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Management of Pulmonary Embolism: State of the Art Treatment and Emerging Research

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Opinion statement

Pulmonary embolism is one of the most important causes of morbidity and mortality in cardiovascular medicine and demands a circumscribed algorithmic treatment approach (Fig. 1). Anticoagulation should be triggered by a high clinical probability and continued based on urgent definitive imaging. Our assessment then continues with evaluation of the clinical severity of the pulmonary embolism to determine whether the patient will benefit from thrombolysis or not. We usually reserve this option for cases of massive pulmonary embolism (sustained hypotension, pulselessness, or persistent profound bradycardia) or patients with a low cardiopulmonary reserve and categorical signs of right ventricle failure. At this juncture, renal function, a diagnosis of active cancer, calculated bleeding risk, and estimated patient compliance will help us gravitate toward specific agent selection for subsequent anticoagulation management. While rivaroxaban is an attractive oral therapy option, it is not an appropriate choice for patients with significant renal disease; patients with cancer are better treated with low molecular weight heparin when possible. Warfarin anticoagulation continues to be a well-known, valid, and cost-effective treatment option. At the end of the primary treatment we assess each patient for the likelihood of thromboembolism recurrence, which will be highest among those patients with idiopathic events or those with cancer-associated thrombosis. We favor prolonged anticoagulation in these scenarios. In addition, we strongly advocate periodic scheduled follow up of patients on long-term anticoagulation for secondary prophylaxis to re-evaluate their bleeding and recurrence risk. We understand both of these extremes are in a dynamic balance, and likewise so should be the anticoagulation directives. As we learn more about recurrence and bleeding prediction, we foresee a personalized approach in which the anticoagulant agent for each patient will be narrowly chosen based on their specific performance.

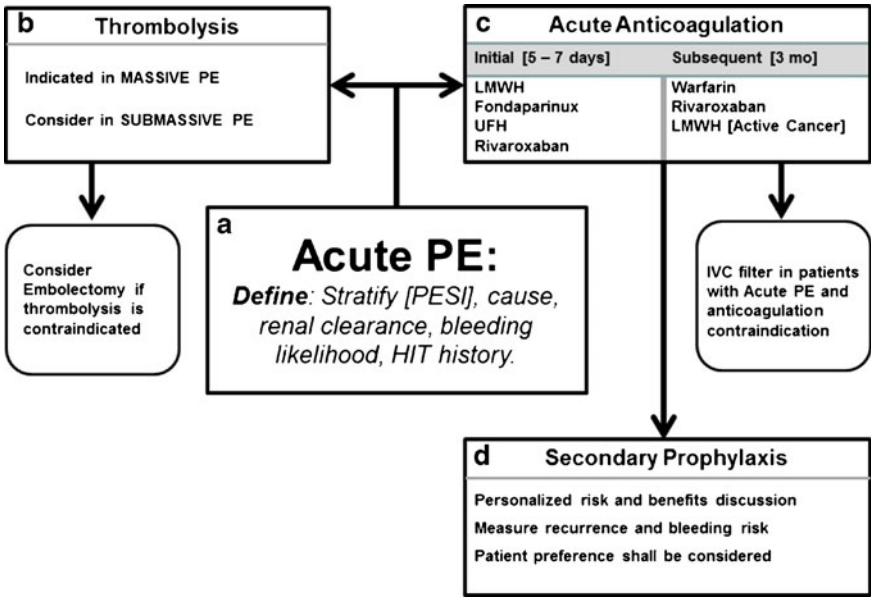

Figure 1. Key components of acute pulmonary embolism treatment. A) Risk assessement, B) Thrombolysis in selected patients, C) All patients should receive anticoagulation unless contraindicated, D) The choice and duration of secondary prophylaxis is an individualized decision based on risk assessement and patient preference.

Introduction

Venous thromboembolism (VTE) is the third most common cardiovascular disease, preceded by acute coronary syndrome and stroke [1–3]. Pulmonary embolism (PE) is the occurrence of direct physical obstruction of the pulmonary arteries and marks the direst event in the spectrum of VTE. Based on data from 2006 reported on the 2010 National Hospital Discharge Survey, a quarter of a million patients are hospitalized with PE in the United States each year [2].

Age and ethnicity are variables that modify risk for venous thromboembolic events. As age increases, so does the incidence, prevalence, morbidity, and mortality of PE, and this in an exponential fashion [2, 4]. Interestingly, it has being found that the incidence of PE is lower in Asian Americans, American Indians, and Alaskan Natives than in African Americans and whites. Ethnicity can be an important therapeutic and diagnostic determinant, as members of ethnic groups share a heritable gene pool and other important socioeconomic factors that could protect or predispose to VTE [2].

Upon clinical suspicion of PE, the use of a clinical prediction model to guide the diagnostic approach is recommended, such as the Wells score [5], the PERC score [6], and the Geneva scores [7], to stratify for pretest probability of VTE [8]. The signs and symptoms of PE are remarkably nonspecific; most patients with PE present with at least one of the following four symptoms: sudden onset dyspnea, chest pain, syncope, and hemoptysis. Sudden onset dyspnea is the most reliable indicator to alert a clinician to consider the possibility of PE [9]. A negative result on D-dimer quantitative rapid ELISA with a low clinical pretest probability of VTE excludes PE; however, the use of D-dimer in the geriatric population is not recommended due to false positive results in this age bracket [10, 11]. In cases of intermediate or high pretest clinical probability, at least one imaging modality should be used to confirm or exclude the diagnosis of PE, computed tomographic angiography (CTA) being the most commonly used in current practice.

Therapeutic goals for PE are: prevention of further embolization, prevention of extension of thrombi, reduction of recurrence, restoration of pulmonary artery patency, and prevention of pulmonary hypertension. Anticoagulation continues to be the initial approach in the treatment of PE, preventing further embolization, extension of thrombi, and reducing recurrence. Fibrinolysis may be required to restore pulmonary artery patency and re-

duce the incidence of pulmonary hypertension [12]. Patients with acute PE and contraindication to anticoagulation should undergo IVC filter placement [13••].

Treatment

The minimal duration of anticoagulation for patients with VTE is three months, after which time there should be re-evaluation of the potential benefit in terms of whether the reduction in recurrence of VTE continues to outweigh the increased risk of bleeding [13••, 14]. The use of aspirin for long-term secondary prevention has been recently evaluated in two studies; the combined results showed a 32 % reduction in the rate of recurrence of VTE, a significant 34 % reduction in the rate of major vascular events, and no excess of bleeding [15, 16]. Therapy should be individualized by taking into consideration hereditary and acquired factors that predispose to venous thromboembolic events. It has been proposed that, in hemodynamically stable patients with low-risk PE and whose home circumstances are adequate, outpatient treatment may be considered with the aid of a prediction rule such as the simplified pulmonary embolism severity index (sPESI) or levels of NT-proBNP [13••, 17, 18•, 19]. This approach, however, is not common practice at this moment, and the majority of patients with PE are initially managed in the hospital setting.

Pulmonary embolism is best managed when appropriately classified according to objective criteria. A useful approach to the management of PE is to categorize events as massive, submassive, and low-risk PE [20••]. This classification uses blood pressure, pulse, heart rate, right ventricular (RV) function and myocardial necrosis as parameters to classify PE. Massive PE is defined as acute PE with sustained hypotension, pulselessness, or persistent profound bradycardia. In patients with evidence of circulatory or respiratory compromise or moderate to severe RV dysfunction, fibrinolytic therapy is recommended [20••]. Submassive PE is defined as acute PE without systemic hypotension but with either RV dysfunction or myocardial necrosis, and low-risk PE is defined as acute PE and the absence of clinical qualifiers of adverse prognosis that define massive or submassive PE [20••]. It is reasonable to consider using thrombolytic therapy in a select group of cases which do not fulfill the unstable hemodynamic criteria for massive PE.

Diet and lifestyle

There is no conclusive evidence with regard to diet and the risk of VTE; nevertheless, some have reported that low vegetable intake is strongly associated with VTE risk and daily alcohol consumption lowers risk of VTE as compared to non-consumers [21–24]. To achieve and maintain a stable therapeutic INR in patients taking vitamin K antagonists (VKA), consistent dietary vitamin K intake is important. This is best achieved by the use of a self-assessment instrument to determine daily intake and variability of dietary vitamin K, as well as a record of all medication changes, over-the-counter drugs, natural products therapy, and vitamin supplementation [25–27].

While increased body mass index is recognized as a risk factor for VTE, increased physical activity is associated with both a decreased and increased risk for VTE depending on the population studied [28, 29]. However, heavy smoking, stress, and low socioeconomic status seem to be associated to an increased risk for VTE [29, 30].

Pharmacological treatment

All patients treated with anticoagulant or thrombolytic medications have an increased risk of bleeding; therefore, when considering the use of these medications as treatment of acute PE, a risk to benefit appraisal should be undertaken.

For patients with acute PE, the initial therapy for acute treatment is intravenous unfractionated heparin. Additional options for acute treatment are low molecular weight heparin (LMWH) and fondaparinux [13••]. In addition, those patients with PE related to cancer are better treated with prolonged LMWH rather than vitamin K antagonists [31]. Those patients who are treated with vitamin K antagonist after acute parenteral treatment must overlap parenteral anticoagulation (bridging therapy) for a minimum of 5 days and until the INR is 2.0 or above for at least 24 hours.

Parenteral agents

Low molecular weight heparin

LMWH is the product of the enzymatic cleavage of UFH producing a mixture of low molecular weight glycosaminoglycans capable of binding AT with an increased affinity to factor Xa [32••].

Standard dosage

Dalteparin: In patients with DVT with or without PE, a SC administration of dalteparin at 200 units/kg once daily or 100 units/kg twice daily is a reasonable choice, particularly in cancer patients with normal renal function [20••].

Enoxaparin:The recommended dose for enoxaparin in patients with VTE with or without PE is SC administration of 1 mg/kg/dose every 12 hours, or 1.5 mg/kg once daily [20••].

Tinzaparin: In patients with PE, SC administration of 175 anti-Xa units/kg once daily can be used up to a maximum of 18,000 anti-Xa units/day.

Fondaparinux

Fondaparinux is a synthetic analog of the antithrombin (AT) binding pentasaccharide, found in UFH and LMWH. Fondaparinux binds the reactive site of AT enhancing its reactivity with factor Xa.

Standard dosage

In patients with acute PE, fondaparinux should be administered once daily by body weight; those patients weighting <50 kg, should receive 5 mg SC daily, those with 50 to 100 kg of body weight 7.5 mg SC daily, and those with > 100 kg 10 mg SC daily [33].

Intravenous unfractionated heparin sodium (UFH)

UFH is a heterogeneous mixture of glycosaminoglycans that bind to AT via a unique pentasaccharide sequence. This linkage induces a conformational change in AT, converting it from a slow inhibitor to a very rapid

inhibitor, which catalyzes the inactivation of thrombin and factors IIa, Xa, IXa, XIa and XIIa [32••].

Standard dosage Although there are various strategies for the use of UFH for treatment of VTE, we favor the weight-based strategy, which uses an infusion of 80 units per kilogram (kg) bolus followed by an 18 units per kg per hour. The target of anticoagulation is a Xa level of 0.3 to 0.7 IU/L. Although it has a high variability, an alternative option is to monitor aPTT with a goal of 1.5 to 2.5 times baseline aPTT. This administration strategy also allows the clinician to titrate medications depending on age group, as there is a definite difference in the metabolism of UFH, particularly in the elderly [34]. Moreover, the IV route avoids the unpredictability of the SC absorption in the extremes, as is the case in the morbidly obese or in patients with severe anasarca.

Contraindications LMWH, fondaparinux and UFH share similar contraindications. Absolute contraindications for anticoagulation are active bleeding and know sensitivity to the drug. A specific example is heparin-induced thrombocytopenia (HIT), where UFH and LMWH are contraindicated as they could trigger thrombosis. Fondaparinux, however, is a promising medication in the setting of HIT and is not formally contraindicated [35]. Relative contraindications for parenteral anticoagulation are potential bleeding lesions due to disease, surgery or trauma in the gastrointestinal, genitourinary, neuroaxial, or central nervous system.

Main drug interactions Concomitant use of drugs known to increase the risk of bleeding, such as antiplatelet agents and thrombolytics, are a concern when using parenteral anticoagulation. The determination of and selection of anticoagulation should be individualized when other agents are used due to the increased risk of bleeding.

Main side effects Bleeding is a strong concern when using parenteral anticoagulation. A low threshold for the detection of clinical or subclinical signs of bleeding should be standard. Due to the possibility of HIT, platelets levels should be periodically evaluated. The use of a clinical scoring system is advised to estimate the probability of HIT if suspected [36]. Hyperkalemia can occur within a few days of UFH administration. Osteopenia and osteoporosis can also occur however, this is more of a concern for prolonged administration of UFH and seldom with LMWH. Subcutaneous administration of UFH, LMWH, and fondaparinux are associated with pain, irritation, hematoma, and ecchymosis at injection sites.

Special points Half-life, drug metabolism and elimination, and monitoring as well as antidote and reversal of anticoagulation, may help determine the preferred agent for acute PE management.

LMWH has a half-life between 3 to 6 hours, is predominantly cleared by the kidneys and is only partially neutralized by protamine sulfate. Protamine sulfate should be administered in doses of 1 mg per 100 anti-Xa units of LMWH if anticoagulant was administered within 8 hours up to a maximum single dose of 50 mg; if a second dose is needed, 0.5 mg protamine sulfate per 100 anti-Xa units should be administered. Monitoring the anticoagulant effect of LMWH with anti-Xa levels is not generally necessary, with the exception of patients with renal insufficiency, the morbidly obese, and in the pregnant or pediatric populations [32••].

Fondaparinux has a long half-life of 17 to 21 hours; its elimination is almost completely dependent on renal clearance and there is no reliable antidote for this drug. Recombinant activated factor VII (rFVIIa) can normalize hemostasis for patients on fondaparinux after a single dose of 90 μgkg [37]. The

monitoring of anticoagulation for fondaparinux is not routinely recommended.
Finally, the half-life of UFH is approximately 60 to 90 minutes; it is metabolized through the reticuloendothelial system and is neutralized by protamine sulfate in doses of approximately 1 mg per 100 U of UFH. Therapeutic ranges should be adapted as per institution sensitivity of the reagent and coagulometer used with therapeutic aPTT usually correlating to Xa level of 0.3 to 0.7 IU/ [32••].

Cost/cost-effectiveness

LMWH:
Dalteparin 10000 units/mL (1 mL vial): $76.99 [38]
Enoxaparin 100 mg/mL (1 mL vial): $79.99 [38]
Fondaparinux 7.5 mg/0.6 mL (0.6 mL vial $140.09 [38]
UFH 10000 units/mL (25 mL vial): $259.20 [38]

Direct thrombin inhibitors

Direct thrombin inhibitors (DTIs) bind directly to thrombin and block its enzymatic activity. Originally isolated from the salivary glands of the medicinal leech, *Hirudo medicinalis*, direct thrombin inhibitors are now raised as recombinant drugs from yeast or are synthetic polypeptides. These drugs are the medication of choice when the pulmonary embolism is associated with HIT.

Standard dosage

Argatroban*:* Administered continuously through IV infusion with an initial dose of 1 to 2 mg/kg/min [32••].
Lepirudin*:* IV recommended dose is 0.15 mg/kg/h with or without an initial bolus of 0.4 mg/kg [39].
Bivalirudin*:* For presenting with HIT and a creatinine clearance greater than 60 ml/minute, the recommended dose is 0.15 mg/kg/hour [40].

Contraindications

As with all anticoagulants, active bleeding is a contraindication. Relative contraindications include potential bleeding lesions due to disease, surgery, or trauma in the gastrointestinal, genitourinary, neuroaxial, or central nervous system. A contraindication specific to lepirudin is a hypersensitivity to hirudins or any component of the formulation, as hirudins are known to raise antibodies in up to 40 % of patients treated with lepirudin [32••].

Main drug interactions

See Parenteral Agents.

Main side effects

See Parenteral Agents. Lepirudin can raise antibodies against hirudin, which could prolong the plasma half-life, resulting in accumulation of the drug [32••]. Moreover, it has been shown in vitro that antibodies against hirudin can cross-react with bivalirudin; however, the consequences of this clinically are uncertain [41].

Special points

Argatroban's half-life is approximately 45 minutes, reaching steady-state plasma concentrations in 10 hours, and it is metabolized in the liver via the cytochrome P450 3A4/5 enzyme system and predominantly excreted through the biliary system. As such, dose adjustments are necessary in patients with hepatic impairment [32••, 42]. The aPTT can be used to monitor its effect; while titrating to maintain an aPTT of 1.5 to 3 times that of baseline. As with other DTI, there is no specific antidote for this drug. When bridging, the combination of a DTI and warfarin will generate a higher INR than the expected by warfarin alone, frequently higher than 4 [43]. Argatroban shall be overlapped for at least 5 days and until the INR has been therapeutic for 2 days. The INR is trend checked again off parenteral medication; premature discontinuation of the DTI may result in an increased risk of recurrent thrombosis [44].

The half-life of lepirudin is approximately 60 min after IV injection and 120 min after SC injection. It is cleared from circulation by the kidneys, and the drug can accumulate in those patients with a creatinine clearance of less than 60 mL/min. The use of a high-flux hemofiltration system is the only available and valid means to manage lepirudin overdose [45]. The dose is adjusted to achieve a target aPTT ratio of 1.5 to 2.5 times baseline [32••, 45]. As of May 31, 2012, Bayer HealthCare stopped shipping lepirudin. The company expects supply from wholesalers to be depleted by mid-2013.

Bivalirudin has a half-life of 25 minutes after IV injection. The half-life of bivalirudin in severe renal failure is sustained to 1 hour, and in dialysis-dependent renal failure, the half-life approaches 4 hours [46]. Only a fraction of the drug (20 %) is cleared through the kidneys, while the rest is metabolized by proteolysis. In the case of overdose, hemodialysis, hemofiltration, and plasmapheresis can remove significant amounts of bivalirudin, although there is no specific antidote for this drug. The aPTT is usually used for monitoring patients treated for HIT for a target of 1.5- to 2.5-fold increase above the patient's baseline aPTT. Nevertheless, this measurement at times may not be reliable since it could be prolonged due to patient's hepatic dysfunction, warfarin administration, DIC and so forth.

Cost/cost-effectiveness

The direct thrombin inhibitors are expensive compared to other agent. For example, the cost of argatroban for 5 days on a 70 Kg individual at 2 mcg/kg/min is $5,400 (100 mg/mL [2.5 mL]: $1350.03 [38]).

Oral agents

Until recently, oral vitamin K antagonists were the only alternative available for chronic anticoagulation. Warfarin requires monitoring to ensure that therapeutic anticoagulation.

Standard dosage

Vitamin K antagonist

VKAs produce their anticoagulant effect by interfering with the cyclic transformation of vitamin K and vitamin K epoxide, therefore modulating clotting factors II, VII, IX, and X and the natural anticoagulants protein C and protein S, rendering them nonfunctional within the clotting cascade.

Warfarin

Most patients can begin therapy with 5 mg of warfarin daily. For elderly patients, those on interacting medications, those with malnutrition, and those with multiple active medical issues, it is reasonable to start with an initial dose of 2–3 mg. A 10-mg initial oral dose can be used for stable patients with low bleeding risk. A parenteral medication must be overlapped until the INR is therapeutic and for at least 5 days [47].

Factor Xa inhibitors

As a family, these medications have good oral bioavailability and rapid onset of action, eliminating the need for bridging therapy with a parenteral anti-

coagulant. Diet has no effect on the activity of the drug, and the potential for drug – drug interactions is much lower when compared to warfarin.

Rivaroxaban

Was approved by the FDA to be used as treatment strategy for pulmonary embolism in November 2012. The recommended dose for acute VTE is 15 mg twice daily for three weeks, followed by 20 mg once daily. This regimen was not inferior to standard therapy for the initial and long term treatment of PE [48].
The efficacy of other factor X inhibitors on VTE treatment, including edoxaban and apixaban, are not yet available [49].

Direct thrombin inhibitor

The oral prodrug dabigatran etexilate, which is converted to dabigatran, acts as a potent reversible direct thrombin inhibitor. Dabigatran has a rapid onset of action, eliminating the need for bridging therapy with a parenteral anticoagulant and lacks interaction with cytochrome P450, food or other drugs.

Dabigatran

A dose of 150 mg twice daily had a similar efficacy and safety profile as warfarin in the treatment of acute symptomatic VTE [50]. Of note, in the RE-COVER trial, initial parenteral anticoagulation was used for both the dabigatran and the warfarin arm. In the United States, this medication has not yet been approved for treatment of VTE.

Contraindications Warfarin is contraindicated during pregnancy because of its teratogenic effect. Current data is insufficient to evaluate the safety of direct thrombin inhibitors and oral factor Xa inhibitors during pregnancy; therefore, the use of oral agents during pregnancy should be avoided [51].

Main drug interactions There are multiple potential drug interactions with warfarin [52]. Rivaroxaban should be avoided with the use of other anticoagulants as may enhance its effect, as well as P-glycoprotein and CYP3A4 inhibitors since it may increase its serum concentration [53]. Amiodarone and droneradone may increase the serum concentration of dabigatran.

Main side effects Hemorrhage is the major adverse effect of all the oral anticoagulants. Bleeding might occur at essentially any site. Bleeding risk is dependent on multiple variables, which includes intensity of anticoagulation, drug-drug/food interactions and patient susceptibility. Fortunately, major bleeding is not a frequent complication; in RECOVER, the rate of major bleeding events with the patients on dabigatran was 1.6 %, and 1.9 % for those on warfarin. In the EINSTEIN PE trial, which represents more than 4000 patients, major bleeding happened for rivaroxaban in 1.1 % of the patients and 2.2 % in the warfarin group (hazard ratio, 0.49; 95 % CI, 0.31 to 0.79, P=0.003) [48].

Special points Warfarin has a long half-life (36 to 42 hours); it reaches maximum concentrations about 90 minutes after oral administration, circulates bound to albumin and accumulates in the liver where it has most of its therapeutic effect. Intensity of anticoagulation is monitored by means of the INR in which the target range for VTE is between 2 to 3. Vitamin K, fresh frozen plasma infusion, recombinant activated factor VII and prothrombin complex concentrate are all alternatives for reversal of anticoagulation [54–56].

Rivaroxaban half-life is approximately 5 to 9 hours; it reaches peak concentrations about 3 hours after oral administration, circulates primarily bound to albumin, and its metabolism is via the liver CYP3A4/5 and CYP2J2. It requires no monitoring and an antidote to rivaroxaban is currently unavailable.
Dabigatran half-life is approximately 12 to 17 hours; it reaches peak concentrations in about 1 hour after oral administration. Dabigatran etexilate is hydrolyzed to its active form by plasma and hepatic esterases; which later undergo hepatic glucoronidation. Routine monitoring of coagulation parameters is not recommended for patients taking dabigatran, due to its predictable pharmacokinetics. There is no formal reversal agent for dabigatran. In case of emergencies, about two thirds of the drug may be dialyzed but it would take up to 4 hours given a large volume of distribution. In addition, activated prothrombin complex concentrate and recombinant factor VIIa have been proposed, but the validity of such approach remains unconfirmed [57].

Cost/cost-effectiveness Warfarin is inexpensive; 5 mg (30 pills): $49.99 [38]. The cost of monitoring however is not factored in this estimate.
Rivaroxaban and dabigatran are more expensive options.

Thrombolytic therapy

In most patients with PE, thrombolytic therapy will not be necessary. The current ACCP guidelines give a grade 2C recommendation for systemic thrombolysis, reserved for patients with PE associated with hypotension and who are not at a high bleeding risk [13••]. Assuming a mortality risk as high as 30 % among patients with massive PE, 1000 patients would need treatment to have 90 fewer deaths [13••, 58]. Among patients with submassive PE, the utility of thrombolytic therapy is still matter of debate. Meta-analyses of patients without hemodynamic compromise have failed to consistently demonstrate the value of systemic thrombolysis [59].

Recently, Stein et al. have analyzed data from more than 2 million hospital discharges of patients hospitalized with acute PE at the national level and compared the outcomes of unstable patients who received thrombolytics [N= 21,390] to those who did not receive thrombolysis [N=50,840] [60]. In this analysis, the case fatality rate attributable to PE was 8.4 % with thrombolytic therapy, compared with 42 % among patients who did not receive thrombolytic therapy [RR 0.20; 95 % CI, 0.19-0.22]. These results, however, should be interpreted with caution, as the groups were dissimilar. The Pulmonary Embolism Thrombolysis [PEITHO] trial is soon to present results and is expected to enroll 1000 patients, more than all patients in previous randomized controlled trials combined. This prospective, multicenter, international, randomized, double-blind study comparing thrombolysis with tenecteplase vs. placebo in patients with submassive PE will likely be a definitive trial [61].

Standard procedure There is a paucity of evidence comparing administration regimens; however, the most efficient administration mechanism is peripheral venous infusion of the thrombolytic agent over <2 h. Bolus administration is appropriate in patients with cardiac arrest [13••]. The administration of thrombolytic therapy via a pulmonary artery catheter is currently discouraged [13••]. Several agents have been used in previous trials, including urokinase (4,400-

U/kg bolus dose, followed by 4,400 U/kg per hour for 24 hours.) [62], streptokinase (250,000-IU loading dose followed by 100,000 IU/h for 24 hours) [63], recombinant tPA, reteplase, tenecteplase (weight-adjusted bolus over 5 sec at a dose ranging from 30 to 50 mg, with a 5-mg step every 10 kg from <60 to ≥90 kg) [64]. The dose of 100 mg recombinant tPA infused over 2 hours is currently the most commonly studied regimen. In a meta-analysis of 11 thrombolysis trials, there was no statistically significant increase in major bleeding events between thrombolysis and heparin alone arms [9.1 % vs. 6.1 %; OR 1.42, 95 % CI 0.81 - 2.46] [65].

Contraindications Absolute contraindications for the use of thrombolysis are: prior intracranial hemorrhage, structural intracranial cerebrovascular disease, malignant intracranial neoplasm, ischemic stroke within 3 months, suspected aortic dissection, active bleeding, recent surgery involving the spinal canal or brain, and recent closed-head or facial trauma with radiographic evidence of bony fracture or brain injury [20••].

Complications The most common complications are non-major bleeding events which happen in as much as 22 % of the patients [65]. In a national-level epidemiological study on 49,500 patients with PE who required thrombolysis, the rate of intracranial bleed was less than 1 % [66]. The prevalence of intracerebral hemorrhage was lower among younger patients (i.e., < 65 years of age) with no renal failure.

Special points In the MOPETT (MOderate Pulmonary Embolism Treated with Thrombolysis) trial, 121 patients were randomized to a lower dose of tissue plasminogen activator [For patients ≥ 50 kg=10 mg in 1 min followed by 40 mg in 2 hours] vs. anticoagulation alone. The authors reported in abstract form that the outcomes of pulmonary hypertension and recurrent PE at 28 months were better for the thrombolysis group. Final results, however, remain unpublished [67].

Cost/cost-effectiveness Thrombolysis may decrease the length of stay, suggesting cost effectiveness [68]. The cost of a 100-mg vial of alteplase is $4,779.71 [69].

Interventional procedures

Inferior vena cava filter placement

In patients with life-threatening PE and bleeding complications during anticoagulation, or those patients with VTE recurrence despite with optimal antithrombotic therapy, an inferior vena cava (IVC) filter should be considered.

IVC filters may be permanent or retrievable; most the filters that are currently placed are retrievable. Over time, the initial beneficial of IVC filters for preventing PE is counterbalanced by an increased incidence of DVT, without a difference in patient mortality [70].

Standard procedure Retrievable filters are deployed according to manufacturer design and specifications. Filters can be placed from femoral, brachial, or jugular venous access. While some versatile filters can be retrieved using a femoral approach, most are retrieved via the jugular vein. Usual deployment of IVC filter is at the infrarenal IVC, as a prophylactic measure for emboli from lower extremities; placement at the superior vena cava is seldom used and not currently recommended for upper extremity DVT (UEDVT). The incidence of PE resulting from UEDVT is approximately 6 %, and less than 1 % is associated with fatal events [71]. The maximum implantation time depends of the filter type and is widely variable, as filter thrombogenicity and patient status are

often the determinant factors that prompt the clinician to expedite or delay filter removal after deployment. In the absence of institutional policy or a local registry, the rate of IVC filter retrieval is often lower than 30 %. A mechanism to follow up outcomes and assess continued need of the IVC filter is strongly recommended [72].

Contraindications There are relatively few absolute contraindications for IVC filter deployment. In general, contraindications are related to the intricacies of the procedure itself, due to the use of radiocontrast in the setting of renal insufficiency, or allergy to iodinated contrast dye. In these scenarios, intravascular venous ultrasound may be used to guide the filter placement [73]. In patients with extensive IVC thrombus, filter deployment may be obstructed by the thrombus itself [74].

Complications The most frequent complication of IVC filters is filter occlusion, and its incidence varies from 6 to 30 % of cases [75]. Other complications include lower extremity DVT with subsequent post-thrombotic syndrome, vena cava perforation, and filter migration, as well as complications from insertion and thrombosis at the insertion site.

Cost/cost-effectiveness Expensive option. In addition, the cost of extraction of a retrievable filter should be considered.

Catheter-directed therapy

Direct administration of thrombolytics into large proximal thromboemboli has being considered in patients with acute PE however this therapeutic approach does not appear to be better than the use of thrombolytics by the peripheral route. One pilot trial has shown that intrapulmonary catheter directed infusion of rt-PA does not offer significant benefit over the intravenous route [76].

Surgery

Embolectomy

Due to historical mortality ranging up to 32 %, emergent pulmonary embolectomy has been relegated as a last option in many institutions [77, 78]. The current ACCP guidelines give surgical embolectomy only a grade 2C recommendation [13••]. Recent reports claim an improved in hospital mortality to levels as low as 6 %; and expert opinion has suggested that it is time to re-explore surgical indications [78–81]. Leacche and colleagues suggested the expansion of the indications also to include hemodynamically stable patients with massive central clot burden and signs of right ventricular dysfunction [80]. Conversely, the Nationwide Inpatient Sample was recently used to report on 2709 adult patients who underwent surgical embolectomy for acute PE from 1999 to 2008 [82]. In this sample, mortality for surgical embolectomy was 27 % [82]. In this large study, the covariates independently associated with mortality were the Charlson comorbidity index and black race.

Surgical embolectomy is primarily indicated for critically ill patients in whom thrombolysis is contraindicated, or for whom it cannot be infused in a timely fashion [77, 78]. A recent study compared outcomes among patients who did not respond to thrombolysis and underwent surgical

	embolectomy or repeat thrombolysis [83]. The authors included 40 cases of failed thrombolysis, from 488 patients who initially required thrombolysis in their registry. The repeated thrombolysis arm had a higher mortality (38 % vs 7 %) than the patients who underwent surgery [OR 0.13 95 % CI 0.003 – 1.12]. Failed thrombolysis, defined as persistent clinical instability and residual echocardiographic right ventricle dysfunction at 36 hours, is potentially an adequate indication for surgical embolectomy [83].
Standard procedure	Direct incision to the pulmonary arteries is required and the thrombotic material is removed using a miniaturized metallic suction device (tip size, 2–6 mm). In addition, both lungs are gently compressed to mobilize smaller peripheral thrombi. After closure of the pulmonary arteries, the right ventricle, atria, and cava are examined. In some institutions post-operatively, routine pulmonary artery angiography is performed. After the procedure, low-dose IV heparin is started 4 hours after surgery [84].
Complications	Recurrent PE is a probable complication after surgical embolectomy, with an incidence of 5 %; therefore, IVC filter placement is often recommended preoperatively [78, 80, 85].
Special points	Thielmann et al. have recently explored the value of pre-operative cardiac troponin as an outcome predictor among patients who have surgery for pulmonary embolism [84]. In-hospital 30-day mortality was increased among patients with elevated troponins [39 vs. 8 %; OR: 9.0; 95 % CI:1.0–215.2; P=0.03]. Furthermore, on a receiver operator curve analysis, a cutoff value of 1.8 ng/ml cTnI had a valuable area under the curve of 0.848 [95 % CI: 0.69–1.0]. The retrospective nature of this study and the heterogeneous characteristics of patients in the normal troponin group limits the interpretation of these results In a retrospective study of 28 patients who underwent embolectomy, compared to 52 patients who underwent thrombolysis for severe PE, the subsequent quality of life measured by SF36, was not different among the two groups; in the physical and psychological components the SF36 subscores favored surgery [86].
Cost/cost-effectiveness	Very expensive.

Emerging therapies

ECMO

Peripheral extracorporeal membrane oxygenation [pECMO] has been recently proposed for high-risk patients with massive PE who do not qualify for either thrombolysis or surgical embolectomy. There is paucity of data on this technique; in a case series of four patients with an APACHE IV predicted mortality of 23 %, all patients survived [87].

Disclosure

Dr. Omar Esponda reported no conflicts of interest relevant to this article.
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