

## Theme Issue Article

# Role of fibrinolysis and interventional therapy for acute venous thromboembolism

Joseph Emmerich<sup>1,2</sup>, Guy Meyer<sup>1,2</sup>, Hervé Decousus<sup>3</sup>, Giancarlo Agnelli<sup>4</sup>

<sup>1</sup>University Paris-Descartes, Hôpital Européen Georges Pompidou, Paris, France; <sup>2</sup>Inserm U765, Paris, France; <sup>3</sup>Inserm, CIE3, CHU Saint-Etienne, Hôpital Bellevue, Service de Médecine Interne et Thérapeutique, Saint-Etienne, France; <sup>4</sup>Department of Internal Medicine, Division of Internal and Vascular Medicine, Stroke Unit, University of Perugia, Perugia, Italy

### Summary

The initial goals of treatment for venous thromboembolism (VTE) are usually achieved with anticoagulation. This review focuses on fibrinolysis and interventional therapy in VTE, treatments whose indications are much more controversial. The benefit-to-risk ratio of fibrinolysis in deep vein thrombosis (DVT) is dubious. Thrombolytic treatment is recommended for unstable patients with pulmonary embolism (PE), although these patients represent less than 5% of all patients hospitalized for PE. The use of thrombolytic treatment in patients with sub-massive PE remains controversial. Two indications are widely recognized for inferior vena cava filters: the first is a permanent or tempor-

ary contraindication to anticoagulation, in patients with proximal DVT or PE. The second is the occurrence of PE or propagation of the thrombus in patients treated for DVT or recurrence in patients with PE. The PREPIC study demonstrated that in acute VTE, vena cava filters reduced the risk of PE but increased that of DVT and had no effect on survival. The fact that prevention of PE is mainly observed during the short initial period following the diagnosis of an acute VTE event justifies a new randomized study with the use of retrievable filters as an adjuvant to anticoagulation in high risk patients with PE.

### Keywords

Deep vein thrombosis, pulmonary embolism, fibrinolysis, thrombolysis, inferior vena cava filter

**Thromb Haemost 2006; 96: 251–7**

### Introduction

The initial goals of treatment for venous thromboembolism (VTE) are to stop clot propagation and prevent early and late recurrence, pulmonary embolism (PE) and pulmonary hypertension (a potential complication of multiple recurrent PEs), and for patients with deep vein thrombosis (DVT) to prevent the post-thrombotic syndrome. These goals are usually achieved with anticoagulation using heparin or low-molecular-weight heparin (LMWH) followed by an oral anticoagulant (1). This article will focus on the role of fibrinolysis and interventional therapy in VTE, whose indications are much more controversial compared with the evidence obtained from numerous trials with heparin and its derivatives followed by oral anticoagulants.

### Fibrinolysis in deep vein thrombosis

The rationale for the use of thrombolysis in DVT is the promise of dissolving the thrombus within the deep venous system, re-

storing a faster patency of valves and preserving their function. If this is achieved, the incidence and severity of post-thrombotic syndrome can theoretically be reduced in the long term. The benefit on mortality is dubious, as mortality in recent trials of anticoagulation treatment in DVT is below 4%, after three months of follow-up (2). Furthermore, mortality related to PE in this population is below 1%. There is no doubt that fibrinolytic treatment induces lysis of the deep vein thrombus more rapidly and more completely than heparin administration in the acute treatment of DVT; the main problem of such an approach in DVT is the benefit-to-risk ratio.

### Systemic fibrinolysis

In a meta-analysis published in 1984, which included a relatively low number of patients, recanalization is obtained 3.7-fold more often in patients receiving fibrinolysis compared with patients treated with heparin ( $p < 0.0001$ ) (3). However, there is a major price to pay for this relative benefit: a 2.9-fold increased risk of major bleeding ( $p < 0.04$ ). In a small trial of 65 patients rando-

Correspondence to:  
Dr. Joseph Emmerich, MD, PhD  
Service de Médecine Vasculaire-HTA  
Hôpital Européen Georges Pompidou  
20 rue Leblanc, 75908 Paris 15, France  
Tel.: +33 1 5609 3051, Fax: +33 1 5609 3065  
E-mail: joseph.emmerich@egp.aphp.fr

Received May 5, 2006  
Accepted after resubmission July 17, 2006

Prepublished online August 16, 2006 doi:10.1160/TH06-05-0244

**Table 1: Results of the Cochrane collaboration concerning thrombolysis for acute deep vein thrombosis (from ref. 5).**

Events	RR (fibrinolysis vs. heparin)	95% CI
Complete clot lysis	0.24	0.07–0.82
Post thrombotic syndrome	0.66	0.47–0.94
Leg ulceration	0.53	0.12–2.43
Normal venous function	0.43	0.06–3.17
Total bleeding	1.73	1.04–2.88
Mortality	1.33	0.34–5.24
Recurrent DVT	1.41	0.37–5.40

mized to receive recombinant tissue type plasminogen activator (rt-PA) alone, rt-PA plus heparin or heparin alone, Goldhaber et al. showed a frequency of around 30% of initial lysis in patients treated with rt-PA alone or associated with heparin. No lysis occurred in patients treated with heparin alone 24–36 hours after randomization. There was one major complication: a non-fatal intracranial hemorrhage in a patient who received rt-PA (4).

Table 1 summarizes the results of the Cochrane Database Systematic Review of Thrombolysis for acute DVT, which included 12 studies (5). Complete clot lysis occurred significantly more often in the treatment group in early follow up (relative risk [RR] 0.24, 95% confidence interval [CI] 0.07–0.82), and in late follow up (RR 0.37, 95% CI 0.25–0.54). There was a significantly lower incidence of post-thrombotic syndrome in patients receiving fibrinolysis (RR 0.66, 95% CI 0.47–0.94). The incidence of leg ulceration, which occurs in the more severe form of post-thrombotic syndrome, was also decreased (RR 0.53, 95% CI 0.12–2.43), but not significantly due to the small number of observed events. Interestingly, it was also shown that the incidence of bleeding appears to decrease over time with the introduction of stricter selection criteria. However, no significant effect on mortality was detected in either early or late follow-up, and the effects on PE and DVT recurrence were inconclusive.

As the long-term benefit on severe post-thrombotic syndrome in DVT remains unproven, and due to the risk of major bleeding, the systemic use of fibrinolysis in patients with DVT is not recommended. Such a conclusion is supported by the seventh ACCP conference on antithrombotic and thrombolytic therapy: “in patients with DVT, we recommend against the routine use of i.v. thrombolytic treatment (Grade 1A)” (1). In very rare patients with iliofemoral DVT and phlegmasia cerulea dolens, i.v. fibrinolysis can be performed due to the high risk of limb gangrene. In these cases, the optimum drug, dose and route of administration have yet to be determined (5).

### Catheter-directed thrombolysis

Catheter-directed thrombolysis has been proposed since the mid-1990s, but all the studies are open or retrospective (6, 7). Most studies of local thrombolysis used urokinase, but rt-PA (0.5–1.0 mg/h) or reteplase (0.5–1.0U/h) can also be used. The largest study with catheter-directed thrombolysis in DVT is the National Venous Thrombolysis Registry, which included 287 patients (71% with iliofemoral DVT) treated with urokinase and

followed up for one year. Complete dissolution of the thrombus was achieved in 31% of cases, and partial dissolution in 52% (8). Preservation of valvular function was demonstrated in 72% of patients with complete thrombolysis. Nevertheless, 34% of the patients also had a stent placed in the thrombotic vein. A randomized study of only 35 patients compared thrombolysis plus anticoagulation versus anticoagulation alone in iliofemoral DVT. Thrombolysis was associated with a six-month improvement in patency rate (71% vs. 12%;  $p < 0.001$ ) and venous valvular function (89% vs. 59%;  $p < 0.04$ ) (10). The long-term benefit of such an approach has not been demonstrated. In fact, catheter-directed thrombolysis is often combined with other invasive techniques, such as mechanical thrombus removal devices or mechanical fragmentation and/or stent placement, for example in the case of DVT caused by May-Thurner syndrome (9–13). The long-term benefit of such an aggressive approach remains to be demonstrated. Furthermore, the long-term risk of recurrence in patients with DVT treated by stent placement has never been adequately assessed after withdrawal of oral anticoagulant. Catheter-directed thrombolysis has been advocated by some authors in the case of phlegmasia cerulea dolens (14).

### Fibrinolysis in PE

The hospital mortality rate of unselected patients with PE has been estimated to 9%, and depends primarily on hemodynamic tolerance and underlying disease (15, 16). For clinically stable patients, the in-hospital mortality rate when using anticoagulant treatment is between 1% and 2% (17, 18). A recent meta-analysis comparing unfractionated heparin with LMWH for the initial treatment of PE reported an in-hospital mortality rate of 1.4% for unfractionated heparin and 1.2% for LMWH (19). However, more than 25% of patients with low blood pressure die during the first two weeks (15, 20, 21). In between these two clinical presentations, several studies have described an intermediate group of patients with normal blood pressure and right ventricular failure, as shown by echocardiography, who have an increased mortality rate compared with patients with normal echocardiography findings (22).

In the ICOPER registry, the mortality was 58% in patients with hemodynamic instability compared with 15% in clinically stable patients (15); a systolic blood pressure  $< 90$  mm Hg was independently associated with an increased mortality (odds ratio [OR]: 2.9; 95% CI 1.7–5.0). In the same study, the in-hospital death rate of patients with right ventricular failure was 18%, although the patients with shock were not analyzed separately. Another large multicenter registry included 1,001 patients with major PE, defined as PE and right heart failure or pulmonary hypertension (21). Four patient groups were prospectively defined: (i) patients with evidence of right ventricular pressure overload or pulmonary hypertension with normal blood pressure; (ii) patients with arterial hypotension (systolic blood pressure  $< 90$  mm Hg or a drop of at least 40 mm Hg for more than 15 minutes) but without cardiogenic shock or need for catecholamine support; (iii) patients with arterial hypotension and cardiogenic shock or catecholamine administration; and (iv) patients who underwent cardiopulmonary resuscitation. The physician in charge decided on the treatment. Hospital mortality was 8.1% in group (i),

15.2% in group (ii), 25% in group (iii) and 62.5% in group (iv) (21).

Recently, cardiac biomarkers have been evaluated to select patients with sub-massive PE. Brain natriuretic peptide, pro-brain natriuretic peptide, and troponins T and I were all associated with an increased risk of death in patients with PE. However, most studies did not carry out separate analyses of patients in a stable hemodynamic condition and patients with shock. In one series, the in-hospital mortality of patients with normal blood pressure, high troponin levels and an enlarged right ventricle was 25% (23). Another study from the same group showed that clinically stable patients with high pro-brain natriuretic peptide levels had a 17% mortality rate (24). Other markers have been studied, such as N-terminal pro-brain natriuretic peptide (NT-proBNP) or troponin. The cut-off level of 1,000 pg/ml for NT-proBNP had a high negative predictive value, but NT-proBNP  $\geq$  1,000 pg/ml did not independently predict an adverse outcome in the absence of right ventricular dysfunction (25).

Based on clinical examination, PE can be classified in two main categories: i) massive PE defined by a systolic blood pressure  $\leq$  90 mm Hg or a pressure drop of  $\geq$  40 mm Hg for at least 15 minutes, and ii) non-massive PE (26). Sub-massive PE is considered as a subgroup of non-massive PE with evidence of right ventricular hypokinesis on echocardiography (26). Thrombolytic treatment is recommended for unstable patients with PE, although these patients represent less than 5% of all patients hospitalized for PE (15). However, the use of thrombolytic treatment in patients with sub-massive PE remains controversial. Some indirect evidence supports the use of thrombolysis in these patients, but controlled studies neither confirm nor exclude a significant reduction in mortality as it was summarized in recent meta-analyses (16, 27). In several studies, the mortality in this group varied from 0–20%, due to the different criteria used for definition of right ventricular dysfunction (23–25, 28–34).

### Beneficial effects of thrombolytic treatment in PE

Thrombolytic treatment induces a rapid decline of pulmonary artery resistance in patients with acute PE and pulmonary hypertension. In the PAIMS 2 study, alteplase, given as a 100-mg dose over two hours, reduced the pulmonary artery mean pressure from  $30.2 \pm 7.8$  mm Hg to  $21.0 \pm 6.7$  mm Hg after two hours, whereas no significant change was observed with heparin (35). Simultaneously, the cardiac index increased significantly in the alteplase group, whereas no change was observed in the heparin group. In the UPET study, no significant change in hemodynamic measurements were observed after 24 hours of heparin infusion, whereas a significant 23% reduction in pulmonary artery mean pressure was observed in the patients who received urokinase (36). Early reversal of right ventricular dysfunction has also been documented by serial echocardiography in patients receiving alteplase compared with patients receiving heparin (37).

Thrombolytic treatment produces a faster decrease in vascular obstruction compared with treatment with heparin. In the PAIMS 2 study, the pulmonary vascular obstruction assessed by the Miller index (an angiographic score of pulmonary vascular obstruction with a maximum value of 34) decreased significantly from  $28.3 \pm 2.9$  to  $24.8 \pm 5.2$  at the end of the alteplase infusion, whereas no significant difference was observed in the pa-

**Table 2: Results of the Cochrane collaboration concerning thrombolysis for pulmonary embolism (from ref. 27).**

Events	RR (fibrinolysis vs. heparin)	95% CI
Death by all causes	0.89	0.45–1.78
Recurrence of PE	0.63	0.33–1.20
Major bleeding	1.61	0.91–2.86
Minor bleeding	1.98	0.68–5.75

tients who received heparin (35). Using lung scanning, Goldhaber et al. observed a larger reduction in vascular obstruction 24 hours after the start of treatment with alteplase (37). However, the difference between thrombolytic therapy and heparin treatment disappeared after seven days (35). These data strongly suggest that thrombolytic therapy produces a much faster improvement in vascular obstruction and hemodynamics than heparin treatment, but that thrombolytic treatment and heparin produce a similar improvement after one week.

### Bleeding and fibrinolysis in PE

A recent meta-analysis of controlled studies compared thrombolytic treatment with heparin in patients with PE (16). It found that the overall rate of major bleeding events was 9.1% in the patients who were allocated to thrombolytic treatment and 6.1% in those who received heparin, a non-significant increase (OR 1.42; 95% CI 0.81–2.46). However, intracranial bleeding remains a major concern in patients receiving thrombolytic treatment; the incidence of intracranial bleeding has been estimated to be 1.9% (95% CI 0.7–4.1) and is higher than in myocardial infarction studies (38). Risk factors for major bleeding include older age and invasive diagnostic procedures (39). As most of the bleeding events occur at the puncture site, it is essential to avoid invasive diagnostic procedures to confirm PE when the use of thrombolytic treatment is considered (40). Thrombolytic therapy can be given through a peripheral line, and a central venous line should be avoided. In the recent Cochrane collaboration review (27), whose clinical events are summarized in Table 2, major bleeding events were not statistically higher in the fibrinolysis group (OR 1.61; 95% CI 0.91–2.86). A slight increase was also observed for minor hemorrhagic events, but this was not statistically significant (OR 1.98; 95% CI 0.68–5.75).

### Results of studies on mortality in massive PE

In patients with massive PE, a single, small randomized trial has compared streptokinase with heparin. Although 40 patients were expected to be recruited, the trial was terminated after only eight patients had been included. All patients had massive PE; four were allocated to streptokinase and survived, and four were allocated to heparin and died from cardiogenic shock during the 72 hours following randomization (41). These results prompted the ethics committee to stop the trial. In a recent meta-analysis of the controlled studies comparing thrombolytic therapy with heparin in patients with PE, a subgroup analysis was performed for the studies that included patients with massive PE and shock (16).

The mortality rate in these studies was 6.2% for the patients allocated to thrombolytic treatment and 12.7% for those allocated to heparin (OR 0.47; 95% CI 0.20–1.10). When recurrent PE and deaths were considered, the difference was significant, with a 9.4% event rate for patients allocated to thrombolytic treatment compared with 19% for those allocated to heparin treatment (OR 0.45; 95% CI 0.22–0.92).

The available evidence suggests that thrombolytic therapy induces a reduction in mortality rate in patients with massive PE. The high mortality rate seen in patients with massive PE, the early hemodynamic improvement observed with thrombolytic therapy, the results of the randomized study by Jerjes-Sanchez et al. and the recent meta-analysis all strongly suggest that thrombolytic therapy should be instituted early in patients with massive PE (16, 41). Guidelines recommend the use of thrombolytic therapy for patients with massive PE (1, 26).

### Results of studies on mortality in sub-massive PE

To date, the largest randomized study assessing thrombolytic treatment for sub-massive PE included 256 patients with PE and normal blood pressure who were allocated to receive either heparin alone or both alteplase and heparin (42). The main endpoint consisted of the combination of in-hospital death and/or clinical deterioration requiring an escalation of treatment. This was achieved in 11% of the patients in the alteplase/heparin group compared with 24.6% in the heparin group ( $p = 0.006$ ). The difference was mainly due to secondary open-label thrombolytic therapy, which was more frequent in the patients assigned to receive heparin (23.2%) than in those receiving alteplase (7.6%;  $p = 0.001$ ). The death rate was 3.4% for the alteplase group and 2.2% for the heparin group. The unexpected low mortality rate in patients receiving heparin may be related to the low (30%) proportion of patients with right ventricular dilatation on echocardiography, or to the early use of rescue thrombolytic treatment for those patients who did not improve with heparin. Ten other controlled studies have been conducted to compare thrombolytic therapy with heparin for patients with PE. These studies were included in a meta-analysis that analyzed the outcome of 748 patients (16). The overall death rate was 4.3% for the patients allocated to thrombolytic therapy compared with 5.9% for those assigned to heparin (OR 0.70; 95% CI 0.37–1.30). In a subset of studies that included only clinically stable patients, the death rate was 3.3% for those receiving thrombolytic therapy compared with 2.4% for those allocated to heparin (OR 1.16; 95% CI 0.44–3.05). The current evidence from controlled studies does not suggest a reduction in the hospital mortality rate among pa-

tients with sub-massive PE receiving thrombolytic treatment. However, even the meta-analysis was not powerful enough to detect a 50% reduction in the mortality rate with thrombolysis. In the Cochrane collaboration review (27), similar results were observed with an OR for death rate in the fibrinolysis group of 0.89 (95% CI 0.45–1.78) (Table 2).

Despite negative results from controlled studies, some indirect evidence suggests that thrombolytic therapy may affect the outcome of patients with sub-massive PE. Goldhaber et al. retrospectively analyzed a subgroup of 36 patients with right ventricular hypokinesia who were included in a controlled study comparing thrombolytic therapy and heparin. They observed five recurrent PE (two fatal) among 18 patients who were treated with heparin but no death or recurrent PE among 18 patients who received thrombolytic treatment (37). In the MAPETT study, the death rate was higher for patients receiving heparin, whereas thrombolytic treatment was the only independent predictor of favorable outcome (32).

The current evidence does not indicate that thrombolytic therapy decreases the mortality rate of patients with sub-massive PE. International experts have recently expressed different opinions regarding the indications for thrombolytic therapy in these patients, demonstrating that a large international randomized study is needed to clarify this controversial issue (27, 43, 44).

### What is the optimal thrombolytic regimen in PE?

Different thrombolytic regimens have been evaluated in controlled trials (Table 3). In the USPET study, urokinase, given as a bolus dose of 4,400 IU/kg followed by a 12- or 24-hour maintenance infusion of 4,400 IU/kg/h, was compared with streptokinase given as a 250,000 IU bolus dose followed by a 100,000 IU/h infusion given over 24 hours (45). The three regimens produced the same degree of hemodynamic and angiographic improvement, with no significant difference regarding major hemorrhage. A subsequent European study found no difference concerning safety or efficacy when the same dose of urokinase was administered over 12 or 24 hours (46).

In two randomized controlled trials, rt-PA given as a two-hour 100 mg infusion was compared with a 4,400 IU/kg/h infusion of urokinase given over 12 or 24 hours (47, 48). In both studies, rt-PA produced a faster hemodynamic and angiographic improvement, but the two drugs achieved the same hemodynamic improvement by the end of the urokinase infusion. A non-significant reduction in major bleeding events was observed in both studies for the patients receiving rt-PA, although the two studies were not powerful enough to detect a difference in the major bleeding rates. The same rt-PA regimen was subsequently compared with a shorter regimen of urokinase, given as a 3-MU infusion over two hours (49). No difference was observed regarding hemodynamic improvement or bleeding between both groups. More recently, two randomized trials have compared rtPA with streptokinase given as a 100,000 IU/h 12-hour infusion or given as a 1.5-MU infusion over two hours (50, 51). Again, the two-hour regimen of rt-PA produced a faster hemodynamic improvement compared with 12-hour of streptokinase infusion, whereas no difference was observed when the two drugs were given over two hours. The rate of major bleeding was lower for patients receiving the two-hour streptokinase infusion than for

**Table 3: Thrombolytic regimens for pulmonary embolism evaluated in prospective controlled studies.**

Streptokinase	250,000 IU over 15 min + 100,000 IU/h, 12–24 h
	1.5 M IU, 2 h
Urokinase	4400 IU/kg over 30 min + 4400 IU/Kg/h, 12–24 h
	3 MIU, 2 h
rt-PA	100 mg, 2 h
	0.6 mg/kg, 15 min

those receiving rt-PA, although this difference was not statistically significant. Two studies compared the efficacy and safety of 0.6 mg/kg body weight of rt-PA given over a period of 15 minutes with 100 mg during two hours (52, 53). Hemodynamic improvement was slightly but significantly faster for the two-hour regimen, although the 0.6 mg/kg dose was associated with a non-significant reduction in major bleeding events.

## The role of inferior vena cava filters in VTE

The role of inferior vena cava (IVC) filters in the management of VTE has recently been reviewed (54). The first IVC filter was the Mobin-Uddin umbrella in the late 1960s and then the Greenfield filter in the early 1970s (55, 56). Compared with IVC ligation and then clips, filters are now easily inserted through a femoral or jugular vein using local anesthesia and fluoroscopic control. However, numerous complications do persist, such as fracture and/or migration of these devices (54). Despite the absence of large evaluations of IVC filters, their rate of implantation has been very high in some countries with, for example, a 50-fold higher rate of implantation in the USA compared with Sweden, during the 1990s (57). A five-fold increase in the number of caval filters implanted in the USA was reported between 1980 and 1996 (58). Furthermore, it is surprising to see in a recent prospective US registry of 5,451 patients with acute DVT that 781 patients (14%) had received filters. Among them, one-third were inserted for prophylaxis rather than accepted indications such as contraindication to anticoagulant treatment (59).

Several IVC filters exist, nine of which have been approved by the FDA (8, 54). There are three kinds of devices: permanent, temporary and retrievable filters. The temporary filters require a permanent catheter to fix the device and tend to be abandoned. Alternatively, the retrievable filters can be left in place like a permanent filter or retrieved as it was the case with a temporary filter. Two of them (the ALN and the RNF filters) can be retrieved up to six months after initial placement; among these new devices the ALN filter is certainly the one that has undergone the most studies (60). However, complication rates and comparison between the different devices are limited due to the small number of studies published to date and their short follow-up.

### Indications for IVC filter placement

Due to their risk of complication, the small number of controlled trials available and the potential cost incurred, filter indications should remain restricted. Table 4 summarizes the indications for IVC filters in VTE. Two indications are widely recognized as being appropriate, despite the fact that most clinical data on IVC filter placement are derived from historic, non-randomized series (1, 8). The first is a permanent or temporary contraindication to anticoagulation in patients with proximal DVT or PE. Absolute contraindications include severe and active visceral hemorrhage, recent history of brain hemorrhage, recent neurosurgical operation or head injury, and the need for major surgery (57). When contraindication to anticoagulants is temporary, the use of a temporary filter and now of a retrievable filter is logical. The second indication is the occurrence of PE or propagation of the thrombus in patients treated for DVT, or recurrence in patients with PE, despite adequate anticoagulation. It is thus

necessary to ascertain the recurrence and that the patient was in the therapeutic range during the period preceding the recurrent event. If not, it is probably more appropriate to equilibrate anticoagulation treatment. Investigation of thrombophilia and/or Trousseau's syndrome is also mandatory in this setting.

Other debated or debatable indications are based on small series, and IVC filter placement in these situations should be addressed by prospective clinical studies. This was realized in a single randomized trial (the PREPIC study) in patients with acute proximal DVT confirmed by bilateral venography, with or without concomitant symptomatic PE, and considered to be at high risk for PE (61). In a two-by-two factorial design, the authors randomized 400 patients with proximal DVT to receive a permanent vena caval filter (200 patients) or no filter (200 patients), and LMWH (enoxaparin, 195 patients) or unfractionated heparin (205 patients), followed by at least three months of vitamin K antagonists. The rates of recurrent VTE, death and major bleeding were analyzed on day 12 and at two years. On day 12, 1.1% of patients assigned to receive filters, compared with 4.8% of patients in the no-filter group, had had symptomatic or asymptomatic PE (OR 0.22; 95% CI 0.05–0.90). By contrast, at two years, 20.8% of patients assigned to the filter group, compared with 11.6% of patients assigned to the no-filter group, had had symptomatic recurrent DVT (OR 1.87; 95% CI 1.10–3.20). There were no significant differences in mortality or in the other outcomes. Recently, the results of an eight-year follow-up of 99% of patients included in the PREPIC study have been reported. Symptomatic PE occurred in nine patients in the filter group (cumulative rate 6.2%) and 24 patients (15.1%) in the no-filter group ( $p = 0.008$ ). DVT occurred in 57 patients (35.7%) in the filter group and 41 (27.5%) in the no-filter group ( $p = 0.042$ ). A similar rate of post-thrombotic syndrome was observed in 70% of both groups, the most common signs reported being edema and varicose veins. At eight years, 201 (50.3%) patients had died (103 and 98 patients

**Table 4: Indications for IVC filters (adapted from ref. 1, 54 and 57).**

<b>Accepted (appropriate) indications</b>
Contraindication (temporary or definitive) to anticoagulant treatment and recent proximal DVT or PE
Failure of adequate anticoagulant treatment: Documented PE Documented propagation of DVT
<b>Debated indications</b>
Pulmonary thromboembolism patients
Post-embolic pulmonary hypertension
Adjuvant preventive treatment before high-risk surgery in high-risk patients or in major trauma patients
<b>Debatable indications</b>
Thrombolysis of ilio-caval thrombus or extensive free-floating iliofemoral thrombus
Proximal DVT or PE and thrombolytic treatment
Cancer patients
Exclusive preventive treatment before high-risk surgery or in major trauma patients

in the filter and no-filter groups, respectively) (62). The take-home message from PREPIC is that vena cava filters reduced the risk of PE but increased that of DVT and had no effect on survival. Although their use may be beneficial in patients at high risk of PE, systematic use in the general population with VTE is not recommended. The fact that prevention of PE is mainly required during the short initial period following the diagnosis of an acute VTE event justifies a new randomized study with the use of retrievable filters as an adjuvant to anticoagulation in high-risk patients. This could demonstrate an initial benefit on PE, without the drawback of an increased rate of late recurrent DVT. Nevertheless, in DVT without concomitant PE it is doubtful that vena cava filters in association with anticoagulation would be useful. High-risk patients, with sub-massive PE, would probably be a better subset of patients in terms of eligibility for adjuvant IVC filters. As recently reported, the PREPIC study, and now the new retrievable filters, raise more questions than they answer (63), highlighting the need for more clinical trials.

### Other invasive approaches in the treatment of PE

The role of mechanical devices and embolectomy in PE has been recently reviewed by Greenfield (64). These techniques are reserved for patients with massive PE, refractory to medical management including thrombolysis, or for patients with an absolute contraindication to thrombolysis. Open pulmonary embolectomy on cardiopulmonary bypass consists, once the patient is safely on bypass, to open the pulmonary artery after sternotomy and to extract the emboli using forceps, balloon catheters, irrigation and manual massage of the lungs. The mortality rate for surgical embolectomy exceeds 30% at experienced centers (65, 66).

Percutaneous embolectomy is a less invasive option than open embolectomy in these patients (64). As this technique is performed in patients with acute pulmonary hypertension, cardiac arrest during the procedure is associated with the injection of contrast material, which must be carried out with caution, using small quantities. Cardiac arrest can also occur as a consequence of fragmentation of the thrombi during the procedure. Several devices, such as rotational catheters, jet-vortex catheters, impeller catheters, rotatable pigtail catheters, and aspiration devices have been designed for percutaneous embolectomy. The principle of percutaneous embolectomy is to fragment, aspirate and migrate to the periphery the part of the thrombi occluding

proximal pulmonary arteries. Rapid relief of central obstruction to the periphery could allow a rapid decrease in obstruction and hypertension associated with an increased cardiac output, based on the premise that the cross-sectional area of the distal arteries is several times that of proximal arteries (8). Percutaneous embolectomy can also be used in conjunction with local administration of fibrinolytic therapy, which will facilitate fragmentation; fragmentation exposing a larger surface area of thrombi will also facilitate thrombolysis (67).

A few cases of pulmonary stenting in the proximal main artery have been reported in life-saving therapy when other percutaneous treatments have failed. The long-term fate of stents in the pulmonary artery is unknown (8, 64).

In DVT, surgical embolectomy, percutaneous mechanical thrombectomy and the association of venous angioplasty and stenting have also been used (reviewed in 7, 8). Recent recommendations have stated that in DVT, surgical thrombectomy is commonly complicated by a local recurrence of thrombosis (1). A high percentage of patients require secondary re-intervention or secondary angioplasty with or without stent and long-term anticoagulation. For these reasons and the absence of proven benefit compared with anticoagulation alone, thrombectomy cannot be recommended in the vast majority of patients with proximal DVT.

### Conclusion

The indications of fibrinolysis, vena cava filters and/or interventional therapies are not indicated in the majority of patients with VTE. In the subset of the most severe patients with a life-threatening disease, these approaches are certainly useful in our armamentarium. In all the other situations, we need some future trials which must be large enough to detect significant clinical outcomes and last long enough to estimate the long-term benefit or harm of the proposed therapeutic strategies.

### Acknowledgements

This manuscript has been developed as part of the Thrombosis Quorum initiative, under the direction of the Thrombosis Quorum Steering Group [G. Agnelli (Chairman), P. Bath, J. Emmerich, B. Gersh, M. Ogren, S. Schulman, and J. Weitz]. Thrombosis Quorum is supported by an unrestricted educational grant from AstraZeneca.

### References

1. Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126 (Suppl 3): 401S–28S.
2. Buller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004; 140: 867–73.
3. Goldhaber SZ, Buring JE, Lipnick RJ, et al. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. *Am J Med* 1984; 76: 393–7.
4. Goldhaber SZ, Meyerovitz MF, Green D, et al. A randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. *Am J Med* 1990; 88: 235–40.
5. Watson LI, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochrane Database System Rev* 2004; 3: Art. No.: CD002783. doi: 10.1002/14651858.CD002783.pub2.
6. Konstantinides S, Marder VJ. Thrombolysis in venous thromboembolic disease. In: Hemostasis and Thrombosis. Basic principles and clinical practice. Lippincott Williams and Wilkins 2006; 1317–29.
7. Augustinos P, Ouriel K. Invasive approaches to treatment of venous thromboembolism. *Circulation* 2004; 110 (Suppl 1): I-27–I-34.
8. Mewissen MW, Seabrook GR, Meissner MH, et al. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. *Radiology* 1999; 211: 39–49.
9. Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. *Eur J Vasc Endovasc Surg* 2002; 24: 209–14.
10. Castaneda F, Li R, Young K, et al. Catheter-directed thrombolysis in deep venous thrombosis with use of reteplase: immediate results and complications from a pilot study. *J Vasc Interv Radiol* 2002; 13: 577–80.
11. Vedantham S, Vesely TM, Parti N, et al. Lower extremity venous thrombolysis with adjunctive mechanical thrombectomy. *J Vasc Interv Radiol* 2002; 13: 1001–8.
12. Laiho MK, Oinonen A, Sugano N, et al. Preservation of venous valve function after catheter-directed and systemic thrombolysis for deep venous thrombosis. *Eur J Vasc Endovasc Surg* 2004; 28: 391–6.
13. Patel NH, Stookey KR, Ketcham DB, et al. Endovascular management of acute extensive iliofemoral deep venous thrombosis caused by May-Thurner syndrome. *J Vasc Interv Radiol* 2000; 11: 1297–302.

14. Patel NH, Plorde JJ, Meissner M. Catheter-directed thrombolysis in the treatment of phlegmasia cerulea dolens. *Ann Vasc Surg* 1998; 12: 471–5.
15. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; 353: 1386–9.
16. Wan S, Quinlan DJ, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation* 2004; 110: 744–9.
17. Buller HR, Davidson BL, Decousus H, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003; 349: 1695–702.
18. Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. *Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire*. *N Engl J Med* 1997; 337: 663–9.
19. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2004; 140: 175–83.
20. Alpert JS, Smith R, Carlson J, et al. Mortality in patients treated for pulmonary embolism. *J Am Med Assoc* 1976; 236: 1477–80.
21. Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. *J Am Coll Cardiol* 1997; 30: 1165–71.
22. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, et al. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. *Am Heart J* 1997; 134: 479–87.
23. Pruszczyk P, Bochowicz A, Torbicki A, et al. Cardiac troponin T monitoring identifies high-risk group of normotensive patients with acute pulmonary embolism. *Chest* 2003; 123: 1947–52.
24. Pruszczyk P, Kostrubiec M, Bochowicz A, et al. N-terminal pro-brain natriuretic peptide in patients with acute pulmonary embolism. *Eur Respir J* 2003; 22: 649–53.
25. Binder L, Pieske B, Olschewski M, et al. N-terminal pro-brain natriuretic peptide or troponin testing followed by echocardiography for risk stratification of acute pulmonary embolism. *Circulation* 2005; 112: 1573–9.
26. No authors listed. Guidelines on diagnosis and management of acute pulmonary embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. *Eur Heart J* 2000; 21: 1301–36.
27. Dong B, Jirong Y, Liu G, Wang Q, Wu T. Thrombolytic treatment for pulmonary embolism. *Cochrane Database System Rev* 2006; 2: Art. No.: CD004437. pub2. doi:10.1002/14651858.CD004437.pub2.
28. Vieillard-Baron A, Page B, Augarde R, et al. Acute cor pulmonale in massive pulmonary embolism: incidence, echocardiographic pattern, clinical implications and recovery rate. *Intensive Care Med* 2001; 27: 1481–6.
29. Kucher N, Rossi E, De Rosa M, et al. Massive pulmonary embolism. *Circulation* 2006; 113: 577–82.
30. Giannitsis E, Muller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. *Circulation* 2000; 102: 211–7.
31. Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation* 2000; 101: 2817–22.
32. Konstantinides S, Geibel A, Olschewski M, et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. *Circulation* 1997; 96: 882–8.
33. Hamel E, Pacouret G, Vincetelli D, et al. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. *Chest* 2001; 120: 120–5.
34. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. *Circulation* 2003; 107: 2545–7.
35. Dalla-Volta S, Palla A, Santolicandro A, et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. *Plasminogen activator Italian multicenter study 2*. *J Am Coll Cardiol* 1992; 20: 520–6.
36. The urokinase pulmonary embolism trial. A national cooperative study. *Circulation* 1973; 47: 111–108.
37. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet* 1993; 341: 507–11.
38. Kanter DS, Mikkola KM, Patel SR, et al. Thrombolytic therapy for pulmonary embolism. Frequency of intracranial hemorrhage and associated risk factors. *Chest* 1997; 111: 1241–5.
39. Mikkola KM, Patel SR, Parker JA, et al. Increasing age is a major risk factor for hemorrhagic complications after pulmonary embolism thrombolysis. *Am Heart J* 1997; 134: 69–72.
40. Meyer G, Gisselbrecht M, Diehl JL, et al. Incidence and predictors of major hemorrhagic complications from thrombolytic therapy in patients with massive pulmonary embolism. *Am J Med* 1998; 105: 472–7.
41. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis* 1995; 2: 227–9.
42. Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002; 347: 1143–50.
43. Konstantinides S. Thrombolysis in submassive pulmonary embolism? Yes. *J Thromb Haemost* 2003; 1: 1127–9.
44. Dalen JE. Thrombolysis in submassive pulmonary embolism? No. *J Thromb Haemost* 2003; 1: 1130–2.
45. Urokinase-streptokinase embolism trial. Phase 2 results. A cooperative study. *J Am Med Assoc* 1974; 229: 1606–13.
46. The UKEP study: multicentre clinical trial on two local regimens of urokinase in massive pulmonary embolism. The UKEP Study Research Group. *Eur Heart J* 1987; 8: 2–10.
47. Goldhaber SZ, Kessler CM, Heit J, et al. Randomised controlled trial of recombinant tissue plasminogen activator versus urokinase in the treatment of acute pulmonary embolism. *Lancet* 1988; 2: 293–8.
48. Meyer G, Sors H, Charbonnier B, et al. Effects of intravenous urokinase versus alteplase on total pulmonary resistance in acute massive pulmonary embolism: a European multicenter double-blind trial. The European Cooperative Study Group for Pulmonary Embolism. *J Am Coll Cardiol* 1992; 19: 239–45.
49. Goldhaber SZ, Kessler CM, Heit JA, et al. Recombinant tissue-type plasminogen activator versus a novel dosing regimen of urokinase in acute pulmonary embolism: a randomized controlled multicenter trial. *J Am Coll Cardiol* 1992; 20: 24–30.
50. Meneveau N, Schiele F, Metz D, et al. Comparative efficacy of a two-hour regimen of streptokinase versus alteplase in acute massive pulmonary embolism: immediate clinical and hemodynamic outcome and one-year follow-up. *J Am Coll Cardiol* 1998; 31: 1057–63.
51. Meneveau N, Schiele F, Vuilleminot A, et al. Streptokinase vs alteplase in massive pulmonary embolism. A randomized trial assessing right heart haemodynamics and pulmonary vascular obstruction. *Eur Heart J* 1997; 18: 1141–8.
52. Goldhaber SZ, Agnelli G, Levine MN. Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis. An international multicenter randomized trial. The Bolus Alteplase Pulmonary Embolism Group. *Chest* 1994; 106: 718–24.
53. Sors H, Pacouret G, Azarian R, et al. Hemodynamic effects of bolus vs 2-h infusion of alteplase in acute massive pulmonary embolism. A randomized controlled multicenter trial. *Chest* 1994; 106: 712–7.
54. Hann CL, Streiff MB. The role of vena caval filters in the management of venous thromboembolism. *Blood Rev* 2005; 19: 179–202.
55. Mobin-Uddin K, McLean R, Jude JR. A new catheter technique of interruption of inferior vena cava for prevention of pulmonary embolism. *Am Surg* 1969; 35: 889–94.
56. Greenfield LJ, McCurdy JR, Brown PP, et al. A new intracaval filter permitting continued flow and resolution of emboli. *Surgery* 1973; 73: 599–606.
57. Girard P, Tardy B, Decousus H. Inferior vena cava interruption: how and when? *Annu Rev Med* 2000; 51: 1–15.
58. Athanasoulis CA, Kaufman JA, Halpern EF, et al. Inferior vena caval filters: review of a 26-year single-center clinical experience. *Radiology* 2000; 216: 54–66.
59. Goldhaber SZ, Tapson VF; DVT FREE Steering Committee. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am J Cardiol* 2004; 93: 259–62.
60. Mismetti P, Rivron-Guillot K, Quenet S, et al. A prospective long-term study of 220 patients with a retrievable vena cava filter for secondary prevention of venous thromboembolism. *Chest* 2006; in press.
61. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group*. *N Engl J Med* 1998; 338: 409–15.
62. The PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. *Circulation* 2005; 112: 416–22.
63. Ansell J. Vena cava filters. Do we know all that we need to know? *Circulation* 2005; 112: 298–9.
64. Greenfield LJ. Mechanical devices and embolectomy. In: Hemostasis and Thrombosis. Basic principles and clinical practice. Lippincott Williams and Wilkins 2006; 1331–8.
65. Meyer G, Tamisier D, Sors H, et al. Pulmonary embolectomy: a 20-year experience at one center. *Ann Thorac Surg* 1991; 5: 232–6.
66. Yalamanchili K, Fleisher AG, Lehrman SG, et al. Open pulmonary embolectomy for treatment of major pulmonary embolism. *Ann Thorac Surg* 2004; 77: 819–23.
67. Timsit JF, Reynaud P, Meyer G, et al. Pulmonary embolectomy by catheter device in massive pulmonary embolism. *Chest* 1991; 100: 655–8.