HEPARIN PLUS ALTEPLASE COMPARED WITH HEPARIN ALONE IN PATIENTS WITH SUBMASSIVE PULMONARY EMBOLISM

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ABSTRACT

Background The use of thrombolytic agents in the treatment of hemodynamically stable patients with acute submassive pulmonary embolism remains controversial.

Methods We conducted a study of patients with acute pulmonary embolism and pulmonary hypertension or right ventricular dysfunction but without arterial hypotension or shock. The patients were randomly assigned in double-blind fashion to receive heparin plus 100 mg of alteplase or heparin plus placebo over a period of two hours. The primary end point was in-hospital death or clinical deterioration requiring an escalation of treatment, which was defined as catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter.

Results Of 256 patients enrolled, 118 were randomly assigned to receive heparin plus alteplase and 138 to receive heparin plus placebo. The incidence of the primary end point was significantly higher in the heparin-plus-placebo group than in the heparin-plus-alteplase group (P=0.006), and the probability of 30-day event-free survival (according to Kaplan–Meier analysis) was higher in the heparin-plus-alteplase group (P=0.005). This difference was due to the higher incidence of treatment escalation in the heparin-plus-placebo group (24.6 percent vs. 10.2 percent, P=0.004), since mortality was low in both groups (3.4 percent in the heparin-plus-alteplase group and 2.2 percent in the heparin-plus-placebo group, P=0.71). Treatment with heparin plus placebo was associated with almost three times the risk of death or treatment escalation that was associated with heparin plus alteplase (P=0.006). No fatal bleeding or cerebral bleeding occurred in patients receiving heparin plus alteplase.

Conclusions When given in conjunction with heparin, alteplase can improve the clinical course of stable patients who have acute submassive pulmonary embolism and can prevent clinical deterioration requiring the escalation of treatment during the hospital stay. (N Engl J Med 2002;347:1143-50.)

THROMBOLYSIS is an established treatment for patients with acute massive pulmonary embolism and hemodynamic instability or cardiogenic shock.[1] In contrast, the effect of thrombolytic agents on the outcome of hemodynamically stable patients who have submassive pulmonary embolism has been debated for decades.[2,3] Several factors have contributed to the ongoing controversy: the lack of a large, randomized study assessing clinical end points,[4] the risk of serious hemorrhage associated with thrombolytic therapy,[1,5-7] and the fact that patients' hemodynamic status may gradually improve with heparin therapy alone.[8,9]

The clinical data currently available underscore the need to identify patients in whom thrombolysis may have a favorable risk–benefit ratio. Studies based on two large, multicenter registries reported that patients with right ventricular dysfunction due to pulmonary embolism had increased rates of in-hospital death, even in the absence of arterial hypotension or shock.[5,10] These findings are in accord with the results of early experimental studies on the pathophysiology of venous thromboembolism.[11] Data from one of these registries also suggested that early thrombolytic therapy might favorably affect the prognosis of these patients.[12] We therefore undertook a randomized, placebo-controlled trial to compare the effects of treatment with heparin plus alteplase with the effects of heparin plus placebo on the outcome of patients with acute submassive pulmonary embolism. We focused on patients with pulmonary hypertension, right ventricular dysfunction, or both, but we excluded those with hemodynamic instability.

METHODS

Study Population

To be included in the trial, patients with acute pulmonary embolism had to fulfill at least one of the following criteria, which were defined a priori: echocardiographically detected right ventricular

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dysfunction, defined as right ventricular enlargement combined with loss of inspiratory collapse of the inferior vena cava, without left ventricular or mitral-valve disease[12]; echocardiographically detected pulmonary-artery hypertension,[13] defined as a tricuspid regurgitant jet velocity greater than 2.8 m per second, followed by confirmation of pulmonary embolism (by ventilation–perfusion lung scanning, spiral computed tomography [CT], or pulmonary angiography); a diagnosis of precapillary pulmonary hypertension based on catheterization of the right side of the heart, defined as a mean pulmonary-artery pressure above 20 mm Hg and a pulmonary-capillary wedge pressure below 18 mm Hg, followed by confirmation of pulmonary embolism; or new electrocardiographic signs of right ventricular strain (defined as complete or incomplete right bundle-branch block, S waves in lead I combined with Q waves in lead III, or inverted T waves in precordial leads V_1, V_2, and V_3), followed by confirmation of pulmonary embolism.

Patients were excluded from the study if they had one or more of the following characteristics: age over 80 years; hemodynamic instability, defined as persistent arterial hypotension (i.e., systolic pressure below 90 mm Hg), with or without signs of cardiogenic shock; onset of symptoms more than 96 hours before diagnosis; thrombolytic treatment, major surgery, or biopsy within the preceding 7 days; major trauma within the preceding 10 days; stroke, transient ischemic attack, craniocerebral trauma, or neurologic surgery within the preceding 6 months; gastrointestinal bleeding within the preceding 3 months; uncontrolled hypertension; a known bleeding disorder; known inability to tolerate alteplase; known diabetic retinopathy; current therapy with an oral anticoagulant; current pregnancy or lactation; a life expectancy of less than 6 months because of underlying disease; or planned use of thrombolytic agents for extensive deep-vein thrombosis.

The study protocol was approved by the local ethics committee at each institution. Written informed consent was obtained from all the patients.

Study Design

The study was designed as a prospective, randomized, double-blind, placebo-controlled trial and was conducted between September 1997 and August 2001 at 49 centers in Germany (see the Appendix) by a committee that included all the authors. Patients believed to have acute submassive pulmonary embolism, as previously defined,[12] received an intravenous bolus of 5000 U of unfractionated heparin before undergoing further diagnostic workup. Patients who met the inclusion criteria and were enrolled in the study were then randomly assigned to receive 100 mg of alteplase (Actilyse, Boehringer Ingelheim Pharma) as a 10-mg bolus, followed by a 90-mg intravenous infusion over a period of two hours, or matching placebo. Randomization was performed on a 1:1 basis with a fixed block size of six patients at each center, according to a standard randomization program. In addition to alteplase or placebo, patients in both groups received an intravenous infusion of unfractionated heparin. The infusion was started at a rate of 1000 U per hour, and the rate was subsequently adjusted to maintain the activated partial-thromboplastin time at 2.0 to 2.5 times the upper limit of normal. Measurements of the activated partial-thromboplastin time were performed at 6-hour intervals on day 1 after randomization, and at 12-hour intervals thereafter for at least four days. Overlapping oral anticoagulant therapy was started on day 3 after randomization, and the dosage was adjusted to maintain an international normalized ratio of 2.5 to 3.5. The trial protocol permitted breaking of the randomization code if additional therapy had to be provided on an emergency basis to a patient whose condition was deteriorating.

Definition of Clinical End Points

Patients were evaluated at the end of their hospital stay or on day 30 after randomization, whichever occurred first. The primary end point was in-hospital death or clinical deterioration that required an escalation of treatment after the infusion of alteplase or placebo was terminated. Escalation of treatment was defined as the use of at least one of the following: infusion of a catecholamine because of persistent arterial hypotension or shock (except for dopamine infused at a rate no more than 5 μg per kilogram of body weight per minute); secondary, or "rescue," thrombolysis (for one of the following indications: worsening clinical symptoms, particularly dyspnea, or worsening respiratory failure due to pulmonary embolism; arterial hypotension or shock; and persistent or worsening pulmonary hypertension or right ventricular dysfunction detected by echocardiography or right heart catheterization); endotracheal intubation; cardiopulmonary resuscitation; and emergency surgical embolectomy or thrombus fragmentation by catheter.

The secondary end points of the study were recurrent pulmonary embolism, major bleeding, and ischemic stroke. Recurrence of pulmonary embolism was confirmed by ventilation–perfusion lung scanning, spiral CT, or pulmonary angiography. Major bleeding was defined as fatal bleeding, hemorrhagic stroke, or a drop in the hemoglobin concentration by at least 4 g per deciliter, with or without the need for red-cell transfusion. Hemorrhagic or ischemic stroke was confirmed by CT or magnetic resonance imaging.

Statistical Analysis

The data were analyzed by an independent clinical research organization that also monitored the study (Parexel, Berlin, Germany). All the authors had full access to the data and participated in the data analysis. The null hypothesis was that there would be no difference between the two treatment groups with regard to the primary end point — that is, that the proportion of patients who reached the primary end point (death or the need for an escalation of therapy) would be the same in each group. On the basis of the data provided by the Management Strategies and Prognosis of Pulmonary Embolism Registry,[12] it was calculated that 217 patients would be required in each group to reject the null hypothesis with a power of 80 percent and at an alpha level of 5 percent, by the detection of a 33 percent relative reduction (or a 13 percent absolute reduction, from 39 to 26 percent) in the incidence of the primary end point. An interim analysis after the enrollment of the first 250 patients was prospectively planned to verify these calculations. The study was terminated after the interim analysis, which demonstrated a statistically significant difference in favor of alteplase treatment at that point.

Statistical analysis was performed according to the intention-to-treat principle. Differences between the treatment groups were examined with the use of Fisher's exact test (for proportions) and Student's t-test (for means of continuous variables). The time from randomization to death or escalation of treatment was analyzed with the use of the log-rank test, and Kaplan–Meier estimates of the probability of event-free survival were calculated. To define further the prognostic importance of treatment and other base-line variables, a proportional-hazards model was applied to the primary end point. The results are presented as relative risks and corresponding 95 percent confidence intervals. All reported P values are two-sided. Plus–minus values are means ±SD, unless stated otherwise.

RESULTS

Characteristics of the Patients

A total of 256 patients underwent randomization. Of these patients, 118 were assigned to the heparin-plus-alteplase group and 138 to the heparin-plus-placebo group. The two groups were well matched with regard to major clinical characteristics at base line (Table 1). There were no significant differences in systolic or diastolic blood pressure, heart rate, or the severity of dyspnea or arterial hypoxemia. Catheterization of the right side of the heart was performed in

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.*

CHARACTERISTIC	HEPARIN PLUS ALTEPLASE (N=118)	HEPARIN PLUS PLACEBO (N=138)	P VALUE
Clinical			
Sex — no. (%)			0.66
Male	54 (45.8)	68 (49.3)	
Female	64 (54.2)	70 (50.7)	
Age — yr			
Men	61.2±10.1	60.5±9.7	0.70
Women	64.4±9.5	62.2±12.4	0.25
Weight — kg			
Men	86.5±16.2	86.7±16.0	0.70
Women	75.2±15.3	75.6±13.6	0.25
Previous or concomitant disease — no. (%)			
Cardiovascular	84 (71.2)	92 (66.7)	0.52
Pulmonary	40 (33.9)	51 (37.0)	0.71
Gastrointestinal or hepatobiliary	38 (32.2)	56 (40.6)	0.21
Diabetes mellitus	46 (39.0)	57 (41.3)	0.80
Renal	28 (23.7)	25 (18.1)	0.34
Musculoskeletal or dermatologic	45 (38.1)	55 (39.9)	0.88
Neurologic	9 (7.6)	12 (8.7)	0.94
Blood pressure — mm Hg			
Systolic	133±19	133±20	1.00
Diastolic	79.7±12.0	80.8±13.0	0.49
Heart rate — beats/min	103±18.9	100±17	0.18
Respiratory rate — breaths/min	23.0±6.3	22.5±6.1	0.52
Partial pressure of arterial oxygen — mm Hg	63.9±28.7	59.6±24.6	0.20
Partial pressure of arterial carbon dioxide — mm Hg	29.4±8.7	28.7±9.9	0.55
Electrocardiographic			
S waves in lead I plus Q waves in lead III — no. (%)	41 (34.7)	76 (55.1)	0.002
Complete right bundle-branch block — no. (%)	12 (10.2)	13 (9.4)	0.99
Incomplete right bundle-branch block — no. (%)	34 (28.8)	50 (36.2)	0.26
Inverted T waves in leads V_1, V_2, and V_3 — no. (%)	53 (44.9)	67 (48.6)	0.65
Echocardiographic†			
Right ventricular dysfunction — no. (%)	37 (31.4)	43 (31.2)	0.92
Laboratory			
Hematocrit — %	40.9±5.0	41.3±4.7	0.51
Platelet count — per mm^3	221,000±73,600	223,000±95,900	0.87

*The numbers shown are based on calculations for the intention-to-treat population. Plus–minus values are means ±SD. Differences between the heparin-plus-alteplase group and the heparin-plus-placebo group were examined with the use of the chi-square test (or Fisher's exact test for neurologic disease) and Student's t-test.

†Echocardiography was performed in 106 patients in the heparin-plus-alteplase group (89.8 percent) and 129 patients in the heparin-plus-placebo group (93.5 percent). Right ventricular dysfunction was defined as the presence of an enlarged right ventricle (end-diastolic diameter >30 mm in the parasternal view or a right ventricle that appeared larger than the left ventricle in the subcostal or apical view) in the absence of inspiratory collapse of the inferior vena cava.

43 patients, 19 (16.1 percent) in the heparin-plus-alteplase group and 24 (17.4 percent) in the heparin-plus-placebo group. There were no significant differences between the two treatment groups with regard to pulmonary-artery pressures (systolic: 55.2±14.0 mm Hg in the heparin-plus-alteplase group and 60.42±15.9 mm Hg in the heparin-plus-placebo group; diastolic: 21.9±8.0 and 23.9±8.9 mm Hg, respectively; mean: 34.0±8.5 and 36.1±10.6 mm Hg, respectively).

Echocardiography was performed in 106 of the patients assigned to receive heparin plus alteplase (89.8 percent), and 129 of those assigned to receive heparin plus placebo (93.5 percent). The incidence of right ventricular dysfunction was almost identical in the two groups (Table 1). Doppler echocardiography revealed that the mean tricuspid regurgitant jet velocity was elevated in both groups (3.23±0.66 m per second in the heparin-plus-alteplase group, and 3.31±0.78 m per second in the heparin-plus-placebo group).

Clinical Outcome during the In-Hospital Phase

Table 2 summarizes in-hospital clinical events in the two study groups. The mean duration of the hospital

TABLE 2. IN-HOSPITAL CLINICAL EVENTS.*

EVENT	HEPARIN PLUS ALTEPLASE (N=118)	HEPARIN PLUS PLACEBO (N=138)	P VALUE†
	no. (%)		
Primary end point	13 (11.0)	34 (24.6)	0.006
Death from all causes	4 (3.4)	3 (2.2)	0.71
Escalation of treatment	12 (10.2)	34 (24.6)	0.004
Catecholamine infusion (for persistent hypotension or shock)	3 (2.5)	8 (5.8)	0.33
Secondary thrombolysis	9 (7.6)	32 (23.2)	0.001
Endotracheal intubation	3 (2.5)	3 (2.2)	0.85
Cardiopulmonary resuscitation	0	1 (0.7)	1.0
Embolectomy or thrombus fragmentation	0	1 (0.7)	1.0
Secondary end points			
Recurrent pulmonary embolism‡	4 (3.4)	4 (2.9)	0.89
Major bleeding§	1 (0.8)	5 (3.6)	0.29
Fatal bleeding	0	1 (0.7)	1.0
Hemorrhagic stroke¶	0	0	—
Ischemic stroke¶	0	1 (0.7)	1.0

*The numbers shown are based on calculations for the intention-to-treat population.

†P values were calculated with the use of Fisher's exact test (two-sided).

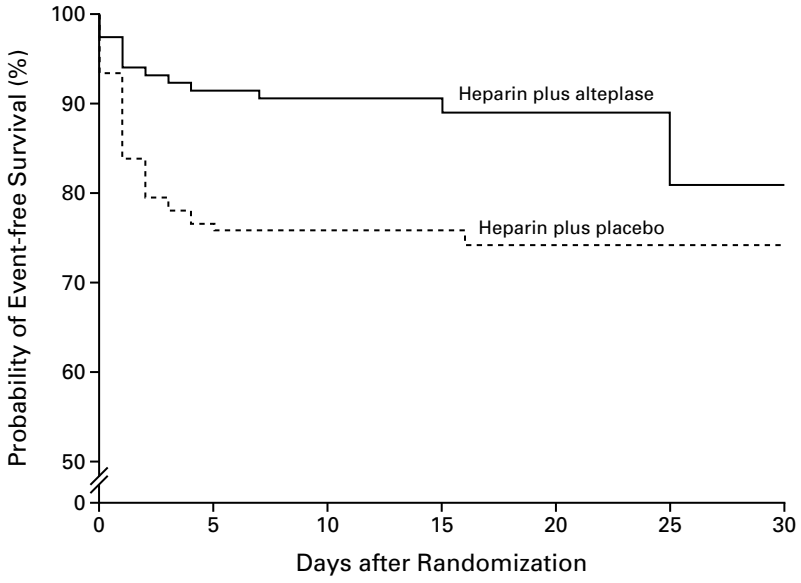
‡Recurrence of pulmonary embolism had to be confirmed by ventilation–perfusion lung scanning, spiral computed tomography, or pulmonary angiography.

§Major bleeding was defined as fatal bleeding, hemorrhagic stroke, or a drop in the hemoglobin concentration by at least 4 g per deciliter, with or without the need for red-cell transfusion.

¶Hemorrhagic or ischemic stroke had to be confirmed by computed tomography or magnetic resonance imaging.

stay was 16.7±8.4 days (range, 2 to 70). The mortality rate was low in both treatment groups. Four patients in the heparin-plus-alteplase group died, two from pulmonary embolism and two from underlying disease. Three patients in the heparin-plus-placebo group died, two from pulmonary embolism and one from a bleeding complication. Although the mortality rate in the two groups was similar, the rate of escalation of treatment because of clinical deterioration was much higher in the heparin-plus-placebo group than in the heparin-plus-alteplase group. For example, secondary (rescue) thrombolysis was performed roughly three times as often in the heparin-plus-placebo group as in the heparin-plus-alteplase group (Table 2). In the heparin-plus-placebo group, the indications for secondary thrombolysis were cardiogenic shock (in 4 patients), arterial hypotension requiring catecholamine infusion (in 4), and worsening symptoms and respiratory failure (in 24 patients, 3 of whom underwent endotracheal intubation and mechanical ventilation). In the heparin-plus-alteplase group, nine patients underwent additional thrombolysis, one because of arterial hypotension and the remaining eight because of worsening symptoms; one of the latter patients underwent endotracheal intubation). Overall, the incidence of the primary end point (death or escalation of treatment) was significantly greater in the heparin-plus-placebo group than in the heparin-plus-alteplase group (34 patients [24.6 percent] vs. 13 patients [11.0 percent], P=0.006).

In accord with these data, the probability of 30-day event-free survival according to Kaplan–Meier analysis was significantly higher in the group of patients treated with heparin plus alteplase than in those treated with heparin plus placebo (P=0.005 by the log-rank test) (Fig. 1). Further analysis with use of the proportional-hazards model confirmed that treatment with heparin plus placebo predicted an unfavorable in-hospital outcome: the relative risk of the primary end point with heparin plus placebo as compared with heparin plus alteplase was 2.63 (P=0.006) (Table 3). As shown in Figure 2, the favorable outcome of the patients assigned to heparin plus alteplase was not due to greater effectiveness of heparin anticoagulation in this group than in the other group, since the activated partial-thromboplastin time reached similar levels in the two treatment groups between 12 and 48 hours after randomization. Of the other baseline variables tested in the proportional-hazards model, age older than 70 years, female sex, and the pres-



No. at Risk							
Heparin plus alteplase	118	107	96	57	26	11	6
Heparin plus placebo	137	105	87	53	24	3	2

Figure 1. Kaplan–Meier Estimates of the Probability of Event-free Survival among Patients with Acute Submassive Pulmonary Embolism, According to Treatment with Heparin plus Alteplase or Heparin plus Placebo.

An event was defined as in-hospital death or clinical deterioration requiring an escalation of treatment after termination of the infusion of the study drug. Escalation of treatment was defined as at least one of the following: infusion of a catecholamine because of arterial hypotension or shock (except for dopamine infused at a rate of no more than 5 μg per kilogram per minute), secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter. P=0.005 by the log-rank test for the overall comparison between the groups.

ence of arterial hypoxemia were also found to predict an increased risk of in-hospital death or escalation of treatment (Table 3).

Secondary End Points, Safety, and Tolerability

The incidence of recurrent pulmonary embolism was low in both treatment groups (Table 2). However, its incidence may have been underestimated because of the relatively strict criteria for confirmation of recurrent thromboembolic events. Bleeding complications were uncommon, and the incidence of bleeding was not higher in the heparin-plus-alteplase group than in the heparin-plus-placebo group. In particular, there was only one fatal bleeding episode (in the heparin-plus-placebo group), and there were no hemorrhagic strokes. Minor symptoms that may have been related to the study medication were reported in 72 patients in the heparin-plus-alteplase group (61.0 percent) and in 78 patients in the heparin-plus-placebo group (56.5 percent) (P=0.55), but they did not result in discontinuation of treatment or breaking of the randomization code.

DISCUSSION

Previous studies have convincingly demonstrated the ability of thrombolytic agents to dissolve pulmonary emboli and to improve pulmonary perfusion and right ventricular function.[14-21] These medications are therefore recommended for the treatment of massive pulmonary embolism. However, the efficacy of thrombolytic agents in the treatment of submassive pulmonary embolism has remained unclear,[1] and identifying the patient population in which the benefits of thrombolysis may outweigh the associated risks of bleeding has been the subject of debate, mostly because of the lack of large-scale clinical trials.[4] Our study was designed to address these issues directly. Our results indicate that alteplase, given with heparin, improves the clinical course of hemodynamically stable patients who have acute submassive pulmonary embolism and that it does so with a low risk of major hemorrhagic complications.

The clinical course and prognosis of patients with acute pulmonary embolism vary widely, depending on their clinical and hemodynamic status at the time

TABLE 3. DETERMINANTS OF THE RISK OF IN-HOSPITAL DEATH OR ESCALATION OF TREATMENT.*

VARIABLE	RELATIVE RISK (95% CI)	P VALUE
Treatment with heparin plus placebo (vs. heparin plus alteplase)	2.63 (1.32–5.26)	0.006
Age >70 yr (vs. ≤70 yr)	2.29 (1.14–4.60)	0.02
Female sex (vs. male)	2.68 (1.34–5.36)	0.005
Presence of previous or concomitant disease (vs. absence)†		
Cardiac disease	1.72 (0.82–3.61)	0.15
Pulmonary disease	1.26 (0.65–2.43)	0.48
Diabetes mellitus	0.70 (0.36–1.37)	0.30
Systolic blood pressure ≤100 mm Hg (vs. >100 mm Hg)‡	1.50 (0.32–7.00)	0.60
Heart rate >100 beats/min (vs. ≤100 beats/min)	1.42 (0.75–2.68)	0.28
Repiratory rate >24 breaths/min (vs. ≤24 breaths/min)	1.50 (0.78–2.85)	0.22
Presence of arterial hypoxemia (vs. absence)§	3.57 (1.55–8.20)	0.003

*Relative risks and P values were calculated with the use of a proportional-hazards model. The relative risk associated with each variable at base line was adjusted for the type of treatment (heparin plus placebo or heparin plus alteplase). CI denotes confidence interval.

†Information on previous or concomitant cardiac disease, pulmonary disease, or diabetes mellitus was provided by the patients' physicians or was obtained from their medical records.

‡Patients who had a systolic blood pressure persistently below 90 mm Hg or who had signs of cardiogenic shock at base line were excluded from the trial.

§Arterial hypoxemia was defined as a partial pressure of arterial oxygen below 70 mm Hg or severe dyspnea requiring the administration of oxygen at a rate greater than 2 liters per minute.

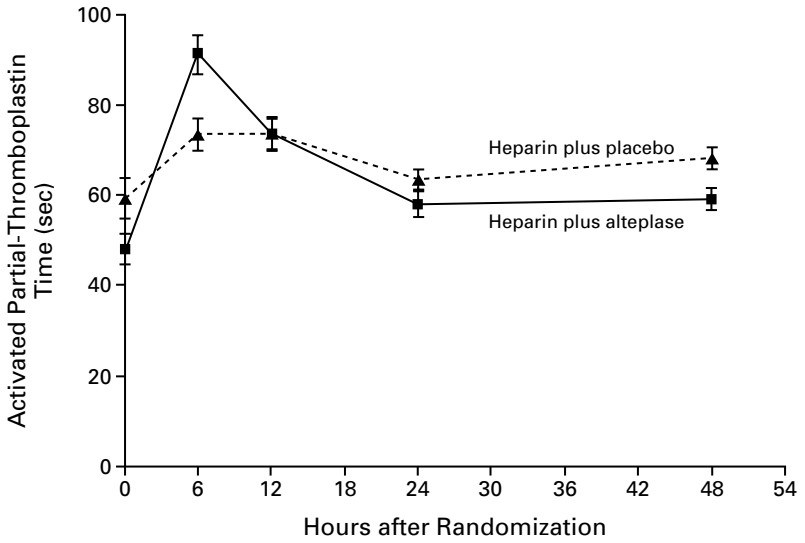


Figure 2. Mean Activated Partial-Thromboplastin Time in Patients with Acute Submassive Pulmonary Embolism, According to Treatment with Heparin plus Alteplase or Heparin plus Placebo.

The first measurement was performed at the time of randomization, after the patient had received 5000 U of heparin as a bolus injection. P=0.02 for the difference between the two treatment groups six hours after randomization. At all other times up to 48 hours, the difference between the groups was not significant. The I bars represent standard errors.

of diagnosis.[22-25] In particular, right ventricular dysfunction has been identified as a predictor of adverse outcome.[5,10,26] Thus, in the current trial, we focused on patients who presented with evidence of pulmonary hypertension, right ventricular dysfunction, or both of these conditions,[27] which were prospectively defined according to strict echocardiographic and hemodynamic criteria.[9,12] We excluded patients with persistent arterial hypotension or shock resulting from overt right ventricular failure; the prognosis of such hemodynamically unstable patients with massive pulmonary embolism is so poor[10] that withholding thrombolytic therapy (or other aggressive treatment) would be considered unethical, even though there is a lack of large clinical trials to prove its efficacy in these patients.[28]

In the current study, the patients in the two treatment groups were well matched with regard to baseline characteristics. Kaplan–Meier analysis showed that the probability of event-free survival during the hospital stay was significantly lower in the patients assigned to receive heparin plus placebo than in those assigned to receive heparin plus alteplase. Although the in-hospital mortality rate was similar in the two groups, the incidence of clinical deterioration requiring escalation of treatment was higher in the heparin-plus-placebo group. In particular, secondary thrombolysis (for predefined clinical and hemodynamic indications) was needed three times as often in the patients assigned to heparin plus placebo. Given the strict randomization and blinding used in the trial, it seems unlikely that the higher incidence of secondary thrombolysis in the heparin-plus-placebo group was due to bias on the part of the investigators in favor of thrombolytic therapy. Therefore, it seems reasonable to assume that delayed resolution (or lack of resolution)[8,9] or recurrence[20] of pulmonary embolism with heparin alone resulted in persistence or deterioration of pulmonary hypertension and right-sided heart failure.[29]

In-hospital mortality rates were low in our study, and there were no significant differences between the two treatment groups. This finding was unexpected, in view of the results of analysis of the Management Strategies and Prognosis of Pulmonary Embolism registry, which showed a mortality rate of 8 percent among hemodynamically stable patients with right ventricular dysfunction.[10] However, patient monitoring is closer and the degree of alertness on the part of caregivers is generally higher in randomized therapeutic trials than in registries, and it is possible that, in the current trial, clinicians' prompt response to early signs of clinical deterioration averted some in-hospital deaths.

Thrombolysis may be associated with a significant increase in the risk of fatal or disabling hemorrhagic complications.[7,12,30] However, the rates of bleeding in our patient population were very low, and no patient had intracranial or fatal hemorrhage after treatment with alteplase. Our findings, combined with those of another controlled trial of thrombolysis in pulmonary embolism,[20] support the notion that alteplase is a safe treatment for hemodynamically stable patients with acute submassive pulmonary embolism, provided that it is not given to patients with contraindications to thrombolysis and provided that the patients' clinical condition and coagulation status are closely monitored.

In conclusion, the findings of this randomized, double-blind, placebo-controlled trial show that treatment with alteplase, given in conjunction with heparin, may improve the clinical course of patients with acute submassive pulmonary embolism and, in particular, that such treatment may prevent further clinical or hemodynamic deterioration requiring the escalation of treatment during the hospital stay. On the basis of these data, we believe that the indications for thrombolysis, which are currently limited to massive pulmonary embolism, can be extended to include submassive pulmonary embolism (manifested as right ventricular pressure overload and dysfunction) in hemodynamically stable patients. Patients thus treated should be carefully monitored to ensure that they are at low risk for serious bleeding complications.

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APPENDIX

The following investigators participated in the Management Strategies and Prognosis of Pulmonary Embolism-3 Trial: **Steering Committee:** W. Kasper, S. Konstantinides, A. Geibel, G. Heusel, E. Bluhmki, F. Heinrich, and K. Rauber; **Participating investigators and centers:** W. Kasper, *St. Josefs Hospital, Wiesbaden;* E. Wolff, *Kreiskrankenhaus, Demmin;* G. Lockert, *Krankenhaus Stade, Stade;* H. Hoetz, *Krankenhaus Ludmillens, Meppen an der Ems;* V. Hitz, *Ruppiner Kliniken, Neuruppin;* W. Rösch and G.C. Cieslinski, *Krankenhaus Nordwest, Frankfurt am Main;* M. Wiersbitzky, *Universitätsklinik, Greifswald;* M. Bollhorst, *Kreiskrankenhaus, Sinsheim;* F. Höltermann, *Kreiskrankenhaus, Weinheim;* W. Sehnert, *Evangelisches Krankenhaus, Herne;* J. Lehmann, *Krankenhaus vom Deutschen Roten Kreuz, Saarlouis;* D. Widmann, *Städtisches Krankenhaus, Pfullendorf;* E. Kauder, *Kreiskrankenhaus, Tuttlingen;* K. Schlotterbeck, *Kreiskrankenhaus, Traunstein;* C. Wonhas, *Kreiskrankenhaus, München-Pasing;* A. Geibel, *Universitätsklinik, Freiburg;* H.D. Bundschuh and M. Haag, *Caritas Krankenhaus, Bad Mergentheim;* R. Thiele, *Universitätsklinik, Jena;* C. Kelbel, *Kreiskrankenhaus, Lüdenscheid;* H.J. Simon, *Krankenhaus Düren, Düren;* G. Krahnstöver, *Katharinen Hospital, Willich;* U. Fahrenkrog, *Klinikum Remscheid, Remscheid;* A. Zeiher, *Universitätsklinik, Frankfurt am Main;* J. Cyran, *Städtisches Krankenhaus, Heilbronn;* F. Forycki, *Krankenhuas Neukölln, Berlin;* J. Kohler, *Klinikum der Stadt Villingen-Schwenningen, Villingen-Schwenningen;* B. Kohler, *Krankenhaus Bruchsal, Bruchsal;* R. Zahn, *Klinikum der Stadt Ludwigshafen, Ludwigshafen;* M. Weise and J. Neidermeyer, *Universitätsklinik, Dresden;* B. Becker, *St. Gertrauden Krankenhaus, Berlin;* P. Limbourg, *Stadtkrankenhaus, Worms;* P. Schweitzer, *Evangelisches Krankenhaus, Bergisch-Gladbach;* H. Ditter, *Städtisches Krankenhaus, Gütersloh;* K.E. Hauptmann, *Krankenhaus der Barmherzigen Brüder, Trier;* D.C. Gulba, *Virchow Klinikum, Humboldt Universität, Berlin;* H. Nebelsieck, *Kreis-*

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