



Local and systemic thrombolytic therapy for acute venous thromboembolism

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Pulmonary embolism (PE) and deep venous thrombosis (DVT), collectively referred to as venous thromboembolism (VTE), are common disorders associated with substantial morbidity and mortality. PE is estimated to occur in approximately 600,000 patients annually in the United States, causing or contributing to 50,000 to 200,000 deaths [1–3]. Autopsy series have shown that PE is responsible for, or at least accompanies, as many as 15% of all in-hospital deaths, further highlighting the significance of this problem [2,4,5]. Moreover, a disturbingly small fraction of patients with this common and lethal disorder is recognized antemortem, with the majority of deaths occurring in the first few hours of presentation [6–9].

The importance of DVT stems from its short- and long-term local complications in the affected extremity, as well as its frequent association with PE, which is seen in as many as 40% to 50% of patients with symptomatic proximal DVT [10–12]. Acutely, DVT results in considerable symptoms. In a small number of cases, extensive venous obstruction may lead to

limb-threatening ischemia, known as phlegmasia cerulea dolens. Long-term, the two major consequences of DVT are recurrent VTE and the development of postthrombotic syndrome (PTS) [13–17].

Currently, anticoagulation remains the standard of care for VTE. Anticoagulation prevents clot propagation and allows endogenous fibrinolytic activity to dissolve existing thrombi, a process that typically occurs over several weeks or months. Nonetheless, incomplete resolution is not uncommon after several months and may result in organization of thromboemboli and obliteration of the pulmonary or deep venous vascular system [18–24].

Thrombolytic therapy, by actively dissolving thromboemboli, offers several potential advantages over anticoagulation in the treatment of patients with VTE (Fig. 1) [25]. By virtue of its ability to produce more rapid clot lysis, thrombolysis may result in earlier improvement in pulmonary perfusion, hemodynamic alterations, gas exchange, and right ventricular function in patients with PE. Thrombolysis also may eliminate venous thrombi, the source of PE, thereby reducing the risk of recurrence. Furthermore, rapid and more complete clot resolution may prevent the development of chronic vascular obstruction and thromboembolic pulmonary hypertension. Through all of these mechanisms, thrombolytic therapy offers the potential to reduce morbidity and mortality from PE. Likewise, thrombolysis offers similar benefits in the treatment of DVT by rapidly improving short-term venous patency, which, in turn, may result in a

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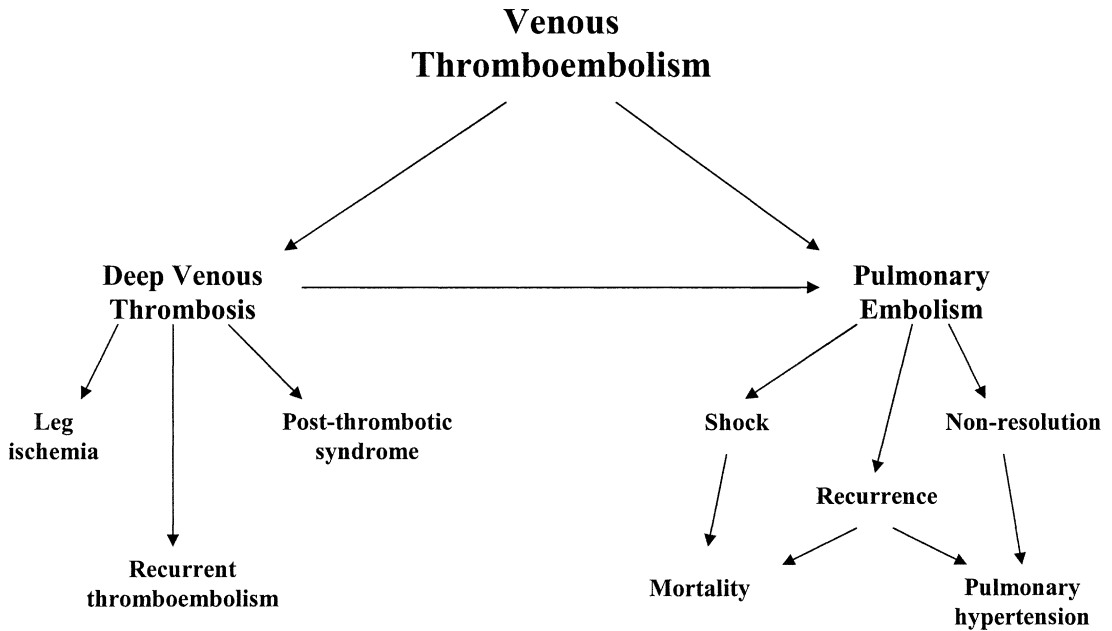


Fig. 1. Adverse outcomes of VTE with potential benefit from thrombolytic therapy.

decrease in the risk of embolization and the development of PTS.

Despite its potential advantages, the widespread interest in its use, and more than 3 decades of investigation, the role of thrombolytic therapy in VTE remains unsettled. A recent report from the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy suggested a highly individualized approach to the use of thrombolytic agents in the treatment of VTE, recommending thrombolysis in patients at low risk for bleeding with hemodynamically unstable PE or massive iliofemoral thrombosis [26].

This article provides a comprehensive review of the literature evaluating the efficacy and safety of thrombolytic therapy in patients with VTE, with a focus on PE. Using data drawn primarily from randomized controlled trials and large registries, the following topics in PE thrombolysis are discussed and recommendations for the use of thrombolytic therapy are provided:

- Efficacy of thrombolytic therapy
- Comparison of thrombolytic agents
- Methods of delivery
- Timing of PE thrombolysis
- Hemorrhagic complications
- Practical aspects of PE thrombolysis
- Special circumstances

Thrombolytic therapy for DVT is discussed briefly, with an emphasis on its short- and long-term efficacy and complications.

Pulmonary embolism

Efficacy of thrombolytic therapy

Data from randomized trials

The National Institutes of Health–sponsored Urokinase Pulmonary Embolism Trial (UPET) was the first study to evaluate PE thrombolysis in a controlled fashion [18]. In this large prospective trial, 160 patients with angiographically documented PE were randomized to receive either a 12-hour infusion of urokinase followed by heparin or heparin alone. At 24 hours, the degree of improvement in hemodynamic measurements and pulmonary blood flow as assessed by angiography and perfusion scan was significantly greater in patients who had received urokinase. Nevertheless, serial perfusion scans performed over 12 months revealed that the quantitative difference in resolution between the two groups decreased progressively after 24 hours such that no difference was found beyond 5 days. Furthermore, no difference in mortality or the rate of PE recurrence was detected between the two groups.

A small subset of 40 patients who were enrolled in either the UPET or the subsequent Urokinase–Streptokinase Embolism Trial (USET) underwent measurements of diffusing capacity and pulmonary capillary blood volume as surrogate markers of small vessel patency 2 weeks and 1 year after therapy with heparin or thrombolytic agents [27]. Although no difference in the degree of perfusion scan resolution had been evident, both of these measurements were initially low in the heparin arm and remained unchanged at 1 year, whereas both values were within the normal range at 2 weeks and improved further by 1 year in the thrombolytic therapy arm. These results are suggestive of more complete resolution of emboli by thrombolysis in small peripheral vessels that are beyond the resolution of perfusion scanning or angiography.

Long-term effects of thrombolytic therapy were assessed by clinical follow-up and hemodynamic studies in the same group of 40 patients more than 7 years after their initial PE [28]. At the end of the follow-up period, more patients in the heparin group had recurrent VTE and dyspnea on exertion when compared with the patients treated with thrombolysis. Twenty-three patients underwent right-sided heart catheterization and measurement of resting and exercise hemodynamics. The group that had received heparin alone had elevated resting pulmonary artery pressure and pulmonary vascular resistance, both of which increased significantly with exercise. The group treated with thrombolytic agents demonstrated normal resting values and normal response to exercise. The observations from this small study suggest that thrombolytic therapy prevents the development of pulmonary hypertension by achieving more complete resolution of emboli and decreasing the risk of subsequent PE recurrence.

Since the UPET trial, eight smaller randomized studies have prospectively compared the efficacy and safety of various thrombolytic agents with heparin in patients with PE [29–36]. In general, these studies, which are summarized in Table 1, were not designed to assess survival as a primary endpoint but focused on various surrogate markers of the degree and rate of clot resolution. The total numbers of patients treated with thrombolysis and heparin were 241 and 220, respectively. The vast majority of the studies revealed that, in the first 24 hours, thrombolytic therapy resulted in more rapid clot resolution than treatment with heparin alone as assessed by angiography, perfusion scan, and hemodynamic measurements [25]. Within 5 to 7 days, both treatments produced similar improvements in pulmonary perfusion as assessed by perfusion scan. Although most of the studies demonstrated no significant differences in

mortality or PE recurrence rates, this finding may be related to inadequate power to detect a difference. Two of the PE thrombolysis studies deserve more detailed discussion.

In 1993, Goldhaber et al reported the results of a randomized trial of 101 normotensive patients treated with either alteplase (rt-PA) or heparin [35]. Baseline right ventricular function was assessed by echocardiography, which was repeated 3 and 24 hours after the start of therapy. In addition, perfusion scans were obtained before and 24 hours after the initiation of treatment. Patients receiving rt-PA had a greater improvement in right ventricular function and pulmonary perfusion than patients receiving heparin alone. Moreover, in the group receiving heparin, there were two fatal and three nonfatal clinically suspected PE recurrences during the first 14 days. None of the patients treated with rt-PA experienced a recurrence, and this difference approached, but did not reach, statistical significance ($P = 0.06$). It is important to note that all of the recurrences occurred in patients with right ventricular dysfunction on baseline echocardiography.

Two years later, Jerjes-Sanchez et al reported the results of a small study in which eight patients with shock owing to massive PE were randomized to receive bolus streptokinase or heparin [36]. No deaths occurred in the streptokinase group, whereas all of the patients receiving heparin alone died, resulting in a statistically significant difference between treatment groups and premature termination of the study. This study was the first and only randomized trial to demonstrate a survival advantage with thrombolytic therapy. Nevertheless, the results are difficult to interpret, because patients receiving heparin presented initially with hemodynamic stability but then experienced severe respiratory failure and shock owing to massive PE recurrence. Therefore, there was a much longer interval between the onset of symptoms and randomization in the heparin group when compared with the patients receiving streptokinase. Additionally, patients receiving streptokinase did not have a PE recurrence before enrollment in the study.

Risk stratification and right ventricular dysfunction

Conflicting data and the lack of a clear advantage of thrombolytic therapy over anticoagulation in reducing clinically important adverse outcomes suggest the possibility that only a subset of patients with PE may benefit from aggressive therapy with thrombolysis. Clearly, the risk–benefit ratio of thrombolytic therapy is expected to be most favorable in patients who are at highest risk for mortality from PE. Hemodynamic instability, defined as hypotension

Table 1
Randomized trials comparing thrombolytic and heparin therapy for pulmonary embolism

Author (year)	Number of patients	Treatment regimens ^{a,b}	Mortality, n (%)	Recurrent PE ^c , n (%)	Major hemorrhage ^d , n (%)
UPET (1970) [18]	78	Heparin	7 (8.9)	15 (19)	21 (27)
	82	UK, 2000 U/lb bolus, 2000 U/lb/h for 12 h	6 (7.3)	12 (15)	37 (45)
Tibbitt et al (1974) [29]	17	Intrapulmonary heparin	1 (5.8)	1 (5.8)	1 (5.8)
	13	Intrapulmonary SK, 600,000 U bolus, 100,000 U/h for 72 h	0	0	1 (8)
Ly et al (1978) [30]	11	Heparin	2 (18.2)	ND	2 (18.2)
	14	SK, 250,000 U bolus, 100,000 U/h for 72 h	1 (7.1)	ND	4 (29)
Marini et al (1988) [31]	10	Heparin	0	0	0
	10	UK, 800,000 U/d infused over 12 h for 3 d	0	0	0
	10	UK, 3,300,000 U infused over 12 h	0	0	0
PIOPED (1990) [32]	4	Heparin	0	ND	0
	9	rt-PA, 40–80 mg over 40–90 min and concomitant heparin	1 (11.1)	ND	1 (11.1)
Levine et al (1990) [33]	25	Heparin	0	0	0
	33	rt-PA, 0.6 mg/kg over 2 min	1 (3)	0	0
PAIMS 2: Dalla-Volta et al (1992) [34]	16	Heparin	1 (6.3)	3 (18.8)	2 (12.5)
	20	rt-PA, 100 mg over 2 h	2 (10)	1 (5)	3 (15)
Goldhaber et al (1993) [35]	55	Heparin	2 (3.6)	5 (9.1)	1 (1.8)
	46	rt-PA, 100 mg over 2 h	0	0	2 (4.3)
Jerjes-Sanchez et al (1995) [36]	4	Heparin	4 (100)	ND	0
	4	SK, 1,500,000 U over 1 h	0 ^e	ND	0

Abbreviations: ND, no data; PE, pulmonary embolism; rt-PA, alteplase; SK, streptokinase; UK, urokinase.

^a Unless specified, treatment was administered intravenously.

^b In all studies, heparin was adjusted to maintain a therapeutic partial thromboplastin time. In most of the studies, thrombolytic therapy was followed by heparin infusion.

^c Recurrent PE rate includes clinically suspected but unconfirmed cases as well as those episodes confirmed by objective tests.

^d The definition of major hemorrhage varied between trials but usually included intracranial hemorrhage, bleeding that required surgery, transfusion, or resulted in death, or a decrease in hematocrit of more than 10 or 15 percentage points.

^e $P < 0.05$. All other comparisons did not reach statistical significance.

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with or without shock, is present in 5% to 10% of patients with PE and has been identified repeatedly as a strong predictor of death, with mortality rates exceeding 50% in hemodynamically unstable patients [18,37–40]. Although thrombolysis has proven beneficial in the setting of hemodynamic instability, these patients represent only a small subset of patients with

PE, because the vast majority of deaths occur before the recognition of PE [36]. This fact has led to the investigation of other markers of adverse outcomes in the remaining majority of patients who are hemodynamically stable. Although several patient and clinical characteristics, including older age, underlying cardiopulmonary disease, certain electrocardio-

graphic findings, elevated cardiac troponins, and the identification of a patent foramen ovale, have been identified as prognostic markers, the echocardiographic finding of right ventricular dysfunction has gained increasing popularity as a component of risk assessment and treatment decisions [40–47]. Recent studies suggest that right ventricular dysfunction is a frequent finding in acute PE, detected in 30% to 50% of patients who undergo echocardiography [40,47–49]. Most of these studies have identified the presence of right ventricular dysfunction in hemodynamically stable patients as a marker of poor prognosis.

Wolfe et al investigated the relationship between right ventricular hypokinesis and the extent of perfusion defects on the initial lung scan in 90 hemodynamically stable patients [48]. Thirty-eight patients (42%) had right ventricular hypokinesis, which was typically identified when the perfusion defect exceeded 30%. All five patients with recurrent symptomatic PE were in the group with right ventricular hypokinesis.

In a study of 126 consecutive patients with PE, echocardiography on the day of diagnosis revealed moderate-to-severe right ventricular dysfunction in 70 (56%) [49]. The overall in-hospital mortality rate was 7.9%, with deaths occurring exclusively in patients with significant right ventricular dysfunction. On multivariate analysis, right ventricular dysfunction was associated with in-hospital and 1-year mortality; however, because systemic blood pressure was not reported, this study does not provide adequate information to determine the independent impact of right ventricular dysfunction on prognosis in patients with PE.

In 1999, the results of the International Cooperative Pulmonary Embolism Registry (ICOPER), investigating the prognostic impact of baseline clinical factors on 3-month mortality were published. In this registry of 2454 consecutive patients with PE, 40% of the patients who underwent baseline echocardiography had right ventricular hypokinesis [40]. The presence of right ventricular hypokinesis was an independent predictor of mortality, doubling the risk of death during the follow-up period.

Recently, Grifoni et al investigated 209 consecutive patients with PE and identified right ventricular dysfunction in 31% of patients with normal systemic blood pressure [47]. In that group, shock owing to PE developed in 10%, resulting in death in half of these patients. In contrast, none of the normotensive patients with normal right ventricular function had a PE-related death.

The initial evidence of the efficacy of thrombolytic therapy in the setting of PE and isolated right

ventricular dysfunction came from the study of Goldhaber et al, as discussed in the previous section. Further support for this concept emerged from the analysis of the Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET), which included 1001 patients [50]. The clinical course of 719 patients presenting with right ventricular dysfunction with or without pulmonary hypertension, excluding those with shock, was reported in 1997. In this nonrandomized study, 169 patients initially received thrombolytic therapy, whereas 550 were treated with heparin alone. There were important baseline differences between treatment groups, including older age and a higher frequency of underlying cardiopulmonary disease in the heparin arm. Moreover, the treatment decision was left to the discretion of the attending physician, with a potential for selection bias. In the group undergoing thrombolysis, mortality at 30 days and the rate of recurrent PE were significantly lower than in the heparin-treated group, but the bleeding rate was much higher. Despite its shortcomings, this study was the first to demonstrate a survival advantage with thrombolytic therapy in patients without shock and supports the trend noted previously by Goldhaber and colleagues for thrombolysis to reduce the risk of recurrent PE.

The findings of Goldhaber et al and the MAPPET have provided justification for thrombolytic therapy in normotensive patients with PE and right ventricular dysfunction [46,51]. The proponents of this approach believe that patients with right ventricular dysfunction have “impending hemodynamic instability” with a larger clot burden and a lower likelihood of tolerating recurrent PE. They argue that rapid improvement in pulmonary blood flow, reversal of right ventricular dysfunction, and elimination of the source of recurrent emboli by thrombolytic therapy will improve the outcomes in this setting. However, although rapid reversal of right ventricular dysfunction can be achieved by thrombolytic therapy, it has never been demonstrated conclusively that the PE recurrence rate can be reduced by thrombolysis [35,52,53]. More importantly, right ventricular dysfunction has a low positive predictive value for mortality; the majority of hemodynamically stable patients with right ventricular dysfunction have a good prognosis and survive when treated with anticoagulation alone [47,54]. The extension of thrombolytic therapy to this large subset of patients with a good prognosis would lead to a significantly increased incidence of bleeding, outweighing any potential benefits of thrombolysis.

Furthermore, a recent report from a single-center registry of 128 patients with massive PE and right ventricular dysfunction sharply contradicts the re-

sults of the MAPPET [55]. In this study, patients treated with thrombolytic therapy had significantly worse outcomes when compared with patients treated with anticoagulation. Although the PE recurrence rate was the same in both groups, significantly higher rates of in-hospital mortality and intracranial and other severe hemorrhage were observed in the thrombolysis arm.

Recommended indications for thrombolytic therapy

Based on the ability of thrombolytic therapy to reduce clot burden rapidly and improve hemodynamic abnormalities and on the survival advantage

demonstrated by Jerjes-Sanchez and colleagues, patients with PE and circulatory shock should be treated with thrombolytic therapy unless an overwhelming contraindication exists [25]. Thrombolysis has never been proven to reduce mortality or the risk of recurrent PE in hemodynamically stable patients. Given the increased risk of major hemorrhage that accompanies thrombolytic therapy, patients in this category should generally be treated with heparin alone. As discussed previously, PE thrombolysis based solely on the presence of right ventricular dysfunction in hemodynamically stable patients is controversial, because insufficient data are available

Table 2
Randomized trials comparing the efficacy and safety of thrombolytic agents

Author (year)	Number of patients	Treatment regimens ^a	Mortality, n (%)	Recurrent PE ^b , n (%)	Major hemorrhage ^c , n (%)
USET Phase 2 (1974) [37]	59	UK, 2000 U/lb bolus, 2,000 U/lb/h for 12 h	4 (7)	1 (1)	8 (14)
	54	UK, 2000 U/lb bolus, 2,000 U/lb/h for 24 h	5 (9)	4 (7)	10 (19)
	54	SK, 250,000 U bolus, 100,000 U/h for 24 h	5 (9)	2 (4)	6 (11)
Goldhaber et al (1988) [56]	23	UK, 2000 U/lb bolus, 2000 U/lb/h for 24 h	2 (8.7)	1 (4)	11 (48)
	22	rt-PA, 100 mg over 2 h	2 (8.7)	0	4 (18)
Meyer et al (1992) [57]	29	UK, 4400 U/kg bolus, 4400 U/kg/h for 12 h	1 (3.4)	2 (6.9)	8 (28)
	34	rt-PA, 80–100 mg over 2 h	3 (8.8)	2 (5.9)	7 (21)
Goldhaber et al (1992) [58]	46	UK, 1,000,000 U over 10 min, 2,000,000 U over 110 min	1 (2)	3 (6.5)	6 (13)
	44	rt-PA, 100 mg over 2 h	2 (4.5)	0	9 (20)
Meneveau et al (1997) [59]	25	SK, 250,000 U bolus, 100,000 U/h for 12 h	1 (4)	2 (8)	3 (12)
	25	rt-PA, 100 mg over 2 h	1 (4)	0	4 (16)
Meneveau et al (1998) [60]	43	SK, 1,500,000 U over 2 h	0	1 (2.3)	3 (7.0)
	23	rt-PA, 100 mg over 2 h	0	2 (8.7)	5 (21.7)
Tebbe et al (1999) [61]	23	Reteplase, 10 U, two injections 30 min apart	1 (4)	0	4 (17.4)
	13	rt-PA, 100 mg over 2 h	2 (15)	1 (7.7)	1 (7.7)

Abbreviations: PE, pulmonary embolism; rt-PA, alteplase; SK, streptokinase; UK, urokinase.

^a In all studies, heparin was adjusted to maintain a therapeutic partial thromboplastin time. In most of the studies, thrombolytic therapy was followed by heparin infusion.

^b Recurrent PE rate includes clinically suspected but unconfirmed cases as well as those episodes confirmed by objective tests.

^c The definition of major hemorrhage varied between trials but usually included intracranial hemorrhage, bleeding that required surgery, transfusion, or resulted in death, or a decrease in hematocrit of more than 10 or 15 percentage points.

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to support this practice. Clearly, a large prospective randomized trial is needed to settle this issue and to identify precisely the subset of patients with right ventricular dysfunction and a higher risk of mortality who would benefit most from thrombolysis. The authors believe that, until such data are available, right ventricular dysfunction alone is not an indication for thrombolytic therapy. Lastly, many experts would consider severe respiratory failure with refractory hypoxemia as another potential indication for thrombolytic therapy, although this view has never been investigated formally.

Comparison of thrombolytic agents

Randomized controlled trials comparing streptokinase, urokinase, rt-PA, and reteplase are summarized in Table 2 [37,56–61]. The earliest and largest of these trials was the USET, which included 167 patients with angiographically demonstrated PE [37]. Patients were randomized to treatment with 12 hours of urokinase, 24 hours of urokinase, or 24 hours of streptokinase. Similar improvements in angiographic severity scores, hemodynamic variables, and perfusion scans were found in all groups at 24 hours, although no difference in the resolution of lung scan defects between groups was detected at 3 or 6 months. The rates of mortality, recurrent PE, and major hemorrhage were not significantly different.

Six subsequent trials have compared 2-hour infusions of rt-PA with 24-, 12-, and 2-hour regimens of urokinase, 12- and 2-hour infusions of streptokinase, and, most recently, two bolus injections of reteplase [56–61]. These trials revealed that a 2-hour infusion of rt-PA resulted in more rapid clot lysis when compared with the 12- or 24-hour regimens of urokinase and streptokinase; however, these agents have comparable efficacy and safety when equivalent doses are delivered at the same rate within the same time period. Similarly, the efficacy and safety of rt-PA and reteplase do not seem to be significantly different. The thrombolytic regimens available for the treatment of VTE are listed in Table 3. Three thrombolytic agents with specific regimens are approved by the United States Food and Drug Administration (FDA) for the treatment of PE.

Methods of delivery

Thrombolytic agents can be administered systemically or locally into the pulmonary artery. Interest in the local delivery of thrombolytic agents is based on several potential advantages over systemic administration [62–66]. Delivery of the drug directly into the

Table 3
Thrombolytic regimens used for treatment of venous thromboembolism

Drug	Regimen ^a
Streptokinase	250,000 U over 30 min followed by 100,000 U/h for 24 h ^{b,c} 250,000 U over 30 min followed by 100,000 U/h for 12 h 1,500,000 U over 1 to 2 h
Urokinase	4400 U/kg over 10 min followed by 4400 U/kg/h for 24 h ^b 4400 U/kg over 10 min followed by 4400 U/kg/h for 12 h ^b 1,000,000 U over 10 min followed by 2,000,000 U over 110 min
rt-PA	100 mg over 2 h ^b
Reteplase	Two injections of 10 U 30 min apart

Abbreviations: rt-PA, alteplase.

^a All agents are administered as a continuous peripheral intravenous infusion.

^b Approved by the US Food and Drug Administration for pulmonary embolism thrombolysis.

^c A 72-hour infusion using the same dose is approved for the treatment of deep venous thrombosis.

pulmonary artery might be accompanied by more rapid or more complete clot lysis, and, because of high local drug concentrations, low doses might be able to achieve the same degree of thrombolysis as higher systemic doses. Furthermore, local therapy might reduce the risk of bleeding, especially if lower doses are used. The major disadvantage of local therapy is the requirement for pulmonary artery catheterization, which is associated with an increased risk of bleeding from the vascular access site.

Only one controlled study has compared intrapulmonary and systemic thrombolysis. Verstraete et al randomized patients with angiographically proven massive PE to receive 50 mg of either intrapulmonary or intravenous rt-PA over 2 hours [67]. Angiography was then repeated, and a second dose of 50 mg was infused over 5 hours if sufficient improvement had not occurred. The rate and degree of improvement in pulmonary hemodynamics and perfusion and the incidence of major hemorrhage were not influenced by the route of drug administration.

A potentially more effective role of local thrombolysis is the combined use of a low-dose thrombolytic agent and mechanical adjuncts to assist in clot disruption, especially in patients with a higher bleeding risk. Local pharmacomechanical thrombolysis using low doses of urokinase or rt-PA and either

intraembolic infusion or mechanical clot disruption has been used in several case series [62–64,66]. In one report, six patients with contraindications to systemic thrombolysis received low-dose intraembolic thrombolytic therapy using specialized catheters, which resulted in an impressive degree of angiographic improvement in all patients and no bleeding [64]. In a more recent larger series of 59 patients with massive PE, mechanical fragmentation and intrapulmonary thrombolysis led to clinical improvement in 56 patients [66].

Bolus thrombolysis is another approach that has been suggested to improve clot lysis and decrease the risk of bleeding by achieving a higher drug concentration over a shorter period of time. Two prospective randomized trials comparing bolus dose rt-PA with the traditional 2-hour regimen revealed no significant intergroup differences in the rate of angiographic, lung scan, and hemodynamic improvement, and bleeding rates [68–70].

In summary, the limited available controlled data do not support the use of bolus therapy or the use of intrapulmonary versus systemic thrombolytic therapy. Further research is needed to determine the precise role of local pharmacomechanical thrombolysis employing low doses of thrombolytic agents, especially in the treatment of patients with PE who are at high risk for bleeding complications.

Timing of pulmonary embolism thrombolysis

Contemporary studies of PE thrombolysis have included patients with symptoms up to 14 days before the diagnosis. Daniels et al combined data from 308 patients who participated in five multicenter trials to study the relationship between the duration of symptoms and the efficacy of thrombolytic therapy [71]. Based on perfusion lung scan improvement, this analysis documented a progressive decrease in the efficacy of thrombolytic therapy with increasing symptom duration; therefore, once the diagnosis is established, thrombolytic therapy should be carried out as early as possible. However, it is important to note that the benefit of thrombolysis extends up to 14 days after symptom onset.

Hemorrhagic complications

Hemorrhage following thrombolytic therapy most commonly occurs at vascular puncture sites, although spontaneous hemorrhage, especially gastrointestinal, retroperitoneal, and intracranial, may also occur. Older age, a higher body mass index, and the performance of pulmonary angiography have been identified as sig-

nificant predictors of bleeding [72]. As shown in Tables 1 and 2, the reported rate of major hemorrhage with thrombolytic and heparin therapy has ranged from 0% to 48% and 0% and 27%, respectively [25]. This wide range can be explained by more aggressive diagnostic and follow-up protocols in earlier studies and by variable definitions of “major hemorrhage.” When major hemorrhage is defined arbitrarily as fatal hemorrhage, intracranial hemorrhage, or bleeding that requires surgery or transfusion, a review of controlled studies comparing thrombolysis and heparin yields an average incidence of 6.3% and 1.8%, respectively (see Table 1) [25]. When data from randomized studies comparing different thrombolytic agents are also considered, the overall incidence of major hemorrhage with PE thrombolysis increases to approximately 12%, with no significant differences in risk between the three agents (Table 2) [25].

The most dreaded bleeding complication is intracranial hemorrhage. An intracranial neoplasm or aneurysm, a recent cerebrovascular accident, and recent central nervous system trauma or surgery clearly increase the risk of intracranial hemorrhage. In addition, an overview of five previously published studies identified elevated diastolic blood pressure at the time of presentation as an additional risk factor for intracranial hemorrhage [73]. Pooled data from 19 randomized studies in which 932 patients received thrombolytic therapy revealed that the overall incidence of intracranial hemorrhage was 1.2%, with death occurring in about half of these patients. It is important to point out that in the ICOPER, the rate of intracranial hemorrhage was much higher at 3% in 304 patients treated with thrombolysis [40]. This higher rate of intracranial hemorrhage based on registry data may be more reflective of the real risk in routine clinical practice, because randomized controlled trials are equipped with multiple mechanisms to ensure safety and prevent complications [45].

Practical aspects of pulmonary embolism thrombolysis

Diagnosis of pulmonary embolism before thrombolytic therapy

A detailed discussion of the diagnostic evaluation of PE is beyond the scope of this article. The comments herein are limited to diagnostic techniques performed in the context of massive PE when thrombolytic therapy is considered. Because thrombolysis is accompanied by a significant risk of major hemorrhage, it is essential to confirm the presence of PE before the initiation of treatment, preferably with noninvasive imaging techniques. For instance, in the

presence of a high pretest clinical suspicion, a high-probability ventilation–perfusion scan is sufficient to establish the diagnosis of PE; however, definitive diagnostic combinations of clinical and ventilation–perfusion scan probabilities are not observed in most patients. Spiral computed tomography of the chest, either as an initial study or in patients with a non-diagnostic ventilation–perfusion scan, is an attractive alternative modality for the detection of emboli in central (segmental or larger) pulmonary arteries. For the diagnosis of central PE, studies comparing spiral CT with angiography have demonstrated positive and negative predictive values exceeding 90% [74–77]. Despite an increased risk of bleeding, pulmonary angiography remains the diagnostic gold standard and should be considered when PE cannot be reliably diagnosed or excluded using noninvasive testing.

In hemodynamically unstable patients who cannot leave the intensive care unit for ventilation–perfusion scanning, spiral CT, or pulmonary angiography, diagnosis must be based on clinical evaluation supplemented by indirect evidence of PE. In this regard, bedside duplex ultrasound of extremities and echocardiography are potential options. Transthoracic or transesophageal echocardiography is extremely useful because of its ability to demonstrate signs of right ventricular pressure overload, including right ventricular hypokinesis or dilatation, interventricular septal flattening and paradoxical motion, and an elevated transtricuspid gradient, and to rule out other causes of shock, such as pericardial tamponade, left ventricular failure, aortic dissection, and valvular insufficiency [78]. Other more specific echocardiographic signs of PE are an altered pattern of right ventricular systolic flow velocity and regional hypokinesis of the right ventricular mid free wall [78–80]. Although it is rare for central emboli to be visualized directly by transthoracic echocardiography, transesophageal echocardiography can identify proximal thromboemboli with sensitivity and specificity figures exceeding 80% in cases of massive PE associated with right ventricular dilatation [81,82]. Finally, right-sided cardiac catheterization may also strengthen the suspicion of massive PE while excluding other causes of shock by demonstrating elevated pulmonary artery and right ventricular pressures, a normal or low pulmonary artery occlusion pressure, and a low cardiac index.

Guidelines for the administration of thrombolytic agents

The drug regimens available for PE thrombolysis are shown in Table 3. Based on studies demonstrating more rapid clot lysis, the authors believe that, among the FDA-approved regimens, rt-PA is the thrombolytic

agent of choice. Other effective alternatives are bolus infusion of streptokinase and the newer agent reteplase. Before therapy is initiated, patients must undergo a thorough evaluation to elicit factors that increase the risk of major hemorrhage (Table 4) [25]. This evaluation includes a detailed history and physical examination to detect signs of intracranial, gastrointestinal, or other organ system disorders that may predispose the patient to a higher risk of bleeding. Initial laboratory tests should include measurement of hemoglobin, hematocrit, platelet count, prothrombin time, and partial thromboplastin time (PTT). A blood sample should be obtained for blood typing in anticipation of the need for transfusion. The decision to use thrombolytic therapy must be based on a careful evaluation of its potential benefits and risks. No contraindication is absolute in the setting of massive PE and shock, and the decision to use thrombolytic therapy must be individualized. As an example, successful thrombolysis has been reported in pregnant and postoperative patients, including postneurosurgical patients [83–85].

Unlike in thrombolytic therapy for myocardial infarction, heparin is generally not infused during PE thrombolysis. Because all regimens employ fixed or weight-based dosages, there is no need to monitor coagulation parameters during the infusion. Following the completion of thrombolytic therapy, the PTT should be measured. Heparin should be started when

Table 4
Relative contraindications to thrombolytic therapy for venous thromboembolism

Recent (within 2 months) cerebrovascular accident, or intracranial or intraspinal trauma or surgery
Active intracranial disease (aneurysm, vascular malformation, neoplasm)
Major internal bleeding within the past 6 months
Uncontrolled hypertension (systolic blood pressure \geq 200 or diastolic blood pressure \geq 110 mm Hg)
Bleeding diathesis, including that associated with severe renal or hepatic disease
Recent ($<$ 10 days) major surgery, puncture of a noncompressible vessel, organ biopsy, or obstetric delivery
Recent major and minor trauma, including cardiopulmonary resuscitation
Infective endocarditis
Pregnancy
Hemorrhagic retinopathy
Pericarditis
Aneurysm

From Arcasoy SM, Kreit JW. Thrombolytic therapy of pulmonary embolism: a comprehensive review of current evidence. Chest 1999;115:1695–707; with permission.

Table 5
Randomized trials comparing systemic thrombolytic and heparin therapy for deep venous thrombosis

Author (year)	Number of patients		Treatment ^a	Venographic results ^b			Mortality, n (%)	PE ^c , n (%)	Major hemorrhage ^d , n (%)
	Total	Evaluable ^e		Complete, n (%)	Partial, n (%)	None, n (%)			
Robertson et al (1968) [105]	16	8	Heparin ^f	0	3 (37)	5 (63)	1 (13)	ND	1 (13)
		8	SK	0	7 (87)	1 (13)	0	ND	3 (38)
Kakkar et al (1969) [106]	20	9	Heparin	2 (22)	2 (22)	5 (56)	2 (20)	1 (10)	2 (20)
		9	SK	6 (67) ^g	1 (11)	2 (22)	0	0	2 (20)
Robertson (1970) [107] ^h	16	7	Heparin ^f	2 (29)		5 (71)	0	0	1 (14)
		9	SK	6 (67)		3 (33)	1 (11)	4 (44)	ND
Tsapogas (1973) [108] ^h	34	15	Heparin	1 (7)		14 (93)	0	1 (7)	ND
		19	SK	10 (53)		9 (47)	0	0	ND
Porter et al (1975) [109]	50	26	Heparin	1 (4)	20 (77)	5 (19)	0	0	1 (4)
		23	SK	6 (26)	15 (65)	2 (9)	1 (4)	0	4 (17)
Arnesen et al (1978) [110] ^h	42	21	Heparin	5 (24)		16 (76)	0	0	3 (14)
		21	SK	15 (71)		6 (29)	0	1 (5)	3 (14)
Elliot et al (1979) [111]	51	25	Heparin	0	ND	ND	2 (8)	2 (8)	0
		23	SK	9 (39)	12 (52)	2 (9)	0	1 (4)	2 (8)
Schulman et al (1986) [112]	38	19	Heparin	2 (11)	ND	ND	0	0	1 (5)
		17	SK	7 (41)	ND	ND	0	0	3 (18)

Turpie I (1990) [113] ^h	24	12	Heparin	2 (17) ⁱ	10 (83)	0	ND	1 (8)	
		12	rt-PA	9 (75)	3 (25)	0	ND	4 (33)	
Turpie II (1990) [113] ^h	59	30	Heparin	7 (23)	23 (77)	0	ND	1 (3)	
		28	rt-PA + heparin	13 (46)	15 (54)	0	ND	1 (3)	
Goldhaber et al (1990) [114]	65	11	Heparin	0 ^j	2 (18)	9 (82)	0	ND	0
		32	rt-PA	2 (6)	18 (56)	12 (38)	0	ND	1 (3)
		17	rt-PA + heparin	1 (6)	8 (47)	8 (47)	0	ND	0
Schweizer et al (2000) [115]	150	50	Heparin	1 (2)	9 (18)	40 (80)	0	0	0
		50	UK + heparin	17 (34)	23 (46)	10 (20)	0	4 (8)	4 (8)
		50	SK + heparin	20 (40)	20 (40)	10 (20)	0	5 (10)	5 (10)

Abbreviations: ND, no data; PE, pulmonary embolism; rt-PA, alteplase; SK, streptokinase; UK, urokinase.

^a In most of the studies, thrombolytic therapy was followed by heparin infusion.

^b Venographic patency was defined as follows: complete (100% resolution), partial (1%–99% resolution), none (no resolution or worse).

^c PE rates include clinically suspected but unconfirmed cases as well as those episodes confirmed by objective tests. PE rates are based on the total number of patients randomized.

^d The definition of major hemorrhage varied between trials but usually included intracranial hemorrhage, retroperitoneal hemorrhage, bleeding that required transfusion, surgery, or resulted in death, or a decrease in the hemoglobin of 2 g or greater. Hemorrhage rates are based on the total number of patients randomized.

^e Evaluable patients include those patients who finished therapy and underwent follow-up venography.

^f Heparin was not adjusted to maintain a therapeutic partial thromboplastin time.

^g $P = 0.05$.

^h Results for venographic patency did not distinguish between complete or partial response.

ⁱ When venographic results are reported as > 50% resolution (0 patients in the heparin group versus 7 patients in the rt-PA group), there is a statistically significant difference between groups, $P = 0.002$.

^j $P = 0.04$.

the PTT is less than 2.5 times the control value and adjusted to maintain the PTT in the range of 1.5 to 2.5 times control. If the initial PTT exceeds this upper limit, it should be remeasured every 2 to 4 hours until it returns to the therapeutic range, at which time heparin may safely be started [25,86,87]. When PTT measurements are not readily available, the authors recommend that heparin infusion be started immediately after the completion of thrombolytic therapy and adjusted based on PTT results.

During thrombolytic therapy, the avoidance of unnecessary invasive procedures minimizes the risk of hemorrhage. Management of hemorrhage depends on its location, severity, and cause. Bleeding from vascular access sites can usually be controlled with manual pressure or compression dressings. In clinically important major hemorrhage, the thrombolytic agent should be discontinued. Cryoprecipitate, fresh frozen plasma, or both may need to be administered to reverse any associated coagulopathy. If an altered mental status or focal neurologic findings develop during or after thrombolysis, the diagnosis of intracranial hemorrhage should be considered, and an emergent noncontrast CT scan of the brain should be obtained. In addition to measures to stop the bleeding, a neurosurgical consultation must be requested.

Special circumstances

Right-sided heart thromboemboli

With the increased use of echocardiography in patients with PE, right-sided heart thromboemboli (RHTE), also referred to as “emboli in transit,” have been identified more frequently, with a reported incidence of 3% to 23%. The majority are found in the right atrium [88–92]. Most, but not all, reports of RHTE suggest a higher mortality rate in patients with this condition and recommend the use of aggressive therapeutic measures, such as surgery or thrombolytic therapy [88,93–96]. Nevertheless, it is unclear whether the presence of RHTE independently increases the risk of mortality or is simply a marker of severe accompanying PE, which is present in the vast majority of patients who have RHTE. A recent systematic review identified 177 patients with RHTE and reported an overall mortality rate of 27.1% [88]. The mortality rates in patients treated with anticoagulation, surgery, or thrombolytic therapy were 28.6%, 23.8%, and 11.3%, respectively. On multivariate analysis, thrombolytic therapy resulted in an odds ratio for mortality of 0.33 (95% confidence interval, 0.11–0.98) when anticoagulation was used as a reference. Previous studies have reported conflicting findings, with better or similar outcomes after

surgery or anticoagulation when compared with thrombolysis [96–98]; therefore, the optimal management strategy for RHTE remains unclear.

Cardiac arrest

Acute PE and myocardial infarction collectively account for 50% to 70% of out-of-hospital cardiac arrests not related to trauma [99]. Several case reports and series have revealed successful stabilization and long-term survival in patients with cardiac arrest owing to PE after thrombolytic therapy [100–102]. In a recent retrospective study, PE was identified as the cause of 4.8% of all cardiac arrests [103]. The initial rhythm was pulseless electrical activity or asystole in the majority of patients with PE, and clinical diagnosis was made antemortem in 42 patients (70% of those with PE). One half of these patients were treated with 100 mg of rt-PA. Although the rate of return of spontaneous circulation was significantly higher in the thrombolysis group (81% versus 43%, $P = 0.03$), only 2 of 21 patients survived to hospital discharge. More recent studies of thrombolysis in cardiac arrest victims have not differentiated patients with PE from those with other disorders and have yielded contrasting and less optimistic results [99,104].

Clearly, thrombolytic therapy for PE leads to much faster improvement in patients with pulmonary vascular obstruction and hemodynamic abnormalities than does treatment with anticoagulation alone. Nevertheless, it has not been established conclusively that this benefit results in a reduction in morbidity or mortality in all patients with PE. In the subset of patients with shock owing to massive PE, the potential benefits of thrombolysis almost certainly prevail over the risk of significant hemorrhage. In patients with small emboli that produce no hemodynamic impact, the risk of thrombolytic therapy is clearly not warranted. Additional information is required to determine the most appropriate therapy for patients who fall between these two extremes, focusing on the role of thrombolytic therapy in patients with right ventricular dysfunction who have no clinical signs of systemic hypoperfusion.

Deep venous thrombosis

Efficacy of thrombolytic therapy

Short-term results

The results of randomized controlled trials assessing the short-term efficacy of streptokinase and rt-PA compared with heparin are summarized in Table 5 [105–115]. Most of these trials demonstrate that

systemic thrombolytic therapy leads to complete or partial resolution more often than does heparin therapy. Overall, some degree of lysis was achieved in approximately 70% of patients treated with thrombolysis compared with 24% of heparin-treated patients. Complete lysis occurred in 28% and 4% of patients, respectively. Data suggest that newer and nonocclusive thrombi are more likely to undergo successful lysis when compared with older and

occlusive thrombi [108,109,111]. Although no differences in the rates of PE and mortality have been reported, studies have not been designed to assess these outcomes adequately.

Long-term results on the development of postthrombotic syndrome

Randomized controlled trials comparing the effects of thrombolytic therapy and heparin on the

Table 6
Long-term results of thrombolytic therapy: postthrombotic syndrome

Author (year)	Number of patients		Mean duration of follow-up (range)	Treatment	Results		
	Initial	Long-term follow-up			Normal, n (%)	Venographic, PTS, n (%)	Clinical PTS, n (%)
Kakkar et al (1969) [116]	20	8	6–12 Months	Heparin	1 (13)	7 (87)	ND
		7		SK	4 (57)	3 (43)	ND
Bieger et al (1976) [117]	10	5	3–4 Months	Heparin	1 (20)	4 (80)	2 (40)
		5		SK	4 (80)	1 (20)	0
Common et al (1976) [118]	50	12	7 Months (4–18)	Heparin	1 (8)	11 (92)	6 (50)
		15		SK	6 (40)	9 (60)	5 (33)
Johansson et al (1979) [119]	57	3	10 Years (9–12)	Heparin	2 (66)	1 (33)	2 (66)
		5 ^a		SK	0	3 (100)	4 (80)
Elliot et al (1979) [111]	51	20	19 Months	Heparin	ND	ND	18 (90)
		23 ^b		SK	10 (50)	10 (50)	8 (35)
Arnesen et al (1982) [120]	42	18	6.5 Years	Heparin	0 ^c	18 (100)	12 (67)
		17 ^c		SK	7 (44)	9 (56)	4 (24)
Schulman et al (1986) [112]	38	18 ^d	60 Months (2–108)	Heparin	4 (36)	7 (64)	11 (61)
		17		SK	1 (14)	6 (86)	11 (65)
Schweizer et al (1998) [121]	69	22	12 Months	Heparin	ND	ND	18 (82)
		22		UK + heparin	ND	ND	12 (54)
		22		rt-PA + heparin	ND	ND	16 (73)
Schweizer et al (2000) [115]	250	46	12 Months	Heparin	5 (11) ^f	41 (89)	41 (89)
		46		SK (systemic) + heparin	23 (50)	23 (50)	23 (50)
		46		UK (systemic) + heparin	14 (30)	32 (70)	32 (70)
		50		UK (locoregional) + heparin	13 (26)	37 (74)	37 (74)
		50		rt-PA + heparin	11 (22)	39 (78)	39 (78)

Abbreviations: ND, no data; PTS, postthrombotic syndrome; rt-PA, alteplase; SK, streptokinase; UK, urokinase.

^a Venographic data available for three patients.

^b Venographic data available for 20 patients.

^c Venographic data available for 16 patients.

^d Venographic results at 1 month. Venographic data available for 11 patients in the heparin arm and 7 patients in the SK arm.

^e $P = 0.004$.

^f $P < 0.001$ for systemic thrombolytic therapy (SK or UK) versus controls (heparin).

development of PTS are summarized in Table 6 [111,112,115–121]. In most of the studies, thrombolytic therapy reduced the rate of venographic PTS, which frequently translated into an improvement in the rate of clinical PTS [116–118,120]. The data also suggest that the long-term benefit of thrombolytic therapy on the development of PTS is observed primarily in patients with an early response to treatment. Nevertheless, these data suffer from several important limitations, including small study populations, variable patient follow-up, and non-standardized clinical assessment at the time of follow-up.

Methods of delivery

Local delivery of thrombolytic agents for the treatment of DVT has been investigated for reasons similar to those discussed in the section on PE. The two main strategies for local therapy that have been employed are regional administration of thrombolytic agents via a peripheral vein in the affected limb and catheter-directed thrombolysis. Limited data from controlled studies do not demonstrate any clear advantages of the use of regional versus systemic therapy [115,122]. Recently, catheter-directed thrombolysis has shown promising results in nonrandomized patient series. In a large registry of 473 patients, catheter-directed urokinase resulted in a “marked” (defined as more than 50%) lysis rate in 83% of patients and complete lysis in 31%. The primary patency rate was 60% at 1 year [123]. The technique and indications for catheter-directed thrombolysis merit further research.

Dosage

The three controlled studies directly comparing different dosages of thrombolytic agents, two using streptokinase and one using rt-PA, demonstrated no evidence of superior efficacy or decreased bleeding rate with the use of lower dosages [124–126]. Currently, streptokinase should be administered in dosages approved by the FDA, that is, a 250,000 U bolus followed by an infusion of 100,000 U/hour for 72 hours (see Table 3). The recommended dosage of rt-PA is 0.5 mg/kg over 8 hours, which can be repeated once 24 hours later if necessary.

Hemorrhagic complications

The rates of major hemorrhage with thrombolytic therapy are listed in Table 5. Pooled data from randomized trials of DVT thrombolysis demonstrate

rates of major hemorrhage similar to those reported in the PE thrombolysis literature, that is, an average incidence of 10% (range, 0% to 38%) with thrombolytic therapy and 5% (range, 0% to 22%) with heparin. The overall incidence of intracranial hemorrhage is 0.5% with thrombolytic therapy and 1.2% with heparin. The incidence of intracranial hemorrhage with DVT thrombolysis seems to be somewhat lower than the incidence reported in controlled clinical trials of PE, most likely reflecting differences in patient populations and treatment regimens [25].

When compared with anticoagulation, thrombolytic therapy for DVT leads to superior short-term venous patency and a higher risk of major hemorrhage but no difference in the rates of PE and mortality. The data also suggest a lower incidence of PTS following thrombolysis, although it is unclear whether the potential benefit of improved early patency and lower incidence of PTS outweighs the risk of increased bleeding and cost associated with thrombolytic therapy. Limited data do not show any advantage of locoregional versus systemic thrombolytic therapy, although catheter-directed techniques warrant further investigation.

Summary

Thrombolytic therapy unquestionably leads to more rapid and complete clot lysis with a significantly higher risk of bleeding when compared with anticoagulation. The most definite indication for thrombolytic therapy in patients with VTE is massive PE associated with hemodynamic instability. Other potential indications, although not widely accepted or proven, include PE-related respiratory failure with severe hypoxemia and massive iliofemoral thrombosis with the risk of phlegmasia cerulea dolens. Routine use of thrombolytic therapy in all other cases of PE and DVT cannot be justified. Future research using randomized controlled studies should focus on the following key questions:

- Do hemodynamically stable patients with PE and right ventricular dysfunction benefit from thrombolysis, and, if so, is there a subset of patients within this group who are most likely to benefit?
- Does thrombolytic therapy improve long-term outcomes of DVT with a favorable risk-to-benefit ratio, and, if so, which patients are most likely to benefit long-term?

- What is the precise role of catheter-directed thrombolysis in the treatment of VTE, particularly the use of a low-dose thrombolytic agent in conjunction with mechanical clot disruption to minimize bleeding in patients at high risk?

Until these questions are answered, clinicians must approach decision-making regarding the use of thrombolytic therapy in PE and DVT with careful consideration of the potential risks and benefits for the patient within the framework of currently available data.

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