Thrombolytic therapy for the treatment of acute pulmonary embolism

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Objectives: To determine whether thrombolytic therapy reduces the rate of death or complications in patients with acute pulmonary embolism and whether a particular thrombolytic regimen is more effective than others.
Data sources: The key words "fibrinolytic agents," "plasminogen activators," "streptokinse," "urokinase" and "pulmonary embolism" were used to search MEDLINE for relevant articles in English; the bibliographies of these articles were reviewed for additional publications.
Study selection: Articles were included if they were of a randomized controlled design; 10 such articles were found.
Data extraction: Ten trials were appraised with the use of the following methodologic criteria: a clear description of the study population; use of objective criteria to diagnose pulmonary embolism and to assess outcomes; use of clinically relevant outcomes; and blinded outcome assessments.
Results: In the nine trials that met the methodologic criteria thrombolytic therapy led to a more rapid resolution of the radiographic and hemodynamic abnormalities associated with acute pulmonary embolism than did anticoagulant therapy alone, although these benefits were short-lived. No difference was detected in the death rate or the resolution of symptoms between patients receiving thrombolytic therapy and those receiving anticoagulant therapy alone. In addition, bleeding complications were more frequent and serious in patients who received lytic therapy, although these events were related to the use of invasive procedures.
Conclusion: There is a lack of evidence that thrombolytic therapy improves clinically relevant outcomes of patients with acute pulmonary embolism. This may be a reflection of the small sample size of the clinical trials. Further research is required to define the role of thrombolytic therapy in the management of patients with acute pulmonary embolism.

Objectifs : Déterminer si le traitement thrombolytique réduit le taux de mortalité ou de complications chez les patients ayant subi une embolie pulmonaire aiguë et si un schéma thrombolytique particulier est plus efficace que les autres.
Sources de données : Les mots clés «agents fibrinolytiques», «activateurs du plasminogène», «streptokinase», «urokinase» et «embolie pulmonaire» ont été utilisés pour rechercher des articles pertinents en anglais dans MEDLINE; on a parcouru les bibliographies de ces articles pour trouver des publications supplémentaires.
Sélection d'études : Les articles étaient étudiés si leur conception était randomisée et contrôlée; on a trouvé 10 articles de ce genre.

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Extraction de données : Dix études ont été évaluées au moyen des critères méthodologiques suivants : une description claire de la population étudiée; utilisation de critères objectifs pour diagnostiquer l'embolie pulmonaire et évaluer les résultats; utilisation des résultats pertinents sur le plan clinique; et évaluations des résultats à l'insu.
Résultats : Dans les neuf essais qui répondaient aux critères méthodologiques, le traitement thrombolytique a donné lieu à une résolution plus rapide des anomalies radiographiques et hémodynamiques reliées à l'embolie pulmonaire aiguë que le seul traitement anticoagulant, bien que ces avantages aient été de courte durée. Aucune différence n'a été décelée quant au taux de mortalité ou à la résolution des symptômes entre les patients à qui l'on a administré le traitement thrombolytique et ceux qui n'ont reçu que le traitement anticoagulant. De plus, les complications hémorragiques étaient plus fréquentes et graves chez les patients à qui l'on a administré un traitement lytique, bien que ces complications soient reliées au recours à des interventions invasives.
Conclusion : Il n'est pas prouvé que le traitement thrombolytique améliore les résultats cliniquement significatifs chez les patients ayant subi une embolie pulmonaire aiguë. Cela peut refléter la faible importance de l'échantillon des essais cliniques. Il faudra mener d'autres recherches pour définir le rôle du traitement thrombolytique chez les patients ayant subi une embolie pulmonaire aiguë.

Acute pulmonary embolism is a serious medical condition that causes approximately 30 000 deaths annually in the United States alone.[1] Anticoagulant therapy has been shown to reduce the rate of death from acute pulmonary embolism, but even with this treatment as many as 10% of patients with the condition die before discharge from hospital.[2,3] There has been renewed interest in the treatment of acute pulmonary embolism with thrombolytic therapy because of the demonstrated reduction in the death rate of patients with acute myocardial infarction who are treated with these agents and because of the development of newer, fibrin-specific thrombolytic drugs.[4,5]

In acute pulmonary embolism the rapid lysis of the embolus is an attractive approach for several reasons: first, lytic therapy could reduce the rate of death from acute pulmonary embolism; second, it could reduce the severity and duration of the associated symptoms; third, by dissolving the deep venous source of the embolus it could reduce the risk of recurrence; and, finally, by reducing the obstruction to pulmonary artery outflow it could prevent the development of chronic pulmonary hypertension secondary to pulmonary embolic disease.

The drawback of thrombolytic therapy is the potential for bleeding.[4] Thrombolytic agents cause hemorrhage primarily by the dissolution of fibrin in the hemostatic plug. Contributing factors may include plasma proteolysis, with its associated depletion of fibrinogen and other coagulation factors, and the production of fibrinogen degradation products, which interfere with fibrin polymerization. Cerebral hemorrhage has occurred in 0.1% to 1.6% of patients treated with these agents for myocardial infarction.[6,7] Other nonfatal bleeding events are more common and occur frequently at the sites of invasive procedures.[8,9] Since the hemorrhagic complications of thrombolytic agents may be life-threatening the risks and benefits of this form of treatment for patients with acute pulmonary embolism must be carefully balanced before lytic therapy can be recommended. We critically appraised the literature to determine whether thrombolytic therapy reduces the rate of death or complications in patients with acute pulmonary embolism and whether any thrombolytic drug is more effective than others.

Methods

Literature review

Relevant articles were obtained from a search of MEDLINE with the use of the key words "fibrinolytic agents," "plasminogen activators," "streptokinase," "urokinase" and "pulmonary embolism." All relevant studies published in English were reviewed, and their bibliographies were searched for additional articles.

Critical appraisal

The articles were classified into different levels of evidence depending on their study design and sample size as previously outlined by Sackett.[10] Level I studies are randomized controlled trials of sufficient sample size to minimize a false-negative, type II error. Level II studies are randomized controlled trials with small samples. We classified trials as level I or II on the basis of the primary outcome measures. Therefore, in our analysis a study could be designated as level I because it found significant differences between therapies on these primary outcome measures, but it could be of insufficient sample size to exclude significant differences in other clinically relevant outcomes, such as death rate. Level III trials were nonrandomized studies that included a concurrent control group not receiv-

ing thrombolytic therapy. Level IV studies were nonrandomized studies that included a historical control group. Level V studies were descriptive series without control groups. Only level I and level II studies were reviewed. These were evaluated according to the following criteria.

- Was there a clear definition of the patient population? We included in the analysis only studies that used thrombolytic agents to treat patients within 2 weeks after the onset of acute symptomatic pulmonary embolism. Emphasis was placed on articles that clearly described patients' demographic and clinical characteristics and the criteria for entry into the study and that gave evidence that an inception cohort was assembled.
- Was the diagnosis of acute pulmonary embolism made according to objective criteria? We included in the analysis only studies that used pulmonary angiography or high-probability ventilation–perfusion lung scanning to confirm the diagnosis.
- Were objective outcome measures used? Emphasis was placed on studies that used the following clinically relevant and objective outcome measures.

Death within 2 weeks of the patient's having received thrombolytic therapy: When possible we tried to determine the rate of death directly attributable to acute pulmonary embolism.

Radiographic parameters: We evaluated improvement in the results of pulmonary angiography and ventilation–perfusion lung scans after thrombolytic therapy, placing the most weight on studies that used predetermined scoring systems to assess the severity of the embolism.

Hemodynamic parameters: We analysed resolution of the hemodynamic abnormalities associated with acute pulmonary embolism, selecting the mean pulmonary artery pressure (PAP) as the primary hemodynamic measure, because it generally reflects the severity of the acute pulmonary embolism (especially in patients without underlying cardiopulmonary disease) and is measured routinely.

Complications: In the short term these consisted of strictly defined symptoms directly related to the embolism (e.g., shortness of breath) and the complications of therapy (e.g., bleeding). The definitions of major and minor bleeding differed between studies. For our appraisal we classified bleeding as major if it was intracranial or retroperitoneal or if it led directly to death or transfusion.[11] All other types of bleeding (including some gastrointestinal and most epistaxis, hematuria, ecchymosis and hemoptysis) were classified as minor. Long-term complications consisted of the cardiopulmonary problems that developed more than 2 weeks after the patients received thrombolytic therapy.

- Were the outcome measurements assessed blindly? Most of the outcome measures could be subject to bias if those assessing them were aware of the treatment that patients had received.

Results

Trials comparing thrombolytic therapy with heparin therapy

Of the six level I or II studies of this type uncovered in the MEDLINE search[8,12–17] five fulfilled most of our methodologic criteria and are included in the analysis[8,12–16] (Table 1).

The first and largest of the studies, classed as level I, was the Urokinase Pulmonary Embolism Trial (UPET), in which 160 patients received either a 12-hour urokinase infusion (a 4400-U/kg bolus plus 4400 U/kg hourly) followed by heparin or heparin alone.[8,12] Angiography after 24 hours showed that patients who had received urokinase had greater thrombus resolution and significantly greater improvements in hemodynamic parameters than did those receiving heparin alone.

Ventilation–perfusion lung scanning was performed before treatment and serially afterwards. Patients who had received urokinase showed a significantly greater resolution of perfusion defects within 24 hours after the initiation of therapy than patients receiving heparin alone. However, this advantage was short-lived: 5 days after treatment the amount of resolution was equivalent in the two groups and remained so over the next 9 days.

Despite the significant early improvements in radiographic and hemodynamic parameters offered by urokinase the study did not demonstrate a decrease in the rate of death or short-term complications of pulmonary embolism in the patients thus treated (Table 1). The death rate within 2 weeks after treatment was 6% in the urokinase group and 7% in the heparin-only group. The authors commented that "three and possibly four" of the patients in the heparin-only group as compared with only one of the patients in the urokinase group died as a result of a direct complication of the pulmonary embolism. However, this modest benefit of lytic therapy was offset by four deaths in which bleeding was either the cause or a contributing cause.[12] No patients in the heparin-only group had fatal bleeding. The death rates were much higher in the subgroup of 14 patients who presented in shock (shock was not defined in the paper): 4 of the 9 (44%) receiving urokinase and 1 of the 5 (20%) receiving heparin alone died in the 2-week follow-up period. This difference was not statistically significant.

The UPET was the only trial that evaluated the resolution of the acute symptoms and signs of pulmonary embolism in a systematic manner with blind observers. It found no significant difference

between groups in the resolution of dyspnea, hemoptysis, pleuritic chest pain or abnormal heart sounds. However, a subgroup analysis revealed that in patients with massive pulmonary embolism (blockage of two or more lobar pulmonary arteries as revealed by pulmonary angiography) there was faster resolution of these symptoms over 2 weeks in the urokinase group than in the heparin-only group.

Bleeding was a frequent complication in this study. There were 22 major episodes in the urokinase group and 11 in the heparin-only group (Table 1). The bleeding-related deaths already mentioned led the authors to use much more stringent exclusion criteria to avoid bleeding complications in their follow-up trial.

Two level I studies compared 72-hour infusions of streptokinase with heparin for the treatment of acute pulmonary embolism.[13,14] Tibbutt and associates[13] assigned 30 patients to groups receiving either streptokinase (a 600 000-U bolus plus 100 000 U/h) followed by coumarin or 7 days of heparin followed by coumarin. This study had a high proportion of patients (6 of 13 treated with streptokinase and 9 of 17 treated with heparin) whose initial systolic blood pressure was less than 100 mm Hg. Perhaps for this reason seven patients did not complete the 72 hours of therapy, six because of prolonged hypotension and one because of death from pulmonary embolism. Two of these patients were in the streptokinase group and five in the heparin group; the authors excluded them from the analysis of the radiographic and hemodynamic outcomes.

The study found that patients in the group receiving streptokinase showed significantly greater resolution of angiographic abnormalities and PAP than the patients in the heparin group. The only death was that of a patient in the heparin group who had massive pulmonary embolism. Bleeding complications were also relatively uncommon, one patient in each group having had a major episode of bleeding.

Ly and collaborators[14] compared 72-hour infusions of streptokinase (a 250 000-U bolus plus 100 000 U/h) followed by heparin with heparin alone. Ten patients were randomly allocated to each group, and five additional patients were allocated nonrandomly, four to the streptokinase and one to the heparin-only group. There was a significant

Table 1: Clinical details of randomized controlled trials comparing thrombolytic therapy with heparin therapy in the treatment of acute pulmonary embolism

Study	Treatment*	n (male/female)	Age† (yr)	No. of deaths‡	No. (and %) of bleeding episodes	
					Major	Minor
UPET[8,12]	UK: 4400-U/kg bolus + 4400 U/kg hourly for 12 h; heparin	82 (47/35)	46 < 50	6 (1)	22 (27)	15 (18)
	Heparin: 165-U/kg bolus + 22 U/kg hourly	78 (45/33)	35 < 50	7 (3)	11 (14)	10 (13)
Tibbutt et al[13]	SK: 600 000-U bolus + 100 000 U/h for 72 h; coumarin	13 (4/9)	51	0	1 (8)	3 (23)
	Heparin: 5000-U bolus + 2500 U/h; coumarin	17 (11/6)	47	1 (1)	1 (6)	3 (18)
Ly et al[14]	SK: 250 000-U bolus + 100 000 U/h for 72 h; heparin	14 (8/6)	51	0	2 (14)	3 (21)
	Heparin: 15 000-U bolus + 30 000 U/d	11 (3/8)	56	1 (1)	1 (9)	3 (27)
PIOPED[15]	TPA: 40-80 mg at 1 mg/min; heparin	9 (5/4)	58	1 (0)	1 (11)	0
	Heparin (no details given)	4 (4/0)	60	0	0	0
Levine et al[16]	TPA: 0.6 mg/kg over 2 min; heparin	33 (18/15)	62	1 (1)	0	15 (45)
	Heparin: 5000-U bolus + 30 000 U/d	25 (11/14)	60	0	0	1 (4)

*UK = urokinase, SK = streptokinase, TPA = tissue plasminogen activator.
†Mean age except for the UPET, which reported the number of patients less than 50 years old.
‡The number of deaths from pulmonary embolism is in parenthesis.

improvement in the resolution of the angiographic abnormalities in the patients receiving streptokinase as compared with those receiving heparin alone, even with the exclusion of the five additional patients. One patient in the heparin group died from pulmonary embolism. Two patients in the streptokinase group and one in the heparin-only group suffered major bleeding.

Two recent studies compared tissue plasminogen activator (tPA) with heparin for the treatment of acute pulmonary embolism.[15,16] The PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study[15] was a level II study in which 13 patients received either an infusion of 40 to 80 mg (at a rate of 1 mg/min) of tPA followed by heparin or heparin alone. A 2:1 randomization scheme was used in this study, nine patients being assigned to the group receiving tPA and four to the group receiving heparin alone. The authors stopped the trial well short of their target sample size of 50 patients because of poor patient accrual. There was no difference in the resolution of angiographic or hemodynamic abnormalities between the two groups or of lung scan abnormalities, although a strong trend favouring the tPA group was seen on both the 1st and the 7th day after treatment. These negative results are in contrast to the findings from the other four level I studies and in view of the small sample are likely the result of type II error.

In the PIOPED study an 81-year-old patient in the tPA group had major bleeding and did not have follow-up radiographic or hemodynamic studies. Although no deaths occurred within 2 weeks after therapy this patient died 19 days afterwards, and the bleeding episode contributed to his death.

Levine and colleagues[16] compared therapy with a bolus of tPA administered over 2 minutes (0.6 mg/kg ideal body weight) followed by heparin and heparin therapy alone in a double-blind study involving 58 patients with acute pulmonary embolism. The primary outcome of this level I study was 50% resolution of the pretreatment perfusion defects as revealed by lung scanning 24 hours after therapy. In the tPA group 11 of the 33 patients showed more than 50% resolution as compared with 3 of the 25 in the heparin-only group ($p = 0.026$). However, by the 7th day the improvements in the two groups were equivalent. The only death was secondary to a saddle embolus in the tPA group. There were no major bleeding events, although minor bleeding was much more common (45% v. 4%) in the tPA group.

Only one level I study examined for possible long-term benefits of thrombolytic therapy for patients with pulmonary embolism.[18] Sharma, Burleson and Sasahara[18] studied 40 patients who were participants in either the UPET or the Urokinase-Streptokinase Pulmonary Embolism Trial (USPET)[9] and examined the diffusion lung capacity and the lung capillary volumes at 2 weeks and 1 year after the embolism. None of these patients had obstructive abnormalities according to initial pulmonary function testing, but otherwise the selection criteria used to include only these patients in the study were not given.

Those receiving thrombolytic therapy as the initial treatment for their embolism had significantly higher diffusion lung capacity and lung capillary volumes at 2 weeks and 1 year than patients receiving only heparin. Although the differences were statistically significant the clinical significance of the findings is unclear.

In a follow-up study 23 of these patients were evaluated 7 years, on average, after thrombolytic treatment.[19] Pulmonary hemodynamic investigations demonstrated that patients who had received heparin alone had persistently higher PAP and pulmonary vascular resistance than those who had received thrombolytic therapy and that these differences were accentuated by exercise. The relation between these findings and symptoms was not described.

Trials comparing thrombolytic regimens

Four level I studies have compared different thrombolytic regimens for the treatment of pulmonary embolism,[9,20-22] and all of them fulfilled our methodologic criteria (Table 2).

The first and largest of these studies was the multicentre USPET[9] (a follow-up to the UPET), in which 167 patients received either a 24-hour streptokinase infusion (a 250 000-U bolus followed by a continuous infusion of 100 000 U/h) or a 12-hour or 24-hour urokinase infusion (a 4400-U/kg bolus followed by a continuous infusion of 4400 U/kg for 12 or 24 hours). In each group thrombolytic therapy was followed by heparin treatment. Each of the lytic treatments led to significant resolution of the pulmonary angiographic and lung scan abnormalities and to reduction in the PAP as compared with the findings in the heparin-only group of the UPET. However, no difference in thrombolytic efficacy, bleeding or number of deaths was detected between the three regimens.

The UKEP trial[20] was a multicentre European study in which 139 patients received either 2000 U/kg hourly of urokinase for 24 hours with simultaneous heparin therapy or 4400 U/kg hourly of urokinase for 12 hours followed by heparin. No difference in resolution of the angiographic abnormalities or in reduction of the PAP was detected between the two groups. The bleeding and death rates were similar with each of the regimens (Table 2). This study was somewhat compromised by the

fact that 31 patients did not have evaluable angiograms before and after treatment, 11 because of death or poor medical condition and 20 because of poor-quality angiograms.

Verstraete and associates[21] performed a multicentre study comparing intrapulmonary tPA with intravenous tPA for the treatment of pulmonary embolism in 34 patients. All patients were given a 10-mg bolus of tPA followed by a 40-mg infusion over 2 hours along with simultaneous heparin therapy. Angiography was then performed, and an additional 50 mg of tPA was given over 5 hours if the 2-hour Miller pulmonary angiographic index[23] was greater than 15/34. There was no difference in resolution of the angiographic abnormalities or in reduction of the PAP between the two groups either after the first or after the second tPA infusion. There were two deaths and five major bleeding events in this trial, but the authors did not specify in which of the two groups these events occurred.

Goldhaber and collaborators[22] performed a multicentre study in which 45 patients were given either a 100-mg tPA infusion over 2 hours or a 24-hour urokinase infusion (a 4400-U/kg bolus and then 4400 U/kg hourly) followed by heparin. After 2 hours of therapy (i.e., at the completion of tPA treatment but after only 1/8 of the urokinase dose) repeat pulmonary angiographic and hemodynamic evaluations were performed. The 2-hour studies demonstrated that tPA led to significantly greater resolution of the angiographic abnormalities and reduction of the PAP as compared with urokinase. However, lung scans performed 24 hours after the initiation of treatment demonstrated equivalent improvement in the two groups. There were two deaths secondary to pulmonary embolism in the urokinase group and one death unrelated to pulmonary embolism in the tPA group. Bleeding complications were more common in the urokinase group, and in eight patients bleeding led to the premature discontinuation of the urokinase infusion.

This study has been criticized[24] because repeat angiography was performed after 2 hours of therapy while the urokinase group was continuing to receive the thrombolytic drug. The timing of the outcome measure increased the likelihood of a favourable result for tPA. In fairness, however, the regimen used in the urokinase group is the one currently approved by the Food and Drug Administration for the treatment of pulmonary embolism, on the basis of the USPET and UPET results.

Discussion

It has been demonstrated in four level I studies that thrombolytic therapy leads to more rapid reso-

Table 2: Clinical details of randomized controlled trials comparing different thrombolytic regimens

Study	Treatment*	n (male/female)	Age† (yr)	No. of deaths‡	No. (and %) of bleeding episodes	
					Major	Minor
USPET[9]	SK: 250 000-U bolus + 100 000 U/h for 24 h; heparin	54 (36/18)	21 < 50	5 (NA)	10 (19)	NA
	UK: 4400-U/kg bolus + 4400 U/kg hourly for 12 h; heparin	59 (39/20)	26 < 50	4 (NA)	10 (17)	NA
	UK: 4400-U/kg bolus + 4400 U/kg hourly for 24 h; heparin	54 (30/24)	25 < 50	5 (NA)	7 (13)	NA
UKEP[20]	UK: 2000 U/kg hourly for 24 h + heparin	67 (33/34)	60	4 (4)	3 (5)	13 (19)
	UK: 4400 U/kg hourly for 12 h; heparin	62 (32/30)	60	3 (3)	2 (3)	16 (26)
Verstraete et al[21]	TPA (IP): 10-mg bolus + 40-90 mg over 2 to 7 h + heparin	19 (11/8)	62	2§ (2)	5§ (15)	11§ (32)
	TPA (IV): as above	15 (9/6)	69			
Goldhaber et al[22]	TPA: 100 mg over 2 h	22 (13/9)	55	1 (0)	0	1 (4)
	UK: 4400-U/kg bolus + 4400 U/kg hourly for 24 h	23 (14/9)	55	2 (2)	1 (4)	7 (30)

*IP = intrapulmonary artery infusion, IV = intravenous infusion.
†Mean age except for the USPET, which reported the number of patients less than 50 years old.
‡The number of deaths from pulmonary embolism is in parenthesis. NA = not available.
§These numbers were not broken down by treatment group.

lution of both the radiographic (pulmonary angiographic and perfusion lung scanning) and the hemodynamic (PAP) abnormalities caused by acute pulmonary embolism than does heparin therapy alone.[8,13,14,16] However, the results of serial lung scan studies suggest that these benefits are short-lived, since by 5 to 7 days after lytic therapy the degree of resolution of perfusion defects is similar to that in patients treated with heparin alone.[8,16]

Despite the early hemodynamic and radiographic improvements no difference was detected in the rate of death or of resolution of symptoms of the patients given thrombolytic therapy as compared with those given heparin alone (Table 1). In addition, bleeding complications were more frequent and serious in patients receiving lytic therapy, although usually these events were related to the use of invasive procedures.[8,9,16,22]

Before concluding that lytic therapy does not cause a significant reduction in the death rate of patients with acute pulmonary embolism, the number of patients required in a trial to demonstrate such a difference should be considered. With a pooled death rate of only 6.7% in the heparin control patients studied in our analysis a sample of about 1000 patients would be needed in order for the study to have 80% power to exclude the possibility that thrombolytic therapy can cause even a 50% reduction in the death rate. This estimate is likely conservative, because many patients who die after acute pulmonary embolism are seriously ill to begin with, and the cause of death may be unrelated to the pulmonary embolism.

Is there a subgroup of patients with acute pulmonary embolism that would be most likely to benefit from thrombolytic therapy? Logically, patients who present in shock might be such a group. The UPET[8] reported a 35% death rate among 15 patients presenting with shock. Tibbutt and associates[13] found that 47% of 15 hypotensive patients were unable to complete the 72-hour trial because of persistent hypotension. The high rate of adverse events in this group together with the likelihood that the hypotension is secondary to the obstruction of large segments of the pulmonary circulation means that the early improvements provided by lytic therapy could be of considerable clinical importance to these patients. A subgroup analysis of patients in the level I studies who were in shock did not demonstrate a significant reduction in the death rate with the use of lytic therapy, but the number of these patients was small, and in the more recent tPA placebo-controlled studies shock was an exclusion criterion.

Despite the lack of clear evidence from randomized trials that thrombolytic therapy improves clinical outcome some experienced clinicians, including those in our own McMaster Thromboembolism Group, will still use thrombolytic therapy for critically ill, hemodynamically compromised patients with acute pulmonary embolism.

Unfortunately, there have been few trials examining the potential long-term benefits of thrombolytic therapy. Sharma and coworkers[18,19] have demonstrated that the pulmonary hemodynamic profiles of patients receiving lytic therapy for the treatment of acute pulmonary embolism are better in the long term than those of patients receiving heparin alone. Although these results are very encouraging they were taken from only a small cohort of patients, and the correlation between them and the patients' symptoms is uncertain. Further research is required to define the role of thrombolytic therapy in the management of acute pulmonary embolism.

References

1. Hillum RF: Pulmonary embolism and thrombophlebitis in the United States, 1970–1985. *Am Heart J* 1987; 114: 1261–1264
2. Barritt DW, Jordan SC: Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. *Lancet* 1960; 1: 1309–1312
3. Dalen JE, Alpert JS: Natural history of pulmonary embolism. *Prog Cardiovasc Dis* 1975; 17: 259–270
4. Marder VJ, Sherry S: Thrombolytic therapy: current status. *N Engl J Med* 1988; 318: 1512–1520, 1585–1595
5. Tiefenbrunn AJ, Sobel BE: The impact of coronary thrombolysis on myocardial infarction. *Fibrinolysis* 1989; 3: 1–15
6. Loscalzo J, Braunwald E: Tissue plasminogen activator. *N Engl J Med* 1988; 319: 925–931
7. Tognoni G, Fresco C, Franzosi MG et al: Thrombolysis in acute myocardial infarction. *Chest* 1991; 99: 121S–127S
8. Urokinase Pulmonary Embolism Trial: phase 1 results. *JAMA* 1970; 214: 2163–2172
9. Urokinase-Streptokinase Embolism Trial: phase 2 results. *JAMA* 1974; 229: 1606–1613
10. Sackett DL: Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989; 95 (suppl): 2S–4S
11. Levine MN, Raskob G, Hirsh J: Hemorrhagic complications of long-term anticoagulant therapy. Ibid: 26S–36S
12. The urokinase pulmonary embolism trial: a national cooperative study. *Circulation* 1973; 47 (suppl II): II-1–II-108
13. Tibbutt DA, Davies JA, Anderson JA et al: Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonary embolism. *BMJ* 1974; 1: 343–347
14. Ly B, Arnesen H, Eie H et al: A controlled clinical trial of streptokinase and heparin in the treatment of major pulmonary embolism. *Acta Med Scand* 1978; 203: 465–470
15. Tissue plasminogen activator for the treatment of acute pulmonary embolism: a collaborative study by the PIOPED investigators. *Chest* 1990; 97: 528–533
16. Levine M, Hirsh J, Weitz J et al: A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. *Chest* 1990; 98: 1473–1479
17. Giuntini C, Marini C, Di Ricco G et al: A controlled clinical trial on the effect of heparin infusion and two regimens of urokinase in acute pulmonary embolism. *G Ital Cardiol* 1984; 14 (suppl 1): 26–29
18. Sharma GVRK, Burleson VA, Sasahara AA: Effect of throm-

bolytic therapy on pulmonary-capillary blood volume in patients with pulmonary embolism. *N Engl J Med* 1980; 303: 842-845
19. Sharma GVRK, Folland ED, McIntyre KM et al: Longterm hemodynamic benefit of thrombolytic therapy in pulmonary embolic disease [abstr]. *J Am Coll Cardiol* 1990; 15: 65A
20. The UKEP Study Research Group: The UKEP study: multicentre clinical trial on two local regimens of urokinase in massive pulmonary embolism. *Eur Heart J* 1987; 8: 2-10
21. Verstraete M, Miller GAH, Bounameaux H et al: Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. *Circulation* 1988; 77: 353-360
22. 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: 293-298
23. Miller GAH, Sutton GC, Kerr IH et al: Comparison of streptokinase and heparin in the treatment of isolated acute massive pulmonary embolism. *BMJ* 1971; 2: 681-684
24. Sasahara AA: Urokinase versus tissue plasminogen activator in pulmonary embolism [C]. *Lancet* 1988; 2: 691

Conferences

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May 22-24, 1992: Okanagan Anesthesia Conference — Postoperative Acute Pain Management: the First 24 Hours
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May 24-28, 1992: International Heart Health Conference: Bridging the Gap — Science and Policy in Action (sponsored in part by the Department of National Health and Welfare, the BC Ministry of Health and the Heart and Stroke Foundation of Canada)
Victoria
International Heart Health Conference Secretariat, c/o Venue West Ltd., 645-375 Water St., Vancouver, BC V6B 5C6; (604) 681-5226, fax (604) 681-2503

May 24-29, 1992: International Conference on Pharmaceutical Sciences and Clinical Pharmacology
Jerusalem
Conference coordinator, Kenes USA, 903-271 Madison Ave., New York, NY 10016; (212) 986-8300

May 24-June 6, 1992: Extended Ibero-American Bioethics Course (in cooperation with the Pan American Health Organization and in conjunction with the May 31-June 6 Intensive Bioethics Course XVIII)
Georgetown University, Washington, DC
Exclusively for Latin-American, Spanish and Portuguese participants, who will then join the 18th Annual Kennedy Institute of Ethics Intensive Bioethics Course (IBC) May 31-June 6. (Some sessions in the first week will be in Spanish.)
Kennedy Institute of Ethics, Georgetown University, Washington, DC 20057; (202) 687-8099, fax (202) 687-6770

May 25-29, 1992: McGill Annual Course in Anesthesia
Montreal
Postgraduate Board, Royal Victoria Hospital, 687 Pine Ave. W, Montreal PQ H3A 1A1; (514) 842-1231, ext. 5300

May 25-29, 1992: 12th International Congress of Hospital Engineering (in concurrence with the Hospital-Health Care International Exhibition)
Congress Hall, Bologna, Italy
Organizing Secretariat, SENAF, Via Michelino 69, 40127 Bologna, Italy; telephone 011-39-51-503318, fax 011-39-51-505282

May 27, 1992: 5th Annual Obstetric/Gynecology Clinic Afternoon
Radisson Hotel, Toronto
Gayle Willoughby, conference coordinator, North York General Hospital, 116-4001 Leslie St., Willowdale, ON M2K 1E1; (416) 756-6538, fax (416) 756-6740

May 27, 1992: Update in Drug Therapy
University Hospital, London, Ont.
Gerry Niles, program assistant, Continuing Medical Education, University of Western Ontario Health Sciences Centre, London, ON N6A 5C1; (519) 661-2074, fax (519) 661-3797

May 27-29, 1992: 7th Annual Update in Geriatrics
Woodward Instructional Resources Centre, University of British Columbia, Vancouver
Continuing Medical Education, 105-2194 Health Sciences Mall, University of British Columbia, Vancouver, BC V6T 1Z3; (604) 822-2626, fax (604) 822-4835

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