REVIEW

When should we thrombolyse patients with pulmonary embolism? A systematic review of the literature

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The early mortality in pulmonary embolism (PE) is largely predicted by the associated cardiovascular response, with progressive right ventricular failure, hypotension, shock, and circulatory arrest being associated with increasing mortality. Thrombolysis may improve the prognosis of PE associated with these varying degrees of circulatory collapse, but has no place in the treatment of small emboli with no cardiovascular compromise, as it carries a significant risk of haemorrhage. This review sets out to guide the emergency physician in deciding which patients with PE may benefit from thrombolysis.

Pulmonary embolism (PE) remains a common disease, with an incidence of about 60–70 per 100 000 of the general population.¹ Postmortem studies, which reflect disease in the whole hospital rather than the emergency department (ED) population, have found that only 30–45% of those who died of PE had the correct antemortem diagnosis.^{2–4} This suggests that although over 80% of patients have a risk factor such as previous thromboembolic disease, immobilisation, morbid obesity, malignancy, cardiac failure, pregnancy, or recent surgery,⁵ PE is underdiagnosed and physicians should have a lower threshold for considering the disease.

Hull⁶ diagnosed PE in 21% of those patients presenting to the ED with pleuritic chest pain. PE associated with reduced cardiac output or right ventricular embarrassment is suggested by non-specific findings including dyspnoea, syncope, hypotension, tachycardia, loud second heart sound (P2), and cyanosis.

This review will concentrate on assessing which patients with pulmonary embolism would benefit from thrombolysis.

SEARCH STRATEGY

An electronic search was performed using MedLine (1966–2002; once with PubMed and once with Ovid) and Embase (1980–2002) using the terms pulmonary embolism, thromboembolism combined with each named thrombolytic agent, thrombolysis, right heart strain/failure, pulmonary hypertension, and shock. This was later repeated using the search engine Google. Relevant papers were obtained and references from these were inspected. No authors were contacted and no unpublished data were obtained.

TREATMENT OPTIONS FOR PE

There are no robust data on the untreated overall mortality of PE, as heparin was introduced in the 1960s before modern imaging was widely available, and thus no placebo arm is included in modern trials. The mortality has been quoted at ~30%, which is reduced to 1–15% with anticoagulation.^{7–9} Recently, low molecular weight heparins have proved to be as effective as or superior to intravenous heparin infusion.^{10–12}

Anticoagulation with heparin prevents clot propagation, tipping the balance in favour of endogenous fibrinolysis and allowing clot dissolution over weeks and months.¹³ Thrombolytics are plasminogen activators, converting plasminogen to plasmin, which then degrades clot bound fibrinogen, resulting in clot lysis. Thrombolysis may result in faster and more complete clot lysis, producing a more rapid improvement in pulmonary flow, right ventricular performance, and oxygenation, which could lower morbidity and mortality.¹⁴ The causal clot may also be more efficiently lysed and so recurrence reduced. However, thrombolysis risks haemorrhage. Is there a subset of patients at high risk of death in whom the potential benefits outweigh the risk?

CAN WE PREDICT WHO IS MOST AT RISK OF DEATH FROM PE?

It is intuitive that large pulmonary emboli in patients with less cardiorespiratory reserve should result in higher mortality. Death occurs from circulatory obstruction, causing right heart failure, systemic shock, and hypoperfusion. In 1976, Alpert found that the presence of right ventricular (RV) failure rather than embolic size determined mortality. Alpert followed 144 patients with angiographically proven PE and found a mortality of 20 (13.8%), of whom 8 were thought to have died despite the PE and 12 (8%) because of it. Nine (75%) of this group had RV failure but the degree of arterial obstruction varied from 25 to 75%. The mortality of those with >50% arterial occlusion on angiogram was 6% in those with no acute right heart failure and 32% where RV failure was present.¹⁵

In 1993, Goldhaber suggested that echocardiographic evidence of RV wall motion abnormality could define a high risk subgroup.¹⁶ The International Cooperative Pulmonary Embolism Registry was set up specifically to look at factors

Abbreviations: CPR, cardiopulmonary resuscitation; ED, emergency department; PE, pulmonary embolism; rTPA, recombinant tissue plasminogen activator; RV, right ventricular

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associated with 3 month mortality from PE.⁹ Data were obtained on 2454 patients from 52 North American and European centres, relying on diagnostic information supplied by the centres.

The following predicted mortality on multiple regression modelling: (a) age >70 years (hazard ratio (HR) 1.6; 95% confidence interval (CI) 1.1 to 2.3); (b) cancer (HR 2.3 CI 1.5 to 3.5); (c) congestive cardiac failure (HR 2.4 CI 1.5 to 3.7); (d) systolic hypotension (HR 2.9 CI 1.7 to 5.0); (e) tachypnoea (HR 2.0 CI 1.2 to 3.2); and (f) RV hypokinesis on echo (HR 2.0 CI 1.3 to 2.9).

The mortality in the haemodynamically unstable (not defined) group was 56 of 96 (58.3%), compared with 317 of 2093 patients (15.1%) who were haemodynamically stable. RV hypokinesis on echo was also associated with higher mortality.

The Management Strategy and Prognosis of Pulmonary Embolism Registry included 1001 patients from 204 German centres divided into 4 subgroups based on cardiac performance.¹⁷ Overall mortality was as follows:

- Group 1: normotensive group but with pulmonary hypertension or RV dysfunction on echocardiogram. Mortality 8.1%.
- Group 2: systemic hypotension (systolic blood pressure <90 or pressure drop >40). Mortality 15%.
- Group 3: cardiogenic shock. Mortality 25%.
- Group 4: those requiring cardiopulmonary resuscitation. Mortality 65%.

In a separate study of 317 patients with clinically suspected PE, Kasper¹⁸ found the in hospital/1 year mortality from PE was 13%/13% in those with echocardiographic evidence of RV dysfunction and 0.9/1.3% in those without. In this study, transthoracic echocardiography was used, with one of the A criteria or two of the B criteria being used to diagnose RV dysfunction (table 1).

If those with acute rather than chronic RV afterload stress are considered alone, then the in hospital mortality rises to 23.5% in this study. Thus the acute mortality of PE is largely dependent on the resulting cardiovascular performance, being worst if the patient is in arrest, better if the patient is in shock, better still if normotensive with RV dysfunction, and best of all with normal pulmonary and systemic haemodynamics.

The simplest way to determine RV function in the ED is by echo. It may also help identify other causes of chest pain and cardiovascular embarrassment such as myocardial infarction and aortic dissection. Its use in the emergent assessment and triage of patients with PE has been advocated by Konstantinides.¹⁹

WHAT IS THE EVIDENCE FOR THE USE OF THROMBOLYSIS IN PE?

The literature search identified 10 randomised trials comparing thrombolysis to heparin in patients with PE as outlined in table 2. Five trials excluded patients with shock (defined usually as systolic blood pressure <90 mmHg). Nine delivered the thrombolysis intravenously and one delivered it into the

pulmonary artery. Five used rTPA, three streptokinase, and two urokinase. None used tenecteplase. Only one trial looked specifically at patients with shock²⁸ and one investigated patients without shock but with ECG/right cardiac catheter/echo evidence of right heart strain or pulmonary hypertension or RV dysfunction.²⁹

The first nine trials in the table, which involved 461 patients in total, were included in a meta-analysis by Thabut *et al* in 2002,³⁰ which concluded that in this unselected group of patients the use of thrombolytics to treat PE was not associated with a reduction in mortality (relative risk (RR) 0.63; 95% CI 0.32 to 1.23) or disease recurrence (RR = 0.59; 95% CI 0.30 to 1.18) but did confer a risk of haemorrhage over heparin (RR = 1.76; 95% CI 1.04 to 2.98). Major haemorrhage is defined here as intracerebral, retroperitoneal, or other bleeding requiring surgery or a blood transfusion. A further meta-analysis of the same 461 patients and 9 trials by Agnelli and colleagues,³¹ also published in 2002, concluded that thrombolytic therapy conferred no mortality advantage over heparin, (RR = 0.59; 95% CI 0.27 to 1.25) but also resulted in no change in disease recurrence (RR = 0.60; 95% CI 0.29 to 1.15) or risk of major haemorrhage (RR = 1.49; 95% CI 0.85 to 2.81). In this paper, major haemorrhage was defined as fatal, intracranial, associated with a decrease in haemoglobin of at least 20 g/l, or requiring a transfusion of two or more units of red blood cells. Agnelli *et al* also examined the combined endpoint of recurrence and/or death, which occurred in 25/241 (10.4%) of patients thrombolysed and 38/220 (17.3%) treated with heparin. This gives a significantly lower relative risk of death/recurrence (RR = 0.55; 95% CI 0.33 to 0.96).

These meta-analyses involved relatively few patients, and the inclusion of so many trials where "shock" was an exclusion criterion weakens their power. With one exception,²⁸ the other trials did not provide enough information to allow subset analysis of those with shock or RV dysfunction.

The trials on thrombolysis in PE may be underpowered to detect a true treatment mortality advantage, or alternatively the benefits of thrombolysis may outweigh the risks in only those few at high risk of death from PE. If thrombolysis is in fact effective, it is essential to use it in a subgroup where the potential benefit of therapy outweighs the risk.

USE OF THROMBOLYSIS IN DIFFERENT GROUPS OF PATIENTS

Patients with PE and systemic hypotension

The use of thrombolysis in this group is widely advocated, reflecting the high mortality rate and encouraging case reports.^{1417 3233} However, only one small randomised trial exists. In 1995, Jerges-Sanches *et al*²⁸ compared thrombolysis with streptokinase to intravenous heparin in eight patients. The trial was stopped early, as all four patients thrombolysed lived whereas the four treated with heparin died.

There was a major difference between the two groups by chance; the four patients who had streptokinase were new presentations to the treating hospital. Those receiving heparin were already receiving heparin treatment in other hospitals for small emboli without compromise, when they suddenly suffered massive pulmonary emboli and were transferred to the trial centre.

Patients with cardiopulmonary arrest

The evidence base of much of what we offer for patients in arrest from PE is not substantiated by clinical trials.³⁴ The mortality in this group has been reported as 65% in the MAPPET registry,¹⁷ and use of thrombolytics is widely advocated.^{14 33} In 2001, Bailen³⁷ reviewed the literature on thrombolysis for fulminant PE with circulatory collapse requiring cardiopulmonary resuscitation (CPR), and found

Table 1 Criteria for RV dysfunction

A criteria: right ventricle appearing larger than left ventricle or right ventricle end diastolic diameter >30 mm
B criteria: tricuspid regurgitation jet velocity >2.8 m/s or >2.5 m/s in absence of IVC inspiratory collapse, pulmonary artery >12 mm/m2 body area or RV wall >5 mm or loss of inspiratory collapse of the inferior vena cava

Table 2 Randomised trials comparing thrombolytic and heparin therapy

Study	Treatment regimens	No. of patients	Mortality, n (%)	Recurrence n (%)	Major haemorrhage,* n (%)	Comments
UPET 1970 ²⁰	IV heparin v UK 2000 U/lb bolus then hourly	78	7 (8.9)	15 (19)	21 (27)	Patients had <5 days of symptoms Angiography used to diagnose and repeated at 24 hours showing improved haemodynamics in UK group SK group had greater improvement in pulmonary perfusion All patients had life threatening PE and angiographic diagnosis Angiographic evidence of improved perfusion with SK All patients >1 lobar artery occluded
		82	6 (7.3)	12 (15)	37 (45)	
Tibbitt <i>et al</i> 1974 ²¹	IP heparin IP SK 600 000 units bolus then 100 000 units/h for 72 hours	17	1 (5.8)	1 (5.8)	1 (5.8)	Patients all >9 segments not perfused on Q scan. By 24 hrs and at 1 year no difference in pulmonary haemodynamics
		13	0	0	1 (8)	
Ly <i>et al</i> 1978 ²²	IV heparin v APTT SK 250000 units bolus and 100000 units per hour 72 hours	11	2 (18.2)	NA	2 (18)	Patients all >9 segments not perfused on Q scan. By 24 hrs and at 1 year no difference in pulmonary haemodynamics
		14	1 (7.1)	0	4 (29)	
Marini <i>et al</i> 1988 ²³	Heparin v APTT UK 800 000 units 12 hourly for 3 days	10	0	0	0	Vascular resistance better for rTPA group at 90 mins but equal at 2 hrs Patient diagnosis by angiogram
		10	0	0	0	
PIOPE 1990 ²⁴	Heparin v APTT rTPA 40–80 mg for 40–90 minutes	4	0	NA	0	Perfusion scan on day 1 better with rTPA but equal by day 7 Diagnosis by angiogram Haemodynamics better at 24 hours in rTPA group but equal day 7 and 30
		9	1 (11.1)	0	1 (11.1)	
Levine <i>et al</i> 1990 ²⁵	Heparin v APTT rTPA 0.6 mg/kg over 2 minutes	25	0	0	0	Perfusion scans and RV function on echo better in rTPA at 24 hours
		33	1 (3)	0	0	
PAIMS 2 1992 ²⁶	Heparin v APTT rTPA 100 mg over 2 hours	16	1 (6.3)	3 (18.8)	2 (12.5)	All patients had shock. 100% mortality in heparin group led to trial being abandoned early
		55	2 (3.6)	5 (9.1)	1 (1.8)	
Goldhaber <i>et al</i> 1993 ²⁷	Heparin infusion v APTT SK 1 500 000 units over 1 hour	46	0	0	2 (4.3)	Unexpectedly low mortality. Composite end point of death or treatment escalation lower in rTPA Group: see text.
		4	4 (100)	NA	0	
Jerges-Sanches <i>et al</i> 1995 ²⁸	Heparin infusion v APTT rTPA 100 mg over 2 hours	4	0	4 (2.9)	5 (3.6)	
		138	3 (2.2)	4 (2.9)	5 (3.6)	
Konstantinides <i>et al</i> 2002 ²⁹	rTPA 100 mg over 2 hours	118	4 (3.4)	4 (3.4)	1 (0.8)	

*Defined as intracranial bleed, bleed requiring surgery, transfusion or fall >10% in haematocrit. IV, intravenous; IP, intrapulmonary; U, units; SK, streptokinase; UK, urokinase; rTPA, recombinant tissue plasminogen activator, infusion followed by intravenous heparin.

about 100 case reports and a retrospective series of 42 patients. In this series, 21 patients received heparin and 21 received thrombolytics, resulting in no mortality difference but a higher return of spontaneous circulation in favour of thrombolysis. Many of this group were young postoperative or postpartum cases. The high number of survivors and paucity of haemorrhagic complications coupled with the poor prognosis of this group suggests that the use of thrombolysis may be beneficial in this setting.

In their 1999 review (predominantly of case reports), Newmann *et al*³⁵ found a survival rate of 75% (50/67) for patients given thrombolysis after undergoing CPR for varied aetiologies. Many of these cases were characterised by long periods of CPR, with surprisingly good neurological recovery. However, this type of study is likely to suffer from reporting bias. Newmann proposes that thrombolysis may have neuroprotective properties through lysing microvascular thrombi and improving cerebral microvascular flow. The use of thrombolysis in arrested patients of unknown cause has been proposed, as the majority are due to thrombolytic responsive disease, coronary ischaemia, or PE.³⁵ Causes such as subarachnoid or intracerebral haemorrhage are contraindications for thrombolysis, but patient prognosis in this setting is dismal and other contraindications such as trauma or gastrointestinal haemorrhage are readily identifiable.

Bottiger³⁶ performed a nonrandomised prospective trial comparing 50 mg of rTPA and intravenous heparin with conventional CPR/advanced life support and no anticoagulation in patients with >15 minutes of arrest (repeated at 30 minutes if no return of spontaneous circulation occurred), and found an improved rate of return of spontaneous circulation (68% v 44%) and higher rate of hospital discharge (15% v 8%) in the treatment arm. Based on this protocol, eight arrested patients would require treatment with thrombolytics to result in one extra survivor.

Patients with PE and with RV dysfunction

RV dysfunction has been shown to predict disease recurrence and mortality as detailed above. In a randomised controlled trial, Goldhaber¹⁶ found RV function improved at 24 hours in 16/18 thrombolysed patients compared with 8/18 treated with heparin.

Konstantinides¹⁹ found a 30 day mortality of 4.7% in 169 patients who received thrombolysis, compared with 11.1% in 550 who were treated with heparin. Recurrence rates were 7.7% and 18.7% respectively. These data were from a multicentre registry (not a randomised trial) of 719 patients with echo or cardiac catheter evidence of RV dysfunction or pulmonary hypertension but systolic pressures >90 mmHg. However, the heparin group were older, and more of them

had congestive cardiac failure and chronic respiratory problems.

In a 2001 retrospective study of patients with echo evidence of RV dysfunction, Hamel³⁸ compared 64 patients treated with thrombolysis with 64 treated with heparin. There were no deaths or bleeding complications in the heparin group, but haemorrhage occurred in 15.6% of the thrombolysed group, and 6.3% died.

In a 2002 randomised trial of 256 patients with PE and evidence of RV dysfunction (defined by echocardiography, right heart catheterisation, or ECG changes), Konstantinides³⁹ found a 30 day mortality of 3.4% in those receiving 100 mg reteplase over 2 hours plus heparin and 2.2% in those treated with heparin alone ($p = 0.71$). The mortality in this study was unexpectedly low. There was only one fatal bleed in the heparin group and bleeding complications were not statistically different between the two groups.

Echocardiography is a widely available bedside test which helps diagnosis, risk stratification, and exclusion of alternate diagnoses such as RV infarct, aortic dissection, and pericardial effusion/tamponade.^{40–41}

WHICH IS THE THROMBOLYTIC OF CHOICE?

Six trials (table 3) with 481 patients have compared various thrombolytic regimens using rTPA, streptokinase, and urokinase, with rTPA being delivered over 2 hours and urokinase and streptokinase delivered over 2–24 hours.^{42–47} No one agent has proved superior.⁴⁴

rTPA regimens showed better pulmonary flow at 2 hours but not subsequently compared with long and short regimens using the other agents.^{43–45–47} Goldhaber⁴⁸ compared rTPA at a dose of 100 mg over 2 hours with the same agent at 0.6 mg/kg over 15 minutes, and found similar improvements in all parameters as measured by echo, angiography, and VQ scan.

Tebe⁴⁹ compared rTPA 100 mg over 2 hours with Reteplase (rTPA) 10 units at baseline and repeated at 30 minutes, and found no difference in all measured pulmonary haemodynamics.

In conclusion, no single agent or regimen has been shown to be more effective than any other, though the theoretical

risk of worsening hypotension with streptokinase in patients with circulatory compromise suggests other thrombolytic agents may be preferable.

HOW SHOULD THROMBOLYTICS BE ADMINISTERED?

Despite the theoretical advantages of higher local concentration at the clot site, the delivery of thrombolysis via pulmonary artery catheter offers no advantage in terms of mortality, morbidity, or haemorrhage risk over peripheral administration and carries the risks of a more invasive procedure, according to the results of a single trial.⁵⁰ Bolus therapy may be expected to produce more rapid thrombolysis with improved outcome but two trials found this method of administration offered no advantage over infusion regimens.^{48–51} Overall, it thus appears there is insufficient evidence to justify the increased risk.

WHAT ARE THE COMPLICATIONS OF THROMBOLYSIS?

The major complication of thrombolysis is haemorrhage, although allergy, hypotension, fever, nausea, and vomiting may occur.⁵² The overall risk of haemorrhage with thrombolysis is reported as 6–20%, with no significant differences between the alternative agents.

The most feared bleeding complication is intracerebral haemorrhage, which has a reported incidence of 0.6–3%.^{9–14–35–53–55} The risk factors associated with intracranial bleeding are increasing age (0.4% at <65 years and 2.1% at >75 years), increasing dose of thrombolytic, chronic hypertension, female sex, low body mass (with weight <70 kg being associated with a four fold increase), and pulmonary catheterisation.^{33–55}

The risk of bleeding largely defines the contraindications to thrombolysis. These relative contraindications are active bleeding, any active or recent (within 6 weeks) intracranial disease, trauma, visceral biopsy, surgery, or gastrointestinal bleed, haemorrhagic disorder, hepatic or renal failure, pregnancy, puncture of a non-compressible vessel, and pericarditis.^{14–56}

Table 3 Randomised trials comparing the efficiency and safety of thrombolytic agents

Study	No. of patients	Treatment regimens	Mortality, n (%)	Recurrence n (%)	Major haemorrhage, n (%)	Comments
USET phase 2 ⁴²	59	UK 2000 U/lb bolus, 2000 U/lb/h over 12 hours	4 (7)	1 (1)	8 (14)	Angiographic diagnosis, repeated at 24 h showing improved pulmonary flow in UK group but equal at day 5
	54	UK 2000 U/lb bolus, 2000 U/lb/h over 24 hours	5 (9)	4 (7)	10 (19)	
	54	SK 250 000 unit bolus, 100 000 U/h over 24 hours	5 (9)	2 (4)	6 (11)	
Goldhaber <i>et al</i> 1988 ⁴³	23	UK 2000 U/lb bolus, 2000 U/lb/h	2 (8.7)	1 (4)	11 (48)	Perfusion/haemodynamics better at 2 h in rTPA but equal by 24 h. Trend towards more haemorrhage UK
	22	Rt-PA 100 mg over 2 hours	2 (8.7)	0	4 (18)	
Meyer <i>et al</i> 1992 ⁴⁴	29	UK 4400 U/lb bolus, 4400 U/lb/h over 24 hours	1 (3.4)	2 (6.9)	8 (28)	2 h pulmonary haemodynamics favour rTPA but equal at 12 h
	34	Rt-PA 80–100 mg over 2 hours	3 (8.8)	2 (5.9)	7 (21)	
Goldhaber <i>et al</i> 1992 ⁴⁵	46	UK 1 000 000 U over 10 mins, 2 000 000 U over 110 mins	1 (2)	3 (6.5)	6 (13)	No difference at 2 h angiogram or 24 h perfusion scan
	44	Rt-PA 100 mg over 2 hours	2 (4.5)	0	9 (20)	
Meneveau <i>et al</i> 1997 ⁴⁶	25	SK 250000 bolus, 1 000 000 U/h over 12 hours	1 (4)	2 (8)	3 (12)	2 h pulmonary haemodynamics favour rTPA but no difference by 12 h
	25	Rt-PA 100 mg over 2 hours	1 (4)	0	4 (16)	
Meneveau <i>et al</i> 1998 ⁴⁷	43	SK 1 500 000 U 2 hours	0	1 (2.3)	3 (7.0)	Identical haemodynamics at 2 h and identical day 2 perfusion scan
	23	Rt-PA	0	2 (8.7)	5 (21.7)	

UK, urokinase; SK, streptokinase; recombinant tissue plasminogen activator, U, units; lb, pound; h, hour

WHAT ARE THE ALTERNATIVES TO THROMBOLYSIS IN CRITICALLY SICK PATIENTS?

Given the risk of haemorrhage with thrombolysis and the improving surgical techniques, alternative methods of treating massive PE have been explored, including pulmonary catheterisation and surgical embolectomy. The former has been shown to improve cardiac output and has a mortality of 11% with a "success" rate of 91% in a series of non-shocked patients with moderate to severe RV dysfunction.⁵⁷ Cardiac catheterisation, mechanical fragmentation techniques, high velocity jet fragmentation, and combinations of mechanical clot disruption with low/usual dose thrombolysis have all been described in case reports/case series but there is no published trial evidence.^{58–65} It is unlikely that adherent clot more than 48–72 hours old is removable.^{58, 59}

There is no randomised trial of medical versus surgical therapy. Surgical embolectomy has been used on critically ill patients and when thrombolysis is contraindicated. Perioperative mortality rates are reported as 29–44% in this group.^{66, 67} Gulba⁶⁸ reported a series of 23 surgically and 24 medically treated patients with systolic blood pressure <100 mmHg, and reported survival rates of 77% and 67% respectively. In a series of 29 patients including those with RV dysfunction but normal systolic blood pressure, Aklog⁶⁹ reported a mortality of 11% at 1 month.

CONCLUSIONS

- The use of thrombolysis in cardiac arrest thought to be due to pulmonary embolus is supported by the available evidence and appears to improve survival to hospital discharge in one study.³⁶
- Thrombolysis may be beneficial in patients with massive PE with systemic hypotension and this approach is widely supported,⁷⁰ although good quality evidence for mortality benefit is lacking.
- In those without shock but with RV dysfunction on echo, there are studies showing more rapid clot lysis and faster normalisation of cardiac function when treated by thrombolysis/heparin as opposed to heparin alone,^{15, 19} but thrombolysis has not been shown to reduce mortality and in this subgroup and confers a risk of haemorrhage. Thrombolysis should only be used in these patients on an individual basis with careful consideration of opposing risk factors.
- For emboli with no cardiovascular compromise, thrombolysis is not advisable.

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