# Thrombolytic therapy in acute venous thromboembolism

**Thita Chiasakul[1,2] and Kenneth A. Bauer[2]**

[1]Division of Hematology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand; and [2]Hematology-Oncology Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

**Although anticoagulation remains the mainstay of treatment of acute venous thromboembolism (VTE), the use of thrombolytic agents or thrombectomy is required to immediately restore blood flow to thrombosed vessels. Nevertheless, systemic thrombolysis has not clearly been shown to improve outcomes in patients with large clot burdens in the lung or legs as compared with anticoagulation alone; this is in part due to the occurrence of intracranial hemorrhage in a small percentage of patients to whom therapeutic doses of a thrombolytic drug are administered. Algorithms have been developed to identify patients at high risk for poor outcomes resulting from large clot burdens and at low risk for major bleeding in an effort to improve outcomes in those receiving thrombolytic therapy. In acute pulmonary embolism (PE), hemodynamic instability is the key determinant of short-term survival and should prompt consideration of immediate thrombolysis. In hemodynamically stable PE, systemic thrombolysis is not recommended and should be used as rescue therapy if clinical deterioration occurs. Evidence is accumulating regarding the efficacy of administering reduced doses of thrombolytic agents systemically or via catheters directly into thrombi in an effort to lower bleed rates. In acute deep venous thrombosis, catheter-directed thrombolysis with thrombectomy can be used in severe or limb-threatening thrombosis but has not been shown to prevent postthrombotic syndrome. Because the management of acute VTE can be complex, having a rapid-response team (ie, PE response team) composed of physicians from different specialties may aid in the management of severely affected patients.**

**LEARNING OBJECTIVES**

- Describe risk stratification strategies in patients with acute pulmonary embolism
- Review current evidence on the efficacy and safety of systemic and catheter-directed thrombolytic therapy in pulmonary embolism and deep vein thrombosis
- Examine the role of pulmonary embolism response teams

## Clinical case

A 36-year-old woman was brought to the emergency department with a 1-day history of progressive shortness of breath and pleuritic chest pain. Vital signs showed pulse of 142 beats per minute, respiratory rate of 38 breaths per minute, blood pressure of 128/94 mmHg, and weight of 200 lbs; before being given oxygen, her oxygen saturation on room air was 75%. D-dimer level was very elevated at 8238 ng/mL, lactate was 3.7 mmol/L (normal range, 0.5-2 mmol/L), and pro–B-type natriuretic peptide (proBNP) was 2636 pg/mL (reference range, 0-178 pg/mL). Computed tomography pulmonary arteriography showed pulmonary emboli with a saddle embolus and extension into all lobar pulmonary arteries; there was evidence of right heart strain, with interventricular septal flattening and right ventricular (RV)/atrial dilatation. Her risk factors were use of an oral contraceptive for 10 years and obesity. She was started on a heparin infusion, and the pulmonary embolism (PE) response team (PERT) was consulted. Shortly after the heparin infusion was initiated, the patient became hypotensive, with BP of 90/60 mmHg. Because she had no contraindications to systemic thrombolysis, she was administered half-dose tissue plasminogen activator (tPA) IV (10 mg bolus followed by 40 mg over 2 hours along with unfractionated heparin). She clinically improved over several hours, with marked improvement of hypoxia. Fibrinogen level was monitored, reaching a nadir at 83 mg/dL (reference range, 180-400 mg/dL); she had a brief episode of epistaxis. She was discharged on therapeutic anticoagulation on the fourth hospital day.

## Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and PE, is a common vascular disease with significant morbidity and mortality. The mortality rate of VTE has substantially decreased over the last few decades as a result of advances in diagnosis and management.[1,2] Nonetheless, early mortality remains a major complication, occurring in 3.1% to 4% of PEs and 0.7% of DVTs.[1,2]

The cornerstone of treatment of VTE is anticoagulation. In a majority of patients, therapeutic anticoagulation is effective in preventing thrombus propagation and distal embolization while allowing the endogenous fibrinolytic system to dissolve the existing clots. In severe cases, such as those with acute RV failure, hemodynamic instability, and sudden cardiac arrest in PE or phlegmasia cerulea dolens in DVT, reperfusion therapy aimed at thrombus dissolution with immediate restoration of vascular patency is warranted to save life or limb function. Methods of reperfusion are categorized as pharmacological (systemic or catheter-directed thrombolysis [CDT]), mechanical (surgical or catheter-based embolectomy), or a combination of both.

In VTE, the potential benefits of thrombolysis include immediate symptom relief, prevention of clinical deterioration and short-term mortality, and prevention of long-term complications, such as chronic thromboembolic pulmonary hypertension and postthrombotic syndrome (PTS). However, evidence supporting the benefits of thrombolysis are inconclusive, and debate continues over whether, when, and which modality of thrombolysis should be used for a given patient with VTE. In this article, we present an update on evidence regarding the efficacy and safety of thrombolytic therapy in PE and DVT.

## PE

### Are we able to effectively stratify high-risk patients who will benefit from thrombolytic therapy?

The clinical presentation of PE represents a continuous spectrum, ranging in severity from no symptoms to hemodynamic instability and sudden death. The prognosis, as well as the risk/benefit ratio of thrombolytic therapy, varies widely based on severity at presentation. During the initial assessment of PE, it is therefore mandatory to identify those patients at risk of early mortality to guide management decisions. An ideal strategy would allow us to identify (1) patients who require immediate reperfusion therapy; (2) patients who require hospitalization and, within this group, those who may benefit from early advanced therapy, and (3) patients who can be safely discharged and treated as outpatients.

The presence of hemodynamic instability is the most important determinant of short-term mortality and should prompt immediate reperfusion therapy. Acute PE with hemodynamic instability, manifested as cardiac arrest, profound bradycardia, or persistent hypotension, represents a high-risk cohort with massive PE.[3,4] In this group, the 90-day mortality rate can be as high as 52.4%.[5] In a metaanalysis of 40 363 patients with acute PE, 3.9% had unstable PE. These patients had increased risk of short-term all-cause mortality (odds ratio [OR], 5.9; 95% confidence interval [CI], 2.7-13.0) and PE-related mortality (OR, 8.2; 95% CI, 3.4-19.7) compared with their stable counterparts.[6] Given this dire prognosis, systemic thrombolytic therapy is justified to rapidly resolve pulmonary vascular obstruction. To date, there has been only 1 randomized control trial (RCT) comparing systemic thrombolysis with anticoagulation alone in patients with massive PE.[7] In this trial, 8 patients with massive PE and cardiogenic shock were enrolled and randomly assigned to receive either 1.5 million IU of streptokinase and heparin or heparin alone. The trial was terminated after all 4 patients (100%) in the heparin group died compared with none (0%) in the streptokinase group. The streptokinase group had clinical and echocardiographic improvement within the first hour of treatment. Notwithstanding its methodological limitations, this early evidence suggests a mortality benefit of systemic thrombolysis in massive PE. In recent VTE registries, unstable PE patients who received thrombolytic therapy had a lower risk of short-term mortality than those who did not (OR, 0.69; 95% CI, 0.49-0.95).[6] Barring contraindications (Table 1), systemic thrombolytic therapy is indicated for acute PE with hemodynamic instability.[3,4] Surgical embolectomy or percutaneous catheter-directed treatment is an alternative for those with contraindications to systemic thrombolysis.

A large majority of hemodynamically stable PE patients (~50% to 60%) fall between the 2 extremes of hemodynamically unstable and low-risk PE. Among these intermediate-risk PE patients, the short-term mortality rate ranges from 3.2% to 11.4%.[8] Many clinical (concomitant DVT and respiratory index), imaging (RV dysfunction on echocardiogram or computed tomography), laboratory (troponin, BNP, N-terminal proBNP, lactate, and heart-type fatty acid-binding protein levels), or combined parameters have been shown to be associated with higher risk of clinical deterioration and early mortality in hemodynamically stable patients with PE.[9] However, none have been shown to effectively identify patients who will benefit from routine early advanced therapies, including systemic thrombolysis.

In hemodynamically stable PE, RV dysfunction, detected by echocardiography or computed tomography, and elevation of myocardial injury markers such as troponins are associated with increased risk of short-term mortality.[10,11] Patients presenting with both are classified as intermediate-high–risk or submassive

**Table 1. Contraindications to thrombolysis[4]**

| Contraindication |
|---|
| **Absolute** |
| History of hemorrhagic stroke or stroke of unknown origin |
| Ischemic stroke in previous 6 mo |
| Central nervous system neoplasm |
| Major trauma, surgery, or head injury in previous 3 wk |
| Bleeding diathesis |
| Active bleeding |
| **Relative** |
| Transient ischemic attack in previous 6 mo |
| Oral anticoagulation |
| Pregnancy or first postpartum week |
| Traumatic resuscitation |
| Refractory hypertension (systolic blood pressure >180 mmHg) |
| Advanced liver disease |
| Infective endocarditis |
| Active peptic ulcer |

PE. The role of early systemic thrombolysis to prevent short-term adverse outcomes in this group of patients has been investigated in the PEITHO trial.[12] In this large RCT, tenecteplase (single weight-based IV bolus; dose range, 30-50 mg) plus heparin was compared with placebo plus heparin in 1005 patients with intermediate-high–risk PE. The primary outcome, which was death or hemodynamic decompensation within 7 days after randomization, occurred more commonly in the placebo group (5.6%) than the tenecteplase group (2.6%; OR, 0.44; 95% CI, 0.23-0.87; $P$ = .02). The effect was largely driven by the difference in hemodynamic decompensation (5.0% vs 1.6%) and not by mortality (1.8% vs 1.2%). The potential benefit was offset by the higher bleeding events from thrombolysis. The tenecteplase group had a fivefold higher risk of major bleeding (11.5% vs 2.4%) and 10-fold higher risk of hemorrhagic stroke (2.0% vs 0.2%). Long-term follow-up was continued in 709 randomly assigned patients from the PEITHO study. Over the median follow-up time of 37.8 months, thrombolysis did not have a positive impact on overall mortality rate, functional limitation, persistent symptoms, or chronic thromboembolic pulmonary hypertension.[13] These results suggest that the combination of RV dysfunction and myocardial injury is not sufficient to identify intermediate-risk PE patients who will benefit from systemic thrombolysis. Nevertheless, given the substantial risk of early hemodynamic deterioration, close monitoring is warranted, and rescue therapy should be considered for patients who develop hemodynamic instability. In a recent metaanalysis, after excluding studies with high risk of bias, systemic thrombolysis did not show a mortality benefit over heparin alone (OR, 0.66; 95% CI, 0.42-1.06; N = 2054; $P$ = .08). Moreover, the incidence of major bleeding was significantly higher in the thrombolysis group (OR, 2.90; 95% CI, 1.95-4.31; N = 1897; $P$ < .001).[14]

In light of this evidence, full-dose systemic thrombolysis is not routinely recommended for intermediate-risk PE and should be reserved for patients presenting with hemodynamic instability or with clinical deterioration after anticoagulation. Additional studies to improve the risk/benefit ratio of thrombolysis should focus on developing more effective risk stratification tools to identify high-risk patients and minimize the bleeding risk from thrombolysis using alternatives such as low-dose or CDT.

## What is the evidence for low-dose thrombolysis?

Because the bleeding risk associated with thrombolysis is dose dependent, lower doses of thrombolytic drugs may provide a more favorable safety profile with comparable efficacy. Several studies have been conducted to explore the feasibility of low-dose thrombolysis. In the MOPETT study, 121 moderate PE patients were randomly assigned to receive low-dose tPA (50 mg for patients ≥50 kg and 0.5 mg/kg for patients <50 kg) or anticoagulation alone. At 28 months, the low-dose tPA group had a lower rate of pulmonary hypertension, with no difference in mortality rate or recurrent PE. Interestingly, bleeding events were not observed in either group.[15] Low-dose tPA was also compared with full-dose tPA in an RCT enrolling 127 acute PE patients with hemodynamic instability or massive obstruction. In this study, 50 mg of tPA (10 mg bolus followed by 40 mg by IV clinical integration over 2 hours) was comparable to 100 mg of tPA (10 mg bolus followed by 90 mg by IV continuous infusion) with respect to improvement of RV dysfunction, lung perfusion defects, and pulmonary obstruction. Although statistical significance was not reached, bleeding was numerically lower in the low-dose group.[16] In a systematic review and metaanalysis, low-dose tPA was associated with lower risk of major bleeding than full-dose tPA (OR, 0.33; 95% CI, 0.12-0.91), with no difference in recurrent PE or all-cause mortality.[17] In contrast, a propensity score–matched analysis of an administrative database concluded that half-dose alteplase was associated with more frequent treatment escalation, with similar rates of mortality and major bleeding.[18] At present, more evidence is needed to support the use of low-dose thrombolysis. PEITHO-III (NCT04430569) is an ongoing placebo-controlled RCT evaluating the efficacy of low-dose alteplase administered as bolus (0.6 mg/kg) in intermediate-high–risk PE; the premise is that bleeding will be reduced if tPA is administered over a short period.[19]

## What is the role of CDT?

In clinical practice, only a fraction (30%) of eligible high-risk PE patients receive systemic thrombolysis, possibly because of contraindications and risk of bleeding.[8] Catheter-directed therapy provides an alternative reperfusion approach that allows localized drug delivery and can be combined with mechanical thrombus removal. Catheter-based modalities include mechanical thrombectomy (thrombus fragmentation, aspiration, and rheolytic thrombectomy), pharmacologic CDT (via thrombolytic infusion catheter or ultrasound-facilitated CDT), or a combination of both.

The major advantage of CDT is the lower bleeding risk. In a metaanalysis of outcomes of CDT in 1168 patients, the rates of major bleeding were 6.7% and 1.4% in high- and intermediate-risk PE, respectively, which seem more favorable than those associated with systemic thrombolysis (up to 20% in high- and 12% in intermediate-risk PE).[20] In a propensity score-matched administrative database analysis, CDT was associated with lower in-hospital mortality and intracranial hemorrhage rates compared with systemic thrombolysis in acute PE.[21] Nevertheless, the bleeding risk associated with CDT is still greater than anticoagulation alone (1.1% to 1.7%).[4] The procedure also requires specialized resources and expertise that might not be readily available in many centers. Most importantly, current evidence supporting the use of CDT in acute PE is limited to a small RCT or single-arm studies focusing on short-term surrogate outcomes rather than clinical outcomes (Table 2).[22-26] Therefore, the decision to use CDT should be based on individualized risk/benefit considerations.

In patients with high-risk PE, CDT is recommended when systemic thrombolysis is contraindicated or has failed.[3,4] In a recent prospective registry, catheter-directed aspiration thrombectomy with low-dose thrombolysis was administered to 54 patients with acute unstable PE. In-hospital PE-related death occurred in 6 patients (11%), whereas hemodynamic stability was achieved in the remaining 48 patients. One patient (2.1%) developed hemorrhagic stroke.[27]

The role of routine CDT in intermediate-risk PE remains controversial. In the ULTIMA trial, ultrasound-assisted CDT was superior to anticoagulation alone in terms of RV/left ventricular ratio reduction from baseline at 24 hours.[22] However, there was no difference in mortality, recurrent VTE, or major bleeding at 90 days. Given the lack of evidence regarding short- and long-term clinical benefits, CDT should be reserved for intermediate-risk PE patients who develop signs of hemodynamic instability despite adequate anticoagulation.[4] Additional studies with larger sample sizes are required to elucidate the optimal use of CDT.

**Table 2. Summary of key studies of DCT in intermediate-risk PE**

| Study | N | Study design | Study population | Treatment | Comparison | Efficacy | Safety |
|---|---|---|---|---|---|---|---|
| ULTIMA[22] | 59 | RCT | Intermediate-risk PE | USAT: tPA at 10 mg via EKOS catheter + therapeutic anticoagulation (n = 30) | UFH alone (n = 29) | Mean difference in RV/LV ratio from baseline to 24 h<br>USAT tPA: 0.30 ± 0.20<br>UFH alone: 0.03 ± 0.16 ($P$ < .001)<br>No difference in hemodynamic decompensation, recurrent VTE, mortality at 90 d | No major bleeding<br>Minor bleeding<br>USAT rtPA: 10%<br>UFH alone: 3% ($P$ = .61) |
| SEATTLE II[23] | 150 | Prospective single arm | Massive PE (n = 31; 21%)<br>Submassive PE (n = 119; 79%) | USAT: tPA at 24 mg via EKOS catheter + therapeutic anticoagulation | None | Mean RV/LV ratio decreased from baseline (1.55) to 48 h (1.13; $P$ < .001)<br>PASP decreased at 48 h | 30-d major bleeding, 10%<br>30-d mortality, 2.7%; no ICH |
| PERFECT[24] | 101 | Prospective single arm | Massive PE (n = 28; 28%)<br>Submassive PE (n = 73; 72%) | Standard CDT (64%) or USAT via EKOS catheter (36%) with tPA at 0.5-1.0 mg/h or urokinase 100 000 IU/hr + therapeutic anticoagulation | None | Clinical success* achieved in 85.7% massive PE and 97.3% submassive PE<br>PASP decreased post-CDT<br>No difference in PASP change, tPA dose, or infusion between USAT and standard CDT | In-hospital mortality, 5.9%<br>No major bleeding or ICH at 30 d |
| OPTALYSE-PE[25] | 101 | Randomized comparison of 4 USAT regimens | Intermediate-risk PE | USAT: tPA at 8-24 mg via EKOS catheter + therapeutic anticoagulation | 4 USAT regimens | Mean RV/LV ratio decreased at 48 h in all 4 regimens | Major bleeding at 72 h, 4%<br>2 ICHs (1 attributable to USAT tPA)<br>Recurrent PE, 1%<br>30-d mortality, 1% |
| FLARE[26] | 104 | Prospective single arm | Intermediate-risk PE | Catheter-directed mechanical thrombectomy without thrombolysis + therapeutic anticoagulation | None | Mean RV/LV ratio decreased from baseline (1.56) to 48 h (1.15; $P$ < .0001) | 1 major bleeding<br>No ICH<br>4 clinical deterioration<br>1 death at 23 d |

EKOS, EndoWave Infusion Catheter System; ICH, intracranial hemorrhage; LV, left ventricular; PASP, pulmonary artery systolic pressure; rtPA, recombinant tPA; UFH, unfractionated heparin; USAT, ultrasound-assisted CDT.
*Clinical success was defined as stabilization of hemodynamics, improvement in pulmonary hypertension and/or right-sided heart strain, and survival to hospital discharge.

### What is the role of a PERT?

Given the limitations of risk stratification and availability of advanced therapies, the optimal management of acute PE can be challenging. Treatment decisions, especially for intermediate- and high-risk PE, require individualized and timely use of these therapies. To aid this process, institutions caring for patients with severe PE have established multidisciplinary PERTs. Although the composition of the team varies by institution, a PERT often includes specialists in cardiology, pulmonology, vascular medicine, critical care, emergency medicine, hematology, interventional radiology, and vascular or cardiothoracic surgery. Upon activation, a PERT evaluates, triages, and provides treatment and follow-up plans for patients with acute PE. The impact of PERTs on management and outcomes has varied among institutions. Compared with historical controls, the initiation of a PERT led to increased use of advanced therapies, particularly CDT, shorter time to therapeutic anticoagulation, and decreased use of inferior vena cava filters.[28-31] The early involvement of interventional radiologists may help facilitate the identification of patients who are suitable for catheter-directed therapies and avoid the bleeding risk from systemic

thrombolysis. Major bleeding and 30-day mortality rates were lower after PERT involvement in 1 study,[31] but this was not demonstrated in others.[32]

In our clinical case, the patient was normotensive on presentation, with an elevated proBNP level and evidence of right heart strain on computed tomography pulmonary arteriography; this placed her in the intermediate-high–risk group. Although immediate systemic thrombolysis was not clearly required, she hemodynamically decompensated after anticoagulation was initiated. Because she was at low risk for bleeding, the recommendation of the PERT was to administer low-dose tPA, which was associated with clinical improvement.

## DVT

### How can we predict the risk of PTS in DVT patients?

In patients with acute DVT that is limb threatening or who have progressive symptoms despite adequate anticoagulation, thrombolysis and/or thrombectomy is indicated to improve blood flow. Another proposed benefit of thrombolysis with or without thrombectomy is the prevention of PTS by rapidly relieving venous obstruction. PTS is a common long-term complication occurring in up to 50% of patients with lower-extremity DVT. Risk factors for PTS include preexisting venous insufficiency, iliofemoral DVT, high body mass index, older age, inadequate anticoagulation during the first 3 months, and ipsilateral DVT recurrence.[33] Several models have been developed to predict the risk of PTS in patients with DVT (Table 3).[34-36] On the basis of these models, the highest risk groups have a risk of 25% to 80.7% for developing PTS. Although external validation is needed, elements of these models may be useful in selecting DVT patients at high risk for PTS who may benefit from strategies employing thrombolysis with or without thrombectomy.

### Should thrombolysis be used to prevent PTS?

In the early clinical trials comparing systemic thrombolysis with anticoagulation alone in DVT, thrombolysis was associated with a nonsignificant reduction of PTS and a twofold higher bleeding risk, particularly intracranial hemorrhage.[37] Therefore, systemic thrombolysis was not recommended as an adjunct to anticoagulation for the initial treatment of DVT. Pharmacological and pharmacomechanical CDT have been investigated to prevent PTS in selected patients with DVT. To date, 3 multicenter RCTs have been conducted to assess the efficacy and safety of these interventions (Table 4).[38-40] In CaVenT, CDT prevented PTS at 2 and 5 years. In contrast, the occurrence of PTS at 2 years was not significantly different in ATTRACT, although CDT decreased PTS severity and rate of moderate to severe PTS in the subgroup with iliofemoral DVT. In CAVA, which enrolled only patients with iliofemoral DVT, the rates of PTS at 1 year were not different between the 2 groups. The risk of bleeding increased with CDT in all studies. Although CDT led to quality of life (QoL) improvement at 1 and 6 months in the ATTRACT trial, none of the studies found long-term QoL to be improved with CDT.

**Table 3. Risk prediction models for PTS**

| | SOX-PTS score[34] | Points | Amin et al[35] | Points | Méan et al[36] | Points |
|---|---|---|---|---|---|---|
| **Age, y** | — | | >56 | 2 | ≥75 | 1 |
| **BMI, kg/m²** | ≥35 | 2 | >30 | 2 | — | |
| **DVT anatomy** | Iliac DVT | 1 | Iliofemoral DVT | 1 | Multilevel thrombosis | 1 |
| **Signs of preexisting venous insufficiency** | Baseline Vilalta score | | Varicose veins | 4 | Prior varicose vein surgery | 1 |
| | >14 (severe) | 2 | | | | |
| | 10-14 (moderate) | 1 | | | | |
| | | | | | N of leg signs and symptoms* | 1 (for each) |
| **Other** | — | | Smoking | 1 | Concomitant antiplatelet/NSAID therapy | 1 |
| | | | Female sex | 1 | | |
| | | | Provoked DVT | 1 | | |
| | | | History of DVT | 1 | | |
| **Risk category** | **Total score** | **PTS risk, %** | **Total score** | **PTS risk, %** | **Total score** | **PTS risk, %** |
| Low | 0 | 6.4 | 0-2 | 10 | 0-3 | 24.4 |
| | 1 | 13.4 | | | | |
| Intermediate | 2 | 16.4 | 3-4 | 20 | 4-5 | 38.4 |
| | 3 | 25 | | | | |
| High | ≥4 | 30 | ≥5 | 40 | ≥6 | 80.7 |

BMI, body mass index; NSAID, nonsteroidal antiinflammatory drug.
*Pain, cramps, heaviness, pruritus, paraesthesias, edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain during calf compression.

**Table 4. Summary of RCTs evaluating CDT in DVT**

| Study | N | Study population | Treatment | Comparison | Efficacy | Safety |
|---|---|---|---|---|---|---|
| CaVENT[38] | 209 | Iliofemoral DVT within 21 d | CDT: tPA at 20 mg + therapeutic anticoagulation (n = 90) | Anticoagulation alone (n = 99) | PTS at 24 mo:<br>CDT, 37 (41.1%) vs control, 55 (55.6%; *P* = .047)<br>PTS at 5 y:<br>CDT, 37 (42.5%) vs control, 63 (70.8%; *P* < .001) | Major bleeding:<br>CDT, 3 (3.3%) vs control, 0 (0%)<br>No intracranial hemorrhage |
| ATTRACT[39] | 692 | Iliac, femoral, common femoral DVT within 14 d | PMCDT: tPA at <35 mg + therapeutic anticoagulation (n = 336) | Anticoagulation alone (n = 355) | PTS at 24 mo:<br>PMCDT, 157 (47%) vs control, 171 (48%)<br>RR, 0.96 (95% CI, 0.82-1.11; *P* = .56)<br>Moderate to severe PTS at 24 mo:<br>PMCDT, 60 (18%) vs control, 84 (24%)<br>RR, 0.73 (95% CI, 0.54-0.98; *P* = .04) | Major bleeding in 10 d:<br>PMCDT, 1.7% vs control, 0.3%<br>RR, 6.18 (95% CI, 0.78-49.2; *P* = .049)<br>No intracranial hemorrhage |
| CAVA[40] | 184 | Iliofemoral DVT within 14 d | USAT: urokinase via EKOS catheter + therapeutic anticoagulation (n = 77) | Anticoagulation alone (n = 75) | PTS at 12 mo:<br>USAT, 22 (29%) vs control, 26 (35%)<br>OR, 0.75 (95% CI, 0.38-1.50) | Major bleeding in 10 d:<br>USAT, 4 (5%) vs control, 0 (0%)<br>OR, 9.25 (95% CI, 0.49-174.7)<br>No intracranial hemorrhage |

EKOS, EndoWave Infusion Catheter System; PMCDT, pharmacomechanical CDT; RR, relative risk; USAT, ultrasound-assisted CDT.

In summary, CDT has not consistently been shown to reduce the occurrence of PTS or improve long-term QoL and is associated with an increased bleeding risk. Therefore, CDT should be restricted to selected patients with severe symptoms and a higher risk of PTS (iliofemoral DVT) who have a low risk of bleeding. The use of validated prediction models for PTS in the future may allow us to successfully reduce its occurrence in future studies of CDT with or without thrombectomy.

Systemic or CDT can lead to a rapid improvement in vascular patency in patients with severe PE and DVT. Because improved clinical outcomes have not clearly been demonstrated in RCTs, the selection of suitable candidates for these therapies remains critical. Management of these patients can be facilitated by taking a multidisciplinary team approach to their care, with consideration of each patient's clinical presentation, disease severity, comorbidities, and bleeding tendency.

### Conflict-of-interest disclosure

K.A.B. has served as a consultant to Bristol-Myers Squibb and Takeda. T.C. declares no competing financial interests.

### Off-label drug use

None disclosed.

### Correspondence

Kenneth A. Bauer, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215; e-mail: kbauer@bidmc.harvard.edu.

### References

1. Bikdeli B, Wang Y, Jimenez D, et al. Pulmonary embolism hospitalization, readmission, and mortality rates in US older adults, 1999-2015. *JAMA*. 2019;322(6):574-576.
2. Brahmandam A, Abougergi MS, Ochoa Chaar CI. National trends in hospitalizations for venous thromboembolism. *J Vasc Surg Venous Lymphat Disord*. 2017;5(5):621-629.e2.
3. Jaff MR, McMurtry MS, Archer SL, et al; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association [published corrections appear in *Circulation*. 2012;126(7):e104 and *Circulation*. 2012;125(11):e495]. *Circulation*. 2011;123(16):1788-1830.
4. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Respir J*. 2019;54(3):1901647.
5. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Massive pulmonary embolism. *Circulation*. 2006;113(4):577-582.
6. 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(4):684-689.
7. 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(3):227-229.
8. Secemsky E, Chang Y, Jain CC, et al. Contemporary management and outcomes of patients with massive and submassive pulmonary embolism. *Am J Med*. 2018;131(12):1506-1514.e0.
9. Barrios D, Morillo R, Yusen RD, Jiménez D. Pulmonary embolism severity assessment and prognostication. *Thromb Res*. 2018;163:246-251.

10. Meinel FG, Nance JW Jr, Schoepf UJ, et al. Predictive value of computed tomography in acute pulmonary embolism: systematic review and meta-analysis. *Am J Med*. 2015;128(7):747-759.e2.
11. Bajaj A, Saleeb M, Rathor P, Sehgal V, Kabak B, Hosur S. Prognostic value of troponins in acute nonmassive pulmonary embolism: a meta-analysis. *Heart Lung*. 2015;44(4):327-334.
12. Meyer G, Vicaut E, Danays T, et al; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014; 370(15):1402-1411.
13. 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(12):1536-1544.
14. Hao Q, Dong BR, Yue J, Wu T, Liu GJ. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev*. 2018;12:CD004437.
15. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M; "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" trial). *Am J Cardiol*. 2013;111(2):273-277.
16. Wang C, Zhai Z, Yang Y, et al; China Venous Thromboembolism (VTE) Study Group. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial. *Chest*. 2010;137(2): 254-262.
17. Zhang Z, Zhai ZG, Liang LR, Liu FF, Yang YH, Wang C. Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: a systematic review and meta-analysis. *Thromb Res*. 2014;133(3):357-363.
18. Kiser TH, Burnham EL, Clark B, et al. Half-dose versus full-dose alteplase for treatment of pulmonary embolism. *Crit Care Med*. 2018;46(10):1617-1625.
19. 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(6):1473-1479.
20. Avgerinos ED, Saadeddin Z, Abou Ali AN, et al. A meta-analysis of outcomes of catheter-directed thrombolysis for high- and intermediate-risk pulmonary embolism. *J Vasc Surg Venous Lymphat Disord*. 2018;6(4):530-540.
21. Patel N, Patel NJ, Agnihotri K, et al. Utilization of catheter-directed thrombolysis in pulmonary embolism and outcome difference between systemic thrombolysis and catheter-directed thrombolysis. *Catheter Cardiovasc Interv*. 2015;86(7):1219-1227.
22. 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(4):479-486.
23. Piazza G, Hohlfelder B, Jaff MR, et al; SEATTLE II Investigators. 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(10):1382-1392.
24. 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(3): 667-673.
25. 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(14):1401-1410.
26. Tu T, Toma C, Tapson VF, et al; FLARE Investigators. A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: the FLARE study. *JACC Cardiovasc Interv*. 2019;12(9):859-869.
27. De Gregorio MA, Guirola JA, Kuo WT, et al. Catheter-directed aspiration thrombectomy and low-dose thrombolysis for patients with acute unstable pulmonary embolism: prospective outcomes from a PE registry. *Int J Cardiol*. 2019;287:106-110.
28. Xenos ES, Davis GA, He Q, Green A, Smyth SS. The implementation of a pulmonary embolism response team in the management of intermediate- or high-risk pulmonary embolism. *J Vasc Surg Venous Lymphat Disord*. 2019;7(4):493-500.
29. Wright C, Elbadawi A, Chen YL, et al. The impact of a pulmonary embolism response team on the efficiency of patient care in the emergency department. *J Thromb Thrombolysis*. 2019;48(2):331-335.
30. Rosovsky R, Chang Y, Rosenfield K, et al. Changes in treatment and outcomes after creation of a pulmonary embolism response team (PERT), a 10-year analysis [published correction appears in *J Thromb Thrombolysis*. 2019;47(1):41]. *J Thromb Thrombolysis*. 2019;47(1):31-40.
31. Chaudhury P, Gadre SK, Schneider E, et al. Impact of multidisciplinary pulmonary embolism response team availability on management and outcomes. *Am J Cardiol*. 2019;124(9):1465-1469.
32. Carroll BJ, Beyer SE, Mehegan T, et al. Changes in care for acute pulmonary embolism through a multidisciplinary pulmonary embolism response team [published online ahead of print 19 May 2020]. *Am J Med*. doi:10.1016/j.amjmed.2020.03.058.
33. Rabinovich A, Kahn SR. How I treat the postthrombotic syndrome. *Blood*. 2018;131(20):2215-2222.
34. Rabinovich A, Ducruet T, Kahn SR; SOX Trial investigators. Development of a clinical prediction model for the postthrombotic syndrome in a prospective cohort of patients with proximal deep vein thrombosis. *J Thromb Haemost*. 2018;16(2):262-270.
35. Amin EE, van Kuijk SMJ, Joore MA, Prandoni P, Ten Cate H, Ten Cate-Hoek AJ. Development and validation of a practical two-step prediction model and clinical risk score for post-thrombotic syndrome. *Thromb Haemost*. 2018;118(7):1242-1249.
36. Méan M, Limacher A, Alatri A, Aujesky D, Mazzolai L. Derivation and validation of a prediction model for risk stratification of post-thrombotic syndrome in elderly patients with a first deep vein thrombosis. *Thromb Haemost*. 2018;118(8):1419-1427.
37. Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochrane Database Syst Rev*. 2016;11:CD002783.
38. Enden T, Haig Y, Kløw N-E, et al; CaVenT Study Group. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet*. 2012;379(9810):31-38.
39. Vedantham S, Goldhaber SZ, Julian JA, et al; ATTRACT Trial Investigators. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med*. 2017;377(23):2240-2252.
40. Notten P, Ten Cate-Hoek AJ, Arnoldussen CWKP, et al. Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA): a single-blind, multicentre, randomised trial. *Lancet Haematol*. 2020;7(1):e40-e49.

DOI 10.1182/hematology.2020000148