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 inhospital 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.


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

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. These findings are in accord with the results of early experimental studies on the pathophysiology of venous thromboembolism. Data from one of these registries also suggested that early thrombolytic therapy might favorably affect the prognosis of these patients. 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...
dysfunction, defined as right ventricular enlargement combined with loss of inspiratory collapse of the inferior vena cava, without left ven-
tricular or mitral-valve disease; 12 echocardiographically detected pul-
monary-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 cath-
eterization of the right side of the heart, defined as a mean pul-
monary-artery pressure above 20 mm Hg and a pulmonary-cali-
per wedge pressure below 18 mm Hg, followed by confirmation of pul-
monary embolism; or new electrocardiographic signs of right ven-
tricular 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 V2, V3, and V4), 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 pre-
ceding 7 days; major trauma within the preceding 10 days; stroke;
transient ischemic attack, cranioencephal trauma, or neurologic sur-
gery 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 antico-
agulant; 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 Sep-
tember 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 previous-
lly defined, 12 received an intravenous bolus of 5000 U of unfraction-
ated 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 ran-
domization program. In addition to alteplase or placebo, patients in
both groups received an intravenous infusion of unfractionated hep-
arin. 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 ran-
domization 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 re-
quired 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 be-
cause of persistent arterial hypotension or shock (except for dopa-
mine 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, particu-
larly dyspnea, or worsening respiratory failure due to pulmonary em-
bolism; arterial hypotension or shock; and persistent or worsening
pulmonary hypertension or right ventricular dysfunction detected
eyechocardiography 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 pulmo-
nary 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 ische-
ic stroke was confirmed by CT or magnetic resonance imaging.

Statistical Analysis

The data were analyzed by an independent clinical research or-
ganization 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 dif-
ference between the two treatment groups with regard to the pri-
mary end point — that is, that the proportion of patients who
reached the primary end point (death or the need for an escala-
tion of therapy) would be the same in each group. On the basis of the
data provided by the Management Strategies and Prognosis of Pul-
monary 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 de-
tection 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 demonstrat-
ed 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 ex-
amined 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 vari-
ables, 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. Catheteriza-
tion of the right side of the heart was performed in

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 60.4±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
The 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 alteplase 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-

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**Table 2. In-Hospital Clinical Events.***

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

*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.
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.*

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

*Relative risks and P values were calculated with the use of a proportional-hazards model. The relative risk associated with each variable at baseline 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 baseline 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.\textsuperscript{22-25} In particular, right ventricular dysfunction has been identified as a predictor of adverse outcome.\textsuperscript{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,\textsuperscript{27} which were prospectively defined according to strict echocardiographic and hemodynamic criteria.\textsuperscript{9,11} 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\textsuperscript{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.\textsuperscript{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)\textsuperscript{8,9} or recurrence\textsuperscript{20} of pulmonary embolism with heparin alone resulted in persistence or deterioration of pulmonary hypertension and right-sided heart failure.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{30} 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**

REFERENCES