are both extensively validated, allowing the assessment, according to clinical suspicion, of low or high PE probability. (2)

Table 1. Predisposing factors for venous thromboembolic disease associated with the patient and the clinical context.

Parameter	Original version (score)	Simplified versión (score)
Wells score		
Prior DVT or PE	1.5	1
HR ≥100 bpm	1.5	1
Immobility or surgery <4 weeks	1.5	1
Hemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
PE is the most probable diagnosis	3	1
Clinical probability		
Low	***0-4***	***0-1***
High	***≥5***	***≥2***
Geneva score		
Age >65 years	1	1
Prior DVT or PE	3	1
Surgery or fracture <1 month	2	1
Active cancer	2	1
Lower limb unilateral pain	3	1
Hemoptysis	2	1
Deep vein pain on palpation and lower limb edema	4	1
HR >75 and <94 bpm	3	1
HR ≥95 bpm	5	1
Clinical probability		
Low	0-5	***0-2***
High	≥6	***≥3***

Biochemical diagnostic markers

No biochemical marker has enough sensitivity and specificity to establish a prognostic value; therefore, they must usually be used together with other clinical elements.

D-dimer

D-dimer level is elevated in the presence of acute thrombosis, as it is a product of fibrinogen degradation.

Negative D-dimer test and normal D-dimer dispel the probability of DVT or PE. However, the diagnosis of PE cannot be exclusively confirmed by a high D-dimer level, as there are other fibrin origins which may elevate

D-dimer, such as cancer, trauma, inflammation, bleeding and necrosis.

Dimer-D sensitivity when ELISA (enzyme-linked immunosorbent assay) or high sensitivity tests are used is close to 95% and hence can be used to rule out PE in patients with moderate to low probability pretest when its result is negative. (3)

The blood latex test and/or the agglutination test have a moderate sensitivity <95% and their negative value would be useful in patients with low clinical probability of PE.

The persistently elevated D-dimer value can also be used as prognostic factor and risk marker of recurrence, being useful for extended anticoagulation (DASH criteria).

Right ventricular dysfunction markers

Right ventricular pressure overload is associated with increased wall stress and brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) release.

Plasma peptide level reflects the severity of hemodynamic involvement and possible RV dysfunction due to PE.

A meta-analysis of 1,132 PE patients revealed that 51% had elevated BNP or NT-proBNP and 10% early mortality. (4)

Another study, however, demonstrated that PE normotensive patients without clinical instability and with high BNP or NT-proBNP had a low positive predictive value for early mortality.

A low BNP or NT-proBNP level could identify patients with a favorable clinical outcome. Hemodynamically stable PE patients with low levels of these markers would be candidates for early hospital discharge.

Myocardial injury markers

Elevated plasma concentration of the different forms of troponin in PE has been associated with adverse prognosis.

In a meta-analysis of 1,985 PE patients, elevated troponin T or I was observed in 50% of patients and was associated with higher mortality. (5) However, other authors ascribe a limited value to high troponin in normotensive patients. The positive predictive value of troponin elevation in PE patients correlates with 12% to 44% early mortality and the negative predictive value is high. There is evidence of the positive predictive value of ultrasensitive troponin, but the cutoff value is still unclear. In a prospective multicenter study with 526 patients, a low ultrasensitive troponin T level <14 pg/ml in PE normotensive patients had a negative predictive value of 98%. (6)

Elevated troponin T or I or high BNP or NT-proBNP have also shown increased risk. Heart-type fatty acid-binding proteins (h-FABP), (7) still unavailable in our setting, consisting of small cytoplasmic proteins present in tissues with enhanced fatty acid metabolic activity are injury markers that have also demonstrated prognostic value in PE.

Chest X-ray

Chest X-ray is an important widely available and cheap tool in the diagnostic algorithm to exclude other entities that may simulate PE. In the ICOPER study, X-ray was abnormal in 75% of patients evaluated with unspecific findings, among which, the most frequent are an increase in the cardiac silhouette (27%), pleural effusion (23%), elevated hemidiaphragm (20%), increased pulmonary artery diameter (19%) and atelectasis (18%).

Electrocardiogram

Sinus tachycardia is the most prevalent disorder. The occurrence of ST-segment elevation in aVR and V1 as expression of severe RV ischemia, acute clockwise rotation of the QRS axis with S1 Q3 T3 configuration, negative T waves from V1 to V4 as expression of RV dilatation and ischemia, and complete or incomplete acute right bundle branch block due to RV moderator band distention involve a worse prognosis. (8, 9)

3. IMAGING DIAGNOSIS

Transthoracic echocardiogram

Echocardiogram is essential in PE patient evaluation as it provides diagnostic suspicion when there is RV dilatation or pulmonary hypertension, and in defined cases, allows risk stratification. It is the diagnostic and stratification tool for PE with hemodynamic involvement. Right ventricular dysfunction is the rule in a patient with shock for PE; therefore, RV normal function dispels the diagnosis of PE shock.

McConnell's sign is a distinct though infrequent finding expressed as hypokinesia of the RV lateral wall with preserved apical wall motion. Other evidence is the presence of systolic pulmonary hypertension, generally with tricuspid regurgitation peak velocity between 3 and 3.6 meters/s. Echocardiogram has prognostic implications,

where RV dilatation and especially significant functional involvement are independent predictors of mortality. Another marker of poor outcome is the presence of thrombus-in-transit in right heart chambers. In this case, the association with patent foramen ovale (present in 22% of the population) adds risk of paradoxical systemic embolism.

Transesophageal echocardiography

Its usefulness lies in the possibility of detecting pulmonary artery trunk or proximal branch thrombi when CT scan is not available and especially in ventilated patients. It is an important second line study when there is no other confirming information. In addition, it allows ruling out other cardiovascular pathologies, as aortic dissection or acute mitral regurgitation.

Ventilation/perfusion (V/Q) scintigraphy

The diagnostic value of V/Q scintigraphy depends on the quality and analysis of the study. It must include 6 imaging positions (anterior, posterior and 4 oblique images) as established in the PIOPED I study. Normal V/Q scintigraphy rules out PE diagnosis. Less than 15% PE have a high PE probability study and most (65%-80%) have intermediate probability, needing another study to confirm the diagnosis. For this reason, multislice computed tomography (angio CT scan) has become relevant in the last years. However, when this last method is not available or is not considered adequate (unstable patient, iodine allergy, pregnancy or severe renal failure), V/Q scintigraphy is still a useful tool, especially in individuals without prior cardiopulmonary disease. A normal chest X-ray significantly increases the specificity of the method. An abnormal pulmonary perfusion scan with a normal chest X-ray suggests PE.

Computed tomography

It is the initial method of choice to confirm PE diagnosis. The presence of intraluminal defects in the trunk or lobar branches of the pulmonary artery have 85% positive predictive value. Subsegmental defects, which constitute 10% to 30% of pulmonary embolisms present more limitations to diagnosis. New multiple head devices increase the chances of diagnosing peripheral thrombi and assessing their degree of organization (indicating their age). It also allows an angiography of the inferior vena cava territory to eventually rule out DVT.
The limitations to perform CT scan are: pregnancy, contrast sensitivity and renal failure.

In the PIOPED II study, performed with multislice CT scan, sensitivity was 83% and specificity 96%. In patients with low-intermediate clinical probability, CT scan has a highly negative predictive value (96%-89%), but in the case of high clinical probability this value decreases significantly (60% positive predictive value); in this instance, when clinical suspicion is high, the diagnosis with the gold standard represented by pulmonary angiography, should be ruled out.

This study demonstrated that the yield of multidetector CT scan evaluation is similar to that of pulmonary angiography.

Doppler ultrasound in deep vein thrombosis

The diagnosis of DVT is an indirect way of determining possible PE. In the presence of PE, DVT is positive in 50% to 70% of cases. Moreover, 50% of DVT patients present evidence of asymptomatic PE. In patients with DVT and clinical PE, presence of pulmonary thrombosis is confirmed in 90% of cases.

Lower limb venous echo Doppler is the most useful, easy and accessible diagnostic method to diagnose DVT. Presence of a non-collapsible vein constitutes the confirmatory support, with more than 90% sensitivity and 95% specificity to diagnose proximal thrombosis. However, lower-limb venous echo Doppler is normal in 30%-50% of PE patients; therefore, it does not rule out PE diagnosis, although it reduces its probability owing to the method sensitivity and the occasional thrombosis in other territories (pelvis, upper limbs, etc). Absence of DVT diagnosed by echo Doppler is accompanied by lower risk of PE recurrence.

Magnetic angioresonance with protocol for PE

It is a non-invasive technique, with similar usefulness as pulmonary angiography, presenting high sensitivity and specificity for PE diagnosis, in addition to allowing RV functional and dilatation assessment. It has some limitations as the potential development of nephrosclerosis by gadolinium and the possible need of sedation as well the prolonged duration of the study.

Pulmonary angiography

It is an invasive method and guide for PE diagnosis and confirmation. It is indicated in patients at high clinical risk and non-invasive negative or dubious tests, and may be negative in 1-5% of patients who have effectively suffered from PE.

It has the advantage of fast image acquisition, possibility of evaluating other entities which might be causing

the symptoms, prognostic evaluation according to thrombus location, magnitude and hemodynamic involvement (possibility of acute pulmonary score evaluation, using the Miller I and II angiographic scores). In critical patients, it allows attempting local reperfusion with thrombolytic therapy and endovascular treatment with catheters.

RECOMMENDATIONS FOR IMAGING DIAGNOSTIC METHODS

Deep vein thrombosis

Class I

- Venous echo Doppler (A).
- Venography with radiologic contrast (limited to center experience) (A).
- Venography associated with pulmonary multislice helical computed tomography (A).

Pulmonary embolism

Class I

- Multislice helical computed tomography (A).
- Pulmonary angiography (A) if it is impossible to confirm the diagnosis by another method or revascularization is decided by vascular or surgical thrombectomy.

Class IIa

- V/Q scintigraphy (A).
- Single-slice helical computed tomography (A)
- Transesophageal echo-Doppler (A).

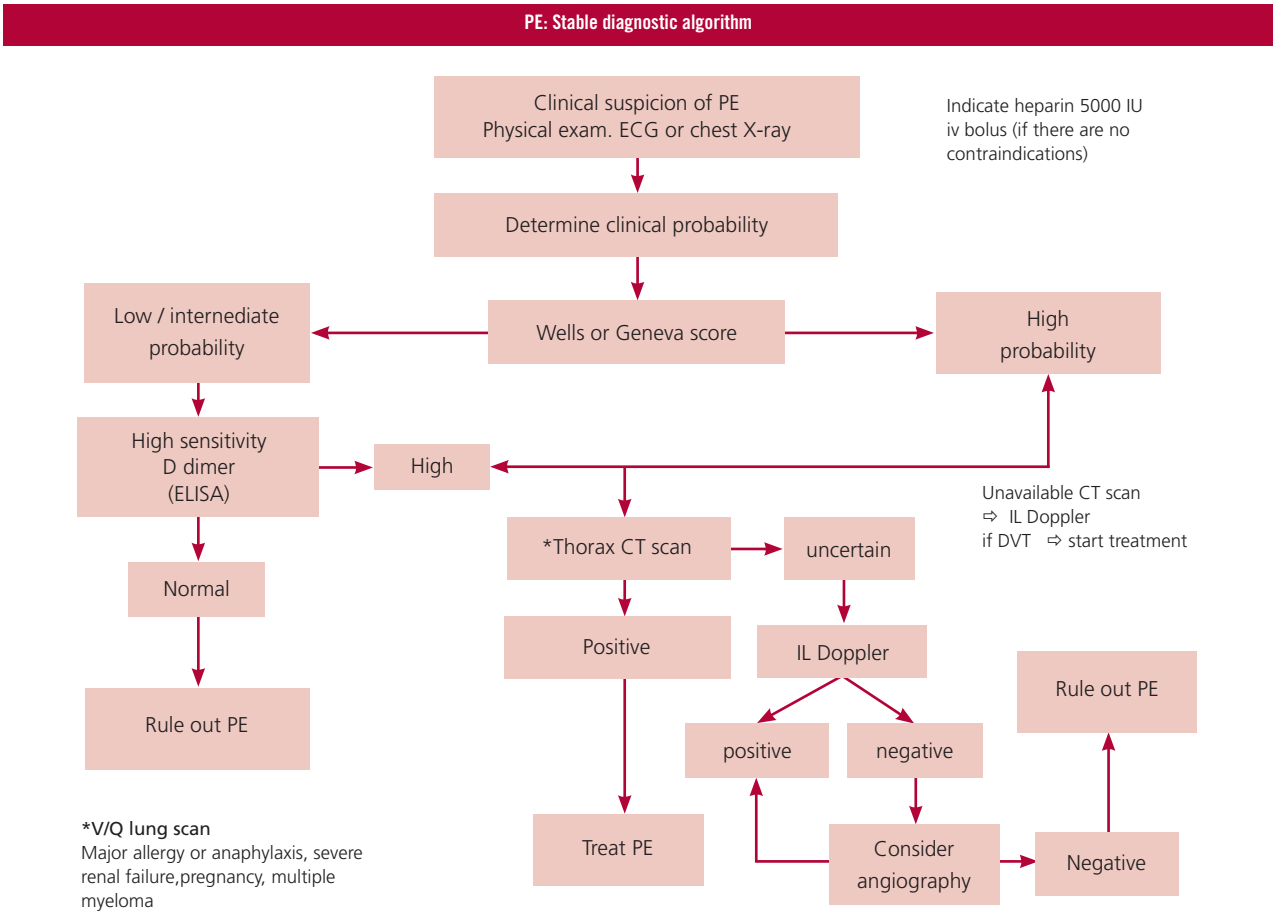

Fig. 1. Diagnostic algorithm for stable patients with clinical suspicion of pulmonary embolism

4. RISK STRATIFICATION

Risk can be stratified using clinical, laboratory, electrocardiographic and imaging variables. This risk classification must not only contemplate the risk of death or hemodynamic decompensation but also major bleeding including intracranial hemorrhage in order to establish clinical conduct and the most adequate treatment. There is no consensus on the exact definition of "submassive" as defined by the American Heart Association (AHA) or "intermediate risk" according to the European Society of Cardiology (ESC). However, different variables have been identified to stratify risk of PE patients.

1) High risk PE represents approximately 5% of all patients, with short-term mortality above 15%; they should therefore receive intensive and eventually invasive treatment.
2) Intermediate risk PE represents approximately 30-50% of all symptomatic patients. It involves a wide range of patients with those at lower risk for presenting only one adverse prognostic variable and those at higher risk with various risk variables or comorbidities. One of these variables is syncope, which in the context of PE must be assumed as fragmented proximal central embolism allowing the reestablishment of circulation.
3) Low risk PE represents most PE patients with short-term mortality below 1%. These patients would benefit with noninvasive anticoagulation therapy and early hospital discharge or in certain cases, eventual ambulatory management.

Different prognostic variables should be used in PE risk stratification. Simple and evident parameters as significant dyspnea (Borg scale >8) may be used for clinical assessment. Persistent tachycardia and especially higher heart rate than systolic blood pressure (shock index=HR/SBP >1), hypoxemia, oxygen desaturation and abnormal tissue perfusion parameters (lactic acid >2 mmol/L, and central venous saturation <70 mmHg) are also useful to assess risk.

The Pulmonary Embolism Severity Index (PESI) score is widely validated and also useful for risk stratification. (10, 11)

Table 3. Risk stratification in pulmonary embolism. Pulmonary Embolism Severity Index (PESI) score

Pulmonary Embolism Severity Index (PESI) score	
Variable	**Score**
Age	**1 point per year of age**
Male gender	**10**
Cancer	**30**
Heart failure	**10**
Chronic pulmonary disease	**10**
Heart rate ≥110 beats per min	**20**
Blood pressure <100 mmHg	**30**
Respiratory rate ≥30 per min	**20**
Axillary temperature <36°C	**20**
Altered mental status	**60**
Oxygen saturation <90%	**20**
Class I (very low risk): *<65 points****; Class II (low risk):*** *65-85 points****; Class III (intermediate risk):*** *86-105 points****; Class IV (high risk):*** *106-125 points****; Class V (very high risk):*** *>125 points*	

Pulmonary Embolism Severity Index (PESI) score	
Variable	**Score**
Age >80 years	**1**
Cancer	**1**
Chronic pulmonary disease	**1**
Heart rate ≥110 beats per min	**1**
Blood pressure <100 mmHg	**1**
Oxygen saturation <90%	**1**
Low risk: *0 points****; High risk*** *≥1 point*	

Right ventricular dilatation measured either by echocardiography or angio-CT scan, the increase of RV diameter/LV diameter index >0.9 and especially severe RV dysfunction have an adverse prognosis. From the information obtained from the angio-TC scan, only RV dilatation and the proximal location of pulmonary artery trunk or lobar branch thrombi have been associated with adverse prognosis. Patients with extensive proximal or bilateral DVT, sessile thrombus or thrombus-in-transit are also considered at high risk.

Table 4. Useful prognostic variables for risk stratification in pulmonary embolism

Useful prognostic variables for risk stratification in PE	
Clinical	• Pulmonary Embolism Severity Index (PESI) score ≥86 • Borg dyspnea score >8 or FC IV dyspnea • Shock index (HR/BP >1) • Abnormal tissue perfusion parameters (lactic acid >2 mmol/L; Central venous saturation <65 mmHg) • Oximetry <90% or PaO2/FiO2 <300
ECG	• ST-segment elevation in AvR and V1, S1Q3T3 pattern, negative T waves in V1-V3, new incomplete or complete right bundle branch block.
Laboratory	• High myocardial injury markers (Troponin T or I) • Elevated high end-diastolic pressure markers (BNP or NT-proBNP) • Elevated Heart-type Fatty Acid-Binding Protein (h-FABP)
Echocardiographic	• Right ventricular systolic function dilatation or impairment
Thorax angio-CT scan	• Proximal thrombi location (pulmonary artery trunk or lobar branches) • Increased right ventricular diameter
Thrombotic load	• Proximal DVT, thrombus-in-transit, or sessile thrombus.

High risk PE

Definition

High risk is defined by hemodynamic instability secondary to RV failure and not by the degree of interruption in the pulmonary vascular tree.

In medical practice, it includes four groups of patients:

1) Clinical signs of tissue hypoperfusion, low cardiac output with imminent shock and poor peripheral perfusion (dyspnea in FC IV, cold extremities, livid blotches, sweating, sensory deterioration, generally with tachycardia and reduced diuretic rhythm).
2) Overt shock with hypotension (SBP <90 mmHg or fall of at least 40 mmHg for 15-30 minutes) unexplained by any other cause (tachyarrhythmia, hypovolemia, cardiac tamponade, sepsis, hypertensive pneumothorax).
3) Sustained hypotension requiring inotropic or vasopressor support, respiratory insufficiency requiring or not mechanical respiratory assistance (MRA).
4) Cardiorespiratory arrest

Hemodynamic instability originates in sudden RV failure secondary to fast increase of pulmonary vascular resistance produced by abrupt obstruction of the pulmonary artery or some of its main branches. The impact of an embolic event depends essentially of thrombus size, its location in the pulmonary vascular tree, preexistent cardiorespiratory reserve and general patient status.

The acute pressure overload increases right intraventricular pressure decreasing coronary perfusion pressure with ischemia, dysfunction and RV dilatation. This effect increases ventricular tension and oxygen consumption sustaining the ischemic state. Acute RV dilatation reduces left ventricular distensibility, with decreased preload and reduced cardiac output and shock. Right ventricular dilatation may also generate significant tricuspid regurgitation leading to decreased RV output, with reduced left ventricular preload and cardiac output.

Although thrombus-in-transit is observed only in 4% of patients, this condition is considered as high risk due to greater mortality and because the association with patent foramen ovale entails risk of systemic, mainly cerebral, embolism. The association of chamber thrombus and patent foramen ovale is one of the surgical indications for PE.

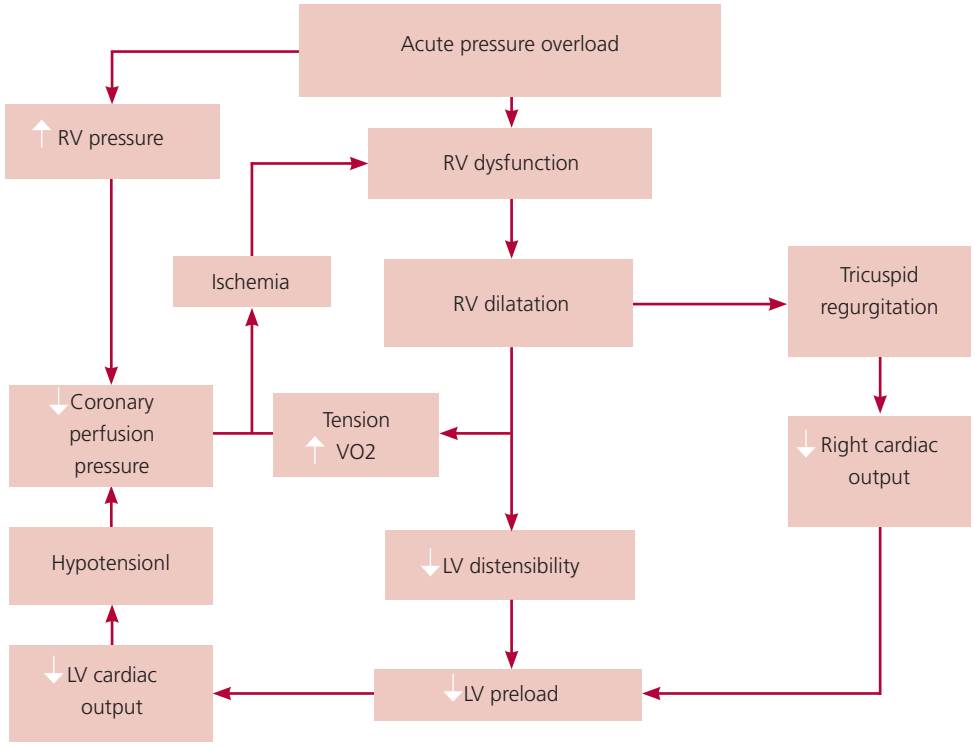

Fig. 2. Pathophysiology of shock in pulmonary embolism

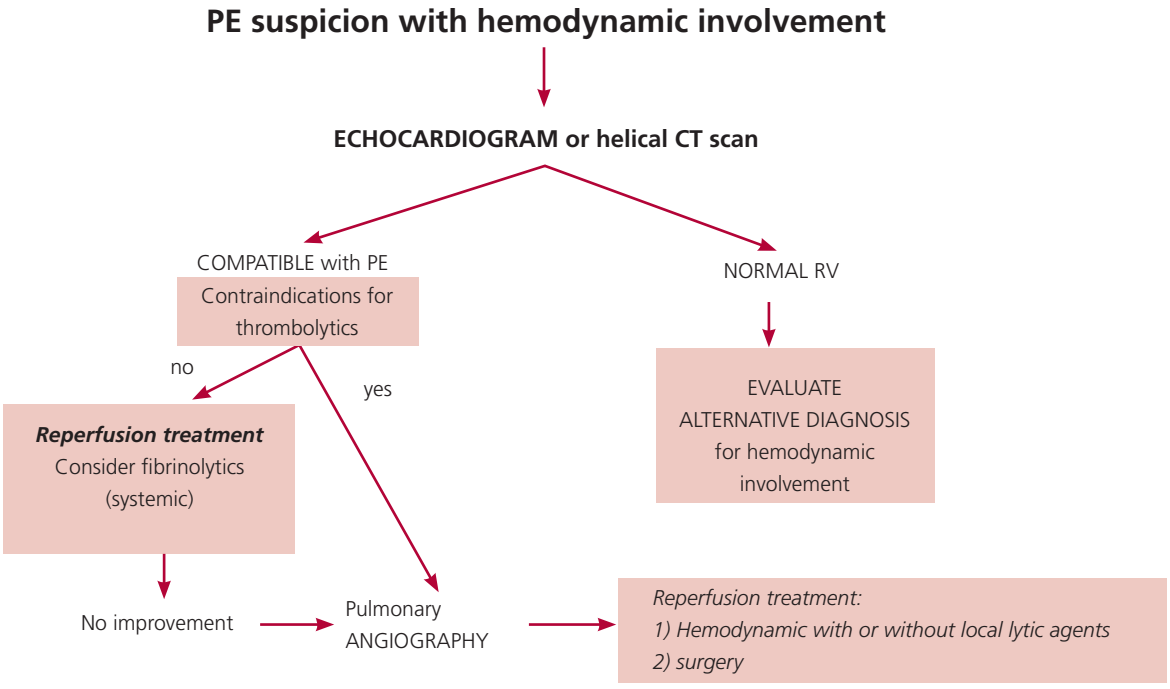

Fig. 3. Initial diagnostic algorithm in a patient with suspected pulmonary embolism and hemodynamic involvement.

Echocardiography

Echocardiography is a useful tool in a hemodynamically unstable patient, since it gives rise to a series of important differential diagnoses: cardiac tamponade, acute myocardial infarction, aortic dissection and acute valvular regurgitation.

It is the first study to be performed at the bedside of the unstable patient, who cannot be transferred to perform complementary studies. Acute RV pressure overload in the absence of valvular or left ventricular disease, with or without pulmonary hypertension, confirms high risk PE suspicion. A normal right ventricle rules out PE as cause of hemodynamic decompensation.

Pulmonary angiography and right heart catheterization

Pulmonary angiography is the gold standard for PE diagnosis. However, the availability of multislice angio-TC has matched it with equivalent sensitivity and specificity. Different meta-analyses demonstrated that a negative multislice angio-TC, same as negative angiography, rules out PE. In the case of high risk PE, catheterization confirms the diagnosis and offers the possibility of performing local reperfusion therapeutic maneuvers, especially in unstable patients at high risk of bleeding who are not candidates for surgical thrombectomy and in those with failed systemic fibrinolysis. In selected cases with strong suspicion of associated coronary heart disease, a diagnostic coronary angiography must also be performed.

Treatment

The appropriate therapy in the PE patient with hemodynamic collapse is immediate reperfusion of the occluded vessels with the most effective method according to the patient (12, 13): systemic thrombolytic agents, endovascular treatment with or without fibrinolytics or surgical thrombectomy. High risk PE patients should receive an adequate hemodynamic support to prevent and treat shock while reperfusion therapy is decided. Patients without contraindications may receive systemic thrombolytic therapy (IB). In patients with contraindications, high risk of bleeding or suspected organized thrombus which will probably not respond to fibrinolytics, surgical thrombectomy (IbC) or hemodynamic thrombectomy (IIaC) may be considered in experienced centers. In patients with thrombus in a cardiac chamber and atrial septal defect, right heart circulatory assistance or ECMO will be preferred to surgical treatment. In case of persistent hemodynamic instability after thrombolytic infusion, hemodynamic or surgical thrombectomy should be considered.

Initial resuscitation

Crystaloid expansion: in most patients with shock of any etiology, empirical volume expansion is one of the first therapeutic approaches. If the cause of shock is due to RV failure, the expansion has a limited role, as overexpansion (central venous pressure >15 mmHg) is deleterious, worsening ischemia and perpetuating or precipitating shock through multiple mechanisms. The increase in right intraventricular pressure may reduce RV coronary perfusion gradient, displace the interventricular septum increasing left ventricular end-diastolic pressures with subsequent cardiac output reduction and consequently decreased coronary perfusion. If the RV is not critically dilated, expansion with crystaloids can be attempted with caution. In case there is no response with 500 to 1,000 ml, interruption of expansion and onset of inotropic and vasopressor therapy is suggested to increase mean arterial pressure (MAP) to 70-80 mmHg and improve the perfusion gradient between the aorta and the right coronary artery while a reperfusion strategy is decided.

Drugs and devices to treat shock associated to PE

It is necessary to maintain an adequate mean pressure to minimize RV ischemia (the RV is irrigated in both diastole and systole). Drug combination is suggested according to the availability and experience of each center (e.g. noradrenaline to support blood pressure together with dobutamine to improve cardiac output and vasodilate the pulmonary vascular bed). It is important to remember that inotropic support should be a bridge to reperfusion in most cases.

Dobutamine: It is a beta-agonist inotropic drug with strong lung and peripheral vasodilator activity. It has positive chronotropic effect so it should be used with caution in patients with tachycardia.

Milrinone: It is a phosphodiesterase III inhibitor, with positive inotropic effect and peripheral and pulmonary vasodilator activity. It is a particularly useful drug in patients with tachycardia requiring inotropic effect.

Noradrenaline: It is the most effective drug to increase MAP. It has strong vasoconstrictor alpha-1 effect, increasing both systemic and pulmonary pressure. It has mild beta-1 inotropic effect making it suitable for tachycardic and hypotensive patients.

Adrenaline: It is a catecholamine with alpha and beta activity. It has inotropic and vasodilator effect at low doses. The alpha-1 effect intensifies at high doses, producing systemic and pulmonary vasoconstriction. High doses should be avoided due to tachycardic effect.

Dopamine: It has beta, alpha and dopaminergic inotropic effect. At low doses (up to 3 μg/kg/min) it has do-

paminergic effect (diuretic) but no systemic vasoconstrictor effect. At higher doses, beta-1, beta-2 and alpha-1 peripheral vasoconstrictor effect is expressed, increasing systemic blood pressure.

Vasopressin: It binds to the specific V1-vascular vasopressin membrane receptors (AVPR1A) in the vascular smooth muscle and stimulates protein kinase C activation as a second messenger, increasing intracellular free calcium concentration and consequently vascular smooth muscle contraction. It is used as a second-order drug when maximal doses of a sympathomimetic agent are reached and MAP increase is not achieved. In medical practice, vasopressin is added when targets with noradrenaline 0.5 μgr /kg/min are not attained. The dose varies between 0.01-0.04 units/min. It is ideal for patients who require increased blood pressure without producing higher tachycardia.

Phenylephrine: It has pure alpha-1 agonist activity thus resulting in vasoconstrictor effect without positive chronotropic effect. The dose is 0.1-0.5 μgr/kg/min.

Nitric oxide (NO): Inhaled NO is a potent, short half-life selective pulmonary vasodilator, without effect on systemic circulation allowing its use in patients with RV failure and hemodynamic instability. Reduction of pulmonary vascular resistance is essential in the treatment of acute pulmonary hypertension with severe RV failure that fails to compensate with inodilators. It is commonly used in ventilated patients, but may be administered by nasal cannula or facial mask. Prolonged administration at high concentrations may cause methemoglobinemia. Removal should be gradual as it may generate a sharp increase in pulmonary vascular resistance by rebound effect. It is an expensive tool and requires experienced handling.

Right ventricular mechanical circulatory support: Its use should be considered in an unstable patient under maximum inodilator and vasopressor doses; its use also allows reducing their doses to attenuate RV ischemic and metabolic insult. Veno-arterial ECMO is a useful tool in PE due to the combination of RV failure associated with hypoxemia. It is an expensive, partial assistance device with short life span, (from 7 to 14 days) that may provide support of up to 4.5 liters ensuring better oxygenation. It may be central (by sternotomy) placed in the operating room or peripheral (by puncture) and available at the patient's bedside. ECMO is not indicated if clotting disorder is present because it requires full anticoagulation. Some authors have obtained good results using this method as bridge to reperfusion by surgical thrombechtomy or endovascular hemodynamics intervention, or as bridge to recovery or long-term care.

Moderate (Levitronic) or long-term (Thoratec, Aviomed) RV or biventricular assist devices are reserved for those patients who require a longer period of time to recover. They are not indicated in patients with severe multiorganic failure and terminal illnesses or neurological disorders.

Table 5. Useful inotropic and vasopressor drugs for hemodynamic instability management

Drug	Mechanism of action	Dose
Adrenaline 1mg ampoule	α- and β-adrenergic agonist	0.1 to 0.5 μg/kg/min (7 to 35 μg/min)
Dobutamine 250 mg ampoule	β1-adrenergic agonist with mild β2 and α effect	5 a 10 μg/kg/min
Dopamine 200 mg ampoule	α1- and β1-adrenergic agonist with mild β2 effect and dopaminergic effect	5 to 10 μg/kg/min
Phenylephrine: 10 mg ampoule	α1-adrenergic agonist	0.1 to 0.5 μg/kg/min
Milrinone 10 mg ampoule	phosphodiesterase III inhibitor	0.375 to 0.75 μg/kg/min Dose adjustment in renal failure
Noradrenaline 4 mg ampoule	α1- and β1-adrenergic agonist without β2 effect	0.1 to 0.5 μg/kg/min (7 to 35 μg/min)
Vasopressin 20 IU ampoule	V1 vascular receptor agonist and protein kinase C activation	0.01 to 0.04 units/min

Treatment of respiratory failure.

Hypoxemia: V/Q mismatch and shunt are the main mechanisms involved in PE hypoxemia. Vasoconstriction in alveolar hypoxia is a physiological response that seeks to redistribute pulmonary flow to better ventilated areas of the lung. There are non-perfused ventilated alveolar areas and non-ventilated perfused areas. The inability

to correct hypoxemia with supplemental oxygen reveals the existence of venous left-to-right shunt through the heart, the lungs, or both. When hypoxia is widespread, diffuse pulmonary arterial vasoconstriction arises resulting in pulmonary hypertension worsening that generates greater RV claudication.

Hypercapnia: The pulmonary vasoconstrictor effect of hypercapnia has been known for some time. The rise in CO2 may significantly increase pulmonary vascular resistance and pulmonary arterial pressure, leading to reduced cardiac output and increased RV end-diastolic volume.

Mechanical respiratory assistance (MRA): Firstly, two important aspects should be considered. One is related to sedation at the moment of patient intubation; this should be made with caution avoiding intravenous bolus which may precipitate shock or generate irreversible hypotension due to RV ischemia and cardio-respiratory arrest.

Endogenous adrenergic discharge secondary to hypoxemia maintains blood pressure and this compensating mechanism may be interrupted with sedation. The other aspect is related to the fact that the administration of positive airway pressure may further increase pulmonary artery pressure precipitating RV claudication and eventually worsening hypoxemia by increased intracardiac right to left shunt, in addition to reducing venous return to the RV by increased intrathoracic pressure.

In our opinion patients should be ventilated when they present: 1) severe shock refractory to hemodynamic support with optimal doses of inotropic drugs and adequate RV preload and 2) respiratory failure with refractory significant hypoxemia (PaO2/FiO2 <200). Non-invasive ventilation should not be indicated in this group of patients. It is strongly recommended to avoid high tidal volumes and high positive expiratory pressure (PEEP).

Some authors recommend controlling plateau pressure, keeping it, if possible, below 28 cm H2O and to avoid PEEP over 5 cm H2O, since PEEP is useful in recruiting alveoli previously closed without over-distending the healthy lung. Over-distension unnecessarily increases pulmonary vascular resistance impairing lung function, with consequent RV depression resulting in greater decrease of cardiac output.

Hyperventilation may be used to lower pulmonary artery pressure (e.g. acidosis induced vasoconstriction). In these cases it is desirable to control airway pressure and flow-time curves to avoid lung hyperinflation that may be induced by high frequencies.

In patients with refractory hypoxemia, use of venovenous ECMO and in case of hemodynamic instability venoarterial ECMO may be considered in experienced centers.

Low-risk PE

Patients with the best prognosis are those that have none of the risk variables that define high-risk or intermediate-risk PE, i.e. they are hemodynamically stable patients without dilatation or RV dysfunction, with no elevation of myocardial damage biomarkers or electrocardiographic changes of risk. They define a subgroup with a mortality rate close to 1%. The use of clinical scales such as PESI or sPESI (simplified PESI) and tomographic risk predictors are very useful and have been widely validated. The highest PESI value identifies low-risk patients. (15-17)

The treatment begins with parenteral anticoagulant administration, usually LMWH for at least five days together with vitamin K antagonists (VKA) to reach a target INR between 2 and 3. Due to the different half-lives of circulating factors, the anticoagulant effect is not achieved before 4-7 days of treatment.

Although VKA may be used from day one, their use is recommended with parenteral ATCG for 48 to 72 hours.

New oral anticoagulants could be considered in this subgroup of patients provided they have the proper clinical conditions (creatinine clearance >30ml/min, no liver failure, medication affordability, good adherence, no active cancer, pregnancy or use of concomitant double antiplatelet therapy). (Figure 4)

Intermediate-risk PE

The current PE definition involves intermediate-risk patients with systolic blood pressure >90 mmHg, presenting one or more risk variables (See Table 2).

However, only hemodynamic instability has demonstrated to have prognostic value. Early PE mortality is caused by acute RV failure and cardiogenic shock. (18) The risk of death during hospitalization is subsequently determined by recurrent embolism and baseline disease or pre-existing medical condition. The primary objectives are early reperfusion to relieve pressure overload on the RV, prevention of recurrent thromboembolic events and improvement of RV function.

The combined use of different variables has shown greater prognostic value.

Fibrinolytic treatment in intermediate-risk PE

Most patients with intermediate-risk PE only treated with anticoagulant therapy have a favorable outcome and a mortality rate close to 3%, so the benefit of fibrinolytic therapy would be eventually neutralized by the risk of bleeding. The rate of major bleeding in different trials is 20%, while that of fatal intracerebral hemorrhage is from 2 to 5%. (19)

To date, no study has shown mortality reduction in intermediate-risk PE. (20) In recent years, several meta-analyses have shown a trend to reduce early mortality in high-risk and intermediate-risk PE, at the expense of a major risk of bleeding, in patients below 65 years of age. (21)

Fibrinolytic therapy is not routinely indicated in intermediate-risk PE. The greatest benefit is obtained in patients under 75 years with RV severe dysfunction in addition to major risk factors: severe persistent hypoxemia (oxygen saturation <90%), elevated troponin levels, a tendency to hypotension, incipient hemodynamic instability or clinical or sub-clinical signs of shock (oliguria, poor peripheral perfusion and persistent tachycardia >110x').

In these patients with multiple variables of adverse prognostic risk, anticoagulation strategy alone, particularly if the patient has low risk of bleeding, exposes him to high mortality shock. Therefore, in this scenario a more effective reperfusion therapy with thrombolytics or thrombectomy (surgical or hemodynamic) should be considered. Patients with mild RV dilatation plus some risk variable theoretically would not be candidates for thrombolytic therapy; they should be re-evaluated closely for signs of incipient instability to consider reperfusion therapy.

The PEITHO study (22) compared tenecteplase (TSE) plus LMWH vs. LMWH alone in normotensive patients with RV dysfunction or dilatation on echocardiography or CT scan and biomarkers of myocardial damage (troponin T or troponin I). It was observed that the mortality rate was 1.2% in the thrombolytic group and 1.8% in the control group while the rate of intracranial hemorrhage was 2% in the thrombolytic group vs. 0.2% in the control group.

In this study, the combined endpoint of death and hemodynamic collapse was reduced within 7 days with an absolute primary end-point reduction of 5.6% vs. 2.6%; RR 3%. In the control group, 3.4% of patients that received only anticoagulation (17/500) presented with clinical instability requiring thrombolytic therapy, suggesting that in these patients, anticoagulation strategy alone may be appropriate in a significant percentage of patients. An increased risk of intracerebral hemorrhage was seen in the PEITHO study in patients over 75 years with full dose TSE. It is noteworthy that the patients included in this study were not high risk patients, as evidenced by the mortality observed in the control group (1.8%).

The MOPETT trial (23) was a small study that enrolled intermediate-risk PE patients. Half-dose alteplase (50 mg) and LMWH vs. LMWH alone was used. Reduced pulmonary artery pressure and recurrent PE was observed at 28-month follow-up without significant increase in bleeding.

The TOPCOAT study (24) was another small study comparing TSE with LMWH in patients with intermediate-risk PE. In this study, in-hospital outcome assessed at 50 days and 3-month follow-up revealed reduced hospital stay and improved SF-36 quality of life survey.

In the last years, evidence has emerged on the usefulness of endovascular treatment in intermediate-high-risk PE and the possibility of using smaller doses of local fibrinolytics with potential lower risk of bleeding. The ULTIMA study (25) (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) included 59 patients with symptomatic PE, with CT evidence of at least one main branch or proximal lower lobe pulmonary artery embolism and RV/LV dimension ratio ≥1 obtained from echocardiographic apical 4-chamber view. It showed that fibrinolytic therapy with 10 to 20 mg rtPA by local catheter-guided infusion during 15 h vs. LMWH anticoagulation alone significantly reduced the RV/LV ratio within 24 hours without increased bleeding risk.

The SEATTLE I study was a retrospective safety and efficacy study of low-dose catheter-guided fibrinolytic treatment. The SEATTLE II study (26) was a prospective, single-arm, multicenter trial evaluating the efficacy of catheter-guided local thrombolytics in 150 patients with high-risk (20%) and intermediate-risk (80 %) PE. Mean preprocedural RV/LV dimension ratio was 1.55 vs. 1.13 48 hours after the procedure ($p < 0.0001$). (Figure 4)

The most widely used fibrinolytics in our setting are streptokinase: 1.5 million IU during 2 hours without concomitant intravenous heparin and with alteplase (rtPA): 100 mg infused during 2 hours or in cases of imminent hemodynamic collapse 0.6 mg/kg for 15 min (maximum dose 50 mg). Concomitant sodium heparin may or may not be considered according to bleeding risk when the rtPA option is adopted.

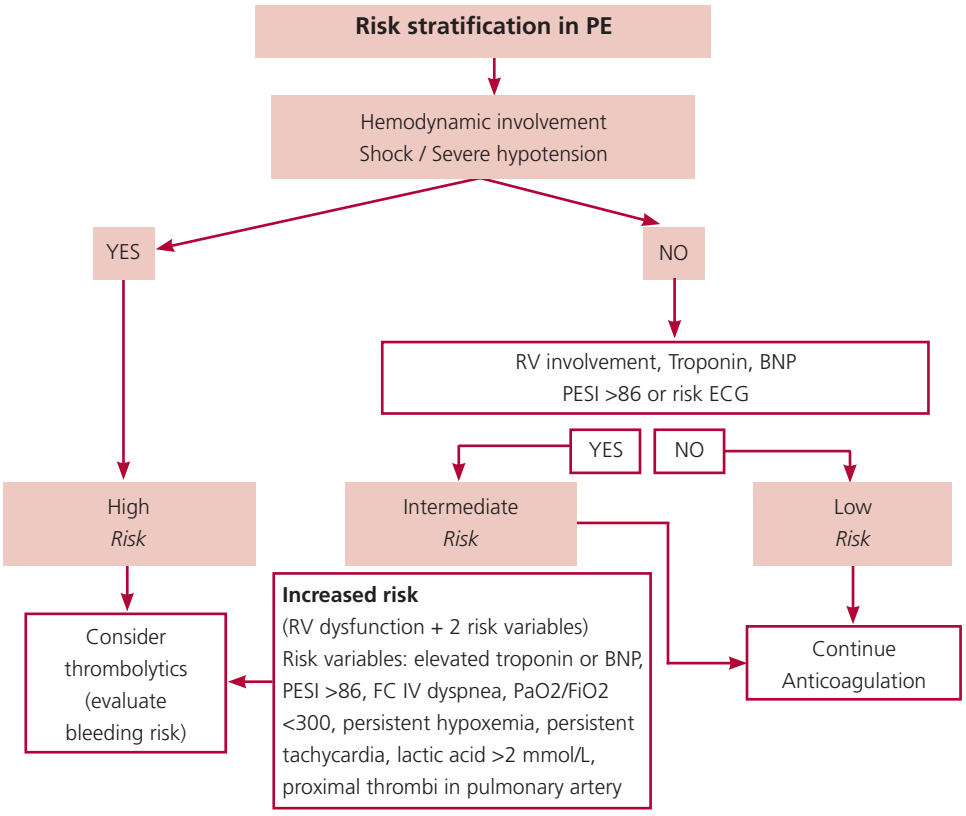

Fig. 4. Initial diagnostic algorithm in a patient with suspected pulmonary embolism and hemodynamic involvement.

Bleeding risk assessment

The use of anticoagulants or thrombolytics involves the identification of patients at increased risk of bleeding. The benefit of fibrinolytic therapy in intermediate-risk PE appears to be less than in high-risk PE due to the elevated risk of major bleeding, especially in patients >65 years. (27)

Currently, we do not have adequately validated scales to assess bleeding risk with thrombolytics, (28, 29) so we have extrapolated data from scales of bleeding risk with anticoagulation. The RIETE registry (30) included mainly patients with DVT but also with PE and classified them into low, intermediate and high risk of bleeding according to the score obtained. The other scale that may be used is that of the American College of Chest Physicians that also divides patients into low, intermediate or high risk of bleeding. Age over 75years alone should be considered as high risk.

Indication of thrombolytics for intermediate-risk PE (in the absence of contraindications) should be considered in patients who present with RV/LV ratio >0.9 by CT scan or echocardiography plus the addition of at least two risk variables (this type of PE is identified as intermediate-high-risk): elevated troponin, BNP or NT-proBNP

Table 6. Risk of bleeding stratification. Modified RIETE score

Modified RIETE score for risk of bleeding	
Variable	**Score**
Recent major hemorrhage (one month)	2.0
Creatinine>1.2mg/dL	1.5
Anemia	1.5
Cancer	1
Age >75 years	5
Low-risk: 0; Intermediate-risk: 1-4; High-risk: >4	

and severe persistent hypoxemia. There are other variables indicating imminent hemodynamic collapse among which we suggest considering: PaO2/FiO2 <300, lactic acid >2 mOsm/L, oxygen saturation of central venous catheter <70%, SBP/HR index >1, and central thrombus in the pulmonary artery. The presence of low to intermediate risk of bleeding, according to the scores, should also be considered. Patients at high risk of bleeding for the use of thrombolytics would be candidates for reperfusion by surgical thrombectomy or by hemodynamic intervention. In our field, this last option is the most advisable considering that surgery requires an experienced surgical team to perform it.

Beyond the already mentioned variables suggestive of hemodynamic collapse, we stress the importance of requesting and interpreting them in the patient's clinical context. The clinical view of the treating physician is of vital importance when an auxiliary diagnostic method is requested as well as when deciding a therapeutic conduct.

General measures and pharmacological treatment

General measures:

In patients with PE/DVT early ambulation is recommended, insofar as it is tolerated and there is no risk clinical condition (extensive iliofemoral thrombosis, mobile thrombus, and clinical or hemodynamic instability). In extensive thrombosis and/or moderate- and high-risk PE, ambulation is recommended from the 5th to 7th day of anticoagulation onset. The use of graduated calf compression socks exerting pressure of 20 mmHg is recommended to reduce the risk of post-thrombotic syndrome.

Anticoagulant therapy

Anticoagulant therapy is similar for DVT and PE as both are manifestations of the same disease known as venous thromboembolic disease (VTE). However, patients with PE have significantly higher mortality, and its recurrence is three times higher in those who have already suffered it.

Anticoagulation is intended to interrupt the progression of thrombotic phenomena while endogenous fibrinolysis acts on already formed thrombi.

In patients with high clinical suspicion of TD, and in the absence of contraindications, it is suggested to start treatment as early as possible until diagnosis may be reliably rejected or confirmed. (Class IC)

If clinical suspicion is intermediate and results are delayed more than 4 hours, it is suggested to start with anticoagulant therapy. IIaC

If clinical suspicion is low, patient treatment is not suggested while awaiting the results of diagnostic tests expected in the next 24 hours. IIaC

In patients with acute DVT of the lower limbs, early initiation of oral anticoagulants (the same day of parenteral anticoagulant onset) is recommended. Parenteral anticoagulation should be continued whenever possible, for a minimum of 5 days until INR ≥2, or for at least 24 hours. Ib

In patients with acute isolated DVT, LWMH, direct oral anticoagulants or fondaparinux instead of intravenous or subcutaneous unfractionated heparin, is suggested. IIa

In patients with acute proximal DVT and contraindication to anticoagulation, inferior vena cava filter is indicated. IB

In patients with PE, oral and parenteral anticoagulant therapy may be started simultaneously, maintaining the latter until INR ≥2 for at least 24 hours. IB

In patients with intermediate to high-risk PE who may be candidates for fibrinolytic therapy, catheter intervention or surgical embolectomy, unfractionated sodium heparin should be used to eventually discontinue it and minimize bleeding risk. IIB

Currently, an accelerated thrombolytic scheme is recommended. IIC

In patients with unprovoked high-risk PE, anticoagulation with enoxaparin is suggested for at least 3 or 4 weeks before rotating to oral administration. IIbC

Vena cava filters should be considered in patients with PE and absolute contraindication to anticoagulation and in those with recurrence despite anticoagulant therapeutic doses. IIaC

In patients in whom it is considered that PE recurrence may cause the patient's death (low cardiorespiratory reserve) it is reasonable to place a removable vena cava filter to overcome this condition. IIBC

In patients who have an inferior vena cava filter with no contraindication to anticoagulation, an optimal anticoagulation level should be ensured for the high risk of thrombosis generated by the device. IIaB

Removable vena cava filters in patients without contraindication to anticoagulation should be withdrawn before 15 or 30 days and once the clinical condition that led to its placement is overcome, due to the associated risk of complications (thrombosis, infection, device migration) coupled with the lack of long-term reduced mortality evidence. IIaB

Following withdrawal of removable inferior vena cava filter, anticoagulation with heparin during the subsequent 48-72 hours may be considered. IIbC

a. Unfractionated heparin (UFH)

Anticoagulation with UFH is the standard initial VTE treatment. The advantages of this biological drug are its short half-life, the inhibition of its anticoagulant effect by protamine and its low cost. Its disadvantage is that it requires constant monitoring. It has been shown that the greater the delay in obtaining adequate anticoagulation times, the greater the chance of thrombosis progression and also the increased possibility of recurrence. This is why it is recommended to achieve useful times within 24 hours of treatment initiation.

The treatment begins with an intravenous bolus of 5000 IU, followed by infusion of 15-18 IU/kg/hour. The aim is to rapidly reach 1.5 to 2.5-fold higher kPTT than the baseline value. It is recommended to control kPTT every 4 hours until the desired value is reached and then every 24 hours adjusting heparin dosing following a nomogram.

Unfractionated heparin treatment is not without complications such as bleeding. Another disadvantage is its variable effect through indirect antithrombin activity and binding to plasma proteins. An important complication observed in 1% to 3% of cases is immune thrombocytopenia which usually appears after the 5th day of treatment. Platelet count should be performed for its detection, and if it falls below 100000/mm^3, or to half the baseline value, treatment with heparin should be discontinued. This risk is somewhat lower when LMWH is used. Bivalirudin may be used in Argentina (not always accessible and expensive) as an alternative anticoagulant, especially in patients with severe kidney failure. It is administered as an initial bolus of 0.10 mg/kg followed by infusion of 0.10-0.25 mg/kg/hour, titrated to maintain kPTT twice the baseline value. The other drugs that may be used in immune thrombocytopenia are fondaparinux or NOACs (rivaroxaban, dabigatran and apixaban).

Unfractionated heparin remains the drug of choice for a certain group of patients (renal failure, morbid obesity and in the perioperative period) due to the possibility of rapid clearance (short half-life) and extrarenal metabolism. The use of heparin is not recommended in intermittent boluses as it greatly increases the risk of bleeding.

b. Low molecular weight heparins (LMWH)

Low molecular weight heparins act on factor Xa and to a lesser extent on thrombin inhibition. Therefore, kPTT is not a suitable parameter to assess its activity. They have nearly 90% bioavailability and long half-life which makes them more predictable.(32) Therefore, except for some special situations (renal failure, pregnancy, extreme obesity) it is not necessary to monitor coagulation. If necessary, factor Xa may be measured at 4 hours of a subcutaneously administered dose. Therapeutic anti-Xa activity for VTE ranges between 0.6 and 1.2 IU/ml.

Low molecular weight heparins have lower incidence of autoimmune thrombocytopenia and osteoporosis. Their effectiveness is at least similar to UFH and in some studies was higher. In patients with cancer they are the treatment of choice during the first 3-6 months. (IIaB) They have the disadvantage of being eliminated almost exclusively via the kidneys and are only partially inhibited by protamine. Therefore, in patients with high risk of bleeding and/or significant renal impairment it is preferred to continue with UFH. Once LMWH is discontinued its effect ceases in about 24 hours.

The recommended doses are: nadroparin 86 IU/kg every 12 hours or 171 IU/kg every 24 hours and enoxaparin 1mg/kg every 12 hours or 1.5 mg/kg subcutaneously every 24 hours.

Pentasaccharides-Fondaparinux. It is an indirect anticoagulant drug, which as heparin acts potentiating antithrombin. But unlike heparin it is a synthetic product with absolute anti-Xa activity. It may be used as parenteral anticoagulant since the acute stage and it is an alternative treatment similar to LMWH. (IA) It is administered in 7.5 mg/day subcutaneous doses for the treatment of patients weighing 50 to 100 kg. In patients under 50 kg doses are 5mg/day and in patients over 100 kg, 10 mg/day. No laboratory controls are required and its half-life is 17 hours, allowing a single application per day. It has no specific antagonist and is as effective and safe as heparin in initial VTE treatment.

Direct oral anticoagulants (NOACs)

They are a valid anticoagulation alternative with vitamin K antagonists. (33) (IB)

Dabigatran (34), rivaroxaban (35), apixaban (36) and edoxaban (37)* are synthetic and specific antagonists against certain coagulation factors and they are approved for the treatment of VTE (*eledoxaban is in the process of approval by the ANMAT). Some advantages of these drugs are the possibility of avoiding the initial use of heparin (in the case of rivaroxaban and apixaban), no coagulation monitoring requirement, no generation of immune thrombocytopenia, a 2-hour onset of activity, no interference with food and rare interactivity with other drugs. Its half-life is short and it has hepatic and renal clearance. On the other hand they cannot be assessed with standard coagulation tests; thus, an element of great importance to assess bleeding, a new thrombotic event or to coordinate emergency surgery is lost. They also have no antidote and only prothrombin complex concentrates have been considered for factor Xa antagonists in case of severe bleeding, but with limited clinical experience, although these drugs seem to have less risk of bleeding.

Both rivaroxaban and apixaban may be used from the onset of the acute phase, albeit with a higher dose, and are an alternative to parenteral treatment associated with vitamin K antagonists.

Hemodynamic invasive treatment

The primary goal is to reduce RV acute pressure overload and to achieve patient hemodynamic stability. The most commonly used devices include catheters and balloons to fragment and displace the emboli, rheolytic lysis and extraction systems, thromboaspiration devices and combined systems for local administration of thrombolytics and mechanical lysis. In a review on the use of different fragmentation systems, use of mechanical lysis and/or aspiration in over 300 patients with massive PE showed that success rate, defined as the immediate improvement of the patient's hemodynamic status, was over 80% and mortality ranged from 0 to 25%, although in a high percentage of cases local or systemic fibrinolytics were also administered. (38) In a meta-analysis (39) of 594 patients in 6 prospective and 29 retrospective studies, where catheters for fragmentation, aspiration or thrombi rheolytic lysis were used with or without fibrinolytics, clinical improvement (hemodynamic stability, improved oxygenation and survival) was obtained in 87% of cases. The authors concluded that catheter thrombectomy is a relatively safe and effective treatment for acute massive PE (IIaC), further suggesting that in experienced centers it should be considered as a first-line treatment in these patients. In intermediate-risk PE, it may also be useful especially in patients with contraindications for thrombolytics, high risk of bleeding, or in whom it is presumed that due to symptom outcome (>14 days) systemic thrombolytic therapy is not effective for being out of the time window for lytic therapy. (IIbB)

Devices and Procedures

- Fragmentation and large proximal thrombi displacement: in the whole vascular anatomy the sum of the cross-sectional areas of peripheral derivation vessels is always higher than the cross-sectional area of the main vessel; therefore, thrombi fragmentation and displacement from proximal vessels to the distal bed allows reducing severe RV overload. The use of conventional or modified angiographic catheters and angioplasty balloons has been described with mixed results, and are the most used devices in our setting. The association of local fibrinolytics with endovascular mechanical treatment allows better results.
- Aspiration rotational embolectomy: there is limited experience with the use of devices capable of fragmenting thrombi through a rotational motion and aspirating and removing residues, which has been presented as an alternative therapy in patients with massive PE. In the most recent series of 16 patients with massive PE, thrombi removal was achieved in 94% of patients treated, with a significant mean pressure drop in the pulmonary artery.
- Aspiration embolectomy: thrombi aspiration using angioplasty catheters or sheaths without valve or cannulas connected to continuous aspiration systems has only been reported anecdotally.
- Rheolytic systems for fragmentation and aspiration: these systems facilitate thrombus maceration by injecting saline solution at high pressure and aspirating the residues, achieving an improvement in pulmonary artery pressure and in the Miller index score.
- Catheter-directed thrombolysis: there are currently two ways to deliver thrombolytics locally within a pulmonary embolus, through multi-perforated catheters or through an infusion catheter with a filament also capable of emitting ultrasonic waves, thus facilitating thrombus rupture and drug penetration.

Conflicts of interest

See author´s conflicts of interest forms in the web / Supplementary Material.

REFERENCES

1. Ubaldini J, Chertcoff J, Sampó E, Casey M, Ceresetto J, Boughen R y cols. Consenso de enfermedad tromboembólica. Consenso Argentino SAC. Rev Argent Cardiol 2009;77:411-28

2. Klok FA, Kruisman E, Spaan J, Nijkeuter M, Righini M, Aujesky D, et al. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. J Thromb Haemost 2008;6:40-4. http://doi.org/dfjwtc

3. Carrier M, Righini M, Djurabi RK, Huisman MV, Perrier A, Wells PS, et al. VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. Thromb Haemost 2009;101:886-92. http://doi.org/c2khwp

4. Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. Am J Respir Crit Care Med 2008;178:425-30. http://doi.org/bgn537

5. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007;116:427-33. http://doi.org/cjqx7t

6. Lankeit M, Jiménez D, Kostrubiec M, Dellas C, Hasenfuss G, Pruszczyk P, et al. Predictive value of the high-sensitivity troponin T assay and the simplified pulmonary embolism severity index in hemodynamically stable patients with acute pulmonary embolism: a prospective validation study. Circulation 2011;124:2716-24. http://doi.org/dbj636

7. Puls M, Dellas C, Lankeit M, Olschewski M, Binder L, Geibel A, et al. Heart-type fatty acid-binding protein permits early risk stratification of pulmonary embolism. Eur Heart J 2007;28:224-9. http://doi.org/cp6wxv

8. Toosi MS, Merlino JD, Leeper KV. Electrocardiographic score and short-term outcomes of acute pulmonary embolism. Am J Cardiol 2007;100:1172-6. http://doi.org/c8fk86

9. Escobar C, Jiménez D, Martí D, Lobo JL, Díaz G, Gallego P et al. Prognostic value of electrocardiographic findings in hemodynamically stable patients with acute symptomatic pulmonary embolism. Rev Esp Cardiol 2008;61:244-50. http://doi.org/fm36xk

10. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. 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) Authors/Task Force Members: Stavros Konstantinides (Chairperson) (Germany/Greece), Adam Torbicki (Co-chairperson) et al. ESC Committee for Practice Guidelines. European Heart Journal. http://doi.org/9vr

11. Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170:1383-9. http://doi.org/dmn7ps

12. Stein PD, Fadi Matta F. The Treatment of Unstable Pulmonary Embolism in the Elderly and Those with Comorbid Conditions. Am J Med 2013;126:304-10. http://doi.org/f2wv6v

13. Marti C, John G, Konstantinides S, Combescure C, Sanchez O, Lankeit M, Meyer G, Perrier A. Systematic throbolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 2015;36:605-14. http://doi.org/9vs

14. Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, et al., for the RIETE investigators. Simplification of the Pulmonary Embolism Severity Index for prognosticating patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170:1383-9. http://doi.org/dmn7ps

15. Binder L, Pieske B, Olschewski M, Geibel A, Klostermann B, Reiner C, et al. N-terminal pro-brain natriuretic peptide or troponin testing followed by echocardiography for risk stratification of acute pulmonary embolism. Circulation 2005;112:1573-9. http://doi.org/bf7dwf

16. Palmieri V, Gallotta G, Rendina D, De Bonis S, Russo V, Postiglione A, et al. Troponin I and right ventricular dysfunction for risk assessment in patients with nonmassive pulmonary embolism in the Emergency Department in combination with clinically based risk score. Intern Emerg Med 2008;3:131-8. http://doi.org/c23mbh

17. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172:1041-6. http://doi.org/dvpgd2

18. Jiménez D, Uresandi F, Otero R, Lobo JL, Monreal M, Martí D, et al.Troponin-based risk stratification of patients with acute nonmassive pulmonary embolism: systematic review and metaanalysis. Chest 2009;136:974-82. http://doi.org/d5n3zt

19. Konstantinides S, Marder VJ, Thrombolysis in venous thromboembolism. In: Colman RW, Marder VJ, Clowes AW, George JN, Goldhaber SZ, editors. Hemostasis and thrombosis. Philadelphia: Lippincott Williams and Wilkins, 2006;13:17-29. http://doi.org/d9z6xm

20. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation 2004;110:744-9. http://doi.org/trc

21. Chatterjee S, Chakraborty A,Weinberg I, Kadakia M, WilenskyRL, Sardar P, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage. A meta-analysis. JAMA 2014;311:2414-21. http://doi.org/9vt

22. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402-11. http://doi.org/9vt

23. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol 2013;111:273-7.

24. Kline JA, Nordenholz KE, Courtney DM, Kabrhel C, Jones AE, Rondina MT, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo controlled randomized trial. J Thromb Haemost 2014;12:459-68. http://doi.org/9vv

25. Kucher N, Boekstegers P, Müller OJ, KupattC, Beyer-Westendorf J, Heitzer T, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479-86. http://doi.org/9vw

26. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM.A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism. SEATTLE II. JACC: Cardiovasc Intervent 2015,8:1382-92. http://doi.org/9vx

27. Mikkola KM, Patel SR, Parker JA, Grodstein F, Goldhaber SZ. Increasing age is a major risk factor for hemorrhagic complications after pulmonary embolism thrombolysis. Am Heart J 1997;134:69-72. http://doi.org/cpvh2k

28. Klok FA1, Niemann C, Dellas C, Hasenfuß G, Konstantinides S, Lankeit M. Performance of five different bleeding-prediction scores in patients with acute pulmonary embolism. J Thromb Thrombolysis 2015 Jun 20. [Epub ahead of print]

29. Curtis GM, Lam SW, Reddy AJ, Bauer SR. Risk factors associated with bleeding after alteplase administration for pulmonary embolism: a case-control study. Pharmacotherapy 2014;34:818-25. http://doi.org/9vz

30. Ruíz-Giménez N, Suárez C, González R, Nieto JA, Todolí JA, Samperiz AL, et al., RIETE Investigators. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. Thromb Haemost 2008;100:26-31

31. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:419S-94S.
32. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism. A meta-analysis of randomized, controlled trials. Ann Intern Med 2004;140:175-83. http://doi.org/9v2
33. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2014;12:320-8. http://doi.org/9v3
34. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009; 361:2342-52. http://doi.org/dsm8kh
35. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363: 2499-510. http://doi.org/dg8w5c
36. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013; 369:799-808. http://doi.org/9v4
37. Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406-15. http://doi.org/9v5
38. Skaf E, Beemath A, Siddiqui T, Janjua M, Patel NR, Stein PD. Catheter-tip embolectomy in the management of acute massive pulmonary embolism. Am J Cardiol 2007;99:415-20. http://doi.org/9v5
39. Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and metaanalysis of modern techniques. J Vasc Interv Radiol. 2009;20:1431-40. http://doi.org/bhc2c3