CONSENSUS STATEMENT ON THROMBOEMBOLIC DISEASE

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1. GRADES OF RECOMMENDATION

Class I: conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful, and effective.

Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: usefulness/efficacy is less well established by evidence/opinion.

2. LEVELS OF EVIDENCE

Level of evidence A: consistent evidence from randomized clinical trials or meta-analyses.

Level of evidence B: data derived from a single randomized trial.

Level of evidence C: data derived from consensus opinion of experts, retrospective studies or registries.

3. BACKGROUND

Pulmonary embolism (PE) is one of the most frequent causes of death in hospitalized patients and constitutes a clinical presentation of thromboembolic disease or venous thromboembolism together with deep venous thrombosis (DVT). (1) The risk of post-thrombotic syndrome, pulmonary hypertension and recurrences of thromboembolic events exists after the acute phase.

Thromboembolic disease is the third cause of cardiovascular morbidity after ischemic heart disease and cerebrovascular disease. The annual incidence is about 100 cases per 100000 person-years and the prevalence in hospitalized patients is 1%. In 1975, Dalen et al. (1) summarized the natural history of venous thromboembolism on the basis of several epidemiological factors and pathological findings. Most deaths which occur in the first hours (Figure 1) can be prevented by prophylaxis. For patients who have received treatment, mortality ranges from 6% to 10%, and reaches 25% - 30% in those cases without diagnosis and treatment. Currently, these figures are similar to those published in 1975, demonstrating that little progress has been achieved in the early diagnosis of this disease. About 70% of cases are still not diagnosed. This situation strengthens the need to improve prevention measures and to intensify early diagnosis strategies starting by a change in physicians' attitudes, as the clinical suspicion of the disease is the first link in this chain. (2)

4. PHYSIOPATHOLOGICAL CONSIDERATIONS

The severity of embolic obstruction depends on the embolus size; in this way, symptomatic embolism usually arises from thrombi originating in the deep venous system of the lower extremities, especially from the iliac and femoral veins. They rarely originate in the pelvic or upper extremity veins, inferior vena cava or the right heart chambers.

Emboli located proximally or producing severe vascular obstruction are associated with severe hemodynamic compromise, which has an inverse correlation with the cardiopulmonary reserve. In occasions, friable thrombi are likely to be fragmented by the pulsatile flow of blood in smaller thrombi that can travel more distally, occluding smaller vessels in the lung periphery where the section area is greater, producing less hemodynamic impairment. More than 50% of pulmonary emboli are multiple, and the lower lobes are involved more commonly than the upper lobes, unilaterally or bilaterally. (3)

Smaller thrombi are lodged directly in the lung periphery producing less hemodynamic impact; they are more likely to produce pleuritic chest pain by initiating an inflammatory response adjacent to the parietal pleura that does not necessarily imply a pulmonary infarction.

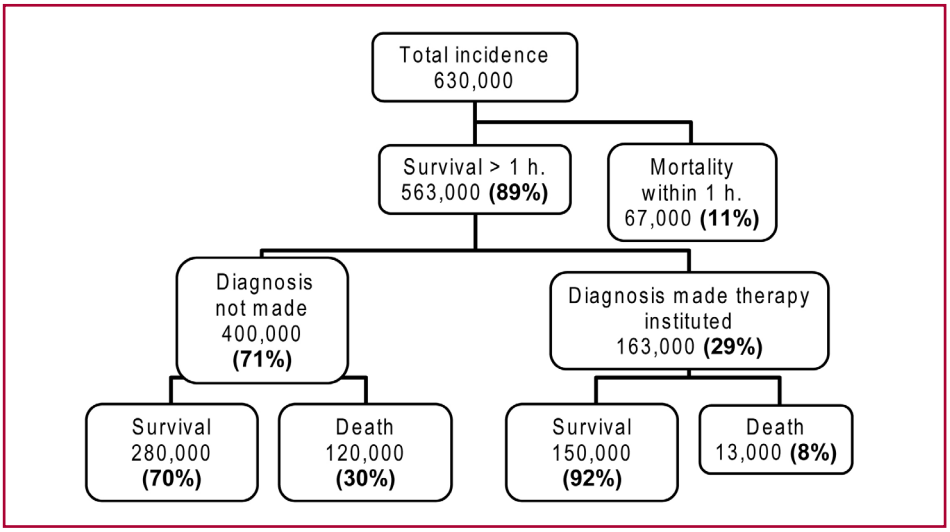

Fig. 1. Incidence of pulmonary embolism per year in the United States.

Larger thrombi may be temporarily trapped in the right atrium or among the tendinous cords of the tricuspid valve and the papillary muscles of the right ventricle (thrombi in transit) and can be detected by echocardiography. (4)

Thrombi in transit may pass through a patent foramen ovale from the right atrium into the left atrium and thus embolize to the arterial circulation. This migration is facilitated by the increased right atrium pressure in the presence of pulmonary hypertension induced by previous pulmonary embolisms.

5. RISK FACTORS

The primary and secondary known risk factors are related to traditional Virchow's triad described in the 19th century (venous stasis, hypercoagulability and endothelial injury); the most important factors are summarized in Table 1.

Although the genetic predisposition for thrombosis is relatively frequent, the real incidence in our environment is unknown. Unexplained DVT should be suspected in persons < 40 years with recurrent PE or DVT and/or a positive family history. (6)

The incidence of thrombotic events increases with the age until the 8th decade and is more frequent in men than in women.

Recurrences are also more frequent in men.

Thromboembolic disease has been reported in 30 - 60% of patients with stroke, 5- 35% of patients with acute myocardial infarction and 12% of patients with congestive heart failure who did not receive prophylaxis.

Immobilization during short periods of time (> 3 days) predisposes to DVT. The incidence of DVT after a simple surgery of inguinal hernia is about 5% and increases to 15% - 30% after major abdominal surgeries, 50% - 70% in hip surgeries and 50% - 100% in severe spinal cord injuries.

It should be noted that 25% of postoperative embolisms may occur after hospital discharge.

Approximately 70% - 90% of thrombi are located in the inferior vena cava, especially at the level of the femoral or iliac veins. Some recent studies have shown that the compromise of the pelvic veins (periprostatic or periuterine veins) has increased.

In 10% - 20% of cases, thrombi originate in the territory of the superior vena cava and are generally associated with diagnostic and therapeutic invasive procedures (insertion of catheters, pacemakers, chemotherapy, etc).

Table 1. Risk factors (5)

Primary risk factors	Secondary risk factors
Antithrombin III deficiency	Trauma
Anti-cardiolipin antibodies	Bed rest (>3 days)
Factor V Leiden	Surgery
Prothrombin 20210 mutation	Stroke
Protein C deficiency	Increasing age
Protein S deficiency	Heart failure
Factor XII deficiency	Chronic obstructive pulmonary
Fibrinogen deficiency	Malignancy
Plasminogen deficiency	Nephrotic syndrome
Hyperhomocysteinemia	Crohn's disease
	Prolonged travel
	Pregnancy/puerperium/oral contraceptive therapy

6. PREVENTION OF DVT (7-10)

The information provided by registries from many countries demonstrates that 50% of patients at risk for DVT do note receive prophylaxis at all or receive ineffective prophylaxis.

6.1 DVT prophylaxis strategies (Table 2)

The methods used for DVT prophylaxis are mechanical or pharmacological. The latter have been extensively studied and are the first indication. Mechanical methods are used when the pharmacological strategies are contraindicated or are associated with them in cases of greater risk.

a. Mechanical methods

These methods are used very little in our environment despite their relatively proved usefulness. Several ongoing studies are evaluating them. Mechanical methods are not as effective as pharmacological methods; for this reason, pharmacological prophylaxis should be initiated again once the risk of complications has disappeared.

- Intermittent pneumatic compression

The way intermittent pneumatic compression (IPC) exerts its action is not completely clear. Some authors think that it increases the blood flow in the lower extremities veins. Another explanation is the release of fibrinolytic substances due to venous walls compression.

- Graduated compression stockings

Graduated compression stockings (GCS) exert a decreasing degree of pressure that is greatest at the ankle and reduces further up the leg, thus increasing the venous return. They offer adequate prophylaxis for moderate-risk patients and may be combined with pharmacological methods in high-risk patients.

Graduated compression stockings have some limitations: a) there is no evidence that their use reduces the risk of lethal PE; b) there is little experience in patients not undergoing surgery; c) they are not well-tolerated

in occasions; and, d) they should be used with care in patients with lower limb ischemia.

They are very useful to prevent recurrences and post-thrombotic syndrome. All patients with thromboembolic disease should wear graduated compression stockings from the moment they start to walk and for two years.

b. Pharmacological methods

- Subcutaneous unfractionated heparin (UFH)

Subcutaneous UFH is the method most often used for DVT prophylaxis.

Prophylaxis with subcutaneous UFH increases the risk of postoperative hematomas but not of major or lethal bleeding. The contraindications to heparin therapy are: previous bleeding disorders, active bleeding and conditions with potential risk for increased bleeding (active ulcer, esophageal varices, severe hypertension, infective endocarditis). Heparin administration should be delayed for a couple of hours after epidural anesthesia. Heparin-induced thrombocytopenia may occur in 0.3% of patients under prophylaxis.

The recommended dose is 5000 units every 12 hours for low-risk patients and every 8 hours for intermediate-risk patients.

Prophylaxis with UFH remains the drug of choice in patients with kidney failure and in elder patients > 75 years.

A complete blood count including platelet count should be taken in all patients before receiving heparin of any kind (UFH, LMWH, etc.). An additional platelet count should be performed 24 hours after starting heparin therapy, on the 4th day, and then every 2 to 4 days until the end of treatment in patients who have received heparin within the last 100 days.

- Low-molecular-weight heparin (LMWH)

Low-molecular-weight heparin has important advantages: 1) once-daily dosing; 2) lower incidence of bleeding complications; and, 3) smaller risk of heparin-induced thrombocytopenia.

Some studies have demonstrated the superiority of LMWH over UFH, especially in high-risk patients.

However, its high cost is the most important disadvantage.

Table 2 details the dose of the drugs more frequently used.

-Pentasaccharides

Pentasaccharides are selective inhibitors of activated factor X. Fondaparinux has been recently incorporated to our environment (Table 2).

One daily subcutaneous injection of a pentasaccharide is more effective than LMWH for the treatment of DVT, especially in patients undergoing major orthopedic surgery. The advantages of fondaparinux are: 1) as a pure factor Xa inhibitor it does not induce thrombocytopenia; 2) in orthopedic surgery the first dose is administered 6 to 24 hours after surgery, allowing for a proper evaluation of perioperative bleeding; and, 3) its relatively long half-life (17 hours).

Table 2. Dosage regime of the drugs most used in our environment

Low-molecular-weight heparin	Usual dosage for prophylaxis
Enoxaparin	40 mg s.c. once daily.
Nandroparine	3400 UAXa s.c. once daily.
Dalteparin	5000 U s.c. once daily.
Pentasaccharides	
Fondaparinux	2.5 mg s.c. once daily.

There is no specific antagonist against fondaparinux. It should not be used in patients with a creatinine clearance < 30 ml/min.

- Oral anticoagulant agents

Coumarin therapy has proved to be effective in patients at moderate and high risk for DVT. Warfarin has been extensively investigated and used in low and escalation dose and should only be recommended for prolonged prophylaxis maintaining an INR between 2 and 3.

New oral anticoagulant agents: three new drugs are currently under investigation. Dabigatran is a direct thrombin inhibitor that is currently available in our environment. Both apixaban y rivaroxaban are Factor Xa inhibitors in the most advanced stages of development.

The dose of dabigatran for DVT prophylaxis is 220 mg once daily. The recommended initial dose of dabigratan is 110 mg given within the first 4 hours postoperatively, followed then by a daily dose of 220 mg.

It should not be used in patients with a creatinine clearance < 30 ml/min.

There is no specific antagonist against dabigatran.

- Antiplatelet agents

Acetyl salicylic acid (ASA), dipyridamole and ticlopidine are not effective and thus not recommended to prevent DVT.

The prevention of DVT in patients undergoing surgery is based on different risk factors, as shown in Table 3.

6.2 General recommendations for prevention of DVT (10)

Class I

Prophylaxis is not recommended for low-risk patients < 40 yr undergoing minor surgery with immobilization < 3 days, or for low-risk medical patients< 40 yr hospitalized for < 3 days.

We suggest early and persistent mobilization (A).

We recommend against prophylaxis in patients undergoing laparoscopic surgery with no additional risk factors (A). (11, 12)

Table 3. Levels of thromboembolism risk in surgical patients without prophylaxis (9)

Level of risk	Calf	Proximal	Clínical	Fatal	Successful prevention strategies
Low risk Minor surgery in patients 40 yr with no additional risk factors	2%	0.4%	0.2%	< 0.01%	Early mobilization
Moderate risk Minor surgery in patients with additional risk factors Surgery in patients aged 40–60 yr with no additional risk factors	10-20%	2-4%	1-2%	0.1-0.4%	UFH (q12h) LMWH once daily GCS IPC
High risk Surgery in patients > 60 yr, or age 40–60 with additional risk actors (prior VTE, cancer, molecular hypercoagulability)	20-40%	4-8%	0.4-1%	0.4-1%	UFH (q8h) LMWH once daily Fondaparinux IPC
Highest risk Surgery in patients with multiple risk factors (age > 40 yr, cancer, prior VTE) Hip or knee arthroplasty, fracture surgery Major trauma; spine cord injury	40-80%	10-20%	4-10%	0.2-5	LMWH once daily Fondaparinux, UFH/ LMWH + IPC/GCS

UFH: Unfractionated heparin LMWH: Low-molecular-weight heparin IPC: Intermittent pneumatic compression GCS: Graduated compression stockings
Geerts, et al. Chest 2004;126:338S-400S.

Class I
- Low-molecular-weight heparin (A)
– Fondaparinux (A).
– UFH 5000 U bid for low-risk patients (A)
– UFH 5000 tid for high-risk patients (A).
– For patients with multiple clinical or surgical risk factors (highest-risk patients), we recommend UFH 5000 U tid or LMWH or fondaparinux plus mechanical prophylaxis with GCS or IPC(C).

We recommend consideration of renal impairment when deciding on doses that are cleared by the kidneys such as LMWH and fondaparinux. We suggest UFH in patients with a creatinine clearance < 30 ml/min or plasma creatinine level > 2.5 mg/dl

Class I
– Intermittent pneumatic compression (B)
– Graduated compression stockings (B).

We recommend that mechanical methods of prophylaxis be used primarily in patients in whom antithrombotic drugs are contraindicated or in those who are at high risk for bleeding.

We recommend against the use of aspirin alone as prophylaxis against VTE for any patient group (A).

6.3 Prophylaxis in special situations

a. Coronary care unit (13) *and cardiovascular surgery* (14)
Prophylaxis with antithrombotic agents is recommended in patients with decompensated heart failure, acute pulmonary edema and in patients with heart diseases who are not receiving anticoagulants and will be immobilized for more 3days.

Class I
– UFH, LMWH (B), fondaparinux (C).

The incidence of catheter-associated thrombosis is greater with fondaparinux than with enoxaparin. An estimated dose of 5000 U of UGH should be administered in patients undergoing cardiac catheterization.

For patients undergoing vascular surgery who do not have additional thromboembolic risk factors we suggest early and persistent mobilization.

For patients undergoing major vascular surgical procedures who have additional thromboembolic risk factors, we recommend prophylaxis with antithrombotic agents.

Class I
– UFH, LMWH (B), fondaparinux (C).

For patients undergoing cardiac surgery (coronary artery bypass graft surgery) or thoracic surgery we recommend prophylaxis.

Class I
- LMWH, UFH (C).
- IPC or GCS for patients with contraindications to antithrombotic agents (C).

b. Intensive care unit (15)

Patients admitted to a critical care unit with recent major surgery, major trauma, sepsis, stroke, congestive heart failure, respiratory failure, history of DVT, extensive burns or elder patients have multiple risk factors for DVT. Additional risk factors are acquired during hospitalization: prolonged immobilization, sedation or paralysis, central venous lines, mechanical ventilation, dialysis, etc. The incidence of DVT ranges between 10% and 90%, reflecting the great variability in the critically ill patients.

Class I
- UFH (A), LMWH (A), fondaparinux (A).
- Mechanical methods for patients with contraindications to antithrombotic agents (C).

c. Burn patients (16)

Burn patients are at increased risk for VTE because of the presence of a profound systemic hypercoagulable state, as well as prolonged bed rest, performance of repeated surgical procedures, venous catheter insertion, and recurrent bouts of sepsis.

Class I
- HUF (A), LMWH (A).

Class I
- We recommend the use of IPC or GCS when anticoagulant prophylaxis is contraindicated (A).

d. Spinal cord injury (17)

More than 50% of spinal cord injury (SCI) patients who are subjected to routine screening have DVT. Despite an increased awareness of DVT as a complication of SCI, PE remains the third leading cause of death and its incidence has not decreased in the recent years.

Prophylaxis with UFN, IPC and/or GSC alone has not proved to be effective. We recommend the use of LMWH alone or associated with mechanical methods.

Class I
- LMWH once primary hemostasis is evident (A).
- UHF combined with a mechanical method (B).
- We recommend mechanical prophylaxis in patients at high risk for hemorrhage or with spinal hematoma (C).

e. Major trauma (18)

Patients recovering from major trauma have the highest risk of developing DVT. Without prophylaxis, these patients have a DVT risk exceeding 50%, with PE being the third leading cause of death in those who survive beyond the first day of hospitalization.

Based on a variety of studies, factors that were associated with an increased risk of VTE include the following: spinal cord injury; lower extremity or pelvic fracture; need for a surgical procedure; femoral venous line insertion and prolonged immobility.

Class I
- LMWH once primary hemostasis is evident (A).
- We recommend mechanical prophylaxis in patients at high risk for bleeding until LMWH can be used safely(C).
- We recommend LMWH associated with a mechanical method in high-risk patients (B).

f. Neurosurgery (19)

Patients undergoing major neurosurgery are known to be at moderately increased risk of postoperative DVT and warrant the routine use of thromboprophylaxis. The risk factors for DVT in neurosurgery patients include intracranial surgery (rather than spinal surgery), active malignancy, more lengthy procedures, prolonged leg weakness, and advanced age. Patients with malignant brain tumors are at particularly high risk for DVT.

Class I
- IPC until LMWH or UFH can be used safely (B).
- LMWH or UFH given 12 to 24 hours following surgery.
- IPC + LMWH in high-risk patients.

g. Hip surgery (11)

Patients undergoing hip arthroplasty are at particularly high risk for DVT, and the incidence of venographic DVT is 50%. The incidence of fatal PE is between 1.4% and 7.5% within 3 months after surgery.

LMWH and pentasaccharides are effective strategies, yet expensive, to prevent DVT. (20)

We recommend that these patients receive extended prophylaxis for up to 28 to 35 days after surgery. The recommended options include fondaparinux, LMWH or oral anticoagulant agents

Class I
- Fondaparinux 2.5 mg started 6 to 24 hours after surgery (A).
- LMWH. LMWH can be started 12 h before surgery or 12 to 24 h after surgery (A).
- We recommend mechanical prophylaxis if anticoagulant prophylaxis is contraindicated because of a high risk of bleeding (A) and then start with antithrombotic agents alone or associated with mechanical methods in high-risk patients (C).

h. Cancer (11, 12)

Cancer is a systemic hypercoagulable state that increases the risk of VTE.

The pathogenic mechanisms of thrombosis in the patient with cancer involve a complex interaction between the tumor cells and the hemostatic system that produces activation of the coagulation system, inhibition of anticoagulant factors and fibrinolytic system, and vascular injury, leading to hypercoagulability. In addition, extrinsic factors such as surgery, chemotherapy and insertion of intravenous catheters play an important role.

Patients with cancer have a sixfold increased risk of VTE compared to those without cancer. Active cancer accounts for almost 20% of all new VTE events occurring in the general population. Cancer patients undergoing surgery have at least twice the risk of postoperative DVT and more than three times the risk of fatal PE than noncancer patients who are undergoing similar procedures.

Cancer is also an independent predictor of lack of response to prophylaxis.

i. Long distance travel (21)

We recommend the following general measures for long-distance travelers, whether by flight or by bus, who travel > 8 h: avoidance of constrictive clothing around the lower extremities or waist; avoidance of dehydration and frequent calf muscle stretching (Class I –C-). For high-risk patients we suggest the use of GCS (Class II -C-), or a single dose of LMWH, injected prior to departure (Class II -C-).

j. Extended prophylaxis

Some patients may require prophylaxis beyond the hospital stay:

- Patients with medical conditions or surgery patients that must stay in bed after hospital discharge should receive prophylaxis as long as immobilization lasts (Class I -A-).
- Patients undergoing complex orthopedic surgery: total hip replacement, total knee replacement (Class I -A-)
- Abdominal or pelvic cancer surgery patients (Class I -B-).

Extended prophylaxis is recommended for 2 to 4 weeks with any of the antithrombotic agents previously mentioned.

k. Prophylaxis and neuraxial analgesia

The use of extended postoperative neuraxial anesthesia is more frequent. Removal of an epidural catheter should be done when the anticoagulant effect is at a minimum (usually just before the next scheduled subcutaneous injection). Anticoagulant prophylaxis should be delayed for at least 2 h after spinal needle or epidural catheter removal.

7. DIAGNOSIS OF DVT (22)

The diagnosis of DVT based exclusively on clinical presentation is not reliable. More than 70% of DVT are asymptomatic and 50% of clinical diagnoses of DVT are wrong. Pain and edema are the most frequent yet unspecific findings. On the contrary, unilateral edema, the most specific clinical sign, is present in only 10% of patients. For these reasons, additional studies are necessary for diagnostic confirmation. In addition, unilateral edema may appear in lower extremity palsy in the absence of thrombosis.

Venography has been described as the gold standard method for the diagnosis of DVT; yet, it is an invasive strategy that is not readily available at all hospitals. The different methods for the diagnosis of DVT and their advantages, disadvantages, sensitivities and specificities are compared in Table 4.

High-speed multidetector computed tomography allows visualization of pulmonary arteries and of the entire venous system with same injection of contrast agent. However, radiation exposure is greater as more images are acquired. In this sense, the alarm has been raised, especially when young patients have to be studied.

8. DIAGNOSIS OF PE

8.1 Clinical presentation

The sensitivity and specificity of symptoms and signs of pulmonary embolism are low (table 5). Yet, the diagnosis of PE is strongly based on the clinical assessment (high, moderate or low clinical probability) that results from the combination of symptoms and signs suggestive of the condition.

Even considering their low predictive value, we should not forget that dyspnea, pleuritic pain, tachy-

Table 4. Methods for diagnosis of DVT

Method	Sensitivity	Specificity	Finantial cost	Desventajas
Venography	100%	100%	Low risk	Invasive Use of contrast agent
Doppler	66-90%	85-95%	Very low	Interobserver variability in its interpretation
LLHCT	95-100%	95-100%	Moderate risk	Use of contrast agent Performed with chest CT
MRI	90-97%	100%	High risk	Scarcely accessible

LLHCT: lower limb helical computed tomography scan. MRI: Magnetic Resonance Imaging.

pnea and tachycardia are the most frequent symptoms and signs. On the contrary, the presence of a fourth heart sound or an increased pulmonary component of the second sound is uncommon yet more specific. The clinical probability of PE is higher in the presence of greater number of symptoms and signs. Complementary tests do not modify the predictive value of clinical manifestations. (23)

Naturally, it is important to correlate the clinical presentation with the presence of risk factors.

The probability of PE is high in the presence of three clinical syndromes which may occur isolated or combined:

Acute unexpected dyspnea. These patients present sudden onset dyspnea, tachypnea and tachycardia. The electrocardiogram and chest X-ray may be normal. Dyspnea may be intermittent and thus may be absent when the patient is examined.

Hemoptisis and/or pleuritic pain. These patients usually present at least three of the following manifestations: pleuritic pain, dyspnea, hemoptisis and radiographic evidence of parenchymal infiltrates. Fever, pleural friction rub and leukocytosis may also be present and a diagnosis of pneumonia should be ruled out.

Cardiogenic shock. Cardiogenic shock is the critical manifestations of massive PE. Patients usually present some degree of loss of consciousness, anxiety, pronounced dyspnea, oppressive chest pain suggestive of myocardial infarction, increased pulmonary component of the second sound and signs of shock.

8.2 Routine laboratory tests (24)

Their usefulness is limited. Increased erythrocyte sedimentation rate and leukocytosis are nonspecific findings.

8.3 Chest X-ray

An abnormal chest X-ray has little value in patients with previous cardiac and respiratory conditions.

Table 6 shows the most common radiographic findings in patients with PE with no previous cardiac disease as described in the PIOPED I study.

8.4 Electrocardiogram

ECG findings depend on the level of pulmonary hypertension and on the presence of previous cardiac and pulmonary disease.

The PIOPED study included 117 patients with no previous cardiac and pulmonary disease. The ECG was normal in 30% of patients and 70% presented nonspecific abnormalities. Sinus tachycardia was the most frequent abnormality.

A S_1 Q_3 T_3 y S_1 S_2 S_3 pattern was described in less than 12% of patients. ST-segment and T-wave abnormalities were observed in 66% of patients. The presence of T-wave inversion in the anterior leads and acute RBBB correlated with the magnitude of PE, with an increase in pulmonary artery pressure and with the severity of right ventricular dysfunction. Occasionally, the magnitude and the morphology of ST-segment elevation in leads V1, V2 and V3 may mimic an anterior myocardial infarction. In fact, these changes represent right ventricular injury and ischemia.

The presence of acute changes in the ECG - arrhythmias, right bundle branch block, S1Q3 pattern or ST-segment changes - is associated with greater 30-day mortality (29% versus 11%).

Table 5. Diagnostic value of isolated symptoms and signs in pulmonary embolism*

Sign or symptom	Sensitivity (%)	Specificity (%)	PPV (%)	NVP (%)
Dyspnea	73	28	32	31
Pleuritic pain	66	41	34	66
Rales (crakles)	51	60	38	28
Fourth heart sound	24	86	45	29
Second heart sound	23	87	45	30

Modified from Stein, et al. Chest 1991;100:598-603.
*Patients with no pre-existing cardiac or pulmonary disease.
PPV: Positive predictive value. NPV: Negative predictive value.

Table 6. Chest radiograph abnormalities in PE patients

Abnormalities (n = 2.315)	%
Cardiomegaly	27
Pleural effusion	23
Elevated diaphragm	20
Prominent central	19
pulmonary artery	
Atelectasis	18
Interstitial infiltrate	17
Pulmonary congestion	14
Decreased pulmonary 8	
vascularity	
Pulmonary infarction	5
Hyperinflation	5

8.5 Arterial blood gases and alveolar-arterial O_2 gradient

Pulmonary embolism is generally associated with hypoxemia, hypocapnia, respiratory alkalosis and increased alveolar-arterial O_2 gradient. This combination is suggestive of PE in the absence of any alternative diagnosis.

However, a normal PaO_2 does not exclude the diagnosis of PE.

In massive PE with shock and ventilatory failure, hypercapnic respiratory acidosis may be combined with metabolic acidosis secondary to severe heart failure.

8.6 D-dimer (25)

Plasma D-dimer is the specific derivative of cross-linked fibrin, which is produced when fibrin is degraded by plasmin. D-dimer levels are elevated in plasma in the presence of an acute clot under a process of fibrinolysis.

Most patients with PE have elevated levels of D-dimer (>500 U/ml). High plasma levels of D-dimer may also be found in elder patients, hospitalized patients, cancer and recent surgery. For this reason, this sensitive marker has low specificity (< 40%) for the diagnosis of VTE (DVT - PE). Thus, the usefulness of the test is low is hospitalized patients as an elevated percentage of patients will have a positive test even in the absence of VTE.

Despite its low specificity, several authors have demonstrated that D-dimer has high sensitivity, PPV and NPV for DVT - PE.

There are a number of available assays with different characteristics:

1. High sensitivity D-dimer assays: these methods have a sensitivity ≥ 98% and a very high negative predictive value.
2. Moderately sensitive D-dimer assays: the sensitivity of these methods ranges from 85% to 98%. Their negative predictive value is not high enough to rule out PE and a negative result requires another diagnostic test.

The conventional latex test used in our environment has low sensitivity (about 70%) and specificity.

In conclusion, a moderately sensitive assay excludes PE only in patients with a low clinical probability, while a negative D-dimer result in a highly sensitive assay has a negative predictive value high enough to be used as a single study.

Recent studies have shown that the magnitude of the increase has a prognostic value and that patients with abnormal D-dimer test have increased risk of recurrent thromboembolism. (26) It has been suggested to continue anticoagulation therapy as long as D-dimer values remain elevated.

8.7 Troponins (27)

Although serum levels of troponin T and I are not useful for the diagnosis of PE due to low specificity, their value as markers of risk is increasing.

Cardiac troponins are elevated in 30-50% of patients with moderate or severe PE.

High cardiac troponin elevation is associated with a 5-fold higher risk of complications compared to moderate elevations, with a greater incidence of cardiogenic shock and in-hospital mortality.

8.8 Transthoracic echocardiography

Transthoracic echocardiography is currently an essential tool for the evaluation of patients with suspected PE. A high percentage of patients with PE have abnormalities in the right heart chambers that can be detected by transthoracic echocardiography.

The Mc Connell sign is the most specific finding: depressed contractility of the RV free wall compared with its apex. Other indirect signs are the presence of tricuspid regurgitation, systolic pulmonary hypertension (not greater than 40 to 50 mm Hg in a previously healthy heart) without apparent cause or right ventricular dilatation with absence of inspiratory collapse of the inferior vena cava. (28)

In patients presenting with shock or hypotension, a normal transthoracic echocardiogram practically excludes PE as a cause of hemodynamic instability.

Once the diagnosis of PE has been confirmed, transthoracic echocardiography is useful for prognosis assessment. Right ventricular compromise is a strong independent predictor of mortality.

The presence of thrombi in transit (4% of echocardiograms) is another indicator of poor outcomes. In this case, the association with a patent foramen ovale increases the risk.

8.9 Transesophageal echocardiography (29)

Bedside transesophageal echocardiography is being used with more frequency. The use of multiplanar transducers increases its performance. An additional advantage of this method is the ability to rule out other severe cardiovascular conditions as aortic dissection.

8.10 Ventilation-perfusion scintigraphy (V/Q scan)

When properly performed, ventilation-perfusion scintigraphy has diagnostic value. The perfusion images should be acquired in the six views established by the PIOPED study (anterior, posterior and four oblique views).

A normal V/Q scan rules out EP, yet this situation is not common. On the other hand, only 10% of PE have a high-probability V/Q scan, while most PE (65-78%) have intermediate-probability scans. For this reason, further studies are necessary to make a diagnosis. In addition, most patients with previous cardiac and pulmonary diseases have intermediate-probability scans. Currently, V/Q scan has been replaced by helical computed tomography (HCT) scan. However, when HCT is not available or is considered inconvenient, V/Q scan is still a useful tool, especially for patients with no pre-existent cardiac and pulmonary conditions. (30) An abnormal chest X-ray markedly increases the specificity of the method.

8.11 Helical computed tomography scan (31)

Although helical computed tomography scan has been used in the last years, it has been recently added to

the diagnostic algorithm. Yet, some aspects should be considered:

1. The positive predict value of HCT to detect intraluminal defects in lobe arteries or in pulmonary artery trunk is 85%, equivalent to a high-probability V/Q scan
2. Subsegmental pulmonary defects are more difficult to visualize with this method.
3. A normal single-slice CT scan reduces the possibility of PE but does not exclude the diagnosis, (similar to a low-probability V/Q scan). In case of high clinical probability of PE, further studies should be performed.
4. Recent studies have determined that a normal HCT rules out the diagnosis of PE without need of additional studies.

It has been shown that 10% to 30% of patients with documented PE present with clots only in subsegmental and smaller arteries. Controversy also exists about the clinical significance of small emboli; yet, they are thought to have prognostic relevance in sujects with a decreased cardiopulmonary reserve.

The most important advantage of multidetector-row spiral CT is improved diagnosis of small peripheral emboli. In addition, it is also useful to evaluate the presence of old, organized emboli and the territory of the inferior vena cava with the same injection of contrast agent.

Its diagnostic yield is equivalent to that of pulmonary angiography.

8.12 Deep venous thrombosis

The diagnosis of DVT is an indirect way to determine the probability of PE, as both treatments are similar.

In the presence of DVT, contrast venography detects DVT in 50% to 70% of patients. In addition, 50% of patients with DVT have asymptomatic PE that is evident if investigated. Even more, in patients with DVT and clinical probability of PE, the latter is confirmed in 90% of patients.

Color-Doppler ultrasound of the lower extremities is the most useful, available and easiest tool fort the diagnosis of DVT; yet, some considerations should be mentioned:

1. A normal ultrasound does not exclude PE in patients with a nondiagnostic V/Q scan or HCT, but it reduces its probability.
2. The absence of DVT diagnosed by Doppler ultrasound is associated with low-risk of PE recurrence.

8.13 Pulmonary angiography (7, 25, 28)

Pulmonary angiography is the gold standard diagnostic test for PE, but is invasive, costly and is not always available at all hospitals. It is currently indicated in critically ill high-risk patients when the results of non-invasive imaging are negative or equivocal. Pulmonary angiography should be performed when mechanical approaches or local pharmacological therapy are indicated. This test may be negative in 1-5% of patients with PE.

9. RECOMMENDATIONS OF DIAGNOSTIC IMAGING TESTS

Deep venous thrombosis

Class I

- Contrast venography (A)
- Venous Doppler ultrasound (A).
- Combined venography and multislice helical computed tomography pulmonary angiography (A).

Pulmonary embolism

Class I

- Pulmonary angiography (A).
- Multislice helical computed tomography (A).

Class IIa

- V/Q scintigraphy scan (A).
- Helical single-slice computed tomography (A).
- Transesophageal echocardiography (A).

10. DIAGNOSTIC AND THERAPEUTIC ALGORITHM (32)

The diagnosis of PE is not simple. Pulmonary embolism is one of the most common unexpected findings at autopsies. Conversely, the diagnosis of PE is frequently empirical and unnecessary treatments are often initiated, increasing the risk of bleeding complications. Moreover, PE is a frequent clinical problem in daily practice.

Diagnostic algorithms specify a particular a set of medical tests to order so as to allow an accurate inclusion and exclusion of patients with this condition. Algorithms should adapt to the specific hospital and provide adequate cost-benefit ratio.

Clinical suspicion is the initial step of any diagnostic strategy and should guide which studies to order. D-dimer (DD), ventilation-perfusion scintigraphy scan (V/Q scan), helical computed tomography (HCT) and 2D-echocardiography should be performed for initial stratification of clinical risk.

Naturally, in patients with clinical signs of deep venous thrombosis (DVT), Doppler ultrasound of the lower limbs should be the initial test as it provides high sensitivity and specificity, is easy to perform and cost-effective.

10. 1 Models for clinical stratification

The initial clinical suspicion may be guided by the clinical experience or ruled by preestablished algorithms. In this sense, there are several models that may be implemented as an initial approach.

Models based on scores

The most frequently used clinical prediction rule is the one developed by Wells, based on symptoms, signs, the presence of an alternative diagnosis and risk factors.

This scheme classifies patients as having low, moderate and high probability of PE (Table 7).

Wells developed this score for the emergency department and found a prevalence of PE of 2% in the low probability group (40% of the patients studied), 19% in the moderate probability group (45% of patients studied), and 50% in the high probability group (8% of patients).

In summary, according to the different studies, there is enough evidence supporting that empiric use of clinical parameters or standardized rules is useful for risk stratification of patients. The expected prevalence of PE is about 10% in patients with low clinical probability, 25% in moderate clinical probability and 60% in those with high clinical probability. (Table 7)

Special situations modifying the diagnostic strategies

1. DD may be positive in hospitalized surgery patients (specificity 7% versus el 47% in outpatients).
2. Cancer patients: 85% with positive DD even in the absence of VTE.
3. Elder patients are more likely to have positive DD and abnormal V/Q scan.
4. PE treatment: heparin significantly decreases the sensitivity of DD due to reduction in plasma levels.
5. A negative high sensitivity DD does not rule out PE in patients with high clinical probability.
6. Previous cardiovascular surgery modifies the result of V/Q scans.

Based on the aforementioned studies, we believe that the last algorithm published by Goldhaber in 2005 is an interesting approach for this condition (Figure 2).

11. HIGH-RISK PE (34)

High-risk PE deserves a special consideration. The current concept of high-risk massive PE is functional rather than anatomical. Massive PE is defined as sustained systolic hypotension (< 90 mm Hg or a reduction > 40 mm Hg in hypertensive patients) for at least 30 minutes, unresponsive to intravenous fluid expansion, that cannot be explained by other coexistent conditions (sepsis, active bleeding, arrhythmias).

The mortality rate within the first hours is extremely high without appropriate treatment.

These massive emboli reduce the pulmonary cross-sectional area and produce an abrupt rise in pulmonary artery pressure, leading to acute right ventricular dilatation. Pulmonary artery pressure increases with more than 50% obstruction of the pulmonary artery bed in patients without coexistent cardiopulmonary disease and with 25% of obstruction or even less in those with prior cardiopulmonary disease.

Patients without prior pulmonary hypertension are unable to generate systolic or mean pulmonary artery pressure of ≥ 50 mm Hg or ≥ 40 mm Hg, respectively, which appear to be the maximal pressure that a healthy ventricle can generate. When the pulmonary artery bed obstruction is > 75% (or less in patients with prior cardiopulmonary disease), right ventricular failure develops, leading to ischemia by increasing myocardial oxygen demand while limiting supply. In turn, cardiac output and systemic blood pressure decrease and intramural pressure elevates. The presence of coronary artery disease worsens the outcomes. Death is then the consequence of unmanageable systolic overload, associated with ischemia and eventually with right ventricular infarction.

The sequence of events leading to acute decompensation of the RV is shown in Figure 3. Acute right ventricular dilatation produces pericardial restraint and leftward shift of the interventricular septum, reducing left ventricular preload and cardiac output, and coronary artery perfusion decrease. These phenomena occur when the right ventricle requirements are increased, needing maximal coronary artery flow.

These concepts explain the elevation of troponin levels in critically ill patients. (28)

Table 7. Clinical prediction rules for PE: Wells scoring system. Score and pretest probability (33)

	Score
Active cancer	1.0
Hemoptysis	1.0
Recent surgery	1.5
Previous DVT	1.5
HR > 100	1.5
Clinical signs of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Pretest probability	
High	≥ 6
Moderate	2.5-5.5
Low	≤ 2

12. TREATMENT OF THROMBOEMBOLIC DISEASE (35)

12.1 High-risk patient (Figure 4)

These patients are admitted to the Intensive Care Unit with hemodynamic impairment and/or severe hypoxemia and require a rapid and efficient management. The first step is to provide hemodynamic support. The combination of hypoxemia and increased pulmonary resistance is very dangerous. The initial treatment of patients in shock is rapid volume expansion (500 to 1000 cm^3). However, in hypotensive patients with severe RV dysfunction excess fluid administration may precipitate further RV deterioration.

Ensuring adequate oxygenation is also important in stabilizing their condition. Mechanical ventilation is indicated for patients with severe hypoxia unresponsive to the initial measures.

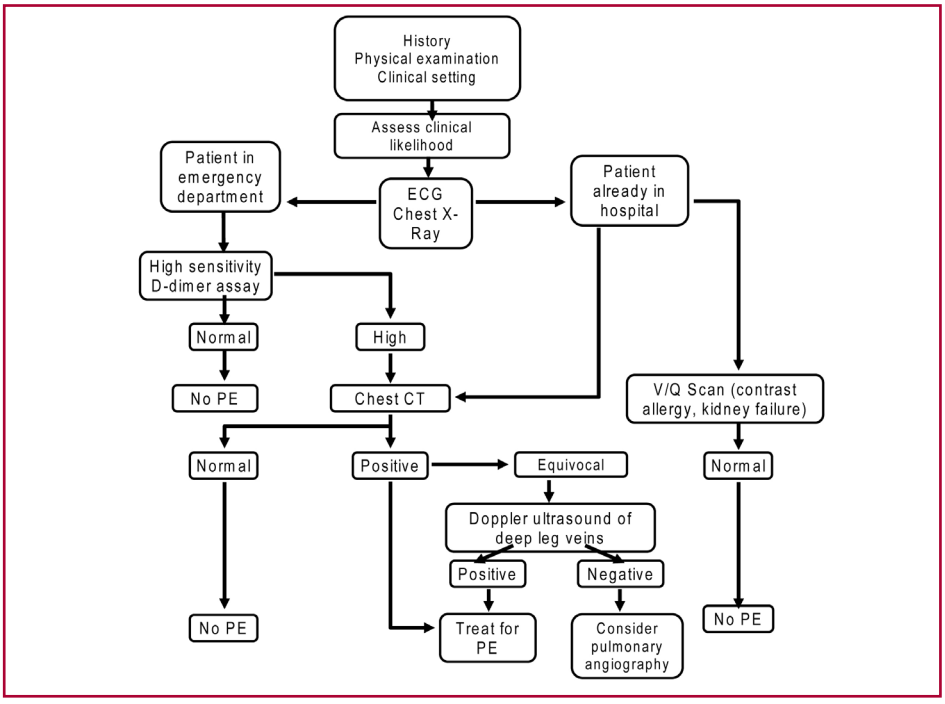

Fig. 2. Diagnostic algorithm. (Adapted from Piazza G, Godhaber SZ. Acute Pulmonary Embolism Part I. Circulation 2006;114:e28-e32.)

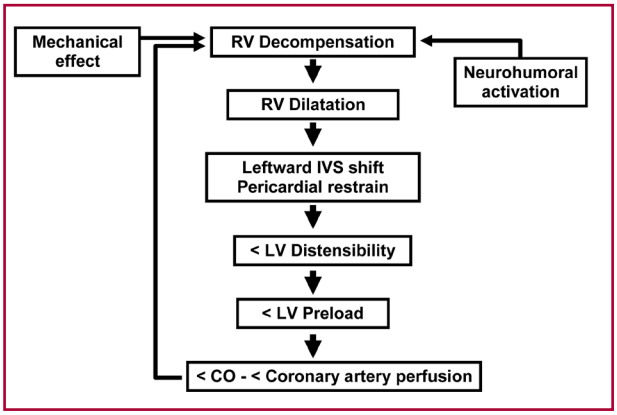

Fig. 3. Physiopathology of massive PE

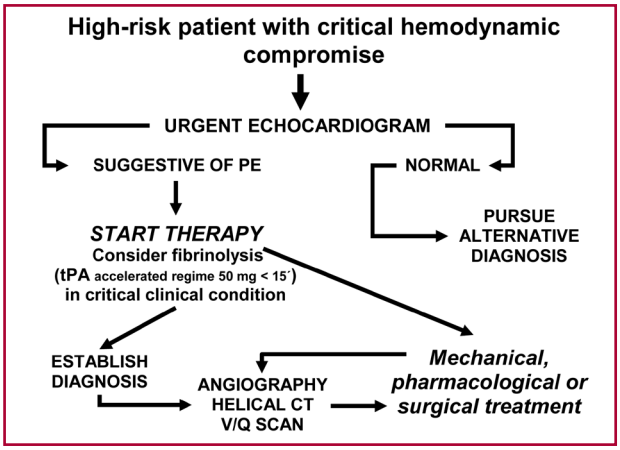

Fig. 4. Diagnostic-therapeutic approach in the patient with critical hemodynamic instability

Inotropic and/or vasoactive agents are added if hemodynamic instability persists, following the guidelines for treatment of cardiogenic shock.

Undoubtedly, thrombolysis or emboli fragmentation are the treatment of choice in hemodinamically unstable patients with PE. When possible, the patient should be transferred to the catheterization lab for diagnostic and therapeutic purposes. If cath lab facilities are not available, intravenous thrombolysis is indicated.

12.2 Low-risk patient:

a. Anticoagulant therapy (28)

Anticoagulant therapy for DVT and PE are similar as both conditions are manifestations of the same disease.

However, mortality is significantly higher and recurrences are three times greater in PE versus DVT without PE. In addition, about 4% of patients with PE will develop significant pulmonary hypertension in the medium term. (36)

The goal of the treatment is to interrupt the progression of the thrombotic phenomena; yet it does not exert any action on the existent clots which are degraded by endogenous fibrinolysis in the medium term.

The duration of anticoagulation with LMWH or UFH is currently 5 days. In the absence of contraindications, therapy with oral vitamin K antagonists starts at the first or second day. An adequate anticoagulation is usually achieved by the fifth day, and heparin can then be discontinued.

In patients with clinical suspicion of thromboembolic disease, and in the absence of contraindications, we suggest starting any heparin treatment until the diagnosis can be ruled out or confirmed.

b. Unfractionated heparin

Anticoagulation with UFH is the classical treatment of VTE. The advantage of UFH is its short half life. However, effective anticoagulation cannot be achieved rapidly due to its low bioavailability. Delays in achieving therapeutic aPTT values are associated with greater likelihood of progression of VTE and recurrences. We recommend achieving target aPTT value within 24 hours from starting therapy with heparin. An initial intravenous bolus injection of 5000 U is followed by an infusion at a rate of 15-18 U/kg/h (mean: 1250 U/h; total dose for average weight subjects: 25200-30240 U/d) administered by infusion pump. Target aPTT value is between 1.5 and 2 times the baseline value. The aPTT should be measured 2–4 h after each dose adjustment and once daily when the target therapeutic dose has been reached. Subsequent doses of unfractionated heparin should be adjusted using a nomogram. We propose the one shown in Table 8.

Unfractionated heparin is still the drug of choice for patients with hemodynamic instability, high risk of bleeding, elder patients > 75 years, those with renal dysfunction and those who will undergo a surgical procedure.

Intermittent boluses are not recommended, having been associated with a higher incidence of bleeding.

Treatment with heparin is not free of complications. Bleeding is the most common side effect. Other disadvantages related to the use of this drug are: the previously mentioned variability in response to a given dose, due to indirect thrombin inhibition through antithrombin III, and heparin resistance caused by heparin binding to plasma proteins with subsequent unpredictable release.

Heparin-induced thrombocytopenia is an important complication that occurs in 1% to 3% of cases. It usually develops between the third and fifth day after treatment started, the moment when platelet count should be ordered. Treatment with heparin should be discontinued if platelet count is < 100.000/mm^3 or if the fall is >50%. The risk of heparin-induced thrombocytopenia is lower with LMWH.

The FDA approved the use of bivalirudin in patients unable to receive heparin, especially in those with heparin-induced thrombocytopenia. An initial IV bolus of bivalirudin of 0.10 mg/kg is followed by a 0.25 mg/kg/h IV infusion to maintain aPTT 2 times the control value.

Fondaparinux, a pure factor Xa inhibitor that does not induce thrombocytopenia and is used subcutaneously, is available in our country.

c. Low-molecular-weight heparins (Table 9)

Unlike unfractionated heparin, an indirect thrombin inhibitor, low-molecular-weight heparin inhibits (LMWH) coagulation factor Xa and, to a lesser extent, thrombin. For this reason, aPTT is not markedly modified by LMWH and thus does not need to be monitored. Monitoring of the anti-Xa level is not required except in the following circumstances: renal dysfunction, pregnancy, extreme obesity.

These agents are more stable and have a more predictable anticoagulant response; in addition, the incidence of heparin-induced thrombocytopenia and osteoporosis is lower compared with UFH. The effectiveness of LMWH for prophylaxis and treatment of VTE is similar to UFH or even greater. In patients with cancer, LMWH therapy has been associated with a significant survival advantage.

Low-molecular-weight heparin has a longer half-life than UFH and is partially inhibited by protamine. Therefore, UFH is recommended in patients at high risk of bleeding, in those who will undergo a surgical procedure, and in renal dysfunction with plasma creatinine level > 2.5 mg/dl.

The anticoagulant effect of LMWH diminishes 6 hours after being discontinued.

Although increasing experience suggests that LMWH is safe in pregnancy, UFH is preferred in this circumstance. (37, 38)

Table 8. Adjustment of intravenous unfractionated heparin dosage

aPTT (s)	Bolus	Change of dosage
< 35	80 UI/kg	Increase infusion rate by 4 U/kg/h
35-50	40 UI/kg	Increase infusion rate by 2 U/kg/h
51-70	———	No change
71-90	———	Reduce infusion rate by 2 U/kg/h
> 90	Stop infusion for 1 h	Reduce infusion rate by 3 U/kg/h

Table 9. LMWH and pentasaccharides for the treatment of thromboembolic disease

LMWH	Recommended dose
Enoxaparin	1 mg/kg s.c. every 12 h (maximum 180 mg)
Nadroparin	85 UAXa/kg s.c. every 12 h
Dalteparin	100 UAXa/kg s.c. every 12 h
Pentasaccharides	
Fondaparinux	7.5 mg s.c. once daily

d. Pentasaccharides (Table 9)

As of 2008, the FDA and our local authorities approved the use of fondaparinux for the prevention and treatment of thromboembolic disease. This synthetic pure factor Xa inhibitor is administered subcutaneously in a single daily dose of 2.5 mg or 7.5 mg for prophylaxis and treatment, respectively. The latter is a fixed dose for patients weighting between 50 and 100 kg. Monitoring of the anti-Xa level is not required except under special circumstances.

It is used once a day due to its long half-life (17 hours). There is no specific antagonist against fondaparinux.

e. Thrombolytic therapy

Thrombolysis seems to be an excellent option, at least in theory; it has a lytic effect in both venous thrombi and pulmonary emboli, which is beneficial in terms of immediate hemodynamic and clinical improvement. However, the number of patients included in randomized trials comparing thrombolytic agents versus placebo is not more than 800.

The MAPPET trial is the most important study recently published that evaluated thrombolysis plus heparin versus heparin alone. (39) The investigators used rtPA and included patients with right ventricular dysfunction. The study was favorable to thrombolytic therapy, yet the methodology used was strongly criticized.

The ICOPER registry (40) included 2454 patients and 304 were treated with thrombolytic drugs. In this study these agents did not improve the survival. Yet, the incidence of intracranial hemorrhage was 3%.

Nine studies with a total of 461 patients were included in a meta-analysis published in 2002. Only three of the trials were double-blind. Most of these studies showed that thrombolytic agents were more effective and rapid than heparin to dissolve the thrombi, especially during the first 24 hours. The most important finding of this meta-analysis was that thrombolysis did not provide any benefit to unselected patients with pulmonary embolism (RR 0.63, 95% CI 0.32-1.93).

There is well established evidence to indicate thrombolysis to patients with severe hemodynamic impairment (systolic blood pressure < 90 mm Hg or a reduction > 40 mm Hg in hypertensive patients) who are unresponsive to intravenous fluid expansion for 30-60 minutes, and require the use of vasopressive drugs, and to patients with refractory hypoxemia. In these high-risk patients, rapid improvement in pulmonary circulation may make the difference between life and death.

Thrombolysis may be indicated in patients with thrombi in transit, especially associated with a patent foramen ovale.

Yet, the indication in patients with right ventricular dysfunction or severe PE with preexistent cardiopulmonary diseases is controversial. In these cases, the decision should be based on the individual patient considering the risk-benefit ratio. (28)

All patients treated with thrombolysis should receive continuous infusion of UFH in the absence of contraindications, following the controls previously mentioned. In patients previously treated with heparin, we recommend to discontinue anticoagulation during thrombolytic therapy. The aPTT should be monitored at the end of thrombolysis and then every two hours. Therapy with heparin is reinitiated when aPTT reaches < 80 s.

Table 10 describes the different therapeutic schedules usually used. The main contraindications are shown in Table 11.

It is recommended to discontinue infusion after 12 hours, as prolonged thrombolytic periods are not effective and are associated with increased risk of bleeding.

The following precautions should be taken into account when thrombolysis is used to treat pulmonary embolism:

– Avoid invasive procedures such as punctures in vessels that cannot be compressed (e.g. subclavian vein) or arterial punctures.
– No coagulation tests are necessary after thrombolysis because the doses of thrombolytic agent are fixed. This treatment should be performed under strict control in an intensive care unit. Infusion should be discontinued if disorders of consciousness suggestive of brain hemorrhage or signs of intraabdominal bleeding develop.

The route of administration is another controversial issue. Traditionally, the intravenous route has been considered as effective as the direct infusion in the pulmonary artery. Yet, some experimental studies suggest that, in patients with massive pulmonary embolism, direct local infusion of a thrombolytic agent via a catheter in the pulmonary artery, at a reduced dosage (10-20% the intravenous dose), might offer better outcomes than systemic infusion, with a lower

Table 10. Dosage regime of the drugs used in our environment

rtPA	100 mg over 2 h in continuous infusion The first 10 mg may be given in bolus
Streptokinase	1500000 U over 2 h in continuous infusion
rtPA	0.6 mg/kg over 5-15 min (maximum dose 60 mg) in critically ill patients

Table 11. Contraindications to thrombolytic therapy

Absolute	Relative
Hemorrhagic stroke	Bleeding disorders or thrombo cytopenia < 100000/mm^3
Central nervous system neoplasms	Refractory hypertension (systolic/diastolic blood pressure >180/110 mmHg)
Recent head surgery or trauma (within preceding 2 months)	Ischemic stroke in the preceding 6 months
Internal bleeding in the preceding 6 months	Surgery in the preceding 10 days

risk of bleeding. This therapeutic strategy has been used in small studies in critically ill patients, with encouraging results.

Time window: classically, there is a 14-day "window" for administration of PE thrombolysis. In fact, in daily practice, most deaths occur within the first hours after the onset of PE.

f. Mechanical and pharmacological treatment in the catheterization laboratory

Nowadays, patients with pulmonary embolism are not referred to the catheterization laboratory only for diagnostic purposes.

Most patients with massive PE undergo cardiac catheterization to confirm the diagnosis and for percutaneous embolectomy and fragmentation to open a partially occluded pulmonary trunk or major pulmonary arteries. The procedure may be performed using specially designed pulmonary catheters or conventional cardiac catheters (e.g. pigtail catheter). Thrombolytic therapy can be administered as adjunctive therapy in doses equivalent to 10% to 20% of the systemic dose.

g. Surgical embolectomy

Traditionally, pulmonary embolectomy has been reserved for patients *in extremis* with PE. The Trendelemburg procedure is no longer used and most centers use cardiopulmonary bypass. Surgical embolectomy is associated with elevated mortality, even in referral centers worldwide. Recently, a group of investigators from Boston has revived this technique with favorable outcomes in patients with severe though not critical PE. We believe that this technique is still an option for tertiary care centers with well-trained surgical staff.

13. THERAPEUTIC RECOMMENDATIONS

Class I

Patients with PE should initiate anticoagulation for 5 days, until achieving target INR levels of $\geq$ 2 for 24 hours with any of the following drugs:

– Unfractionated heparin in continuous infusion (A).
– Low-molecular-weight heparin (A)
– Pentassacharides: fondaparinux (A).

Anticoagulation with unfractionated heparin should be initiated in patients with shock and in those in whom subcutaneous drug absorption cannot be warranted.

In the absence of contraindications, all patients with suspected PE and a high pretest probability should be treated with anticoagulant agents until the diagnosis is confirmed or excluded (C).

Class IIa

– Use of bivalirudin or fondaparinux is the recommended form of initial treatment for patients in whom heparin is contraindicated (B).

Class I

– Fibrinolytic therapy in patients with shock (C).
- rtPA 100 mg over 2 h.
- Streptokinase 1500000 IU over 90 minutes.

Class IIa

– Fibrinolytic therapy in patients with refractory hypoxemia under mechanical ventilation and high fraction of inspired O_2 (C).
– Fibrinolytic therapy in patients with thrombi in transit (C).
– Mechanical therapy with or without fibrinolytic therapy associated in PE (A)
– Surgical embolectomy (B).
– rtPA in bolus injection of 50 mg over 15 minutes in patients with impending circulatory arrest (C).

Class IIb

– Fibrinolytic therapy in PE patients with signs of right ventricular dysfunction on echocardiography without hemodynamic impairment. (B)

14. VENA CAVAL FILTERS

Recommendations for vena caval filters

Class I

– Patients with active bleeding (C)
– Patients with recurrent embolism despite adequate anticoagulation treatment (C).
– Patients with bleeding during adequate anticoagulation treatment (C).

Other indications: the indication of vena caval filters for prevention of recurrent embolism in patients with massive PE, inadequate cardiopulmonary reserve or in those undergoing a previous surgical or percutaneous embolectomy is still under debate. Under these special circumstances, clinical management decisions will continue to be individualized and based on updated guidelines.

Exceptionally, venous filters have been inserted in the superior vena cava.

Retrievable devices, currently available may be removed within 2 weeks of implantation or left *in situ* for longer periods of time.

The percentage of patients who receive vena caval filters is low (3% to 5%). At present, there is no evidence showing a significant reduction on mortality; yet, a moderate reduction in short-term morbidity has been demonstrated.

15. COUMARIN THERAPY

Coumarin therapy is indicated for long-term anticoagulation treatment to prevent recurrences. These drugs are vitamin K antagonists. These drugs prolong the prothrombin time; yet the maximum effect occurs five days after the initial dose when all the factors involved in the coagulation cascade are effectively inhibited.

Therefore, in patients with PE or DVT heparin and coumarin therapies should overlap for approximately four to five days; heparin is discontinued thereafter and vitamin K antagonists are administered alone. The duration of oral anticoagulation has not been precisely established by reliable trials. In consequence, we suggest the guidelines recommended by the American College of Chest Physicians (Table 12).

Proper duration of therapy is unclear in first event with:

- Factor V Leiden, homocystinemia, deficiency of protein C or S;
- Thrombophilias with reversible risk factors (Hyers TM, et al. Chest 2001;169:176S).

If severe hemorrhage develops, infusion of cryoprecipitates or 2 units of fresh frozen plasma should be rapidly initiated. Intravenous injection of 10 mg of vitamin K reverses oral anticoagulant therapy in 6 to 12 hours; refractoriness to subsequent anticoagulant therapy persists for 10 to 15 days.

16. RECOMMENDATIONS FOR SECONDARY PREVENTION

- Early mobilization is indicated in patients with DVT, if tolerated (Class I -B-).
- We recommend starting therapy with vitamin K antagonists together with heparin therapy, and overlapping both drugs for 3 to 5 days (Class I -B-).
- Anticoagulant agents should be given at doses adjusted to maintain a target INR of 2 to 3 (Class I -A-).
- We recommend lifetime anticoagulation in patients with 2 or more thromboembolic events (Class II -A-).
- We recommend anticoagulation therapy for 3 months in patients with DVT and reversible or time-limited risk factor (Class I -A-).
- In cancer patients with DVT we recommend anticoagulation therapy with LMWH for 3 to 6 months and lifetime anticoagulation until resolved (Class I -C-).
- In patients with anticardiolipin antibodies or multiple thrombophilias we recommend anticoagulation therapy for 12 months (Class I -C-).

Table 12. Duration of anticoagulant therapy

3-6 months First event with reversible or time-limited risk factor
6 months Idiopathic VTE, first event
12 months to lifetime First event with cancer, until resolved – Anticardiolipin antibody – Recurrent event, idiopathic – Recurrent event with thrombophilia

Lifetime anticoagulation is also suggested (Class II -C-).

- Lifetime anticoagulation should be considered in idiopathic DVT (Class II -A-).
- Recommendations for lifetime anticoagulation are subject to modification considering the individual risk-benefit ratio (Class I -C-).

17. PREGNANCY

Pregnant women, those in the post-partum period or under hormone therapy, are at high risk of thromboembolic disease. The risk of VTE in the puerperal period increases 5-fold as compared to the antepartum period, and the risk of PE is 15 times higher.

The diagnostic tools should not interfere with the fetus; CT scanning may be used providing effective protection to the fetus.

Low molecular weight heparins are recommended in the usual dose. Thrombolytic therapy may be indicated in life-threatening PE (reports from isolated cases, with favorable outcomes) Low-molecular-weight heparin is indicated as coumarins have teratogenic effects.

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