كلية الطب بنات جامعة الأزهر

Role of Thrombolysis in Pulmonary Embolism

By

Abeer Ahmed Elmalah,

Lecturer of Cardiology, Faculty of Medicine "Girls"

Contents

Pulmonary embolism 1

Definition 1

Epidemiology 1

Classification 1

Reperfusion treatment 4

Systemic thrombolysis 4

Indication 4

Contraindication 9

Type of thrombolytic agents 10

Administration 11

Regimens 12

Catheter directed thrombolysis 16

Outcome 19

Mortality 19

Complications 20

Hemodynamic benefits 21

Side effects 22

Surgical embolectomy 22

Inferior vena cava filters 23

Regimens and treatment duration with non VKA oral anticoagulants and antithrombotic drugs 24

New agents 26

References 27

Pulmonary embolism (PE)

Definition:

Pulmonary embolus (PE) refers to obstruction of the pulmonary artery or one of its branches by material (eg, thrombus, tumor, air, or fat) that originated elsewhere in the body [1].

The majority of pulmonary emboli arise in the deep veins of the legs, but they may also arise from the deep veins of the arms, particularly when central venous catheters are present. Other veins, such as renal and pelvic veins, are uncommon sources of pulmonary emboli [2].

Epidemiology:

Pulmonary embolism is a common disease, occurring in 60 to 112 of every 100,000 individuals. It is the third most common cause of cardiovascular mortality and is responsible for 100,000 to 180,000 deaths annually [2]. PE may cause ≤300,000 deaths per year in the US, ranking high among the causes of cardiovascular mortality [3]. In epidemiological studies, the annual incidence rates for PE range from 39-115 per 100,000 populations [3&4]. Cross-sectional data show that the incidence of VTE is almost eight times higher in individuals aged ≥80 years than in the fifth decade of life [3]. In parallel, longitudinal studies have revealed a rising tendency in annual PE incidence rates over time [5,6&7].

Classification:

One useful clinical classification of pulmonary embolism divides the condition into massive pulmonary embolism, submassive pulmonary embolism, and low-risk (for mortality) pulmonary embolism [8].

While classifying pulmonary embolism, it is reasonable to consider not only size of the embolus but also the underlying cardiopulmonary reserve. Therefore, the best way to classify pulmonary embolism depends on the hemodynamic consequences (hemodynamically unstable or stable): Hemodynamically unstable PE is also called "massive" or "high-risk" PE. Hemodynamically stable PE is called "submassive" or "intermediate-risk" PE if there is associated right ventricular strain or "low-risk" PE if there is no evidence of RV strain [9].

Hemodynamically unstable PE (massive) is that which results in hypotension. Hypotension is defined as a systolic blood pressure <90 mmHg or

a drop in systolic blood pressure of ≥40 mmHg from baseline for a period >15 minutes or hypotension that requires vasopressors or inotropic support and is not explained by other causes. In addition, nonspecific symptoms, patients with acute massive PE also present with persistent profound bradycardia, or cardiogenic shock (Table 1) [9].

Table 1: Definition of haemodynamic instability and high-risk PE [1]

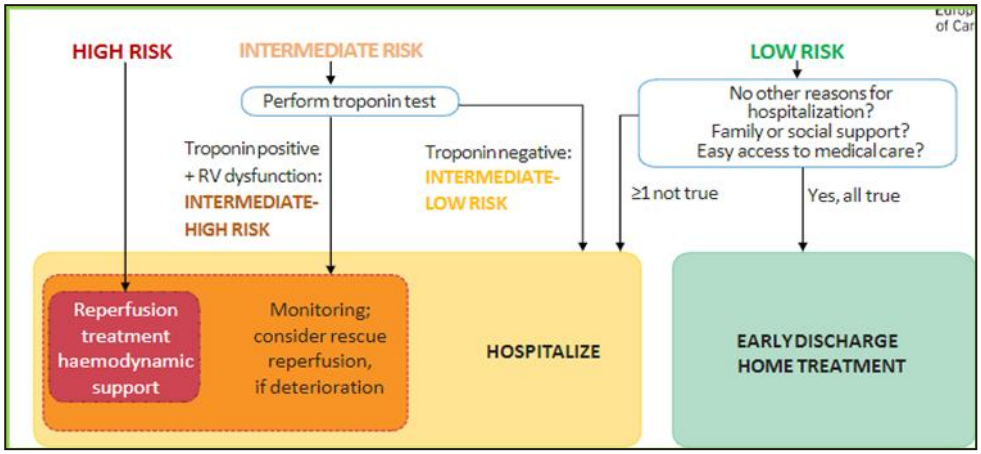
(1) Cardiac arrest	(2) Obstructive shock	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP <90 mmHg, or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status ***And*** End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	Systolic BP <90 mmHg, or systolic BP drop ≥40 mmHg, either lasting longer than 15 minutes and not caused by new-onset arrhythmia, hypovolaemia, or sepsis

Although hemodynamically unstable PE is often caused by large (ie, massive) PE, it can sometimes be due to small PE in patients with underlying cardiopulmonary disease. Thus, the term "massive" PE does not necessarily describe the size of the PE as much as it's hemodynamic effect.

Hemodynamically stable PE is defined as PE that does not meet the definition of hemodynamically unstable PE. There is a spectrum of severity within this population ranging from patients who present with small, mildly symptomatic or asymptomatic PE (also known as "low-risk PE") to those who present with mild or borderline hypotension that stabilizes in response to fluid therapy, or those who present with right ventricle dysfunction [10]. Submassive PE is defined as an acute PE without systemic hypotension (systolic blood pressure >90 mm Hg) but with either RV dysfunction or myocardial necrosis [11].

Clinical evidence of instability in this subgroup of patients could present as a decrease in systolic BP that remains above 90 mm Hg, tachycardia, poor tissue perfusion, RV dysfunction or enlargement, worsening respiratory insufficiency or major myocardial necrosis [11]. The ninth edition of the American College of Chest Physicians (ACCP) guidelines for antithrombotic and thrombolytic therapy recommended the use of thrombolytic therapy in patients with acute PE associated with hypotension and in a subgroup of patients who are hemodynamically stable at presentation but are at high risk for hypotension (Figure 1) [11].

Figure 1: Risk-adjusted management strategy for acute PE [1]



Bozbay et al suggested that levels of creatinine kinase isoenzyme-MB (CK-MB) may be used as a prognostic marker for inpatients with PE treated with tPA [12]. In their study of 148 patients with acute PE who received tPA, those with high CK-MB levels at admission (>31.5 U/L) had higher rates of inpatient mortality (37.1%) than those with low CK-MB levels at admission (1.7%). Long-term outcomes were similar for the two groups with regard to recurrent PE, major/minor bleeding, and mortality [13]. Patients with pulmonary thromboembolism often decompensate suddenly, and once hemodynamic compromise has developed, mortality is extremely high. When the decision is made to use thrombolysis, the fastest-acting available thrombolytic agent with an acceptable safety and efficacy profile should be chosen. Many centers prefer off-label regimens to the slower on-label regimens that have been approved by the US Food and Drug Administration (FDA) [14].

Unfractionated heparin (UFH) should not be given concomitantly with fibrinolytic therapy in acute massive PE. After fibrinolytic therapy, anticoagulation treatment is recommended to prevent recurrent thrombosis. Heparin should not be started until the activated partial thromboplastin time (aPTT) has decreased to less than twice the normal control value [15].

In the worst clinical scenario, PE can cause cardiac arrest. The most common cardiac arrest initial rhythms documented include pulseless electrical activity and asystole. Cardiac arrest in the event of PE carries a mortality of 66-95% [15].

Numerous case reports state the use of thrombolytic boluses in cardiac arrest due to PE, with apparent heroic results. According to the British Thoracic Society 2003 recommendations, immediate administration of 50 mg of alteplase may be lifesaving for patients in cardiac arrest believed to be caused

by PE. The clinician's focus should be on preventing the cardiac arrest and identifying patients who are candidates for thrombolytic therapy in the event of a PE [15].

The three thrombolytic agents currently approved by the FDA for use in patients with acute PE are alteplase, urokinase, and streptokinase. Tenecteplase is being studied for use in PE; however, it is not yet approved for this indication. In Steering Committee single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury [15].

Reperfusion treatment in PE

Systemic thrombolysis

The history of thrombolytic therapy began in 1933, when it was discovered that filtrates of broth cultures of certain streptococcal strains (beta-hemolytic streptococci) could dissolve a fibrin clot [16].

Thrombolytic agents activate plasminogen to form plasmin, resulting in the accelerated lysis of thrombi. As a result, thrombolytic agents have been used in a variety of thrombotic disorders including acute myocardial infarction, stroke, acute pulmonary embolism (PE), and deep vein thrombosis (DVT) [17].

Indications:

Persistent hypotension or shock (ie, a systolic blood pressure <90 mmHg or a decrease in the systolic blood pressure by ≥40 mmHg from baseline) due to acute PE is the only widely accepted indication for systemic thrombolysis [11]. In most cases, systemic thrombolytic therapy should be considered only after acute PE has been confirmed because the adverse effects of this therapy can be severe. Because a pulmonary arteriogram immediately precedes catheter-based therapy, PE can be confirmed at that time when this procedure is undertaken [18].

The decision to administer thrombolysis is strongly influenced by clinical factors that are unique to the individual. For example, while a patient with proven PE-induced shock who is unconscious requiring very high doses of vasopressors is a candidate for immediate intravenous thrombolytic therapy, the indication is not as apparent in a patient who has low blood pressure for 20 minutes but who is awake, alert, and comfortable with low oxygenation requirement. Thus, when feasible, it is prudent to adopt a multidisciplinary

approach to facilitate management of patients with PE and help with the decision of thrombolysis; some centers have incorporated a "pulmonary embolism response team" (PERT) to facilitate this process (disciplines including, for example, cardiology, pulmonology, haematology, vascular medicine, anaesthesiology/intensive care, cardiothoracic surgery, and interventional radiology) [19&20].

Most clinicians and society guidelines accept that thrombolysis in patients with acute PE who present with hypotension is likely beneficial and therefore is a widely accepted indication [11&21]. A similar approach is also appropriate in those whose course is complicated by hypotension assessed to be due to recurrent PE despite anticoagulation.

They lead to faster improvements in pulmonary obstruction, pulmonary artery pressure, and peripheral vascular resistance accompanied by reduction of RV dilatation in echocardiography [22&23].

Few trials have evaluated the effects of systemic thrombolytic therapy in hemodynamically unstable patients, but those that did found a consistent trend toward improved mortality [24-28]. A meta-analysis that included those trials did a subgroup analysis of 154 patients with massive (high-risk) PE and found that systemic thrombolytic therapy decreased the composite endpoint of death and recurrent thromboembolism (9.4 versus 19%) [29]. Another meta-analysis reported a reduced short-term all-cause mortality in unstable patients with PE treated with thrombolytic therapy compared with those not treated with thrombolytics [30].

Hemodynamically stable patients: For most patients with acute PE who do not have hemodynamic compromise thrombolytic therapy is not warranted. Under occasional circumstances, thrombolysis may be considered on a case-by-case basis when the benefits are assessed by the clinician to outweigh the risk of hemorrhage and the patient's values and preferences have been taken into consideration [11&21].

The following are situations during which clinicians typically contemplate thrombolysis, particularly when patients develop:

- Severe or worsening right ventricular dysfunction (submassive PE)
- Cardiopulmonary arrest due to PE (eg, BP >90 mmHg after resuscitation)
- Extensive clot burden (large perfusion defects on ventilation/perfusion scan or extensive embolic burden on computed tomography)

- Free-floating right atrial or ventricular thrombus
- Signs of deterioration (increasing tachycardia, clinical signs of shock, worsening blood pressure, significant hypoxemia) despite maintaining a systolic blood pressure >90 mmHg [31-35].

Although most patients listed above may not be initially treated with thrombolysis, they should be anticoagulated and monitored closely since they are at risk of deterioration and a decision to administer thrombolytics may need to be made promptly.

Assessing patients based upon a validated clinical prognostic score, preferably the PESI (or sPESI, its simplified version) (Table 2), has been recommended (2014 ESC/ERS PE Guidelines) to distinguish between intermediate-low risk (abnormal sPESI + abnormal RV function OR abnormal BNP or troponin) and intermediate-high risk (abnormal sPESI + abnormal RV function and abnormal BNP or troponin), this stratification cannot be utilized as a definitive means to decide whether thrombolytic or catheter-directed therapy should be administered. Although retrospective reports suggest that outcomes may be no different between anticoagulation and reperfusion therapies among patients with evidence of right heart thrombus, This population considered for catheter-based or surgical-based clot removal on an individual basis [36&37].

Table 2: The original pulmonary embolism severity index (PESI) and simplified (sPESI) clinical risk scores [1]

Parameter	PESI	s-PESI
Age	Age in years	1 point (if >80 years)
Male sex	+10 points	-
Cancer diagnosis	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 beats per minute	+20 points	1 point
Systolic blood pressure <100 mmHg	+30 points	1 point
Respiratory rate ≥30 breaths per minute	+20 points	-
Temperature <36°C	+20 points	-
Altered mental status	+60 points	-
Arterial oxyhemoglobin saturation <90 %	+20 points	1 point
Risk stratification		
Class I: ≤65 points	Very low 30-day mortality risk (0–1.5 %)	
Class II: 66–85 points	Low mortality risk (1.7–3.5 %)	
Class III: 86–105 points	Moderate mortality risk (3.2–7.1 %)	
Class IV: 106–125 points	High mortality risk (4–11.4 %)	
Class V: >125 points	Very high mortality risk (10–24.5 %)	
Simplified PESI Score		
0 points = 30-day mortality risk 1 % (95 % CI 0–2.1 %)		
≥ 1 point(s) = 30-day mortality risk 10.9 % (95 % CI 8.5–13.2 %)		

Right ventricular dysfunction:

The most controversial situation in which thrombolytic therapy is often considered is right ventricular (RV) dilation or hypokinesis without systemic hypotension (also known as "submassive" or "intermediate-risk" PE). The rationale for thrombolysis in this population is based upon the observation that severe RV dysfunction is associated with a worse prognosis than mild or no RV dysfunction [37].

However, randomized trials have not shown a convincing mortality benefit in these patients. This may be because clinical trials of thrombolytic therapy have not stratified this population based upon the degree of RV enlargement or the severity of RV dysfunction. As an example, this population of patients with acute PE constitutes a spectrum of severity such that patients with severe or worsening RV dysfunction and a markedly elevated brain natriuretic peptide level, with a substantial oxygen requirement and an elevated heart rate (>120/minute), is likely different than patients with mild RV dysfunction, a normal heart rate and no oxygen requirement. Thus, thrombolytic therapy in this population should be individualized and benefits and risks (of bleeding) should be carefully weighed on a case-by-case basis. Several studies have shown improved RV function in association with the administration of thrombolytic agents (systemic and catheter-directed) and one meta-analysis has suggested a possible mortality benefit [38-44].

The largest of these trials was the randomized multicenter trial (PEITHO) trial that compared thrombolytic therapy (tenecteplase) plus heparin with placebo plus heparin in 1005 patients with acute PE who were normotensive and had evidence of RV dysfunction (ie, "intermediate-risk PE") [38]. RV dysfunction was confirmed by echocardiography or computed tomography and a positive troponin (I or T). Tenecteplase was administered as an IV push with weight-based dosing and heparin was either unfractionated or low molecular weight heparin. Compared with heparin alone, thrombolysis resulted in a reduction in the primary endpoint of death or hemodynamic decompensation at seven days following randomization (6 vs 3%). Subgroup analysis indicated that the differences in outcome were affected largely by the prevention of further decompensation; there was no difference in 7 day or 30 day mortality (2.4 vs 3.2% at 30 days). The administration of thrombolytic agents was associated with increased extracranial bleeding (6 vs 1%), major bleeding (12 vs 2%), and hemorrhagic stroke (2 vs 0.2%). In a prespecified subgroup analysis of patients older than 75 years, benefits of therapy were maintained but rates of extracranial bleeding were higher (11 vs 0.6%), suggesting that risk benefit may be more favorable in those 75 years-old or

younger. Long-term follow up of these patients (approximately 3.5 years) reported no difference in mortality (20 vs 18%) and no difference in dyspnea or exercise capacity, right ventricular dysfunction, or chronic thromboembolic pulmonary hypertension (2 vs 3%) [45].

Further randomized trials are needed to identify subpopulations of patients with RV dysfunction where the benefits in mortality clearly outweigh the risk of hemorrhage before it can be routinely used to treat hemodynamically stable acute PE with RV dysfunction. Specifically, more data further stratifying intermediate-risk PE based on severity of RV dysfunction, biomarkers (troponin/brain natriuretic peptide), oxygen requirement, residual DVT, and simple vital sign parameters such as heart and respiratory rate are necessary [46].

Cardiopulmonary resuscitation:

Case reports and series have reported some success from systemic thrombolytic therapy during cardiopulmonary resuscitation when the cardiac arrest is due to suspected or confirmed acute PE [47-49].

One retrospective study reported a 5% incidence of PE (diagnosed by autopsy, clinically, or echocardiography) in 1246 cardiac arrest victims [48]. Subgroup analysis suggested that thrombolysis was associated with a greater rate of return of spontaneous circulation compared with those who did not receive thrombolysis. Another retrospective study of 23 patients with pulseless electrical activity (PEA) due to confirmed massive PE reported return of spontaneous circulation within two to 15 minutes after the administration of tissue plasminogen activator at a reduced dose of 50 mg intravenous push [49]. In contrast, another randomized study of 233 patients who presented with PEA arrest of unknown etiology reported that compared to placebo, thrombolysis did not improve survival or return of spontaneous circulation [50].

There are insufficient data to debate for or against the routine use of thrombolytic therapy during cardiac arrest; however, the decision to administer treatment as a potentially lifesaving maneuver for suspected PE-induced cardiac arrest can be considered on a case-by-case basis.

Extensive clot burden:

A large clot burden may elevate pulmonary arterial pressure without causing significant RV dysfunction or hemodynamic collapse. A large retrospective study suggested that an obstruction index by CTA in acute PE >40% was associated with an 11-fold increase in mortality [51]. However, there

was no proof that systemic thrombolysis would reduce this mortality with an acceptable bleeding rate.

Other indications:

Although there is no clear indication for thrombolytic therapy in patients with severe hypoxemia, a free-floating right atrial or ventricular thrombus (with or without a patent foramen ovale), the administration of thrombolytic therapy in such rare circumstances may be considered on an individual basis. Some patients with paradoxical embolism and a large patent foramen ovale (PFO) may need surgical closure. There is no clear algorithm for patient selection for PFO closure [51].

Contraindications:

In every patient in whom thrombolysis is contemplated, the risk of bleeding should always be considered. The importance of the contraindication depends on the strength of the indication [52]. As an example, a contraindication is of more concern if the indication for systemic thrombolytic therapy is RV dyskinesis, than if the indication is shock.

Absolute contraindications are active bleeding or bleeding diathesis, ischemic stroke within 2-3 months, history of hemorrhagic stroke, intracranial neoplasm, recent (<2 months) intracranial or spinal surgery or trauma.

Relative contraindications include a major operation within 10 days, multiple trauma within 2 weeks, neurosurgery or ophthalmologic operations within 1 month, and similar conditions, severe uncontrolled hypertension (systolic blood pressure >200 mmHg or diastolic blood pressure >110 mmHg), nonhemorrhagic stroke older than three months, surgery within the previous 10 days, and pregnancy [53-58]. However, these relative contraindications are also associated with inducible risks for PE. Therefore, thrombolytic therapy may still be appropriate for patients with severe PE complicated by relative contraindications [11&59] (Table 3).

Table 3: Contraindications to thrombolysis

Absolute contraindication
• Haemorrhagic stroke or stroke of unknown origin at any time
• Ischaemic stroke in the preceding 6 months
• Central nervous system damage or neoplasms
• Recent major trauma/surgery/head injury in the preceding 3 weeks
• Gastrointestinal bleeding within the last month
• Known bleeding risk
Relative contraindications
• Transient ischaemic attack in the preceding 6 months
• Oral anticoagulant therapy
• Pregnancy, or within one week postpartum
• Non-compressible puncture site
• Traumatic resuscitation
• Refractory hypertension (systolic blood pressure >180 mmHg)
• Advanced liver disease
• Infective endocarditis
• Active peptic ulcer

Thrombolytic therapy may cause moderate bleeding in menstruating women, but it has rarely been associated with major hemorrhage. Therefore, menstruation is not a contraindication to thrombolytic therapy.

Type of Thrombolytic agents:

Fibrinolytic agents, sometimes referred to as plasminogen activators, are divided into the following two categories:

Fibrin-specific agents: include alteplase (tPA), reteplase (recombinant plasminogen activator [r-PA]), and tenecteplase, produce limited plasminogen conversion in the absence of fibrin.

Non–fibrin-specific agents: streptokinase (catalyze systemic fibrinolysis), urokinase, prourokinase and Anisoylated purified streptokinase activator complex (APSAC; anistreplase).

Fibrinolytic agents can be administered systematically or can be delivered directly into the area of the thrombus [60].

Recombinant tissue type plasminogen activator (tPA also known as alteplase), streptokinase (SK), and recombinant human urokinase (UK) are the best studied thrombolytic agents for the treatment of acute PE, that are approved by the US Food and Drug Administration (FDA).

tPA is a naturally occurring enzyme produced by a number of tissues including endothelial cells. tPA binds to fibrin, which increases its affinity for plasminogen and enhances plasminogen activation [61&62].

SK is a polypeptide derived from beta-hemolytic streptococcus cultures. It binds to plasminogen, forming an active enzyme that activates plasmin [61&63]. Because streptokinase is produced from streptococcal bacteria, it often causes febrile reactions and other allergic problems. It can also cause hypotension that appears to be dose-related. Streptokinase usually cannot be administered safely a second time within 6 months, because it is highly antigenic and results in high levels of antistreptococcal antibodies [64].

Streptokinase:

It is the least expensive fibrinolytic agent, but unfortunately, its antigenicity and its high incidence of untoward reactions limit its usefulness in the clinical setting. Although other fibrinolytic agents are more popular in developed nations such as the United States, streptokinase continues to be widely used in developing nations [64].

Urokinase:

It is also a plasminogen activator that is normally present in the urine. It is the major activator of fibrinolysis in the extravascular compartment, in contrast to tPA which is largely responsible for initiating intravascular fibrinolysis. Because the FDA-approved duration for tPA delivery is two hours, the use of streptokinase and urokinase decreased and these drugs are no longer available for use in the United States for acute PE but is still used elsewhere because of its lower cost [64].

Prourokinase:

Prourokinase is a fibrinolytic agent that is undergoing clinical trials for a variety of indications. It is a relatively inactive precursor that must be converted to urokinase before it becomes active in vivo. The need for such conversion has handicapped therapeutic exploitation of the fibrin-specific physiologic properties of prourokinase.

The relative fibrin-specificity of prourokinase is explained by preferential activation of fibrin-bound plasminogen found in a thrombus over the free plasminogen in flowing blood. This agent has been studied in the settings of acute myocardial infarction, AIS, and peripheral arterial occlusion [65].

Anisoylated purified streptokinase activator complex (APSAC):

Anistreplase is a complex of streptokinase and plasminogen that doesn't require free circulating plasminogen to be effective. It has many theoretical benefits over streptokinase but suffers antigenic problems similar to those of the parent compound. Like streptokinase, anistreplase does not distinguish between fibrin-bound and circulating plasminogen; consequently, it produces a systemic lytic state. The half-life of APSAC in plasma is somewhere between 40 and 90 minutes [66].

Administration:

Once the decision to administer thrombolytic therapy has been made, the thrombolytic agent is typically administered via a peripheral intravenous catheter as an infusion [11]. Although bolus and catheter-directed routes of administration have been studied, there are less available data. Unnecessary invasive procedures (particularly arterial punctures) should be minimized while thrombolytic therapy is being administered, and extreme caution should be

taken with patients who have had PE-induced syncope with resultant head trauma even if the brain computed tomography (CT) is negative.

Anticoagulant therapy is generally discontinued during the thrombolytic infusion. Discontinuing anticoagulants during thrombolysis is consistent with that most commonly performed in trials done in the United States. However, in other trials, particularly in Europe, this has not been the case. The potential risk of bleeding with continued anticoagulation and the risk of recurrent embolism while anticoagulation is discontinued is unknown. Full anticoagulation (usually heparin followed by an oral anticoagulant) following clot lysis is typically undertaken. The optimal duration of intravenous heparin following thrombolysis is unknown. Similarly, the duration of long term anticoagulation, once the patient is stabilized depends on a number of factors primarily focused on perceived risk for recurrence an absolute minimum of three months is required [11].

Some researchers have proposed that anticoagulation therapy with heparin will prevent the development of new fibrin on the thrombus, thereby facilitating lysis by thrombolytic agents and reducing the risk of re-extension after thrombolysis [67]. Unfractionated heparin infusion can be continued during recombinant t-PA infusion.

Thrombolytic regimens

Alteplase

The FDA-approved alteplase regimen for PE is 100 mg as a continuous infusion over 2 hours. A 15-mg bolus is administered first, followed by 85 mg administered over 2 hours. Heparin drip must be discontinued during alteplase infusion.

Some centers prefer to use an accelerated 90-minute regimen that appears to be faster-acting, safer, and more efficacious than the 2-hour infusion. For patients weighing less than 67 kg, the drug is administered as a 15-mg IV bolus followed by 0.75 mg/kg over the next 30 minutes (maximum, 50 mg) and then 0.50 mg/kg over the next 60 minutes (maximum, 35 mg). For patients weighing more than 67 kg, 100 mg is administered as an 15-mg IV bolus followed by 50 mg over the next 30 minutes and then 35 mg over the next 60 minutes [68].

Urokinase

The FDA-approved urokinase regimen for PE consists of 4400 U/kg as a loading dose given at a rate of 90 mL/hr over a period of 10 minutes, followed by continuous infusion of 4400 U/kg/hr at a rate of 15 mL/hr for 12 hours [66].

Streptokinase

The FDA-approved streptokinase regimen for PE consists of 250,000 U as a loading dose over 30 minutes, followed by 100,000 U/hr over 12-24 hours. Monitor closely for hypotension, anaphylaxis, asthma, and allergic reactions. Mild adverse reactions may respond favorably to a decreased infusion rate [11].

Reteplase

Reteplase has not been approved by the FDA for any indication except acute myocardial infarction (AMI), but it is widely used for acute deep vein thrombosis (DVT) and PE. The dosing used is the same as that approved for patients with AMI: two IV boluses of 10 U each, administered 30 minutes apart [11].

Although tPA (alteplase) is the most commonly used thrombolytic, superiority of any agent or regimen over another has not been established. Studied regimens include tPA administration over 15 minutes or two hours, urokinase administration over two hours or 24 hours, and streptokinase administration over two hours, 12 hours, or 24 hours. The evidence from small randomized trials suggests that shorter infusions (ie, ≤2 hours) achieve more rapid clot lysis and are associated with lower rates of bleeding than longer infusions (ie, ≥12 hours) [11]. The FDA-approved infusion duration for tPA of two hours, being much shorter than for SK or UK, has been the main reason why this drug is commonly chosen and is the only thrombolytic agent that is FDA-approved for acute PE.

An activated partial thromboplastin time (aPTT) can be measured when infusion of the thrombolytic therapy is complete. Heparin should be resumed without a loading dose when the aPTT is less than twice its upper limit of normal. If the aPTT exceeds this value, the test should be repeated every four hours until it is less than twice its upper limit of normal, at which time heparin should be resumed. Another option is to simply restart the heparin infusion without a bolus when the thrombolytic infusion has been infused.

Coagulation assays are unnecessary during infusion of the thrombolytic agent since thrombolytic agents are administered as fixed doses [11].

Reduced-dose thrombolytic therapy:

The question of whether a lower dose of thrombolytic therapy could expedite resolution of pulmonary hypertension due to a "moderate" acute PE without major adverse effects was examined in the Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) trial [69]. Moderate PE was defined as the presence of signs and symptoms of PE plus CT pulmonary angiography demonstrating >70% involvement with embolism in ≥2 lobar arteries or main pulmonary arteries or by a high probability ventilation/perfusion (V/Q) scan showing V/Q mismatch in ≥2 lobes. The 121 patients were randomly assigned to receive heparin (unfractionated or low molecular weight) alone or the combination of lower-dose tissue type plasminogen activator (alteplase) plus heparin. This dose of tPA was ≤50% of the standard dose (100 mg) for patients weighing 50 kg or more and 0.5 mg/kg for those weighing less than 50 kg. Compared with conventional therapy, this lower-dose regimen of tPA resulted in the following:

- Lower rates of pulmonary hypertension (by echocardiography; 57 versus 16 percent)
- Lower pulmonary artery systolic pressures at 28 months (43 ± 6 versus 28 ± 7 mmHg)
- Faster resolution of pulmonary hypertension (50 ± 6 mmHg versus 51 ± 7 mmHg on admission; 43 ± 6 mmHg versus 28 ± 7 mmHg at 28 months)
- Similar rates of bleeding (0% in each group)
- Recurrent PE (5 vs 0%), and
- Mortality (5 vs 1.6%) [70].

Statistical significance for a rate reduction in recurrent PE was only reached when it was combined with pulmonary hypertension or mortality as a composite outcome. The sample size was small and the prevalence of RV dysfunction (<25%) and RV hypokinesis (<7%) in this study was low. In addition, echocardiography is not the optimal tool for determining pulmonary artery pressure, thus there is no proof that any of the patients with elevated PA pressure had chronic thromboembolic pulmonary hypertension [71].

A retrospective propensity-matched study reported that compared with patients treated with full-dose alteplase (100 mg), patients treated with half-dose alteplase (50 mg) required vasopressor therapy and invasive ventilation less often but needed rapid increase of therapy more often [71]. Hospital mortality and rates of significant bleeding were similar.

One retrospective analysis compared reduced-dose (half-dose) thrombolysis with catheter-directed thrombolysis and found that both therapies led to similar reductions in the pulmonary artery systolic pressure and RV/LV ratio but that half-dose thrombolysis reduced the duration and cost of hospitalization [72]. Further studies are required before firm conclusions can be drawn from this retrospective study.

Based on this limited evidence, a recommendation cannot be made to implement this lower-dose regimen of tPA for "moderate" PE. Further prospective studies are needed to validate its efficacy in a larger population of patients with moderate acute PE [73].

Bolus injections:

Bolus infusion of thrombolytics may be effective without excess bleeding complications [74&75]. However, this has not been directly compared to a two-hour infusion of tPA (alteplase). More trials comparing the regimens are necessary before routine bolus infusion replace the more conventional two hour regimen.

An exception is that bolus infusion of thrombolytic therapy is indicated for patients with imminent or actual PE-related cardiac arrest [11].

The impact of bolus infusion was illustrated by a double-blind trial in which 58 patients with acute PE were randomly assigned to receive tPA (alteplase) (0.6 mg/kg over two minutes) plus heparin or placebo plus heparin [74]. Patients who received tPA were more likely to have >50% clot resolution and increased perfusion within 24 hours, although there were no detectable differences by the seventh day. There was no major bleeding in either group.

However, during an arrest or impending arrest it is more practical to give tPA (alteplase) using an entire 50 mg vial rather than calculating and preparing a fractional dose based upon patient weight. In adult patients with PE-related arrest, a 50 mg IV bolus of tPA (alteplase) can be given over two minutes and repeated after 15 minutes in the absence of return of spontaneous circulation. This regimen is generally consistent with American Heart Association 2015 guidelines on cardiopulmonary resuscitation, section on arrest in special circumstances, and 2012 guidelines of American College of Chest Physicians on antithrombotic therapy for VTE [76].

If tPA (alteplase) is unavailable, but tenecteplase is available, a single IV dose of tenecteplase given over five seconds can be given for PE-related

cardiac arrest, based upon patient weight (30 mg for ≤60 kg; 35 mg for 61 to 69 kg; 40 mg for 70 to 79 kg; 45 mg for 80 to 89; 50 mg for ≥90 kg).

Thrombolytics for PE-related arrest are given with systemic anticoagulation (unfractionated heparin infusion) [76].

Catheter-directed thrombolysis

Thrombolytic agents can be infused directly into the pulmonary artery via a pulmonary arterial catheter [40,43,77&78]. Guidelines suggest that catheter-directed thrombolysis may be considered for patients with persistent hemodynamic instability despite systemic thrombolysis, those at risk of death before systemic thrombolysis can manifest effectiveness, and those at high risk of bleeding [21].

It should be kept in mind that in spite of this guideline recommendation, catheter-based therapy can, in fact, almost never be performed faster than systemic lysis. Catheter-directed thrombolysis (CDT) should be reserved for use in centers with appropriate expertise. The potential advantage of catheter-administered thrombolytics is that lower doses of lytic agent can be administered, thereby reducing the risk of bleeding when compared with systemic therapy. In addition, other mechanical interventions can be simultaneously performed to aid clot dissolution (eg, ultrasound) or mechanical removal (eg, embolectomy) [79].

As an alternative to thrombolytic therapy, CDT may be warranted if the necessary resources and expertise are available. However, it was believed that systemic thrombolysis, even delivered over two hours, is generally faster than a CDT with or without lysis, although this may depend on how quickly the latter procedure can be arranged.

Percutaneous catheter-directed treatment:

Catheter-directed treatment (CDT) is an alternative to surgery if immediate access to cardiopulmonary bypass is unavailable [80].

The objective of CDT is the removal of obstructing thrombi from the main pulmonary arteries to facilitate RV recovery and improve symptoms and survival [81].

Interventional options include thrombus fragmentation with a pigtail or balloon catheter, clotlytic thrombectomy with hydrodynamic catheter devices, suction thrombectomy with aspiration catheters and mechanical thrombectomy

that break up the clot. With respect to thrombus fragmentation, the fact that the cross-sectional area of the distal arterioles is more than four times that of the central circulation and that the volume of the peripheral circulatory bed is about twice that of the pulmonary arteries suggests that the redistribution of large central clots into smaller clots in the peripheral pulmonary arteries may acutely improve cardiopulmonary hemodynamics, with significant increases in the total pulmonary blood flow and RV function [82] The action of these thrombectomy devices can sometimes be facilitated by softening the thrombotic mass using thrombolytic therapy, which helps to speed up the debulking and fragmentation of the occlusive clots. Fragmentation can also be used as a complement to thrombolytic therapy because fragmentation of a large clot exposes fresh surfaces on which endogenous urokinase and infused thrombolytic drugs can work to further break down the resulting emboli [82].

One review on CDT included 35 nonrandomized studies involving 594 patients [83]. The rate of clinical success, defined as stabilization of hemodynamic parameters, resolution of hypoxia, and survival to discharge, was 87%. The contribution of the mechanical catheter intervention per se to clinical success is unclear because 67% of patients also received adjunctive local thrombolysis. Publication bias probably resulted in underreporting of major complications (reportedly affecting 2% of interventions), which may include death from worsening RV failure, distal embolization, pulmonary artery perforation with lung hemorrhage, systemic bleeding complications, pericardial tamponade, heart block or bradycardia, hemolysis, contrast-induced nephropathy, and puncture-related complications [81]. While anticoagulation with heparin alone has little effect on improvement of RV size and performance within the first 24 to 48 h, the extent of early RV recovery after low-dose catheter-directed thrombolysis appears comparable with that after standard-dose systemic thrombolysis.

In a randomized controlled clinical trial of 59 patients with intermediate-risk PE, when compared with treatment by heparin alone, catheter-directed ultrasound-accelerated thrombolysis (administration of 10 mg t-PA per treated lung over 15 h) significantly reduced the subannular RV/LV dimension ratio between baseline and the 24-h follow-up without an increase in bleeding complications [84].

According to a guideline [80], CDT should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed.

Data regarding this approach come from small prospective trials with mixed results. As examples:

The initial catheter-directed thrombolysis trial was a study of 34 patients published in 1988, and included 34 patients with persistent hypotension due to acute PE (ie, high-risk PE). CDT was compared with intravenous tPA (alteplase) (100 mg for each route) [82]. In the catheter-based group, the tPA was delivered directly into the pulmonary arteries with no form of mechanical lysis attempted. The route of administration had no impact on degree of reduction of clot burden (determined by pulmonary angiogram) or the mean pulmonary arterial pressure. Both catheter-directed and intravenous tPA (alteplase) were associated with bleeding at surgical, puncture, and catheter insertion sites.

The ultrasound accelerated thrombolysis of pulmonary embolism (ULTIMA) randomized 59 patients with acute intermediate risk pulmonary embolism to ultrasound-assisted catheter-directed thrombolysis (USAT) followed by intravenous heparin or intravenous heparin alone [40]. Intermediate risk PE was defined as PE of the main or lower lobe pulmonary artery and echocardiographic evidence of right ventricular enlargement (RV: LV ratio ≥1). The USAT regimen consisted of high frequency ultrasound combined with 10 to 20 mg of tPA infused over 15 hours. At 24 hours, compared to conventional anticoagulation, USAT resulted in an improved RV:LV ratio (mean difference 0.3 versus 0.03), suggesting a hemodynamic benefit. At 90 days, there was no difference in mortality or major bleeding between the groups.

Another single-arm prospective trial in a similar population (SEATTLE II) described similar results [43]. This system is approved by the FDA.

A retrospective review of 105 cases of massive and submassive PE reported an improved RV/LV ratio in patients treated with CDT-thrombolysis compared with heparin alone without any difference in 90-day mortality or major bleeding [85].

Limitations of these trials include small sample size, inadequate power to estimate survival benefit, use of echocardiography to assess pulmonary hypertension, and lack of data describing the effect of thrombolysis over a more extended period (weeks to months) on clinically meaningful outcomes. Further randomized studies will be needed to clarify the population that would benefit from this approach before CDT can be routinely used for patients with acute PE [80].

Outcomes:

The effects of thrombolytic therapy followed by anticoagulant therapy have been compared to those of anticoagulant therapy alone. The evidence consistently indicates that thrombolytic therapy leads to early hemodynamic improvement, but at a cost of increased major bleeding. Although thrombolytic therapy has been shown in one meta-analysis to improve mortality, methodologic flaws limited the analysis such that the specific population that may potentially derive benefit as well as the optimal agent, dose, and delivery system (catheter-directed or systemic) remain unknown [80].

Mortality:

Thrombolytic therapy has been shown in one meta-analysis of patients with acute PE to improve mortality, although the data was not robust for any one specific patient population nor was the optimal agent or dose identified.

This meta-analysis of 16 trials comprising 2115 patients reported that, compared to anticoagulation alone, thrombolytic therapy (mostly systemic agents) was associated with a lower all-cause mortality (2.2 versus 3.9%) [80]. The mortality benefit was maintained in a pre-specified analysis of the eight trials that enrolled only hemodynamically stable patients with right ventricle dysfunction (1.4 versus 2.9%). In contrast, the mortality benefit was not significant in patients older than 65 years (2.1 versus 3.6%). Importantly, any mortality benefit from thrombolysis came at the expense of an increased risk of major hemorrhage (9.2 versus 3.4%). To put these opposing risks and benefits in context, 59 patients would need to be treated to prevent one death, while a major bleed occurs with every 18 patients treated, according to this analysis [86].

In addition, this meta-analysis was limited by the inclusion of different thrombolytic agents at varying doses and poor definitions of hemodynamic stability/instability and was not able to distinguish benefit from systemic versus catheter-directed therapy [80]. Randomized trials that clearly demonstrate a mortality benefit in select populations of patients with acute PE (other than high-risk PE) will be needed before thrombolytic therapy can be administered routinely.

Recurrent thromboembolism:

A meta-analysis of 16 trials reported reduced rates of recurrent thromboembolism with thrombolytic therapy compared to anticoagulation alone (1.2 vs 3%) [80]. However, recurrence rates were assessed at varying time points, such that the effect on recurrent thromboembolism remains in question.

Complications:

Bleeding:

Systemic thrombolytic therapy increases the risk of major bleeding including intracranial hemorrhage. A meta-analysis of pooled data from trials using various thrombolytic agents and regimens showed an intracranial bleeding rate of 1.46% [86]. In a meta-analysis comparing thrombolysis vs. anticoagulation with UFH alone [87] major bleeding including intracranial or retroperitoneal bleeding, bleeding requiring blood transfusion, or bleeding requiring surgical hemostasis was observed significantly more often in patients undergoing thrombolysis than anticoagulation (13.7 vs. 7.7%, respectively). In the subgroup analysis of that study [87] major bleeding was not significantly increased in patients aged ≤65 years. However, there was an association with a greater risk of major bleeding in those aged >65 years. Increasing age and the presence of comorbidities including cancer, diabetes, a high prothrombin time, high international normalized ratio, or concomitant use of catecholamines have been associated with a higher risk of bleeding complications [88]. In a study, a strategy using reduced-dose recombinant t-PA appeared to be safe in patients with hemodynamic instability or massive pulmonary embolism [89]. In patients with mobile right heart thrombi, the therapeutic benefits of thrombolysis remain controversial [90].

One meta-analysis of 16 trials compared bleeding rates with thrombolytic agents to that associated with anticoagulant therapy (usually heparin) [80]. The use of thrombolytic agents was associated with greater overall rates of major bleeding (9.2 versus 3.4%), as well as higher rates of intracranial hemorrhage (1.5 vs 0.2%). In a subgroup analysis, the risk of thrombolysis-associated bleeding was three-times greater in those older compared to those younger than 65 years (12.9 vs 4.1%). Older patients also did not derive a mortality benefit from thrombolysis in this same analysis.

Few studies have sought to identify risk factors for bleeding during thrombolytic therapy. In a retrospective analysis of 104 patients with acute PE who received IV tPA (alteplase), 20 patients (19%) had major bleeding [91]. The principal site of bleeding was unknown in nine patients (45%), gastrointestinal in six patients (30%), retroperitoneal in three patients (15%), intracranial in one patient (5%), and splenic in one patient (5%). Independent predictors of major hemorrhage were administration of catecholamines for systemic arterial hypotension, malignancy, diabetes mellitus and an elevated international normalized ratio (INR) [91].

Bleeding during thrombolytic therapy occurs most commonly at sites of invasive procedures such as pulmonary arteriography or arterial puncture [93&94]. Invasive procedures should be minimized when thrombolytic therapy is contemplated and while it is being administered. Bleeding from vascular puncture sites should be controlled with manual compression followed by a pressure dressing.

In practice, patients with significant or refractory bleeding are typically transfused ten units of cryoprecipitate and two units of fresh frozen plasma, then reassessed. In addition, protamine sulfate should be considered to reverse the effect of any heparin that may remain in the patient's plasma. When considering reversal, the relative severity of the bleeding and the thromboembolic process must be weighed in view of the potential to exacerbate the thromboembolic process.

The most devastating complication associated with systemic thrombolytic therapy is intracranial hemorrhage [94]. Clinical trials suggest that this complication occurs in up to 3% of patients who receive thrombolytic therapy for acute PE, which is higher than the rate of intracranial hemorrhage reported after thrombolysis for acute coronary occlusion [33,80,92&95]. If intracranial bleeding is suspected clinically, infusion of the thrombolytic agent should be immediately discontinued. Following stabilization, a noncontrast-enhanced computed tomographic scan of the brain and emergent neurologic/neurosurgical consultation should be obtained.

Hemodynamics benefits:

Thrombolytic therapy improves pulmonary arterial blood pressure, RV function, and pulmonary perfusion in the short-term [70,96-99]. However, it is uncertain whether these beneficial effects persist because the data are contradictory. This was best illustrated by two studies:

In a prospective, nonrandomized trial of 40 consecutive patients with acute PE, patients who received thrombolytic therapy had improved RV function 12 hours after the initiation of therapy, compared to patients who received anticoagulation alone [96]. One week later, there was no difference in RV function. This suggests that either the improvement of RV function seen in patients who received thrombolytic therapy was transient and short-lived or that RV function improved later in patients who did not receive thrombolytic therapy. The latter seems more likely.

In another trial, 40 patients with acute PE were randomly assigned to receive thrombolysis or anticoagulation alone [97&98]. Follow-up two weeks and

one year after the initiation of therapy demonstrated more complete resolution of emboli in the group that received thrombolytic therapy (determined by diffusing capacity and pulmonary capillary blood volume) [97]. Longer-term follow-up (an average of seven years) revealed that patients who had been treated with thrombolytic therapy had lower pulmonary artery pressure and pulmonary vascular resistance, compared to patients who had received anticoagulant therapy alone, suggesting that the hemodynamic benefits of thrombolytic therapy were persistent [99].

Side effects:

There are adverse effects that are specific for certain thrombolytic agents. As an example, streptokinase is associated with allergic reactions and hypotension:

Streptokinase (SK) is antigenic and can cause immunologic sensitization and allergic reactions, particularly with repeat administration. Major reactions are rare, with anaphylaxis occurring in less than 0.5% of patients. However, less severe symptoms such as shivering, pyrexia, or rash may occur in up to 10 percent of patients. The efficacy of SK is not reduced by an allergic reaction; however, anti-SK antibodies remain elevated for up to 7.5 years after treatment, suggesting that a suboptimal response and/or an allergic reaction may occur even if SK is readministered many years later [100&101].

Hypotension may occur during streptokinase infusion (particularly if the infusion rate is increased above 500 units/kg/min). The decreased blood pressure usually responds to cessation or slowing of the infusion, intravenous fluids, or vasopressors.

Surgical embolectomy

Traditionally, surgical embolectomy has been reserved for patients with PE who may need cardiopulmonary resuscitation. It is also performed in patients with contraindications or inadequate responses to thrombolysis and in those with patent foramen ovale and intracardiac thrombi [80]. Pulmonary embolectomy is technically a relatively simple operation. Extra-corporal membrane oxygenation (ECMO) can be helpful in critical situations, ensuring circulation and oxygenation until a definitive diagnosis is obtained [102].

After rapid transfer to the operating room and induction of anesthesia and median sternotomy, normothermic cardiopulmonary bypass should be instituted. Aortic cross-clamping and cardioplegic cardiac arrest should be

avoided [103]. With bilateral pulmonary artery incisions, clots can be removed from both pulmonary arteries down to the segmental level under direct vision. Prolonged periods of postoperative cardiopulmonary bypass and weaning may be necessary for recovery of RV function. With a rapid multidisciplinary approach and individualized indications for embolectomy before hemodynamic collapse, perioperative mortality rates of ≤6% have been reported [103&104].

Preoperative thrombolysis increases the risk of bleeding, but it is not an absolute contraindication to surgical embolectomy [105]. The long-term postoperative survival rate, World Health Organization functional class, and quality of life were favorable [102&106].

Patients presenting with an episode of acute PE superimposed on a history of chronic dyspnea and pulmonary hypertension are likely to develop chronic thromboembolic pulmonary hypertension. These patients should be transferred to an expert center for pulmonary endarterectomy [106].

Inferior vena cava filters

In general, inferior vena cava (IVC) filters are indicated in patients with acute PE who have absolute contraindications to anticoagulant drugs and in patients with objectively confirmed recurrent PE despite adequate anticoagulation treatment. Observational studies have suggested that insertion of a venous filter might reduce PE-related mortality rates in the acute phase [107&108], this benefit possibly coming at the cost of an increased risk of recurrence of venous thromboembolism (VTE) [108].

Although complications associated with permanent IVC filters are common, they are rarely fatal [109]. Overall, early complications, which include insertion-site thrombosis, occur in approximately 10% of patients. Late complications are more frequent and include recurrent DVT in approximately 20% of patients and post-thrombotic syndrome in up to 40% of patients. Occlusion of the IVC affects approximately 22% of patients at 5 years and 33% at 9 years, regardless of the use and duration of anticoagulation [110]. Impermanent IVC filters are classified as temporary or retrievable devices. Temporary filters must be removed within a few days, while retrievable filters can be left in place for longer periods. Impermanent filters should be removed as soon as it is safe to use anticoagulants [111].

The prevention of pulmonary embolism in Cave II trial enrolled patients with acute symptomatic PE with concomitant DVT and at least one independent risk factor for fatal PE (age of >75 years, RV dysfunction and/or

elevated troponin and/or hypotension, bilateral DVT and/or iliocaval DVT, active cancer, or chronic cardiac or respiratory failure). The primary end point was fatal and nonfatal PE recurrence at 3 months. The investigators found no significant reduction in the primary end point for patients who received an IVC filter [111].

Although some observational data suggest that IVC filter placement in addition to anticoagulation might improve survival in patients with unstable PE or after thrombolytic therapy, controlled data do not support its routine use in patients at high risk of death unless there is a contraindication to anticoagulant therapy [108]. There are no data to support the routine use of venous filters in patients with high-risk PE.

Regimens and treatment durations with non-vitamin K antagonist oral anticoagulants, and with other non-vitamin K antagonist antithrombotic drugs:

All patients with PE should be treated with anticoagulants for ≥3 months [112]. Beyond this period, the balance between the risk of VTE recurrence and that of bleeding, which has been used to select candidates for extended anticoagulation after a first VTE event in the VKA era, is currently being revisited based on the lower bleeding rates with NOACs. However, despite the improved safety of these drugs compared with VKAs, treatment with NOACs is not without risk. Phase III clinical trials on the extended treatment of VTE have shown that the rate of major bleeding may be 1%, and that of clinically relevant non-major (CRNM) bleeding as high as 6%. Bleeding rates may be higher in every day clinical practice [113].

In all studies, patients with PE made up approximately one-third of the entire study population, while the remaining two-thirds were patients with proximal DVT but no clinically overt PE. Patients needed to have completed the initial and long-term anticoagulation phase to be included in the extended studies. *Dabigatran* was compared with warfarin or placebo in two different studies [114]. In these studies, dabigatran was non-inferior to warfarin for the prevention of confirmed recurrent symptomatic VTE or VTE-related death, and more effective than placebo for the prevention of symptomatic recurrent VTE or unexplained death [114]. The rate of major bleeding was 0.9% with dabigatran compared to 1.8% with warfarin [114].

Rivaroxaban was compared with placebo or aspirin in two different studies in patients who had completed 6-12 months of anticoagulation treatment for a first VTE event. Treatment with rivaroxaban [20 mg once a day

(o.d.)] reduced recurrent VTE by 80%, with a 6.0% incidence of major or CRNM bleeding as compared to 1.2% with placebo. [115].

Rivaroxaban given at a dose of 20 or 10 mg o.d. was compared with aspirin (100 mg o.d.) in 3365 patients [116]. Both doses of rivaroxaban reduced symptomatic recurrent fatal or non-fatal VTE by 70% in comparison with aspirin. No significant differences in the rates of major or CRNM bleeding were shown between either dose of rivaroxaban and aspirin [116].

Patients with VTE were randomized to receive two different doses of *apixaban* [2.5 or 5 mg twice a day or placebo after 6-12 months of initial anticoagulation [117].

Both doses of apixaban reduced the incidence of symptomatic recurrent VTE or death from any cause compared with placebo, with no safety concerns [117]. Patients at high bleeding risk based on the investigator's judgement, the patient's medical history, and the results of laboratory examinations were excluded from the extension studies; this was also the case for studies on extended anticoagulation with VKAs [118&119]. This fact should be taken into account during triage of a patient for extended anticoagulation with one of the above regimens [120].

In a randomized, open-label study in high-risk patients with antiphospholipid syndrome (testing triple positive for lupus anticoagulant, anticardiolipin, and anti-b2-glycoprotein I), rivaroxaban was associated with an increased rate of thromboembolic and major bleeding events compared with warfarin [120]. NOACs are not an alternative to VKAs for patients with antiphospholipid syndrome. In two trials with a total of 1224 patients, extended therapy with aspirin (after termination of standard oral anticoagulation) was associated with a 30-35% reduction in the risk of recurrence compared with placebo [121&122].

However, more recently, another trial demonstrated the superiority of anticoagulation with rivaroxaban, either 20 or 10 mg once per day, over aspirin for secondary prophylax is of VTE recurrence [116].

A randomized, placebo controlled study evaluated sulodexide (low molecular weight heparin) for the prevention of recurrence in 615 patients with a first VTE event without an identifiable risk factor, who had completed 3-12 months of oral anticoagulant treatment. Sulodexide reduced the risk of recurrence by 50% with no apparent increase in bleeding events. However, only 8% of patients in this study had PE as the index VTE event [123].

New agents

Single-chain antibody-prothrombotic serine-protease thrombin (SCE5-HtPlg)**:** Thrombolytic therapy for acute thrombosis is limited by life-threatening side effects such as major bleeding and neurotoxicity. New treatment options with enhanced fibrinolytic potential are therefore required [124]. Thrombin is a key enzyme of the blood coagulation cascade as it activates platelets, catalyzes the polymerization of fibrinogen into fibrin, and converts factors V, VIII, XI, and XIII into their activated form [125].

A recombinant microplasminogen modified to be activated by the prothrombotic serine-protease thrombin (HtPlg), fused to an activation-specific anti–glycoprotein IIb/IIIa single-chain antibody (SCE5), thereby hijacking the coagulation system to initiate thrombolysis in blood samples collected from human volunteers. The resulting fusion protein named SCE5-HtPlg shows in vitro targeting towards the highly abundant activated form of the fibrinogen receptor glycoprotein IIb/IIIa expressed on activated human platelets. Following thrombin formation, SCE5-HtPlg is activated to contain active microplasmin.

Administration of SCE5-HtPlg resulted in effective thrombolysis 20 minutes after injection. It is a potent and effective treatment for thrombosis that enables in vivo thrombolysis without bleeding time prolongation. The activation of this construct by thrombin generated within the clot itself rather than by a plasminogen activator, which needs to be delivered systemically, provides a targeted approach to improve thrombolysis [124].

Role of clopidogrel in PE:

A previous study revealed that clopidogrel may provide additional safe & effective treatment strategies for acute PE. Clinical effectiveness of clopidogrel has been tested in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial comparing either daily aspirin or clopidogrel. After a mean follow-up of 2 yrs, patients treated with clopidogrel had an annual risk of ischemic stroke, MI or vascular death of 5.3% compared with 5.8% in the aspirin arm [126].

References

1. Konstantinides SV, Meyer G, Becattini C, et al. ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). European Heart Journal. 2019; 00: 1
2. Ramesh D, Setty HS, Kumarswamy, et al. Timely embolectomy in acute massive pulmonary embolism prevents catastrophe: An experience from two cases. J Nat Sci Biol Med. 2016; 7: 176.
3. Martin C, Sobolewski K, Bridgeman P and Boutsikaris D. Systemic Thrombolysis for Pulmonary Embolism: A Review. Pulmonary and therapeutic. 2016; 41: 770.
4. Wendelboe AM and Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circ Res 2016; 118: 1340.
5. Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J. 2019; 00: 1.
6. de Miguel-Diez J, Jimenez-Garcia R, Jimenez D, et al. Trends in hospital admissions for pulmonary embolism in Spain from 2002 to 2011. Eur Respir J. 2014; 44: 942.
7. Dentali F, Ageno W, Pomero F, et al. Time trends and case fatality rate of in-hospital treated pulmonary embolism during 11 years of observation in Northwestern Italy. ThrombHaemost. 2016; 115: 399.
8. Lehnert P, Lange T, Moller CH, et al. Acute pulmonary embolism in a national Danish cohort: increasing incidence and decreasing mortality. Thromb Haemost. 2018; 118: 539.
9. Bělohlávek J, Dytrych V and Linhart A. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp Clin Cardiol. 2013; 18: 129.
10. Kucher N and Goldwater SZ. Management of massive pulmonary embolism. Circulation. 2005; 112:e28.
11. Fangled BT and Brady WJ. Fibrinolysis therapy in pulmonary embolism: an evidence-based treatment algorithm. Am J Emerg Med. 2009; 27: 84.

12. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141: e419S.

13. van der Meer RW, Pattynama PM, van Strijen MJ, et al. Right ventricular dysfunction and pulmonary obstruction index at helical CT: prediction of clinical outcome during 3-month follow-up in patients with acute pulmonary embolism. Radiology 2005; 235: 798.

14. Bozbay M, Uyarel H, Avsar S, et al. Creatinine kinase isoenzyme-MB: A simple prognostic biomarker in patients with pulmonary embolism treated with thrombolytic therapy. J Crit Care. 2015; 30: 1179.

15. Yamamoto T. Management of patients with high-risk pulmonary embolism: a narrative review. J Intensive Care. 2018; 6: 16.

16. Pulmonary embolism thrombolysis study (PETHO). An observational study, rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J. 2012; 163: 33e1.

17. Ouriel K. A history of thrombolytic therapy. J Endovasc Ther. 2004; 2: II128.

18. Tapson, VF, Weinberg, AS, Mandel J and Finlay G. Thrombolytic (Fibrinolytic) Therapy in Acute Pulmonary Embolism and Lower Extremity Deep Vein Thrombosis. Uptodate. 2018

19. Konstantinides SV, Torbicki A, Agnelli G, et al. ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014; 35: 30.

20. Kabrhel C, Jaff MR, Channick RN, et al. A multidisciplinary pulmonary embolism response team. Chest. 2013; 144: 1738.

21. Dudzinski DM and Piazza G. Multidisciplinary Pulmonary Embolism Response Teams. Circulation 2016; 133: 98.

22. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016; 149: 315.

23. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost. 2014; 12: 459.

24. Becattini C, Agnelli G, Salvi A, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res. 2010; 125: e82.

25. Dotter CT, Seamon AJ, Rosch J. Streptokinase and heparin in the treatment of acute pulmonary embolism. VascSurg. 1979; 13: 42.

26. Jerjes-Sanchez C, Ramírez-Rivera A, de Lourdes García M, et al. Streptokinase and Heparin versus Heparin Alone in Massive Pulmonary Embolism: A Randomized Controlled Trial. J Thromb Thrombolysis. 1995; 2: 227.

27. Ly B, Arnesen H, Eie H, Hol R. A controlled clinical trial of streptokinase and heparin in the treatment of major pulmonary embolism. Acta Med Scand. 1978; 203: 465.

28. Tibbutt DA, Davies JA, Anderson JA, et al. Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonay embolism. Br Med J. 1974; 1: 343.

29. Urokinase pulmonary embolism trial. Phase 1 results: a cooperative study. JAMA. 1970; 214: 2163.

30. Wan S, Quinlan DJ, Agnelli G and Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation. 2004; 110: 744.

31. Quezada CA, Bikdeli B, Barrios D, et al. Meta-Analysis of Prevalence and Short-Term Prognosis of Hemodynamically Unstable Patients With Symptomatic Acute Pulmonary Embolism. Am J Cardiol. 2019; 123: 684.

32. Guidelines on diagnosis and management of acute pulmonary embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. Eur Heart J. 2000; 21: 1301.

33. Dalen JE. The uncertain role of thrombolytic therapy in the treatment of pulmonary embolism. Arch Intern Med. 2002; 162: 2521.

34. Goldhaber SZ. Modern treatment of pulmonary embolism. Eur Respir J. 2002; 35: 22s.

35. Goldhaber SZ. Echocardiography in the management of pulmonary embolism. Ann Intern Med. 2002; 136: 691.

36. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA. 2014; 311: 2414.

37. Koć M, Kostrubiec M, Elikowski W, et al. Outcome of patients with right heart thrombi: the Right Heart Thrombi European Registry. Eur Respir J. 2016; 47: 869.

38. Barrios D, Chavant J, Jiménez D, et al. Treatment of Right Heart Thrombi Associated with Acute Pulmonary Embolism. Am J Med. 2017; 130: 588.

39. Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000; 101: 2817.

40. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014; 370: 1402.

41. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014; 129: 479.

42. Becattini C, Agnelli G, Salvi A, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res. 2010; 125: e82.

43. Engelberger RP, Moschovitis A, Fahrni J, et al. Fixed low-dose ultrasound-assisted catheter-directed thrombolysis for intermediate and high-risk pulmonary embolism. Eur Heart J. 2015; 36: 597.

44. Piazza G, Hohlfelder B, Jaff MR, et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. The SEATTLE II Study. J Am Coll Cardio. 2015; 8: 1382.

45. Kuo WT, Banerjee A, Kim PS, et al. Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): Initial Results From a Prospective Multicenter Registry. Chest. 2015; 148: 667.

46. Konstantinides SV, Vicaut E, Danays T, et al. Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism. J Am Coll. Cardiol 2017; 69: 1536.

47. Vyas PA and Donato AA. Thrombolysis in Acute Pulmonary Thromboembolism. 2012 Southern Medical Association. 2012; 105: 560.

48. Bailén MR, Cuadra JA and Aguayo De Hoyos E. Thrombolysis during cardiopulmonary resuscitation in fulminant pulmonary embolism: a review. Crit Care Med. 2001; 29: 2211.

49. Kürkciyan I, Meron G, Sterz F, et al. Pulmonary embolism as a cause of cardiac arrest: presentation and outcome. Arch Intern Med. 2000; 160: 1529.

50. Sharifi M, Berger J, Beeston P, et al. Pulseless electrical activity in pulmonary embolism treated with thrombolysis (from the "PEAPETT" study). Am J Emerg Med. 2016; 34:1963.

51. Abu-Laban RB, Christenson JM, Innes GD, et al. Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. N Engl J Med. 2002; 346:1522.

52. van der Meer RW, Pattynama PM, van Strijen MJ, et al. Right ventricular dysfunction and pulmonary obstruction index at helical CT: prediction of clinical outcome during 3-month follow-up in patients with acute pulmonary embolism. Radiology. 2005; 235:798.

53. Papanikolaou J, Spathoulas K, Makris D and Zakynthinos E. Thrombolysis for Massive Pulmonary Embolism in a Patient with Hemorrhagic Shock. Am J Respir Crit Care Med. 2016; 194: e15.

54. Meyer G. Massive acute pulmonary embolism. In: Jeremias A, Brown D, editors. Cardiac intensive care. Philadelphia: Saunders; 2010. pp.

55. Nijkeuter M, Geleijns J, De Roos A, et al. Diagnosing pulmonary embolism in pregnancy: rationalizing fetal radiation exposure in radiological procedures. J Thromb Haemost. 2004; 2: 1857.

56. Tromeur C, van der Pol LM, Klok FA, et al. Pitfalls in the diagnostic management of pulmonary embolism in pregnancy. Thromb Res. 2017; 151: S86.

57. Schembri GP, Miller AE and Smart R. Radiation dosimetry and safety issues in the investigation of pulmonary embolism. Semin Nucl Med. 2010; 40: 442.

58. Ramsay R, Byrd L, Tower C, James J, Prescott M, Thachil J. The problem of pulmonary embolism diagnosis in pregnancy. Br J Haematol. 2015; 170: 727

59. Bourjeily G, Khalil H, Raker C, et al. Outcomes of negative multidetector computed tomography with pulmonary angiography in pregnant women suspected of pulmonary embolism. Lung. 2012; 190: 105

60. Lavonas EJ, Drennan IR, Gabrielli A, et al. Part 10: special circumstances of resuscitation: American Heart Association guidelines update for

cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015; 132:501.

61. Hoffman R, Benz EJ, Shattil SJ, et al. Antithrombotic drugs. Hematology: Basic Principles and Practice. 5th ed. Philadelphia: Churchill Livingston Elsevier; 2008. chap 137.

62. Anderson HV and Willerson JT. Thrombolysis in acute myocardial infarction. N Engl J Med. 1993; 329: 703.

63. Van Zonneveld AJ, Veerman H and Pannekoek H. Autonomous functions of structural domains on human tissue-type plasminogen activator. Proc Natl Acad Sci. 1986; 83: 4670.

64. Kalyan NK, Lee SG, Wilhelm J, et al. Structure-function analysis with tissue-type plasminogen activator. Effect of deletion of NH2-terminal domains on its biochemical and biological properties. J Biol Chem. 1988; 263: 3971.

65. Siki N, Bardia A.A history of streptokinase use in acute myocardial infarction.Tex Heart Inst J. 2007; 34: 318.

66. Gurewich V, Pannell R, Simmons-Byrd A, et al. Thrombolysis vs bleeding from hemostatic sites by a prourokinase mutant compared with tissue plasminogen activator. J Thromb Haemost. 2006; 4: 1559.

67. Rivera-Bou WL, Schraga ED and Cabañas JG, et al. What is the mechanism of action for anisoylated purified streptokinase activator complex (APSAC) in thrombolytic therapy? Updated: 2017.

68. Agnelli G and Parise P. Bolus thrombolysis in venous thromboembolism. Chest. 1992; 101: 172.

69. Katsanos AH and Tsivgoulis G. Is intravenous thrombolysis still necessary in patients who undergo mechanical thrombectomy? Curr. Opin. Neurol. 2019; 32: 3.

70. Sharifi M, Bay C, Skrocki L, et al. Moderate Pulmonary Embolism Treated With Thrombolysis (from the "MOPETT" Trial). The American Journal of Cardiology. 2013; 111: 273.

71. Kiser TH, Burnham EL, Clark B, et al. Half-Dose Versus Full-Dose Alteplase for Treatment of Pulmonary Embolism. Crit Care Med. 2018; 46: 1617.

72. Sharifi M, Awdisho A, Schroeder B, et al. Retrospective comparison of ultrasound facilitated catheter-directed thrombolysis and systemically

administered half-dose thrombolysis in treatment of pulmonary embolism. Vasc Med. 2019; 24: 103.

73. Abraham P, Arroyo DA, Giraud R, et al. Understanding haemorrhagic risk following thrombolytic therapy in patients with intermediate-risk and high-risk pulmonary embolism: a hypothesis paper. Open Heart. 2018; 5: e000735.

74. Levine M, Hirsh J, Weitz J, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. Chest. 1990; 98:1473.

75. Meneveau N, Schiele F, Metz D, et al. Comparative efficacy of a two-hour regimen of streptokinase versus alteplase in acute massive pulmonary embolism: immediate clinical and hemodynamic outcome and one-year follow-up. J Am Coll Cardiol. 1998; 31:1057.

76. Lavonas EJ, Drennan IR, Gabrielli A, et al. Part 10: Special Circumstances of Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015; 132: S501.

77. Fengler BT, Brady WJ. Fibrinolytic therapy in pulmonary embolism: an evidence-based treatment algorithm. Am J Emerg Med. 2009; 27: 84.

78. McCabe JM, Huang PH, Riedl L, et al. Usefulness and safety of ultrasound-assisted catheter-directed thrombolysis for submassive pulmonary emboli. Am J Cardiol. 2015; 115: 821.

79. Tapson VF, Jimenez D. Catheter-Based Approaches for the Treatment of Acute Pulmonary Embolism. Semin Respir Crit Care Med. 2017; 38: 73.

80. Konstantinides SV, Torbicki A, Agnelli G, et al., Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014; 35: 3033.

81. Engelberger RP, Kucher N. Catheter-based reperfusion treatment of pulmonary embolism. Circulation. 2011; 124: 2139.

82. Tajima H, Murata S, Kumazaki T, et al. Hybrid treatment of acute massive pulmonary thromboembolism: mechanical fragmentation with a modified rotating pigtail catheter, local fibrinolytic therapy, and clot aspiration followed by systemic fibrinolytic therapy. AJR Am J Roentgenol. 2004; 183: 589.

83. Kuo WT, Gould MK, Louie JD, et al. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. J Vasc Interv Radiol. 2009; 20: 1431.

84. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014; 129: 479.

85. Hennemeyer C, Khan A, McGregor H, et al. Outcomes of Catheter-Directed Therapy Plus Anticoagulation Versus Anticoagulation Alone for Submassive and Massive Pulmonary Embolism. Am J Med. 2019; 132: 240.

86. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA. 2014; 311: 2414.

87. Thabut G, Thabut D, Myers RP, et al. Thrombolytic therapy of pulmonary embolism: a meta-analysis. J Am Coll Cardiol. 2002; 40: 1660.

88. Fiumara K, Kucher N, Fanikos J, et al. Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. Am J Cardiol. 2006; 97: 127.

89. Wang C, Zhai Z, Yang Y, et al. Thromboembolism (VTE) Study Group Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial. Chest. 2010; 137: 254.

90. Torbicki A,Galié N, Covezzoli A, et al. Study Group Right heart thrombi in pulmonary embolism: results from the International Cooperative Pulmonary Embolism Registry. J Am Coll Cardiol. 2003; 41: 2245

91. Fiumara K, Kucher N, Fanikos J and Goldhaber SZ. Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. Am J Cardiol. 2006; 97: 127.

92. Meyer G, Gisselbrecht M, Diehl JL, et al. Incidence and predictors of major hemorrhagic complications from thrombolytic therapy in patients with massive pulmonary embolism. Am J Med. 1998; 105: 472.

93. Sadiq I, Goldhaber SZ, Liu PY, et al. Risk factors for major bleeding in the SEATTLE II trial. Vasc Med. 2017; 22: 44.

94. Gore JM. Prevention of severe neurologic events in the thrombolytic era. Chest. 1992; 101: 124S.

95. Kanter DS, Mikkola KM, Patel SR, et al. Thrombolytic therapy for pulmonary embolism. Frequency of intracranial hemorrhage and associated risk factors. Chest. 1997; 111: 1241.

96. Konstantinides S, Tiede N, Geibel A, et al. Comparison of alteplase versus heparin for resolution of major pulmonary embolism. Am J Cardiol. 1998; 82: 966.

97. Sharma GV, Burleson VA, Sasahara AA. Effect of thrombolytic therapy on pulmonary-capillary blood volume in patients with pulmonary embolism. N Engl J Med. 1980; 303: 842.

98. Come PC. Echocardiographic evaluation of pulmonary embolism and its response to therapeutic interventions. Chest. 1992; 101: 151S.

99. Sharma GV, Folland ED, McIntyre KM, et al. Longterm hemodynamic benefit of thrombolytic therapy in pulmonary embolic disease (abstract). J Am Coll Cardiol. 1990; 15:65A.

100. Tsang TS, Califf RM, Stebbins AL, et al. Incidence and impact on outcome of streptokinase allergy in the GUSTO-I trial. Global Utilization of Streptokinase and t-PA in Occluded Coronary Arteries. Am J Cardiol 1997; 79: 1232.

101. Squire IB, Lawley W, Fletcher S, et al. Humoral and cellular immune responses up to 7.5 years after administration of streptokinase for acute myocardial infarction. Eur Heart J. 1999; 20: 1245.

102. Takahashi H, Okada K, Matsumori M, et al. Aggressive surgical treatment of acute pulmonary embolism with circulatory collapse. Ann Thorac Surg. 2012; 94: 785.

103. Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg. 2005; 129: 1018.

104. Fukuda I, Taniguchi S, Fukui K, et al. Improved outcome of surgical pulmonary embolectomy by aggressive intervention for critically ill patients. Ann Thorac Surg. 2011; 91: 728.

105. Aklog L, Williams CS, Byrne JG and Goldhaber SZ. Acute pulmonary embolectomy: a contemporary approach. Circulation. 2002; 105: 1416.

106. Vohra HA, Whistance RN, Mattam K, et al. Early and late clinical outcomes of pulmonary embolectomy for acute massive pulmonary embolism. Ann Thorac Surg. 2010; 90: 1747.

107. Stein PD, Matta F, Keyes DC and Willyerd GL. Impact of vena cava filters on in-hospital case fatality rate from pulmonary embolism. Am J Med. 2012; 125: 478.

108. Muriel A, Jime'nez D, Aujesky D, et al. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. J Am Coll Cardiol. 2014; 63: 1675.

109. Hann CL and Streiff MB. The role of vena caval filters in the management of venous thromboembolism. Blood Rev. 2005; 19: 179.

110. Partovi S, Davidson JC, and Indravadan J. Implications and limitations of the PREPIC2 (Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption) study: the interventionist's perspective. Cardiovasc Diagn Ther. 2016; 6: 259.

111. Author information Article notes Copyright and LicensMismetti P, Laporte S, Pellerin O, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. JAMA. 2015; 313: 1627.

112. Boutitie F, Pinede L, Schulman S, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. BMJ. 2011; 342: d30.

113. Helmert S, Marten S, Mizera H, et al. Effectiveness and safety of apixaban therapy in daily-care patients with atrial fibrillation: results from the Dresden NOAC Registry. J Thromb Thrombolysis. 2017; 44: 169.

114. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013; 368: 709

115. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010; 363: 2499.

116. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med. 2017; 376: 1211.

117. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013; 368: 699.

118. Couturaud F, Sanchez O, Pernod G, et al. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: the PADIS-PE randomized clinical trial. JAMA. 2015; 314: 31.

119. Agnelli G, Prandoni P, Becattini C, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med. 2003; 139: 19.

120. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood. 2018; 132: 1365.

121. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med. 2012; 367: 1979.

122. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012; 366: 1959.

123. Andreozzi GM, Bignamini AA, Davı G, et al. Sulodexide for the prevention of recurrent venous thromboembolism: the Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) study: a multicenter, randomized, double-blind, placebo-controlled trial. Circulation. 2015; 132: 1891.

124. Bonnard T, Tennant Z, Niego BE, et al. Novel Thrombolytic Drug Based on Thrombin Cleavable Microplasminogen Coupled to a Single-Chain Antibody Specific for Activated GPIIb/IIIa. J Am Heart Assoc. 2017; 6: e004535.

125. Di Cera E. Thrombin. Mol Aspects Med. 2008; 29: 203.

126. Sobieszczyk P, Fishbein MC, and Goldhaber SZ. Acute Pulmonary Embolism: Don’t Ignore the Platelet. Circulation. 2002; 106: 1748.