Approach to thrombolytic (fibrinolytic) therapy in acute pulmonary embolism: Patient selection and administration

AUTHORS: Belinda Rivera-Lebron, MD, MS, FCCP, Aaron S Weinberg, MD, MPhil
SECTION EDITOR: Jess Mandel, MD, MACP, ATSF, FRCP
DEPUTY EDITOR: Geraldine Finlay, MD

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INTRODUCTION

Thrombolytic agents activate plasminogen to form plasmin, which accelerates lysis of thromboemboli. Thrombolytic therapy is used in patients with acute pulmonary embolism (PE) to rapidly dissolve the embolic burden and improve cardiorespiratory hemodynamics. However, thrombolytic therapy is associated with bleeding which can be catastrophic. Thus, careful patient selection is critical to the success of this therapy.

The indications, contraindications, and adverse effects of thrombolytic therapy in acute PE are discussed here. Thrombolysis for deep vein thrombosis of the upper and lower extremities are discussed elsewhere. (See "Catheter-directed thrombolytic therapy in deep venous thrombosis of the lower extremity: Patient selection and administration" and "Primary (spontaneous) upper extremity deep vein thrombosis", section on 'Thrombolytic therapy'.)

MAKING THE DECISION

Because the adverse effects of bleeding can be devastating, only compromised patients in whom the diagnosis of acute PE is highly suspected or confirmed and in whom risk/benefit appears favorable should be considered for thrombolytic therapy. In most patients, the diagnosis is made by computed tomographic pulmonary angiography (CTPA). However,

ventilation perfusion scanning or pulmonary arteriography, which often immediately precedes catheter-directed thrombolytic therapy (CDT), may also be confirmatory [1]. Occasionally, thrombolytic therapy is administered when a diagnosis is made with bedside echocardiography. Thrombolytic therapy can be administered using an empiric clinical diagnosis during cardiopulmonary resuscitation, but it is rarely successful in refractory pulseless electrical activity arrest. The diagnosis of PE is discussed in detail separately. (See "Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism", section on 'Hemodynamically unstable patients' and "Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism", section on 'Computed tomography pulmonary angiography'.)

Pulmonary embolism response team — Because the decision to administer thrombolysis is fraught with difficulty, we support a multidisciplinary approach that comprises a team of experts including pulmonologists, intensivists, cardiologists, thoracic surgeons, interventional radiologists, vascular surgeons, emergency department clinicians, and/or pharmacists. Many centers have created PE response teams (PERTs) to facilitate rapid diagnosis and management of patients with PE who may be candidates for thrombolysis or other interventions [2,3]. When making the decision regarding whether, when (immediate or delayed), and how (systemic, catheter-directed, with or without mechanical clot lysis) to administer thrombolytic therapy, most experts consider early involvement of PERT or other similar teams as critical. Data that support PERT are discussed elsewhere. (See "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults".)

Factors that influence the decision — Experts should evaluate the risk of death from PE (table 1) and the risk of bleeding from the thrombolytic agent (table 2). We believe that the importance placed on the risk of bleeding is relative to the strength of the indication (ie, the risk of death from PE). As an example, the risk of bleeding from surgical trauma has greater weight if the indication for systemic thrombolytic therapy is, for example, mild right ventricular (RV) hypokinesis with normal biomarkers (intermediate-low-risk PE), than if the indication is shock or cardiac arrest (high-risk PE). As another example, while a patient with PE-induced shock who is unconscious requiring very high doses of vasopressors (high-risk PE) is likely to benefit from immediate intravenous (IV) systemic thrombolytic therapy, the indication is not as apparent in a patient who has low blood pressure for 20 minutes but is awake, alert, and comfortable with low oxygenation requirement. Despite a paucity of supporting data, PERTs help individualized decision-making. (See 'Pulmonary embolism response team' above.)

Once the decision is made to proceed with thrombolysis (table 3), the clinician needs to decide the optimal mode and timing of administration. While this evaluation is ongoing,

patients should be anticoagulated with IV unfractionated heparin or low molecular weight heparin.

Assessing risk of death from pulmonary embolism — The clinician should thoroughly evaluate each individual for any one or more of the following factors that are thought to increase the risk of death from PE. Other than refractory hypotension and shock due to PE in patients with a low bleeding risk, **none** of the listed factors by itself is an absolute indication for thrombolytic therapy. Rather, all other factors are considered **collectively** so that the risk of death from PE can be assessed appropriately. These risk factors are summarized in the tables (table 1 and table 4). (See "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults".)

When considering patients for thrombolysis, most expert clinicians use a combination of clinical variables and their overall gestalt to **stratify** patients according to the risk of death from PE as the following [1]:

- **High risk** – Patients in this category are considered hemodynamically unstable, the definition of which is discussed separately (see "Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism", section on 'Hemodynamically unstable patients' and 'Hemodynamically unstable patients (high-risk pulmonary embolism)' below). However, it needs to be acknowledged that significant heterogeneity exists among this group (eg, ranging from marginal hypotension to refractory hypotension, shock, and cardiac arrest). Nonetheless, patients at high risk of death from PE are generally considered good candidates for thrombolytic therapy, assuming that the bleeding risk is low. (See 'Hemodynamically unstable patients (high-risk pulmonary embolism)' below and 'Cardiopulmonary resuscitation' below.)

- **Intermediate risk** – The intermediate-risk group is the most challenging and is the most heterogeneous. Within this category, significant variation of the derived benefit from thrombolysis is likely. Thus, selecting those most likely to benefit requires additional assessment. As a general rule, most experts consider intermediate-risk PE as acute PE that is associated with biochemical, echocardiographic, and/or imaging evidence of RV dilation or hypokinesis **without** systemic hypotension. Accordingly, while not absolute, many patients in this category typically have a simplified pulmonary embolism severity index (sPESI) score >0 (table 4). While many patients in this category do not need thrombolysis, a select group may benefit. Thus, some experts have subdivided this group into patients on the high end of the intermediate-risk category (intermediate-high) and patients on the low end of the intermediate-risk category (intermediate-low). We believe that patients in the intermediate-low-risk category are unlikely to benefit from

thrombolytic therapy and should simply be anticoagulated in the vast majority of cases, while patients in the intermediate-high risk-category may benefit from thrombolytic therapy. The distinction between intermediate-high-risk and intermediate-low-risk patients involves the following:

- Intermediate-low-risk PE – Abnormal RV function **or** elevated brain natriuretic peptide (BNP) or troponin
- Intermediate-high-risk PE – Abnormal RV function **and** elevated BNP or troponin

A patient with an sPESI >1 also meets definition for intermediate-risk PE, but we believe that such patients must have abnormal RV function **and** an elevated BNP or troponin before considering thrombolytic therapy.

However, this risk stratification needs further validation and cannot be utilized as the only measure to definitively decide whether or how thrombolytic therapy is administered. Thus, careful clinical assessment and gestalt are often necessary to supplement the available information. For example, clinical features that should be taken into consideration during this assessment include the following:

- Evidence of RV dysfunction may be present despite a calculated sPESI of 0, and such patients may potentially benefit from thrombolysis if they meet other high-risk criteria (table 1).
- Certain older adult patients, or those with underlying cardiac disease or on beta blockers, may have an inappropriately low heart rate response to the stress of PE.
- Some patients with acute PE may have an oxygen saturation of >90 percent at rest but desaturate significantly with exertion (eg, sitting up in bed) or have postural hypotension. These features are not accounted for in the sPESI.

While patients with extensive clot burden have been defined by some groups as "moderate PE," this definition is not consistent in the medical literature and not every patient with extensive clot burden has RV dysfunction or needs thrombolysis [4]. (See 'Intermediate-high-risk pulmonary embolism' below and 'Extensive clot burden' below.)

- **Low risk** – Patients with low-risk PE do not require thrombolytic therapy and should be treated with anticoagulation alone. (See "Venous thromboembolism: Initiation of anticoagulation".)

The location of the emboli (eg, peripheral, central) should also be assessed at this time since the location may affect methods chosen for clot removal (eg, bulky central emboli may require

additional ablation locally [eg, surgical or mechanical clot extraction], clot in transit may also require specific expertise).

Assessing risk of bleeding and contraindications — Absolute contraindications to systemic thrombolytic therapy in acute PE include an intracranial neoplasm, recent (ie, <2 months) intracranial or spinal surgery or trauma, history of a hemorrhagic stroke, active bleeding or bleeding diathesis (eg, severe thrombocytopenia), or nonhemorrhagic stroke within the previous three months. Relative contraindications include severe uncontrolled hypertension (ie, systolic blood pressure >200 mmHg or diastolic blood pressure >110 mmHg), non-hemorrhagic stroke more than three months prior, surgery within the previous 10 days, pregnancy, and others that are listed in the table (table 2)[5].

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.

Agents such as aspirin or dual antiplatelet therapy increase the risk of bleeding but, in isolation, are not contraindications to thrombolytic therapy.

Caution is advised in patients who have had PE-induced syncope with resultant head trauma, even if brain CT shows no hemorrhage; in such cases, the risk of bleeding may be increased due to the trauma that may be undetected by head CT.

For those in whom contraindications or high bleeding risk truly prohibit thrombolytic therapy, an inferior vena cava filter and catheter/mechanical or surgical embolectomy are options, provided that the necessary resources and expertise are available; additional details are provided separately. (See "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults", section on 'Embolectomy' and "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults", section on 'Inferior vena cava filters' and "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults", section on 'Inferior vena cava filter'.)

Timing and method of administration — In most patients, thrombolytic therapy is administered immediately when the indication is clear (eg, shock due to PE or high-risk PE without a contraindication). However, in some cases when the indication is uncertain (eg, intermediate-risk PE or high-risk with a relative contraindication), some experts, including our group, observe the response to anticoagulation during the first 24 hours following the diagnosis. If during that time the patient improves (based on vitals, oxygenation, tissue perfusion), we do not proceed with thrombolytic therapy. In contrast, if during that period, patients have persistent or worsening signs of distress (eg, severe tachycardia, borderline blood

pressure, poor oxygenation and tissue perfusion), we may proceed with thrombolytic therapy since the benefits likely outweigh the risk, at that point.

Once it is decided that thrombolytic therapy is indicated, the method of administration (eg, catheter-directed versus systemic) and dosing (full or reduced dose, infusion versus bolus) depend on factors including hemodynamic instability, risk of bleeding, available expertise, oxygen requirement, and extent of the emboli. Further details on our preferred method of administration are provided in the individual sections below. (See 'Hemodynamically unstable patients (high-risk pulmonary embolism)' below and 'Hemodynamically stable patients' below and 'Special populations' below.)

HEMODYNAMICALLY UNSTABLE PATIENTS (HIGH-RISK PULMONARY EMBOLISM)

In patients with a low bleeding risk, the only widely accepted indication for full-dose intravenous (IV) systemic thrombolysis is acute PE (PE first or recurrent event) causing shock or persistent hypotension (ie, a systolic blood pressure <90 mmHg, need for vasopressors, or a decrease in the systolic blood pressure by ≥40 mmHg from baseline for 15 minutes or longer despite resuscitation) (table 3)[5,6]. Evidence from randomized and retrospective observational studies indicate that systemic thrombolytic therapy leads to early and rapid hemodynamic improvement (eg, improved pulmonary arterial blood pressure, right ventricular [RV] function, and pulmonary perfusion). Most experts believe that the benefit of rapid resolution of emboli causing shock or near-shock, is sufficient to justify thrombolytic therapy despite the increased risk of major or catastrophic bleeding. This strategy applies to patients who present with unstable PE. (See 'Efficacy' below.)

However, it may also be considered in those with intermediate-high-risk PE who deteriorate while on anticoagulant therapy (eg, worsening gas exchange, falling blood pressure without meeting the shock or hypotension definition criteria, rising heart rate), although most experts would prefer catheter-directed thrombolysis or catheter/mechanical embolectomy in this population. (See 'Catheter-directed thrombolytic therapy' below.)

In patients at moderate or high risk of bleeding who are unstable due to PE, societal guidelines suggest catheter-directed therapies (eg, ultrasound, saline, rotational device, suction) with or without thrombolysis [5,6] rather than full-dose systemic thrombolytic therapy. However, reduced-dose systemic thrombolysis may be an alternative if catheter-directed approaches are unavailable. While patients in this category may not be ideal for any form of thrombolytic therapy, some experts administer catheter-directed thrombolytics when the benefit is believed

to outweigh the risk (eg, life-threatening unstable PE in patients with a minor fracture or compressible surgical wound). Catheter-based therapies are also an option for those in whom systemic thrombolysis fails (to reverse shock), provided that the necessary local expertise is available [7].

In patients with hemodynamically unstable PE in whom thrombolysis is contraindicated, surgical or catheter-directed embolectomy are options. (See "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults", section on 'Embolectomy'.)

While the American College of Chest Physicians support the administration of catheter-directed therapies with or without thrombolysis as an option in hemodynamically unstable patients in whom death is likely to occur before systemic thrombolysis can manifest effectiveness (ie, within hours), we believe that implementing systemic thrombolysis, even delivered over two hours, is, in fact, nearly always faster than a catheter-directed approach [5,6].

Extracorporeal membrane oxygenation (ECMO) is a useful adjunct for supporting patients with refractory shock, hypoxemia from PE, or after cardiac arrest [8]. (See "Extracorporeal life support in adults in the intensive care unit: Overview".)

We prefer that a specialist in anesthesia perform intubation in these patients, if feasible, since a sudden increase in pressure from intubation and mechanical ventilation and hypotension from sedatives may have significant adverse effects of the already compromised RV and precipitate RV shock.

Systemic infusion (full-dose thrombolytic) — In hemodynamically **unstable** patients with low bleeding risk, we and others prefer systemic thrombolysis with, typically, tissue-type plasminogen activator (tPA); this preference is based on the widespread availability and clinical experience with this agent, as well as the rapidity with which it can be administered in life-threatening situations [5]. IV access needs to be secure, and central access is not required.

Necessary invasive procedures (eg, IV access) should be quickly performed while the infusion is being prepared and all other invasive procedures delayed until after the infusion is complete. (See "Anesthesia for noncardiac surgery in patients with pulmonary hypertension or right heart failure".)

Anticoagulation during thrombolysis — For patients who are hemodynamically unstable from PE and who are already receiving systemic anticoagulation, which is typically unfractionated heparin (UFH), we discontinue the anticoagulant therapy immediately before and during the thrombolytic infusion to minimize the risk of bleeding, although some clinicians may continue anticoagulation during the thrombolytic infusion. Regardless of the practice, the

potential risk of bleeding (when anticoagulation is continued) and the potential risk of recurrent embolism (when anticoagulation is discontinued) are unknown. The use of low molecular weight heparin prior to thrombolysis is not a contraindication.

Dosing (continuous infusion) — Full-dose IV thrombolytic infusion regimens are the most common method of administering these agents. Recombinant tPA (eg, alteplase, tenecteplase), streptokinase (SK), and recombinant human urokinase (UK), the best studied thrombolytic agents for the treatment of acute PE. No agent has proven to be superior. However, SK and UK are no longer available for this indication in the United States. This, coupled with a shorter infusion time, has resulted in tPA (in particular alteplase) being the most common agent used for patients with acute PE. Other related formulations of tPA, including lanoteplase and reteplase, have not been studied in the treatment of acute PE. The biologic characteristics of thrombolytic agents and their role in acute myocardial infarction and stroke are discussed in detail separately. (See "Intravenous thrombolytic therapy for acute ischemic stroke: Therapeutic use" and "Acute ST-elevation myocardial infarction: Management of fibrinolysis".)

The US Food and Drug Administration-approved dosing regimen for IV tPA (alteplase) is 100 mg administered over two hours. In more urgent situations, it is appropriate to administer tPA as a bolus, as an infusion over 15 minutes, or as a 50 mg IV bolus followed by an infusion of 50 mg over the next two hours [5,9,10]. However, none of these regimens has been directly compared with a two-hour infusion of tPA. Evidence from small randomized trials suggests that shorter infusions (ie, ≤2 hours for tPA) achieve more rapid clot lysis and are associated with lower rates of bleeding than longer infusions (ie, ≥12 to 24 hours for UK and SK, respectively) [5,9]. A bolus infusion of thrombolytic therapy (50 mg tPA) is indicated for patients with PE-related cardiac arrest [5]. (See 'Cardiopulmonary resuscitation' below.)

Tenecteplase is rarely used in the United States. However, it was administered as a weight-based bolus infusion for hemodynamically **stable** patients with RV dysfunction due to PE (the PEITHO trial), the details of which are provided below. (See 'Systemic full-dose thrombolytic therapy' below.)

Monitoring and management of bleeding — During the infusion, the patient should be monitored closely for stability or improvement of vital signs and oxygenation, development of neurologic deficits, and hemodynamic or obvious signs of bleeding. Generally, clinical improvement is noted within the first hour of the infusion. When infusion of the thrombolytic agent is complete, IV UFH is restarted, as discussed below. (See 'Anticoagulation following thrombolysis' below.)

Considerable clinical judgment is needed when patients have bleeding while on thrombolytic therapy. Minor bleeding during thrombolytic therapy is common and is not generally an indication to stop therapy. However, the definition of minor bleeding is unclear. In our opinion, minor bleeding is that which occurs at sites of invasive procedures such as venipuncture or arterial puncture sites or in the skin and gums [11,12]. Bleeding from vascular puncture sites should be controlled with manual compression followed by a pressure dressing. Many experts also tolerate bleeding from menstruation and bleeding that can be controlled at compressible sites (eg, epistaxis or wounds). Minor bleeding from the gastrointestinal or genitourinary tract may also be managed by following clinically (eg, vital signs and hemoglobin).

However, signs of major bleeding (eg, hemodynamic compromise, mental status changes, significant reductions in hemoglobin [eg, by 1 to 2 g/dL], need for transfusion, and copious amounts of bleeding) are indications to immediately stop the infusion and treat the bleeding. If intracranial bleeding is suspected clinically, infusion of the thrombolytic agent should be **immediately** discontinued; following stabilization, a non-contrast-enhanced CT scan of the brain and emergent neurologic/neurosurgical consultation should be obtained. (See "Spontaneous intracerebral hemorrhage: Acute treatment and prognosis" and "Spontaneous intracerebral hemorrhage: Pathogenesis, clinical features, and diagnosis".)

There is a paucity of data regarding indications for reversal of thrombolytics. If patients continue to have significant or refractory bleeding despite cessation of the thrombolytic agent, we typically transfuse patients with 10 units of cryoprecipitate with or without two units of fresh frozen plasma and then reassess. 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 thrombosis. This approach is based on our experience and that of other intensivists for the management of thrombolytic-related intracranial hemorrhage (ICH) in patients with stroke [13]. Further details regarding reversal of thrombolytic agents and of heparin are provided separately. The dose and administration of protamine sulfate are discussed in detail elsewhere. (See "Heparin and LMW heparin: Dosing and adverse effects", section on 'Bleeding' and "Intravenous thrombolytic therapy for acute ischemic stroke: Therapeutic use", section on 'Management of symptomatic intracerebral hemorrhage' and "Reversal of anticoagulation in intracranial hemorrhage".)

Anticoagulation following thrombolysis — Following thrombolysis, patients should be fully anticoagulated with IV UFH. We generally avoid initiating longer-acting anticoagulants (eg, low molecular weight heparin) and oral agents (eg, direct oral anticoagulants [DOAC], warfarin) for at least 24 hours to ensure that there is no delayed bleeding that would require immediate

cessation of anticoagulation. After the thrombolytic infusion is complete, some experts start a heparin infusion without a bolus. However, to minimize the risk of bleeding, most would check an activated partial thromboplastin time (aPTT) and resume UFH without a loading dose when the aPTT is less than twice its upper limit of normal. If the aPTT exceeds this value, we repeat it every four hours until it is less than twice its upper limit of normal, at which time, we resume a heparin infusion. The protocol used to administer UFH is the same as that administered to patients with acute PE. (See "Venous thromboembolism: Initiation of anticoagulation".)

Once stable for 24 to 48 hours, patients should be transitioned to an oral agent (eg, DOAC or warfarin). The duration of long-term anticoagulation following thrombolysis is generally the same as for patients who have not received a thrombolytic agent. (See "Venous thromboembolism: Anticoagulation after initial management".)

Efficacy — Most trials that have evaluated the effect of systemic thrombolytic therapy in patients with unstable PE are either small, randomized trials or observational studies that compared the effects of thrombolytic therapy followed by anticoagulant therapy with anticoagulant therapy alone. Many of the trials are limited by issues including small sample size and patient crossover between the groups. In addition, many studies included variable populations of patients with PE (unstable, stable) and had variable types of thrombolysis agents, methods of administration, and dosing. Nonetheless, a consistent finding among studies is that thrombolytic therapy leads to early hemodynamic improvement and, although a mortality benefit may exist, it occurs at a cost of increased major bleeding [14-21]. The effect on recurrent venous thromboembolism is unclear.

- **Pulmonary hemodynamics** – Thrombolytic therapy improves pulmonary arterial blood pressure, RV function, and pulmonary perfusion more quickly than heparin alone [4,22-25]. Improvement generally occurs over the first several days. However, it is uncertain whether these beneficial effects are persistent. This was best illustrated by the following sentinel studies:

  - In one trial, 40 patients with acute PE were randomly assigned to receive thrombolytic therapy or anticoagulation alone [23]. 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; resolution was determined by diffusing capacity and pulmonary capillary blood volume (which is not the optimal way to determine this outcome). 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 with patients who had received

anticoagulant therapy alone [26]. These results suggested that the hemodynamic benefits of thrombolytic therapy were persistent.

- In a prospective, 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 with patients who received anticoagulation alone [22]. However, unlike the study described above, one week later, there was no difference in RV function. This suggests RV function improved later in patients who did not receive thrombolytic therapy.

Since these sentinel studies, several other studies have confirmed rapid clot lysis when thrombolytic is administered in other populations either systemically or using a catheter-directed approach. (See 'Catheter-directed approaches' below and 'Efficacy' below.)

- **Mortality** – Thrombolytic therapy has been shown in several meta-analyses of patients with acute PE to improve mortality at the expense of increased rates of bleeding. However, studies are, in general, small; flawed (eg, crossover between groups); use different agents, methods of administration, and dosing strategies; and include different populations of patients with PE. As examples:

  - In one 2014 meta-analysis of 16 randomized trials comprising 2115 patients (with stable and unstable PE), thrombolytic therapy (mostly systemic agents; UK, SK, tenecteplase, tPA [alteplase]) was associated with a lower all-cause mortality compared with anticoagulation alone (2.2 versus 3.9 percent; odds ratio [OR] 0.53, 95% CI 0.32-0.88) [21]. However, the mortality benefit was not significant in patients older than 65 years (2.1 versus 3.6 percent; OR 0.55, 95% CI 0.29-1.05). Importantly, any mortality benefit from thrombolysis came at the expense of an increased risk of major hemorrhage (9.2 versus 3.4 percent) and, in particular, a higher rate of ICH (1.5 versus 0.2 percent, OR 4.63). However, major bleeding was not significantly increased in patients 65 years and younger (OR 1.25, 95% CI 0.50-3.14), suggesting that the higher bleeding rates occurred in older patients. Using these data, 59 patients would need to be treated to prevent one death, while a major bleed would occur with every 18 patients treated. Although most of the agents were administered systemically, this meta-analysis was not able to distinguish benefit from systemic versus catheter-directed therapy. The wide CIs also suggest variability in the effect.

  - In another 2019 meta-analysis of registry data that enrolled 1574 patients with unstable PE, thrombolytic therapy resulted in a reduced short-term all-cause mortality

(OR 0.66, 95% CI 0.45-0.97) as well as PE-related mortality (OR 0.69, 95% CI 0.49-0.95), compared with those not treated with thrombolytics [20].

- In a 2004 meta-analysis of 11 trials that performed a subgroup analysis in the 154 patients with massive (high-risk) PE, systemic thrombolytic therapy decreased the composite endpoint of death and recurrent thromboembolism (9.4 versus 19 percent; OR 0.45, 95% CI 0.22-0.92) [19]. The same difference was not appreciated in patients with nonmassive (intermediate-risk) PE.

- In a 2021 meta-analysis of 29 studies of patients with acute PE (massive and submassive), compared with heparin alone, thrombolysis resulted in a reduction in mortality (OR 0.59, 95% CI 0.37-0.87; 2.8 versus 4.9 percent) and PE recurrence (OR 0.51, 95% CI 0.29-0.89; 2 versus 3.9 percent) but at the expense of major bleeding (OR 2.9, 95% CI 1.95-4.31; 10.4 versus 3.8 percent) [6].

- **Recurrent thromboembolism** – A meta-analysis of 16 trials reported reduced rates of recurrent thromboembolism with thrombolytic therapy compared with anticoagulation alone (1.2 versus 3 percent; OR 0.40, 95% CI 0.22-0.74) [21]. However, recurrence rates were assessed at varying time points and the CIs were wide, suggesting variability in this effect.

The efficacy of reduced-dose systemic thrombolytic therapy has been inadequately studied in unstable patients with acute PE. However, one study, in whom one-third of patients were hemodynamically unstable due to acute PE, reported a possible mortality benefit from reduced-dose tPA. Further details of this study and of other studies that examined the efficacy of reduced-dose tPA in patients with stable PE are provided below. (See 'Reduced-dose systemic thrombolytic therapy' below.)

Follow-up — Patients should be monitored for continued signs of improvement (eg, reduced heart rate and respiratory rate and improved oxygenation and blood pressure) following the infusion. Generally, clinical improvement may continue for a few hours and days beyond completion of the infusion. Although not routine, many experts also perform echocardiography 24 hours following the infusion to examine the size and function of the RV. While many cases demonstrate improved RV size and function, complete RV recovery may lag behind clinical improvement. (See "Echocardiographic assessment of the right heart".)

Routine follow-up while the patient is receiving long-term anticoagulation is described separately. (See "Echocardiographic assessment of the right heart" and "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults", section on 'Monitoring and follow-up'

and "Venous thromboembolism: Anticoagulation after initial management", section on 'Monitoring'.)

Catheter-directed approaches — Thrombolytic agents can be infused directly into the pulmonary artery via a pulmonary arterial catheter (ie, CDT) [27-37]. CDT has the potential advantage that lower doses of lytic agent can be administered, thereby reducing the risk of bleeding compared with systemic therapy. Clot removal can also be performed using a catheter-directed approach (eg, mechanical, ultrasound, or jet saline lysis). Both thrombolysis and clot removal can be performed in isolation or in combination. Typical access sites are internal jugular and femoral veins. Procedural details of CDT are discussed below. (See 'Intermediate-high-risk pulmonary embolism' below.)

We agree with guidelines that suggest that catheter-directed approaches are options for patients with persistent hemodynamic instability despite systemic thrombolysis and those with hemodynamic instability due to PE who are at moderate to high risk of bleeding [6]. Importantly, catheter-directed techniques should be reserved for use in centers with appropriate expertise since they are not without risk (eg, further hemodynamic instability, bleeding at insertion sites, arrhythmias). Further details regarding catheter-directed embolectomy are provided separately. (See "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults", section on 'Embolectomy'.)

Data describing the efficacy of CDT in hemodynamically unstable patients are limited and are comprised of observational data that also includes systemic therapy. Limitations of these trials include small sample size, inadequate power to estimate survival benefit, use of surrogate outcome measures (eg, echocardiography for measuring pulmonary pressures), and lack of data describing the effect of thrombolysis over a more extended period (weeks to months) on clinically meaningful outcomes, such as survival. 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 hemodynamically unstable acute PE. As examples:

- The sentinel CDT trial that suggested benefit in patients with hemodynamic instability from acute PE was a study published in 1988 that included 34 patients with persistent hypotension due to acute PE (ie, high-risk PE). CDT (without any form of mechanical removal) was compared with IV tPA (alteplase 100 mg for each route) [32]. Both modalities had a similar impact on the degree of reduction of clot burden (determined by pulmonary angiography) and the mean pulmonary arterial pressure. Both catheter-directed and IV tPA were associated with similar rates of bleeding at surgical, puncture, and catheter insertion sites. Bleeding complications were noted in 50 percent of patients and were serious in 12 percent. However, comparatively lower doses of tPA are now typically

administered during CDT and bleeding rates are now likely in the region of less than 4 percent. It should also be recognized that the technique in this trial is also different when compared with more modern techniques in that the catheter was placed in the pulmonary artery (proximal to the embolus) rather than being "buried" in the embolus.

- A subsequent 2019 retrospective review of 105 cases of both massive and submassive PE reported an improved RV/left ventricular ratio in patients treated with CDT compared with heparin alone without any difference in 90-day mortality or major bleeding [38].

- A meta-analysis of 28 studies totaling 2135 patients, 47 percent of whom had high-risk PE, reported significant improvement in cardiopulmonary hemodynamics with ultrasound-assisted catheter-directed thrombolysis [39]. This study is discussed in further detail below. (See 'Catheter-directed thrombolytic therapy' below.)

- A single-arm prospective trial of 150 patients, 20 percent of whom were considered to have "massive" PE (SEATTLE II), reported that at 48 hours, CDT resulted in a significant reduction in pulmonary artery pressure without any episodes of major bleeding [40]. No ICHs were reported. This study is discussed in further detail below. (See 'Catheter-directed thrombolytic therapy' below.)

Data that describe the role of CDT in intermediate-risk PE (ie, "submassive" PE) are discussed below. (See 'Catheter-directed thrombolytic therapy' below.)

HEMODYNAMICALLY STABLE PATIENTS

For most patients with acute PE who do not have hemodynamic compromise, thrombolytic therapy is **not** warranted. However, thrombolysis may be considered on a case-by-case basis when the benefits of rapid lysis are assessed by the clinician to outweigh the risk of hemorrhage, the bleeding risk is low, and the patient's values and preferences have been taken into consideration [5,6].

The following are situations in which we and other experts typically contemplate thrombolysis in the hemodynamically stable patient with PE (table 3)[1,21,41-45]:

- Intermediate-high-risk PE (previously known as "submassive PE") and defined as right ventricular (RV) dysfunction together with an elevated troponin or brain natriuretic peptide (BNP), particularly when there are other supportive findings such as significant tachycardia, severe hypoxemia, respiratory distress, or extensive clot burden (eg, large perfusion defects on ventilation/perfusion scan or extensive embolic burden on chest CT).

Assessing the risk of death from PE is described above, and data supporting thrombolysis in this population are discussed below. (See 'Intermediate-high-risk pulmonary embolism' below and 'Assessing risk of death from pulmonary embolism' above.)

- Patients with acute PE who are clearly deteriorating but not yet hypotensive (ie, showing signs of failing anticoagulation). Other patients are rarely considered for thrombolytic therapy in the absence of RV dysfunction. (See 'Other' below.)

Although most patients described above may not need to be urgently treated with thrombolytic therapy, they should be rapidly anticoagulated. They should also be monitored closely since they are at risk of deterioration, and a decision to administer thrombolytic therapy may need to be made promptly. In general, clinicians have time to discuss relevant options with the patient and with other experts (eg, interventional radiology, pulmonary/critical care, cardiology, or cardiothoracic/vascular surgery). Factors that weigh into the decision process, the value of PE response teams (PERTs), and timing of thrombolysis are discussed above. (See 'Making the decision' above.)

If patients have intermediate-high-risk PE but are at a moderate or high risk of bleeding or have contraindications to thrombolytic therapy, catheter-directed thrombolysis and/or clot extraction or surgical embolectomy are options. (See "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults", section on 'Embolectomy'.)

Intermediate-high-risk pulmonary embolism — The most controversial situation in which thrombolytic therapy is considered is in patients with "intermediate-high-risk" PE ("submassive PE"). The most widely accepted definition of intermediate-high-risk PE is acute PE without hypotension but with evidence of abnormal RV function by echocardiography (or a clearly dilated RV by CT pulmonary angiography) **and** an elevated troponin and/or BNP level; patients in this category typically have a simplified pulmonary embolism severity index score >0 (table 4)[1]. Further discussion of what constitutes intermediate-risk PE is discussed above. (See 'Assessing risk of death from pulmonary embolism' above.)

- **Rationale** – The rationale for thrombolysis in this population is based on the observation that severe RV dysfunction is associated with a worse prognosis than mild or no RV dysfunction [46]. However, randomized trials have not shown a convincing or consistent mortality benefit from thrombolytic therapy in patients with RV dysfunction. This is likely because this population constitutes a wide spectrum; thus, selecting patients at highest risk of death from RV dysfunction due to PE is likely critical to the success of thrombolytic therapy. As an example, patients with severe or worsening RV dysfunction and a markedly elevated troponin/BNP level, with a substantial oxygen requirement and an elevated heart

rate (eg, >120/minute), are probably more likely to benefit from thrombolysis than patients with mild RV dysfunction, a normal heart rate, and no or minimal oxygen requirement. (See 'Efficacy' below.)

- **Patient selection** – We suggest that thrombolytic therapy in patients with intermediate-high-risk PE be individualized and based on a thorough assessment of clinical, echocardiographic, and imaging data that support a high mortality from PE. We believe that careful assessment by **knowledgeable experts** of those who are at intermediate-high risk of death from PE is the cornerstone of appropriate patient selection in this contentious group. (See 'Assessing risk of death from pulmonary embolism' above and 'Pulmonary embolism response team' above.)

- **Method of administration** – When the decision is made to administer thrombolytic therapy to hemodynamically **stable** patients with intermediate-high-risk PE, the optimal method of administration remains unknown. However, we prefer catheter-directed thrombolytic therapy (CDT) rather than systemic therapy, provided that the expertise is available and the bleeding risk is low. Systemic thrombolytic therapy is a suitable alternative if local expertise is not available. Clinical trials of low-dose systemic thrombolysis (ie, doses in the range utilized for CDT) are underway (NCT03988842).

  Our preference for CDT is based on our clinical experience and the likelihood of a lower risk of bleeding with CDT compared with systemic agents; the lower bleeding risk is likely due to the lower total dose of agent administered (eg, 8 to approximately 24 mg during CDT versus 50 to 100 mg for intravenous [IV] tissue-type plasminogen activator [tPA]). In addition, during CDT, other mechanical interventions can be simultaneously performed to aid clot dissolution (eg, ultrasound, saline) or mechanical removal (eg, embolectomy, aspiration, rotational devices) to either supplement clot lysis or to be used independently in the event that thrombolysis is contraindicated [47]. Further details regarding catheter-directed clot extraction and data describing the efficacy of CDT in patients with intermediate-risk PE are provided separately. (See "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults" and 'Efficacy' below.)

- **Procedure and dosing** – For CDT, catheters are placed under fluoroscopic guidance with the patient supine. Choosing how many catheters to place, whether a bolus of thrombolytic agent is administered before the infusion, and whether lysis should be combined with other clot removal procedures is individualized and dependent on the operator, their experience, and the location and volume of emboli. For example, the presence of large central main pulmonary artery embolus in addition to significant peripheral segmental/subsegmental embolus might prompt debulking with percutaneous

clot extraction devices followed by infusion with CDT lysis. This is individual preference, and no randomized data exist to support this approach. In contrast, for those with just central main pulmonary artery embolus or right atrial clot in transit, mechanical clot extraction alone may be enough. For thrombolytic infusions, one catheter is typically placed per affected lung (ie, two for bilateral PE and one for unilateral PE). In addition, we prefer shorter duration infusions with lower doses to reduce the risk of bleeding. An example would be 1 mg/hour per lung over four to six hours (ie, 12 mg tPA [alteplase] total) [48].

There are no universally accepted anticoagulation protocols for CDT. We reduce the unfractionated heparin (UFH) infusion dose to 300 to 500 units/hour while infusing tPA. Following the infusion of tPA, we then hold the heparin for 30 minutes, remove the sheaths, and restart UFH at full dose. Alternatively, if the patient is already receiving therapeutic low molecular weight heparin, no anticoagulant is needed during CDT.

If systemic lysis is chosen, it should be administered as described above for patients who have unstable PE, although reduced doses may be an option. (See 'Systemic infusion (full-dose thrombolytic)' above and 'Reduced-dose systemic thrombolytic therapy' below.)

Efficacy — Data to support thrombolytic therapy in patients with intermediate-high-risk PE suggest that the administration of systemic or catheter-directed thrombolysis results in rapid and early improvement in indices of RV function; however, the impact on mortality is unclear [21,27,37,49-52]. Our preference is for CDT, based on a rationale that is explained above. (See 'Intermediate-high-risk pulmonary embolism' above.)

Catheter-directed thrombolytic therapy — Several trials have examined CDT in patients with acute PE who are hemodynamically stable [27,38,40,48,53-56]:

- A meta-analysis of 44 mostly observational studies also reported that compared with systemic thrombolysis, CDT was associated with reduced risk of death (odds ratio [OR] 0.43, 95% CI 0.32-0.57), intracerebral hemorrhage (OR 0.44, 95% CI 0.29-0.64), and major bleeding (OR 0.61, 95% CI 0.53-0.70) [57]. Compared with anticoagulation, CDT was also associated with decreased risk of death (OR 0.36, 95% CI 0.25-0.52) and no difference in the risk of intracerebral hemorrhage or major bleeding.

  An older meta-analysis of 28 studies (randomized trials and observational studies) totaling 2135 patients, 53 percent of whom had intermediate-risk PE, reported significant improvement in cardiopulmonary hemodynamics with ultrasound-assisted CDT (USAT) [39]. This included an improvement in the RV/left ventricle (LV) ratio (mean decrease 0.35, 95% CI -0.4 to -0.3), mean pulmonary artery pressure (mPAP; mean decrease -12.13

mmHg, 95% CI -14.67 to -9.59), cardiac index (mean increase 0.68 L/m^2, 95% CI 0.49-0.87), and Miller index score (mean decrease by 10.55, 95% CI -12.98 to -8.12). The in-hospital mortality was 2.9 percent, and long-term mortality (30 days to 3 years) was 4.1 percent. Major bleeding occurred in 5.4 percent, and recurrent venous thromboembolism was seen in 0.2 percent.

- The only CDT trial which randomized patients to either CDT plus anticoagulation or anticoagulation alone was the ULTIMA trial. In ULTIMA, 59 patients with intermediate-high-risk PE were randomized to USAT followed by IV heparin or to IV heparin alone [27]. Intermediate-high-risk PE was defined as PE of the main or lower lobe pulmonary artery and echocardiographic evidence of RV enlargement (RV/LV ratio ≥1). The USAT regimen consisted of high-frequency ultrasound combined with 10 (one lung) to 20 mg (two lungs) of tPA infused over 15 hours. At 24 hours, compared with conventional anticoagulation, USAT resulted in a statistically significantly improved RV/LV ratio (mean difference 0.3 versus 0.03), supporting a hemodynamic benefit. At 90 days, there was significantly improved RV/LV ratio in the IV heparin group, no difference in mortality, and no major bleeding events or intracranial hemorrhage (ICH) in either group. In another preliminary study of 12 patients with intermediate-high-risk PE, a different USAT regimen that consisted of high-frequency ultrasound combined with 10 mg of tPA infused over five hours resulted in a reduction in mPAP and an increase in cardiac index, with only one episode of access-site related bleeding [58]. Whether limited versions of USAT such as this should be routinely used in patients with intermediate-high-risk PE requires further study.

- In a single-arm prospective trial (SEATTLE II) of 150 patients with massive (n = 31) and intermediate-high-risk (n = 119) PE, CDT with USAT resulted in a reduction in the mean RV/LV ratio at 48 hours post-thrombolysis, compared with baseline (1.55 versus 1.13) [40]. CDT also reduced the mean pulmonary artery systolic pressure (51.4 versus 36.9 mmHg). No ICHs were reported.

- The OPTALYSE trial was subsequently designed to optimize USAT tPA doses and infusion durations [48]. In OPTALYSE, 101 patients with acute intermediate-high-risk PE were randomized to one of four tPA CDT regimens: 4 mg/lung over two hours, 4 mg/lung over four hours, 6 mg/lung over six hours, and 12 mg/lung over six hours. Each of the regimens significantly improved the RV/LV ratio (by approximately 24 percent) compared with baseline. In addition, tPA incrementally reduced the clot burden at 48 hours, ranging from 5 percent reduction in patients receiving 4 mg/lung over four hours to 26 percent reduction in those receiving 12 mg/lung over six hours. The overall bleeding rate was 4 percent, with one ICH in a patient given 4 mg/lung over four hours. There was no heparin

control arm. Outcomes at one year showed sustained recovery of the RV/LV ratio as well as improvements in functional status and quality of life [59].

- In the SUNSET trial, 81 patients with submassive PE were randomized to receive either USAT or standard CDT [60]. There was no difference in thrombus score reduction between the groups, although there was one stroke and one vaginal bleed requiring transfusion in the USAT group.

A comparison between CDT-directed and one-half-dose thrombolysis found similar reductions in pulmonary pressures between the two modalities [53]. (See 'Reduced-dose systemic thrombolytic therapy' below.)

Further research is ongoing.

Systemic full-dose thrombolytic therapy — One randomized trial (PEITHO) compared systemic thrombolytic therapy (tenecteplase) plus heparin with placebo plus heparin in 1005 patients with acute intermediate-high-risk PE [49]. RV dysfunction was confirmed by echocardiography or CT and a positive troponin I or troponin T (see 'Assessing risk of death from pulmonary embolism' above). Tenecteplase was administered as an IV push with weight-based dosing (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), and heparin was either unfractionated or low molecular weight heparin. Thrombolysis resulted in a reduction in the combined primary endpoint of death or hemodynamic decompensation at seven days compared with heparin alone (6 versus 3 percent; OR 0.44, 95% CI 0.23-0.87). However, this endpoint was largely driven by a significant reduction in hemodynamic decompensation (1.6 versus 5 percent) rather than a reduction in 7- or 30-day mortality, which, as an independent outcome, was not significantly changed by tenecteplase (1.2 versus 1.8 percent at 7 days, 2.4 versus 3.2 percent at 30 days). The administration of tenecteplase was associated with increased extracranial bleeding (6 versus 1 percent), major bleeding (12 versus 2 percent), and hemorrhagic stroke (2 versus 0.2 percent). In a prespecified subgroup analysis of patients older than 75 years, benefits of therapy were maintained but rates of extracranial bleeding were higher (11 versus 0.6 percent), 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 versus 18 percent) and no difference in dyspnea or exercise capacity, RV dysfunction, or chronic thromboembolic pulmonary hypertension (2 versus 3 percent) [61].

A meta-analysis of 16 randomized trials that included patients with both high-risk (massive) and intermediate-high-risk (submassive) PE reported a mortality benefit from thrombolytic therapy (mostly systemic agents) in the subgroup of patients with acute PE who had RV dysfunction (ie,

intermediate-high risk) when compared with anticoagulation alone (1.4 versus 2.9 percent; OR 0.48, 95% CI 0.25-0.92) [21]. Further details regarding this study including the high rates of bleeding, reduced efficacy in older patients, and its flaws are discussed above. (See 'Efficacy' above.)

In another meta-analysis of 21 trials that included patients with both unstable and stable PE, the administration of thrombolytic agents followed by heparin reduced the odds of death and recurrent PE compared with heparin alone, although the certainty of the effect was low (OR 0.58, 95% CI 0.38-0.88 [death]; OR 0.54, 95% CI 0.32-0.91 [recurrence]) [62]. Both outcomes were weakened significantly when one study at high risk of bias was removed from the analysis. The risk of major bleeding was increased in those who received the thrombolytic therapy (OR 2.84, 95% CI 1.92-4.20) as was the risk of hemorrhagic stroke (OR 7.59, 95% CI 1.38-41.72).

In a 2021 meta-analysis of 29 studies of patients with acute PE, a subgroup analysis of those with intermediate-risk PE reported that compared with heparin alone, thrombolysis resulted in a reduction in mortality (OR 0.6, 95% CI 0.36-1.01; 2.3 versus 3.9 percent) and PE recurrence (OR 0.39, 95% CI 0.17-0.896; 0.8 versus 2.4 percent) but at the expense of major bleeding (OR 3.35, 95% CI 2.06-5.45; 8.5 versus 2.6 percent) [6].

Reduced-dose systemic thrombolytic therapy — Based on the rationale that reduced doses of a thrombolytic agent may be sufficient to lyse clot effectively while minimizing the risk of bleeding, several trials have examined the efficacy and safety of reduced doses of systemic thrombolytic agents in patients with acute PE [4,53,63]. However, data are flawed such that a recommendation cannot be made to routinely implement this lower-dose regimen of tPA for any category of PE patients.

- The Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) trial examined reduced-dose IV tPA (alteplase) [4]. Moderate PE was defined as the presence of signs and symptoms of PE plus CT pulmonary angiography demonstrating >70 percent involvement with embolism in ≥2 lobar arteries or main pulmonary arteries or by a high probability ventilation/perfusion scan showing ventilation/perfusion mismatch in ≥2 lobes. In MOPETT, 121 patients were randomly assigned to receive heparin (unfractionated or low molecular weight) alone or the combination of lower-dose tPA plus heparin. This dose of tPA was ≤50 percent 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 at 28 months:
    - Lower rates of pulmonary hypertension by echocardiography (57 versus 16 percent)
    - Lower pulmonary artery systolic pressures (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 percent in each group)
- Statistically nonsignificant lower rates of recurrent PE (0 versus 5 percent) and mortality (1.6 versus 5 percent)

However, criticisms included the small sample size and the low prevalence of RV dysfunction (<25 percent) and RV hypokinesis (<7 percent). Additionally, "moderate PE" is not an accepted definition; thus, applicability to patients with intermediate-high-risk PE is limited. In addition, echocardiography is not adequate for diagnosing pulmonary hypertension and this study did not prove that systemic thrombolysis prevents the ultimate development of pulmonary hypertension.

- One randomized trial of 118 patients with acute PE, two-thirds of whom had significant pulmonary artery obstruction and RV dysfunction (ie, intermediate-high-risk PE) and one-third of whom were hemodynamically unstable (ie, high-risk PE), compared low-dose tPA (50 mg IV) with full-dose tPA (100 mg IV). Low-dose tPA resulted in a lower mortality rate (2 versus 6 percent) and bleeding rate (3 versus 10 percent) [64].

- A retrospective database study of patients with PE undergoing thrombolysis (both hemodynamically stable and unstable) reported that patients treated with one-half-dose alteplase (50 mg) required less vasopressor therapy and invasive ventilation but needed escalation of therapy more often than patients treated with full-dose alteplase (tPA 100 mg) [63]. Hospital mortality and rates of significant bleeding were similar. Another retrospective analysis compared one-,half-dose systemic thrombolysis with ultrasound-facilitated CDT 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 [53]. However, interpretation is limited due to the retrospective nature of these studies.

- A case study of four patients reported successful use of "ultra" low-dose and slow infusion of tPA (25 mg at 1 mg/hour), with all four patients demonstrating improved hemodynamics within hours of administration [65].

Other

Failure to improve or deterioration despite anticoagulation — Hemodynamically stable patients with known acute PE who do not improve or who fail despite anticoagulation are sometimes considered for thrombolysis. However, data to support this practice are lacking. However, guideline groups support the use of thrombolysis in non-high-risk patients who are

deteriorating [1,6]. The mode of administration should be individualized, but we prefer CDT based on what we believe is a lower risk of bleeding.

Severe hypoxemia — Severe hypoxemia may occur in the absence of hypotension, and, while such cases do not neatly fit in intermediate- or high-risk PE categories, we individualize such patients and believe that aggressive therapy should be considered. We occasionally administer thrombolytic therapy in patients with severe hypoxemia (particularly those with limited cardiorespiratory reserve) to avoid further deterioration or intubation and mechanical ventilation. However, there are no data to support this practice. The mode of administration should be individualized, but we prefer CDT based on the lower risk of bleeding. (See 'Catheter-directed thrombolytic therapy' above.)

As an alternative to thrombolysis, supporting the severely hypoxemic patient with oxygen delivered via high-flow nasal cannulae, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) while receiving anticoagulation is also appropriate. Because of the concern that induction agents and positive pressure ventilation can lead to further decompensation, we advise intubation by providers with expertise in intubating patients with RV dysfunction. (See "Anesthesia for noncardiac surgery in patients with pulmonary hypertension or right heart failure".)

Extensive clot burden — We sometimes consider thrombolysis in patients assessed to have a high clot burden, particularly when other high-risk factors for death from PE are present. However, high clot burden is poorly defined and robust data to support either an increased mortality from PE or a reduction in mortality with thrombolytic therapy in this population are lacking. The mode of administration should be individualized, but we prefer CDT based on the lower risk of bleeding.

A large clot burden may elevate pulmonary arterial pressure without causing significant RV dysfunction or hemodynamic collapse. One large retrospective study suggested that an obstruction index by CTPA in acute PE >40 percent was associated with an 11-fold increase in mortality [66]. However, the obstructive index is not a routine read-out and we have no robust proof that systemic thrombolysis would reduce this mortality in this population with an acceptable bleeding rate. The MOPETT trial defined large clot burden as >70 percent involvement of the pulmonary vascular bed with embolism in ≥2 lobar arteries or main pulmonary arteries on CT pulmonary angiography or by a high probability ventilation/perfusion scan showing ventilation/perfusion mismatch in ≥2 lobes [4]. However, reduced-dose systemic thrombolysis in this population did not result in reduced mortality when assessed as an independent outcome; further details of this study are provided above. (See 'Reduced-dose systemic thrombolytic therapy' above.)

SPECIAL POPULATIONS

Cardiopulmonary resuscitation — Thrombolytic therapy should **not** be routinely administered in patients during cardiac arrest. However, the decision to administer treatment as a potentially lifesaving maneuver for suspected PE-induced cardiac arrest (or impending arrest) can be considered on a case-by-case basis. Another option for treatment of PE during cardiac arrest includes anticoagulation and use of extracorporeal membrane oxygenation (ECMO). (See "Supportive data for advanced cardiac life support in adults with sudden cardiac arrest".)

Efficacy — Case series have reported some success from systemic thrombolytic therapy during cardiopulmonary resuscitation when the cardiac arrest is due to suspected or confirmed acute PE [67-70]. Thrombolysis may be more successful when there is intermittent recovery during resuscitation.

- In a retrospective study of patients with out-of-hospital cardiac arrest, patients who were treated with thrombolysis prehospitalization ("mobile intensive care unit") and found subsequently to have confirmed PE had a higher 30-day survival compared with controls [70].
- One retrospective study reported a 5 percent incidence of PE (diagnosed by autopsy, clinically, or echocardiography) in 1246 cardiac arrest patients [68]. Subgroup analysis suggested that thrombolysis was associated with a greater rate of return of spontaneous circulation (ROSC) compared with those who did not receive thrombolysis.
- Another retrospective study of 23 patients with pulseless electrical activity due to confirmed massive PE reported ROSC within 2 to 15 minutes after the administration of tissue-type plasminogen activator (tPA; alteplase) at a reduced dose of 50 mg intravenous (IV) push [69].
- In contrast, another randomized study of 233 patients who presented with pulseless electrical activity arrest of unknown etiology reported that thrombolysis did not improve survival or ROSC that compared with placebo [71].

Data regarding thrombolysis in sudden cardiac arrest not due to PE are discussed in more detail separately. (See "Therapies of uncertain benefit in basic and advanced cardiac life support", section on 'Fibrinolysis'.)

Dosing (bolus injections) — During a cardiac arrest or impending cardiac arrest, it is more practical to give tPA (alteplase) as an IV bolus using an entire 50 mg vial over two minutes rather than preparing an infusion to be administered over two hours, which is typical for noncardiac

arrest patients. The bolus can be repeated after 15 minutes in the absence of ROSC. This regimen is generally consistent with American Heart Association guidelines on cardiopulmonary resuscitation, section on arrest in special circumstances, and with the American College of Chest Physicians guidelines on antithrombotic therapy for venous thromboembolism [5,72,73].

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 on patient weight, as follows [74]:

- <60 kg – 30 mg
- ≥60 to <70 kg – 35 mg
- ≥70 to <80 kg – 40 mg
- ≥80 to <90 kg – 45 mg
- ≥90 kg – 50 mg

In general, thrombolytic therapy for patients with PE-related cardiac arrest is given with systemic anticoagulation (eg, unfractionated heparin infusion); in other words, the anticoagulant is not withheld [72]. (See 'Anticoagulation during thrombolysis' above.)

Clot-in-transit — Some patients present with a free-floating right atrial or right ventricle (RV) thrombus or thrombus in a patent foramen ovale (PFO). Options in this population include anticoagulation alone, thrombolysis, catheter-based or surgical-based clot removal, or surgical embolectomy.

There are limited data to support choosing one option over another. While mortality may be higher in this population, retrospective reports suggest that outcomes may be no different between anticoagulation and reperfusion therapies, at least among patients with evidence of right heart thrombus [75-77]. Another retrospective study reported that only 20 percent received advanced therapy in combination with anticoagulation [78]. Large thrombus size and high body mass index predicted worse outcomes.

We prefer an individualized approach that involves expert consultation and assessment of factors including clot size and location and consequence of embolization. For example, patients with large thrombus in the right atrium or RV may be candidates for catheter-directed extraction together with CDT; systemic thrombolysis or surgical thrombectomy is an alternative. In contrast, patients with smaller thrombi may be simply anticoagulated. Patients with a large thrombus who also have a PFO may be better suited to surgical removal and closure of the PFO (at a later date). (See 'Pulmonary embolism response team' above and "Stroke associated with patent foramen ovale (PFO): Evaluation" and "Atrial septal abnormalities (PFO, ASD, and ASA) and risk of cerebral emboli in adults".)

Failed systemic thrombolysis — In patients who fail systemic thrombolysis, options include repeat systemic thrombolysis (full- or half-dose), catheter-directed thrombolytic therapy (CDT), catheter-directed clot extraction, or surgical embolectomy; choosing among these is dependent on available resources and local expertise. (See "Extracorporeal life support in adults in the intensive care unit: Overview".)

Pregnancy — Thrombolysis is relatively contraindicated in patients who are pregnant but should be strongly considered in high-risk PE. Further details are provided separately. (See "Venous thromboembolism in pregnancy and postpartum: Treatment", section on 'Thrombolysis/thrombectomy'.)

BLEEDING

Thrombolytic therapy increases the risk of major bleeding. The frequency varies depending on the route of administration, and older age (>65 years) is a risk factor:

- Systemic – One meta-analysis of 16 trials compared bleeding rates with thrombolytic agents (mostly systemic agents) to that associated with anticoagulant therapy (usually heparin) [21]. The use of thrombolytic agents was associated with greater overall rates of major bleeding (9.2 versus 3.4 percent; odds ratio [OR] 2.73, 95% CI 1.91-3.91), as well as higher rates of intracranial hemorrhage (ICH; 1.5 versus 0.2 percent; OR 4.63, 95% CI 1.78-12.04). In a subgroup analysis, the risk of thrombolysis-associated bleeding was three times greater in those older, compared with those who were 65 years or younger (12.9 versus 4.1 percent; OR 3.10, 95% CI 2.10-4.56). This higher bleeding rate may explain the lack of a mortality benefit seen in older patients.

  The most potentially devastating complication associated with systemic thrombolytic therapy is ICH [79]. Clinical trials suggest that ICH occurs in up to 5 percent (on average 2 to 3 percent) of patients who receive systemic thrombolytic therapy for acute PE, which is higher than the rate of ICH reported after thrombolysis for acute coronary occlusion [11,21,44,80]. (See 'Systemic infusion (full-dose thrombolytic)' above.)

- Catheter-directed – Among the major studies (totaling over 300 patients) that examined the efficacy of catheter-directed thrombolysis (CDT) [27,40,48,58], rates of major bleeding ranged from 0 to 4 percent and only two patients had ICH (<1 percent). Although bleeding rates have not been directly compared, the incidence of bleeding in patients undergoing CDT is lower than that reported in studies of systemic agents (ie, approximately 10 to 20

percent for major bleeding and 2 to 5 percent for ICH) [21,49]. (See 'Catheter-directed thrombolytic therapy' above.)

Few studies have identified risk factors for bleeding during thrombolytic therapy, other than route of administration and age. In a retrospective analysis of 104 patients with acute PE who received intravenous tissue-type plasminogen activator (tPA; alteplase), 20 patients (19 percent) had major bleeding [81]. The principal site of bleeding was unknown in nine patients (45 percent), gastrointestinal in six patients (30 percent), retroperitoneal in three patients (15 percent), intracranial in one patient (5 percent), and splenic in one patient (5 percent). Independent predictors of major hemorrhage were administration of catecholamines for systemic arterial hypotension (OR 115, 95% CI 9.4-1411), malignancy (OR 16, 95% CI 3.2-80), diabetes mellitus (OR 9.6, 95% CI 1.7-54), and elevated international normalized ratio (OR 6, 95% CI 1.5-22).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Superficial vein thrombosis, deep vein thrombosis, and pulmonary embolism".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Deep vein thrombosis (DVT) (Beyond the Basics)" and "Patient education: Pulmonary embolism (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Factors influencing the decision** – Thrombolytic therapy is typically only administered to select patients in whom the diagnosis of acute pulmonary embolism (PE) has been confirmed, although exceptions exist (eg, during cardiopulmonary resuscitation). For patients in whom thrombolytic therapy is being considered, we support a multidisciplinary approach (eg, PE response team). The approach should integrate several clinical factors that stratify the risk of death from acute PE (low, intermediate, high risk) (table 1) and the risk of bleeding from the agent (table 2). (See 'Making the decision' above.)

- **Hemodynamically unstable patients**

  Patients who are unstable and are at low risk of bleeding – For patients who have imminently life-threatening shock due to acute PE (first or recurrent event) and are **at low** risk of bleeding, we recommend systemic thrombolytic therapy followed by anticoagulation, rather than anticoagulation alone (**Grade 1C**); for patients with persistent hypotension due to PE and are **at low** risk of bleeding, we suggest systemic thrombolytic therapy followed by anticoagulation, rather than anticoagulation alone (**Grade 2C**) (table 3).

  - Persistent hypotension is defined as a systolic blood pressure <90 mmHg, vasopressor requirement, or a drop in systolic blood pressure of ≥40 mmHg from baseline for 15 minutes despite resuscitation.

  - The rationale for thrombolysis in this population is derived from small randomized and observational studies that demonstrate a faster resolution of thrombus, which, in an unstable patient, can be lifesaving; while evidence supports a possible mortality benefit, it may be limited to patients younger than 65 years and occurs at the expense of an increased risk of major bleeding, which can sometimes be catastrophic. (See 'Hemodynamically unstable patients (high-risk pulmonary embolism)' above and 'Efficacy' above.)

  - In unstable patients due to acute PE in whom systemic thrombolytic therapy is indicated, the following approach to administration is appropriate:

    - **Dosing and infusion times** – We prefer short infusion times (ie, infusion of 100 mg tissue plasminogen activator [tPA; alteplase] over ≤2 hours) since this strategy is associated with lower rates of bleeding compared with longer infusion times. (See 'Systemic infusion (full-dose thrombolytic)' above.)

- **Anticoagulation** – We typically discontinue anticoagulation during the infusion, when feasible, although this is not universally performed by all experts. During the infusion, the patient should be monitored closely for stability or improvement of vital signs and oxygenation, development of neurologic signs, and hemodynamic or other obvious signs of bleeding. Clinical improvement is typically noted within the first hour of the infusion. Signs of major bleeding (eg, hemodynamic compromise, mental status changes, reduction in hemoglobin [eg, 1 to 2 g/dL], need for transfusion, and copious amounts of bleeding) are indications to immediately stop the infusion and investigate, locate, and treat the source. Following thrombolysis, patients should be fully anticoagulated with unfractionated heparin (UFH) infusion without a bolus; we prefer to wait until the activated partial thromboplastin time is less than twice its upper limit of normal before starting the UFH infusion. (See 'Anticoagulation during thrombolysis' above and 'Monitoring and management of bleeding' above and 'Anticoagulation following thrombolysis' above.)

Patients who are unstable and are at moderate risk of bleeding – For patients who are unstable due to PE and are at moderate risk of bleeding, we suggest catheter-directed thrombolysis (CDT) or catheter-directed thrombectomy if expertise is available rather than systemic thrombolysis (**Grade 2C**). This approach is based on limited data that suggest similar rapid clot resolution but lower bleeding rates than that seen with systemic thrombolysis. In some cases, CDT may be combined with a clot extraction procedure (eg, mechanical, ultrasound, or jet saline lysis). (See 'Catheter-directed approaches' above.)

Patents with contraindications – For those who are unstable due to PE and have contraindications to thrombolysis or are at high risk of bleeding or for patients who fail systemic thrombolysis, catheter-directed clot extraction procedures or surgical embolectomy are appropriate options. (See 'Catheter-directed approaches' above and "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults", section on 'Embolectomy'.)

- **Stable patients** – For **most** patients who do not have hemodynamic compromise due to acute PE, we recommend **against** thrombolytic therapy (**Grade 1C**). However, thrombolysis may be administered on a case-by-case basis in those assessed to be at the highest risk of death from PE, in whom the benefits are considered by the clinician to outweigh the risk of hemorrhage (table 1). For example:

  - **Patients withintermediate-high-risk PE** – Patients with intermediate-high-risk PE may benefit from thrombolysis. This population typically comprises acute PE associated with

biochemical and echocardiographic (or CT pulmonary angiographic) evidence of right ventricle (RV) dilation or hypokinesis.

The rationale for thrombolysis in this population is based on the observation that severe RV dysfunction is associated with a worse prognosis than mild or no RV dysfunction. However, randomized trials have not shown a convincing or consistent mortality benefit from thrombolytic therapy in patients with RV dysfunction. This may be because this heterogeneous population constitutes a fairly wide spectrum such that selecting patients at highest risk of death from RV dysfunction due to PE is likely critical to the benefit of thrombolytic therapy.

For those in whom thrombolytic therapy is selected, we suggest CDT rather than systemic therapy, provided that the expertise is available and bleeding risk is low (**Grade 2C**). Our preference for CDT is based on our clinical experience and the likelihood of a lower risk of bleeding with this method of administration compared with systemic thrombolysis since lower doses of agent are administered during CDT. Full-dose systemic thrombolytic therapy is a suitable alternative if local expertise is not available or the patient is not suitable or cannot be transferred for CDT; while there are relatively few data, reduced-dose systemic tPA may also be a reasonable option when CDT is not available. (See 'Intermediate-high-risk pulmonary embolism' above.)

- **Patients who do not improve or deteriorate despite anticoagulation** – Patients who do not improve or deteriorate despite anticoagulation may be considered for thrombolysis (systemic or CDT), an indication that is supported by guidelines. Patients assessed to have a high clot burden and/or severe hypoxemia are sometimes considered for thrombolysis, particularly when these features are combined with other high-risk factors for death from PE. However, these populations are poorly defined and robust data to support either an increased mortality from PE or a reduction in mortality with thrombolytic therapy are lacking. The mode of administration is preferably CDT, based on the same rationale as for those with intermediate-high risk PE. (See 'Other' above.)

- **Special populations** – Thrombolytic therapy in select populations requiring special consideration includes those who present with cardiac arrest or clot-in-transit, patients who fail systemic thrombolytic therapy, and pregnant women. The approach to thrombolysis should be individualized in these populations. (See 'Special populations' above.)

- **Bleeding** – Bleeding rates vary among studies. In general, rates of major bleeding range from 10 to 20 percent for systemic agents, while lower rates in the region of 4 percent or less have been reported for CDT. Similarly, approximately 2 to 5 percent may experience intracranial hemorrhage with systemic agents, while rates of <1 percent are reported in those who receive CDT. (See 'Bleeding' above.)

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REFERENCES

1. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014; 35:3033.
2. Kabrhel C, Jaff MR, Channick RN, et al. A multidisciplinary pulmonary embolism response team. Chest 2013; 144:1738.
3. Dudzinski DM, Piazza G. Multidisciplinary Pulmonary Embolism Response Teams. Circulation 2016; 133:98.
4. Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol 2013; 111:273.
5. 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.
6. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest 2021; 160:e545.
7. Weinberg AS, Dohad S, Ramzy D, et al. Clot Extraction With the FlowTriever Device in Acute Massive Pulmonary Embolism. J Intensive Care Med 2016; 31:676.
8. Elbadawi A, Mentias A, Elgendy IY, et al. National trends and outcomes for extra-corporeal membrane oxygenation use in high-risk pulmonary embolism. Vasc Med 2019; 24:230.
9. 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.

10. 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.
11. 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.
12. Sadiq I, Goldhaber SZ, Liu PY, et al. Risk factors for major bleeding in the SEATTLE II trial. Vasc Med 2017; 22:44.
13. Frontera JA, Lewin JJ 3rd, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care 2016; 24:6.
14. Dotter CT, Seamon AJ, Rosch J. Streptokinase and heparin in the treatment of acute pulmonary embolism. Vasc Surg 1979; 13:42.
15. 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.
16. 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.
17. 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.
18. Urokinase pulmonary embolism trial. Phase 1 results: a cooperative study. JAMA 1970; 214:2163.
19. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation 2004; 110:744.
20. 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.
21. 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.
22. 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.

23. 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.
24. Come PC. Echocardiographic evaluation of pulmonary embolism and its response to therapeutic interventions. Chest 1992; 101:151S.
25. 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.
26. Sharma GV, Folland ED, McIntyre KM, Sasahara AA. Long-term benefit of thrombolytic therapy in patients with pulmonary embolism. Vasc Med 2000; 5:91.
27. 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.
28. Leeper KV Jr, Popovich J Jr, Lesser BA, et al. Treatment of massive acute pulmonary embolism. The use of low doses of intrapulmonary arterial streptokinase combined with full doses of systemic heparin. Chest 1988; 93:234.
29. Barberena J. Intraarterial infusion of urokinase in the treatment of acute pulmonary thromboembolism: preliminary observations. AJR Am J Roentgenol 1983; 140:883.
30. Schwarz F, Stehr H, Zimmermann R, et al. Sustained improvement of pulmonary hemodynamics in patients at rest and during exercise after thrombolytic treatment of massive pulmonary embolism. Circulation 1985; 71:117.
31. The UKEP study: multicentre clinical trial on two local regimens of urokinase in massive pulmonary embolism. The UKEP Study Research Group. Eur Heart J 1987; 8:2.
32. Verstraete M, Miller GA, Bounameaux H, et al. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. Circulation 1988; 77:353.
33. Cuculi F, Kobza R, Bergner M, Erne P. Usefulness of aspiration of pulmonary emboli and prolonged local thrombolysis to treat pulmonary embolism. Am J Cardiol 2012; 110:1841.
34. Tapson VF, Gurbel PA, Witty LA, et al. Pharmacomechanical thrombolysis of experimental pulmonary emboli. Rapid low-dose intraembolic therapy. Chest 1994; 106:1558.
35. Akin H, Al-Jubouri M, Assi Z, et al. Catheter-directed thrombolytic intervention is effective for patients with massive and submassive pulmonary embolism. Ann Vasc Surg 2014; 28:1589.
36. 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.

37. 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 Cardiol Intv 2015; 8:1382.
38. 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.
39. Pei DT, Liu J, Yaqoob M, et al. Meta-Analysis of Catheter Directed Ultrasound-Assisted Thrombolysis in Pulmonary Embolism. Am J Cardiol 2019; 124:1470.
40. 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. JACC Cardiovasc Interv 2015; 8:1382.
41. Dalen JE. The uncertain role of thrombolytic therapy in the treatment of pulmonary embolism. Arch Intern Med 2002; 162:2521.
42. Hyers TM, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. Chest 1998; 114:561S.
43. Goldhaber SZ. Contemporary pulmonary embolism thrombolysis. Chest 1995; 107:45S.
44. Goldhaber SZ. Modern treatment of pulmonary embolism. Eur Respir J Suppl 2002; 35:22s.
45. Goldhaber SZ. Echocardiography in the management of pulmonary embolism. Ann Intern Med 2002; 136:691.
46. 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.
47. Tapson VF, Jimenez D. Catheter-Based Approaches for the Treatment of Acute Pulmonary Embolism. Semin Respir Crit Care Med 2017; 38:73.
48. Tapson VF, Sterling K, Jones N, et al. A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism: The OPTALYSE PE Trial. JACC Cardiovasc Interv 2018; 11:1401.
49. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014; 370:1402.
50. 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.
51. 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.

52. 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.
53. 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.
54. Rothschild DP, Goldstein JA, Ciacci J, Bowers TR. Ultrasound-accelerated thrombolysis (USAT) versus standard catheter-directed thrombolysis (CDT) for treatment of pulmonary embolism: A retrospective analysis. Vasc Med 2019; 24:234.
55. Rao G, Xu H, Wang JJ, et al. Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute pulmonary embolism: A multicenter comparison of patient-centered outcomes. Vasc Med 2019; 24:241.
56. Bashir R, Foster M, Iskander A, et al. Pharmacomechanical Catheter-Directed Thrombolysis With the Bashir Endovascular Catheter for Acute Pulmonary Embolism: The RESCUE Study. JACC Cardiovasc Interv 2022; 15:2427.
57. Planer D, Yanko S, Matok I, et al. Catheter-directed thrombolysis compared with systemic thrombolysis and anticoagulation in patients with intermediate- or high-risk pulmonary embolism: systematic review and network meta-analysis. CMAJ 2023; 195:E833.
58. Stępniewski J, Kopeć G, Musiałek P, et al. Hemodynamic Effects of Ultrasound-Assisted, Catheter-Directed, Very Low-Dose, Short-Time Duration Thrombolysis in Acute Intermediate-High Risk Pulmonary Embolism (from the EKOS-PL Study). Am J Cardiol 2021; 141:133.
59. Piazza G, Sterling KM, Tapson VF, et al. One-Year Echocardiographic, Functional, and Quality of Life Outcomes After Ultrasound-Facilitated Catheter-Based Fibrinolysis for Pulmonary Embolism. Circ Cardiovasc Interv 2020; 13:e009012.
60. Avgerinos ED, Jaber W, Lacomis J, et al. Randomized Trial Comparing Standard Versus Ultrasound-Assisted Thrombolysis for Submassive Pulmonary Embolism: The SUNSET sPE Trial. JACC Cardiovasc Interv 2021; 14:1364.
61. 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.
62. Zuo Z, Yue J, Dong BR, et al. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev 2021; 4:CD004437.

63. 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.

64. Wang C, Zhai Z, Yang Y, et al. 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.

65. Guru PK, Giri AR, Sanghavi DK, Ritchie C. Ultra-Low-Dose Systemic Tissue Plasminogen Activator in High-Risk Submassive Pulmonary Embolism. Mayo Clin Proc 2022; 97:1158.

66. 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.

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

68. 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.

69. 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.

70. Javaudin F, Lascarrou JB, Le Bastard Q, et al. Thrombolysis During Resuscitation for Out-of-Hospital Cardiac Arrest Caused by Pulmonary Embolism Increases 30-Day Survival: Findings From the French National Cardiac Arrest Registry. Chest 2019; 156:1167.

71. 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.

72. 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.

73. Soar J, Donnino MW, Maconochie I, et al. 2018 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations Summary. Resuscitation 2018; 133:194.

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

75. 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.

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

77. Islam M, Nesheim D, Acquah S, et al. Right Heart Thrombi: Patient Outcomes by Treatment Modality and Predictors of Mortality: A Pooled Analysis. J Intensive Care Med 2019; 34:930.

78. Watson NW, Dicks AB, Carroll BJ, et al. Predictors of Thrombus Resolution Among Patients Who Undergo Anticoagulation for a Right Heart Thrombus. Chest 2023; 164:1298.

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

80. 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.

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

Topic 8259 Version 78.0

GRAPHICS

High-risk factors in pulmonary embolism that predict poor prognosis

- Persistent hypotension* or shock despite adequate resuscitation
- New or worsening RV dysfunction by any 1 or combination of the following:
  - Echocardiography (eg, enlarged RV, increased RV/LV ratio ≥1, bulging of the RV septum into the LV, reduced RV ejection fraction)
  - Chest CT (eg, enlarged RV, increased RV/LV ratio, contrast observed in the liver)¶
  - Elevated biomarkers, including troponin and BNP
  - Absence of comorbidities that affect RV function (eg, significant left-sided heart disease or known poor RV function from chronic lung disease, or septic shock)
- An sPESI ≥1Δ
- Proximal deep venous thrombosis in the lower extremities
- Significant hypoxemia (eg, <90%) and/or respiratory distress
- Tachycardia >120 beats per minute
- Poor cardiopulmonary reserve◇
- The presence of right-sided cardiac thrombus (ie, clot-in-transit; thrombus in inferior vena cava, right atrium, RV, or left atrium [if a patent foramen ovale is present])

Other than refractory hypotension and shock due to acute PE in patients with a low bleeding risk, none of the listed factors by itself is an absolute indication for thrombolytic therapy. Rather, all factors are considered collectively so that the risk of death from PE can be assessed appropriately. Other reported factors include hyponatremia, elevated lactate and white cell count, poor performance, and older age >65 years.

BNP: brain natriuretic peptide; BP: blood pressure; CT: computed tomography; LV: left ventricle; PE: pulmonary embolism; RV: right ventricle; sPESI: simplified pulmonary embolism index.

* Clinically significant hypotension is defined as a systolic BP <90 mmHg or hypotension that requires vasopressors or inotropic support despite adequate filling status in combination with end-organ hypoperfusion; persistent hypotension or a drop in systolic BP of ≥40 mmHg from baseline for a period >15 minutes; hypotension is not explained by other causes such as hypovolemia, sepsis, arrhythmia, or left ventricular dysfunction from acute myocardial ischemia or infarction.

¶ Other than contrast in the liver, chest CT is imprecise for RV assessment, especially when compared with echocardiography. In most cases, if feasible, CT findings of RV enlargement should prompt echocardiography.

Δ An sPESI score is calculated based upon a cumulative point system for age >80 years (1 point), history of cancer (1 point), chronic cardiopulmonary disease (1 point), pulse ≥110/minute (1 point), systolic BP

<100 mmHg (1 point), and arterial oxygen saturation <90% (1 point); low-risk PE is a score of 0 while high-risk is any score >0. It is more useful at initial presentation and less useful for evaluating clinical deterioration following diagnosis.

◇ Small PE in patients with limited cardiopulmonary reserve may precipitate RV dysfunction and cardiac arrest.

Graphic 127558 Version 5.0

Contraindications to fibrinolytic therapy for deep venous thrombosis or acute pulmonary embolism

Absolute contraindications
▪ Prior intracranial hemorrhage ▪ Known structural cerebral vascular lesion ▪ Known malignant intracranial neoplasm ▪ Ischemic stroke within 3 months (excluding stroke within 3 hours*) ▪ Suspected aortic dissection ▪ Active bleeding or bleeding diathesis (excluding menses) ▪ Significant closed-head trauma or facial trauma within 3 months
Relative contraindications
▪ History of chronic, severe, poorly controlled hypertension ▪ Severe uncontrolled hypertension on presentation (SBP >180 mmHg or DBP >110 mmHg) ▪ History of ischemic stroke >3 months prior ▪ Traumatic or prolonged (>10 minutes) CPR or major surgery <3 weeks ▪ Recent (within 2 to 4 weeks) internal bleeding ▪ Noncompressible vascular punctures ▪ Recent invasive procedure ▪ For streptokinase/anistreplase – Prior exposure (>5 days ago) or prior allergic reaction to these agents ▪ Pregnancy ▪ Active peptic ulcer ▪ Pericarditis or pericardial fluid ▪ Current use of anticoagulant (eg, warfarin sodium) that has produced an elevated INR >1.7 or PT >15 seconds ▪ Age >75 years ▪ Diabetic retinopathy

SBP: systolic blood pressure; DBP: diastolic blood pressure; CPR: cardiopulmonary resuscitation; INR: international normalized ratio; PT: prothrombin time.

* The American College of Cardiology suggests that select patients with stroke may benefit from thrombolytic therapy within 4.5 hours of the onset of symptoms.

Graphic 95035 Version 5.0

Indications and potential indications for thrombolytic therapy in venous thromboembolism

Indication
▪ High-risk (massive) PE (ie, presence of hypotension related to PE)*
Potential indication
▪ Patients with severe right ventricular dysfunction due to PE (ie, intermediate risk PE) ▪ Others: • Presence of severe hypoxemia (particularly in those with a contribution from concomitant cardiopulmonary disease) • Patients with acute PE who appear to be decompensating but are not yet hypotensive • Extensive clot burden

PE: pulmonary embolism.

* This indication is widely accepted; the other potential indications require careful review of the risks of thrombolytic therapy and potential benefits.

Graphic 82171 Version 4.0

Pulmonary embolism severity index scores: Full and simplified

Pulmonary embolism severity index (PESI) - Full		
Clinical feature		**Points**
Age		x (eg, 65)
Male gender		10
History of cancer		30
Heart failure		10
Chronic lung disease		10
Pulse ≥110/min		20
Systolic blood pressure <100 mmHg		30
Respiratory rate ≥30/min		20
Temperature <36° Celcius		20
Altered mental status		60
Arterial oxygen saturation <90 percent		20
Class I	Low risk	<66
Class II		66 to 85
Class III	High risk	86 to 105
Class IV		106 to 125
Class V		>125

Simplified pulmonary embolism severity index (sPESI)	
Clinical feature	**Points**
Age >80 years	1
History of cancer	1
Chronic cardiopulmonary disease	1
Pulse ≥110/min	1
Systolic blood pressure <100 mmHg	1
Arterial oxygen saturation <90 percent	1
Low risk	0
High risk	≥1

The full PESI score is rarely calculated in clinical practice since it is generally considered cumbersome. In contrast, sPESI is brief, contains a limited number of easily accessible parameters, and is therefore, much more practical.

Adapted from:

1. *Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005; 172:1041.*
2. *Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010; 170:1383.*

Graphic 90549 Version 4.0

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